

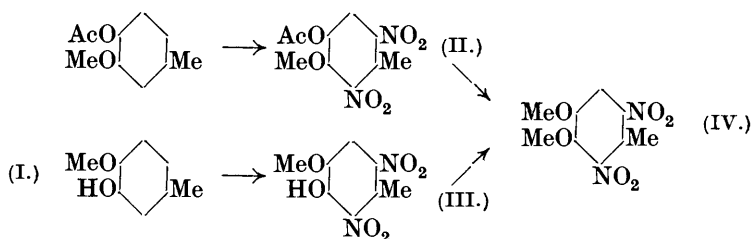
CCLXII.—*Derivatives of Homocatechol. Part I.*

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A RECENT publication of Oberlin (*Arch. Pharm.*, 1925, **263**, 641) includes a description of the preparation of 2:6-dinitrohomoveratrole (IV) from creosol by successive acetylation, nitration, hydrolysis and methylation. We therefore submit an account of experiments in this field in which we have been engaged during the past 10 years with the ultimate object of synthesising *apomorphine*.

3 x\* 2

The annexed scheme indicates the methods which have been employed.



Pollecöff and Robinson (J., 1918, **113**, 645) showed that 2-methoxyphenyl carbonate is nitrated in the *o*- and *p*- positions with respect to the methoxyl groups alone, and this observation suggested the extension to the preparation of 2:6-dinitrocreosol. *iso*Creosol (I) was first obtained in poor yield by Limpach (*Ber.*, 1889, **22**, 350) by the decomposition of diazotised *m*-cresidine and was described as a yellow oil, b. p. 185°. De Vries (*Rec. trav. chim.*, 1909, **28**, 276) showed, however, that the substance has b. p. 220—222° and m. p. 35.5°, and we now submit details of a satisfactory method of preparation and confirm the properties quoted by de Vries. The phenol yields its dinitro-derivative when submitted to the action of nitrous acid or its decomposition products in ethereal solution.

#### EXPERIMENTAL.

*iso*Creosol (I).—The *m*-cresidine employed in this preparation must be of good quality, since impurities cause a decrease in the yield quite disproportionate to their amount.

Sodium nitrite (25 g.) dissolved in water (150 c.c.) was gradually added to a mechanically stirred solution of 3-amino-4-methoxytoluene (50 g.) in water (400 c.c.) and sulphuric acid (57 c.c.; *d* 1.84), maintained below 10°. The diazo-solution\* was diluted with half its volume of water and dropped gradually on hydrated copper sulphate (100 g.) contained in a 1½-litre round-bottomed flask fitted with a condenser, a steam jet passing to the bottom of the vessel, and a thermometer with the bulb touching the copper sulphate. The flask was heated at 170° and a fine jet of steam was blown through the liquid in the flask during the reaction. This had the effect, not only of removing the *isocresol* formed from the mixture, but also of breaking up the tarry scum on the surface

\* In later experiments the diazo-solution was neutralised at a low temperature by the addition of copper carbonate; more regular yields (about 65%) were thus obtained.

and thus allowing the diazo-solution to come into immediate contact with the copper sulphate. The internal temperature remained almost constant at  $103^{\circ}$ . A light brown oil passed over with the steam, and the rate of addition was regulated so as to be equal to that of distillation. The addition occupied 2 hours and the steam was passed for  $\frac{1}{2}$  hour longer. The oil was isolated by means of ether and distilled. The fraction b. p.  $200\text{--}220^{\circ}$  (about 30 g.) was sufficiently pure for most purposes and on distillation gave 24 g., b. p.  $217\text{--}218^{\circ}$ . The colourless oil rapidly crystallised in large plates, m. p.  $35\text{--}36^{\circ}$  (Found: C, 69.5; H, 7.3. Calc. for  $C_8H_{10}O_2$ : C, 69.5; H, 7.2%).

*iso*Creosol gives with alcoholic ferric chloride a transitory green coloration, quickly becoming bluish-green.

*Acetyl derivative.* The phenol was acetylated by a boiling mixture of twice its weight of acetic anhydride and its own weight of sodium acetate for 3 hours (yield almost theoretical). The substance crystallised from a mixture of acetic acid (5 vols.) and water (3 vols.) in colourless needles, m. p.  $56\text{--}57^{\circ}$  (Found: C, 66.4; H, 6.7.  $C_{10}H_{12}O_3$  requires C, 66.7; H, 6.7%). The crystals which separate from aqueous alcohol and from light petroleum are flat prisms and long needles respectively.

The *benzoyl* derivative, obtained by the usual method, crystallised from alcohol in colourless, hexagonal plates, m. p.  $80\text{--}81^{\circ}$  (Found: C, 73.8; H, 5.8.  $C_{15}H_{14}O_3$  requires C, 74.4; H, 5.8%).

2 : 6-*Dinitro-isocreosol* (III).—A mixture of concentrated hydrochloric acid (170 c.c.) and water (200 c.c.) was gradually added with shaking to a solution of sodium nitrite (100 g.) in water (400 c.c.) underlying one of *isocreosol* (10 g.) in ether (300 c.c.). The ethereal layer became deep red and brown fumes were copiously evolved. On the following day, the ethereal solution was separated, washed with water and aqueous sodium acetate, and stirred in a concentrated solution of sodium carbonate. The precipitated yellow sodium salt was collected, washed with ether, and dried (10 g.). Its solution in water was acidified and the *dinitroisocreosol* precipitated was employed in further experiments.

The substance crystallises from water in pale yellow needles, m. p.  $152\text{--}153^{\circ}$  (decomp.) or from benzene-light petroleum in flat, yellow needles of the same m. p. (Found in material dried at  $100^{\circ}$ : N, 12.3.  $C_8H_8O_6N_2$  requires N, 12.3%). The compound gives a reddish-brown coloration with alcoholic ferric chloride and its solution in sulphuric acid is orange. The yellow *sodium* salt crystallises from alcohol in felted needles and gives red solutions.

When the reaction described above was interrupted after 6 hours,

a mixture of nitrophenols could be isolated, but separation was not effected. After methylation, however, pure 6-nitrohomoveratrole, m. p. 117°, was obtained and identified.

The dinitroisocresol was readily soluble in cold acetic anhydride, but was not acetylated. Reaction occurred on boiling the solution, and the resulting *acetyl* derivative crystallised from alcohol in colourless needles, m. p. 106° (Found: C, 44.9; H, 3.8; N, 10.3.  $C_{10}H_{10}O_7N_2$  requires C, 44.4; H, 3.7; N, 10.4%). It gave the original compound on hydrolysis with 2*N*-sodium hydroxide on the steam-bath. It is therefore improbable that either of the nitro-groups is in the *o*- or *p*- position with respect to the methoxyl. On reduction and condensation with phenanthraquinone no phenanthraquinazine derivative was produced.

The *phenylhydrazine* salt was prepared in toluene solution and crystallised from alcohol in flat, orange needles, m. p. 109° with evolution of gas (Found: C, 45.5; H, 5.4; N, 15.8.  $C_8H_8O_6N_2 \cdot C_6H_5N_2 \cdot 2H_2O$  requires C, 45.2; H, 5.4; N, 15.1%). It was partially hydrolysed by boiling water and was resolved into its constituents by acids or alkalis. The *hydroxylamine* salt crystallised from water in bright orange needles which became pasty at 166° and melted to a brown liquid at 208°, a sequence not affected by recrystallisation from water or ethyl acetate (Found: C, 36.2; H, 4.4.  $C_8H_8O_6N_2 \cdot NH_3O$  requires C, 36.8; H, 4.2%). On heating at 100°, the salt lost hydroxylamine, and the residue, m. p. 151°, consisted of pure dinitroisocresol.

*2 : 6-Dinitroacetylcreosol* [*2 : 6-Dinitro - 4 - acetoxy-m-tolyl methyl ether*] (II).—Beechwood creosote was distilled through an efficient column and the fraction, b. p. 210—223°, was redistilled, the portion, b. p. 219—222°, being collected. The sodium salt was then isolated and the phenol recovered and distilled; the material, b. p. 219—221°, consisted of creosol which was sufficiently pure to be employed for most purposes.

*6-Nitroacetylcreosol* [*6-nitro-4-acetoxy-m-tolyl methyl ether*] (Cardwell and Robinson, J., 1915, 107, 256) is best prepared by one of the following methods. (A) Acetylcreosol (25 g.) was gradually added to nitric acid (200 c.c.; *d* 1.42) cooled to  $-10^\circ$  and mechanically stirred. The product was precipitated by the addition of water (500 c.c.) and isolated. The nitric acid employed was previously boiled, but a trace of sodium nitrite was added just before the experiment was commenced. (B) A solution of nitric acid (10 g.; *d* 1.42) in acetic anhydride (5 c.c.) to which a crystal of urea had been added was gradually introduced into a mixture of acetylcreosol (10 g.) and acetic anhydride (10 c.c.) cooled to  $-10^\circ$ . Water was added 15 minutes later, and the product collected. This

material (which can be used for the next stage) crystallised from alcohol in colourless, silky needles, m. p. 136—137°.

When, however, the crude product was extracted from a benzene solution with aqueous sodium hydroxide, a by-product could be isolated. The red alkaline solution was acidified with hydrochloric acid and extracted with chloroform. On evaporation of the dried extract there remained 2 g. of a yellow, crystalline mass, which crystallised from water, in which it was moderately readily soluble, in stout, yellow, hexagonal prisms, m. p. 172° (decomp.) (Found : N, 13.1.  $C_7H_6O_6N_2$  requires N, 13.1%). This indicated a *dinitrohomocatechol*, and the deep cherry-red colour of its solution in aqueous alkalis as well as the rich bluish-green coloration which it gave with ferric chloride confirmed this view. On methylation with a large excess of methyl iodide and boiling alcoholic sodium ethoxide, 2 : 6-dinitrohomoveratrole, m. p. 92° (see below), was obtained. This by-product is therefore 2 : 6-dinitrohomocatechol. It is difficult to explain the demethylation which must have occurred.

6-Nitroacetylcreosol (4 g.) was nitrated in 1 hour by means of nitric acid (30 c.c.;  $d$  1.5) below 10°. The substance crystallised from alcohol in hexagonal plates, m. p. 103° (Found : N, 10.3. Calc. for  $C_{10}H_{10}O_7N_2$  : N, 10.4%). On hydrolysis with 2*N*-sodium hydroxide or, better, with hot aqueous alcoholic sodium carbonate, 2 : 6-dinitrocreosol was obtained; this crystallised from benzene in yellow, prismatic needles, m. p. 108° (Found : C, 42.4; H, 3.6; N, 12.3.  $C_8H_8O_6N_2$  requires C, 42.1; H, 3.5; N, 12.3%). When this phenol was treated with cold nitric acid ( $d$  1.42), and the solution diluted with water, no precipitation occurred, but addition of a solution of quinoline in dilute sulphuric acid precipitated characteristic, bright red prisms of a *quinoline* salt; this crystallised from acetic acid in chocolate-brown, rectangular, prismatic needles, m. p. 110° (decomp.). The *quinoline* salt of 3 : 5 : 6-trinitroguaiacol (Pollecioff and Robinson, *loc. cit.*) was prepared for comparison and this crystallised from alcohol in slender, yellow needles, m. p. 185° (decomp.) (Found : N, 14.4.  $C_{16}H_{12}O_8N_4$  requires N, 14.4%).

2 : 6-Dinitrohomoveratrole (IV) was obtained by methylation of dinitroisocresol and of dinitrocreosol. In the latter case (compare Oberlin, *loc. cit.*) the aqueous alkali-methyl sulphate and the xylene-methyl sulphate-potassium carbonate method both give excellent results. A mixture of the sodium salt of dinitroisocresol, anhydrous potassium carbonate ( $\frac{1}{2}$  mol.), and methyl sulphate (about 2.5 mols.) was heated at 125° for 2 hours (yield almost quantitative). 2 : 6-Dinitrohomoveratrole crystallises from alcohol or light

petroleum (b. p. 60—80°) in colourless needles, m. p. 92° (Found : C, 44·6; H, 4·3; N, 11·5. Calc. for  $C_9H_{10}O_6N_2$  : C, 44·5; H, 4·1; N, 11·5%).

*Anhydrocotarnine-2 : 6-dinitrohomoveratrole,*



—A mixture of 2 : 6-dinitrohomoveratrole (3 g.), cotarnine (3 g.), and methyl alcohol (20 c.c.) was boiled under reflux. Crystals appeared in about 5 minutes and the reaction was completed in 10 minutes. After cooling, the substance was collected, washed with methyl alcohol, and dried in a vacuum (yield, 4·5 g.). The base crystallised from ethyl alcohol in orange-yellow, diamond-shaped plates, often arranged in stellar aggregates, m. p. 141° to a red liquid (Found : C, 54·4; H, 5·0.  $C_{21}H_{23}O_9N_3$  requires C, 54·7; H, 5·0%). This substance is moderately readily soluble in benzene and, on boiling with glacial acetic acid, it is decomposed with formation of its generators.

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