205. Cannabis Indica. *Part III. The Synthesis of Dibenzopyran Derivatives, including an Isomer of Cannabinol.*

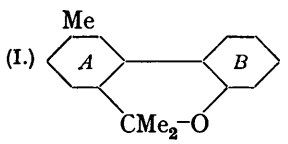
By R. Ghosh, D. C. S. Pascall, and A. R. Todd.

3-*N*-Nitrosoacetamido-4-cyanotoluene condensed with quinol dimethyl ether to give 2′-*cyano*-2 : 5-*dimethoxy*-5′-*methyldiphenyl*, from which by acid treatment 6-*hydroxy*-5′-*methyl*-3 : 4-*benzocoumarin* (V; R = H) was readily obtained. The acetate of (V; R = H) gave with methylmagnesium iodide the corresponding derivative (VI; R = H) of 2 : 2-dimethyldibenzopyran. In similar fashion 5″-*hydroxy*-2 : 2 : 5′-*trimethyl*-4″-n-*amyldibenzopyran* (VI; R = C_5H_{11}) was synthesised; this product is an isomer of cannabinol, a constituent of Indian and Egyptian hashish. Like cannabinol, (VI; R = C_5H_{11}) was inactive in the Gayer test on rabbits at a dose of 5 mg./kg. Attempts to apply the synthetic method to orcinol dimethyl ether and to ethyl veratrate were unsuccessful.

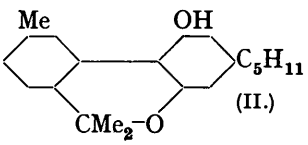
Degradative experiments on cannabinol by Bergel, Cahn, and others led to the conclusion that this constituent of *Cannabis* resins is a derivative of 2 : 2 : 5′-trimethyldibenzopyran (I) bearing in ring *B* a hydroxy- and an *n*-amyl group whose positions could not be established with certainty (Cahn, J., 1932, 1342). Consideration of this structure shows that it would be difficult to obtain any more accurate information as to the location of substituents in ring *B* by oxidative experiments. Cahn (J., 1933, 1400) described an acid fission of cannabinol which gave an unidentified dihydroxydiphenyl derivative by opening of the heterocyclic ring and loss of three carbon atoms; this product seemed a possible starting point for further investigations, but, unfortunately, the extreme conditions employed gave rise, in our experiments, to a series of accidents whereby most of the available material was lost. We therefore decided to devote our attention to a solution of the problem by synthesis of some of the possible structures. A number of routes suggest themselves for this purpose and some of the results so far obtained with them are now described. Although it has recently been shown by Jacob and Todd (*Nature*, 1940, **145**, 350) that cannabinol gives a positive indophenol test, indicating that the *p*-position to the hydroxyl is unsubstituted, and that this, coupled with the results of Adams, Hunt, and Clark (*J. Amer. Chem. Soc.*, 1940, **62**, 735) on cannabidiol, makes (II) the most probable structure for cannabinol (Jacob and Todd, this vol., p. 649), this was not known at the commencement of the synthetic experiments. Indeed, it was considered possible that cannabinol, on the grounds of its weak reducing properties, might be a quinol or catechol derivative. The idea that it might be the quinol derivative (VI; R = C_5H_{11}) seemed attractive in that such a structure might arise in the first instance from a terpene–quinol condensation such as is met with in vitamins E and K.

Cahn (J., 1933, 1400) has described the synthesis of a few simple dibenzopyran derivatives; his method involved formation of 3 : 4-benzocoumarins from diazotised anthranilic acid and phenols, followed by treatment with methylmagnesium iodide and cyclisation of the resulting tertiary alcohols. The yields obtained by Cahn were rather poor and we were

unsuccessful in attempts to apply his method to quinol derivatives. It was thus necessary to alter the method employed for the initial stage in the series. The reaction between *N*-nitrosoacylarylamines and benzene derivatives to give substituted diphenyls, discovered by Bamberger (*Ber.*, 1897, **30**, 366) and recently developed greatly by Heilbron, Hey, and their collaborators, can be adapted to our requirements as regards dibenzopyrans derived from quinol (*e.g.*, VI). 3-Acetamido-4-cyanotoluene (III) (Bogert and Hoffman, *J. Amer. Chem. Soc.*, 1905, **27**, 1295) readily yielded an unstable nitroso-derivative on treatment with nitrous fumes, and this product reacted readily with benzene to give 2-*cyano*-5-*methyldiphenyl*. When condensed with quinol dimethyl ether, it gave similarly 2′-*cyano*-2 : 5-*dimethoxy*-5′-*methyldiphenyl* (IV); the corresponding *diethoxy*-compound was also prepared by means of quinol diethyl ether. When heated with concentrated hydrobromic acid, (IV) underwent hydrolysis of the nitrile group, demethylation, and lactonisation, the product being 6-*hydroxy*-5′-*methyl*-3 : 4-*benzocoumarin* (V; R = H). The *acetate* of this substance, treated with excess of methylmagnesium iodide and worked up in the normal manner, furnished 5″-*hydroxy*-2 : 2 : 5′-*trimethyldibenzopyran* (VI : R = H). No indication was obtained of the presence of the tertiary alcohol which might have been expected as an initial product, although substances of this nature were obtained by Cahn (J., 1933, 1400). A similar series of reactions, 2 : 5-dimethoxy-*n*-amylbenzene being used in place of quinol dimethyl ether, yielded in turn 6-*hydroxy*-5′-*methyl*-7-n-*amyl*-3 : 4-*benzocoumarin* (V; R = C_5H_{11}) and 5″-*hydroxy*-2 : 2 : 5′-*trimethyl*-4″-n-*amyldibenzopyran* (VI; R = C_5H_{11}). The latter product, a colourless crystalline compound, is isomeric but not identical with cannabinol.



(I.)



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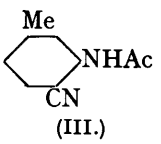

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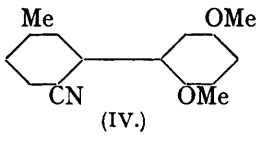
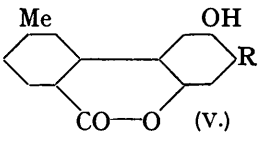


(IV.)



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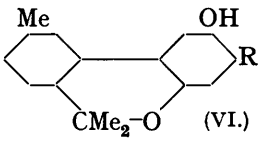

(VI.)

The precise orientation of these compounds has not been rigidly proved, but the structures allotted are, from the mode of synthesis, almost certainly correct. Up to the present little work has been done on the reaction of nitrosoacylarylamines with heavily substituted benzene derivatives, but it has been established that in the case of monosubstituted compounds the substituent phenyl residue enters in the *p*-position and to a lesser extent in the *o*-position; it seems, therefore, reasonable to conclude that in this case substitution would occur in the position indicated by the above structure (V; R = C_5H_{11}). Like cannabinol, the isomeric substance (VI; R = C_5H_{11}) gives a negative result in the Gayer test for *Cannabis* on rabbits. Prof. A. D. Macdonald, to whom we are deeply indebted for the pharmacological tests, found that the compound was inactive at a dose level of 5 mg./kg.; this dose is some 50 times greater than the amount of some of our Indian hashish fractions necessary to evoke a full response.

Attempts were made to extend the synthetic method just described to derivatives of catechol and resorcinol. The sole product isolated from the reaction of 3-*N*-nitroso-acetamido-4-cyanotoluene with orcinol dimethyl ether was a bright red compound which from its analysis was probably 2-*cyano*-2′ : 6′-*dimethoxy*-4′ : 5-*dimethylazobenzene*. Efforts to condense 3-*N*-nitrosoacetamidotoluene with ethyl veratrate yielded only tarry products. Of other possible routes to dibenzopyrans which were explored, the following may be mentioned. The reaction between benzoquinone and diazonium compounds described by Kvalnes (*J. Amer. Chem. Soc.*, 1934, **56**, 2478) was investigated, a number of aromatic amines being used bearing in the *o*-position a group (*e.g.*, CN) which could subsequently be utilised for lactone formation. Like Kvalnes, we found that the

presence of the *o*-substituent prevented the formation of diphenyls. Efforts to convert phenyl anthranilate into a 3 : 4-benzocoumarin were similarly unsuccessful.

Experimental.

3-N-*Nitrosoacetamido*-4-*cyanotoluene*.—Through a solution of 3-acetamido-4-cyanotoluene (III) (2 g.) (Bogert and Hoffman, *loc. cit.*) in a mixture of glacial acetic acid (10 c.c.) and acetic anhydride (2 c.c.) at 0°, dry nitrous fumes were rapidly passed for *ca.* 2 hours. The deep green solution was poured into ice-water, the mixture shaken for a few minutes, and the pale yellow, granular solid collected, washed with ice-water, and dried on porous plate (yield, 90%). The nitroso-compound is very unstable and decomposes explosively on heating.

2-*Cyano*-5-*methyldiphenyl*.—The yellow solution of the above nitroso-compound (1·75 g.) in cold benzene (150 c.c.) gradually became deep red and nitrogen was evolved. After 24 hours, the benzene was distilled off, and the residue sublimed at 150°/0·01 mm. The pale yellow sublimate furnished on recrystallisation from light petroleum (b. p. 40—60°) colourless stout prisms (0·83 g.), m. p. 87—88° (Found: C, 87·3; H, 5·7; N, 6·9. $C_{14}H_{11}N$ requires C, 87·1; H, 5·7; N, 7·2%).

2′-*Cyano*-2 : 5-*dimethoxy*-5′-*methyldiphenyl* (IV).—3-*N*-Nitrosoacetamido-4-cyanotoluene (19 g.) was added during several hours to quinol dimethyl ether (250 g.), maintained at 60° during and for 8 hours after the addition; steam-distillation then removed the excess of quinol dimethyl ether. The residual oil was taken up in ether, and the solution dried and evaporated. Sublimation of the residue at 130—140°/10^{-3} mm. gave a solid, which crystallised from alcohol in colourless needles, m. p. 97° (yield, 41%) (Found: C, 75·9; H, 6·0; N, 5·9. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 5·9; N, 5·5%).

2′-*Cyano*-2 : 5-*diethoxy*-5′-*methyldiphenyl*, prepared similarly from quinol diethyl ether at 75°, formed colourless needles, m. p. 72—73° (Found: C, 76·5; H, 6·5; N, 4·9; OEt, 32·0. $C_{18}H_{19}O_2N$ requires C, 76·8; H, 6·7; N, 5·0; OEt, 32·0%). The low yield (24%) was probably due to the high temperature necessary to keep the quinol diethyl ether liquid during the reaction.

6-*Hydroxy*-5′-*methyl*-3 : 4-*benzocoumarin* (V; R = H).—2′-Cyano-2 : 5-dimethoxy-5′-methyldiphenyl (9 g.) was refluxed during 3 hours with concentrated hydrobromic acid (70 c.c. of 48%); the mixture was then diluted with water, and the solid product collected. After recrystallisation from alcohol (charcoal) the *benzocoumarin* was obtained in clusters of colourless needles (8 g.), m. p. 233—234° (decomp.) (Found: C, 74·4; H, 5·1. $C_{14}H_{10}O_3$ requires C, 74·3; H, 4·5%). The *acetate*, obtained by refluxing with acetic anhydride in pyridine solution, crystallised from alcohol in short stout needles, m. p. 155° (Found: C, 71·3; H, 4·7. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%).

5″-*Hydroxy*-2 : 2 : 5′-*trimethyldibenzopyran* (VI; R = H).—The above acetate (5 g.), dissolved in dry anisole (150 c.c.), was added to a solution of methylmagnesium iodide (from 22·5 g. of methyl iodide) in ether–anisole (200 c.c.). A heavy white precipitate formed and the mixture was heated on the steam-bath with constant stirring during 2 hours. The mixture was decomposed with ice and dilute sulphuric acid, anisole removed by steam-distillation, the product taken up in ether, and the solution dried and evaporated. The residual oil on distillation at 150°/0·015 mm. yielded a pale yellow resin, which crystallised from light petroleum (b. p. 60—80°) in colourless needles (4 g.), m. p. 118° (Found: C, 80·1; H, 6·6. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%). The *dibenzopyran* dissolved in aqueous or alcoholic alkali to give colourless solutions. Its *acetate*, prepared by refluxing with acetic anhydride in pyridine solution, crystallised from light petroleum (b. p. 40—60°) in colourless needles, m. p. 86—87° (Found: C, 75·9; H, 6·2. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%). Treatment with 3 : 5-dinitrobenzoyl chloride in pyridine solution gave a 3 : 5-*dinitrobenzoate*, crystallising from acetic acid in yellow needles, m. p. 169° (Found: C, 63·5; H, 4·0; N, 6·4. $C_{23}H_{18}O_4N_2$ requires C, 63·6; H, 4·1; N, 6·4%).

2 : 5-*Dimethoxy*-n-*amylbenzene*.—The procedure of Cruickshank and Robinson (J., 1938, 2066) was followed, save that the following method was found much more satisfactory for the preparation of the initial 2-hydroxy-5-methoxy-*n*-valerophenone: Valeric acid (61 g.) was heated under reflux for 4 hours with thionyl chloride (72 g.), the excess of the latter removed, and the crude chloride added dropwise to a boiling mixture of carbon disulphide (300 c.c.), quinol dimethyl ether (60 g.), and anhydrous aluminium chloride (100 g.). Heating was continued for 4 hours, and the mixture left overnight; the carbon disulphide layer was then decanted, and the residue decomposed with ice and concentrated hydrochloric acid. Unchanged material was removed by steam-distillation, the residue, which solidified on cooling,

extracted with chloroform, and the extract dried and evaporated, The product distilled at 135—145°/0·1 mm. Recrystallised from light petroleum, it had m. p. 62° and gave a 2 : 4-dinitrophenylhydrazone, m. p. 185°. Cruickshank and Robinson (*loc. cit.*) give m. p. 62°; 2 : 4-dinitrophenylhydrazone, m. p. 186°. The yield of ketone was 70 g.

Acetylation by means of acetic anhydride in pyridine solution gave 2-*acetoxy*-5-*methoxy*-*valerophenone*, forming yellowish prisms from alcohol, m. p. 72—73° (Found : C, 66·8; H, 7·1. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%). Treatment of the ketone in alcoholic solution with semicarbazide hydrochloride and sodium acetate yielded two products, which were readily separated by reason of their differing solubility in alcohol. The less soluble product formed long yellow needles, m. p. 161—162°, and appeared to be the *ketazine* (Found : C, 70·0; H, 8·5; N, 6·8. $C_{24}H_{32}O_4N_2$ requires C, 70·0; H, 8·0; N, 6·8%). The other was a pale greenish, microcrystalline powder, m. p. 159—160°, whose nitrogen content indicated it to be the *semicarbazone* (Found : N, 15·4. $C_{13}H_{19}O_3N_3$ requires N, 15·8%).

2′-*Cyano*-2 : 5-*dimethoxy*-5′-*methyl*-4-n-*amyldiphenyl*.—3-*N*-Nitrosoacetamido-4-cyanotoluene (8 g.) was added during 3—4 hours to 2 : 5-dimethoxy-*n*-amylbenzene (68 g.) maintained at 45—50°. Nitrogen was evolved and, after standing overnight, the deep red solution was worked up as before. The product was a thick oil which distilled fairly steadily at 95—100°/0·036 mm. (Found : C, 77·6; H, 8·5; N, 4·2. $C_{21}H_{25}O_2N$ requires C, 78·0; H, 7·7; N, 4·3%). Yield, 3·5 g.

6-*Hydroxy*-5′-*methyl*-7-n-*amyl*-3 : 4-*benzocoumarin* (V; R = C_5H_{11}).—The above nitrile (1·25 g.) was refluxed with hydrobromic acid (25 c. c. of 48%) during 5 hours, and the product worked up in the usual way. The *benzocoumarin* crystallised from alcohol in needles, m. p. 191—192° (Found : C, 76·9; H, 6·9. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·8%). The *acetate*, prepared by refluxing with acetic anhydride in pyridine solution, crystallised from alcohol in needles, m. p. 138—139° (Found : C, 74·9; H, 7·1. $C_{21}H_{22}O_4$ requires C, 74·6; H, 6·5%).

5″-*Hydroxy*-2 : 2 : 5′-*trimethyl*-4″-n-*amyldibenzopyran* (VI; R = C_5H_{11}).—The above acetate was treated with excess of methylmagnesium iodide in anisole solution in a manner analogous to that described for the preparation of (VI; R = H). Recrystallised from light petroleum (b. p. 60—80°), the *product* formed colourless plates, m. p. 110—111° (Found : C, 81·3; H, 8·8. $C_{21}H_{26}O_2$ requires C, 81·3; H, 8·4%). The substance gave no coloration with alcoholic potash or with 2 : 6-dichloroquinonechloroimide. In alcoholic solution it showed absorption maxima at 2475 A. (ε 11,550), 2765 A. (ε 10,560), and 3400 A. (ε 7450).

Condensation of Orcinol Dimethyl Ether with 3-N-*Nitrosoacetamido*-4-*cyanotoluene*.—The reaction was carried out at room temperature. Although the solution turned deep red, very little evolution of nitrogen occurred and, on working up, a bright red solid was obtained. It crystallised from alcohol in needles, m. p. 126°, and was almost certainly 2-*cyano*-2′ : 6′-*dimethoxy*-4′ : 5-*dimeth lazobenzene* (Found : N, 14·2. $C_{17}H_{17}O_2N_3$ requires N, 14·0%).

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