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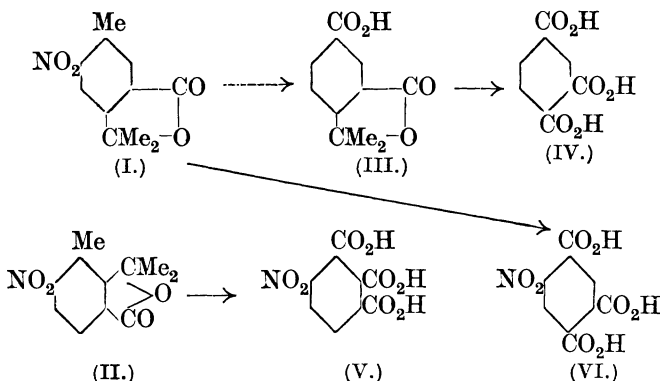
174. *Cannabis indica Resin. Part III. The Constitution of Cannabinol.*

By ROBERT SIDNEY CAHN.

OWING to the improved method (J., 1931, 630) of isolating cannabinol from the high-boiling, pharmacologically active fraction of *Cannabis indica* resin (hashish, etc.), it has become possible to examine the reactions of this substance in greater detail and to suggest tentatively a formula for it.

Cannabinol has the molecular formula  $C_{21}H_{26}O_2$ . The formula  $C_{20}H_{26}O_2$ , which is not conclusively excluded by the analytical data, is shown below to be inconsistent with chemical evidence. Cannabinol readily forms a trinitro-derivative, which on oxidation affords nitrocannabinolactone,  $C_{11}H_{11}O_2 \cdot NO_2$  (*loc. cit.*). In a previous paper (J., 1930, 986) it was shown that the last substance is probably represented by formula (I) or (II). It can be converted into the lactonic acid, cannabinolactonic acid (Wood, Spivey, and Easterfield, J., 1899, 75, 20), which is represented by (III) or the corresponding formula derived from (II). This acid has now been oxidised to trimellitic acid (IV), and it follows that cannabinolactonic acid must be represented by formula (III) and nitrocannabinolactone by formula (I). This has been confirmed by a repetition of

Bargellini and Forli-Forti's synthesis of the acid (III) (*Gazzetta*, 1910, **40**, ii, 74; compare Tasman, *Rec. trav. chim.*, 1927, **46**, 653);



the synthetic acid is identical with cannabinolactonic acid. Dr. Bergel has informed the author that he has synthesised cannabinolactone and cannabinolactonic acid, and is now in agreement with the views here put forward.

A tribasic nitro-acid,  $\text{C}_9\text{H}_5\text{O}_8\text{N}$ , m. p. 228—230°, was obtained by Wood, Spivey, and Easterfield by nitric acid oxidation of nitrocannabinolactone. Schultz and Herzfeld (*Ber.*, 1909, **42**, 3607) ascribe the structure (VI) to an acid, m. p. 175°, which they obtained by oxidation of 6-nitro- $\psi$ -cumene; the orientation of this appears to be well established,\* and it was concluded in Part I of this series that the acid, m. p. 228—230°, must be 4-nitrohemimellitic acid (V) and that nitrocannabinolactone must be represented by the alternative formula (II). Since, however, formulation of nitrocannabinolactone as (I) is now beyond dispute, it is concluded that the acid, m. p. 228—230°, is 5-nitrotrimellitic acid (VI). It is possible that the acid, m. p. 175°, described by Schultz and Herzfeld was a nitrodimethylbenzoic or nitromethylphthalic acid, since they used a quantity of chromic acid which was sufficient for oxidation of only two methyl groups.

Examination of trinitrocannabinol led previously to the conclusion that it was a polynitrophenol; and it followed that cannabinol itself was a phenol, although it does not give a colour with ferric chloride and is insoluble in alkali. This view has been confirmed by further investigation. First, treatment of cannabinol with methyl iodide or sulphate in acetone solution in the presence of potassium carbonate yields a *methyl* ether, m. p. 66°. Ready methylation by the former method is generally considered to be diagnostic of phenolic

\* The orientation of the nitro-group in nitrocannabinolactone is conclusively proved by previous work of the present author.

hydroxyl groups (King and Robertson, J., 1931, 1705; compare also J., 1928, 22; 1930, 2434). Secondly, nitration of cannabinol methyl ether by fuming nitric acid in cold acetic acid gives a *dinitro*-derivative (probably a mixture of dinitro-isomerides), but no trinitro-derivative; similar nitration of cannabinol gives trinitrocannabinol, the methyl ether of which is rapidly hydrolysed by hot piperidine. This peculiar hydrolysis has been shown (J., 1931, 1121) to occur with a number of nitrophenols. Dinitrocannabinol methyl ether is only slowly hydrolysed by piperidine. The resulting *dinitrocannabinol* is readily nitrated to form trinitrocannabinol. Since all the nitrations were carried out under similar conditions, these relations are most readily harmonised with consideration of cannabinol as a phenol. Thirdly, independent evidence to the same effect is that cannabinol has a "critical oxidation potential" of 0.995 volt (compare Fieser, *J. Amer. Chem. Soc.*, 1930, 52, 5204). The author is greatly indebted to Professor L. F. Fieser for this determination. He writes: "Cannabinol behaves like a substituted phenol; the potential is close to that of  $\beta$ -naphthol. I have studied many alcohols and aryl carbinols, and in no case is there any sign of a potential." This view also explains the instability of cannabinol towards cold permanganate as contrasted with the stability of its acyl derivatives and methyl ether.

In the previous investigation it was tentatively concluded that the second oxygen atom of cannabinol was ethereal. Further evidence, still unfortunately negative, to the same effect is now brought forward: cannabinol does not react with 2:4-dinitrophenylhydrazine; the methyl ether does not react with sodium and cannot be acylated; and with phosphorus pentachloride in ether, substitution but not replacement of hydroxyl by chlorine occurs.

Attempts to reduce cannabinol, acetylcannabinol, and the crude high-boiling resin catalytically failed. When the resistance of the methyl ether and acyl derivatives to oxidation (*vide infra*) is also considered, it must be concluded that cannabinol does not contain an ethylenic linking.

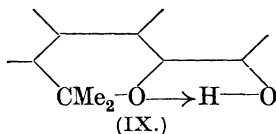
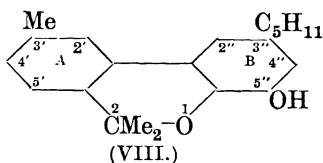
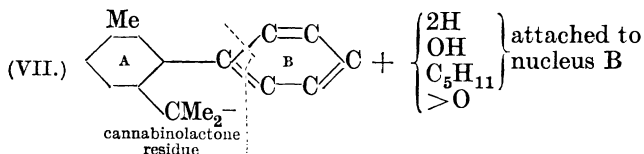
Oxidation of cannabinol with permanganate or with nitric acid destroyed the phenolic portion of the molecule, and milder oxidising agents gave intractable products which were probably polymolecular. To obtain further information concerning the ten carbon atoms not represented by cannabinolactone, derivatives in which the phenolic group was protected were examined. The *benzenesulphonyl* and *m-nitrobenzenesulphonyl* derivatives were prepared, but the former proved difficult to crystallise and was not investigated in detail. The latter, as well as acetylcannabinol and cannabinol methyl ether, is stable to cold permanganate, but heating with this reagent causes

deep-seated degradation. The methyl ether was largely recovered unchanged, the portion attacked having been completely disintegrated. Oxidation of the *m*-nitrobenzenesulphonyl derivative in hot acetic acid yielded *potassium m-nitrobenzenesulphonate*. This result indicated that the phenolic nucleus was being attacked as with cannabinol itself.

Attempts to achieve a graduated oxidation having thus failed, a large quantity of cannabinol was oxidised. With potassium permanganate in cold acetone, an amorphous substance was formed which was almost insoluble in acetone and thus escaped further oxidation. This substance could not be purified and was accordingly further oxidised with permanganate in hot aqueous pyridine, whereupon cannabinolactone, cannabinolactonic acid, and a mixture of aliphatic acids were obtained. The least volatile fraction of the acid mixture contained *n*-hexoic acid, which was identified as its anilide. *n*-Hexoic acid has frequently been reported as a product of oxidation of crude high-boiling *Cannabis* resins (e.g., Casparis, *Pharm. Helv. Acta*, 1926, **1**, 210; Bergel, *Annalen*, 1930, **482**, 55), but, as was previously pointed out, this is without significance for a consideration of the pure substance, cannabinol. Wood, Spivey, and Easterfield obtained 1.85 g. of impure hexoic acid by oxidation of 120 g. of trinitrocannabinol, which is a true derivative of cannabinol; but confirmation of this result was highly desirable, since trinitrocannabinol is exceedingly difficult to obtain pure (J., 1931, 630) and it could not be assumed that the hexoic acid was derived from cannabinol rather than from an impurity. This doubt has now been removed by isolation of hexoic acid on oxidation of cannabinol prepared from the carefully purified crystalline acetyl derivative.

It is now clear that cannabinol contains the carbon skeleton of cannabinolactone (11 carbon atoms), a second (phenolic) benzene nucleus, an ethereal oxygen atom, and a straight chain  $C_5H_{11}\cdot C$ . These components contain 23 carbon atoms, whereas cannabinol has only 21. The carboxyl groups of hexoic acid and cannabinolactone must therefore be derived by oxidation of the phenolic nucleus. The alternative formula  $C_{20}H_{26}O_2$  cannot be reconciled with the products of oxidation. The partial formula (VII) is thus proved, and the most satisfactory way of completing it is that typified in formula (VIII). The hydroxyl and the *n*-amyl group must be attached to nucleus B, but the evidence in favour of the positions actually allotted to them in formula (VIII) is slender. The hydroxyl group is placed at position 5'' because co-ordination of its hydrogen atom with the ethereal oxygen atom, as shown in the partial formula (IX), might account for the fact that cannabinol will not react with diazomethane in ethereal solution; the guaicol structure is also in

accord with the ready oxidation of cannabinol. If the hydroxyl group be placed in position 5'', consideration of the ease of disubstitu-



tion of nucleus B favours position 3'' for the amyl group. It may be expected that a substance of type (VIII) will behave towards substituting agents primarily as a diphenyl derivative; thus, nitration of cannabinol methyl ether leads primarily to the 4' : 4''-dinitro-compound,\* together with some 2''- or 2'-isomeride. The methoxyl group in position 5'' will tend to increase the amount of substitution in position 2'', thus accounting for the large amount of isomeride formed in the dinitration of the ether. The 4' : 4''-dinitrophenol obtained on hydrolysis of the ether has no substituent in the position para to the hydroxyl group and is accordingly very readily and homogeneously further nitrated.

Whilst 3 : 4 : 5 : 6-dibenzo-1 : 2-pyrans have not, so far as the author is aware, been observed hitherto to occur in nature, various portions of formula (VIII) may be recognised. *o*-Hydroxy-*o*'-carboxydiphenyl derivatives occur in tannin substances; embelin contains an aliphatic (C<sub>11</sub>) side chain attached to a phenolic nucleus; the left-hand portion of the formula contains the *p*-cymene skeleton; and the oxygen atoms are in the *p*- and *m*-positions with regard to the side chain. (It is not, of course, contended that all these relations are simultaneously of phylogenetic importance.) Nevertheless, formula (VIII) is regarded as tentative only, particularly with respect to the position of the substituents in nucleus B, and, whilst degradative experiments with cannabinol will be continued, substances of the type considered will be synthesised and examined for comparative purposes.

#### EXPERIMENTAL.

*Benzenesulphonylcannabinol*.—Benzenesulphonyl chloride (2 c.c.) was heated with cannabinol (2 g.) in dry pyridine (4 c.c.) for 30

\* The proved structure of nitrocannabinolactone proves the position (4') of the nitro-group entering nucleus A, in accordance with the above speculations.

minutes, the mixture added to water, and the precipitated uncrystallisable oil refluxed for 2 hours with alcoholic potassium hydroxide; on cooling, *benzenesulphonylcannabinol* separated as an oil which crystallised after 2 days; recrystallised from alcohol, in which it was sparingly soluble, it formed colourless needles, m. p. 70·5° (Found: C, 71·8; H, 6·8; S, 7·15.  $C_{27}H_{30}O_4S$  requires C, 71·95; H, 6·7; S, 7·1%). The yield was poor.

*m-Nitrobenzenesulphonylcannabinol*.—(i) Cannabinol (1·9 g.), *m*-nitrobenzenesulphonyl chloride (1·5 g.), and pyridine (6 c.c.) were heated on the water-bath for 2·5 hours; when the cooled mixture was poured into alcohol, *m-nitrobenzenesulphonylcannabinol* (2·0 g.) separated; after two crystallisations from a mixture of alcohol and a little benzene, it formed pale yellow, diamond-shaped plates, m. p. 125—126° after sintering at 123° (Found: C, 65·6; H, 5·95; S, 6·4; N, 2·8.  $C_{27}H_{29}O_6NS$  requires C, 65·4; H, 5·9; S, 6·5; N, 2·8%). It is sparingly soluble in alcohol and cold acetic acid, readily soluble in the latter when hot, and in benzene and acetone; it is slowly resinified by sodium hydroxide in hot aqueous acetone.

(ii) "Crude cannabinol" (fraction E; J., 1931, 634; 7·7 g.), pyridine (25 c.c.), and *m*-nitrobenzenesulphonyl chloride (15 g.) were heated on the water-bath for 3 hours, cooled, and shaken with benzene and an excess of dilute hydrochloric acid; a considerable amount of black tar (from which no workable product could be isolated) remained insoluble in both layers. The benzene solution, when dried and evaporated, gave a black resin; this, when dissolved in acetic acid and cooled, deposited *m*-nitrobenzenesulphonylcannabinol (3·55 g.; 28% theor.), m. p. 121°, which after recrystallisation from acetic acid melted at 125° alone or when mixed with the product obtained from pure cannabinol. A further small quantity slowly separated when the original mother-liquors were exposed to the air. An attempt to prepare the benzenesulphonyl compound similarly from crude cannabinol failed.

Powdered potassium permanganate (25 g.) was added gradually to a solution of the above compound (4 g.) in acetic acid (40 c.c.) heated on the water-bath. The mixture, when worked up in the usual way, afforded *potassium m-nitrobenzenesulphonate*, which crystallised unchanged from acetic acid in large colourless needles, m. p. above 310° (Found: C, 29·85; H, 1·8; ash, 32·65; N, 5·45; S, 13·2.  $C_6H_4O_5NSK$  requires C, 29·85; H, 1·7;  $K_2SO_4$ , 36·1; N, 5·8; S, 13·2%); it is fairly readily soluble in water, from which it can, however, be recrystallised.

*Cannabinol Methyl Ether*.—Cannabinol (7 g.), methyl sulphate (21 c.c.), acetone (40 c.c.), and anhydrous potassium carbonate (40 g.) were heated under reflux for 2 hours; the mixture was

cooled, treated cautiously with aqueous ammonia (20 c.c.,  $d$  0.880), and then with water (100 c.c.); the methyl ether separated as an oil, which soon solidified, and when crystallised from methyl alcohol formed colourless plates (6.0 g.), m. p.  $66^{\circ}$ , b. p.  $265^{\circ}/32$  mm. (Found : C, 81.1; H, 8.7; MeO, 6.2.  $C_{21}H_{25}O \cdot OMe$  requires C, 81.4; H, 8.7; MeO, 9.6%). Explosions occurred at the end of the distillation of the crude (but not of the pure) product. The ether is very soluble in benzene, ligroin, acetone, and ether, but can be crystallised from methyl or ethyl alcohol or acetic acid. The same ether (mixed m. p.) was obtained when methyl iodide was substituted for methyl sulphate. It (m. p.  $65^{\circ}$  alone or when mixed with the above product) was also obtained from "crude cannabinal" (fraction E; *loc. cit.*; 18 g.) by use of methyl sulphate, after a tedious series of distillations and fractionation by solvents; cannabinal methyl ether became concentrated in the fractions of intermediate solubility in methyl alcohol, and solubility relations are considered to account for the low yield (0.6 g.).

Cannabinal and acetylcannabinal did not react with ethereal diazomethane. Acetylcannabinal was recovered unchanged after heating under reflux with acetone and anhydrous potassium carbonate for 2 hours, addition of methyl sulphate, and heating for a further 2 hours. Addition of silver oxide to a cold solution of cannabinal in methyl iodide, or heating cannabinal with benzene, methyl iodide, and silver oxide, led to amorphous substances, probably polymolecular oxidation products.

The methyl ether was recovered unchanged after heating at  $100^{\circ}$  for 1 hour with acetic anhydride and a few drops of pyridine, and after heating at  $190$ — $210^{\circ}$  for 4 hours with aniline (10 parts) and aniline hydrochloride (5 parts). In the latter case a little dark blue insoluble material was formed.

The methyl ether is stable to boiling aqueous alkaline potassium permanganate, but is slowly oxidised in acid solution. The ether (5 g.) was slowly oxidised in boiling acetone (40 c.c.), addition of 20 g. of permanganate requiring 8 hours; 4.7 g. of the ether were thereafter recovered unchanged, together with a trace of an acid which could not be purified. The ether (4.7 g.) in pyridine (25 c.c.) did not reduce potassium permanganate when cold, but reaction set in slowly when the mixture was boiled; after addition of 18 g. of permanganate, the mixture was worked up in the usual way and gave 3.2 g. of slightly impure ether and a trace only of insoluble acidic material.

*Chlorination of Cannabinal Methyl Ether.*—Cannabinal methyl ether (1 g.), phosphorus pentachloride (1 g.), and dry ether (10 c.c.) were heated under reflux for 8 hours. The cooled solution was shaken

successively with cold water, sodium carbonate solution, and water, dried, and evaporated. The residual oil was dissolved in hot alcohol. On cooling, crystals, m. p. 118—121°, separated; on recrystallisation a mixture of long prismatic needles and thick diamond-shaped plates, m. p. 122—124°, was obtained (0.35 g.). According to analyses [Found: C, 74.5; H, 7.9; Cl, 8.8; MeO, 7.4.  $C_{21}H_{24}OCl \cdot OMe$  (A) requires C, 73.6; H, 7.6; Cl, 9.9; MeO, 8.6.  $C_{21}H_{24}Cl \cdot OMe$  (B) requires C, 77.0; H, 8.9; Cl, 10.35; MeO, 9.05%] the product is a mixture of chlorocannabinol methyl ether (A) and unchanged cannabinol methyl ether (but see below), and not the product (B) formed by replacement of the hydroxyl group by chlorine. The material did not suffice for further purification, as the products exhibited similar solubilities in all the solvents tried. The product was unaffected by hot aqueous-alcoholic potassium hydroxide solution and by hot piperidine; the halogen has, therefore, entered an aromatic nucleus.

Cannabinol methyl ether and chloramine-T (equivalent to 1 mol. of available chlorine) in acetic acid gave a mixture from which a small quantity of the characteristic diamond-shaped plates, m. p. 126—127°, was obtained. It appeared to contain some dichloro-derivative (Found: Cl, 10.45%). Mixed with the first product, it melted at 125—126°, thus confirming the conclusion that the latter is a substitution product.

Passage of chlorine into a solution of cannabinol methyl ether in cold glacial acetic acid gave an amorphous, pale yellow, phototropic substance, which could not be purified.

*Dinitrocannabinol Methyl Ether.*—Cannabinol methyl ether (1 g.) was added during 15 minutes to a mechanically stirred mixture of acetic acid (5 c.c.) and nitric acid (3 c.c., *d* 1.5). After being kept in ice for 30 minutes, the *dinitro*-ether which had separated was collected, washed with acetic acid, and crystallised from ethyl alcohol containing a little benzene; it formed pale yellow plates or needles (0.3 g.), m. p. 174—175° [Found: C, 63.25; H, 6.2; N, 7.0; MeO (determined as NMe), 9.2.  $C_{21}H_{23}O(OMe)(NO_2)_2$  requires C, 63.75; H, 6.3; N, 6.8; MeO, 7.5%]. A micro-methoxyl determination gave only a trace of silver iodide. The same phenomenon was observed with trinitrocannabinol methyl ether and to a lesser extent with the ethers of cannabinol and chlorocannabinol. Larger amounts of low-melting mixtures (which could not be separated) were obtained from the mother-liquors in the above preparation. A similar experiment (on a smaller scale), in which the temperature was allowed to rise, gave the same substance as main product, thus indicating that there is little tendency for trinitration to occur. The impurities are, therefore, presumably position isomerides.



*Dinitrocannabinol*.—The above dinitro-ether (0.3 g.) was only slightly hydrolysed by piperidine (2 c.c.) during 80 minutes at 100°. After boiling under reflux for 48 hours, the orange solution was poured into dilute acid, and the precipitate coagulated by warming and collected. When rubbed with dilute sodium hydroxide solution, it formed a bright yellow sodium salt, which dissolved in much hot water to an orange solution; acidification of the filtered solution precipitated *dinitrocannabinol*, which was coagulated by warming and collected; it formed pale yellow, felted needles (from slightly diluted acetic acid), m. p. 182—183° [Found: C, 62.6; H, 6.2; N, 6.6.  $C_{21}H_{24}O_2(NO_2)_2$  requires C, 63.0; H, 6.0; N, 7.0%]. When the phenol (13 mg.) was added to a cold mixture of acetic acid (0.4 c.c.) and nitric acid (0.22 c.c., *d* 1.5), kept for 15 minutes, and the product precipitated with ice and recrystallised from acetic acid, trinitrocannabinol, m. p. 160° alone or mixed with an authentic specimen, was obtained.

*Oxidation of Cannabinol*.—When finely powdered potassium permanganate (50 g.) was added gradually to cannabinol (40 g., from recrystallised acetylcannabinol) in acetone (190 c.c.), decoloration, at first rapid, became later extremely slow. When the mixture was worked up, very small quantities of a lactone, a fatty acid, and a non-volatile acid (mainly cannabinolactonic acid) were obtained. The main product was recovered from the oxides of manganese by sulphur dioxide; it formed a brown amorphous substance (45 g.) (A), insoluble in acetone, acetic acid, or alkalis, slightly soluble in hot pyridine, rather more so in hot acetic anhydride, separating therefrom in an amorphous state on cooling; it dissolved in hot nitrobenzene, toluene, and anisole, but did not separate from these solvents on cooling; it was readily soluble in ether. A similar product was obtained on treating cannabinol (1.5 g.) in acetic acid with chromic acid (0.65 g.) at 25°.

Powdered potassium permanganate (200 g.) was added during 40 hours to a solution of the substance A (40 g.) in pyridine (233 c.c.) and water (148 c.c.), which was heated on the water-bath; decoloration, at first rapid, became later very slow. The manganese dioxide was filtered off, well washed with pyridine, and then boiled out five times with water (750 c.c. portions); it still contained 1 g. of amorphous substance, probably unchanged A. The filtrate and washings were distilled in steam until the distillate no longer became turbid when saturated with ammonium sulphate. Pyridine distilled first and then an oil which was only slightly soluble in water; the distillates were acidified, saturated with ammonium sulphate, and extracted twice with ether; the oil obtained on drying and removal of the ether distilled at 165°/27 mm. (yield, 1.3 g.) and was identified

as cannabinolactone by hydrolysis with boiling aqueous-alcoholic alkali (2 hours), removal of the alcohol, and subsequent oxidation with permanganate to cannabinolactonic acid, m. p. 202—204° (Wood, Spivey, and Easterfield state that cannabinolactone boils at 290.5°/768 mm. and 126°/20 mm.; the latter b. p. is presumably a misprint for 156°/20 mm., as a specimen prepared during the present work from nitrocannabinolactone by their method had b. p. 150°/16 mm., which is also in better accord with the figure for 768 mm.). The liquors from the steam distillation were concentrated, acidified with sulphuric acid, and again distilled in steam. The distillate was saturated with ammonium sulphate and extracted five times with ether; the ethereal solution was concentrated (column) and shaken twice with sodium carbonate solution. The ethereal solution, when dried and evaporated, now gave only a small amount of a neutral oil (? lactone) which partly solidified; the quantity was insufficient for further investigation. The alkaline extracts were acidified, saturated with ammonium sulphate, and extracted five times with ether; after drying and removal of the ether, liquid acids remained, which smelt strongly of the lower fatty acids; these gave on distillation the following fractions: (i) below 120°, ether and 0.2 g. of acid; (ii) 120—160°, 0.7 g.; (iii) 160—190°, mostly 176—182°, 1.7 g.; (iv) residue, ca. 0.5 g. Eight determinations of the boiling point of fraction (iii) by Emich's method (*Monatsh.*, 1917, **38**, 219) gave values from 175° to 185°; two of the residue gave 180°; two controls with pure *n*-hexoic acid gave the correct b. p. 205°. As these fractions contained mostly *n*-hexoic acid with some lower acids, it appears, as might be expected, that Emich's method, though accurate for pure substances, indicates the boiling point of the more volatile component of mixtures. Fraction (iii) gave an anilide, m. p. 74—77°, which after three crystallisations from ligroin (b. p. 60—80°) had m. p. 80—81°. Fraction (iv) gave an anilide, m. p. 81—83°, which after five crystallisations melted at 88.5—90° alone (Found: C, 75.2; H, 8.8; N, 7.3. Calc. for C<sub>12</sub>H<sub>17</sub>ON: C, 75.4; H, 9.0; N, 7.3. Calc. for C<sub>11</sub>H<sub>15</sub>ON: C, 74.5; H, 8.5; N, 7.9%), at 68—99° when mixed with *isovaler*anilide, and at 93—94° when mixed with *n*-hexoanilide (m. p. 95°). *n*-Valerianilide melts at 63°. The experimental evidence indicates that both the above fractions consisted of *n*-hexoic acid mixed with some *n*-valerianilide.

The acid liquor from the second steam distillation was basified with sodium carbonate, filtered from amorphous material (8 g., soluble in ether; apparently unchanged A), concentrated, and acidified. The precipitated acid was dissolved in ether (a little dark impurity was insoluble), and obtained on evaporation as a slightly

sticky, red solid; several extractions with cold benzene removed a red oil (*ca.* 1 g.); the brown insoluble portion (5.5 g.) yielded on extraction with hot water (60 c.c.) 1 g. of cannabinolactonic acid, and on crystallisation of the residue from a little glacial acetic acid and then from water (charcoal) a further 2.7 g. of this acid, m. p. 204—205°. This acid did not depress the melting point of synthetic 4-carboxydimethylphthalide (III).\* The latter process is well suited for the purification of this acid. Only indefinite substances were obtained from the acetic acid mother-liquors.

The residual aqueous acid solution, when extracted continuously with ether, gave *ca.* 1 g. of a yellow oil, from which concentrated hydrochloric acid separated a quantity of solid material too small for purification.

*Dinitrocannabinolactone.*—Trinitrocannabinol methyl ether (1 g.) was heated under reflux for 2 hours with nitric acid (*d* 1.5; 10 c.c.); more acid (5 c.c.) was then added, and the whole heated for a further 6 hours. On addition to ice, an oil separated which rapidly solidified. After being washed, it was dissolved in boiling sodium carbonate solution, filtered, and reprecipitated by acidification. When crystallised twice from alcohol, it formed pale yellowish-brown plates (? prisms), m. p. 161° (yield, 30 mg.). It is slightly soluble in hot water, insoluble in cold alkalis, dissolves slowly in boiling aqueous sodium carbonate and more rapidly in hot sodium hydroxide solution; it is precipitated unchanged from its solution in alkalis by acidification, and appears to be 6:2 (or 5)-*dinitrocannabinolactone* (Found: C, 49.6; H, 3.8; N, 10.5.  $C_{11}H_{10}O_6N_2$  requires C, 49.5; H, 4.0; N, 10.5%).

*Oxidation of Cannabinolactonic Acid.*—Cannabinolactonic acid (1 g.) was heated with nitric acid (*d* 1.2; 20 c.c.) for 24 hours at 185—195°, and the resulting solution evaporated; the residue was crystallised from 5*N*-hydrochloric acid, freed from nitro-acid by tin and hydrochloric acid, the tin salts removed by hydrogen sulphide, and the solution concentrated; trimellitic acid crystallised in bunches of needles, m. p. 220° alone or mixed with an authentic specimen which was kindly supplied by Professor Ruzicka. The methyl ester was an oil, and the potassium salt was soluble in water (distinction from hemimellitic acid).

*Critical Oxidation Potential of Cannabinol.*—Professor L. F. Fieser

\* The Sandmeyer reaction, applied to 4-aminodimethylphthalide, did not give the compound, m. p. 211—212°, reported by Bargellini and Forli-Forti (*loc. cit.*), nor did it proceed as smoothly as indicated by Tasman (*loc. cit.*). It yielded indeterminate compounds, which with hot alkalis gave copper oxide and cyanide ions; the lactonic acid was obtained in good yield by prolonged hydrolysis of the complex of lactonic nitrile and copper compound by means of hot 50% potassium hydroxide solution.

reports the following figures, the symbols having the same significance as in his papers (*loc. cit.*):

$E_c$ , Mo, v. ....	1.0198	1.0252	1.0284	1.0401	1.0490
% Oxidation .....	20	25	28	32	45
Corr. 2.0 mv.					

whence by a somewhat long extrapolation  $E_c = 0.995 \pm 0.010$  v.

*Colour Reactions of Cannabinol and its Derivatives.*—Cannabinol gives no colour when dissolved in absolute ethyl-alcoholic hydrogen chloride, or when a drop of hydrochloric or sulphuric acid is added to its solution in acetic acid. It dissolves in concentrated sulphuric acid to give a greenish-yellow solution with a slight green fluorescence (strong when viewed in an arc light); on warming or addition of a crystal of potassium dichromate, a deep brown colour (oxidation) develops. Acetylcannabinol and cannabinol methyl ether give similar fluorescent solutions in sulphuric acid. When a few drops of concentrated hydrogen peroxide are added to a solution of cannabinol in glacial acetic acid, no change occurs in the cold (even after addition of ferrous sulphate), but on warming a deep reddish-purple colour rapidly develops. Acetylcannabinol and the methyl ether give similar, but much weaker colours, somewhat more slowly.

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