sodium hydroxide solution, filtered and acidified, the resultant gelatinous precipitate changing to a flocculent one on boiling. The product melted at 358–359° uncor. after sintering about 348° and failed to depress the melting point of an authentic sample prepared from the ester. Owing to an accident part of the product was lost and the yield cannot be reported.

Indole Series

Indole-2,3-dicarboxylic Acid Cyclohydrazide (I, X = NH).—Dimethyl indole-2,3-dicarboxylate (1.0 g. = 0.0043 mole) dissolved in alcohol (6 ml.) and treated with 43% hydrazine hydrate solution (1.5 g. = 0.0129 mole) was heated overnight at 100° in a sealed tube. The mixture (which contained a precipitate of yellow needles) was cooled, diluted with water (20 ml.), treated with dilute sodium hydroxide and warmed until complete solution resulted. To this was added acetone (20 ml.) and an excess of concentrated hydrochloric acid. The resultant yellow precipitate was filtered off, washed and reprecipitated with hydrochloric acid from its solution in hot dilute ammonium hydroxide. The yield was 0.65 g. corresponding to 76%, and did not melt up to 360°.

Anal. Calcd. for $C_{10}H_7O_2N_3$: C, 59.7; H, 3.5; N, 20.9; neut. eq. (for mono-enol), 201.2. Found: C, 59.4, 59.8; H, 3.9, 5.1; N, 20.7, 20.7; neut. eq., 201.9.

The nearly white product was almost insoluble in hot or cold water, ethanol, ether, ethyl acetate, acetone, glacial acetic acid or benzene. It dissolved in dilute sodium hydroxide or in warm sodium carbonate or bicarbonate solution. It did not reduce ammoniacal silver nitrate but gave a deep red-orange color with ferric chloride.

Monoacetyl Derivative.—Indole-2,3-dicarboxylic acid cyclohydrazide (0.2 g.) dissolved in 10% sodium hydroxide (20 ml.) was cooled to 4° and shaken with excess acetic anhydride at this temperature. The resultant white precipitate was filtered off, washed and dried. It failed to show a definite melting point but gradually decomposed above about 270° with charring and gas evolution.

Anal. Calcd. for $C_{12}H_9O_3N_3$: C, 59.3; H, 3.7; sap. equiv. (for monoacetate), 121.6; (for diacetate), 243.2. Found: C, 59.2, 59.0; H, 3.9, 4.3; sap. equiv., 122.7.

Summary

1. The preparation of coumarone-2,3-dicarboxylic acid from coumarandione-2,3 has been developed to a one-step process giving ten times the yields previously reported.

2. The conversion of isatin to coumarandione-2,3 has been developed to give seven times the previously reported yields.

3. The hitherto unknown cyclohydrazides of coumarone-, thionaphthene- and indole-2,3-dicarboxylic acids, together with the corresponding monoacetates, have been prepared and characterized.

4. Two (presumably desmotropic) forms of coumarone-2,3-dicarboxylic acid cyclohydrazide have been isolated.

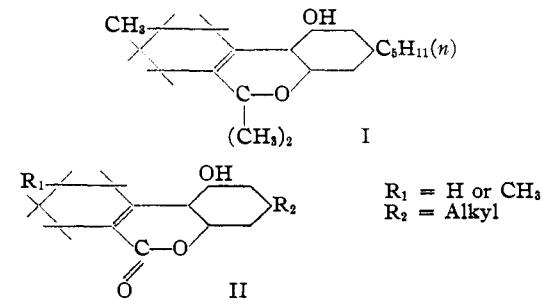
CAMBRIDGE, MASS. RECEIVED AUGUST 2, 1941

[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

(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).

(6) Gosh, Todd and Wright, *J. Chem. Soc.*, 137 (1941).

(7) Powell, Salmon, Walton and Bembry, *Science*, **93**, 522 (1941).

TABLE I

Compound, 7,8,9,10-Tetrahydro-6-dibenzopyrane	Description	Formula	Anal., % calcd. C	calcd. H	found C	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-

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

(9) Adams, Smith and Loewe, THIS JOURNAL, **63**, 1973 (1941).

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.

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

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

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF NEW HAMPSHIRE]

Rearrangement of N-Triphenylmethyl-*o*-toluidine. Direct Synthesis of 3-Methyl-4-aminophenyltriphenylmethane

BY H. A. IDDLES AND A. S. HUSSEY

The rearrangement of N-triphenylmethyl-*o*-toluidine when heated with zinc chloride or the direct action of *o*-toluidine hydrochloride with triphenylcarbinol in an acid medium was interpreted by Van Alphen[1] as a migration of the triphenylmethyl group to the methyl side chain of the *o*-toluidine. This interpretation was postulated by analogy to similar studies made by Schorigin[2] and Van Alphen[3] in the case of the triphenylmethyl ether of *o*-cresol.

However, in previous work from this Laboratory the non-identity of Schorigin's methylated cryptophenol, m. p. 162–163°, with two different preparations of α-2-methoxyphenyl-β,β,β-triphenylethane, m. p. 142–143°, has been established,[4] whereas a synthetic 3-methyl-4-methoxyphenyltriphenylmethane, m. p. 162°, proved to be identical with the methylated rearranged ether.[5] These observations supported the interpretation of a migration to the para ring position for the rearrangement.

In the light of this later evidence, the interpretation offered by Van Alphen[1] for the analogous case of *o*-toluidine required reinvestigation. Further, a discrepancy occurring in his proof of structure remained unexplained, for the postulated unsymmetrical tetraphenylethane produced by diazotization and replacement of the amino group with hydrogen, m. p. 143°, when compared with an authentic synthetic sample, m. p. 144°, depressed the melting point to 110°.

To elucidate these questionable points it seemed desirable to directly synthesize *m*-tolyltriphenylmethane and 3-methyl-4-aminophenyltriphenylmethane, the two compounds which would definitely prove the contention of nuclear migration of

(1) Van Alphen, *Rec. trav. chim.*, **46**, 501 (1927).
(2) Schorigin, *Ber.*, **59**, 2502 (1926).
(3) Van Alphen, *Rec. trav. chim.*, **46**, 287 (1927).
(4) Iddles, French and Mellon, THIS JOURNAL, **61**, 3192 (1939).
(5) Iddles and Minckler, *ibid.*, **62**, 2757 (1940).