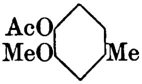
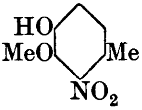
CCLVI.—*Nitro-derivatives of the Homopyrocatechol Ethers.*

By ALBERT EDWARD OXFORD.

IT has previously been shown (Oxford, J., 1926, 2004) that the action of acetyl nitrate on *o*-methoxyphenyl acetate at −15° gives rise to 3-nitro- and 5-nitro-2-methoxyphenyl acetates in about equal quantities. It was hoped that the application of this method to *m*-methoxy-*p*-tolyl acetate (I) would yield a relatively considerable proportion of the 2-nitro-derivative and provide a new and more direct route to 2-nitrohomoveratrole, although it was, of course, recognised that the effect of the methyl group would be to suppress substitution in the position between it and the methoxyl group (compare the nitration of aceto-*m*-toluidide, Cohen and Dakin, J., 1903, **83**, 331; and of *m*-cresol, Gibson, J., 1923, **123**, 1269). In point of fact, the effect was such that the yield of the 2-nitro-derivative could not be raised above 5%, although nearly every possible variation in the experimental conditions was tried, including a nitration at − 40°. The method did, however, provide a means of preparing the hitherto unknown nitro-derivatives of creosol and homoveratrole, *viz.*, 2-*nitrocreosol* (II), 2 : 5-*dinitrocreosol* (III) (readily obtained by nitrating II in acetic acid solution), and 2 : 5-*dinitrohomoveratrole* (IV).



(I.)



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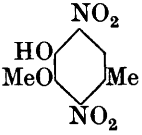

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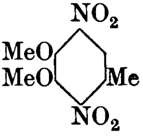
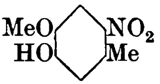


(IV.)

In view of the interest attaching to 2-nitrohomoveratrole (see Oberlin, *Arch. Pharm.*, 1925, **263**, 641; Gulland and Robinson, J., 1926, 1976; compare also Dadswell and Kenner, this vol., p. 580), and of the strong probability that, like homoveratrole and 2-nitro-*m*-tolyl methyl ether, it should be a solid at the ordinary temperature, a method for its complete separation from 6-nitrohomoveratrole was much needed. It was found that under conditions of alkaline hydrolysis which leave the 2-nitro-isomeride unaffected, 6-nitrohomoveratrole is quantitatively demethylated to 6-nitro*iso*creosol (V), and a specimen of 2-nitrohomoveratrole prepared from 2 : 6-dinitrohomoveratrole according to Oberlin's details, after being submitted to this treatment, was found to contain only a trace of 6-nitrohomoveratrole. The purified 2-nitrohomoveratrole could then for the first time be obtained crystalline, having m. p. 6—7·5°. Apparently sodium sulphide (the reducing agent used by Gulland and Robinson, whose final product was undoubtedly a mixture of the two nitrohomoveratroles) attacks both nitro-groups in 2 : 6-dinitrohomoveratrole, whilst ammonium sulphide (the reducing agent used by Oberlin), being milder and more specific in its action, reduces only the 6-nitro-group.

In conclusion, some comparative experiments have been carried out in the *o*-creosol series. The nitration of *o*-homoveratrole by concentrated nitric acid yields only the 5-nitro-derivative (VI) (Cain and Simonsen, J., 1914, **105**, 156; Majima and Okazaki, *Ber.*, 1916, **49**, 1482), and the same result is obtained if acetyl nitrate at —15° is the nitrating agent. The nitration of 3-methoxy-*o*-tolyl acetate (VII) under conditions which convert *o*-methoxyphenyl acetate into its 5-nitro-derivative only, yields chiefly the 4-nitro-derivative (VIII) and not, as might be expected, the 6-nitro-derivative.



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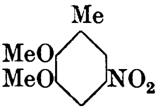

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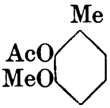
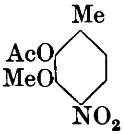


(VII.)



(VIII.)

EXPERIMENTAL.

Nitration of m-*Methoxy*-p-*tolyl Acetate* (I).—A mechanically stirred solution of the acetate (32·2 g.) and redistilled acetyl chloride (35 c.c.) in pure dry carbon tetrachloride (140 c.c.), cooled in a freezing mixture and protected from moisture, was treated during 2½ hours with dry, very finely powdered silver nitrate (36 g.). The 6-nitro-derivative began to crystallise just before all the silver nitrate had been added. Stirring was continued for a further hour, the reaction mixture filtered, and the precipitate—which contained the greater part of the 6-nitro-derivative mixed with silver salts—washed with carbon tetrachloride. The deep red filtrate was shaken twice with water, dried over anhydrous sodium sulphate, and, after evaporation of the solvent, distilled in a vacuum, three fractions being collected : (i) (Up to 167°/13 mm.) 5 g. of a red liquid ; (ii) (167—177°/13 mm.) 8 g., mostly liquid ; (iii) (177—210°/13 mm.) 5 g. of a solid (6-nitro-3-methoxy-*p*-tolyl acetate) ; (i) and the liquid part of (ii) were combined and hydrolysed by warming on the steam-bath with 2*N*-sodium hydroxide.

6(?)-*Chlorocreosol*.—The crude phenolic mixture was steam-distilled ; the brown, semi-solid material (about 4 g.) that came over, after repeated crystallisation from water, was obtained in colourless, glistening, rectangular leaflets, m. p. 71° (Found : Cl, 19·7 ; *M*, in camphor, 174. $C_8H_9O_2Cl$ requires Cl, 20·5% ; *M*, 172). It is sparingly soluble in cold water and dissolves readily in all organic solvents with the exception of light petroleum. It has a faint, guaiacol odour, gives no coloration with ferric chloride, and does not dissolve chemically in sodium bicarbonate solution.

Its *acetyl* derivative crystallises from light petroleum in colourless, thick tablets, m. p. 61° [Found : MeO (micro-Zeisel), 14·2. $C_{10}H_{11}O_3Cl$ requires MeO, 14·5%]. It is readily soluble in ethyl and methyl alcohols and moderately easily soluble in hot water.

The *methyl ether*, obtained by the xylene–methyl sulphate–potassium carbonate method, crystallises from aqueous alcohol in colourless, shining leaflets, m. p. 37—38°. It has an almost ethereal odour recalling that of *m*-methoxy-*p*-tolyl acetate, and gives a yellow coloration with concentrated sulphuric acid. In order to decide which position (2 or 6) is occupied by the chlorine atom, the behaviour of this ether on nitration was investigated. It dissolved in concentrated nitric acid to a red solution, from which nothing was precipitated by addition of water at the end of 10 minutes, but when nitrated in acetic anhydride solution at 0°, by concentrated nitric acid, it yielded a minute amount of a brown solid which crystallised from light petroleum in colourless, well-defined prisms, m. p. 89°. The amount of this substance obtained was insufficient for further investigation, but the behaviour of the chlorocreosol towards nitrating agents recalls that of 6-nitrohomoveratrole and is quite unlike that of 2-nitrohomoveratrole, which is readily nitrated to 2 : 6-dinitrohomoveratrole.

2-*Nitrocreosol* (II).—The nitrocreosols remaining in the distillation flask after the removal of chlorocreosol * were extracted with ether, and after evaporation of the solvent a dark oil remained, the solution of which in boiling light petroleum (b. p. 60—80°) deposited, on cooling, 6-nitrocreosol mixed with a little tar. After evaporation of the mother-liquor, a yellow oil remained (1·5 g.) which proved to be fairly pure 2-nitrocreosol. It was again heated with a little light petroleum, and the undissolved oil (1 g.), which would not crystallise at − 15°, was used in the experiments described below.

2-*Nitro*-3-*methoxy*-4-p-*nitrobenzyloxytoluene*.—The benzoyl derivative of 2-nitrocreosol was an uncrystallisable oil, and the phenol had to be characterised by the preparation of its p-*nitrobenzyl ether*. 2-Nitrocreosol (1·6 g., a slight excess) together with *p*-nitrobenzyl bromide (1·83 g.) was dissolved in a solution of sodium (0·19 g.) in absolute alcohol (60 c.c.), and the whole boiled under reflux for 3½ hours; much water was then added. The precipitate (m. p. 100°) obtained, after five crystallisations from alcohol, separated in fern-like aggregates of minute, colourless, flat rods, m. p. 114—114·5°, unaltered by further crystallisations from alcohol or light petroleum (Found: N, 9·1, 8·9. $C_{15}H_{14}O_6N_2$ requires N, 8·8%). It is readily soluble in most organic solvents.

6-*Nitro*-3-*methoxy*-4-p-*nitrobenzyloxytoluene* was prepared from 6-nitrocreosol by an exactly similar method. It was crystallised from hot alcohol, in which it was very sparingly soluble, and then from benzene, separating in pale yellow, feathery needles, m. p. 202—203° (Found: C, 56·1; H, 4·8. $C_{15}H_{14}O_6N_2$ requires C, 56·6; H, 4·4%).

2 : 5-*Dinitrocreosol* (III).—2-Nitrocreosol (2·6 g.) dissolved in glacial acetic acid (9 c.c.) was nitrated by the addition of a solution of nitric acid (*d* 1·42; 3·5 c.c.) in glacial acetic acid (3 c.c.) with constant stirring and cooling in ice-water, the first half of this solution being added during 10 minutes and the rest during 1 minute. Water was added immediately and the product was collected, washed, and dried (yield, 0·67 g., *i.e.*, 25% of the theoretical). It separated from light petroleum (b. p. 40—60°) in yellow leaflets, m. p. 86—87°, not altered by a second crystallisation from that solvent, from which it was also deposited in flat needles

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* By substituting acetic anhydride for the excess of acetyl chloride used in the nitration, the formation of chlorocreosol can largely be suppressed; the yield of 2-nitrocreosol is, however, if anything diminished.

by rapid crystallisation from a saturated solution (Found : N, 12·1. $C_8H_8O_6N_2$ requires N, 12·3%). It is readily soluble in hot, but only sparingly soluble in cold water, dissolves in aqueous sodium carbonate to a red solution, and gives no coloration with ferric chloride.

Its *acetyl* derivative, obtained by boiling the phenol with excess of acetic anhydride for several hours, crystallises from light petroleum in flat rods, m. p. 53—54°. It is readily soluble in alcohol and gives a pale yellow colour with concentrated sulphuric acid.

The aqueous mother-liquor from the nitration of 2-nitrocreosol was made alkaline with caustic soda, then neutralised with dilute sulphuric acid and extracted with ether. A solid remained after evaporation of the solvent which, when repeatedly crystallised from light petroleum, eventually yielded pure 5 : 6-dinitrocreosol. This observation proves that the 2-nitrocreosol originally used contained a considerable proportion of the 6-nitro-isomeride.

2 : 5-*Dinitrohomoveratrole* (IV).—2 : 5-Dinitrocreosol (0·45 g.) dissolved in dry xylene (7 c.c.) was boiled under reflux with methyl sulphate (0·5 c.c.) and anhydrous potassium carbonate (2 g.). After 30 minutes, a further 0·2 c.c. of methyl sulphate was added, and the liquid was boiled for a further 20 minutes and then worked up in the usual way. When the crude product was distilled, four drops of a nearly colourless oil came over at 190°/15 mm. Its solidification was effected by first cooling in solid carbon dioxide, when it set to a glass, and then transferring it to an ice–salt mixture and scratching vigorously; almost immediate crystallisation then set in.* The solid was obtained in colourless, six-sided plates, m. p. 36°, after two crystallisations from aqueous alcohol (Found : N, 11·5. $C_9H_{10}O_6N_2$ requires N, 11·6%). It gives a pale yellow colour with concentrated sulphuric acid, and the diamine it yields on reduction will not condense with phenanthraquinone to a derivative of phenazine.

2-*Nitrohomoveratrole from* 2-*Nitrocreosol.*—Distillation in steam, followed by repeated fractional distillation in a vacuum, provides a fairly efficient means of separating the two nitrohomoveratroles. The nitrocreosols remaining after all the chlorocreosol had been removed (see p. 1966) were therefore methylated (preferably with methyl iodide) and the methyl ethers were isolated and submitted to steam distillation until the liquid distilling over no longer con-

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* This method was applied with equal success to the purified 2-nitrohomoveratrole (see p. 1965) and to 3-nitro-2-methoxyphenyl acetate (Oxford, *loc. cit.*), an oil which had also previously resisted all attempts at crystallisation. This acetate separates from slightly aqueous alcohol in colourless, well-defined, hexagonal tablets, m. p. 29—30°.

tained any trace of oily drops. 6-Nitrohomoveratrole is appreciably volatile in steam (to the extent of 0·5 g. per litre), although much less so than its isomeride. The distillate was kept for several days in the ice-chest, filtered from 6-nitrohomoveratrole, and extracted with ether. A further separation of the two isomerides by repeated fractional distillation in a vacuum is possible, 2-nitrohomoveratrole being slightly the more volatile (Found in the best fraction: C, 54·9; H, 5·6. Calc. for $C_9H_{11}O_4N$: C, 54·8; H, 5·6%). The proportion of 2-nitrohomoveratrole in a given fraction can roughly be estimated by nitration to 2 : 6-dinitrohomoveratrole under the following conditions: The oil (about 1 g.) is nitrated by stirring with nitric acid (*d* 1·42; 3 c.c., previously boiled) for 2·5 minutes (cooling by means of running water). Much water is then added and the precipitate, after standing for a while, is collected in a Gooch crucible, dried, and weighed. Under these conditions, 6-nitrohomoveratrole gives only a 9·7% yield of somewhat impure 5 : 6-dinitrohomoveratrole. Three different specimens of 2-nitrohomoveratrole, prepared from impure 2-nitrocreosol and purified as outlined above, were found to contain at the least 77%, 80%, and 66% of that constituent respectively. On further nitration, they all gave specimens of almost pure 2 : 6-dinitrohomoveratrole with m. p. 85—89° instead of 90—91°.

5 : 6-*Dinitrohomoveratrole.*—According to Oberlin (*loc. cit.*), the direct nitration of 6-nitrohomoveratrole by fuming nitric acid below 5° gives 5 : 6-dinitrohomoveratrole in 36% yield. The present author found the yield could be increased to 60% by allowing a solution of 6-nitrohomoveratrole (0·7 g.) in acetic anhydride (5 c.c.) mixed with nitric acid (*d* 1·42; 1 c.c.) to stand for ½ hour, the temperature being maintained at 0°.

6-*Nitro*iso*creosol* (V).—6-Nitrohomoveratrole (6 g.) was boiled under reflux during 28 hours with a solution of caustic potash (23 g.) in water (150 c.c.). A further quantity of caustic potash solution (6 g. in 25 c.c. of water) was then added, and the boiling continued for a further 9 hours until 6-nitrohomoveratrole could no longer be seen in the condenser. On cooling, the deep red liquid deposited slender, orange needles of the potassium salt of the nitro*iso*creosol. Sufficient water was added to dissolve the crystals, and on addition of dilute sulphuric acid nearly pure 6-nitro*iso*creosol was precipitated. It was crystallised from very dilute hydrochloric acid (charcoal) and then from benzene, from which it separated in long, slender, pale yellow needles, m. p. 168—170°. The nitro*iso*creosol, m. p. 166—167°, isolated in small amount by Gulland and Robinson (*loc. cit.*) in some experiments on the nitration of *iso*creosol in ethereal solution, must therefore be the 6-nitro-derivative (Found : C, 52·7; H, 4·9. $C_8H_9O_4N$ requires C, 52·5; H, 4 9%).

6-Nitro*iso*creosol is readily soluble in alcohol and ethyl acetate, moderately easily soluble in chloroform in the cold, and very sparingly soluble in cold benzene and carbon tetrachloride. Its golden-orange solution in saturated aqueous sodium carbonate deposits the bright yellow *sodium* salt on addition of concentrated sodium hydroxide. It gives no coloration with ferric chloride.

Its constitution was proved by methylation to 6-nitrohomoveratrole, the methylation being almost complete after 2 hours' boiling with methyl sulphate, xylene, and potassium carbonate.

The *acetyl* derivative was obtained by boiling the nitrophenol with excess of acetic anhydride for 2 hours. It crystallises from alcohol in pale yellow leaflets, m. p. 98—98·5°, and gives a deep red coloration with concentrated sulphuric acid.

Separation of the Two Nitrohomoveratroles.—When a mixture of about equal quantities of 2- and 6-nitrohomoveratroles is demethylated under the foregoing conditions, the oil remaining unattacked contains less than 5% of 6-nitrohomoveratrole. If the original mixture consists largely of 2-nitrohomoveratrole, the removal of the 6-nitro-isomeride is complete. The accumulated mother-liquors from which crude 6-nitro*iso*creosol had been precipitated by acidification were extracted with ether, and the residue remaining after the evaporation of the solvent was submitted to distillation in steam in the hope of isolating 2-nitro*iso*creosol, but the distillate contained only 6-nitro*iso*creosol, which is slightly volatile in steam.

6-Bromo-2-nitrohomoveratrole.—Bromine (6 g.; 1½ equivs.) was added drop by drop with shaking to a solution of 2-nitrohomoveratrole (4·8 g.; 1 equiv., prepared from 2 : 6-dinitrohomoveratrole by Oberlin's method, but not further purified by the alkali treatment) in glacial acetic acid (10 c.c.). Considerable heat was developed. The liquid was kept at room temperature for 48 hours, a considerable proportion of the bromo-derivative crystallising, and then shaken with a large volume of sodium bisulphite solution. The precipitate, after being thoroughly washed with water and dried (yield, 5·8 g. or 86% of the theoretical; m. p. 99—100°), crystallised from methyl alcohol in large, colourless, four-sided tablets, m. p. 102—103° (Found : Br, 28·5. $C_9H_{10}O_4NBr$ requires Br, 29·0%) and was readily soluble in all the usual organic solvents with the exception of cold methyl and ethyl alcohols, and light petroleum, in which it was moderately easily soluble when hot and very sparingly soluble in the cold.

5 : *6-Dinitro*iso*creosol.*—A solution of the acetyl derivative of 6-nitro*iso*creosol (0·6 g.) in ice-cold nitric acid (*d* 1·5; 3·5 c.c.)

was kept at 0° for 3 hours. Water was then added, and the precipitate collected, washed, and dried (0·2 g.). The filtrate became deep red on the addition of alkali, hence considerable demethylation had taken place. The crude acetyl derivative crystallised from aqueous alcohol in colourless, flat needles, m. p. 109—110°. It was then hydrolysed by warming with sodium carbonate solution and alcohol on the steam-bath. The crude nitrophenol, precipitatated by the addition of hydrochloric acid, was recrystallised from water several times, forming very pale yellow, minute, slender needles, m. p. 128—129° (Found : N, 12·3. $C_8H_8O_6N_2$ requires N, 12·3%). It is readily soluble in alcohol, moderately easily soluble in cold benzene, and sparingly soluble in light petroleum and cold carbon tetrachloride. Its orange-coloured solution in saturated aqueous sodium carbonate deposits orange-yellow, flat, pointed rods of the *sodium* salt on addition of concentrated caustic soda. It gives a brownish-red coloration with alcoholic ferric chloride. Its constitution follows from the fact that it yields 5 : 6-dinitrohomoveratrole (m. p. 119—120°) on methylation.

Nitration of 3-*Methoxy*-o-*tolyl Acetate* (VII).—This was carried out according to the details given by Graesser-Thomas, Gulland, and Robinson (J., 1926, 1973) for the preparation of 6-nitro-*m*-methoxy-*p*-tolyl acetate (method B). A solution of nitric acid (1·8 c.c.; *d* 1·4) in acetic anhydride (2 c.c.) to which a few small crystals of urea had been added was very slowly introduced, drop by drop, into a mixture of the acetate (2·5 g.) and acetic anhydride (2·5 c.c.) cooled to − 15°. Addition of water after 15 minutes precipitated an oil, which was hydrolysed by warming it on the steam-bath with *N*-caustic soda. Acidification with dilute sulphuric acid then precipitated an oil; this, after a tedious treatment with light petroleum followed by two crystallisations from water, yielded a minute quantity of a substance, m. p. 60—61°, which crystallised from water in colourless, silky needles, gave no coloration with ferric chloride, and dissolved in saturated sodium carbonate to a golden-yellow solution. It was probably 4-nitro-*o*-creosol, since it yielded a nitrophenol when nitrated in acetic acid solution, the aminophenol from which condensed with phenanthraquinone to give a derivative of phenazine which gave a dull cherry-red colour with concentrated sulphuric acid and exhibited a perceptible green fluorescence in benzene solution (compare the behaviour of 3 : 4-dinitroguaiacol; Oxford, *loc. cit.*).

The various aqueous mother-liquors from the foregoing operations were extracted with ether, the extract was added to the light petroleum mother-liquors, and the residue remaining after evaporation of the combined extracts was methylated by the xylene–

methyl sulphate–potassium carbonate method. The methyl ethers were nitrated by heating them on the steam-bath for 10 minutes with a considerable excess of fuming nitric acid diluted with an equal volume of glacial acetic acid. Addition of water then precipitated almost pure 4 : 5-dinitro-*o*-homoveratrole, m. p. 125—127° after one crystallisation from alcohol (Majima and Okazaki, *loc. cit.*, record m. p. 126—127°). Further proof of the position of the nitro-groups was afforded by condensing the diamine obtained by reduction with zinc and hydrochloric acid, with phenanthraquinone; a substance exhibiting all the colour reactions of a 1 : 2-dimethoxyphenanthraphenazine was then obtained.

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