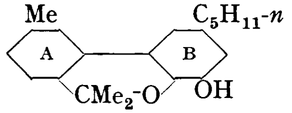
326. Cannabis Indica *Resin. Part IV. The Synthesis of Some 2 : 2-Dimethyldibenzopyrans, and Confirmation of the Structure of Cannabinol.*

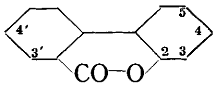
By R. S. Cahn.

It was suggested recently (J., 1932, 1342) that cannabinol was (?)3″-hydroxy-2 : 2 : 5′-trimethyl-(?)5″-*n*-amyldibenzopyran (I). Since the methods of degradation hitherto attempted brought no further evidence of structure, it was decided to synthesise the parent substance, 2 : 2-dimethyldibenzopyran (IV), and a few simple derivatives as a preliminary to further experiments with the natural product. A study of this ring system appeared to have an enhanced interest, since, although the analogous 2 : 2-dimethylcoumaran system, containing one benzene ring fused to a 1 : 2-pyran ring, is present in tephrosin and deguelin, two of the constituents of derris root, cannabinol is the first substance shown to have a dibenzo-1 : 2-pyran structure.

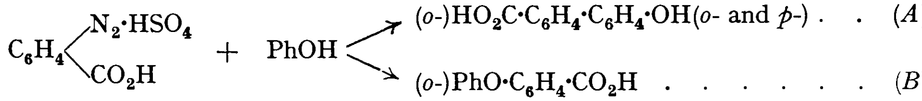
(I.)



(II.)



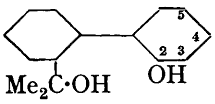
The lactone (II) proved to be a suitable initial material: it reacts with two molecules of a simple alkyl Grignard reagent. Attempts to prepare it from *o-bromophenyl o-bromobenzoate* and from phenyl anthranilate failed. Recourse was then taken to the reaction of anthranilic acid diazonium sulphate with phenol, which proceeds in two directions (Graebe and Schestakov, *Annalen*, 1894, **284**, 317; compare Griess, *Ber.*, 1888, **21**, 981):



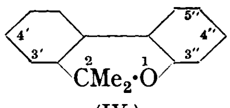
$$C_6H_4\left\langle\begin{matrix}N_2\cdot HSO_4\\CO_2H\end{matrix}\right. + PhOH \begin{matrix}\nearrow (o\text{-})HO_2C\cdot C_6H_4\cdot C_6H_4\cdot OH(o\text{- and } p\text{-}) \quad . \quad . \quad (A)\\ \searrow (o\text{-})PhO\cdot C_6H_4\cdot CO_2H \quad . \quad . \quad . \quad . \quad . \quad . \quad (B)\end{matrix}$$

The *o*-hydroxy-*o*'-carboxylic acid loses water spontaneously to form the lactone (II). The yield is only 22%, and other recorded methods of preparing the substance (Richter, *J. pr. Chem.*, 1883, **28**, 294; Dobbie, Fox, and Gauge, J., 1913, **103**, 36) are unsuitable. When *p*-cresol is used instead of phenol, *o*-(*p*-tolyloxy)benzoic acid and the 5-*methyl-lactone* are obtained, and, since condensation by reaction (*A*) cannot in this case occur in the *p*-position, the yield of lactone is somewhat better (30—35%). When guaiacol is used, the yield of 3-*methoxy-lactone* is only 2—3%, but the only other substance which could be isolated from the reaction mixture was a little salicylic acid.

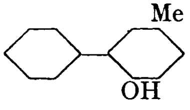
Addition of these lactones to an excess of the Grignard reagent leads to phenolic *alcohols* of type (III), which are dehydrated by phosphoric oxide in boiling xylene to the pyran derivatives. The yields in both these reactions are almost quantitative. 2 : 2-*Dimethyldibenzopyran* (IV) and its 3''-methoxy-derivative are oils.



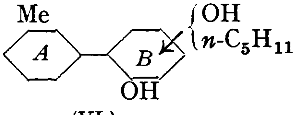
(III.)



(IV.)



(V.)

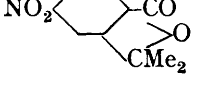


(VI.)

The 5''-*methyl* derivative is crystalline and was chosen for detailed investigation. The new ring system is remarkably stable, as also is cannabinol. The 5''-methyl compound is unchanged by sodium amyloxide at 140° or sodium ethoxide at 160—180°, by fusion with sodium hydroxide at 250°, by alcoholic ammonia at 140°, or by boiling 50% sulphuric acid. It is decomposed by short boiling with 80% (volume) sulphuric acid or longer boiling with a mixture of equal volumes of acetic and sulphuric acids. A method of degradation was, however, eventually found. With concentrated hydrochloric acid at 200°, better with addition of acetic acid to assist solution, it gives a crystalline phenol which, from analyses of itself and of its crystalline *benzoyl* derivative and *methyl ether*, appears to be 2-*hydroxy*-5-*methyldiphenyl* (V). This somewhat remarkable hydrolysis involves loss of acetone and resembles the fission of dimethylphthalide by fusion with alkali to acetone and benzoic acid. The phenol (V) and the phenolic alcohols of type (III) give no colour with aqueous ferric chloride, before or after addition of sodium acetate; in alcohol they develop a pale green colour, changed to reddish-brown by sodium acetate, but both colours are barely distinguishable from those of ferric chloride alone. They show the normal solubility relations of phenols in alkali, but the phenol (V) (not the phenolic alcohols) is only slowly removed from ether by sodium hydroxide solution.

Application of the acid fission to cannabinol, $C_{21}H_{26}O_2$, gives a crystalline *phenol*, $C_{18}H_{22}O_2$, which is exactly similar to (V) in its solubility relations and in ferric chloride reactions. It is considered to be formed by a similar loss of acetone and to be (VI). It gives an oily nitro-derivative, which is oxidised by hot nitric acid to 6-nitro-*m*-toluic acid

(VII.)

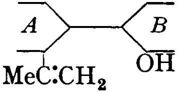


(VIII.)

(VII). The presence of the methyl group in this acid shows that it is derived from ring (*A*) of cannabinol. Since exactly similar treatment of cannabinol affords nitrocannabinolactone

(VIII), this oxidation, coupled with the analytical results, is believed to prove conclusively that the fission by acid involves loss of the CMe_2 group in the manner suggested above.

The phenol (VI) rapidly develops a purple colour in alkaline solution, owing to atmospheric oxidation. This suggests that it may be a catechol or quinol derivative, but attempts to prepare a quinone, a methylene ether, and condensation products with *o*-phenylenediamine and antimony trichloride, failed. No great reliance can, however, be placed on these negative results, since only small quantities of material were available. On the other hand, the similarity of (VI) to (V) in its solubility relations, and to (V) and the phenols of type (III) in ferric chloride colours, suggests that both hydroxyl groups may be in the *o*-position with regard to the tolyl nucleus (*A*). Actually, it has not been possible to prove even the presence of two hydroxyl groups, since no crystalline derivatives could be obtained, but this assumption can hardly be avoided when the method by which the substance is formed from the monohydric phenol, cannabinol, is considered, and it is supported by the ready oxidation of (VI) as contrasted with the stability of (V), of cannabinol, and of the oil, presumably a (di)methyl ether, obtained from (VI) by means of methyl iodide and potassium carbonate in boiling acetone. Although the work described above does not, then, afford any evidence as to the positions of the substituents in ring (*B*), it is held that, taken in conjunction with the experiments previously recorded, it proves the structure of cannabinol in all except this particular.

A further point of importance arises out of the synthetical work. The phenolic alcohols of type (III) are partly dehydrated by distillation at 30 mm., or by heating with acetic anhydride. Since cannabinol is isolated from *Cannabis* resin by distillation, followed by acetylation, the possibility arises that it might be formed from a phenolic alcohol in either or both of these processes. However, formation of water has not been observed during distillation of the high-boiling fractions of the resin, and this could not have escaped observation during the handling of large quantities of material. The second possibility, dehydration by acetylation, is definitely excluded, since acetyl chloride and pyridine at 0° give a higher yield of acetylcannabinol than does boiling acetic anhydride, and it is found that the 5-methyl derivative of the alcohol (III) is acetylated and not dehydrated by the former reagents. It is, therefore, still considered that cannabinol exists as such in the crude resin. On the other hand, the crude resin is unstable in alkaline solution, giving the same purple colour (Beam's test) as is given by the dihydric phenol (VI); moreover, the boiling point of (VI) is only slightly lower than that of cannabinol, so that the two substances would be inseparable by distillation. It is probable, therefore, that some substance, or substances, resembling (VI) also exist in the crude resin. This may be (VI) itself, or small amounts of a phenolic alcohol of type (III), but there is also another alternative. Bergel (*Annalen*, 1930, **482**, 55) showed that the high-boiling fraction of his *Cannabis* resin could be reduced catalytically; it is possible that the unsaturated substance present in his resin was a derivative containing the *iso*propenyl group, as in , since this structure is closely related to the dibenzopyran system, which it would yield by intramolecular ring closure.

According to experiments kindly carried out by Dr. H. R. Ing at University College, London, and, through the courtesy of Dr. F. Bergel, by Dr. H. Marx at the Medizinische Klinik, Heidelberg, cannabinol is not the pharmacologically active principle of *Cannabis* resin. S. Fränkel (*Arch. exp. Path. Pharm.*, 1903, **49**, 266) quotes Wood, Spivey, and Easterfield (J., 1899, **75**, 20) as having made a similar statement, but the present author has been unable to find in any of their publications more than a statement of *optical* inactivity. Fränkel himself never obtained pure cannabinol.

EXPERIMENTAL.

Unsuccessful Attempts to synthesise the Lactone (II).—(1) o-*Bromophenyl* o-*bromobenzoate*, prepared by the Schotten–Baumann method or, better, in pyridine, and distilled (b. p. 246–247°/26 mm.), forms colourless needles, m. p. 39°, from ligroin (b. p. 60—80°), methyl or ethyl alcohol (Found : Br, 45·4. $C_{13}H_8O_2Br_2$ requires Br, 44·9%). It did not react with magnesium in boiling dry ether, even after activation with methyl iodide, or in a mixture of ether and xylene at 100°, and only very slightly with copper powder (0·5 part) in xylene (1 part) at 180°. When it was heated with copper powder (0·5 part) alone at 285—305° for 6 hours, a mobile fraction (25%), b. p. 200—250°/25 mm., containing halogen, and a viscous oil (25%), b. p. about 260°/25 mm., were obtained; neither fraction could be obtained solid.

(2) Phenyl *o*-nitrobenzoate, prepared by the Schotten–Baumann method, forms prisms, m. p. 42—43°, from not too concentrated solution in alcohol; it boils at 164—165°/21 mm. With palladised norite (1 g.; 10% palladium) in acetone (100 c.c.), the ester (15·8 g.) absorbed 4340 c.c. (N.T.P.) of hydrogen (3 mols. = 4600 c.c.) in 2 hours. The oily phenyl anthranilate, obtained by filtration and removal of the solvent, crystallised when rubbed, and formed long needles, m. p. 71° (lit. 70°), from ligroin (b. p. 60—80°); yield, 12 g. (87% theor.). Diazotisation and elimination of nitrogen under a variety of conditions failed to yield the lactone (II).

Phenol Series. 2 : 2-*Dimethyldibenzopyran* (IV).—The following method for the preparation of the lactone (II) is preferable to that given by Graebe and Schestakov (*loc. cit.*), particularly with regard to the preparation of the diazonium salt. Concentrated sulphuric acid (10 c.c.) was added with cooling to anthranilic acid (25 g.) dissolved by stirring in acetic acid (200 c.c.). To the resultant paste, amyl nitrite (25 c.c., freshly distilled) was added in 1—2 minutes; the temperature rose to about 30°, the amine sulphate dissolved, and a crystalline precipitate of the diazonium sulphate formed. After 2 hours this was collected, washed with acetic acid and ether, and dried in the air. Yield, 38—42 g. (*ca.* 90% theor.). This salt was heated with phenol (100 g.) on the water-bath until nitrogen was briskly evolved; reaction then usually proceeded without external heating (but sometimes required moderation by cooling) and appeared complete in 10—20 minutes; the mixture was heated for a further 1—2 hours on the water-bath, the phenol removed in steam, and the oily residue triturated with sodium carbonate solution. The acids gradually dissolved, leaving the lactone (II) of 2-hydroxydiphenyl-2′-carboxylic acid, which finally (several hours) completely solidified. The yield of lactone, after crystallisation from alcohol, was 8 g.; m. p. 94—95°; Griess (*loc. cit.*) records m. p. 96°, Graebe 92·5°. When copper powder (5 g.) was added to the mixture, nitrogen was evolved more smoothly and at a lower temperature, but the yield of lactone was unaffected. When the diazonium salt was added gradually to phenol at (*a*) 90—95° and (*b*) 115—125°, the yield of lactone was (*a*) unaltered and (*b*) decreased by 35%. No reaction took place below about 85°.

When the lactone (14·7 g.) was added in portions to a cooled solution of methylmagnesium iodide [from 7 g. (4 atoms) of magnesium] in ether (250 c.c.), vigorous reaction took place. The mixture was heated on the water-bath for 2 hours, cooled, and decomposed with ice and sulphuric acid. 2-*Hydroxy*-2′-α-*hydroxy*iso*propyldiphenyl* (III) separated as a solid, the ether retaining only a little oily material. The solid was collected, washed with water, ether, and sodium bisulphite solution, and recrystallised from benzene; needles, m. p. 147—150° (14·5 g.) (Found : C, 78·6; H, 7·1. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·1%). It can also be crystallised, but less well, from alcohol or a little chloroform. It is soluble in cold sodium hydroxide solution, whence it is reprecipitated by carbon dioxide or ammonium chloride. With acetic anhydride and 2*N*-sodium hydroxide solution it gave low-melting products.

Phosphoric oxide (14·5 g.) was added to the phenol (14·5 g.) in dry xylene (100 c.c.). Heat was evolved. The mixture was boiled under reflux for 6 hours. The cooled solution was decanted, washed with sodium hydroxide solution and then with water, and dried with calcium chloride, and the xylene removed by distillation. The residual 2 : 2-*dimethyldibenzopyran* (IV), after distillation, formed a colourless, fairly mobile oil, b. p. 186—187°/27 mm. (Found : C, 85·3; H, 6·7. $C_{15}H_{14}O$ requires C, 85·7; H, 6·7%). Yield, 12 g. (90% theor.). Ring closure was only partly effected by distilling the phenol at 30 mm. or heating it at 175° for 45 mins.

p-*Cresol Series.* 2 : 2 : 5″-*Trimethyldibenzopyran.*—Anthranilic acid diazonium sulphate (40 g.) and *p*-cresol (100 g.) required heating to a slightly higher temperature than the phenol mixture and the reaction, once started, was rather more violent. By working as in the phenol series, there were obtained 10—13 g. of the *lactone* of 2-*hydroxy*-5-*methyldiphenyl*-2′-*carboxylic acid*, needles from alcohol, m. p. 134—135° (Found : C, 79·7; H, 4·8. $C_{14}H_{10}O_2$ requires C, 80·0; H, 4·8%). Acidification of the sodium carbonate extract gave 2-*p*-tolyloxybenzoic acid (4 g.), needles from ligroin (b. p. 60—80°), m. p. 127·5—128·5° (Ullman and Slokasov, *Ber.*, 1905, **38**, 2115, record m. p. 118·5°) (Found : C, 73·6; H, 5·6. Calc. for $C_{14}H_{12}O_3$: C, 73·6; H, 5·3%). In two experiments in which copper powder (5 g.) was added, reaction took place at a lower temperature and was easier to control, but the yields of lactone fell to 5·1 and 5·4 g.

The Grignard reaction was carried out as in the phenol series, but the resultant alcohol remained entirely in the ethereal layer; iodine was removed by sodium bisulphite solution, and the phenol then extracted by sodium hydroxide solution and recovered by precipitation by carbon dioxide. 2-*Hydroxy*-5-*methyl*-2′-α-*hydroxy*iso*propyldiphenyl* formed prisms, m. p. 112°, from ligroin (Found : C, 79·4; H, 7·2. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·5%). Yield, nearly quantitative. When crystallised from benzene, it formed colourless transparent needles, which went matt when dried in the air; the m. p. 110—112°, of a fresh specimen fell gradually when the substance was kept; it appeared to contain benzene of crystallisation (Found in a specimen melting at 94—104° : C, 80·2; H, 7·4%).

Acetyl chloride (3 c.c.) was added gradually to the phenol (2 g.) in dry pyridine (10 c.c.) at 0°; the mixture was kept at room temperature for 2 hours, decomposed with ice and dilute hydrochloric acid, and the precipitated oil, which gradually solidified, was triturated with dilute alkali (which removed only a trace of phenol); by two crystallisations from ligroin (b. p. 40—60°) 2-*acetoxy*-5-*methyl*-2′-α-*hydroxy*iso*propyldiphenyl* was obtained as needles, m. p. 78—79° (Found : C, 75·6; H, 7·3. $C_{18}H_{20}O_3$ requires C, 76·0; H, 7·1%). This substance decomposes slightly when distilled. The position of the acetyl group is proved by the insolubility of the substance in caustic alkali; the non-reactivity of the tertiary hydroxyl group is not surprising.

2-*Methoxy*-5-*methyl*-2′-α-*hydroxy*iso*propyldiphenyl*, prepared by means of methyl sulphate and 2*N*-sodium hydroxide, crystallised from alcohol in a mixture of rods and prisms, m. p. 122° (Found : C, 79·3; H, 7·6. $C_{17}H_{20}O_2$ requires C, 79·6; H, 7·9%).

The above phenol (24·8 g.) and phosphoric oxide (25 g.), when heated under reflux in xylene (100 c.c.) for 3 hours, gave 16 g. (73% theor.) of distilled 2 : 2 : 5″-*trimethyldibenzopyran*, b. p. 201°/30 mm., m. p. 57°. Crystallisation from methyl or ethyl alcohol gave plates, m. p. 58° (Found : C, 85·2; H, 7·5. $C_{16}H_{16}O$ requires C, 85·7; H, 7·2%). The same product (mixed m. p.) was obtained when the phenol was heated with a large excess of acetic anhydride on the water-bath for 90 minutes. The behaviour of this compound towards reagents is indicated on p. 1401.

Guaiacol Series. 5″-*Methoxy*-2 : 2-*dimethyldibenzopyran.*—Reaction between anthranilic acid diazonium sulphate (39 g.) and guaiacol (100 g.) set in only slowly, but was then violent and required careful control. The mixture, when treated as in the other series, gave a semi-solid, alkali-insoluble product, whence by trituration with alcohol the *lactone* of 2-*hydroxy*-3-*methoxy*-*diphenyl*-2′-*carboxylic acid* was obtained; yield, after two crystallisations from alcohol, 1·0 g.; m. p. 167° (Found : C, 74·3; H, 4·5. $C_{14}H_{10}O_3$ requires C, 73·9; H, 4·3%). Acidification of the sodium carbonate solution gave an oily mixture of acids; trituration with cold benzene separated 1·2 g. of salicylic acid, needles from benzene, m. p. 159—159·5° alone or mixed with an authentic specimen (methyl salicylate test positive) (Found : C, 61·0; H, 4·5. Calc. for $C_7H_6O_3$: C, 60·9; H, 4·3%).

The lactone (0·8 g.) gave by the Grignard reaction 0·6 g. of 2-hydroxy-3-methoxy-2′-α-hydroxy*iso*propyldiphenyl, which crystallised from benzene–ligroin in needles. As with the corresponding 5-methyl compound, these apparently contained solvent, since the m. p. fell from 132—134° to 118—125° when the substance was dried in a vacuum over sulphuric acid and phosphoric oxide for 16 hours. When the phenol (0·5 g.) was boiled with phosphoric oxide (1 g.) in dry benzene (6 c.c.) for 2 hours, 3″-methoxy-2 : 2-dimethyldibenzopyran was obtained as a pale yellow resin; it distilled without decomposition at 30 mm., but could not be crystallised and was not pure (Found : C, 81·7; H, 7·3. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%).

Acid Fission of 2 : 2 : 5″-*Trimethyldibenzopyran.*—The pyran (2·5 g.) was heated for 8 hours at 200° with a mixture (20 c.c.) of acetic acid (1 part) and concentrated hydrochloric acid (3 parts), saturated with hydrogen chloride at 0° (called below " acetic-hydrochloric acid mixture "). After dilution, the oily insoluble product was collected, dissolved in acetone, and poured into an excess of 2*N*-sodium hydroxide. Acidification of the diluted and filtered solution precipitated 1·6 g. of 2-*hydroxy*-5-*methyldiphenyl* (V). The crude product, m. p. 108°, was best purified by distillation in a vacuum, followed by crystallisation from ligroin (b. p. 60—80°), from which it separated in rods, m. p. 110—111° (Found : C, 84·9, 84·6; H, 6·7, 6·9. $C_{13}H_{12}O_2$ requires C, 84·8; H, 6·5%). Mixed with 2-hydroxy-5-methyl-2′-α-hydroxy*iso*propyldiphenyl (m. p. 112°), the product which would be formed by simple hydrolytic opening of the oxide ring, it melted indefinitely at 80—105°. This phenol is very soluble in most organic solvents. The acetyl derivative (acetic anhydride at 100°, or acetyl chloride and pyridine at 0°) was hard to purify; it is very soluble in the usual organic solvents, but can be crystallised with difficulty from diluted acetic acid and then has m. p. 63—65°. The *methyl ether* (methyl sulphate and alkali) formed rods from alcohol, m. p. 90° (Found : C, 84·5; H, 7·7. $C_{14}H_{14}O$ requires C, 84·8;

H, 7·1%). The *benzoyl* derivative (Schotten–Baumann method) formed small stout prisms from alcohol, m. p. 109—110° (Found : C, 83·5, 83·6; H, 6·4, 5·5. $C_{20}H_{16}O_2$ requires C, 83·3; H, 5·5%).

When the pyran derivative (5 g.) was heated with concentrated hydrochloric acid (without acetic acid) for 8 hours at 200°, 0·7 g. of the same phenol (mixed m. p.) and 3·9 g. of unchanged material (mixed m. p.) were obtained.

When the phenol (0·8 g.) in acetic acid (4 c.c.) was treated gradually with nitric acid (7 c.c., *d* 1·42) and warmed on the water-bath for 15 hours with occasional addition of more nitric and acetic acids, nitration was followed by oxidation. The mixture was evaporated to dryness, the residue extracted with much hot water, and crystallised from benzene, best with addition of a little acetone. This *substance*, m. p. 199—200° (Found : C, 56·45; H, 3·8; N, 6·6%), is apparently not the expected nitrobenzoic acid (Calc. : C, 50·3; H, 3·0; N, 8·47%), and its nature is obscure.

Acid Fission of Cannabinol.—Acetylcannabinol (7·5 g.) and "acetic-hydrochloric acid mixture" (55 c.c.) were heated at 180—220° for 20 hours. The mixture was diluted and extracted with ether. The ethereal layer was shaken seven times with 2*N*-sodium hydroxide, and the *phenol* (VI) isolated by acidification, extraction with ether, and distillation. This gave a red oil (1·6 g.), b. p. about 255°/27 mm., which began to crystallise after 10 days. It was very soluble in most organic solvents, but crystallised from ligroin (b. p. 40—60°) and then had m. p. 61—62° (Found : C, 79·3, 79·6; H, 7·8, 8·0. $C_{18}H_{22}O_2$ requires C, 79·95; H, 8·2%).

The phenol (0·5 g.) in acetic acid (2 c.c.) was treated with cooling with nitric acid (1 c.c., *d* 1·5), and after 3 hours with water; the solution was decanted from the precipitated gum, which could not be crystallised. This was dissolved in acetic acid (10 c.c.) and nitric acid (10 c.c., *d* 1·42), and heated on the water-bath for 20 hours, more nitric acid (30 c.c.) being gradually added. The clear solution was evaporated to dryness, the residue extracted with hot water (15 c.c.), and the less soluble 6-nitro-*m*-toluic acid (VII) recrystallised from benzene; it melted at 210·5—211·5°, and at 213—214° when mixed with an authentic specimen (m. p. 216°) (Found : C, 53·2; H, 3·75. Calc. for $C_8H_7O_4N$: C, 53·0; H, 3·9%).

The preparation of 6-nitro-*m*-toluic acid from *m*-toluidine is easier than might be inferred from the literature. 32 G. of the base gave, by Nölting and Stoecklin's method (*Ber.*, 1891, **24**, 564), 21·5 g. of 6-nitro-derivative, m. p. 137° (m. p. 138°, when pure), after only two crystallisations, and doubtless more was present in the mother-liquors. 10 G. of the nitro-amine gave 6·0 g. of 6-nitro-*m*-toluonitrile, m. p. 76—78° (80°, when pure), according to Gabriel and Thieme's directions (*Ber.*, 1919, **52**, 1090), although these authors report only 1·7 g. from 7 g. of base. Hydrolysis of the nitrile by concentrated hydrochloric acid at 160° during 4 hours is almost quantitative; the acid crystallises best from benzene containing a little acetone.

When trinitrocannabinol (1·1 g.) and "acetic-hydrochloric acid mixture" (22 c.c.) were heated at 200° for 20 hours, a carbonaceous mass resulted.

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