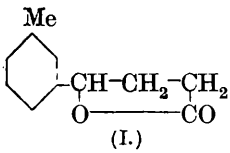
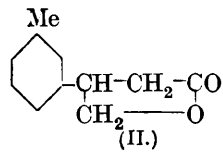
CXXI.—Cannabis Indica *Resin. Part I. The Constitution of Nitrocannabinolactone (Oxycannabin).*

By Robert Sidney Cahn.

The general problem presented by *Cannabis Indica* resin, the essential portion of the drug known as hashish, bhang, etc., will be considered in a later communication. The present paper is confined to oxycannabin, which is a product of oxidation by concentrated nitric acid of the higher-boiling portions of the resin.

Oxycannabin has been assigned various formulæ, *viz.*, $C_{20}H_{20}O_7N_2$ (Bolas and Francis, J., 1869, **22**, 417; *Chem. News*, 1871, **24**, 77), $C_{10}H_{11}O_4N$ (Dunstan and Henry, P., 1898, 44), and $C_{11}H_{11}O_4N$ (Wood, Spivey, and Easterfield, J., 1899, **75**, 20), the last of which has been confirmed in the present investigation. Wood, Spivey, and Easterfield removed the nitro-group, *via* the amino- and iodo-groups, to obtain the substance $C_{11}H_{12}O_2$; this they termed cannabinolactone, renaming oxycannabin as nitrocannabinolactone. Among other results they showed that cannabinolactone on fusion with potassium hydroxide yielded *m*-toluic acid, and as, further, it contains an excessively stable lactone group, they concluded that it must be represented by one of the γ-lactonic formulæ (I)—(III).


(I.)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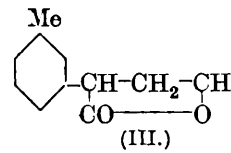
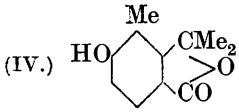

(III.)

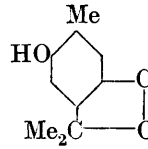
They did not, however, consider the possibility of its being a phthalide derivative, although these are known readily to yield derivatives of benzoic acid on fusion with alkali.

Hydroxycannabinolactone was chosen as the starting point of the present investigation, as it was hoped by means of this substance to determine also the position of the substituent group (compare Bauer, *Ber.*, 1908, **41**, 503, who obtained *m*-hydroxybenzoic acid from methoxy-αα′-diethylphthalide). Hydroxycannabinolactone (prepared by boiling a diazotised solution of the amino-compound) on fusion with potassium hydroxide at 290—300° yielded 6-hydroxy-*m*-toluic acid and acetone, which are the products to be expected from a substance having either formula (IV) or (V) (Gucci, *R. Accad. Lincei*, 1897, **6**, i, 295). The production of acetone renders untenable formulæ (II) and (III) for cannabinolactone (also those representing it as an ethylphthalide), but is not incompatible with

formula (I). In this last case oxidation, starting at the carbon atom carrying the hydroxyl group formed by opening of the lactone



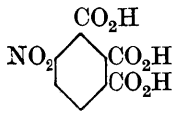
(IV.)



(V.)

ring, would yield potassium malonate, from which acetone would be formed. Wood, Spivey, and Easterfield, however, showed that only the methyl group of cannabinolactone was oxidised by excess of alkaline potassium permanganate solution, and the present author found that under similar conditions nitrocannabinolactone absorbs only the three atoms of oxygen necessary for oxidation of the methyl group. On account of the stability of the alcoholic hydroxyl group, which must be present in alkaline solutions of cannabinolactone and its nitro-compound, it is impossible to regard these substances as primary or secondary alcohols.* The only constitution which gives rise to a tertiary alcoholic group on ring opening is that of a dimethylphthalide, for which the two possibilities (IV) and (V) remain.

A by-product in the nitric acid oxidation of nitrocannabinolactone was a tribasic acid, $C_9H_5O_8N$, m. p. 228—230°, the formation of which Wood, Easterfield, and Spivey were unable satisfactorily to explain on the basis of their formulæ (I)—(III). However, the dimethylphthalide formulation being assumed, this acid clearly has the structure represented by (VI) or (VII). The former has not



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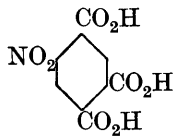

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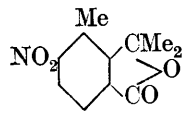


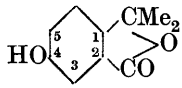
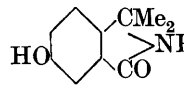
(VIII.)

been synthesised. The latter melts at 175° (Schultz, *Ber.*, 1909, **42**, 3607) and thus cannot be identical with the acid from nitrocannabinolactone, which must, therefore, be (VI). Nitrocannabinolactone itself must then be represented by formula (VIII).

During the preliminary experiments on the alkali fusion of hydroxycannabinolactone it was found that there was considerable danger of loss of carbon dioxide from the hydroxy-acid formed. In order to determine the conditions of the reaction, *4-hydroxydimethylphthalide* (IX) was prepared from the corresponding amino-

* *E.g.*, mandelic acid was found to be readily oxidised under the conditions used for nitrocannabinolactone.

compound * (Teppema, *Rec. trav. chim.*, 1923, **42**, 30; Tasman, *ibid.*, 1927, **46**, 653). The cannabinolactone derivatives behave very similarly to those encountered in this preparation, the methylation of the hydroxy-derivative being particularly noteworthy, and the relative stability of the nitro-, amino-, and methoxy-compounds agrees qualitatively with that established by Tasman (*loc. cit.*) for phthalide derivatives. In an attempt to effect fission by a

(IX.)   (X.)

method in which the possibility of oxidation was excluded, 4-hydroxydimethylphthalide was heated with aniline to 300°. A nearly quantitative yield of 4-*hydroxy*-N-*phenyl*-αα-*dimethylphthalimidine* (X) resulted : the same compound was also obtained by heating with aniline and aniline hydrochloride to 210° (compare Emmert and Meyer, *Ber.*, 1921, **54**, 210).

Experimental.

Nitrocannabinolactone (oxycannabin), prepared according to the directions of Wood, Spivey, and Easterfield (*loc. cit.*), had the properties described by these authors (Found † : C, 59·8, 59·6; H, 5·1, 5·0; N, 6·6, 6·55; *M*, in camphor, 206, 196, 203, 212. Calc. for $C_{11}H_{11}O_4N$: C, 60·0; H, 5·0; N, 6·35%; *M*, 221). The working up of the hashish used for this preparation will be described in a later communication.

Aminocannabinolactone.—The following modification of Wood, Spivey, and Easterfield's method of preparation is more convenient and gives an improved yield. Red phosphorus (5 g.) was added to a solution of nitrocannabinolactone (9 g.) in glacial acetic acid (36 c.c.) and hydriodic acid (27 c.c., *d* 1·7), and the whole heated under reflux for 2—3 hours. The solution was diluted with water (300 c.c.) and filtered hot into a hot solution of sodium hydroxide (34 g.) in water (500 c.c.). The weakly acid solution was again filtered hot from a small amount of gummy impurity, which was washed with boiling water. On cooling, aminocannabinolactone (5·3 g.) separated as an oil which at once crystallised when seeded and was quite pure, m. p. 120° (Wood, Spivey, and Easterfield give m. p. 119°). By concentration of the mother-liquor (charcoal) a further quantity (0·5 g.) was obtained, m. p. 117—118° (total yield, 74·5% of the theoretical).

* Named 5-aminodimethylphthalide by these authors, who start numbering from the carbonyl group.

† All analyses marked thus are microanalyses by Dr. Ing. A. Schoeller of Berlin.

Hydroxycannabinolactone (IV).—When potassium nitrite (2·54 g. in a little water) was added to a cold solution of aminocannabinolactone (5·7 g.) in 20% sulphuric acid (110 c.c.), and the mixture subsequently warmed on the water-bath until evolution of gas ceased, *hydroxycannabinolactone* separated in quantitative yield as an apricot-coloured powder. Recrystallised from aqueous alcohol or, better, from benzene, it formed pale yellow needles, m. p. 198—199° (Found † : C, 68·5; H, 6·3. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·3%). The colour cannot be removed by ordinary methods, but the substance was recovered quite colourless from low-temperature potash fusions. Hydroxycannabinolactone dissolves immediately in cold sodium hydroxide and slowly in sodium bicarbonate solutions (to give bright yellow solutions, if the coloured substance is used), and is precipitated unchanged on acidification. An alcoholic solution does not, however, evolve carbon dioxide on treatment with sodium bicarbonate solution. Acetylation by acetic anhydride was not satisfactory, but *acetoxycannabinolactone* was readily obtained by addition of acetyl chloride to an ice-cold solution of the substance in pyridine and subsequent treatment with water. It crystallised from a little alcohol in colourless needles, m. p. 93° (Found † : C, 66·3; H, 6·1. $C_{13}H_{14}O_4$ requires C, 66·6; H, 6·0%).

Methoxycannabinolactone.—On shaking a solution of hydroxycannabinolactone (0·9 g.) in 8% sodium hydroxide solution with methyl sulphate (20 c.c., added in portions), a homogeneous solution was obtained, from which *methoxycannabinolactone* was precipitated on acidification. It crystallised from methyl alcohol in colourless prisms, m. p. 182° [Found † : C, 69·6; H, 6·9; MeO, 14·1. $C_{11}H_{11}O_2(OMe)$ requires C, 69·9; H, 6·8; MeO, 15·05%].

Once precipitated, the methoxy-compound is insoluble in sodium hydroxide solution, and the phthalide ring is only slowly opened; *e.g.*, after the methoxy-compound (0·3 g.) had been refluxed with 10% aqueous-alcoholic potassium hydroxide solution (1 : 1) for 1 hour, addition of water precipitated 0·1 g. which had not undergone ring fission, the remainder being precipitated on acidification (compare Tasman, *loc. cit.*). As the methoxy-compound, when first formed, remained dissolved in the alkaline solution, it must have been formed as $OH{\cdot}CMe_2{\cdot}C_6H_2Me(OMe){\cdot}CO{\cdot}O^-$. Whence it follows that the dimethylphthalide ring of the hydroxy-compound is opened on solution in cold alkali, and that the doubts of Tasman, who did not investigate hydroxy-compounds, as to the quinonoid structure of phenolphthalein compounds are unfounded.

Methoxycannabinolactone was also obtained by heating the hydroxy-compound in benzene solution with methyl iodide and

freshly prepared silver oxide, and by heating the silver salt with methyl iodide in benzene.

Fusion of Hydroxycannabinolactone.—The lactone (1 g.) was added during 8 minutes to molten potassium hydroxide at 290—300°, this temperature being maintained for a further 10 minutes. The cooled melt was dissolved in water, acidified, and then made alkaline with sodium bicarbonate. Extraction with ether removed a small amount of cresol and unchanged phthalide. Re-acidification of the alkaline liquid and extraction with ether yielded impure 6-hydroxy-*m*-toluic acid, which after recrystallisation from water formed needles containing $\frac{1}{2}H_2O$ of crystallisation (Found : H_2O, 5·95, 6·4. Calc. for $C_8H_8O_3,\frac{1}{2}H_2O$: H_2O, 5·6%). When dried, it melted at 172—173° (Found : C, 63·45; H, 5·25. Calc. for $C_8H_8O_3$: C, 63·15; H, 5·3%). Yield after one crystallisation, 0·3 g. The acid gave no colour with ferric chloride solution.

The distillate from a similar fusion was collected under water and gave positive results with the following tests for acetone : iodoform, sodium nitroprusside–alkali–acetic acid, Denigès's test.

Oxidation of Nitrocannabinolactone.—4% Potassium permanganate solution was added in portions of 1 c.c. to a solution of nitrocannabinolactone (0·47 g.) and sodium hydroxide (1 g.) in water (15 c.c.) heated on the water-bath. Decolorisation, at first complete in 15 seconds, grew progressively slower until, when 16·4 c.c. (3 atoms of oxygen) had been added, 20 minutes were required. Thereafter, decolorisation was exceedingly slow, and on addition of a further 5·5 c.c. (1 atom of oxygen) and continued heating for 1 hour, very little reduction took place. After cooling, excess of sodium bisulphite and hydrochloric acid were added, which precipitated a rapidly crystallising gum. Recrystallised from water, it formed plates (0·2 g.), m. p. 227—229° (Wood, Spivey, and Easterfield give the melting point of cannabinolactonic acid as 229—230°).

4-*Hydroxy*-αα-*dimethylphthalide* (IX). —4-Aminodimethylphthalide (Teppema, *loc. cit.*; Tasman, *loc. cit.*) was prepared (*a*) by the method described above for aminocannabinolactone, the pure compound crystallising (m. p. 117°) in 78% yield, or (*b*) by suitable modification of West's method (J., 1925, **127**, 494), in 70% yield. For transformation into the hydroxy-compound the following conditions should be adhered to, deviations leading to much reduced yields. 4-Aminodimethylphthalide (8·85 g.) in water (100 c.c.) and concentrated sulphuric acid (10 c.c.) was diazotised at 10° by potassium nitrite (4·25 g. in a little water), and the cooled solution dropped slowly into boiling, mechanically stirred 1% sulphuric acid (500 c.c.). Boiling and stirring were continued for a further 2 hours and the solution was then filtered hot from a little tar. On standing

in the ice-chest, 4-*hydroxy*-αα-*dimethylphthalide* (6·9 g.; 78% of the theoretical yield) was deposited in pale yellow crystals. It separated from benzene in very pale yellow crystals, m. p. 149—150° (Found : C, 67·5; H, 5·8. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·7%). The substance was purified beyond this point only with difficulty, but was recovered from low-temperature potash fusions quite colourless and melting at 152°.

The acetyl derivative was prepared by the pyridine and acetyl chloride method, and crystallised from dilute acetic acid; it melted at 84°.

When the hydroxy-compound (0·5 g.), dissolved in 10% sodium hydroxide solution (20 c.c.), was shaken with methyl sulphate (3 c.c.), added in portions, a homogeneous solution was obtained, from which on acidification 4-*methoxydimethylphthalide* was precipitated; after being washed with dilute alkali (in which it was now insoluble) and recrystallised from aqueous methyl alcohol, it melted at 100° (Found : C, 68·5; H, 6·4. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·3%).

4-Hydroxydimethylphthalide can be distilled in a vacuum and is unaffected by prolonged boiling with concentrated hydrochloric acid, 50% (by weight) sulphuric acid, or by fusion with potassium hydroxide below *ca.* 250°. On fusion with potassium hydroxide for 10 minutes at 280—300°, acetone, *m*-hydroxybenzoic acid, and some phenol were obtained.

4-*Hydroxy*-N-*phenyl*-αα-*dimethylphthalimidine* (X).—4-Hydroxydimethylphthalide (2 g.) and aniline (10 c.c.) were heated for 2 hours at 300°. The violet liquid obtained was diluted with ether, and the aniline removed by dilute acid. The 4-*hydroxy*-N-*phenyl*-αα-*dimethylphthalimidine*, which was only partly dissolved in the ether, was shaken into dilute sodium hydroxide solution and obtained on acidification as a pale blue powder. It crystallised from a little ethyl alcohol with one molecule of water of crystallisation (Found : C, lost; H, 6·3; H_2O, 6·5. $C_{16}H_{15}O_2N,H_2O$ requires H, 6·3; H_2O, 6·6%); or, better, from methyl alcohol, from which it formed colourless pseudo-rhombic crystals (showing well-developed domal faces), containing one molecule of methyl alcohol of crystallisation (Found : MeOH, 11·7; C, 71·4; H, 6·8. Found in dried material : C, 76·05; H, 6·1. $C_{16}H_{15}O_2N$,MeOH requires C, 71·6; H, 6·7; MeOH, 11·2%. $C_{16}H_{15}O_2N$ requires C, 75·85; H, 6·0%). Both crystalline forms and the anhydrous material melt at 214—215°.

The same substance was formed on heating 4-hydroxydimethylphthalide (1 g.) with aniline (5 c.c.) and aniline hydrochloride (5 g.) for 2 hours at 210° (but not on refluxing with aniline alone). In this case, however, considerably more of the coloured impurity

(possibly the phenylimide of X) was formed. On distillation with soda-lime, aniline was evolved in quantity.

The *acetoxy*-derivative was prepared (*a*) from the crystallised material by warming on the water-bath for 1 hour with ten times the quantity of acetic anhydride, and (*b*) from the dried material by the pyridine and acetyl chloride method. After crystallisation from methyl alcohol, both specimens, alone or mixed, melted at 219° (Found : C, 73·3; H, 5·9. $C_{18}H_{17}O_3N$ requires C, 73·2; H, 5·8%). Mixed with the hydroxy-compound, the substance melted from 174° to 198°.

3 : 5-*Dibromo*-4-*hydroxy*-αα-*dimethylphthalide*.—When bromine (0·9 g.) in a little acetic acid was gradually added to 4-hydroxydimethylphthalide (0·5 g.) in 50% acetic acid (10 c.c.), and the mixture kept for 30 minutes, 3 : 5-*dibromo*-4-*hydroxy*-αα-*dimethylphthalide* (0·72 g.; 76% yield) separated. Recrystallised from 50% acetic acid, it formed plates with one molecule of water of crystallisation, which did not melt sharply. When dried, it melted at 125° (Found : H_2O, 5·2. Found in dried material : Br, 47·6. $C_{10}H_8O_3Br_2,H_2O$ requires H_2O, 5·1%. $C_{10}H_8O_3Br_2$ requires Br, 47·6%).

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