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Name: THOMAS H. BEMBRY

Present position: INSTRUCTOR OF CHEMISTRY
COLLEGE OF THE CITY OF NEW YORK, N.Y.C.

Address: 143-50 FERNDALE AVE
JAMAICA, NEW YORK

Significant recent activities:
RESEASCH CHEMIST
WAR RESEARCH PROGRAM
COLUMBIA UNIVERSITY, NEW YORK, N.Y.

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COMPOUNDS OF THE CANNABINOL TYPE

DISSERTATION

Submitted in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy
in the Faculty of Pure Science
of Columbia University

BY

THOMAS HENRY BEMBRY

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TO MY WIFE

ACKNOWLEDGMENT

The author wishes to express his deep gratitude to Professor Garfield Powell under whose guidance this research was carried out, for his invaluable advice and encouragement throughout the course of this work. The author also wishes to express his appreciation to Smith, Kine and French and to the Rosenwald Fund for financial assistance in this work.

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APPENDIX

TABLE III.

Marihuana Activity of Cannabinol Types*

	Name of Compound Dibenzopyranes	Activity	Maximum Deviation
1.	2,6,6-trimethyl-7,8,9,10-tetrahydro—(VII)	0	
2.	1-Hydroxy-3,6,6,9-tetramethyl-tetrahydro—(XXVIII)	0	
3.	1-Hydroxy-3-n-amyl-6,6,9-trimethyl-tetrahydro—(XLV)	10	± 3
4.	1-Methoxy-3-n-amyl-6,6,9-trimethyl-tetrahydro—(XLVII)	No marihuana but narcotic	
5.	1-Amyloxy-3-n-amyl-6,6,9-trimethyl-tetrahydro—(XLVIII)	No marihuana but narcotic	
6.	Bromine product of 1-hydroxy-3-n-amyl-6,6,9-trimethyl-tetrahydro—(XLVI)	12	± 3
7.	1-Hydroxy-3-methyl-6,6-diethyl-tetrahydro—(XIV)	No marihuana but narcotic	
8.	1-Hydroxy-3-methyl-6,6-dipropyl-tetrahydro—(XV)	No marihuana but narcotic	
9.	1-Hydroxy-3-methyl-6,6-dibutyl-tetrahydro—(XVI)	No marihuana but narcotic	
10.	1-Hydroxy-3-methyl-6,6-di-amyl-tetrahydro—(XVII)	No marihuana but narcotic	
11.	1-Hydroxy-3-n-amyl-6,6-diethyl-9-methyl-tetrahydro—(L)	1	
12.	1-Hydroxy-3-n-amyl-6,6-dipropyl-9-methyl-tetrahydro—(LI)	1 or less	
13.	1-Hydroxy-3-n-amyl-6,6-dibutyl-9-methyl-tetrahydro—(LII)	1 or less	
14.	1-Hydroxy-3-n-amyl-6,6-dimethyl-tetrahydro—(XLII)	No marihuana but narcotic	
15.	Red oil distillates	80	± 25

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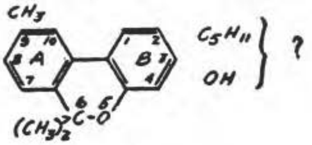
* The above activities were determined by Dr. R. P. Walton of the University of Mississippi, using dogs as experimental animals. The activities are expressed in terms of a standard U. S. P. extract of cannabis.

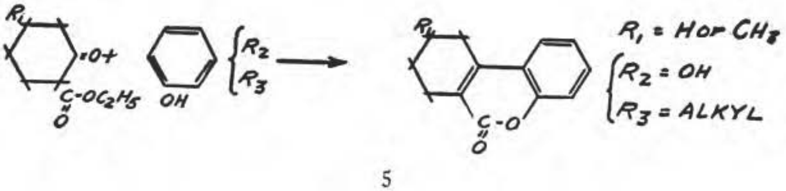
COMPOUNDS OF THE CANNABINOL TYPE

INTRODUCTION

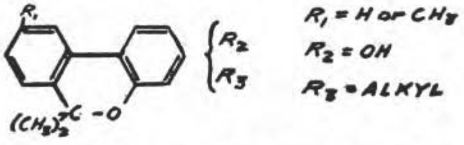
In the inquiry into the nature of the principle of the hemp plant (Cannabis sativa) responsible for marihuana effects, the place of cannabinol is important. This compound, isolated in high yields from active distillates, is toxic but does not give the typical marihuana effects. Nevertheless, because the chemical properties of the most active distillates resemble very closely the chemical properties of cannabinol and because the analyses of such distillates lie very close to that of cannabinol itself, it has long been suspected that the active principle is a near relative of cannabinol. Investigation into the constitution of cannabinol has therefore been pursued by many workers,[1,2,3,5,6,7] and at the beginning of this research it was formulated as a 6, 6-dimethyl-dibenzopyrane of the following constitution with doubt only as to the position of the hydroxyl and amyl group on ring B:



It was the purpose of this study to exploit synthetic methods for approaching compounds of the cannabinol type with the view to settling the constitution of cannabinol and of providing related compounds for physiological study. Examination of the literature indicated that probably the most useful route to such compounds would be an extension of the method of Sen and Basu[10] for the preparation of the substituted tetrahydrobenzocoumarins in excellent yields according to the following general reaction:

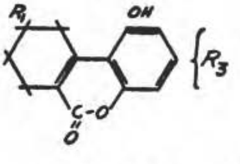


The next step would be either dehydrogenation followed by the use of the Grignard to give the type;

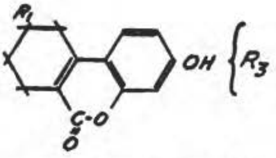


or in the opposite order, that is, the use of the Grignard first followed by dehydrogenation.

Since the reaction of Sen and Basu[10] is known to occur with dihydric phenols and since the cyclohexanones are available, the method would lead to substances closely resembling the formulated cannabinol. Assuming that these suggested reactions are successful, the only item to be decided in reference to the use of the dihydric phenols would be the position of the condensation of the two rings with reference to the hydroxyl groups. Since only one compound was reported in each of these condensations and on the basis of the high yields obtained, the reaction must have proceeded mainly in one direction and it is predicted that of the two possibilities outlined below for the dihydric phenols, the one with the rings joining between the two hydroxyls seems most reasonable:



OR



However, the final proof of the position will have to be given in the course of work on representative compounds.

This reaction was tested and found very satisfactory on orcinol and other representative phenols (See Bembry and Powell,[9] also for reactions involved see Flow Sheet I, Series A) and was used to prepare compounds related to cannabinol. The position of the condensation between the two rings was settled meanwhile by Adams and Baker[17] and cannabinol itself was also synthesized.[16] The method was then used for the most part to prepare the tetrahydro-dibenzopyrane derivatives and others described below. These derivatives are the most important ones for consideration in dealing with marihuana activity, since it has been established only recently by Adams and his co-workers[15] that the tetrahydrocannabinols possess marihuana activity.

RESULTS AND CONCLUSIONS

1. The method of Sen and Basu[10] for the preparation of the tetrahydrobenzo-coumarins has been extended to the study of the cannabinol types.

2. The extended method is a convenient way to obtain either the cannabinol- or the partially reduced cannabinol-types.

3. 2-Methyl-7, 8, 9, 10-tetrahydro-dibenzopyrone (V) when dehydrogenated with sulphur gave 2-methyl-dibenzopyrone (VI) which was identical with that prepared by Kahn[6] by a less practical method.

4. 2, 6, 6-Trimethyl-7, 8, 9, 10-tetrahydro-dibenzopyrane (VII) was dehydrogenated to give directly the corresponding pyrane (VIII) which corresponds to the basic cannabinol type.

5. In the preparation of olivetol (5-n-amyl-resorcinol) the procedure of Suter and Weston[19] involving the reaction of butyl magnesium bromide on dimethoxy-benzamide to form dimethoxy-valerophenone failed when applied to the reaction of the same Grignard on 3, 4, 5-trimethoxy-benzamide, instead a mixture of substances was formed from which was isolated a dimethoxy-butyl-valerophenone instead of the expected trimethoxy-valerophenone.

6. Likewise as in 5 above the reaction of butyl magnesium bromide on trimethoxy-benzonitrile (XXXVII) failed to give the expected trimethoxy-valeriophenone (XXXVIII) but instead gave mainly the identical ketone obtained in 5 above. Here are presented additional examples of the lability of the 4-methoxy in 3, 4, 5-trimethoxy-benzo derivatives as have been observed in other instances by Kostanecki,[26] Semmler[27] and Thomas.[28]

7. A series of tetrahydro-dibenzopyranes was synthesized, including tetrahydrocannabinol itself (XLV), as well as tetrahydrocannabinols in which the 9-methyl is substituted by hydrogen

(XLII) and in another case where the 3-n-amyl is substituted by a methyl (XXVIII).

8. Compounds possessing marihuana activity were prepared in the course of this work.

9. Typical marihuana activity was associated with partially reduced cannabinol itself and was lost through slight departure from the basic cannabinol structure. Although typical marihuana activity was lost by such a departure, the compounds still possessed some narcotic properties.

10. Homologs up to 6,6-di-n-amyl of 1-hydroxy-3,6,6-trimethyl-tetrahydro-dibenzopyrane and up to 6,6-di-n-butyl of tetrahydrocannabinol were prepared through extended application of the pyrane synthesis developed.

11. The hydrogen content of the tetrahydro-dibenzopyrane molecule was reduced to values between the tetrahydro and the completely dehydrogenated pyrane by treatment with one mole of bromine. In the case of such treatment on tetrahydrocannabinol the resulting product possessed a higher marihuana activity than did the original tetrahydrocannabinol. The possibility of deep-seated changes within the molecule by bromine treatment was not excluded.

12. Study of the bio-assays of the synthetic compounds suggest that the active principle of the red oil is a compound or mixture of compounds where ring A of cannabinol is partially reduced to di- or tetra-hydro or both where the essential difference between the synthetic compounds and the naturally occurring product is in the difference in the position of the double bond in this ring.

13. The following new compounds were prepared in the course of this work:

(1). 2-Methyl-7,8,9,10-tetrahydro-6-dibenzopyrone (V)

(2). 2,6,6-Trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrane (VII)

(3). 2-(Methyl-4'-methyl-6'-cyclohexene$\Delta^{1'-6'}$-1'-carboxylate) 1,3-dimethoxy-5-methyl-benzene (XXVI)

(4). 2-(4'-methyl-6'-cyclohexene$\Delta^{1'-6'}$-1'-carboxylic acid) 1,3-dimethoxy-5-methyl-benzene (XXVII)

(5). 1-Acetoxy-3,9-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyrone (XXIIIa)

(6). 1-Methoxy-3,9-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyrone (XXIV)

(7). 1-Acetoxy-3,6,6,9-tetramethyl-7,8,9,10-tetrahydro-6-dibenzopyrane (XXIX)

(8). 2-(1'-Isopropyloxy-4'-methyl-6'-cyclohexene$\Delta^{1'-6'}$–) 1-methoxy-3-hydroxy-5-methyl-benzene (XXIVa)

(9). 1-Hydroxy-3-n-amyl-7,8,9,10-tetrahydro-6-dibenzopyrone (XLI)

(10). 1-Hydroxy-3-n-amyl-6,6-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyrane (XLII)

(11). 3,5-Dinitrophenyl-urethane of 1-hydroxy-5-n-amyl-6,6-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyrane (XLIII)

(12). 3,5-Dinitrophenyl urethane of tetrahydrocannabinol (XLIX)

(13). Semicarbazone of dimethoxy-butyl-valerophenone

(14). 1-Methoxy-3-n-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrane (XLVII)

(15). 1-Amyloxy-3-n-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrane (XLVIII)

(16). 1-Hydroxy-3-methyl-6,6-diethyl-7,8,9,10-tetrahydro-6-dibenzopyrane (XIV)

(17). 1-Hydroxy-3-methyl-6,6-di-n-propyl-7,8,9,10-tetrahydro-6-dibenzopyrane (XV)

(18). 1-Hydroxy-3-methyl-6,6-di-n-butyl-7,8,9,10-tetrahydro-6-dibenzopyrane (XVI)

(19). 1-Hydroxy-3-methyl-6,6-di-n-amyl-7,8,9,10-tetrahydro-6-dibenzopyrane (XVII)

(20). 1-Hydroxy-3-n-amyl-6,6-diethyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrane (L)

(21). 1-Hydroxy-3-n-amyl-6,6-di-n-propyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrane (LI)

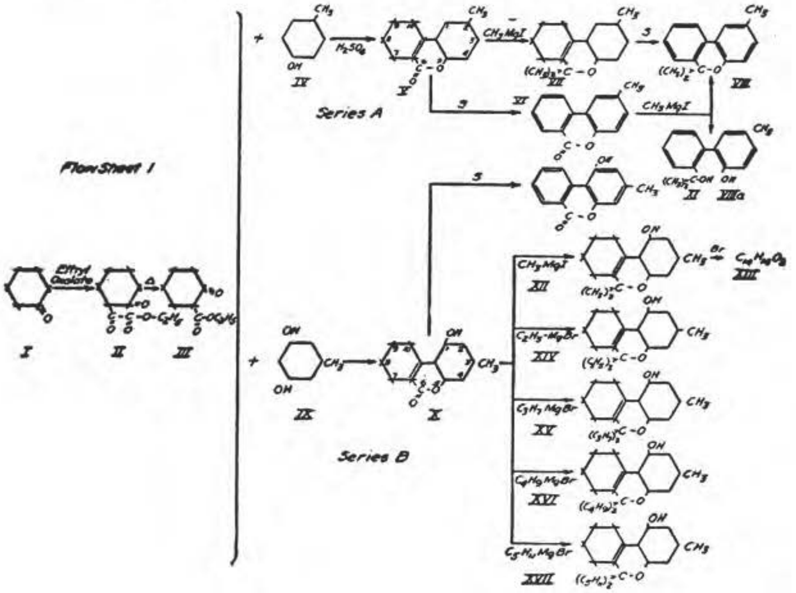
(22). 1-Hydroxy-3-n-amyl-6,6-di-n-butyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrane (LII)

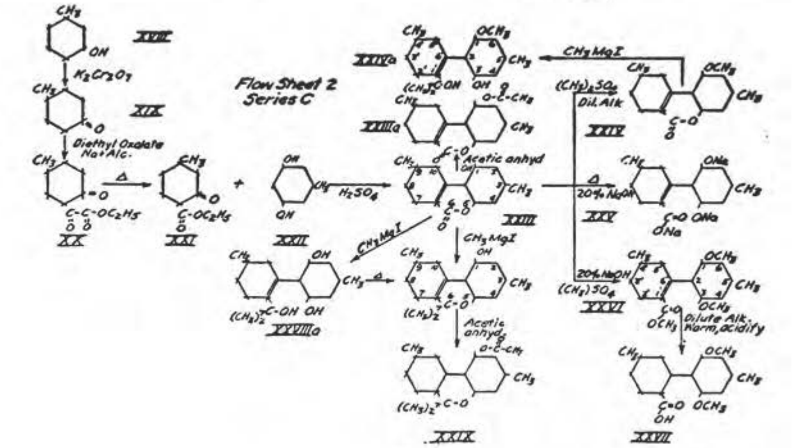
NOMENCLATURE

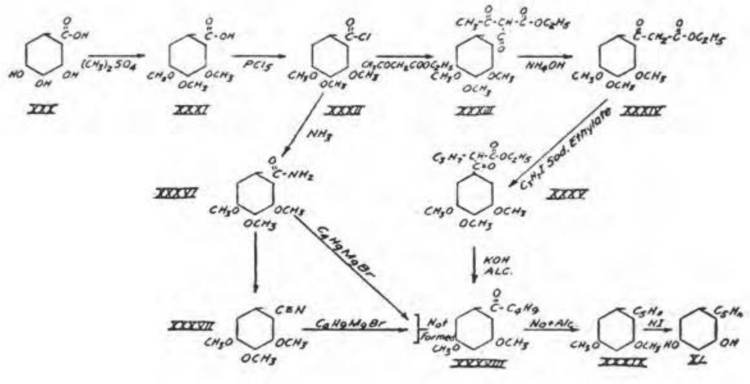
The system of nomenclature used in this dissertation is that of the Chemical Abstracts.

Roman numerals refer to compounds of the Flow Sheet.

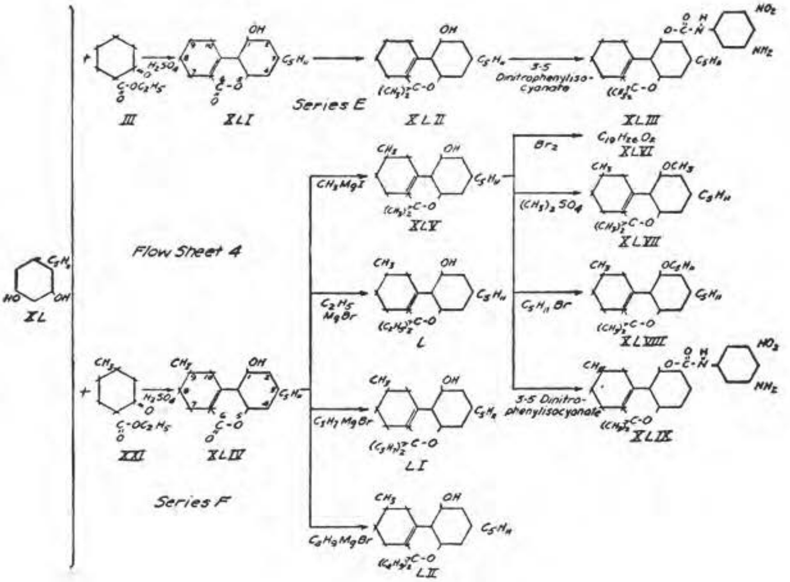
Arabic numerals in the text refer to bibliography.







Flow Sheet 3
Series D



DISCUSSION

The Model Pyrane: 2,6,6-Trimethyl-6-dibenzopyrane (VIII)

The synthesis of 2,6,6-trimethyl-dibenzopyrane was chosen as the first step in this work, because it is one of the pyranes prepared by Kahn[6] and its preparation at the outset will offer a direct test of the proposed synthetic method. Accordingly p-cresol was condensed with ethyl-cyclohexanone-2-carboxylate (III), prepared from cyclohexanone and oxalic ester after the method of Kotz and Michels[11] in the presence of sulphuric acid to give the 2-methyl-7,8,9,10-tetrahydro-dibenzopyrone (V). This was smoothly dehydrogenated with sulphur to the corresponding dehydro-pyrone (VI), and which was in turn allowed to react with methyl magnesium iodide to form Kahn's 2,6,6-trimethyl-dibenzopyrane (VIII). In fact the tetrahydro-pyrone first formed could be converted to the tetrahydropyrane directly by treatment with the Grignard and then the tetrahydropyrane formed dehydrogenated to Kahn's dibenzopyrane. Of the two paths opened for proceeding to the pyrane, it was more practical for the purposes of this research to proceed at once to the tetrahydro-dibenzopyrane and allow the dehydrogenation to be a secondary reaction, because the tetrahydro-dibenzopyranes are sufficiently close to cannabinol to warrant study themselves.

Pyranes Derived from the Condensation of 5-Methyl-resorcinol with Both Ethyl- and Ethyl-5-methyl-cyclohexanone-2-carboxylate

With the success of the model experiment, and because of the complex types of phenols, the various substituted ethyl-cyclohexanone-2-carboxylates as well as the variation in the type of Grignard agents which could be used, it was at once evident that there was at hand a practical method for synthesizing cannabinol as well as a wide variety of cannabinol types. For the purpose of synthesizing the cannabinol types, the phenols showing the greatest promise were the dihydroxy-alkyl-benzenes, because Kahn had already shown the phenolic ring of cannabinol to be a dihydroxyl-amyl-benzene in which one hydroxy group was involved in the formation of the lactone ring. Whether the orientation of the phenolic ring was that of catechol or resorcinol or whether the alkyl was 1-2 or 1-3 in either of these systems, Kahn[6] was not able to decide on the basis of the chemical evidence accumulated.

Upon the examination of known structures of other plant products, it was observed that 5-n-amyl resorcinol was a constituent of the depsides olivetoric acid and physodic acid which are found in several species of Japanese lichens.[12] The observation indicated the possibility that the dihydroxy-amyl-benzene of cannabinol might have the 5-n-amyl-resorcinol arrangement. With this suggestion the phenols chosen for the preparation of the pyranes were 5-methyl resorcinol (orcinol) and 5-n-amyl-resorcinol (olivetol). While this work was well on its way and already a definite route to the synthesis of the cannabinol types had been established (See Bembry and Powell [9]), Adams and his co-workers[13] showed that cannabidiol, a new product recently isolated by them[14] from the red oil of Minnesota hemp, could be cleaved to give olivetol (5-n-amyl-resorcinol) and p-cymene and that cannabidiol and cannabinol had the same orientation of constituents by isomerizing the former into the latter.[15] This showed definitely, therefore, that the phenolic ring of cannabinol was that of 5-n-amyl-resorcinol.

Before using 5-n-amyl resorcinol in these condensations, the readily available 5-methyl resorcinol (IX) was first used. This phenol was condensed with ethyl-cyclohexanone-2-carboxylate (III) primarily for the purpose of verifying the position of the rings in the condensation reaction, for Adams and Baker[17] had prepared 1-hydroxy-3-methyl-dibenzopyrone (XI) by a method which involves the reaction of o-brombenzoic acid with dihydro-orcinol, and which leaves no doubt as to the orientation of the rings, which in this case was between the two hydroxyls. Now if the tetrahydro-dibenzopyrone (X) obtained in this work from orcinol and ethyl-cyclohexanone-2-carboxylate were dehydrogenated, a pyrone comparable to that of Adams and Baker would be produced. Accordingly the orcinol condensation product was dehydrogenated with sulphur, and the resulting 1-hydroxy-3-methyl-dibenzopyrone (XI) was identical in every detail with that prepared by Adams and Baker. Therefore, the condensation of the 5-alkyl resorcinols with the cyclohexanone-2-carboxylates takes place between the two hydroxyl groups as predicted.

The next application of the orcinol condensation was to test it in a reaction with ethyl-methyl-cyclohexanone-2-carboxylate (XXI), a reaction which approaches more closely the basic cannabinol structure by introducing a methyl group in the 9-position of the tetrahydro-dibenzopyrone formed (XXIII). This reaction proceeded as readily as the unsubstituted cyclohexanone-2-carboxylate.

These hydroxy-alkyl-tetrahydro-dibenzopyrones exhibit interesting properties. The stability of the lactone bridge is remarkable, being only broken by prolonged boiling with concentrated sodium hydroxide and immediately reformed upon acidification. For a somewhat detailed study of these hydroxy-alkyl-tetrahydro-dibenzopyrones, 1-hydroxy-3,9-dimethyl-7,8,9,10-tetrahydro-dibenzopyrone (XXIII) was used. This readily formed a monomethyl ether (XXIV) with dimethyl sulphate and alkali, the lactone bridge being entirely undisturbed by this reaction. On the other hand if the lactone is refluxed with 20 per cent sodium hydroxide for thirty minutes, the lactone ring was broken (XXV) and then on treatment with dimethyl sulphate the dimethyl ether (XXVI) was formed as well as the methyl ester of the carboxyl freed by the lactone breaking. The methyl ester of the dimethoxy-diphenyl-carboxylic acid (XXVI) could be hydrolized to the corresponding acid (XXVII) by warming with dilute alkali.

In order to convert the hydroxy-alkyl-tetrahydro-dibenzopyrones (X, XXIII) into the corresponding tetrahydro-pyranes (XII, XXVIII) they were treated with methyl magnesium iodide. If the free phenol is used the reaction is slow and an excess of 10 to 15 moles of the Grignard must be used and prolonged refluxing in benzene is necessary in order to complete the reaction. Whereas if the monomethyl ether (XXIV) is used the reaction is over in a few hours. Although the action of the Grignard on the ether was much smoother than on the free phenol, this method was not used throughout in order to avoid complications which might present themselves in the subsequent splitting of the ether in order to obtain the desired free phenol. When the Grignard reacts with the phenolic tetrahydro-pyranes, glycols (XXIVa, XXVIIIa) were formed as an intermediate step. In this work the glycols were not isolated but treated directly with a dehydrating agent such as phosphorous pentoxide and a high boiling solvent such as xylene. As a matter of fact, direct distillation of these glycols was sufficient to dehydrate them and form the pyrane ring, but it was observed that the yield as well as the quality of the product were somewhat better when the glycols were dehydrated in order to effect ring closure before distillation.

Synthesis of 5-n-amyl-resorcinol (Olivetol) (XL)

With the condensation of the 5-n-alkyl resorcinol and the cyclohexanone carboxylates, the ready conversion of the tetrahydro-pyrones into the 6,6-dimethyl-tetrahydro-pyranes by treatment with methyl magnesium iodide and the possible dehydrogenation to the 6,6-dimethyl pyranes well established by the foregoing experiments, it was now time to apply these procedures to the synthesis of compounds which were more closely related to cannabinol. For this purpose ethyl-cyclohexanone-2-carboxylate (III) and ethyl-5-methyl-cyclohexanone-2-carboxylate (XXI) were to be condensed with olivetol (XL). Olivetol was not readily available, having already been synthesized by two rather cumbersome methods involving a large number of steps. The first method by Asahina[18] required gallic acid as the starting material which was converted into olivetol through a series of eight transformations (Flow Sheet 3, Series D) involving the formation of trimethylgallic acid (XXXI), trimethoxy-benzoyl-chloride (XXXII), trimethoxy-benzoyl-acetoacetic ester (XXXIII), trimethoxy-benzoyl-acetic ester (XXXIV) and trimethoxy-benzoyl-propyl-acetic ester (XXXV), which undergoes ketone decomposition to give trimethoxy-valerophenone (XXXVIII). This was reduced with sodium and alcohol to the hydrocarbon, losing simultaneously the p-methoxy group. The resulting dimethyl ether (XXXIX) was cleaved to olivetol. The last five steps are oily products and considerable practice with the procedure was necessary before maximum yields of 25 grams of pure olivetol could be obtained from 500 grams of gallic acid.

The second method by Suter and Weston[19] had the serious disadvantage of starting with the difficultly accessible 3,5-dihydroxybenzoic acid. This was converted into dimethoxy-benzamide, which was allowed to react with butyl magnesium bromide to give at once the dimethoxy-valerophenone, which in turn was reduced and cleaved to give olivetol. Once the dihydroxy-benzoic acid is available there is no doubt that this method has considerable advantage over that of Asahina.

In order to combine the advantage of readily available starting materials of the method of Asahina and the advantage of the more direct addition of the butyl group through the use of the Grignard of the method of Suter and Weston, an attempt was made to prepare olivetol by allowing the easily accessible trimethoxy-benzamide (XXXVI) to react with the butyl Grignard to give directly the desired trimethoxy-valerophenone (XXXVIII). In this reaction, however, none of the desired valerophenone was formed, but instead a ketone which was minus one methoxy group and carried an extra butyl group was isolated from the reaction mixture. When trimethoxy-benzonitrile (XXXVII) was substituted for the amide in this reaction the identical ketone was obtained which indicates the generality of this behavior of the 3,4,5-trimethoxy-benzo derivatives towards the butyl Grignard under the conditions of these experiments. An explanation of this behavior is possibly based on the peculiar properties of the p-methoxy group between two other methoxy groups as have been observed in other instances.[26, 27, 28]

Nor-tetrahydrocannabinol (XLII) and Tetrahydrocannabinol (XLV)

The condensation of 5-n-amyl resorcinol with ethyl- and ethyl-5-methyl-cyclohexanone-2-carboxylate and the reaction of the tetrahydro-n-amyl-pyrones (XLI), (XLIV) formed with the methyl Grignard proceed with equal readiness as with the 5-methyl-resorcinol reactions to give *nor*-tetrahydrocannabinol and tetrahydrocannabinol respectively as colorless viscous liquids which redden on exposure to air. The oils were identified through their 3,5-dinitro-phenyl-urethanes (XLIII), (XLIX).

Adams and his co-workers[15] reported the isomerization of cannabidiol into a tetrahydrocannabinol which possessed typical marihuana activity. The interest, therefore, of this investigation was at once centered upon the tetrahydrocannabinols as showing greatest promise. The methyl ether (XLVII) and the n-amyl ether (XLVIII) of tetrahydrocannabinol were prepared for study and in addition the syntheses were extended to include certain homologs of both the orcinol (5-methyl resorcinol) and the olivetol (5-n-amyl-resorcinol) series.

Homologs of the 6,6-Dimethyl-tetrahydro-dibenzopyranes (XII, XLV)

The existence of the tetrahydro-dibenzopyrones as intermediate compounds in the synthesis of the pyranes, offered at once the opportunity for preparing homologs involving the 6-carbon atom. For the purpose of preparing homologs, two pyrones were used; 1-hydroxy-3-methyl-7,8,9,10-tetrahydro-dibenzopyrone (X) as a type pyrone because of its availability and 1-hydroxy-3-n-amyl-9-methyl-7,8,9,10-tetrahydro-dibenzopyrone (XLIV) because of the marihuana activity which its 6,6-dimethyl-pyrane possessed. These respective pyrones were allowed to react with the appropriate Grignard to form homologs up to n-amyl of the corresponding 6,6-dimethyl-7,8,9,10-tetrahydro-dibenzopyranes (XII), (XLV). Slightly longer refluxing of the Grignard reaction mixture was necessary to complete the reaction for the higher homologs. The products were all obtained as distillable liquids. See Tables I and II, and Flow Sheet Compounds XIV-XVII and L-LII.

The Action of Bromine of the Tetrahydro-pyranes

The action of bromine on the tetrahydro-pyranes was studied as a possible method by which the lower hydrogenated pyranes might be prepared. For this purpose two tetrahydro-pyranes were chosen; the 1-hydroxy-3,6,6-trimethyl (XII) and the 1-hydroxy-3-n-amyl-6,6,9-trimethyl (XLV), the former pyrane (a high melting solid) was expected to give solid bromination products and the latter pyrane, a physiologically active one, to study the effect of bromine action on marihuana activity. The respective pyranes were treated with one mole of bromine in chloroform solution and vigorous evolution of hydrogen bromide took place. The 1-hydroxy-3,6,6-trimethyl-tetrahydro-dibenzopyrane gave a crystalline product which did not contain bromine and which had a definitely lower hydrogen content. Tetrahydrocannabinol when treated in the same manner gave an oil which did not contain bromine and had also a lower hydrogen content. The oil possessed a higher marihuana activity than did the original tetrahydrocannabinol.

The solid bromination product obtained from the trimethyl-tetrahydro-dibenzopyrane has all the characteristics of a pure chemical individual. Although too much credence could not be placed in the melting point because the product melted with decomposition, the analyses of entirely different runs substantially indicated the individuality of the product isolated. The nature of this compound is unknown, since the formation of common phenolic derivatives such as the acetate, benzoate and methyl ether could not be induced. In fact the analytical data for both products, the one derived from the bromine treatment of the trimethyl-pyrane and the one derived from bromine treatment of tetrahydrocannabinol, indicated the possiblity that a change in the molecule more deep-seated than the mere loss of hydrogen may have taken place, as a result of the action of bromine on these pyranes.

EXPERIMENTAL

All melting points reported by the author have been corrected. The analyses were performed by Mr. Saul Gottlieb in these laboratories.

1. Ethyl-cyclohexanone-2-carboxylate (III)

Two hundred grams of cyclohexanone were condensed with 300 grams of diethyl oxalate in the presence of sodium ethylate and the cyclohexanone-oxalester thus formed decomposed by heating under reduced pressure up to 100 degrees, according to the method of Kotz and Michels[11] to give ethyl-clclohexanone-2-

carboxylate in 70 per cent yield. The product was obtained as a colorless liquid boiling at 120-123° / 23 mm. pressure.

2. 2-Methyl-7,8,9,10-tetrahydro-dibenzopyrone (V)

The method used for the condensation of ethyl cyclohexanone-2-carboxylate with p-cresol is based on the procedure used by Sen and Basu[10] for the corresponding carboxylate with m-cresol. To a mixture of 65 grams of cyclohexanone-2-carboxylate and 40 grams of p-cresol, 35 cc. of concentrated sulphuric acid were added slowly, with shaking and without allowing the temperature to rise. The whole was allowed to stand over night at room temperature and then poured over cracked ice. The solid mass which separated was filtered off and taken up with ethyl alcohol from which the product separated as long white needles, leaving a clear green mother liquor. Yield 60.1 grams or 76 per cent. M. P. 131°.

Analysis:

Calcd. for $C_{14}H_{14}O_2$	C, 78.50; H, 6.58
Found	C, 78.47; H, 6.79

3. 2,6,6-Trimethyl-7,8,9,10-tetrahydro-dibenzopyrane (VII)

To a Grignard prepared from 2.4 grams of magnesium, 15 grams of methyl iodide and 40 cc. of dry ether, 3.5 grams of 2-methyl-7,8,9,10-tetrahydro-dibenzopyrone were added in small portions. The lactone reacted immediately. After the addition the reaction was completed by warming on the water bath for 2 hours. The reaction mixture was then poured over cracked ice acidified with sulphuric acid, the ether layer separated, washed with sodium thiosulphate followed by 10 per cent sodium hydroxide, the latter wash did not contain any of the product. The ether solution was then washed with dilute hydrochloric acid followed by a solution of sodium bicarbonate and finally with water. The ether layer after having been dried over anhydrous sodium sulphate, was evaporated leaving a thick colorless oil which soon solidified. The product was crystallized from ethyl alcohol giving white plates melting at 72-73°. Yield 3 grams or 80 per cent.

Analysis:

Calcd. for $C_{16}H_{20}O$	C, 84.28; H, 8.77
Found	C, 84.24; H, 8.98

4. 2,6,6-Trimethyl-dibenzopyrane (VIII)

Five grams of 2,6,6-trimethyl-7,8,9,10-tetrahydro-dibenzopyrane were placed in a side arm test tube and heated with two atoms of sulphur at 200 to 240° C. in a metal bath. Vigorous evolution of hydrogensulphide took place which had practically ceased after five hours of heating. The reaction mixture was while still hot poured into a mortar and allowed to solidify. It was then ground to a powder and the powder extracted several times with hot petroleum ether (b.p. 60-110°). The petroleum ether extracts were combined and fractionated, collecting the fraction boiling between 193 and 195° at 25 mm., to give an oil which on standing solidified. The product was recrystallized from methanol giving white plates which melted at 58°. Yield 1.1 grams. Kahn[6] reported plates melting at 58°.

Analysis:

Calcd. for $C_{16}H_{16}O$	C, 85.7 ; H, 7.2
Found	C, 85.92; H, 7.35
Kahn Found	C, 85.2 ; H, 7.5

5. 2-Methyl-dibenzopyrone (VI)

Prepared in the same manner as for 2,6,6-trimethyl-dibenzopyrone (procedure 4). The combined petroleum ether (b.p. 60-110°) extracts on cooling deposited which were filtered off and recrystallized from ethyl alcohol giving white needles which melted at 133.5°-134.5°. Yield 1 gram of pure material. Kahn[6] reported white needles melting at 134-135°.

Analysis:

Calcd. for $C_{14}H_{10}O_2$	C, 80.00; H, 4.78
Found	C, 80.19; H, 5.08
Kahn found	C, 79.7 ; H, 4.8

6. 5-Methyl-2-hydroxy-2′-isopropyloxy-diphenyl (VIIIa)

This compound was prepared according to the method of Kahn.[6] The Grignard prepared from 1.6 grams of magnesium, 10 grams of methyl iodide and 30 cc. of dry ether reacted with 2.7 grams of 3-methyl-dibenzopyrone to give a 90 per cent yield of the product in the form of long white needles which melted at 98°. Kahn reported the melting point as 94-104°.

Analysis:

Calcd. for $C_{16}H_{18}O_2$	C, 79.3 ; H, 7.49
Found	C, 79.21 ; H, 7.49
Kahn found	C, 80.2 ; H, 7.4

7. 2,6,6-Trimethyl-dibenzopyrane (VIII)

The ring closure of the glycol (VIIIa) obtained in experiment 6, was effected by the method of Kahn[6]. Five grams of the glycol were heated in xylene solution with 5 grams of phosphorous pentoxide for three hours. The product distilled at 195-198° at 28 mm. with solidification. Plates from methyl alcohol melting at 58° were obtained in 88 per cent yield. A mixed melting point of this pyrane and the one synthesized in Experiment 4 showed no depression. Kahn[6] reported the melting point of this compound to be 58°.

8. Ethyl-5-methyl-cyclohexanone-2-carboxylate (XXI)

(a) Oxidation of 5-methyl cyclohexanol

The oxidation of 5-methyl cyclohexanol was effected according to the procedure of Signaigo and Cramer[20] in 70 per cent yields. The product (XIX) was obtained as a colorless oil boiling at 168-169°.

(b) Condensation of the Cyclohexanone of (a) with Diethyl oxalate

The condensation of 5-methyl-cyclohexanone with diethyl oxalate and the subsequent decomposition of the oxalester formed by heating up to 220° under reduced pressure to form ethyl-5-methyl-cyclohexanone-2-carboxylate were carried out according to the procedure of Kotz and Hesse.[21] The product (XXI) was obtained in 30 to 40 per cent yields as a heavy oil boiling at 134-135° at 20 mm. Kotz and Hesse reported 134.5° at 20 mm.

9. 1-Hydroxy-3-methyl-7,8,9,10-tetrahydro-dibenzopyrone (X)

To a suspension of 8 grams of orcinol and 14 grams of ethyl-cyclohexanone-2-carboxylate, 20 cc. of concentrated sulphuric acid were added drop by drop over a period of two hours without allowing the temperature to rise. The orcinol dissolved and the solution became bright red. The whole was allowed to stand over night and then poured over cracked ice, whereupon a solid separated which was filtered off, washed with water and light petroleum ether. The product crystallized from ethyl alcohol in the form of white needles which melted at 242-243°. The yield was 12.6 grams or 74 per cent.

Analysis:
Calcd. for $C_{14}H_{14}O_3$ C, 73.04; H, 6.09
Found C, 73.05; H, 6.20

10. 1-Hydroxy-3,6,6-trimethyl-7,8,9,10-tetrahydro-dibenzopyrane (XII)

To an ether solution of methyl magnesium iodide prepared from 4 grams of magnesium, 24 grams of methyl iodide and 70 cc. of dry ether, 3.5 grams of 1-hydroxy-3-methyl-7,8,9,10-tetrahydro-dibenzopyrone suspended in 70 cc. of benzene were added. The light green precipitate which first formed soon dissolved and the whole was refluxed for fifteen hours in order to complete the reaction. The Grignard reaction product was decomposed by pouring it over cracked ice acidified with 10 cc. of concentrated hydrochloric acid. The benzene-ether layer was separated, washed with water, a solution of sodium bicarbonate and again with water, dried over anhydrous sodium sulphate, filtered and the solvent distilled off leaving a brown colored oil. In order to close completely the ring to the pyrane before distillation, the oil was refluxed for two hours in xylene solution in the presence of 2 grams of phosphorous pentoxide. The solution was filtered and the solvent evaporated off leaving a dark green oil which was distilled collecting the portion boiling at 145-147° / .5 mm. A portion of the product sublimed along the walls of the flask during distillation. The reddish-brown viscous liquid collected soon solidified to a glass which was broken up and crystallized from 80 per cent ethyl alcohol giving white crystals which melted at 134°-136°. The yield was 70 per cent.

Analysis:
Calcd. for $C_{16}H_{20}O_2$ C, 78.66; H, 8.23
Found C, 78.31; H, 8.43

11. 1-Hydroxy-3-methyl-6-dibenzopyrone (XI)

Five grams of 1-hydroxy-3-methyl-7,8,9,10-tetrahydro-dibenzopyrone was heated with two atoms (1.4 grams) of sulphur for one hour at 250-270°, at the end of which time the evolution of hydrogen sulphide had practically ceased. The product which solidified on cooling was removed from the reaction flask and powdered, washed twice with cold acetone and the residue purified by sublimation at 250° bath temperature and .5 mm. pressure. The white solid which was formed, was crystallized from ethyl alcohol from which it separated in the form of white prisms melting at 249-250°. Yield 3.2 grams or 65 per cent. Adams[17] reported the melting point as 249-251°.

Analysis:
Calcd. for $C_{14}H_{10}O_3$ C, 74.31; H, 4.47
Found C, 74.15; H, 4.74

12. 1-Hydroxy-3,9-dimethyl-7,8,9,10-tetrahydro-dibenzopyrone (XXIII)

The method of Sen and Basu[10] was used in this preparation. Six grams of ethyl-5-methyl-cyclohexanone-2-carboxylate and 4 grams of orcinol were mixed and 20 cc. of concentrated sulphuric acid were added drop by drop without allowing the temperature to rise. The whole was allowed to stand over night and the reaction product poured over cracked ice, from which the product separated as a yellow mass. This was filtered off and crystallized from ethyl alcohol containing a few drops of water giving white needles which melted at 253-254°. The yield of the pure product was 4.5 grams or 60 per cent. (m.p. reported by Sen and Basu 249°.)

Analysis:
Calcd. for $C_{15}H_{16}O_3$ C, 73.77; H, 6.56
Found C, 73.99; H, 6.69

13. Acetate of 1-Hydroxy-3,9-dimethyl-7,8,9,10-tetrahydro-dibenzopyrone (XXIIIa)

A solution of 0.5 gram of the lactone prepared in experiment 12 in 4 cc. of dry pyridine was refluxed for 5 minutes with 3 cc. of acetic anhydride. The reaction product was cooled, diluted with water and the solid filtered off. The product separated from ethyl alcohol as white needles which melted at 133°.

Analysis:

Calcd. for $C_{17}H_{18}O_4$	C, 71.33; H, 6.29
Found	C, 71.10; H, 6.46

14. Monomethyl Ether of 1-Hydroxy-3,9-dimethyl-7,8,9,10-tetrahydro-dibenzopyrone (XXIV)

To a suspension of 2 grams of the lactone from experiment 12 and 20 cc. of methyl alcohol, 10 cc. of dimethyl sulphate were added and warmed on the water bath under a reflux. To the warm solution 20 cc. of 20 per cent solution of potassium hydroxide in methyl alcohol were slowly added always keeping the solution slightly alkaline. As the reaction proceeded solution took place. After the addition the reaction mixture was refluxed for 10 minutes on the water bath. On cooling a solid separated out. The mixture was diluted with water and filtered. The product was crystallized from methyl alcohol forming long silky needles which melted at 149-150°. Yield 1.75 grams.

Analysis:

Calcd. for $C_{16}H_{18}O_3$	C, 74.4 ; H, 6.98
Found	C, 74.43; H, 7.13

15. 2-(Methyl-4'-methyl-6'-cyclohexene$\triangle^{1'-6'}$-carboxylate) 1,3-dimethoxy-5-methyl-benzene (XXVI)

The solution obtained by heating 5 grams of the lactone from experiment 12 with 25 cc. of 30 per cent sodium hydroxide for 30 minutes, was cooled and sufficient water added to dissolve any of the sodium salt which might have been salted out. The whole was then shaken for 15 to 20 minutes with 20 cc. of dimethyl sulphate, keeping the reaction flask in cold running water in order to take away the large amount of heat produced by the reaction. An oil separated which was extracted with ether and after having dried over anhydrous sodium sulphate, the solution was filtered and the ether evaporated off. The viscous oil which made up the residue was taken up with alcohol and the alcohol solution diluted with water to the point of permanent turbidity and the turbidity just displaced by adding additional alcohol. On standing crystals separated in the form of white pearly flakes which melted at 93-94°. Yield 2.5 grams or 42 per cent. About one gram of an oil could be recovered from the acidified residue which was possibly a mixture of the monomethyl ether and the free acid. No attempt was made to purify this oily residue.

Analysis:

Calcd. for $C_{18}H_{24}O_4$	C, 71.05; H, 7.89
Found	C, 71.09; H, 7.90

16. 2-(4'-Methyl-6'-cyclohexene$\Delta^{1'-6'}$-carboxylic acid) 1,3-dimethoxy-5-methyl-benzene (XXVII)

The methyl cyclohexene carboxylate obtained in procedure 15 was hydrolized by warming 5 grams of the ester in 50 cc. of 10 per cent aqueous sodium hydroxide on the steam bath for one hour or until all the ester had dissolved. The hydrolysis mixture was acidified whereupon a precipitate formed which was extracted with ether and after the ether had been evaporated off, the residue was crystallized from 60 per cent alcohol, from which the product separated in fine white needles. Yield 3.7 grams or 78 per cent. The product melted at 175-176°.

Analysis:

Calcd. for $C_{17}H_{22}O_4$	C, 70.34; H, 7.58
Found	C, 70.35; H, 7.62

17. 1-Hydroxy-3,6,6,9-tetramethyl-7,8,9,10-tetrahydro-dibenzopyrane (XXVIII)

This compound was prepared in the same manner as 1-hydroxy-3,6,6-trimethyl-7,8,9,10-tetrahydro-dibenzopyrane (Experiment 10). The reaction of the Grignard prepared from 4 grams of magnesium, 24 grams of methyl iodide and 50 cc. of dry ether with 2 grams of 1-hydroxy-3,9-dimethyl-7,8,9,10-tetarhydro-dibenzopyrone and after having been heated with xylene and phosphorous pentoxide to assure ring closure, gave a product which distilled at 178-180° at 1 mm. in a yield of 1.5 grams or 71 per cent yield. The product on standing solidified to a light brown glass.

Analysis:

Calcd. for $C_{17}H_{22}O_2$	C, 79.00; H, 8.52
Found	C, 79.01; H, 8.39

18. Acetate of 1-Hydroxy-3,6,6,9-tetramethyl-7,8,9,10-tetrahydro-dibenzopyrane (XXIX)

To a solution of 0.5 gram of 1-hydroxy-3,6,6,9-tetramethyl-7,8,9,10-tetrahydro-dibenzopyrane in 5 cc. of dry pyridine, 4 cc. of acetic anhydride were added and the whole refluxed for 5 minutes. The reaction product was cooled, diluted with water and the solid filtered off. It separated from ethyl alcohol in leaflets which melted at 125°. The yield was .4 gram.

Analysis:

Calcd. for $C_{19}H_{24}O_3$	C, 76.00; H, 8.00
Found	C, 76.21; H, 8.00

19. 2-(1'-Isopropyloxy-4'-methyl-6'-cyclohexene $\Delta^{1'-6'}$) 1-methoxy-3-hydroxy-5-methyl-benzene (XXIVa)

To methyl magnesium iodide prepared from 0.6 gram of magnesium, 8 grams of methyl iodide and 25 cc. of dry ether, 2 grams of 1-methoxy-3,9-dimethyl-7,8,9,10-tetrahydro-dibenzopyrone suspended in 25 cc. of dry ether were slowly added. Reaction took place at once, the lactone dissolving as soon as it came in contact with the Grignard. After the addition the whole was refluxed for two hours and then decomposed with ice acidified with 10 cc. of sulphuric acid. The ether layer was separated, washed with sodium thiosulphate, 10 per cent sodium hydroxide, dilute hydrochloric acid, sodium bicarbonate solution and finally with water. The sodium hydroxide wash contained only a small fraction of the product, the bulk remaining in the ether layer. The ether solution after having been dried over anhydrous sodium sulphate and filtered, was evaporated leaving an oil which solidified to a white mass. This was taken up with petroleum ether (b.p. 30-60°)

from which the product crystallized in branches of fine white needles which melted at 106-107°. Yield 2 grams or 84 per cent. Several attempts to demethylate the product resulted in alkali insoluble substances with the odor of terpenes.

Analysis:

Calcd. for $C_{18}H_{26}O_3$	C, 74.5 ; H, 8.96
Found	C, 74.47; H, 8.98

20. Olivetol (5-n-amyl-resorcinol) Method I

(1). Gallic acid trimethyl ether (XXXI)

Both the methods of Perkin and Weizman[22] and Hahn and Wassmuth[23] were tried in this preparation, and the latter was found to be more practical for the preparation of gallic acid trimethyl ether in large quantities such as are required in the olivetol synthesis. The product was obtained in yields of 70-75 per cent in the form of white needles melting at 169°.

(2). Gallyl chloride trimethyl ether (XXXII)

This compound was prepared from trimethyl gallic acid and phosphorous pentoxide in almost quantitative yields according to the method of Perkin and Weizman.[22] The acid chloride distilled over at 188° at 20 mm. Perkin and Weizman report 180° at 18 mm. The acid chloride separates from a mixture of benzene and petroleum ether (b.p. 60-110°) in colorless needles which melt at 77-78°. In this synthesis it was found more practicable to use the freshly distilled material directly in the following step, than to attempt further purification by recrystallization from the above solvent, because in the first place, the time required for crystallizing large quantities was of such length that impurities were introduced through hydrolysis of the acid chloride, and in the second place, the yields in the following steps were much better when the freshly distilled material was used.

(3). Sodium Salt of Ethyl 3,4,5-trimethyl-benzoyl-acetoacetate (XXXIII)

Gallyl chloride trimethyl ether was condensed with acetoacetic ester in the presence of sodium ethylate according to the procedure of Perkin and Weizman[22] to form the sodium salt of ethyl 3,4,5,-trimethoxy-benzoyl-acetoacetate.

(4). Ethyl 3,4,5,-benzoyl-acetate (XXXIV)

This procedure is an adaptation of the method of Perkin and Weizman.[22] The crude wet sodium salt from experiment (3) above obtained from 138 grams of trimethyl-gallyl-chloride was suspended in 1.5 liters of water to which was added 60 grams of ammonium chloride and 300 cc. of a 15 per cent ammonium hydroxide solution. The whole was shaken occasionally over a period of thirty minutes, being careful not to keep the flask tightly stoppered. The reaction was then warmed up to 45 degrees and allowed to stand an additional thirty minutes with shaking. The solid ester which separated out was filtered and crystallized from methyl alcohol from which the ester separated in the form of colorless hexagonal plates which melted at 87°. Perkin and Weizman reported 95° and Asahina[18] reported 87°. The yield of pure product was 66 grams or 42 per cent based on the acid chloride used.

Analysis:

Calcd. for $C_{14}H_{18}O_6$	C, 59.57; H, 6.38
Found	C, 59.40; H, 6.69

(5). Ethyl 3,4,5,-trimethoxy-benzoyl-propyl acetate (XXXV)

This compound was prepared according to the procedure of Asahina.[18]

(6). 3,4,5,-Trimethoxy-valerophenone (XXXVIII)

The preparation of this ketone is an adaptation of the procedure by Asahina.[18] A solution of 150 grams of trimethoxy-benzoylacetic ester in 1.5 liters of ethyl alcohol containing 75 grams of potassium hydroxide, was warmed for two hours on a water bath at 50°. The potassium carbonate formed was filtered off and the alcohol recovered by distilling under reduced pressure never allowing the temperature of the bath to rise above 50°. The residue was diluted with water, extracted with ether and the ether extract washed in turn with sodium carbonate solution, dilute acid and finally several times with water. After drying the ether solution over anhydrous sodium sulphate, the residue was distilled, the product coming over as a colorless oil at 202° and 18 mm., which solidifies and melts at 27° and which readily forms a semicarbazone which melts at 145-146°. Yield of the ketone was 100 grams.

Asahina reported for the product; distills at 192° and 6 mm., melts at 27° and semicarbazone melts at 145-146°.

(7). Olivetol dimethyl ether (XXXIX)

This compound was prepared according to the procedure of Asahina.[18]

(8). Olivetol (5-n-amyl-resorcinol) (XL)

The free phenol was prepared according to the procedure of Asahina.[18] The product was obtained as a colorless viscous liquid boiling at 140-145° at .5 mm. which darkens on exposure to air and solidifies to a glass on cooling. The liquid crystallizes from water giving needles which melted at 41°. Asahina reported the melting point of this compound as 41°. The yield of olivetol from 500 grams of gallic acid was 25 grams.

20. Olivetol Continued, Method II

(1). 3,4,5-Trimethoxy-benzamide (XXXVI)

The following is an adaptation of the procedure of Graebe and Suter[24] for the preparation of the same compound. Thirty grams of the distilled acid chloride were dissolved in 200 cc. of benzene. Dry ammonia gas, generated by dropping ammonium hydroxide on sodium hydroxide and dried by passing through calcium chloride, was passed in while keeping the flask cooled, until the precipitate formed became so thick as to hinder further free passing of the gas. The precipitate was then filtered off on a dry suction funnel and the mother liquor returned for further treatment with ammonia gas. This was repeated until no more precipitate formed. The precipitates were combined shaken with water and the water suspension filtered. The solid was crystallized from 50 per cent ethyl alcohol to give white needles which melted at 176-177°. Yield 25 grams or 86 per cent. Graebe and Suter reported m.p. as 176-177°.

(2). 3,4,5-Trimethoxy-valerophenone (XXXVIII)

An attempt was made to prepare this compound by the method of Suter and Weston,[19] who prepared 3,5-dimethoxy-valerophenone. To one mole of the Grignard prepared from 24.3 grams of magnesium, 137 grams of butyl bromide and 500 cc. of dry ether, .25 mole (52.5 grams) of trimethoxy-benzamide was added. The whole was refluxed with stirring for fifty hours in an atmosphere of hydrogen. The reaction mixture was decomposed by pouring over cracked ice acidified with 25 cc. of concentrated sulphuric acid. The ether layer was separated, washed with water, sodium bicarbonate solution followed by water, and the ether, after having been dried over sodium sulphate, was distilled off and the oily residue was fractionated collecting the portion boiling between 200 and 220° at 25 mm. The product was a slightly colored oil and the yield was 50 grams. Semicarbazone formation could only be induced after repeated trials and then in very low yields, less than 25 per cent. The above procedure was varied using an ether benzene solution in equal volumes for the Grignard instead of ether alone, but an oil was always obtained distilling over the same range and offering the same difficulty in semicarbazone formation. The oils obtained from the several runs were then combined and refractionated. The fraction boiling between 200° and 205° gave a semicarbazone at once, the 205-210° fraction gave a semicarbazone with difficulty and in low yields and in the higher boiling fractions, no semicarbazone formation could be induced.

(3). Semicarbazone of Compound from (2)

One gram of the ketone from (2), fraction boiling at 200-205°, was dissolved in alcohol and sufficient water added to produce cloudiness, which was just displaced by adding more alcohol. A mixture of 1 gram of semicarbazide hydrochloride and 1.5 grams of sodium acetate were added and the whole shaken until the solids dissolved. The reaction mixture was then warmed on the water bath for 15 minutes and after cooling, crystals of the semicarbazone separated. After being crystallized several times from dilute alcohol white crystals were obtained which had a constant melting point of 128°. Yield of the crude product was about .5 gram while the purified material amounted to about .1 gram. Melting point of trimethoxy-valerophenone was 145-146°.

Analyses of the Semicarbazones of:

Trimethoxy-valerophenone requires	C, 58.22; H, 7.39
Butyl-dimethoxy-valerophenone req.	C, 64.48; H, 8.65
Found	C, 64.60; H, 8.43

(4). Reduction of the Ketone-rich Fraction from (2)

The reduction of the ketone-rich fraction was carried out according to the directions of Asahina[18] for reducing valerophenone. 11 grams of the crude material were dissolved in 100 cc. of absolute alcohol and while warming intermittently on a calcium chloride bath, treated with large pieces of sodium and the alternate addition of alcohol until 60 grams of sodium and 600 cc. of alcohol were used. The reaction mixture was diluted with water, acidified, the alcohol distilled off and the residue extracted with ether. The residue from the ether extract gave an oil which distilled at 172-174° at 18 mm. (6 grams) and a high boiling residue (2 grams) which distilled at 188-190° at 18 mm.

When the main fraction was demethylated with hydriodic acid (sp. gr. 1.7), 4 grams of a red oil boiling at 140-150° / .5 mm., which solidified to a glass, was obtained. When this was condensed with ethyl-5-methyl-cyclohexanone-2-carboxylate in the presence of 15 cc. of concentrated sulphuric acid a crystalline solid was obtained which was crystallized from ethyl alcohol giving white prisms which melted at 165-166°. The identical product was obtained from the crude non-fractionated oil.

Analysis:

Olivetol condensation prod. requires:	C, 76.00; H, 8.1
Butyl olivetol cond. prod. requires:	C, 77.53; H, 9.00
Found Analysis No. 1	C, 77.74; H, 9.38
Found Analysis No. 2 (repeated preparation)	C, 77.68; H, 9.16

20. Olivetol Continued Method III

(1). 3,4,5-Trimethoxy-benzonitrile (XXXVII)

Equimolecular quantities of trimethoxy-benzamide and phosphorous pentachloride were mixed in the presence of a few cc. of benzene and heated for 2 hours on a boiling water bath according to the procedure of Harding.[25] The benzene and the phosphorous oxychloride were distilled off and the residue crystallized from methyl alcohol giving white crystals which melted at 93°. The yield of the product was 80 per cent.

(2). 3,4,5-Trimethoxy-velerophenone (XXXVIII)

An attempted preparation of this compound was made on trimethoxy-benzonitrile using the Grignard in the same manner as for trimethoxy-benzamide. To the Grignard prepared from 4.84 grams of magnesium (0.2 mole), 27.4 grams of butyl bromide (0.2 mole) and 250 cc. of ether, was added 9.65 grams (0.05 mole) of trimethoxy-benzonitrile and the whole was refluxed with stirring for 24 hours. The product was obtained as a light colored oil distilling from 205-210° at 28 mm. The yield was 9 grams.

The product gave a semicarbazone when treated with semicarbazide hydrochloride in the presence of sodium acetate, which separated from dilute alcohol in the form of white crystals which melted at 127° in a yield of about 70 per cent. A mixed melting point of this product and the semicarbazone obtained from the product by the action of butyl magnesium bromide on trimethoxy-benzamide showed no depression.

Analysis:

Semicarbazone of trimethoxy-valerophenone
requires C, 58.22; H, 7.49
Semicarbazone of dimethoxy-butyl-valerophenone
requires C, 64.48; H, 8.65
Found C, 64.84; H, 8.56

21. 1-Hydroxy-3n-amyl-7,8,9,10-tetrahydro-dibenzopyrone (XLI)

To a mixture of 2 grams of olivetol and 2.3 grams of ethyl-cyclohexanone-2-carboxylate, 10 cc, of concentrated sulphuric acid were added in the same manner as for the condensations in experiments 9 and 12. The product separated from alcohol in the form of fine white needles which melted at 182-183°. The yield was 2.1 grams.

Analysis:

Calcd. for $C_{18}H_{22}O_3$ C, 75.60; H, 7.69
Found C, 75.82; H, 7.76

22. 1-Hydroxy-3-n-amyl-6,6-dimethyl-7,8,9,10-tetrahydro-dibenzopyrane, *nor*-tetrahydrocannabinol (XLII)

This compound was prepared in the same manner as the pyranes in experiments 10 and 17. The Grignard prepared from 2 grams of magnesium, 5 cc. of methyl iodide and 30 cc. of dry ether, reacted with 1.8 grams of 1-hydroxy-3-n-amyl-7,8,9,10-tetrahydro-dibenzopyrone to give 1.9 grams of a colorless oil which became reddish-brown when exposed to air. The oil distilled at 175-176° at 0.5 mm.

3,5-Dinitrophenyl urethane: 0.6 gram of *nor*-tetrahydro-cannabinol in 10 cc. of dry benzene was allowed to react with 2 grams of 3,5-dinitrobenzazide, prepared by the action of equivalent quantities of 3,5-dinitrobenzoyl chloride and sodium azide in water acetone solution. The reaction mixture was refluxed for three hours and then an additional hour with 10 cc. of 95 per cent alcohol, and filtered while hot. On cooling crystals of the urethane separated which were filtered off and crystallized from 80 per cent alcohol, giving light yellow shining plates which melted at 190-191°.

Analysis:

Calcd. for $C_{27}H_{31}O_7N_3$	C, 63.67; H, 6.09
Found	C, 64.00; H, 6.14

23. 1-Hydroxy-3-n-amyl-9-methyl-7,8,9,10-tetrahydro-dibenzopyrone (XLIV)

Prepared in the same manner as the lactones in experiments 9 and 12. One gram of olivetol was condensed with 1.5 grams of ethyl-5-methyl-cyclohexanone-2-carboxylate in the presence of 10 cc. of sulphuric acid to give 1.1 grams of the lactone which separated from alcohol as fine white needles which melted at 179-180°.

Analysis:

Calcd. for $C_{19}H_{24}O_3$	C, 76.00; H, 8.1
Found	C, 75.77; H, 8.24

24. 1-Hydroxy-3-n-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-dibenzopyrane; Tetrahydrocannabinol (XLV)

The Grignard prepared from 2 grams of magnesium, 5 cc. of methyl iodide and 30 cc. of ether reacted in the same manner as the pyranes in experiments 10, 17, and 22 with 1.8 grams of the 1-hydroxy-3-n-amyl-9-methyl-7,8,9,10-tetrahydro-dibenzopyrone to give tetrahydro cannabinol, which distilled as a colorless viscous liquid at 170° / .4 mm. and became reddish brown when exposed to air. Yield 1.7 grams.

Analysis:

Calcd. for $C_{21}H_{30}O_2$	C, 80.25; H, 9.62
Found	C, 80.25; H, 9.40

3,5-Dinitrophenyl urethane: Prepared in the same manner as for *nor*-tetrahydrocannabinol, Experiment 22. The product separated from alcohol as pale yellow crystals which melted at 210-212° with small evolution of a gas as the temperature was raised above this point.

Analysis:

Calcd. for $C_{28}H_{33}O_7N_3$	C, 64.2 ; H, 6.35
Found	C, 64.28; H, 6.14

25. Tetrahydrocannabinol methyl ether (XLVII)

One-half gram of tetrahydrocannabinol was dissolved in 10 cc. of methyl alcohol and 5 cc. of dimethyl sulphate added. To this was added with shaking 10 cc. of a 10 per cent aqueous sodium hydroxide solution. After the addition, the reaction mixture was warmed on the water bath for 10 minutes, then cooled, diluted with water, extracted with ether and the ether extract dried over anhydrous sodium sulphate. The residue was distilled giving a colorless oil which came over at 200-210° / 15 mm. The yield was .45 gram.

Analysis:

Calcd. for $C_{26}H_{40}O_2$	C, 80.73; H, 9.47
Found	C, 80.50; H, 9.56

26. Tetrahydrocannabinol amyl ether (XLVIII)

One-half gram of tetrahydrocannabinol was dissolved in sodium ethylate prepared from 0.04 gram of sodium and 10 cc. of absolute alcohol. The solution was refluxed for 30 minutes with a slight excess of amyl bromide. The reaction was then cooled, diluted with water, extracted with ether and the ether extract dried over anhydrous sodium sulphate. The residue distilled to give a light yellow oil which came over at 244° / 13 mm. The yield was .5 gram.

Analysis:

Calcd. for $C_{26}H_{40}O_2$	C, 81.25; H, 10.42
Found	C, 81.23; H, 10.58

Homologs of the Model Pyrane: 1-Hydroxy-3,6,6-trimethyl-7,8,9,10-tetrahydro-dibenzopyrane (XIV-XVII)

27. 1-Hydroxy-3-methyl-6,6-diethyl-7,8,9,10-tetrahydro-dibenzopyrane (XIV)

To the Grignard reagent prepared from 4.04 grams (0.166 mole) of magnesium, 18.1 grams of ethyl bromide (0.166 mole) and 50 cc. of dry ether were added 3.4 grams (0.015 mole) of

1-hydroxy-3-methyl-7,8,9,10-tetrahydro-dibenzopyrone suspended in 50 cc. of dry benzene. The precipitate which first formed soon dissolved and the clear solution was refluxed for twenty hours. The Grignard reaction compound was decomposed with hydrochloric acid and ice and the benzene-ether layer separated, washed with water, sodium bicarbonate solution and again with water, dried over anhydrous sodium sulphate, filtered, the solvent distilled off and the residue taken up with 50 cc. of xylene. Two grams of phosphorous pentoxide were added and the xylene solution refluxed for two hours after which the reaction mixture was filtered and the solvent distilled off. The residual oil was distilled coming over at 160-162° / 0.5 mm. as a red viscous oil. The yield of the product was 2.8 grams. The propyl, butyl and amyl homologs were prepared in yields ranging from 70 to 75 per cent in the same manner as the ethyl homolog employing the appropriate n-alkyl Grignard in each case. See Table I below. The oily products formed from the reaction of p-nitro- and 3,5-dinitro-phenylisocyanates as well as the 3,5-dinitro-benzoates did not crystallize after several weeks standing.

TABLE I.

Homologs of 1-hydroxy-3,6,6-trimethyl-tetrahydro-dibenzopyrane

Homolog	Description	Calcd. for	Found
6,6-Diethyl	Light-red vis.	$C_{18}H_{24}O_2$	
	liq. 160-2° / .5 mm.	C 79.41; H, 8.82	C, 79.20; H, 8.72
6,6-Dipropyl	Red viscous	$C_{20}H_{28}O_2$	
(n)	liq. 164-5° / .5 mm.	C, 79.93; H, 9.39	C, 79.56; H, 9.65
6,6-Dibutyl	Red-brown vis.	$C_{22}H_{32}O_2$	
(n)	liq. 173-5° / .5 mm.	C, 80.43; H, 9.82	C, 80.23; H, 9.67
6,6-Diamyl	Red viscous	$C_{24}H_{36}O_2$	
(n)	liq. 183-5° / .5 mm.	C, 80.84; H, 10.18	C, 80.44; H, 10.04

28. Homologs of Tetrahydrocannabinol (XLV)

These homologs were prepared in exactly the same manner as for the 3,6,6-trimethyl pyrane above (Exp. No. 27). See Table II. The p-nitro- and 3,5-dinitro-phenyl urethanes of these homologs were also oily products.

TABLE II.

Homologs of Tetrahydrocannabinol

Homolog	Description	Calcd. for	Found
6,6-Diethyl	Red-brown vis. liq. 178-80° / .5 mm.	$C_{23}H_{34}O_2$ C, 80.64; H, 10.01	C, 80.85; H, 9.93
6,6-Dipropyl (n)	Red-brown vis. liq. 190-2° / .5 mm.	$C_{25}H_{38}O_2$ C, 81.02; H, 10.34	C, 80.96; H, 10.54
6,6-Dibutyl (n)	Red viscous liq. 198-200° / .5 mm.	$C_{27}H_{42}O_2$ C, 81.31; H, 10.62	C, 81.19; H, 10.64

29. Reaction of Bromine with 1-Hydroxy-3,6,6-trimethyl-7,8,9,10-tetrahydro-dibenzopyrane (XII)

A solution of one mole of bromine (0.7 gram) in 15 cc. of chloroform was added drop by drop with shaking to a solution of 1 mole (1 gram) of the tetrahydro-pyrane in 15 cc. of chloroform at room temperature. No noticeable heat of reaction was produced. The reaction solution changed to a deep purple in color and clouds of hydrogen bromide were liberated. After the addition the whole was allowed to stand over night and then the chloroform solution was filtered, washed with water, sodium bicarbonate solution, with water again and finally dried over sodium sulphate. The solvent was evaporated off leaving a dark blue resinous material which solidified. This was ground to a powder and dissolved in 95 per cent alcohol. On cooling about .4 gram of a light gray solid separated. An additional amount of the material was obtained by adding a few drops of water to the alcohol solution bringing the total yield to about .8 gram. On recrystallizing from 85 per cent alcohol the product was obtained as a white powder which decomposed while melting when heated up to about 200 degrees. On rapid heating the decomposition point could be raised to 220 to 230°. The decomposition took place with vigorous evolution of a gas. A test for bromine proved it to be absent.

Analysis:

Repeat analyses were made on different runs, not only involving the bromination step but the entire pyrane synthesis.

Original product requires:	$C_{16}H_{20}O_2$	C, 78.66;	H, 8.23
Found for bromination prod.	1—	C, 78.52;	H, 6.77
	2—	C, 78.76;	H, 6.63
	3—	C, 78.60;	H, 6.72
	4—	C, 78.71;	H, 6.82
Calcd. for $C_{14}H_{14}O_2$		C, 78.48;	H, 6.59

30. Reaction of Bromine with Tetrahydrocannabinol (XLV)

When tetrahydrocannabinol was treated with one mole of bromine in the same manner as in experiment 29, exactly the same behavior was exhibited as with the 3,6,6-trimethyl-pyrane. Hydrogen bromide was liberated and a series of color changes ranging from dark red to almost black ending up in a light red took place. The oily residue left after the chloroform was evaporated off, was distilled giving a light brown oil coming over at 174-175° / .4 mm. The yield was .5 gram from .82 gram of the tetrahydrocannabinol.

Analysis:

Tetrahydrocannabinol requires;	$C_{21}H_{30}O_2$	C, 80.25;	H, 9.62
Found for bromination product		C, 79.56;	H, 9.15
Calculated for bromination prod.	$C_{19}H_{26}O_2$	C, 79.56;	H, 9.11

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VITA

Thomas H. Bembry was born in Hawkinsville, Georgia, on December 19, 1907. He completed his early education in the Public School System and at Georgia State College in Savannah. He entered Howard University in 1924 and received the degree of Bachelor of Science in 1929. After entering the Graduate School of Columbia University under the Faculty of Pure Science in the fall of 1932 he received the degree of Master of Arts in 1933. From 1933 to 1939 he was a member of the faculty of Livingstone College as teacher of Chemistry. He is a member of Phi Beta Sigma, Sigma Xi, and of the American Chemical Society.

APPENDIX

TABLE III.

Marihuana Activity of Cannabinol Types*

	Name of Compound Dibenzopyranes	Activity	Maximum Deviation
1.	2,6,6-trimethyl-7,8,9,10-tetrahydro—(VII)	0	
2.	1-Hydroxy-3,6,6,9-tetramethyl-tetrahydro—(XXVIII)	0	
3.	1-Hydroxy-3-n-amyl-6,6,9-trimethyl-tetrahydro—(XLV)	10	± 3
4.	1-Methoxy-3-n-amyl-6,6,9-trimethyl-tetrahydro—(XLVII)	No marihuana but narcotic	
5.	1-Amyloxy-3-n-amyl-6,6,9-trimethyl-tetrahydro—(XLVIII)	No marihuana but narcotic	
6.	Bromine product of 1-hydroxy-3-n-amyl-6,6,9-trimethyl-tetrahydro—(XLVI)	12	± 3
7.	1-Hydroxy-3-methyl-6,6-diethyl-tetrahydro—(XIV)	No marihuana but narcotic	
8.	1-Hydroxy-3-methyl-6,6-dipropyl-tetrahydro—(XV)	No marihuana but narcotic	
9.	1-Hydroxy-3-methyl-6,6-dibutyl-tetrahydro—(XVI)	No marihuana but narcotic	
10.	1-Hydroxy-3-methyl-6,6-di-amyl-tetrahydro—(XVII)	No marihuana but narcotic	
11.	1-Hydroxy-3-n-amyl-6,6-diethyl-9-methyl-tetrahydro—(L)	1	
12.	1-Hydroxy-3-n-amyl-6,6-dipropyl-9-methyl-tetrahydro—(LI)	1 or less	
13.	1-Hydroxy-3-n-amyl-6,6-dibutyl-9-methyl-tetrahydro—(LII)	1 or less	
14.	1-Hydroxy-3-n-amyl-6,6-dimethyl-tetrahydro—(XLII)	No marihuana but narcotic	
15.	Red oil distillates	80	± 25

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* The above activities were determined by Dr. R. P. Walton of the University of Mississippi, using dogs as experimental animals. The activities are expressed in terms of a standard U. S. P. extract of cannabis.

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Compounds of the Cannabinol Type. I. Synthesis of Some Compounds Related to Tetrahydrocannabinol

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By T. H. Bembry and G. Powell

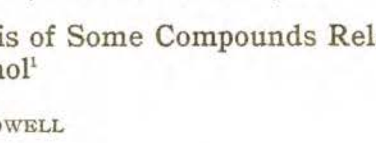
[Reprinted from the Journal of the American Chemical Society, 63, 2766 (1941).]

[Contribution from the Department of Chemistry, Columbia University]

Compounds of the Cannabinol Type. I. Synthesis of Some Compounds Related to Tetrahydrocannabinol[1]

T. H. Bembry and G. Powell

A convenient method for the preparation of certain tetrahydrodibenzopyranes related to tetrahydrocannabinol (I) has been described.[2,3] It involves the use of the substituted tetrahydrobenzocoumarins of the type (II) as intermediates, which are accessible readily by the method of Sen and Basu.[4] As established by Adams and Baker,[2] the condensation of the cyclohexanone carboxylic esters with the 5-alkylresorcinols takes place between the two hydroxyl groups and the tetrahydrobenzocoumarins are unequivocally of constitution II. For inquiry into the relationship between marihuana activity and structure, since it has been demonstrated that the tetrahydrocannabinols possess marihuana activity first by Adams[5] and his associates and confirmed by other workers,[6,7] we have prepared a number of such



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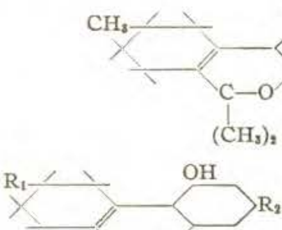

II

R_1 = H or CH_3
R_2 = Alkyl

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[1] A portion of a thesis by Thomas H. Bembry submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science of Columbia University.

[2] R. Adams and B. R. Baker, This Journal, **62**, 2405 (1940).

[3] G. Powell and T. H. Bembry, *ibid.*, **62**, 2568 (1940).

[4] Sen and Basu, *J. Indian Chem. Soc.*, **5**, 467 (1928).

[5] Adams, Pease, Cain and Clark, This Journal, **62**, 2402 (1940).

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TABLE I

Compound, 7,8,9,10-Tetrahydro-6-dibenzopyrane	Description	Formula	Anal., % calcd. C	Anal., % calcd. H	Anal., % found C	Anal., % found H
2,6,6-Trimethyl-	White plates from alc., m. p. 72–73°	$C_{16}H_{20}O$	84.28	8.77	84.24	8.98
1-Hydroxy-3-*n*-amyl-6,6-dimethyl-[a]	Colorless liq., b. p. 175–6° (0.5 mm.)	$C_{20}H_{28}O_2$	79.92	9.39	79.80	9.72
1-Methoxy-3-*n*-amyl-6,6,9-trimethyl-	Colorless liq., b. p. 200–10° (15 mm.)	$C_{22}H_{32}O_2$	80.43	9.82	80.50	9.56
1-Amyloxy-3-*n*-amyl-6,6,9-trimethyl-	Light yellow liq., b. p. 244° (13 mm.)	$C_{26}H_{40}O_2$	81.25	10.42	81.23	10.58
1-Hydroxy-3-methyl-6,6-diethyl-	Light red vis. liq., b. p. 160–2° (0.5 mm.)	$C_{18}H_{24}O_2$	79.41	8.82	79.20	8.72
1-Hydroxy-3-methyl-6,6-di-*n*-propyl-	Red vis. liq., b. p. 164–5° (0.5 mm.)	$C_{20}H_{28}O_2$	79.93	9.39	79.56	9.65
1-Hydroxy-3-methyl-6,6-di-*n*-butyl-	Red-brown vis. liq., b. p. 173–5° (0.5 mm.)	$C_{22}H_{32}O_2$	80.43	9.82	80.23	9.67
1-Hydroxy-3-methyl-6,6-di-*n*-amyl-	Red vis. liq., b. p. 183–5° (0.5 mm.)	$C_{24}H_{36}O_2$	80.84	10.18	80.44	10.04
1-Hydroxy-3-*n*-amyl-9-methyl-6,6-diethyl-[a]	Red-brown vis. liq., b. p. 178–9° (0.5 mm.)	$C_{23}H_{34}O_2$	80.64	10.01	80.85	9.93
1-Hydroxy-3-*n*-amyl-9-methyl-6,6-di-*n*-propyl-[a]	Red-brown vis. liq., b. p. 190–2° (0.5 mm.)	$C_{25}H_{38}O_2$	81.02	10.34	80.96	10.54
1-Hydroxy-3-*n*-amyl-9-methyl-6,6-di-*n*-butyl-	Red vis. liq., b. p. 198–200° (0.5 mm.)	$C_{27}H_{42}O_2$	81.31	10.62	81.19	10.64

[a] A description of these compounds appeared in the literature[9] after submission of manuscript.

tetrahydrodibenzopyranes and their derivatives by this method as described below.

The compounds listed in Table I have been examined for physiological activity by the method of Walton, Martin and Keller.[8] The results will be published separately, but it is of interest to note here that many of them, particularly the higher homologs of tetrahydrocannabinol, exhibit a narcotic activity comparable to but not quite typical of marihuana.

Experimental

The tetrahydrobenzocoumarins used in the preparation of the various substituted tetrahydrodibenzopyranes were obtained by condensing the properly substituted cyclohexanone-2-carboxylate with the required phenol in the presence of sulfuric acid according to the method of Sen and Basu.[4]

1-Hydroxy-3-*n*-amyl-9-methyl-6,6-diethyl-7,8,9,10-tetrahydro-6-dibenzopyrane.—The tetrahydrodibenzopyranes listed in Table I were prepared by the reaction of the proper alkylmagnesium halide on the corresponding tetrahydrobenzocoumarin according to the procedure given here for the 1-hydroxy-3-*n*-amyl-9-methyl-6,6-diethyl derivative. To the Grignard reagent prepared from 4.04 g. (0.166 mole) of magnesium, 18.1 g. (0.166 mole) of ethyl bromide and 50 cc. of dry ether was added 4.98 g. (0.0166 mole) of 1-hydroxy-3-*n*-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone suspended in 50 cc. of dry benzene. The precipitate which first formed soon dissolved and the clear solution was refluxed for twenty hours. The Grignard reaction compound was decomposed with hydrochloric acid and ice and the benzene–ether layer separated, washed with water, sodium bicarbonate solution and again with water, dried over anhydrous sodium sulfate, filtered, the solvent distilled off and the residue taken up with 50 cc. of xylene. Two grams of phosphorus pentoxide was added and the whole refluxed for two hours in order to form completely the pyrane ring before distillation. The reaction mixture was filtered and the solvent distilled off. The residual oil was distilled, coming over at 178–179° and 0.5 mm. as a red-brown viscous liquid; yield 71%. Analytical data and physical constants for the tetrahydrodibenzopyranes thus prepared are given in Table I. The yields of these pyranes ranged from 70 to 75%. In the case of the 2,6,6-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrane only two hours of refluxing was needed to complete the reaction, since in this pyrane there is no free phenolic group.

Derivatives of the Tetrahydro-pyranes

1-Methoxy-3-*n*-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrane (tetrahydrocannabinol methyl ether).—One-half gram of tetrahydrocannabinol was dissolved in 10 cc. of methyl alcohol and 5 cc. of dimethyl sulfate was added. To this was added with shaking 10 cc. of a 10% aqueous sodium hydroxide solution. After the addition the reaction mixture was warmed on the water-bath for ten minutes, then cooled, diluted with water, extracted with ether and the ether extract dried over sodium sulfate. The residual product distilled to give a colorless oil coming over between 200 and 210° at 15 mm.; yield 0.45 g.

1-Amyloxy-3-*n*-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrane (tetrahydrocannabinol amyl ether).—One-half gram of tetrahydrocannabinol was dissolved in sodium ethylate prepared from 0.04 g. of sodium and 10 cc. of absolute ethyl alcohol. This solution was refluxed for thirty minutes with a slight excess of amyl bromide. The reaction mixture was then cooled, diluted with water, extracted with ether and the ether extract dried over sodium sulfate. The residue distilled to give a light yellow oil which came over at 244° and 13 mm.; yield 0.5 g.

3,5-Dinitrophenyl-urethan of 1-Hydroxy-3-*n*-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrane (urethan of tetrahydrocannabinol).—To a solution of 0.6 g. of tetrahydrocannabinol and 10 cc. of dry benzene, 2 g. of 3,5-dinitrobenzazide, prepared by the action of 3,5-dinitroben-

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(8) Walton, Martin and Keller, *J. Pharm. and Exp. Therap.*, **62**, 239 (1938).

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zoyl chloride on sodium azide in water–acetone solution, was added. The reaction mixture was refluxed for three hours in an apparatus well protected from moisture, after which 10 cc. of absolute ethyl alcohol was added, the refluxing continued for an additional hour, and the solution filtered while hot. On cooling crystals of the urethan separated, which were filtered and recrystallized from 80% ethyl alcohol giving pale yellow crystals which melted at 210–212° (cor.) with small evolution of a gas as the temperature was raised above this point.

Anal. Calcd. for $C_{28}H_{33}O_7N_3$: C, 64.24; H, 6.35. Found: C, 64.28; H, 6.14.

3,5-Dinitrophenyl-urethan of 1-Hydroxy-3-*n*-amyl-6,6-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyrane.—Prepared in the same manner as the 3,5-dinitrophenylurethan of 1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrane as light yellow crystals from 80% ethyl alcohol, which melted without decomposition at 191–192° (cor.).

Anal. Calcd. for $C_{27}H_{31}O_7N_3$: C, 63.67; H, 6.09. Found: C, 64.00; H, 6.14.

Dehydro Derivative of 2,6,6-Trimethyl-7,8,9,10-tetrahydro-6-dibenzoypyrane.—Five grams of 2,6,6-trimethyl-7,8,9 10-tetrahydro-6-dibenzopyrane was placed in a side-arm test-tube and heated with two gram atoms of sulfur at 200 to 240° in a metal bath. Vigorous evolution of hydrogen sulfide took place which had practically ceased after five hours of heating. The reaction mixture while still hot was poured into a mortar and allowed to solidify. It was then ground to a powder and extracted several times with hot petroleum ether (b. p. 60–110°). The petroleum ether extracts were combined and fractionated, collecting the fraction boiling between 193–195° at 25 mm. The oily product which was obtained soon solidified and was crystallized from methanol giving white plates which melted at 58° in agreement with the report of Cahn.[10] The yield of pure product was 1.1 g.

Anal. Calcd for $C_{16}H_{16}O$: C, 85.71; H, 7.14. Found: C, 85.92; H, 7.35.

Acknowledgment.—The authors wish to express their thanks to Smith, Kline and French and to the Rosenwald Fund for financial assistance in this work. The authors also wish to express their appreciation to Mr. Saul Gottlieb of this Laboratory for making the microanalyses.

Summary

Compounds related to tetrahydrocannabinol have been prepared from the tetrahydrobenzocoumarins for physiological study.

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[10] Cahn, *J. Chem. Soc.*, 1400 (1933).

NEW YORK, N. Y. RECEIVED JULY 7, 1941

B. Jewett, president of the National Academy of Sciences; Alfred N. Richards, professor of pharmacology, University of Pennsylvania; William J. Robbins, director of the New York Botanical Garden; Harlow Shapley, director of the Harvard College Observatory, and Tom K. Smith, president, the Boatmen's National Bank, St. Louis. Members of the executive committee are Winthrop W. Aldrich, Albert F. Blakeslee, Frank B. Jewett, William J. Robbins and Harlow Shapley.

THE Carnegie Corporation has renewed the grant to finance the Committee of Private Research of Western Reserve University for another year. Established a year ago as the outgrowth of the work of the late Dr. Robert C. Binkley, the committee encourages research and private scholarship. Dr. Harold A. Blaine will continue as director of the committee, and William S. Dicks as research associate.

AN Associated Press dispatch reports that the building of the Royal College of Surgeons in London was among the places damaged in recent air raids. It reads: "Valuable museum specimens were lost when the structure, twice slightly damaged in earlier raids, was hit by high explosive and fire bombs. The bulk of the famous Hunterian collection made by Dr. John Hunter, known as the founder of modern surgery, was buried under a pile of fire-swept débris. This collection was bought by the Government for £15,000 two years after Dr. Hunter's death in 1793."

Nature writes: "Owing to the generosity of the Rockefeller Foundation, which has provided a grant for the purpose, the Royal Society is in a position to give some assistance to scientific societies and associations which, as a result of war conditions, are experiencing financial difficulties in the publication of scientific journals."

THE Pharmaceutical Society of Great Britain celebrated in London on May 15 the centenary of its foundation. A thanksgiving service was held in the morning in the parish church of St. Pancras, and a commemoration meeting at Conway Hall was followed by a play, "Jacob Bell and Some Others," which recalled scenes surrounding the actual foundation of the society. The society received congratulations on its century of useful work from many medical associations, learned bodies, manufacturing and trading organizations in Great Britain and from pharmaceutical societies in all parts of the Empire and in the United States.

THE general meetings of the Linnean Society of London, according to *Nature,* were resumed, beginning on March 6. The centenary of the Royal Botanic Gardens, Kew, as a Government institution, occurred on April 1, and at the meeting on April 3, Sir Arthur W. Hill, director of the Royal Gardens, gave some account of the work of Kew during the past hundred years. At the meeting on May 1, the society observed the tercentenary of the birth of Nehemiah Grew, when Dr. Agnes Arber gave an account of his work and that of Marcellus Malpighi. The anniversary meeting was held on May 24, when the president addressed the society. The council is considering the possibility of prolonging the session into July.

DISCUSSION

IS EVOLUTION INSCRUTABLE?

THE undeniable importance of Professor Goldschmidt's recent volume on evolution,[1] and the weight which its author's name justly carries, make it doubly needful that certain of its implications be fully recognized. Dobzhansky's assertion[2] that the acceptance of Goldschmidt's central theory demands a "belief in miracles" seems to me to be literally true, though the statement deserves some amplification.

The difficulties which beset the Darwinian theory of evolution through the natural selection of small variations were recognized by many of Darwin's contemporaries, and were discussed at great length by Darwin himself. Alternative theories of "saltation" or progress through large, discontinuous "jumps" were proposed by contemporary critics, notably by St. George Mivart.[3] Indeed, the rudiments of this idea long antedated Darwin, as witness Geoffroy St. Hilaire.

Mivart's evolutionism, as is well known, was strongly tinged with theology. The continuous intervention of the Creator in the evolutionary drama was fundamental in his world outlook. There was nothing disturbing to him in the notion that complex, adaptive structures could arise abruptly, since all this happened under divine guidance. The "innate tendency" to vary he conceived to be "an harmonious one, calculated to simultaneously adjust the various parts of the organism to their new relations."

It is needless to say that Professor Goldschmidt entertains no such theological interpretation of natural phenomena. Nor can we suspect him of sympathy with "vitalism," "teleology," "innate tendencies" or other forms of biological mysticism. Indeed, Goldschmidt's position would perhaps be more understand-

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[1] "The Material Basis of Evolution." Yale University Press, 1940.

[2] SCIENCE, October 18, 1940.

[3] "The Genesis of Species." Macmillan and Company, 1871.

FELLOWSHIPS

Bembry, Thomas

able if he did cherish such views. For he contends that "macroevolution" (*i.e., real* evolution) comes to pass through single, abrupt genetic changes ("macromutations"), capable of bringing about phenotypic alterations of specific, generic or even much greater magnitude. The role of selection is limited to the "immediate acceptance or rejection" of the finished product. Even St. Hilaire's suggested origin of the first bird from a reptile's egg, as repeated by a recent paleontologist, is cited by Goldschmidt with seeming approval.

We should surely need the guiding hand of an entelechy here, if not the direct intervention of the Creator himself. That a single, small, genetic change can produce varied and far-reaching somatic changes no one is better qualified to tell us than Professor Goldschmidt. That somatic changes produced in this way have any necessary tendency to be functionally integrated he has not, however, shown to be probable. Yet the most casual examination of any complex organ shows that it is made up of innumerable interrelated parts, harmoniously adjusted to one another. Consider the structure of even a bird's feather! Only the wave of a magician's wand could have transformed the scales of a reptile forthright into the plumage of a bird.

The trouble here is not so much that we are concerned with very great changes, structural and functional, but that these changes must involve the harmonious modification of parts which are to a large extent independent of one another genetically. Goldschmidt's assurance that "a simple shift in the velocity of one of the integrating processes relative to the others will account for the primary change with all the later unavoidable consequences during subsequent development" may suggest a partial solution of some of the difficulties. It can hardly apply, however, to cases involving the simultaneous though not necessarily parallel, modification of different organ-systems, and particularly to the appearance of fundamentally new structures in some of these. Mivart realized the difficulty of accounting for such functional integration in a theory of evolution by "jumps" and called in a supernatural agent to help him out.

Recent biology has sometimes shown itself so unsympathetic toward the conception of "adaptation" that it has even tended to overlook the facts to which this term is applied. Darwin was largely concerned with the endeavor to explain these facts. We can not, indeed, take them for granted, unless we are prepared to abandon the search for a naturalistic explanation.

It is significant that Goldschmidt's most voluminous line of evidence for the production of major bodily changes through single genetic steps is drawn from the field of rudimentation. Under this head, he has assembled a mass of highly interesting facts. It has long been known that even a single gene mutation may result in the degradation or loss of such important structures as an insect's wings or eyes. It is, however, easy to misinterpret such facts. May I repeat a doubtless unoriginal utterance of my own on this subject: "That a single and extremely simple alteration may effect a radical change in an object, even to its complete annihilation, proves nothing as to the degree of complexity of the object itself or of the processes necessary to bring it into existence."[4]

If Professor Goldschmidt can point to any one case in which a new, complex, adaptive structure has arisen through a single genetic change, and if this same genetic change is shown to have involved the necessary correlative changes in many other parts of the body, he will have gone a long way toward proving his main contention. But he will, at the same time, have left naturalistic biology in a most embarrassing position.

F. B. SUMNER
SCRIPPS INSTITUTION OF OCEANOGRAPHY

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[4] *American Naturalist*, March–April, 1934.

THE ACTIVE PRINCIPLE OF MARIHUANA

FROM red oil distillates, Haagen-Smith *et al.*,[1] have reported the isolation of a crystalline product having marihuana activity. No other unmodified products possessing such activity have been isolated directly from the red oil, though it is known that synthetic tetrahydro-cannabinol possesses such activity,[2] that cannabidiol can be converted into active products by ring closure,[3] and that hydrogenated cannabinol acetate gives physiologically active products.[4]

We have subjected red oil distillates of high physiological activity to distribution between petroleum ether and methanol. This was followed by extraction repeatedly with alkali and distillation of the residues at 175–210° C (0.2 mm). Chromatographic adsorption on alumina gives a fraction (reddish-blue in ultra violet light) which yields about 30 per cent. of a crystalline 3,5-dinito-phenyl urethane. This urethane on hydrolysis gives an active product. Activities are expressed below in terms of a standard U.S.P. extract of cannabis, Parke Davis, according to procedures previously described.[5]

	Potency	Max. Dev.
Tetrahydro-cannabinol (synthetic)	10	± 3
Hydrolysate from urethane	25	± 10
A potent red oil fraction	85	± 10

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[1] Haagen-Smith *et al.*, SCIENCE, 91: 602, 1940.

[2] Adams and Baker, *Jour. Am. Chem. Soc.*, 62: 2405, 1940.

[3] Adams, Pease, Cain and Clark, *Jour. Am. Chem. Soc.*, 62: 2402, 1940.

[4] Bergel and Wagner, *Ann*, 482: 55, 1930.

[5] Walton, Martin and Keller, *Jour. Pharm. and Exp. Therap.*, 62: 239, 1938.

(over)

The urethane resembles the corresponding urethane of synthetic tetrahydro-cannabinol in solubilities, but was a higher melting point (about 216° C with reddening and gas evolution compared with that of tetrahydro-cannabinol at about 208° C with reddening and gas evolution). The analysis suggests a derivative of methyl cannabinol: C 65.12; H 6.00. The preparation could be repeated. A derivative of an active product which is possibly a tetrahydro-cannabinol has been obtained directly from the red oil.

G. POWELL
M. SALMON
T. H. BEMBRY

COLUMBIA UNIVERSITY
DEPARTMENT OF CHEMISTRY

R. P. WALTON

UNIVERSITY OF MISSISSIPPI,
DEPARTMENT OF PHARMACOLOGY

DESIGNATION OF LOCATIONS ON MAPS AND PHOTOGRAPHS

IN recent issues of SCIENCE, two methods of location designation have been described. One of these is a "gridiron" system,[1] the other employs "latitudes and departures."[2] Both are entirely workable within reasonable limits; neither is suitable, without some or much modification, for use with maps or photographs which are to be reproduced on a scale differing from that of the original.

A third method, which may be called a method of intersection, in which the designation remains unchanged regardless of the enlargement or reduction of the original, is here presented. Through the point to be designated and the lower left corner of the map, draw a line. Record the angle between this line and the lower margin of the map. Repeat the process with a line through the point and the lower right corner. A typical actual designation, using this system, is: *Lake Nokoni*, Rocky Mountain National Park Quadrangle, L 51½°, R 56½°. The letters R and L before the angles refer to the right and left corner angles, respectively.

It will be noted that these designations are unaltered by any change in scale of the map, through reproduction or otherwise, and that they may be used with equal facility on photographs or sketches.

RONALD L. IVES

BOULDER, COLO.

KARL FRIEDRICH GAUSS AND HIS FAMILY RELATIVES

IN this crisis of civilization the reflections of one too old for active service turn toward the history of the human progress that is now at stake. The appearance of a familiar name in the American news is a reminder of the great achievements coming from the classic ground of the Georgia Augusta at Göttingen, the famous foundation of King George the Second. In the early years of the last century a young assistant at the observatory, already a great mathematician, directed his attention to the philosophy of geodesy. He recognized that an observer at station A could make his survey of his neighborhood by use of the fixed stars as a frame of reference; while an observer at a distant terrestrial station B could likewise make a local survey, by aid of the same framework of stars now however in quite different relative position. The two observers or any set of such pairs could know nothing more about their mutual relations if they were outside each other's range of vision owing to the protuberance of the earth's curvature; unless they had the property of locomotion, and could carry measuring chains about with them. The philosophical question of the relation of the results of survey by astronomical angular observations to the results of a chain triangulation of the non-spherical surface, and the foundations required to express their mutual consistency in a single scheme impressed the attention of Gauss so far as even to entice him to undertake a practical survey in the kingdom of Hanover with that end in view. This was the beginning from which the famous mathematical theory of a surface, like that of the earth, arose, considered as a self-contained region standing by itself without any support from a frame of space such as the stars had provided in the practical geodesic problem. Building on his foundation Riemann, also at Göttingen, extended it far beyond this self-contained surface of two dimensions to cognate loci of many dimensions, in results which were made available to the public only many years later, after his premature death. And more recently the Italian geometers Ricci and Levi-Civika condensed its complications into a very remarkable system of general classification of a system of related abstract concepts. This in turn has been annexed during the last great war as a foundation for a universe of mathematical relativity, which by abolishing time and space and evading all dependence of expression of results on frames of reference, has presented a mathematical model of a concise new physical world free from observational imperfections that insisted on arising from the fact of the delay in time of transmission of influences, which is in fact necessary if there is to be any analyzable medium of transmission at all.

This digression leads to my query. Long ago the great mathematician Felix Klein, well known in America, mentioned to me that he understood that

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[1] C. F. Reed, SCIENCE, 93: 68, 1941.

[2] L. Hubrecht and R. O. Erickson, SCIENCE, 93: 288, 1941.

descendants of Gauss were still alive in America; and the recent occurrence of this unusual name in diplomacy has suggested that exploration in this direction would be of interest as relating to a conspicuous illustration of the dispersal of Central European centers of learning.

JOSEPH LARMOR

HOLYWOOD, NORTHERN IRELAND

SCIENTIFIC BOOKS

THE COMPARATIVE PHYSIOLOGY OF RESPIRATORY MECHANISMS

The Comparative Physiology of Respiratory Mechanisms. By AUGUST KROGH. vii + 172 pp. 84 figures. University of Pennsylvania Press. $3.00.

IN the spring of 1939, Professor Krogh delivered a series of lectures on "The Comparative Physiology of Respiratory Mechanisms" at Swarthmore College, and these lectures have now been prepared by him in a publication of about one hundred and fifty pages. The principal theme is shown by the title. It is approached through a discussion of the quantity of oxygen needed by various organisms at rest and in activity. The maximum steady metabolism indicates the maximum capacity of the animal's respiratory apparatus. Oxygen is available in the air and water at tensions differing according to the particular environment, and it is the difference between the tension in the environment and at the metabolizing tissues which determines the force available for diffusion in the respiratory exchange.

The external exchange is effected in special devices like gills and lungs, which secure the exchange in many different structures suited to the various animals, their habitat and activity. Special requirements, like heavy work or the restricted supply of oxygen during diving, show the adjustments of respiration under stress.

The blood of animals shows that there are several different chemical mechanisms utilized to facilitate transfer to the respiring tissues. The final transfer of oxygen and carbon dioxide between blood and tissues is related to the distribution and regulation of the capillary circulation, but the details for this last step in the respiratory exchange are still obscure.

The tracheal respiration of insects has particularly interested Professor Krogh. He develops this subject in detail, presenting many descriptions of analyses of the mechanisms involved which originate from his own laboratory, or as a result of his suggestions. There are so many intricate variations in the organs and methods of tracheal respiration, and Professor Krogh's knowledge and appreciation of them is so precise that this is one of the most interesting chapters of the book.

The book is written in a very succinct style, and the examples and illustrations are clear and appropriate. Printing, illustration and arrangement have been very nicely done. Each detail of the exposition is presented separately and distinctly, but the order of material and the brief conclusions always lead toward the complete picture of respiration suited to maintain the animal at its own level of activity and in its own environment.

LAURENCE IRVING

SWARTHMORE COLLEGE

ULTRAVIOLET RAYS

The Chemical Action of Ultraviolet Rays. By CARLETON ELLIS and ALFRED A. WELLS. ix + 961 pp. Illus. New York: Reinhold Publishing Corporation. 1941. $12.00

PHOTOCHEMISTRY, more than most branches of physical chemistry, has suffered from the fact that guiding principles and accurate experimental methods have been slow in their development. This is due partly to the fact that many chemists have been inadequately trained in the use of the physical methods necessary for prosecution of sound research work in this field and partly because of the very complexity of the subject itself. During recent years, however, much progress has been made, and to-day there is a growing appreciation of the importance of the study of the effects of electromagnetic radiation both from the standpoint of the pure chemist and of the biologist.

"The Chemical Action of Ultraviolet Rays" is an attempt to provide a comprehensive survey of the effects of visible and ultraviolet light on chemical systems. A glance at the chapter headings will indicate the breadth of the subject covered. Experimental methods, quantum theory, spectroscopy, photochemical reactions, applications to industrial products and applications in biology are all treated. The number of literature references runs into the thousands.

Any book which attempts to cover as much ground as this one will necessarily be open to several criticisms. The uninitiated would have some difficulty in learning much about theories of spectroscopy and of reaction kinetics from a treatment as brief as the one given, but the list of references on experimental methods is very valuable.

The authors have done a real service to photochemists in covering the literature very thoroughly. One will find cited all the important references on nearly all reactions which have been shown to be light sensitive. The reader will thus be able to ascertain many of the facts in this field. It would be much more difficult for him to obtain a clear idea of the mechanisms

CROSS REFERENCE RECORD

FIRM NAME OR SUBJECT FELLOWSHIPS BEMBRY THOMAS HENRY **FILE NO.**

DATE	REMARKS
	6 extra copies of each of the pamphlets included in Mr. Bembry's report of progress.

SEE EXHIBIT FILE **FILE NO.**

DATE

SIGNED

FILE CROSS REFERENCE RECORD UNDER NAME OR SUBJECT LISTED AT TOP OF THIS SHEET, AND IN PROPER DATE ORDER.
THE PAPERS REFERRED TO SHOULD BE FILED UNDER NAME OR SUBJECT LISTED UNDER "SEE"

YAWMAN AND ERBE MFG. CO.
ROCHESTER, N. Y.

FORM NO. 099CR

1941 JULIUS ROSENWALD FUND FELLOWS

Name THOMAS H. BEMBRY

Present position INSTRUCTOR OF CHEMISTRY College of City of New York,

Address 446 ST. NICHOLAS AVE. NEW YORK, N.Y.

Permanent address 446 ST. NICHOLAS AVE, NEW YORK, N.Y.

Since your fellowship was awarded, have you received a promotion in rank? If so, please describe.

Degree received during fellowship tenure, or since, or progress made toward degree.

PH. D. 1942

Title of dissertation COMPOUNDS OF THE CANNABINOL TYPE

Publications, if any. (Please give titles, date, and place of publication.)

1. SYNTHESIS OF CANNABINOL JOUR. AM. CHEM. SOC. 62, 2568 (1940)
2. COMPOUNDS RELATED TO TETRAHYDROCANNABINOL " " " " 63, 2706 (1941)
3. SYNTHESIS OF PHENOLIC GLYCOSIDES " " " " 64 (1942)

Special honors or activities ELECTED TO SIGMA XI

If in armed service, please give details.

General remarks The above dissertation and publications have to do with the elucidation of the problem of the chemical nature of the active principle of marihuana, responsible for its peculiar physiological and psychological effects. I am continuing research in this field

Thomas H. Bembry

Julius Rosenwald Fund

4901 Ellis Avenue
CHICAGO

FELLOWSHIPS

To Mr. Thomas H. Bembry
446 St. Nicholas Avenue, Apt. 3-B
New York City

Payment Voucher No. 4622

Date May 29, 1942

Final payment on extension to fellowship granted 3/27/42 - - - - - - - $225.00

Ck. #26904

Accounts	Appropriation No.	Debit	Credit
Negro Fellowships	40-11	$225.00	

Prepared by	Checked by	Posted by	
McK			Comptroller

Julius Rosenwald Fund

4901 Ellis Avenue
CHICAGO

FELLOWSHIPS

To
Mr. Thomas Henry Bembry
446 St. Nicholas Avenue (Apt. 3-B)
New York City

Payment Voucher No. 9293

Date April 30, 1942

First payment on expansion to fellowship grant - - - - - $200.00

Ck.#9293 W. F.

Accounts	Appropriation No.	Debit	Credit
Negro Fellowships	40-11	$200.00	

Prepared by	Checked by	Posted by	Comptroller
AM			

FELLOWSHIPS

April 13, 1942

Dear Mr. Bembry: We shall be glad to make payment of the extension to your fellowship grant in two installments as requested in your letter of April 8. A check for $200 will be sent you on May 1, and one for $225 on June 1.

Very truly yours,

DOROTHY A. ELVIDGE

DAE*AM

Mr. Thomas H. Bembry
446 ~~St. Nicholas Avenue~~
Apt. 3 B
New York City

FELLOWSHIPS

446 St. Nicholas Ave.
Apt. 3 B
New York, N. Y.
April 8, 1942

Miss Dorothy A. Elvidge, Comptroller
Julius Rosenwald Fund
4901 Ellis Ave.
Chicago, Ill.

	DE	4/10	DE am	4/13

Dear Miss Elvidge:

In accordance with Mr. Haygood's request that I write you to arrange a plan of payment of the $425 extension to my Fellowship, I would like to say that, since I am already obligated to the amount of this extension, the payments be made as soon as possible and I would like to suggest that a payment of $200 be made May 1 and $225 on June 1. I trust that this arrangement will be satisfactory to you.

noted on form
am

Very truly yours
Thomas H. Bembry
Thomas H. Bembry

FELLOWSHIPS

April 2, 1942

Dear Mr. Bembry: I have your letter of March 31, accepting the Committee's award of a $425 extension to your fellowship. Please write Miss Elvidge and arrange a plan of payment with her.

Sincerely yours,

WILLIAM C. HAYGOOD

WCH:McK

Mr. Thomas H. Bembry
446 St. Nicholas Avenue
Apt. 3 B
New York City

FELLOWSHIPS

446 St. Nicholas Ave.
Apt. 3 B
New York, N. Y.
March 31, 1942

	WCH	4/1	WCH	2

Mr. Willian C. Haygood
Director of Fellowships
Julius Rosenwald Fund
Chicago, Ill.

Dear Mr. Haygood:

I received your letter of March 27th. stating that the Committee could not grant my request for full renewal of Fellowship but it would grant me an extension of $425. I realize that the Committee has many new and worthy applicants for consideration and it is difficult to comply with requests for renewals irrespective of the indespensibility in the mind of the applicant for his particular project. However, I am deeply appreciative of the concerned interest which the Committee has shown in my work as well as for the invaluable material aid which was given and I do trust that in time the Committee will be well pleased as a result of having fostered a research program which has proven to be so valuable to the well-being of society.

Although I shall not be able to expand my activities in reference to my research as hoped, the $425 will be of invaluable service and I shall be very pleased to accept it.

Sincerely yours
Thomas H. Bembry
Thomas H. Bembry

FELLOWSHIPS

November 29, 1941

Dear Mr. Bembry: Your report of the work done under your fellowship grant and the publications have come during Mr. Haygood's absence from the office, but I shall be glad to bring them to his attention when he returns next week.

Requests for renewal of fellowship grants are made in brief form, and are due around the middle of February. I shall be glad to send you a set of blanks as soon as they are ready for distribution.

Sincerely yours,

MLU

MARGARET L. UTLEY

Mr. Thomas H. Bembry
446 St. Nicholas Avenue, Apt. 3 B
New York, N. Y.

Fup 12/15

FELLOWSHIPS

446 St. Nicholas Avenue
Apt. 3 B
New York, N. Y.
November 27, 1941

Bembry, Thomas

WCH	12/1	WCH	11
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Mr. William C. Haygood
Director of Fellowships
Julius Rosenwald Fund
4901 Ellis Avenue
Chicago, Illinoise

Dear Mr. Haygood:-

May I express again my deep appreciation to you and the Committee on Fellowships for the grant from the Rosenwald Fund to do research on the Marihuana Problem, which grant has just terminated. Through it's use, very definite accomplishments of great value towards the total elucidation of this problem as stated in the outset have been realized. I am outlining, herewith, the specific accomplishments together with published results to substantiate them, also what yet remains to be done on the problem as well as my future plans.

I have divided the work on the Marihuana Problem into four stages:

1- The synthesis of compounds possessing marihuana activity
2- The study of the relationship between physiological activity and chemical constitution
3- The standardization, localization and interpretation of the physiological effects
4- To find useful application in the field of medicine for the compounds thus prepared and studied

I am happy to state that the first two stages of this research program have been completed as a result of the application of the grant from the Rosenwald Fund. Details of these results are to be found in the publications which I am enclosing. The third and fourth stages, which represent the ultimate aim of the work in this field, remain yet to be done. Because I would like to

Fup 1/15

realize, at least to some degree, the full aim of this work, I have availed myself for another years work on this problem. To start the work for next year Smith, Kline and French have made available fifteen-hundred dollars, however, the work is not only time consuming but very expensive to carry on and there is no doubt that this fund will be exhausted in the first six or seven months of work even with greatest conservation. In order, therefore, to be able to do a full years work additional funds will be necessary and it is for this reason that I would like to apply to the Rosenwald Fund for a <u>second grant of one-thousand dollars</u> to begin in the spring of 1942 so that the research can be carried through the entire year without interruption until the following October. I trust that you will find it possible to consider this request favorably.

In reference to your letter of November 17, in which you requested my co-operation in helping to locate individuals of promising fellowship material for 1942, I must say that I consider it a great honor to do this and you may be assured that you will have my full support in urging scholars of superior calabre to apply.

Very truly yours
Thomas H. Bembry
Thomas H. Bembry

WCH 6 WEH 0

FELLOWSHIPS

446 St.Nicholas Avenue
Apt. 3 B
New York, N. Y.
October 4, 1941

Mr. George M. Reynolds
Director of Fellowships
Julius Rosenwald Fund
Chicago, Ill.

Dear Mr. Reynolds:

I have just received the final installment on the grant of nine-hundred dollars which you and your Committee were so generous to make. I want to express my deep appreciation and to assure you, at this early date, that much has been accomplished through it's use.

I am preparing a detailed account of accomplishments together with published results and will be able to complete it within the next 30 to 60 days. I shall forward this report to you within this time.

Thanking the Committee again for this Fellowship, I am,

Sincerely yours

Thomas H. Bembry

Julius Rosenwald Fund

4901 Ellis Avenue
CHICAGO

FELLOWSHIPS

Payment Voucher No. 3505

Date September 30, 1941

To

Mr. Thomas H. Dembry
446 St. Nicholas Avenue - Apt. 3 B
New York City

Final payment on fellowship grant - - - - - - - - - - - - - - - $140.00

Ck.#25655

Accounts	Appropriation No.	Debit	Credit
Negro Fellowships	39-7	$140.00	

Prepared by	Checked by	Posted by	
AM			Comptroller

Julius Rosenwald Fund

4901 Ellis Avenue
CHICAGO

FELLOWSHIPS

To Mr. Thomas H. Benbry
446 St. Nicholas Avenue - Apt. 3 B
New York City

Payment Voucher No. 3339

Date August 29, 1941

Fifth payment on fellowship granted 4/11/41 - - - - - - - - - - $140.00

Ck. #25471

Accounts	Appropriation No.	Debit	Credit
Negro Fellowships	39-7	$140.00	

Prepared by	Checked by	Posted by	
McK			Comptroller

Julius Rosenwald Fund

4901 Ellis Avenue
CHICAGO

FELLOWSHIPS

To

Mr. Thomas H. Bembry

446 St. Nicholas Avenue - Apt. 3-B

New York City

Payment Voucher No. 3269

Date July 31, 1941

Fourth payment on fellowship grant - - - - - - - - - - - - $140.00

Ck.#25369

Accounts	Appropriation No.	Debit	Credit
Negro Fellowships	39-7	$140.00	

Prepared by	Checked by	Posted by	Comptroller
AM			

FELLOWSHIPS

446 St Nicholas Ave.
Apt. 3 B
New York, N. Y.
July 21, 1941

Miss Dorothy A. Elvidge, Comptroller
Julius Rosenwald Fund
4901 Ellis Avenue
Chicago, Ill.

	DE	7/22	DE	°
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	aul	—	—	0

Dear Miss Elvidge:

My address has been changed from 210 W. 133rd. Street to 446 St Nicholas Ave., Apt. 3 B, New York, N. Y. Will you kindly send my installment checks and other communications to this new address.

noted on form

Very truly yours
Thomas H. Bembry
Thomas H. Bembry

Julius Rosenwald Fund

4901 Ellis Avenue
CHICAGO

FELLOWSHIPS

To

Mr. Thomas H. Bembry

210 West 133rd Street

New York City

Payment Voucher No. 3210

Date July 1, 1941

Third installment on fellowship grant - - - - - - - - - - - - - - $140.00

Ck.#25306

Accounts	Appropriation No.	Debit	Credit
Negro Fellowships	39-7	$140.00	

Prepared by	Checked by	Posted by	
AM			Comptroller

Julius Rosenwald Fund

4901 Ellis Avenue
CHICAGO

FELLOWSHIPS

To
Mr. Thomas H. Bembry
210 West 133rd Street
New York City

Payment Voucher No. 2985

Date May 29, 1941

Second payment on fellowship grant - - - - - - - - - - - - - - - - $140.00

Ck.#25047

Accounts	Appropriation No.	Debit	Credit
Negro Fellowships	39-7	$140.00	

Prepared by	Checked by	Posted by	Comptroller
AM			

Julius Rosenwald Fund

4901 Ellis Avenue
CHICAGO

FELLOWSHIPS

To

Mr. Thomas H. Bembry

210 West 133rd Street

New York City

Payment Voucher No. 2843

Date April 30, 1941

First payment on fellowship grant - - - - - - - - - - - - - - - - $200.00

Ck.#24901

Accounts	Appropriation No.	Debit	Credit
Negro Fellowships	39-7	$200.00	

Prepared by	Checked by	Posted by	Comptroller
AM			

mLw mco

FELLOWSHIPS

April 29, 1941

Dear Mr. Bembry: The payment plan which you have outlined is entirely agreeable to us. The May 1st installment of $200 is enclosed with this letter. I shall continue to send the monthly checks to this address until I am notified to the contrary.

Very truly yours,

DOROTHY A. ELVIDGE

DAE:RW

Mr. Thomas H. Bembry
210 West 133rd Street
New York City

FELLOWSHIPS

210 W. 133rd. Street
New York, N. Y.
April 25, 1941

Miss Dorothy A. Elvidge, Comptroller
Julius Rosenwald Fund
4901 Ellis Avenue
Chicago, Ill.

	DE	4/28	DE	29
	MLW		MLE	0

Dear Miss Elvidge:

Work is already in progress on the proposed project and I am eagerly awaiting the expansion of activities in my research program which the Fellowship award will afford me.

In accordance with the request in your letter of April 22, I am submitting the following payment plan which I believe will meet my needs very well:

Total 900.

An initial payment of $ 200.00 May 1, 1941

The balance to be divided into five equal payments to be paid on the first of each following month.

$ 140.00 ea

Very truly yours
Thomas H. Bembry
Thomas H. Bembry

OK DE.

Negro Fellowship
39-7

FELLOWSHIPS

April 22, 1941

Dear Mr. Bembry: When you are ready to begin work under your fellowship grant, kindly submit a payment plan that will meet your needs. It is customary for Fellows to prefer payment either in monthly or quarterly installments, but if another plan is more agreeable to you do not hesitate to suggest it.

Very truly yours,

DOROTHY A. ELVIDGE

DAE:RH

Mr. Thomas H. Bembry
[redacted]
New York City

FELLOWSHIPS

	GMR	21	ES	4/22
			JRC	o

210 W. I33rd. Street
New York, N. Y.
April I7, I94I

Mr. George M. Reynolds
Director of Fellowships
Julius Rosenwald Fund
490I Ellis Avenue
Chicago, Ill.

Dear Mr. Reynolds:

I am deeply grateful for the favorable consideration given my application by the Committee to the Rosemwald Fund for aid to continue my researches on the marihuana problem.

I do readily accept the grant under the terms stated and I am certain, that, since through it work on this important problem can be continued, such results will be obtained which will represent an important contribution to society.

Very respectfully yours
Thomas H. Bembry
Thomas H. Bembry

FELLOWSHIPS

2I0 W. I33rd. Street
New York, New York
February 8, I94I

GMD	10	SL	0

Mr. George M. Reynolds
Director of Fellowships
Julius Rosenwald Fund
Chicago, Ill.

Dear Mr. Reynolds

I am glad to inclose additional references as per your suggestion in your letter of January 3I. They are as follows:

sent 2/10

I. Dr. Marston T. Bogert, Professor of Organic Chemistry
Chandler Laboratories
Columbia University, New York, N. Y.

2. Dr. M. L. Caldwell, Professor of Chemistry
Chemistry Department
Columbia University, New York, N. Y.

3. Dr. Robert P. Walton, Professor of Pharmacology
Department of Pharmacology
School of Medicine
University of Mississippi, University, Miss.

I am inclosing the name of Dr. Walton of the University of Mississippi because he and I have worked in close collaboration and he is quite familiar with the progress and importance of my work. Since he is the leading authority in the United States in the field in which I am working, I feel that a statement from him will have some weight.

Very truly yours
Thomas H. Bembry
Thomas H. Bembry

FELLOWSHIPS

January 31, 1941

Dear Mr. Bembry: I have just been going over your application for a fellowship. It seems to be in good order except for the number of references which you have given. It has been our experience that three are hardly enough to give our Committee a well rounded idea of a candidate and his plan, and I am wondering, therefore, if you would not like to send me the name of at least one more person at Columbia University who is familiar with the work you did there. If you can suggest two persons, all the better.

Very truly yours,

GMR*MLU

Mr. Thomas H. Bembry
210 West 133rd Street
New York, N. Y.

FELLOWSHIPS

Chemistry Department
Columbia University
New York, N. Y.
c/o Powell
December 30, I940.

GMR

Mr. George M. Reynolds
Director of Fellowships
Julius Rosenwald Fund
490I Ellis Ave.
Chicago, Ill.

Dear Mr. Reynolds:

In reference to your letter of December 9 to Dr. Powell and me, I am glad to say that the Smith, Kline and French Laboratories have graciously consented to extend their fellowship to me until May I, I940, therefore it will not be necessary to interrupt the work at this present date.

I am enclosing an application for the I94I fund and will appreciate through you the kind as well as favorable consideration of the Committee.

Very truly yours
Thomas H. Bembry
Thomas H. Bembry

FELLOWSHIPS

December 9, 1940

Dear Mr. Bembry: I am enclosing a copy of a letter which I have just sent to Mr. Powell. I very much hope that there will be no interruption in your work during the next few months. I am sorry that it will be impossible for us to be of assistance in this emergency.

I am also enclosing a set of application blanks for the 1941 competition, which you may use if you wish to apply for one of our regular fellowships. There is no way of predicting the action of the Committee on any application, but I can assure you that if you apply you will receive the careful consideration of our group.

Very truly yours,

GEORGE M. REYNOLDS

GMR*MLU

Mr. Thomas Henry Bembry
Department of Chemistry
Columbia University
New York, N. Y.

a

Livingstone College
Salisbury, N. C.

Please return

December 15, 1938

GMR 19

Mr. George M. Reynolds, Director of Fellowships
Julius Rosenwald Fund
4901 Ellis Avenue
Chicago, Illinois

Dear Mr. Reynolds:

Professor Thomas H. Bembry, who has the Chair of Chemistry and Physics at Livingstone College, is making application to the Rosenwald Fund for a fellowship to complete his work for the doctorate in the field of chemistry. Mr. Bembry is a very fine student and an excellent teacher. For the past six years he has been interested in heart stimulants and has been making a special study in that particular field.

Mr. Bembry has the ability to do an outstanding piece of work in research. I am recommending him, and am happy to do so, to you for consideration. This further study would further equip him to render greater service in his work here at Livingstone College. Whatever consideration you may be able to give him will be more than appreciated by not only the President and Faculty, but also by the Trustees of Livingstone College.

Yours very truly,

W. J. Trent, President

WJT:nw

JULIUS ROSENWALD FUND
4901 ELLIS AVENUE
CHICAGO

Confidential Report on Candidate for Fellowship

Name of Candidate Mr. Thomas Henry Bembry

Report Requested of Professor Marston T. Bogert
Chemistry Department, Columbia University, New York City

The above-named candidate has applied to this Fund for a fellowship and has given your name as a reference. The candidate's plan of work is attached. Please return it with your statement.

We shall appreciate your frank opinion of this applicant's qualifications, and an appraisal of his plan of work and of his ability to make a noteworthy contribution in his field. *An early reply will be of great assistance in allowing the Fellowship Committee sufficient time for adequate consideration of the large number of candidates.*

We request candid and critical comment. Your reply will be held in strict confidence.

William C. Haygood
Director for Fellowships

REPORT

February 17, 1941

As to the candidate's qualifications, Mr. Bembry is, in my opinion, an exceptionally able and well trained organic chemist. In fact, he is, I think, the ablest negro chemist with whom I have ever had any professional relations, in a rather long career. My judgment of him is based upon his performances in classes I have been directing for graduate students.

The plan of work he suggests is intelligently drawn, covers an exceptionally important field, and he has already obtained successful results in its early stages. I believe, therefore, that there is an excellent chance of his making a noteworthy contribution to our knowledge of the subject. In other words, I regard him as an exceptionally worthy candidate for the award of the fellowship for which he is an applicant.

OVER

Is the candidate free from personality handicaps which would make it difficult to obtain and hold a position giving him opportunity to utilize his abilities?

I know of no such handicaps, unless his being a negro constitutes such a one.

Signed Marston T. Bogert,

Position or Title Professor of Organic Chemistry

Address Columbia University

New York, N. Y.

Date February 17, 1942

Please return to the Director for Fellowships, Julius Rosenwald Fund,
4901 Ellis Avenue, Chicago, Illinois. Addressed, stamped envelope is enclosed.

FELLOWSHIPS

December 9, 1940

Dear Mr. Powell: I have read with interest your letter of December 4 regarding Mr. Thomas H. Bembry. I wish we could consider giving him assistance, but since all awards for this academic year were made last April, it is impossible for us to do anything for him now.

Should Mr. Bembry find it possible to carry on for the next few months, and should he wish to be considered for a 1941 grant, I shall be glad to see that his application receives the careful consideration of the Committee. Unfortunately for Mr. Bembry, the 1941 Fellows will not be selected until April, and payments under one of the new grants do not begin until May. I realize that even if he is successful in his application this year he is left with a period of months unprovided for; I am sorry that I can suggest nothing helpful.

Very truly yours,

GEORGE M. REYNOLDS

GMR*MLU
CC Mr. Bembry

Mr. Garfield Powell
Department of Chemistry
Columbia University
New York, N. Y.

FELLOWSHIPS

Columbia University
in the City of New York
DEPARTMENT OF CHEMISTRY

December 4, 1940

GMR	6	GR	9

Mr. George M. Reynolds,
Director of Fellowships,
Julius Rosenwald Fund
4901 Ellis Avenue
Chicago, Illinois

Dear Mr. Reynolds:

For the past year I have been engaged in Chemical research at Columbia University on a phase of the marihuana problem, in which I am synthesizing compounds possessing marihuana activity, with the view to learning more about the physiological effect of the natural drug. Through the generous aid of the Smith, Kline fellowship, I have reached such a point in the research, where definite results are assured, as will be indicated from an enclosed reprint of a preliminary report made last August.

The Smith-Kline fellowship has been exhausted and there yet remains six or eight more months of work before the completion of this most important problem. I am, therefore, in urgent need of additional funds to continue and complete this work. This is to apply for aid from the Rosenwald fund and I do trust that you will find it possible to extend me the help of this fund in order that this work so nearly completed, will not have to be curtailed.

I am working under the direction of Dr. Garfield Powell. I believe you should have on file a formal application made to this fund in 1939, from which you may get whatever personal information you may need.

I am, Sir,

Very truly yours,

Thomas H. Bembry.

THB:vb

Thomas H. Bembry

FELLOWSHIPS

Columbia University
in the City of New York

DEPARTMENT OF CHEMISTRY

December 4, 1940

GMR	6	GL	9

Mr. George M. Reynolds,
Director of Fellowships,
Julius Rosenwald Fund
4901 Ellis Avenue
Chicago, Illinois

Dear Mr. Reynolds:

I would beg your consideration of this application for a temporary fellowship for Mr. Thomas H. Bembry of Columbia University who is now working with me for his Ph.D in Organic Chemistry.

Mr. Bembry, aged 32, race Negro, is married and has two small children. He is a teacher at Livingston College, Salisbury, North Carolina, now on leave of absence to do research work in Organic Chemistry. In September of this year he was well on with a problem on marihuana (see enclosed publication) which involves at this time competitive activity in publication. He had completed one year of work and was due to return to Livingston College in order to earn enough money to complete his Ph.D at a later time.

In view of the importance of the work I persuaded Mr. Bembry to carry on with it as fast as possible and gave to his use the Smith, Kline and French fellowship under my direction. This, at the rate of $150. a month, is unfortunately running out at the end of December and I am very much concerned to get him enough money to live till next June when he should have completed his Ph. D and also a very creditable piece of work. I wish to say, at this time, that I consider Bembry to be a very good example of the kind of man and student to whom I would give support: he is hard working, generous in mind, and trustworthy.

I am enclosing his personal application and I would be very grateful for any help that could be extended to him to complete the work. I am glad to refer you to Professor J. M. Nelson or Professor Marston T. Bogert of this university for comments if desired. These Professors are outstanding Organic Chemists who are well acquainted with Bembry personally and with the importance of his work.

Sincerely yours,

Garfield Powell

Garfield Powell,
Assistant Professor of Chemistry

GP:vb

[Reprinted from the Journal of the American Chemical Society, **62**, 2568 (1940).]

SYNTHESIS OF CANNABINOL

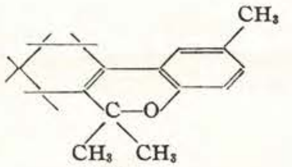
Sir:

We note in a recent communication (This Journal, **62**, 2245 (1940)) that Adams and his co-workers have reported a method for the preparation of compounds analogous to cannabinol which involves the condensation of 5-methylcyclohexanone-2-carboxylate with orcinol in the presence of phosphorous oxychloride, followed by treatment with methylmagnesium iodide. One instance of the use of this method was reported to give a tetrahydropyran.

We wish to report that we have been using this method for some time in the synthesis of compounds analogous to cannabinol with the view to the synthesis of cannabinol itself. The condensation of cyclohexanone-2-carboxylate as well as 5-methylcyclohexanone-2-carboxylate with *p*-cresol, orcinol and olivetol in the presence of sulfuric acid have been carried out with subsequent treatment with methylmagnesium iodide to give the tetrahydropyran I (plates from alcohol, m. p. 69°, found: C, 84.24; H, 8.98; calcd.: C, 84.2; H, 8.77) and the glycol III (white crystals, m. p. 105–106°, found: C, 74.47; H, 8.98; calcd.: C, 74.5; H, 8.98).

Some of these tetrahydropyrans have been dehydrogenated (II, white plates, m. p. 58°, found: C, 85.9; H, 7.35; calcd.: C, 85.7; H, 7.2) to establish the feasibility of passing from these to the pyrans of the cannabinol type. The condensation with orcinol has been carried out and the monomethyl ether of the condensation product treated with methylmagnesium iodide to give the glycol III which was dehydrogenated, after the loss of the elements of water to close the pyran ring, to give a cannabinol type of compound, IV.

This route to cannabinol having been thus fairly well examined, we condensed 5-methylcyclohexanone-2-carboxylate with olivetol, giving a compound which we believe to be V (light brown crystals, m. p. 172–173°, found: C, 75.77; H, 8.2; calcd.: C, 76.0; H, 8.1). Work is now in progress in the treatment of pyrone V or its methyl ether with methylmagnesium iodide with the view of dehydrogenating it to cannabinol.



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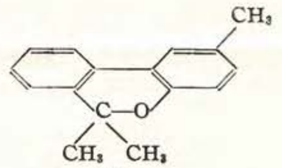

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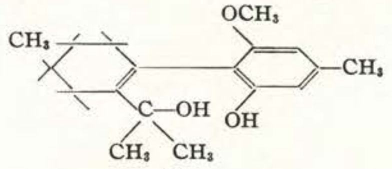
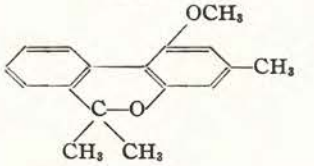
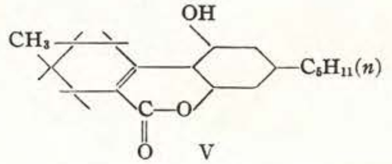


III



IV



V

Isomerism is not excluded in these condensations with the dihydroxybenzenes, and we have refrained from reporting our results. The publication of the note by Adams and his co-workers makes it desirable to point out what has already been done in this type of condensation in these Laboratories.

Chemistry Laboratories
Columbia University
New York, N. Y.

Garfield Powell
Thomas H. Bembry

Received August 12, 1940

FELLOWSHIPS

Columbia University
in the City of New York

DEPARTMENT OF CHEMISTRY

a

January 29, 1942.

Dr. William C. Haygood,
Director of Fellowships,
Julius Rosenwald Foundation
4901 Ellis Avenue
Chicago, Illinois

Dear Doctor Haygood:

I beg to support the application of Thomas H. Bembry for a Rosenwald Foundation Fund to enable him to complete this year of advanced research work with me. As you may remember, the Rosenwald Foundation helped him last year and enabled him to carry on research work on the important marihuana problem. Because of this support he has completed a lot of good work and you will now find that he has been a co-author of four papers on the subject. For 1941-42 I was enabled to get $1500. for him and on this he has continued the research work up to this time. From now on until September, when I hope to have him fixed in a college, there is something of a financial problem. Having a wife and two children he cannot neglect a responsibility for their maintenance and I have, therefore, arranged that, if the worst comes he would be paid out of my own salary to the extent of $425.

If the Rosenwald Foundation can again help him out this year, he will not have to draw on my personal salary for maintenance and I believe that he would be the happier for such an arrangement. I beg, therefore, to support his application for a fellowship from May 1 to October 1. At that time undoubtedly he will be established in some college and have completed more research work on the problem of marihuana.

I believe that the work that Mr. Bembry has done while being supported by the Rosenwald Foundation is very creditable. With the work now in progress added to what he has already done, I am sure that he will be established as a chemist of repute and worthy to take up university research work anywhere. I shall be glad to give details of his work or publications or to give reference to other chemists. In particular I would name Professor John M. Nelson of Columbia University, well-known for his research work in enzymes. He is well acquainted with Bembry.

Sincerely yours,
Garfield Powell
Assistant Professor of Chemistry

GP:vb

JULIUS ROSENWALD FUND

4901 ELLIS AVENUE

CHICAGO

a

Committee folder

Confidential Report on Candidate for Fellowship

Name of Candidate **Mr. Thomas H. Bembry**

Report Requested of **Dr. Percy L. Julian**

Glidden Company, 5165 West Moffat Street, Chicago, Illinois

The above-named candidate has applied to this Fund for a fellowship and has given your name as a reference. The candidate's plan of work is attached. Please return it with your statement.

We shall appreciate your frank opinion of this applicant's qualifications, and an appraisal of his plan of work and of his ability to make a noteworthy contribution in his field. *An early reply will be of great assistance in allowing the Fellowship Committee sufficient time for adequate consideration of the large number of candidates.*

We request candid and critical comment. Your reply will be held in strict confidence.

William C. Haygood

Director for Fellowships

REPORT

Dr. Thomas H. Bembry was under my tutelage as an undergraduate at Howard University some years ago. He made a creditable record as an undergraduate. I have since observed his teaching work and am pleased to say that he did an excellent job under very discouraging conditions. I found him doing research where few would have done anything but grumble over their lack of facilities.

In obvious personality he has never been too strong and should, therefore, find his future in pure research, if possible. He grows on one as acquaintance lengthens.

His work on Marihuana is sound and his results up to the present show progress as I glean from his dissertation, copy of which he kindly sent me sometime ago.

The so-called "Plan of Work" which is presented is indeed poor. No reputable scientist would award a man aid for so important a piece of work on this "layman" presentation. His plan sounds almost like a request for aid to discover,

"A New Method for Synthesizing Rubber".

OVER

It is entirely too general, and were I not familiar with his work, I should reply by saying that there is nothing to be judged. It would appear to me that the Rosenwald Fund in such cases should have competent scientists examine the data accumulated by the applicant.

Indeed in this particular case it would be very pertinent to have the opinion of Dr. Roger Adams of the University of Illinois who is doing at present the most outstanding work on Marihuana in this country.

Is the candidate free from personality handicaps which would make it difficult to obtain and hold a position giving him opportunity to utilize his abilities?

Not in the field of research –

Signed Percy L. Julian

Position or Title Director of Research

Address The Glidden Co., 5165 W. Moffat St.

Chicago, Ill. Date 4/14/42

Please return to the Director for Fellowships, Julius Rosenwald Fund,
4901 Ellis Avenue, Chicago, Illinois. Addressed, stamped envelope is enclosed.

a

JULIUS ROSENWALD FUND

4901 ELLIS AVENUE
CHICAGO

Confidential Report on Candidate for Fellowship

Name of Candidate Mr. Thomas H. Bembry

Report Requested of Dr. M. L. Caldwell

Department of Chemistry, Columbia University, New York

The above-named candidate has applied to this Fund for a fellowship and has given your name as a reference. The candidate's plan of work is attached. Please return it with your statement.

We shall appreciate your frank opinion of this applicant's qualifications, and an appraisal of his plan of work and of his ability to make a noteworthy contribution in his field. *An early reply will be of great assistance in allowing the Fellowship Committee sufficient time for adequate consideration of the large number of candidates.*

We request candid and critical comment. Your reply will be held in strict confidence.

Director for Fellowships

REPORT

Your request for a confidential report on Mr. Thomas H. Bembry, addressed to Dr. M. L. Caldwell, has been referred to me for reply. I can give you the following information: I have the highest regard for Mr. Bembry, both in a personal sense and for his ability as an organic chemist, and have no doubt whatsoever that he is capable of prosecuting a problem of the difficulty of the one in mind.

The only question in my mind concerning the proposed work is whether the competition in this field, which is coming from the University of Illinois, will result in the Illinois people outstripping Mr. Bembry. I have followed this work casually and my impression at present is that the problem is well on the way to being solved through the efforts of the latter group. I hope that this will not be taken in any way as a reflection on Mr. Bembry but merely as my opinion concerning the problem.

OVER

Is the candidate free from personality handicaps which would make it difficult to obtain and hold a position giving him opportunity to utilize his abilities? yes

Signed Robert C. Elderfield

Position or Title Associate Professor of Chemistry

Address Columbia University

New York, N. Y.

Date March 5, 1941

Please return to the Director for Fellowships, Julius Rosenwald Fund,
4901 Ellis Avenue, Chicago, Illinois. Addressed, stamped envelope is enclosed.

A

JULIUS ROSENWALD FUND

4901 ELLIS AVENUE

CHICAGO

Confidential Report on Candidate for Fellowship

Name of Candidate Mr. Thomas H. Bembry

Report Requested of Dr. W. J. Trent, President

Livingstone College, Salisbury, N. C.

The above-named candidate has applied to this Fund for a fellowship and has given your name as a reference. The candidate's plan of work is attached. Please return it with your statement.

We shall appreciate your frank opinion of this applicant's qualifications, and an appraisal of his plan of work and of his ability to make a noteworthy contribution in his field. *An early reply will be of great assistance in allowing the Fellowship Committee sufficient time for adequate consideration of the large number of candidates.*

We request candid and critical comment. Your reply will be held in strict confidence.

George M. Reynolds

Director for Fellowships

REPORT

Dear Mr. Reynolds: I have no additions or subtractions to make in connection with the attached recommendation, which I sent you for Mr. Bembry last year. I heartily reaffirm the statements made in same.

Yours very truly,

W. J. Trent, President

OVER

Is the candidate free from personality handicaps which would make it difficult to obtain and hold a position giving him opportunity to utilize his abilities? Yes.

Signed W. J. Trent

Position or Title President of Livingstone College

Address Salisbury, North Carolina

Date January 28, 1941

Please return to the Director for Fellowships, Julius Rosenwald Fund, 4901 Ellis Avenue, Chicago, Illinois. Addressed, stamped envelope is enclosed.

JULIUS ROSENWALD FUND

4901 ELLIS AVENUE

CHICAGO

Confidential Report on Candidate for Fellowship

Name of Candidate Mr. Thomas H. Bembry

Report Requested of Dr. Robert P. Walton
School of Medicine, University of Mississippi

The above-named candidate has applied to this Fund for a fellowship and has given your name as a reference. The candidate's plan of work is attached. Please return it with your statement.

We shall appreciate your frank opinion of this applicant's qualifications, and an appraisal of his plan of work and of his ability to make a noteworthy contribution in his field. *An early reply will be of great assistance in allowing the Fellowship Committee sufficient time for adequate consideration of the large number of candidates.*

We request candid and critical comment. Your reply will be held in strict confidence.

Director for Fellowships

REPORT

Mr. Bembry has been associated for more than a year with our project directed toward the study of marihuana. His accomplishment to date has demonstrated exceptional ability as a synthetic organic chemist. He has synthesized and turned over to me a material which has typical marihuana activity. The product is less active on a weight basis than some of the most concentrated extracts which we have obtained. Nevertheless, its physiological effects appear to be entirely characteristic. This synthesis followed by one or two months a report of synthesis from a group working at the University of Illinois and Cornell University. Their work will no doubt be recorded as the first synthetic preparation of this important compound. The methods of synthesis, however, were developed by Mr. Bembry independently and prior to the Illinois work. This, I believe, is a good demonstration of Mr. Bembry's ability to accomplish difficult investigative work and indicates good prospects of subsequent productiveness.

OVER

Mr. Bembry is in process of preparing further compounds and we have good expectation that his work will lead to important new information. Since he has made such excellent progress up to this point, I believe any scholarship subsidy which enables the continuation of this work will be exceptionally well placed. As he points out, the information being developed by this program is fundamental knowledge with potentialities of very real usefulness in several different fields. As a sociological problem, the physiological basis of the marihuana effects should be known as fully as possible, as an entirely new field of correlation between chemical constitution and pharmacological action this work is significant and as a direction of experimentation which may develop new therapeutic agents it has definite promise. We hope to continue collaboration along these lines for an indefinite period.

Is the candidate free from personality handicaps which would make it difficult to obtain and hold a position giving him opportunity to utilize his abilities?

I am acquainted with Mr. Bembry only through the correspondence of this collaboration. He has done this work as a graduate student with Dr. Garfield Powell, who was a class-mate of mine at Columbia. Such impressions as may be obtained through such collaborative work have indicated that Mr. Bembry's personal qualifications were satisfactory.

Signed Robt. P. Walton Robt. P. Walton

Position or Title Professor of Pharmacology

Address University, Mississippi.

Date 2-13-41

Please return to the Director for Fellowships, Julius Rosenwald Fund, 4901 Ellis Avenue, Chicago, Illinois. Addressed, stamped envelope is enclosed.

A

JULIUS ROSENWALD FUND

4901 ELLIS AVENUE
CHICAGO

Confidential Report on Candidate for Fellowship

Name of Candidate Mr. Thomas H. Bembry

Report Requested of Dr. Marston T. Bogert
Columbia University, New York, N. Y.

The above-named candidate has applied to this Fund for a fellowship and has given your name as a reference. The candidate's plan of work is attached. Please return it with your statement.

We shall appreciate your frank opinion of this applicant's qualifications, and an appraisal of his plan of work and of his ability to make a noteworthy contribution in his field. *An early reply will be of great assistance in allowing the Fellowship Committee sufficient time for adequate consideration of the large number of candidates.*

We request candid and critical comment. Your reply will be held in strict confidence.

Director for Fellowships

REPORT

February 24, 1941

I have had experience with Mr. Bembry in my organic Seminar during the current academic year, and have formed a very favorable opinion indeed of his ability, energy and resourcefulness. He has already done some fine work in the field which he wishes to follow, namely that of compounds possessing marihuana activity, and the problem he outlines is, in my opinion, a very important one. He is, I think, the ablest colored boy who has come under my personal observation here at Columbia, and I believe he thoroughly merits whatever support you may find it possible to accord him.

OVER

Is the candidate free from personality handicaps which would make it difficult to obtain and hold a position giving him opportunity to utilize his abilities? Yes.

Signed Marston T. Bogert

Position or Title Professor Emeritus of Organic Chemistry in Residence

Address Columbia University

New York, N. Y.

Date Feb. 24, 1941

Please return to the Director for Fellowships, Julius Rosenwald Fund,
4901 Ellis Avenue, Chicago, Illinois. Addressed, stamped envelope is enclosed

JULIUS ROSENWALD FUND

4901 ELLIS AVENUE
CHICAGO

Confidential Report on Candidate for Fellowship

Name of Candidate	Mr. Thomas H. Bembry
Report Requested of	Dr. Garfield Powell Columbia University, New York City

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The above-named candidate has applied to this Fund for a fellowship and has given your name as a reference. The candidate's plan of work is attached. Please return it with your statement.

We shall appreciate your frank opinion of this applicant's qualifications, and an appraisal of his plan of work and of his ability to make a noteworthy contribution in his field. *An early reply will be of great assistance in allowing the Fellowship Committee sufficient time for adequate consideration of the large number of candidates.*

We request candid and critical comment. Your reply will be held in strict confidence.

George M. Reynolds
Director for Fellowships

REPORT

Bembry is a good worker. He has been trained here for research work and has been able to go ahead with a minimum of supervision after some months of work.

The work now in progress competes with that of a full staff of graduate Ph.D workers in Illinois who started some two years before us. That

OVER

he anticipated the best synthetic for cannabinol types and worked on it before the people in Illinois shows good sense, care, and some imagination. The attached note illustrates this matter.

He has ideas which he ought to be allowed to try out. I have obtained a Smith Kline Fellowship to May by special advance from next year but after that he must depend on himself.

He is good research worker. He should be a credit to his race and locality and I believe he should be given every opportunity to continue his research and to hold responsibility.

Is the candidate free from personality handicaps which would make it difficult to obtain and hold a position giving him opportunity to utilize his abilities?

Yes. He is well liked, married, and has two children.

Signed Garfield Powell

Position or Title Asst Prof Chem / Asst Dean Columbia College

Address Columbia College (or University)

New York, N.Y. Date Jan 8 1940

Please return to the Director for Fellowships, Julius Rosenwald Fund,
4901 Ellis Avenue, Chicago, Illinois. Addressed, stamped envelope is enclosed.

A

JULIUS ROSENWALD FUND

4901 ELLIS AVENUE

CHICAGO

Confidential Report on Candidate for Fellowship 39

Name of Candidate Mr. Thomas H. Bembry

Report Requested of Dr. Percy Julian, Glidden Company, 5865 West Moffat Street
Chicago, Illinois

The above-named candidate has applied to this Fund for a fellowship and has given your name as a reference. The candidate's plan of work is attached. Please return it with your statement.

We shall appreciate your frank opinion of this applicant's abilities and personal characteristics, and an appraisal of his plan of work. *An early reply to this inquiry will be of great assistance in allowing the Fellowship Committee sufficient time for an adequate review of the large number of candidates who apply for grants.*

Your reply will be held in strictest confidence.

George M. Reynolds
Director for Fellowships

REPORT

~~The candidate,~~ Mr. Bembry, was under my tutelage as an under-graduate for four years at Howard University. He proved to be an excellent student and a conscientious worker. ~~Later he received his Master's Degree at Columbia University and~~ I had the privilege of visiting him at Livingstone College during the school years, 1935 and 1936. It was an inspiration to see how he was keeping alive, chemically, in the midst of handicaps which would have discouraged a chemist with less determination to forge ahead. I think that of all men of the Negro race who are chemists, I am in a position to point out possibilities as far as creative work is concerned. During the past few years I have called upon possibly 40 or 50 chemistry teachers in the Southern Negro Colleges, and I have yet to find more than 2 or 3 who are trying to do some research work even with handicaps in the same manner in which Bembry is doing at Livingstone College. The Rosenwald Fund will make no mistake in granting him the year's study he is asking for; in fact it would do well to enable him to finish his work for the Doctor's Degree if such is possible. There is a dearth of talent among Negroes in the chemical field. It has been my experience that the teachers of these young Negroes are inclined to evaluate them in a separate category from their white students. From the record of my researches, published under grants from the Rosenwald Fund, I believe it will be evident that I am anxious to avoid this type of evaluation in the case of young Bembry. I believe he will be a good research worker and that he has the type of imagination suited to chemical research. I would like to add that he is happily married and has a beautiful family life. I should greatly appreciate it if you would inform me of your decision with reference to him.

OVER

Is the candidate free from personality handicaps which would make it difficult to obtain and hold a position giving him opportunity to utilize his abilities?

Yes.

Signed Percy L. Julian

Position or Title Director of Research

Address The Glidden Company, Soya Products, Division, 5165 W. Moffat Street

Chicago, Illinois

Date

(Please return to the Director for Fellowships, Julius Rosenwald Fund, 4901 Ellis Avenue, Chicago, Illinois. Addressed, stamped envelope is enclosed.)

Thomas H. Bembry

[Reprinted from the Journal of the American Chemical Society, **62**, 2568 (1940).]

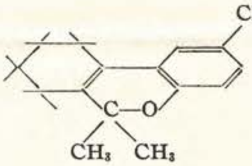
SYNTHESIS OF CANNABINOL

Sir:

We note in a recent communication (THIS JOURNAL, **62,** 2245 (1940)) that Adams and his coworkers have reported a method for the preparation of compounds analogous to cannabinol which involves the condensation of 5-methylcyclohexanone-2-carboxylate with orcinol in the presence of phosphorous oxychloride, followed by treatment with methylmagnesium iodide. One instance of the use of this method was reported to give a tetrahydropyran.

We wish to report that we have been using this method for some time in the synthesis of compounds analogous to cannabinol with the view to the synthesis of cannabinol itself. The condensation of cyclohexanone-2-carboxylate as well as 5-methylcyclohexanone-2-carboxylate with *p*-cresol, orcinol and olivetol in the presence of sulfuric acid have been carried out with subsequent treatment with methylmagnesium iodide to give the tetrahydropyran I (plates from alcohol, m. p. 69°, found: C, 84.24; H, 8.98; calcd.: C, 84.2; H, 8.77) and the g'ycol III (white crystals, m. p. 105–106°, found: C, 74.47; H, 8.98; calcd.: C, 74.5; H, 8.98).

Some of these tetrahydropyrans have been dehydrogenated (II, white plates, m. p. 58°, found: C, 85.9; H, 7.35; calcd.: C, 85.7; H, 7.2) to establish the feasibility of passing from these to the pyrans of the cannabinol type. The condensation with orcinol has been carried out and the monomethyl ether of the condensation product treated with methylmagnesium iodide to give the glycol III which was dehydrogenated, after the loss of the elements of water to close the pyran ring, to give a cannabinol type of compound, IV.



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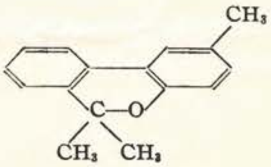
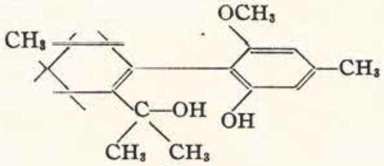
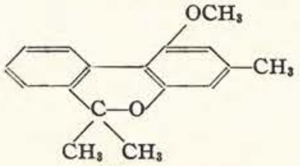


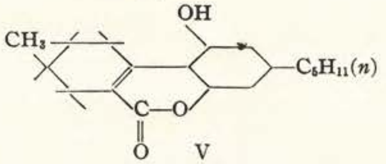
II



III



IV



This route to cannabinol having been thus fairly well examined, we condensed 5-methylcyclohexanone-2-carboxylate with olivetol, giving a compound which we believe to be V (light brown crystals, m. p. 172–173°, found: C, 75.77; H, 8.2; calcd.: C, 76.0; H, 8.1). Work is now in progress in the treatment of pyrone V or its methyl ether with methylmagnesium iodide with the view of dehydrogenating it to cannabinol.

Isomerism is not excluded in these condensations with the dihydroxybenzenes, and we have refrained from reporting our results. The publication of the note by Adams and his co-workers makes it desirable to point out what has already been done in this type of condensation in these Laboratories.

CHEMISTRY LABORATORIES
COLUMBIA UNIVERSITY
NEW YORK, N. Y.

GARFIELD POWELL
THOMAS H. BEMBRY

RECEIVED AUGUST 12, 1940

1942

JULIUS ROSENWALD FUND

DR.1941

APPLICATION FOR RENEWAL OF FELLOWSHIP

Application for reappointment should be filed by February 16, 1942.

Please attach seven copies of a report of progress under your grant, and of your plan of work for the coming year.

Name in full Thomas Henry Bembry

Present address 446 St. Nicholas Avenue, Apt. 3 B
New York, N. Y.

Permanent address 928 W. Monroe Street
Salisbury, North Carolina

FIELD OF INTEREST Chemistry

Concise statement of plan of work To continue work on the Marihuana Problem with particular emphasis now on the standardization, localization and interpretation of the physiological activity of marihuana with the view of finding useful applications for it in the field of medicine.

Institution you wish to attend Columbia University, New York

Under whose supervision will you work? Professor Garfield Powell

Will any time be spent in field work? If so, how much, and where? No

If you do not plan to have an institutional connection, how do you propose to spend your time?

For what period are you requesting a renewal? May 1, 1942 to October 1, 1942

Present status of work toward your degree Ph.D. already obtained

Are you applying elsewhere for a fellowship? If so, please give details.

At present in possession of Smith, Kline and French Fellowship
since Oct.1,1942 and will be exhausted by March 1,1942

Publications since you were awarded a fellowship. (Title, date, place of publication)

Compounds of the Cannabinol Type, Columbia Dissertation, June 1941
Synthesis of Compounds Related to Tetrahydrocannabinol, Jour. of the American Chemical Society, 63, 2766 (1941)
The Active Principle of Marihuana, Science 93, 522, 1941

Do you plan to return to your former position? Yes, if available. Necessary to resign to continue this research

rec'd

References Dr. Garfield Powell, Chemistry Dept. Columbia University, N. Y.
Professor Marston T. Bogert, Chemistry Department
Columbia University, N. Y.
Dr. Percy L. Julian, Director of Research, Glidden Company
5165 W. Moffat Street, Chicago, ill.

Budget estimate

Room and board	$ 500
Clothing	75
Insurance	50
Tuition (Allowed to work at Columbia without tuition)	
Transportation	25
Miscellaneous (Chemicals, Special apparatus, Publications)	600
Total amount needed	1250
Amount applicant can provide	250
Amount requested from Fund	1000

1942 McK

Name Thomas Henry Bembry REAPPOINTMENT **Field:** Chemistry

Student, Columbia University
446 St. Nicholas Avenue, Apt. 3B, New York City

Plan of Work

To continue work on the Marihuana Problem with particular emphasis now on the standardization, localization and interpretation of the physiological activity of marihuana with the view of finding useful applications for it in the field of medicine.

Wishes to work at Columbia University under Professor Garfield Powell, for five months beginning May 1, 1942.

Personal Data Born Hawkinsville, Georgia, December 1907. **Age:** 34
Married, two children.

Undergraduate Work Howard University, B. S., 1929.

Graduate Work Columbia University, M. A. 1932; Ph. D. 1941.

Experience Science teacher, Spencer High School, North Carolina, 1931-32, $810; head, department of chemistry, Livingstone College, 1932- , $1,620.

Accomplishments Articles in Journal of the American Chemical Society, and in Science.

Doctor's Dissertation: "Compounds of the Cannabinol Type"

Smith, Kline and French Fellowship, Columbia University, 1940-41, 1941-42.

Julius Rosenwald Fund Fellowship, 1941, $900.

References

Dr. Garfield Powell, Columbia University
Professor Marston T. Bogert, Columbia University
Dr. Percy L. Julian, Director of Research,
Glidden Company, Chicago

Budget Summary

Total Amount Needed	$1,250
From Applicant	250
From Fund	$1,000

AMOUNT GRANTED

Report of Progress and Plan of Work for the Future

Thomas H. Bembry

Subject: The Study of the Nature of the Active Principle of Marihuana with the View of Finding for It useful Applications in the Field of Medicine

Report of Progress:

I have divided the work on the Marihuana Problem into the following four stages:

I. The synthesis of compounds possessing marihuana activity in order to determine the chemical nature of the principle in marihuana responsible for it's peculiar physiological and psychological properties.

II. The study of the relationship between physiological activity and chemical constitution in an attempt to find the particular part of the chemical molecule responsible for what particular physiological or psychological effect.

III. The standardization, localization and interpretation of the physiological and psychological effects.

IV. To find useful applications in the field of medicine for marihuana.

I am happy to say that the basic work for the first two stages has already been completed through the use of the first Rosenwald Grant of $ 900.00. Details of this study are to be found in published results which are attached.

Plan of Future Work:

The third and fourth stages, which indeed represent the ultimate aim of the whole study, constitute the object of future work on the marihuana problem. In order to realize the successful completion of the third stage one main problem must be solved; and that is, the synthetic compounds of definite constitution and capable of being reproduced at will as obtained in stage I,. must now be so transformed that they can be used as a standard in the interpretation and localization of the physiological and psychological effects. These compounds must retain not only their original marihuana activity, but also must be soluble in water so that they will be readily absorbed by the cellular fluids of the body. In addition they must produce always the same effect when given to a standard test animal under prescribed conditions. The necessary transformations in order to procure such compounds are already well under way, as a result of the use of a Smith, Klime and French Fellowship which I have been using since October, 1941 and is now about to be exhausted. I can say with confidence that the work on this stage has reached such a point in it's development that success is definitely assured by October, 1942.

The realization of the objectives of the fourth stage can come only as a result of the materials and information obtained through the previous steps, particularly the third stage. Even with the information obtained already, there is suggested the possibility of using these marihuana possessing compounds in the field of obstetrics. There is one thing, however, I am certain of and that is, once the information and materials of the first three stages are available there will be no lag in interest in testing the compounds thus standardized in all branches of medicine, for already the medical schools of three universities, Temple University, the University of Mississippi and the University of Chicago, have expressed their desire to collaborate on the problem of finding useful applications for marihuana in the field of medicine..

LETTERS OF REFERENCE

Thomas H. Bembry

Mr. Garfield Powell, Assistant Professor of Chemistry, Columbia University

I wish to support the application of Thomas H. Bembry for a Rosenwald Fund Fellowship to enable him to complete this year of advanced research work with me. As you may remember, the Rosenwald Fund helped him last year and enabled him to carry on research work on the important marihuana problem. Becuase of this support he has completed a lot of good work and you will now find that he has been a co-author of four papers on the subject. For 1941-42 I was enabled to get $1,500 for him and on this he has continued the research work up to this time. From now on until September, when I hope to have him fixed in a college, there is something of a financial problem. Having a wife and two children he cannot neglect a responsibility for their maintenance and I have, therefore, arranged that, if the worst comes, he would be paid out of my own salary to the extent of $425.

If the Rosenwald Fund can again help him out this year, he will not have to draw on my personal salary for maintenance and I believe that he would be the happier for such an arrangement. I beg, therefore, to support his application for a fellowship from May 1 to October 1. At that time undoubtedly he will be established in some college and have completed more research work on the problem of marihuana.

I believe that the work that Mr. Bembry has done while being supported by the Rosenwald Fund is very creditable. With the work now in progress added to what he has already done, I am sure that he will be established as a chemist of repute and worthy to take up university research work anywhere. I shall be glad to give details of his work or publications, or to give reference to other chemists. In particular I would name Professor

John M. Nelson of Columbia University, well-known for his research work in enzymes. He is well acquainted with Bembry.

- - - - -

Professor Marston T. Bogert, Instructor of Organic Chemistry, Columbia University

As to the candidate's qualifications, Mr. Bembry is, in my opinion, an exceptionally able and well trained organic chemist. In fact, he is, I think, the ablest Negro chemist with whom I have ever had any professional relations, in a rather long career. My judgment of him is based upon his performances in classes I have been directing for graduate students.

The plan of work he suggests is intelligently drawn, covers an exceptionally important field, and he has already obtained successful results in its early stages. I believe, therefore, that there is an excellent chance of his making a noteworthy contribution to our knowledge of the subject. In other words, I regard him as an exceptionally worthy candidate for the award of the fellowship for which he is an applicant.

- - - - -

1941. JW

Name Thomas Henry Bembry **Field:** Chemistry

Head, Department of Chemistry (on leave)
Livingstone College, Salisbury, North Carolina
210 West 133rd Street, New York City

Plan of Work

Synthesis of compounds possessing marihuana activity with the view of ascertaining the nature of the physiologically active natural product.

Wishes to attend Columbia University, working for Ph.D. under Dr. Garfield Powell. Has been admitted. Probable duration of study five months, beginning May, 1941. Will return to present position.

Applied in 1939.

Personal Data Born Hawkinsville, Georgia, December, 1907. **Age:** 33
Married, two children.

Undergraduate Work Howard University, B. S., 1929.

Graduate Work Columbia University, M. A., 1932.

Columbia University, 1937-38, 1939 -

Experience Science teacher, Spencer High School, North Carolina, 1931-32, $810; head, department of chemistry, Livingstone College, 1932 - , $1620.

Accomplishments Article in Journal of the American Chemical Society.

Smith-Kline and French Fellowship, Columbia University, 1940-41, $1000; extended to May 1, 1941, $750.

References

Garfield Powell, Columbia University
W. J. Trent, Livingstone College
Percy Julian, Glidden Company, Chicago
Marston T. Bogert, Columbia University
M. L. Caldwell, Columbia University
Robert P. Walton, University of Mississippi

Budget Summary

Total Amount Needed	$ 900
From Applicant	- -
From Fund	$ 900

AMOUNT GRANTED

FILE COPY

Thomas H. Bembry

Synthesis of Compounds Possessing Marihuana Activity

Plan of Work

There has been in the United States within the past fifteen years a rapid increase in the use of hemp extracts, known as marihuana, as a narcotic. The widespread use of marihuana has given rise to a very serious social problem in this country. An understanding of the nature of this drug which is responsible for peculiar psychical de-arrangements in human beings is highly desirable, both in reference to its physiological activity and chemical constitution. Through such information, not only will a more intelligent and effective basis for the control of the use of the drug be gained, but also there will be the possibility of discovering ways by which the drug itself may be turned to special benefit of man, as for example, in the contol or cure of certain diseases.

It is with this view in mind, that I have undertaken to synthesize compounds possessing marihuana activity in order to gain information concerning the particular constituent of the drug which is responsible for its peculiar physiological effect. I have been engaged in this phase of the marihuana problem since October I939, here at Columbia University. Progress of the work up to August I940 can be seen from the attached preliminary report made in the Journal of the American Chemical Society. Since August, I have actually succeeded in synthesizing a compound which possesses marihuana activity according to an assay made by Dr. Robert P. Walton of the University of Mississippi. The results of this assay are now in preparation for publication.

There yet remains the problem of finding out the structural relationship of this synthetic compound to the actual constituent of the natural product. This I intend to do by varying the structure of the synthetic material and comparing the activity of the different synthetic substances with the activity of the natural product. Since I know the structure of these synthetic compounds, the nature of the naturally occurring substance can be predicted.

Through the kindness of the Smith, Kline and French Laboratories, their fellowship to me has been extended to May I94I. From this date about five or six additional months work will be required to conclude the problem. The results of this work will be published in the Journal of the American Chemical Society, and the findings, although within themselves make a contribution to the previously stated purpose of the research, will form the basis of much further work in this field, which I intend to carry on when I return to Livingstone College where I am the Head of the Department of Chemistry.

Thomas H. Bembry

Thomas H. Bembry

[Reprinted from the Journal of the American Chemical Society, **62**, 2568 (1940).]

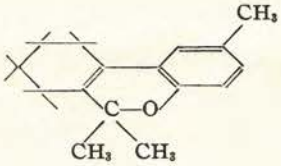
SYNTHESIS OF CANNABINOL

Sir:

We note in a recent communication (THIS JOURNAL, **62**, 2245 (1940)) that Adams and his co-workers have reported a method for the preparation of compounds analogous to cannabinol which involves the condensation of 5-methylcyclohexanone-2-carboxylate with orcinol in the presence of phosphorous oxychloride, followed by treatment with methylmagnesium iodide. One instance of the use of this method was reported to give a tetrahydropyran.

We wish to report that we have been using this method for some time in the synthesis of compounds analogous to cannabinol with the view to the synthesis of cannabinol itself. The condensation of cyclohexanone-2-carboxylate as well as 5-methylcyclohexanone-2-carboxylate with *p*-cresol, orcinol and olivetol in the presence of sulfuric acid have been carried out with subsequent treatment with methylmagnesium iodide to give the tetrahydropyran I (plates from alcohol, m. p. 69°, found: C, 84.24; H, 8.98; calcd.: C, 84.2; H, 8.77) and the glycol III (white crystals, m. p. 105–106°, found: C, 74.47; H, 8.98; calcd.: C, 74.5; H, 8.98).

Some of these tetrahydropyrans have been dehydrogenated (II, white plates, m. p. 58°, found: C, 85.9; H, 7.35; calcd.: C, 85.7; H, 7.2) to establish the feasibility of passing from these to the pyrans of the cannabinol type. The condensation with orcinol has been carried out and the monomethyl ether of the condensation product treated with methylmagnesium iodide to give the glycol III which was dehydrogenated, after the loss of the elements of water to close the pyran ring, to give a cannabinol type of compound, IV.



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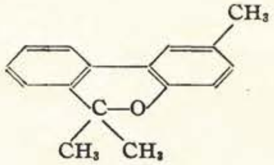

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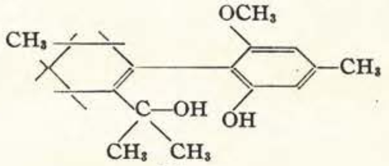
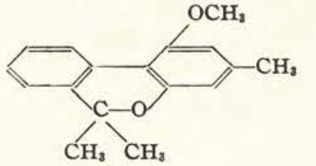
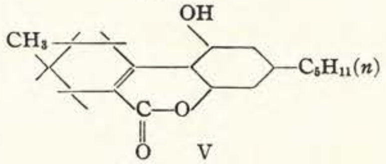


III



IV



V

This route to cannabinol having been thus fairly well examined, we condensed 5-methylcyclohexanone-2-carboxylate with olivetol, giving a compound which we believe to be V (light brown crystals, m. p. 172–173°, found: C, 75.77; H, 8.2; calcd.: C, 76.0; H, 8.1). Work is now in progress in the treatment of pyrone V or its methyl ether with methylmagnesium iodide with the view of dehydrogenating it to cannabinol.

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CHEMISTRY LABORATORIES
COLUMBIA UNIVERSITY
NEW YORK, N. Y.

GARFIELD POWELL
THOMAS H. BEMBRY

RECEIVED AUGUST 12, 1940

For explanation of all terms used see the back of this sheet.

Howard University

WASHINGTON, D. C.
OFFICE OF THE REGISTRAR

Official Transcript of the Record of—

Bembry, Thomas Henry in the College of Liberal Arts and Graduate School

Howard University, Washington, D. C.

I. Attendance. Admitted September 28, 1925

Graduated 8-14-29 Degree S.B. Withdrew 4-19-30

Attended ______ semesters (18 weeks)
______ quarters (12 week)
and ______ summer sessions (8 weeks)

II. Status Received degree of S.B. August 14, 1929

III. Entrance Credits. Sources of credits: (1) Georgia State College, Savannah, Ga.

(2) ______ (3) ______

[Numbers in the third column ("Source") below refer to these numbers.]

Subjects	*Units*	*Source*	*Subjects*	*Units*	*Source*	*Subjects*	*Units*	*Source*	*Subjects*	*Units*	*Source*
English	3		German			Physiology					
Algebra	1½		History	3		General Science					
Geometry	1½		Civics			Com'rcial Subjects					
Trigonometry			Physics	1		Drawing					
Greek			Chemistry	1		Shop Work					
Latin			Physiography	1		Home Economics					
French			Botany			Agriculture	½				
Spanish			Zoology			Other Subjs.	1½		Total	15	

How admitted Unconditioned

IV. College Credits.

Term	Course Number in Catalog	Descriptive Title of Course	No. Wk.	Hours per week Rec.	Lab.	Grade	Unit
Autumn Qr.	Phy. Ed.	Physical Education	12	5	0	B	
1925	Bot. 1	General Botany	12	3	6	C	1
	Germ. 1	Elementary German	12	5	0	C	1
......	Eng. 1	Composition	12	5	0	C	1
Winter Qr.	Phy. Ed.	Physical Education	12	5	0	C	
1926	Math. 3	Plane Trigonometry	12	5	0	C	1
	Eng. 2	Composition	12	5	0	D	1
......	Germ. 2	Elementary German	12	5	0	B	1
Spring Qr.	Phy. Ed.	Physical Education	12	5	0	B	
1926	Zoo. 9	General Zoology	12	3	6	B	1
	Germ. 5	Scientific German Prose	12	5	0	B	1
	Econ. 1	The Principles of Economics	12	5	0	B	1
......	F. L.	Freshman Lectures				S	
Autumn Qr.	Phy. Ed.	Physical Education	12	5	0	A	
1926	Chem. 1	General Inorganic Chemistry	12	4	6	B	1
	Math. 5	Analytic Geometry	12	5	0	D	1
......	Rom. 1	Elementary French	12	5	0	B	1
		Continued on page 2					

*Counted for Entrance Credit.

EXPLANATION

Status

An undergraduate student who withdraws from the University is either—

- (a) *In good standing;* or—
- (b) *On probation;* or—
- (c) *Dropped,* for poor scholarship or excessive absence; or—
- (d) *Under suspension;* or—
- (e) *Dismissed.*

(a) A student *in good standing* is entitled to honorable dismissal in every sense of the term. *No separate letter is necessary.*

(b) A student is *on probation* either for poor scholarship or for disciplinary reasons. If for the former, the University will interpose no objection to his admission to any other school subject to his record here; if for the latter, the nature of the offence will determine the action.

(c) A student is *dropped* for poor scholarship by rule following an unsuccessful probationary period or by special action of the Faculty at any time.

(d) A student may be *under suspension* for cause. Such a student must be reinstated before being honorably dismissed.

(e) A student is *dismissed* only for disciplinary reasons.

Entrance Credits

The term *unit* as applying to secondary work is used in its usual sense—the work in a subject covering 36 weeks of four or five periods each, a period running not less than 40 minutes, with two periods in laboratory, shop or other practice counting as one in recitation.

A student is admitted—

- (a) *Unconditioned.* When 15 units are presented.
- (b) *Unclassified.* To be admitted as unclassified a student must be at least twenty-one years of age and must show preparation for the branches of study chosen.

College Credits

A *semester hour* is the work of a class meeting one hour a week for *eighteen weeks* or the equivalent in laboratory, shop or other practice.

A *college unit* as used in this transcript is the work of a class meeting five hours a week for *twelve weeks.* It is equivalent to 3 1-3 semester hours and to 5 quarter hours.

Marking System

Prior to September 1919 when the semester plan was in operation, grades on the scale 100 were used, the passing mark being 60. From 59 to 50 indicated a condition which could be removed by examination. Below 50 indicated failure which could be removed only by repeating the course.

From September 1919 to June 1933 the quarter plan was in operation and the following grades were in use with significance as indicated:

A—90-100, Excellent; B—80-89, Good; C—70-79, Fair; D—60-69, Poor; E—50-59, Conditioned (Beginning with the Autumn Quarter, 1928, E became a degree of failure); F—less than 50, Failure; WP—Withdrew while passing; WF—Withdrew while failing.

Since September 1933, when the semester plan went into operation the following grades have been in use:
A, B, C, D,—Passing; E, F,—Failure; I—Incomplete; WP—Withdrew while passing; WF—Withdrew while failing.

Graduate School:

S—Satisfactory } Since February, 1934
U—UnSatisfactory }

Term	Course Number in Catalog	Descriptive Title of Course	No. Wks.	Hours per week Rec.	Hours per week Lab.	Grade	Units
		Dembry, Thomas H. p.2.					
Winter Qr.	Phy.Ed.	Physical Education	12	5	0	B	
1927	Rom. 2	Elementary French	12	5	0	A	1
	Chem. 2	General Inorganic Chemistry	12	4	6	C	1
......	Phys. 1	General Physics	12	3	4	F	-
Spring Qr.	Phy. Ed.	Physical Education	12	5	0	[illegible]	
1927	Phys. 1	General Physics	12	3	4	B	1
	Chem. 3	Qualitative Analysis	12	4	6	A	1
......	Germ. 3	Intermediate German	12	5	0	B	1
Autumn Qr.	Phy. Ed.	Physical Education	12	5	0	B	
1927	Chem. 125	Organic Chemistry	12	4	6	B	1
	Eng. 3	Composition	12	5	0	D	1
	Eng. 11	The Elements of Expression	12	5	0	C	1
......	ROTC	R. O.T. C.	12	5	0	B	.5
Winter Qr.	Phy. Ed.	Physical Education	12	5	0	A	
1928	Chem. 126	Organic Chemistry	12	4	6	B	1
	Psy. 1	General Psychology	12	5	0	B	1
	Rom. 3	Intermediate French	12	5	0	D	1
......	ROTC	R. O. T. C.	12	5	0	A	.5
Spring Qr.	Phy. Ed.	Physical Education	12	5	0	B	
1928	Chem. 1251	Organic Chemistry	12	4	6	B	1
	Rom. 4	Intermediate French	12	5	0	C	1
	P.S. 1	The Principles of Political Science	12	5	0	B	1
......	ROTC	R. O. T. C.	12	5	0	B	.5
Autumn Qr.	Chem. 146	Organic Chemistry	12	4	6	B	1
1928	Chem. 4	Elementary Quantitiative Analysis	12	4	6	B	1
......	Econ. 3	Economic Problems	12	5	0	B	1
Winter Qr.	Chem. 147	Organic Chemistry	12	4	6	B	1
1929	Math. 126	Differential Calculus	12	5	0	D	1
....	Chem. 5	Elementary Quantitative Analysis	12	4	6	B	1
Spring Qr.	Chem. 148	Organic Chemistry	12	4	6	C	1
1929	Chem. 130	Physiological Chemistry	12	4	6	D	1
......	Math. 127	Integral Calculus	12	5	0	D	1
Summer 1929	Soc. 125	The Principles of Sociology	8	5	0	B	1
		Graduate					
Autumn Qr. 1929	Chem. 203	Research in Organic Chemistry	12	4	6	B	1
Winter Qr. 1930	Chem. 200	Conference of Chemiscal Literature	12	1	0	-	-

LLW-
TAR
12-12-38

F. A. Wilkinson
Registrar.

EXPLANATION OF MARKS, ABBREVIATIONS AND SYMBOLS: P=Passed. H=Credit for attendance only (residence credit). F=Failure. Also A=Excellent. B=Good. C=Fair. D=Poor (not passing). Abs.=Absent from examination. Wd.=Withdrew. Dr.=Course dropped by student. Inc.=Work incomplete. N.C.=No credit. N.M.=No mark reported by instructor. N.R.=No record of student in course.

UNIT OF VALUE: A point signifies one hour weekly of attendance in classroom or two hours weekly in laboratory or drafting-room for a winter or spring session, or the equivalent.

Columbia University
in the City of New York

Name Thomas Henry Bembry

COURSES	VALUE Points Winter	Spring	Summer	MARKS Winter Final	Winter Def. Exam.	Spring Final	Spring Def. Exam.	Summer
1931 - 1932								
Chemistry 121-122	3	3		P		P		
Chemistry 147-148	2	3		P		B		
Chemistry 161	2			P				
Chemistry 163	5			P				
Chemistry 175	3			P				
Chemistry 124		5				P		
Chemistry 152		4				B		
Summer Session 1934								
Chemistry s110			3					B
Chemistry s162			3					P
1937 - 1938								
Chemistry 101	3			B				
Chemistry 127-128	3	3		P		B		
Chemistry 151	4			B				
Chemistry 301-302	3	3		P		P		
Chemistry 112a		3				C		
Chemistry 242		3				C		

RECORD IN THE GRADUATE
FACULTIES OF POLITICAL SCIENCE
PHILOSOPHY AND PURE SCIENCE

Admitted as Regular ~~Unclassified~~ ~~Non-matriculated~~ Graduate Student

in Faculty of Pure Science

Sept 1931 Date Admission verified MMW

Previous education and degrees:

BS 1929 Howard Univ.

Subject of major interest Chemistry

Counting points

in partial fulfillment of requirements

RESIDENCE REQUIREMENTS
for matriculated students:

For A.M. 30 tuition points

For Ph.D. 60 tuition points

A.M. degree conferred June 1, 1932 Date

Title of Essay

Not Required

Ph.D. degree conferred Date

Title of Dissertation

Committee actions, remarks, etc.

Certified as a correct copy

Registrar

Date

One copy of a student's record is furnished free of charge, each additional copy will cost one dollar.

Form Grad. 7—July '33—5000

For purposes of certifications, reproduced copy of original record shall not be valid without impression seal and actual signature.

LETTERS OF REFERENCE

Thomas H. Bembry

W. J. Trent, President, Livingstone College, Salisbury, North Carolina.

1939 Mr. Bembry is a very fine student and an excellent teacher. For the past six years he has been interested in heart stimulants and has been making a special study in that particular field.

Mr. Bembry has the ability to do an outstanding piece of work in research. I am recommending him, and am happy to do so, to you for consideration. This further study would further equip him to render greater service in his work here at Livingstone College. Whatever consideration you may be able to give him will be more than appreciated by not only the President and faculty, but also by the Trustees of Livingstone College.

1941: I heartily reaffirm the statements made two years ago.

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Robert P. Walton, Professor of Pharmacology, University of Mississippi.

Mr. Bembry has been associated for more than a year with our project directed toward the study of marihuana. His accomplishment to date has demonstrated exceptional ability as a synthetic organic chemist. He has synthesized and turned over to me a material which has typical marihuana activity. The product is less active on a weight basis than some of the most concentrated extracts which we have obtained. Nevertheless, its physiological effects appear to be entirely characteristic. This synthesis followed by one or two months a report of synthesis from a group working at the University of Illinois and Cornell University. Their work will no doubt be recorded as the first synthetic preparation of this important compound. The methods of synthesis, however, were developed by Mr. Bembry independently and prior to the Illinois work. This, I believe, is a good demonstration of Mr. Bembry's ability to accomplish difficult investigative work and indicates good prospects of subsequent productiveness.

Mr. Bembry is in process of preparing further compounds and we have good expectation that his work will lead to important new information. Since he has made such excellent progress up to this point, I believe any scholarship subsidy which enables the continuation of this work will be exceptionally well placed. As he points out, the information being developed by this program is fundamental knowledge with potentialities of very real usefulness in several different fields. As a sociological problem, the physiological basis of the marihuana effects should be known as fully as possible, as an entirely new field of correlation between chemical constitution and pharmacological section this work is significant and as a direction of experimentation which may develop new therapeutic agents it has definite promise. We hope to continue collaboration along these lines for an indefinite period.

I am acquainted with Mr. Bembry only through the correspondence of this collaboration.

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Marston T. Bogert, Professor Emeritus of Organic Chemistry in Residence,
Columbia University.

I have had experience with Mr. Bembry in my organic seminar during the current academic year, and have formed a very favorable opinion indeed of his ability, energy and resourcefulness. He has already done some fine work in the field which he wishes to follow, namely that of compounds possessing marihuana activity, and the problem he outlines is, in my opinion, a very important one. He is, I think, the ablest colored boy who has come under my personal observation here at Columbia, and I believe he thoroughly merits whatever support you may find it possible to accord him.

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Garfield Powell, Assistant Professor of Chemistry, Columbia University.

Bembry is a good worker. He has been trained here for research work and has been able to go ahead with a minimum of supervision after some months of work.

The work now in progress competes with that of a full staff of graduate Ph.D. workers in Illinois who started some two years before us. That he anticipated the best synthetic for cannabriol types and worked on it before the people in Illinois. Shows good sense, care, and some imagination.

He has ideas which he ought to be allowed to try out. I have obtained a Smith Kline Fellowship to May by special advance from next year, but after that he must depend on himself.

He is a good research worker. He should be a credit to his race and locality and I believe he should be given every opportunity to continue his research and to hold responsibility.

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Percy Julian, Glidden Company, Chicago, Illinois.

1939: Mr. Bembry was under my tutelage as an undergraduate for four years at Howard University. He proved to be an excellent student and a conscientious worker. I had the privilege of visiting him at Livingstone College during the school years, 1935 and 1936. It was an inspiration to see how he was keeping alive, chemically, in the midst of handicaps which would have discouraged a chemist with less determination to forge ahead. I think that of all men of the Negro race who are chemists, I am in a position to point out possibilities as far as creative work is concerned. During the past few years I have called upon possibly 40 or 50 chemistry teachers in the Southern Negro colleges, and I have yet to find more than two or three who are trying to do some research work even with handicaps in the same manner in which Bembry is doing at Livingstone College. The Rosenwald Fund will make no mistake in granting him the year's study he is asking for; in fact it would do well to enable him to finish his work for the doctor's degree if such is possible. There is a dearth of talent among Negroes in the chemical field. It has been my experience that the teachers of these young Negroes are inclined to evaluate them in a separate category from their white students. From the record of my researches, published under grants from the Rosenwald Fund, I believe it will be evident that I am anxious to avoid this type of evaluation in the case of young Bembry. I believe he will be a good research worker and that he has the type of imagination suited to chemical research. I would like to add that he is happily married and has a beautiful family life.

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RW

FELLOWSHIPS

ACCOUNT Negro Fellowships APPROPRIATION No. 40-11

NAME OF STUDENT Thomas Henry Bembry

ADDRESS [redacted]

Institution Attending - Columbia University

INSTITUTIONal Position - Head of Department of Chemistry, Livingstone College

Specific Field ~~RECOMMENDED BY~~ - Chemistry

STATEMENT OF OFFER

WCH to Mr. Bembry - 3/27/42: Extension

"At a recent meeting of the Fellowship Committee, your application for a renewal of your fellowship was discussed. The Committee did not feel that it could grant your request for a full renewal, but did grant you an extension of $425 to help you to maintain your present program of research."

AMOUNT OF OFFER $425 PAYMENT DATES

CHECKS PAYABLE TO

TIME PERIOD OF OFFER

APPROVED BY AUTHORIZED BY

PAYMENTS

DATE	EXPLANATION	AMOUNT	DATE	EXPLANATION	AMOUNT

FELLOWSHIPS

ACCOUNT Negro Fellowships APPROPRIATION No. 39-7

NAME OF STUDENT Thomas Henry Bembry

ADDRESS

Institution Attending - Columbia University

INSTITUTIONal Position - Head of Department of Chemistry, Livingstone College

Specific Field - Chemistry

STATEMENT OF OFFER

GMR to Mr. Bembry - 4/11/41

"It is a pleasure to inform you that you have been selected by the Committee on Fellowships of the Julius Rosenwald Fund to receive a grant of nine hundred dollars ($900) to assist you in carrying forward your studies in chemistry at Columbia University for a minimum period of five months, beginning in May of 1941."

AMOUNT OF OFFER $900 PAYMENT DATES

CHECKS PAYABLE TO

TIME PERIOD OF OFFER Not less than five months, beginning in May of 1941.

APPROVED BY AUTHORIZED BY

PAYMENTS

DATE	EXPLANATION	AMOUNT	DATE	EXPLANATION	AMOUNT

FELLOWSHIPS

March 27, 1942

Dear Mr. Bembry: At a recent meeting of the Fellowship Committee, your application for a renewal of your fellowship was discussed. The Committee did not feel that it could grant your request for a full renewal, but did grant you an extension of $425 to help you to maintain your present program of research. If you decide to accept this offer, will you please let me know as soon as you conveniently can?

Sincerely yours,

WILLIAM C. HAYGOOD

WCH:McK

Mr. Thomas H. Bembry
446 St. Nicholas Avenue, Apt. 3B
New York City

FELLOWSHIPS

April 11, 1941

My dear Mr. Bembry: It is a pleasure to inform you that you have been selected by the Committee on Fellowships of the Julius Rosenwald Fund to receive a grant of nine hundred dollars ($900) to assist you in carrying forward your studies in chemistry at Columbia University for a minimum period of five months, beginning in May of 1941.

Will you please let us know at once whether or not you can accept this grant? An official announcement of the Committee's selections will be made soon and it can include only those from whom acceptances have been received.

Very truly yours,

GEORGE M. REYNOLDS

GMR:MLU

Mr. Thomas Henry Bembry
210 West 133rd Street
New York, N. Y.