CCLXIII.—*Derivatives of Homocatechol. Part II.*

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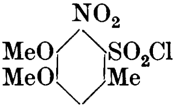
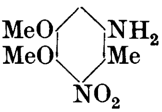
The experiments here described were made with the object of preparing 2-nitrohomoveratrole, and the following points arising from the investigation require comment.

The nitration of homoveratrole-6-sulphonyl chloride (I) yields its 5-nitro-derivative (II) in agreement with the rule of Jones and Robinson (J., 1917, **111**, 907; compare Rây and Robinson, J., 1925, **127**, 1618).

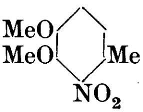
(I.)



(II.)



(III.)



(IV.)

Oberlin (*Arch. Pharm.*, 1925, **263**, 641) reduced 2 : 6-dinitrohomoveratrole with ammonium sulphide and obtained a nitroamine, m. p. 92—93°, or 104—105°, which he considered to be homogeneous and converted into an oily nitrohomoveratrole by deamination.

Since, on oxidation, 2-nitroveratric acid was obtained, the above substances were regarded as 2-nitro-6-aminohomoveratrole (III) and 2-nitrohomoveratrole (IV), respectively.

We had traversed independently much the same ground, but our compounds were undoubtedly mixtures. Employing sodium sulphide as the reducing agent, we obtained a nitroaminohomoveratrole of m. p. 90—100°, and oxidation of the oily nitrohomoveratrole therefrom gave a mixture of nitroveratric acids.

EXPERIMENTAL.

5-*Nitrohomoveratrole*-6-*sulphonyl Chloride* (II).—Chlorosulphonic acid (80 c.c.) in chloroform (100 c.c.) was gradually added to a cooled, mechanically stirred solution of homoveratrole (100 g.) in chloroform (100 c.c.); as the sulphonic acid crystallised in needles, more chloroform (100 c.c.) was added. After 15 minutes, 137 g. of phosphorus pentachloride were added in four portions. The mixture was gently heated and after an hour the solution was shaken with ice-cold water, dried, and the solvent removed. The residue was triturated with light petroleum, dried (140 g.; yield 85%), and recrystallised from this solvent, homoveratrole-6-sulphonyl chloride being obtained in glistening plates, m. p. 75° (Found: S, 13·0. Calc. for $C_9H_{11}O_4ClS$: S, 12·8%). Homoveratrole-6-sulphonamide, prepared from the chloride, had m. p. 193—194° (Brown and Robinson, J., 1917, **111**, 955, describe the chloride as an oil yielding a sulphonamide, m. p. 191°).

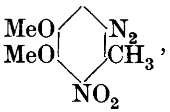
Powdered homoveratrolesulphonyl chloride (10 g.) was gradually added to stirred nitric acid (60 c.c.; *d* 1·46), maintained below 10°, and 15 minutes later the mixture was poured into water. The product (yield, 72%) crystallised from benzene in colourless prisms, m. p. 140—141° (Found: C, 36·8; H, 3·6; N, 4·9. $C_9H_{10}O_6NClS$ requires C, 36·5; H, 3·4; N, 4·7%). To determine the position of the nitro-group, a hot solution of nitrohomoveratrolesulphonyl chloride (6 g.) in aqueous potassium hydroxide (3 g. in 80 c.c.) was cooled, the potassium salt of the sulphonic acid crystallising in elongated, rectangular plates, and concentrated sulphuric acid (70 c.c.) introduced. Superheated steam removed a yellow oil, which solidified (3·7 g.) and was then crystallised from alcohol. (i) The yellow needles (2·8 g.) were recrystallised and had m. p. 57—59° (Found: C, 54·4; H, 5·3%); after removal of a minute amount of a nitrophenol, the substance crystallised from alcohol in colourless, flat needles, which, alone or mixed with 5-nitrohomoveratrole prepared by Cousin's method (*Ann. Chim.*, 1898, **13**, 537), melted at 59° (Found: C, 54·4; H, 5·5. Calc. for $C_9H_{11}O_4N$: C, 54·8; H, 5·6%). (ii) The alcoholic mother-liquor was evaporated, the residue extracted with cold aqueous sodium hydroxide, and the solution filtered (residue, 0·3 g. of nitrohomoveratrole). The precipitate (0·5 g.) obtained on acidification and cooling in ice crystallised from aqueous alcohol in long, orange needles, m. p. 80° (Found: N, 7·8. Calc. for $C_8H_9O_4N$: N, 7·7%). This substance yielded the above-described nitrohomoveratrole, m. p. 59°, on methylation and was unaltered in m. p. when mixed with 5-nitrocreosol (compare Oberlin, *loc. cit.*), m. p. 79—80° (Found: N, 7·6%), prepared by the nitration of creosol in ethereal solution.

*Nitration of Acetyl*iso*creosol* [3-*Acetoxy*-p-*tolyl methyl ether*].—A series of experiments was made on the nitration of *iso*creosol in ethereal solution under various conditions and small quantities of a compound which was volatile in steam were isolated. The substance crystallised from water in needles, m. p. 166—167°, and gave a red solution in aqueous alkali, but the amount obtained did not allow of complete investigation. Under some conditions 2 : 6-dinitro*iso*creosol was obtained.

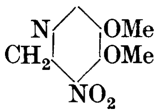
Acetyl*iso*creosol (7 g.) was gradually added to mechanically stirred and ice-cooled nitric acid (100 c.c.; *d* 1·42), the temperature being maintained below 5°. After 15 minutes, the product was precipitated by ice-water as an oil which solidified over-night (6 g.). Fractional crystallisation from alcohol gave two products. (A) The more sparingly soluble substance (yield 5 g.) crystallised from 80% alcohol in flat, yellow needles, m. p. 104—105° (Found: C, 51·0; H, 4·2; N, 6·6. $C_9H_9O_5N$ requires C, 51·2; H, 4·3; N, 6·6%). The compound gave a reddish-brown colour with ferric chloride and dissolved in aqueous alkalis to permanganate-coloured solutions. These properties and the analytical figures suggest that the substance is a nitroacetylhomocatechol the production of which would involve demethylation. After treatment for 15 minutes with boiling 2*N*-alcoholic potassium hydroxide a nitrophenol was obtained which crystallised from water in golden-yellow leaflets, m. p. 80° (unsharp), and then from light petroleum in golden-yellow needles; these melted at 82—83°, and at the same temperature when mixed with an authentic specimen of 5-nitrohomocatechol (Cousin, *loc. cit.*). In all probability, therefore, the substance, m. p. 104—105°, is 5-nitro-3-acetoxy-*p*-cresol. (B) The more soluble constituent (yield 1 g.), which was to some extent obtained from the solution by the addition of water, crystallised from light petroleum in lemon-yellow prisms, m. p. 60—61° (Found: N, 6·2. $C_{10}H_{11}O_5N$ requires N, 6·2%). It was insoluble in cold alkalis, but on boiling dissolved to an orange-red solution. The compound is doubtless a nitroacetyl*iso*creosol and very probably it is 5-*nitro*-3-*acetoxy*-p-*tolyl methyl ether*.

2-*Nitro*-6-*amino*iso*creosol*, $MeO{\cdot}C_6HMe(OH)(NH_2){\cdot}NO_2$.—Sodium sulphide (5 mols.) was added to a boiling solution of 2 : 6-dinitro*iso*creosol (1 mol.) in the calculated quantity of 2% aqueous sodium hydroxide. After ¾ hour, the liquid was just acidified with hydrochloric acid, filtered while hot from sulphur, cooled, and treated with sodium acetate until it was no longer acid to Congo-red. The feathery needles obtained (yield, 25%) crystallised from methyl alcohol and then from benzene–light petroleum in orange-yellow prisms, m. p. 168—169° (decomp.) (Found: C, 49·3; H, 5·1. $C_8H_{10}O_4N_2$ requires C, 48·5; H, 5·0%). This compound is very prone to discoloration as the result of oxidation; its solution in aqueous alkalis is deep red, and it gives a green colour with alcoholic ferric chloride. The *acetyl* derivative, readily produced by the action of acetic anhydride, crystallised from water in colourless needles, m. p. 183° after slight softening at 180°. After drying in a vacuum the substance lost 6·0% at 110° (Found in dried material: N, 11·7. $C_{10}H_{12}O_5N_2,H_2O$ requires H_2O, 6·9%. $C_{10}H_{12}O_5N_2$ requires N, 11·7%). Its solution in aqueous sodium hydroxide is bright red and, on cooling to 0°, deposits the sodium salt in yellow needles. Clearly the acetyl group is attached to nitrogen, and the non-formation of a benzoxazole is one of the reasons for the assignment of the *p*-aminophenol structure to the semi-reduction product of dinitro*iso*creosol.

Nitroaminohomoveratroles and Various Derivatives.—A hot solution of crystallised sodium sulphide (25 g.) and sulphur (7·5 g.) in water (100 c.c.) was added to a boiling mixture of 2 : 6-dinitrohomoveratrole (10 g.), alcohol (50 c.c.), and water (400 c.c.). The whole was boiled under reflux for 1¼ hours, then cooled, and the precipitate of golden-yellow needles was collected and freed from sulphur by solution in hot dilute hydrochloric acid and reprecipitation by ammonia. The dry product (7·5 g.; 85%) crystallised from aqueous alcohol in golden-yellow needles, m. p. 90—100°, and no separation was effected by recrystallisation (Found: N, 13·4. Calc. for $C_9H_{12}O_4N_2$: N, 13·2%). There is no doubt that this substance is a mixture, the chief constituent of which is 2-nitro-6-aminohomoveratrole (III). The *hydrochloride*, m. p. about 210°, is hydrolysed by hot water, giving golden-yellow needles, m. p. 90—92°. The *acetyl* derivative, colourless needles, m. p. 173—175°, from alcohol, on hydrolysis yielded the original base, m. p. 90—100°. 6-*Bromo*-2-*nitrohomoveratrole*, obtained in good yield by the Sandmeyer reaction (along with a sparingly soluble *by-product*, orange needles, m. p. 241°, from ethyl acetate), crystallised from ethyl acetate in buff columns, m. p. 102° (Found: N, 5·3. $C_9H_{10}O_4NBr$ requires N, 5·1%). The action of sulphurous acid on the diazo-sulphate from nitroaminohomoveratrole in presence of copper powder led to the production of two substances, one of which was neutral and crystallised from alcohol in golden-yellow needles, m. p. 142° (Found in material dried at 100° : C, 45·9; H, 4·3; N, 14·3; S, 6·6. $C_{18}H_{19}O_9N_5S$ requires C, 44·9; H, 4·0; N, 14·6; S, 6·7%). This curious compound, which constitutes the major product, is stable in boiling 2*N*-sodium hydroxide and dissolves in sulphuric acid to a purple solution which quickly becomes red. Apparently the following fragments



S, O,



must be pieced together by suitable rearrangements in order to construct a possible constitutional formula for the substance, and this can be done in many ways. The second product from the reaction was a small amount of nitrohomoveratrolesulphinic acid. This was oxidised by permanganate, and the resulting sulphonic acid hydrolysed with superheated steam in presence of sulphuric acid. An alkali-insoluble oil and a nitrophenol, crystallising from light petroleum in needles, m. p. 62° (Found : N, 7·6. $C_8H_9O_4N$ requires N, 7·6%), were obtained. Since this nitrophenol is volatile in steam, gives a red solution in aqueous sodium hydroxide, and a green coloration with ferric chloride, it is probably *2-nitro-3-hydroxy-*p*-tolyl methyl ether.* The nitrohomoveratrolediazonium chloride was reduced by stannous chloride; the resulting *nitrohydrazinohomoveratrole* crystallised from methyl alcohol in orange leaflets, m. p. 146—166°. The *piperonylidene* derivative of this hydrazine crystallised from alcohol as a mixture of small, orange-yellow tablets and large, orange-yellow plates, m. p. 171—175°. On repeated crystallisation a small amount of the plates was obtained in a homogeneous condition, m. p. 172—173°.

Nitroaminohomoveratrole itself was condensed with piperonal, and a considerable quantity of an apparently homogeneous *piperonylidene* derivative obtained which crystallised from methyl alcohol in lemon-yellow needles, m. p. 130—132° (Found : C, 59·3; H, 4·7. $C_{17}H_{16}O_6N_2$ requires C, 58·9; H, 4·7%). On hydrolysis this purified material gave a nitroaminohomoveratrole, m. p. 90—92° (Found : C, 51·2; H, 5·7. Calc. for $C_9H_{12}O_4N_2$: C, 50·9; H, 5·7%). The hydrazine prepared from this specimen crystallised from alcohol in orange leaflets, m. p. 147—149°, and in a second physical modification, m. p. 163—164° after softening at 148° (Found : N, 18·4. $C_9H_{13}O_4N_3$ requires N, 18·5%). On oxidation with copper sulphate in dilute acetic acid solution, the last-mentioned specimen of the hydrazine gave an almost colourless oil, volatile in steam. This afforded, on oxidation with potassium permanganate, a substance, crystallising from water in needles and plates, m. p. 180—198°, which proved to be a mixture of 2-nitro- and 6-nitro-veratric acids.

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