55. *Cinnolines. Part XI. 8-Nitro-4-hydroxycinnoline.*

By J. C. E. Simpson.

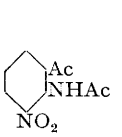
The substance previously formulated as 5-nitro-4-hydroxycinnoline (Schofield and Simpson, *J.*, 1945, 512) is shown to be the 8-nitro-isomer by an unambiguous synthesis from 3-nitro-2-aminoacetophenone.

It was recently shown (*loc. cit.*) that the nitration of 4-hydroxycinnoline produces three mononitro-derivatives. Of these, one, m. p. 331°, was identified as the 6-nitro-compound, a second, m. p. 185°, was regarded as the 5-isomer on account of its failure to react with acetic anhydride, this being attributed to steric causes, and the third isomer, m. p. 277°, was accordingly formulated as 7 (or 8)-nitro-4-hydroxycinnoline.

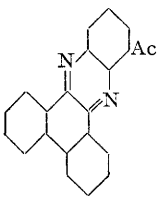
The nitration of *o*-acetamidoacetophenone was previously stated (*J.*, 1945, 646) to give only 5-nitro-2-acetamidoacetophenone, but under somewhat different conditions 3-*nitro*-2-*acetamidoacetophenone* (I) is also formed, together with a small amount of an unidentified *substance*, $C_{10}H_9O_2N_3$, which appears to be neither a primary amine nor an acetamido-compound. Hydrolysis of (I) gave 3-nitro-2-aminoacetophenone, originally obtained in small amount by Bamberger (*Ber.*, 1915, **48**, 537) from 2-nitroaminoacetophenone, but not oriented by him; its constitution has now been proved by conversion into the phenazine (II), previously obtained (*J.*, 1945, 646) from 2-nitro-3-aminoacetophenone.

Diazotisation and cyclisation of 3-nitro-2-aminoacetophenone gave a product identical with the nitro-hydroxycinnoline, m. p. 185°, referred to above; this substance is, therefore, the 8-, and not the 5-, isomer. Its failure to react with acetic anhydride is therefore to be

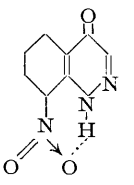
ascribed to chelation, and it must accordingly be represented by (III) rather than by (IV). The substance has been examined spectrographically by Professor R. A. Morton, and the results,



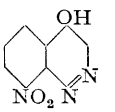
(I.)



(II.)



(III.)



(IV.)

which will be published later, are in conformity with the structure advocated, as also is the comparatively low melting point of the compound.

Experimental.

Melting points are uncorrected.

Nitration of o-Acetamidoacetophenone.—The ketone (50 g.) was added in small portions to a mixture of nitric acid (250 c.c., *d* 1·48) and concentrated sulphuric acid (50 c.c.) with stirring; the addition was made as rapidly as possible (½—¾ hour) consistent with a reaction temperature of 0° to − 8°. The mixture was then added to crushed ice (600 g.) and water (200 c.c.), and the crude nitration product filtered off and washed (filtrate A). The solid from three runs was digested with boiling alcohol (1 l.) and filtered off cold, yielding a product, m. p. *ca.* 130—145°. Crystallisation from the minimum volume of boiling alcohol (*ca.* 3·5 l.) gave a mixture of needles and stout yellow prisms, the former predominating. After rough manual separation, the needles were recrystallised from alcohol and gave pure 5-nitro-2-acetamidoacetophenone, m. p. 154—155°; the prisms, recrystallised from benzene, yielded 3-*nitro*-2-*acetamidoacetophenone*, which formed very pale yellow prisms, m. p. 152—153° (*ca.* 125—130° when mixed with the 5-nitro-isomer) (Found: C, 54·0; H, 4·65. $C_{10}H_{10}O_4N_2$ requires C, 54·0; H, 4·55%). A further crop of the 3-nitro-isomer was obtained from the first two alcoholic filtrates.

All alcoholic mother-liquors then remaining, including those from the nitration of two 25-g. batches under the earlier conditions (*J.*, 1945, 646), were bulked, solvent removed, and the residue repeatedly crystallised from benzene, yielding pure 5-nitro-2-aminoacetophenone (3 g.; m. p. and mixed m. p.). More of this amine was obtained from the total benzene filtrates by removal of solvent, acid hydrolysis, and crystallisation of the mixed amines from benzene.

The filtrates (A) were made just alkaline (ice and ammonia) and thoroughly extracted with ether. The extract was washed with a little water, dried, and evaporated, and the residue crystallised from methanol and finally from ethanol, yielding a sparingly soluble *base*, m. p. 201—202° (slight shrinking at 190°) (Found: C, 59·0, 59·2; H, 4·7, 4·6; N, 20·3, 20·5. $C_{10}H_9O_2N_3$ requires C, 59·1; H, 4·4; N, 20·7%). The compound formed deep yellow, brittle needles, insoluble in cold aqueous sodium bicarbonate or hydroxide, and soluble in cold 2N-hydrochloric acid. It was not attacked by 4N-hydrochloric acid (1½ hours on the steam-bath), and did not visibly couple with alkaline β-naphthol after diazotisation.

The methanol filtrate from the foregoing compound gave a small crop of 3-nitro-2-acetamidoacetophenone; evidence of traces of other compounds was obtained, but these were not investigated. After hydrolysis of the 5-nitro-compound, the final yields from 200 g. of *o*-acetamidoacetophenone were 133 g. of 5-nitro-2-aminoacetophenone, 21 g. of 3-nitro-2-acetamidoacetophenone, and 4·3 g. of the substance, m. p. 201—202°. 3-Nitro-2-acetamidoacetophenone is more soluble than the 5-nitro-isomer in alcohol, but less so in benzene; the 5-nitro-amine, on the other hand, is less soluble in benzene than the 3-nitro-amine, and separates from this solvent in either reddish-brown, stout, brittle needles or light yellow, soft plates.

3-*Nitro*-2-*aminoacetophenone.*—The acetamido-compound (1 g.) was heated for 1 hour at 95° with alcohol (20 c.c.), water (10 c.c.), and concentrated hydrochloric acid (10 c.c.), giving 3-nitro-2-aminoacetophenone as long golden-yellow needles, m. p. 95—96°, from aqueous alcohol (Found: N, 15·5. Calc. for $C_8H_8O_3N_2$: N, 15·55%); Bamberger (*loc. cit.*) gives m. p. 93°. For proof of structure, the nitro-amine (100 mg.) was reduced with iron powder (0·3 g.), acetic acid (2 c.c.), and water (2 c.c.) by the method previously described (*J.*, 1945, 646); the product, isolated with ether, was refluxed with phenanthraquinone (*ca.* 20 mg.) in alcohol (4 c.c.), and the phenazine was crystallised from acetic acid, giving yellow needles, m. p. 226—227° alone and when mixed with the sample previously described (*loc. cit.*).

8-*Nitro*-4-*hydroxycinnoline.*—A cold solution of 3-nitro-2-aminoacetophenone (0·45 g.) in acetic acid (4·5 c.c.) was treated with 1·5 c.c. of a mixture of concentrated sulphuric acid (5 c.c.) and water (1 c.c.). Powdered sodium nitrite (0·2 g.) was then added in portions, after which the mixture was heated on the steam-bath until it gave only a weak coupling reaction (½ hour). The solid (0·25 g.) obtained by dilution with water (2 vols.) was filtered off, washed, and recrystallised from alcohol, from which 8-nitro-4-hydroxycinnoline separated in brown needles, m. p. 185·5—186·5° alone and mixed with the sample described by Schofield and Simpson (*loc. cit.*).

The author is indebted to Imperial Chemical Industries Limited (Dyestuffs Division) for facilities in connection with this work, and to the Medical Research Council for financial support.

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[*Received, June 17th*, 1946.]