

237. *The Chemistry of the Pyrrocolines. Part II. Nitroso-derivatives of Some Substituted Pyrrocolines.*

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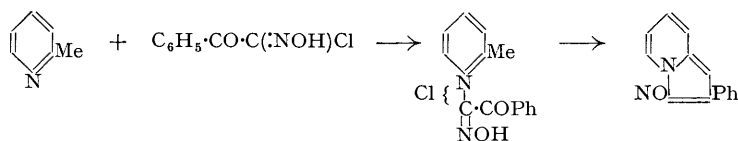
Nitrosation of several substituted pyrrocolines has been effected and the positions of the substituents established.

THERE appears to be only one recorded case of the direct introduction of a nitroso-group into the pyrrocoline nucleus: Kondo and Nischizawa (*J. Pharm. Soc. Japan*, 1936, **56**, 1; *Chem. Zentr.*, 1936, **107**, i, 4158), by the action of nitrous acid on 3-acetyl-2-methylpyrrocoline, prepared its 1-nitroso-derivative. We have applied this procedure to the preparation of the 2-phenyl analogue. Further, we have found that 1-nitroso-3-acetyl-2-methylpyrrocoline can be oxidised to α -picolinic acid *N*-oxide, thus rendering it highly probable that the nitroso-group has entered the one free position in the pyrrole ring of the pyrrocoline nucleus.

Furthermore, the method has been extended to 2-methyl- and 2-phenyl-pyrrocolines to yield two nitroso-compounds, later proved to be the 3-nitroso-derivatives. Oxidation showed that these also contained the nitroso-group in the pyrrole ring, for the principal product of the reaction was α -picolinic acid *N*-oxide, accompanied by benzoic acid in the case of the 2-phenylpyrrocoline derivative.

Although 3-acetyl-2-methyl- and -2-phenyl-pyrrocolines undergo deacetylation very readily (cf. Part I), the corresponding 1-nitroso-derivatives of both compounds proved more resistant to acid hydrolysis and underwent extensive decomposition as the vigour of the treatment was increased; nor was it found possible to introduce an acetyl group into 3-nitroso-derivatives of 2-methyl- and -phenyl-pyrrocoline by means of acetic anhydride or the Friedel-Crafts reaction. During the application of the latter reaction the two compounds were found to form quaternary compounds with acetyl chloride. Attention was directed therefore to the oxidation of the nitroso-derivatives of 2-methyl- and 2-phenyl-pyrrocoline with a view to orienting the groups in these compounds. The former was oxidised by hydrogen peroxide to 3-nitro-2-methylpyrrocoline (Part III). Numerous experiments were carried out before optimum conditions were established and analytically pure compounds obtained; even so, the yield was small. It was not found possible to oxidise the nitroso-derivative of the phenyl analogue to a nitro-compound, but evidence that it was the 3-nitroso-compound was furnished by the synthesis of

3-nitroso-2-phenylpyrrocoline by ring closure of ω -isotonitrosophenacyl- α -picolinium chloride, the preparation of which is described in the Experimental section.



Several attempts to effect ring closure in the usual manner, with cold or boiling aqueous sodium hydrogen carbonate, failed to produce more than a very small quantity of crude nitroso-compound which was accompanied by much intractable material. However, with cold aqueous 2*N*-sodium hydroxide ring closure occurred with surprising ease, and the overall yield of 3-nitroso-2-phenylpyrrocoline from α -picoline was 86%.

Addition of sodium hydrogen carbonate or hydroxide to an aqueous solution of ω -isotonitrosophenacyl- α -picolinium chloride yielded a colourless *sodio*-derivative, m. p. 86°, which contains both sodium and chloride ions. It is converted readily into ω -isotonitrosophenacyl- α -picolinium chloroplatinate and *picrate* by treatment of its aqueous solution with chloroplatinic and picric acid, respectively.

A feature of true unimolecular nitroso-compounds is their blue or green colour in all states of aggregation (cf. Sidgwick, "The Organic Chemistry of Nitrogen," 1942, 204) and the nitroso-compounds described herein appear to belong to this class. However, 3-nitroso-2-methylpyrrocoline and the 1-nitroso-3-acetyl derivatives of 2-methyl- and 2-phenyl-pyrrocoline produce yellow, and 3-nitroso-2-phenylpyrrocoline red solutions in dilute hydrochloric acid. Hence, as cations they do not seem to contain a true nitroso-group and resemble the *p*-nitrosoanilines (cf. Sidgwick, *op. cit.*, p. 217). Furthermore, 3-nitroso-2-methylpyrrocoline, which is very soluble in water, gave a blood-red solution, whilst the phenyl analogue, which is less soluble, is greenish-yellow. By the preparation of 1-nitroso-2-methyl-3-ethylpyrrocoline, which yields a red aqueous solution, it is shown that the loss of the true nitroso-structure by solution in water is not restricted to 3-nitroso-derivatives. The solubilities of these nitroso-compounds in water are not increased by the presence of alkalis.

It would seem from these results that the pyrrocoline nucleus undergoes nitrosation without difficulty by the action of sodium nitrite in acid solution, an observation in marked contrast to the rare success of such a method when applied to pyrroles and indoles.

EXPERIMENTAL.

(All m. p.'s are uncorrected.)

1-Nitroso-3-acetyl-2-methylpyrrocoline.—A solution of sodium nitrite (12 g.; 1.5 mols.) in water (50 c.c.) was slowly added to a stirred solution of 3-acetyl-2-methylpyrrocoline (20 g.) in glacial acetic acid (100 c.c.), the temperature being kept below 15°. After 15 mins. the resulting brown solution was poured into water, and the green precipitate, m. p. 138—141°, collected, washed with water until free from acetic acid, and dried in a vacuum (20 g.; 86%). 1-Nitroso-3-acetyl-2-methylpyrrocoline separates from acetone in small, dark green needles when the solution is cooled quickly, or in long, brilliant blue needles on slow cooling; both forms melt at 146—147.5° to a brown liquid [Kondo and Nischizawa, *loc. cit.*, give m. p. 146.5° (decomp.)] (Found: C, 65.4; H, 5.0; N, 14.3. Calc.: C, 65.3; H, 5.0; N, 13.9%).

The nitroso-compound (0.5 g.) was heated under reflux with acetic acid (5 c.c.) and perhydrol (5 c.c.) until the solution became almost colourless. Evaporation of the solution and extraction of the residue with methanol yielded α -picolinic acid *N*-oxide, m. p. and mixed m. p. with an authentic specimen 160° (decomp.).

1-Nitroso-3-acetyl-2-phenylpyrrocoline.—A solution of sodium nitrite (6 g.) in water (30 c.c.) was added dropwise to a solution of 3-acetyl-2-phenylpyrrocoline (20 g.) in glacial acetic acid (100 c.c.) the temperature of which was lowered from 20° to 10° as the reaction proceeded. The thick crystalline magma was removed by filtration and washed with water; addition of sodium hydroxide to the filtrate yielded a further crop of the same material. The nitroso-compound (18.7 g.; 83%) separates from aqueous alcohol in olive-green needles, m. p. 154—154.5°, which sublime at 130°/0.007 mm. (Found: C, 73.0; H, 4.8; N, 10.3. C₁₆H₁₂O₂N₂ requires C, 72.7; H, 4.5; N, 10.6%). It yields a *monopicrate*, which separates from methyl cyanide in deep orange needles, m. p. 179° (decomp.) (Found: N, 14.0. C₂₂H₁₅O₉N₅ requires N, 14.2%).

3-Nitroso-2-methylpyrrocoline.—A solution of sodium nitrite (20 g.; 1.3 mols.) in water (100 c.c.) was added dropwise to a stirred solution of 2-methylpyrrocoline (30 g.) in hydrochloric acid (200 c.c. + 400 c.c. of water) at 0—5°. After 15 minutes the yellow solution was made alkaline by addition of sodium hydrogen carbonate, and the resulting red solution extracted three times with chloroform. Evaporation of the dried (CaCl₂) bright green solution in a vacuum yielded the nitroso-compound (30 g.; 82%), m. p. 103.5—106°; it separates from dry ethyl acetate in very dark green needles, m. p. 106—107° (Found: C, 67.3; H, 5.2; N, 17.5. C₉H₈ON₂ requires C, 67.5; H, 5.0; N, 17.5%). Oxidation of this compound by perhydrol in glacial acetic acid solution yielded α -picolinic acid *N*-oxide, m. p. 159—160° (decomp.) alone or mixed with an authentic specimen.

On exposure to a moist atmosphere, the nitroso-compound gradually changes into black needles possessing a blue sheen and increases in weight by 10.9%, corresponding to formation of a *monohydrate* (C₉H₈ON₂·H₂O requires increase, 11.25%): it melts at 76—106°. The molecule of water is completely removed after 56 hrs. in a vacuum desiccator.

3-Nitroso-2-phenylpyrrocoline.—2-Phenylpyrrocoline (25 g.) was dissolved in concentrated hydrochloric acid (80 c.c.), and the solution diluted at 35° with water (160 c.c.). To this solution an aqueous solution of sodium nitrite (12.5 g. in 65 c.c. of water) was added dropwise with stirring; an orange-red crystalline precipitate gradually separated which became a thick magma when the mixture was cooled to room temperature. After 20 mins. the crystals were filtered off and the filtrate (I) kept for further examination. The red crystals, m. p. 200° (decomp.), separated from warm water in red needles, unchanged in m. p.; from a solution in *hot* water, however, there separated 3-nitroso-2-phenylpyrrocoline *semihydrochloride dihydrate*, rust-red needles, m. p. 115—116°, in poor yield. The major proportion was precipitated by the addition of 2*N*-sodium hydrogen carbonate (50 c.c.); the green filtrate (II) was kept. Recrystallisation of the *semihydrochloride* from dilute alcohol (charcoal) yielded fine needles (24.5 g.; 73%), m. p. 113—114° [Found: C, 65.2; H, 4.8; N, 10.8; Cl, 6.9. (C₁₄H₁₀ON₂)₂·HCl·2H₂O requires C, 65.1; H, 4.8; N, 10.8; Cl, 6.9%]. Determination of the water of crystallisation proved unsatisfactory and accordingly the active hydrogen content was determined [Found: Active H (Zerewitinoff), 0.92. Calc. for 5H: 0.97%].

Addition of an excess of sodium hydrogen carbonate to the combined filtrates I and II, followed by extraction with

ether, yielded crude 3-nitroso-2-phenylpyrrocoline (5.6 g.; 19%), which separated from aqueous alcohol in deep green needles with a blue tint by reflected light, m. p. 97.5—98° (Found: C, 75.4; H, 4.5; N, 12.6. $C_{14}H_{10}ON_2$ requires C, 75.7; H, 4.5; N, 12.6%). This compound was obtained also by decomposing the above semihydrochloride with bicarbonate. The reverse of this conversion was effected by dissolving the nitroso-compound in concentrated hydrochloric acid and precipitating the semihydrochloride by addition of sodium hydrogen carbonate solution. The picrate, prepared in the usual way, separates from alcohol or aqueous acetone in orange-red needles, m. p. 196—197° (decomp.) (Found: C, 53.3; H, 3.5; N, 15.2. $C_{20}H_{13}O_8N_5$ requires C, 53.2; H, 2.9; N, 15.5%).

3-Nitroso-1-acetyl-2-phenylpyrrocolinium Chloride.—Acetyl chloride in excess was added to the nitroso-compound (0.25 g.) dissolved in carbon disulphide (15 c.c.), the additive compound separating as a red solid, m. p. 99° (decomp.) (Found: N, 9.8; Cl, 12.1. $C_{14}H_{10}ON_2 \cdot CH_3 \cdot COCl$ requires N, 9.3; Cl, 11.8%).

Oxidation of 3-Nitroso-2-phenylpyrrocoline.—The pyrrocoline (4 g.) in glacial acetic acid (35 c.c.), oxidised with perhydrol (50 c.c.), yielded benzoic acid and α -picolinic acid *N*-oxide, m. p. 161° (decomp.) alone or mixed with an authentic specimen.

Oxidation of 3-Nitroso- to 3-Nitro-2-methylpyrrocoline.—A solution of the nitroso-compound (2 g.) in water (16 c.c.) was mixed with perhydrol (40 c.c.) and gradually heated to 65—70°; the mixture was removed from the water-bath and stirred for 10 minutes, after which the buff-coloured precipitate was removed and washed well with water and finally with a little acetone. The precipitate was discarded, and extraction of the combined filtrate and washings with chloroform yielded a green solid (0.75 g.) from which water extracted unchanged nitroso-compound (0.6 g.), leaving a dark solid (0.12 g.). The latter, in acetone solution, was passed through a small pad of alumina and there was obtained a yellow crystalline compound which separated from alcohol in yellow needles, m. p. 101—103°, alone or admixed with authentic 3-nitro-2-methylpyrrocoline prepared by direct nitration (Found: N, 16.0. $C_9H_8O_2N_2$ requires N, 15.9%).

ω -isoNitrosophenacyl- α -picolinium Chloride.— ω -Chloroisnitrosoacetophenone (10 g.) (*Org. Synth.*, 1944, 24, 25) was gradually added to a solution of α -picoline (4.35 c.c.; 0.81 mol.) in dry benzene (150 c.c.). The resulting solution, on standing in a refrigerator, deposited the crystalline quaternary compound which, after desiccation in a vacuum over paraffin wax, weighed 13.9 g. and had m. p. 102—103° (decomp. with gas evolution). This quaternary chloride appeared to contain benzene of crystallisation which it readily lost on crystallisation from alcohol-ether; interlaced soft needles, m. p. 122—123° (decomp.) (Found: C, 60.6; H, 4.8; N, 10.0; Cl, 13.0. $C_{14}H_{13}O_2N_2Cl$ requires C, 60.7; H, 4.7; N, 10.1; Cl, 12.8%).

Addition of chloroplatinic acid to an aqueous solution of the quaternary chloride precipitated the chloroplatinate as a buff-coloured powder, m. p. 199° (decomp.) [Found: N, 6.2; Pt, 21.9. $(C_{14}H_{13}O_2N_2)_2PtCl_6$ requires N, 6.3; Pt, 21.9%]. The picrate was precipitated from an alcoholic solution of the quaternary chloride, on addition of picric acid in the same solvent, as yellow crystalline leaflets, m. p. 176° (decomp.) (Found: Cl, 51.3; H, 3.5; N, 14.8. $C_{20}H_{15}O_9N_5$ requires C, 51.2; H, 3.2; N, 14.9%).

Formation of 3-Nitroso-2-phenylpyrrocoline from ω -isoNitrosophenacyl- α -picolinium Chloride.—A solution of the quaternary chloride (8 g.) in water (60 c.c.) was covered with ether (30 c.c.) and then mixed with sodium hydroxide (40 c.c., 2N), and the whole well shaken at intervals during 30 mins. Filtration removed the crystalline precipitate of 3-nitroso-2-phenylpyrrocoline (4.2 g., 71%), m. p. 97—98°, which had been rapidly formed. The ethereal layer yielded a further 0.88 g. of the same product contaminated with α -picoline. The 3-nitroso-2-phenylpyrrocoline separated from aqueous alcohol in dark green needles, m. p. 97.5—98° alone, or when mixed with the compound produced by nitrosation of 2-phenylpyrrocoline (Found: C, 75.4; H, 4.9; N, 12.6%). Further confirmation was afforded by the conversion of this 3-nitroso-2-phenylpyrrocoline into its picrate (Found: N, 15.3%), and its semihydrochloride, the properties of which were identical with those of the compounds prepared as described above.

1-Nitroso-2-methyl-3-ethylpyrrocoline.—A solution of sodium nitrite (2.4 g.) in water (20 c.c.) was slowly added to a stirred solution, at 0°, of 2-methyl-3-ethylpyrrocoline (5 g.) in hydrochloric acid (15 c.c. + water 30 c.c.). After 30 minutes the solution was made alkaline with sodium hydroxide and the red solution, entraining an oil having the odour of unchanged pyrrocoline, extracted with chloroform. A green oily solid (5.6 g.) was thus obtained, which after being washed with ligroin and crystallised from benzene, yielded 1-nitroso-2-methyl-3-ethylpyrrocoline (2.6 g.), very dark green microscopic irregular crystals, m. p. 110—111° (Found: C, 70.3; H, 6.3; N, 15.4. $C_{11}H_{12}ON_2$ requires C, 70.2; H, 6.4; N, 14.9%). Exposure to a moist atmosphere converts this nitroso-derivative into a red-brown trihydrate which melts indefinitely at 52—86°, the gain in weight being 28.6% ($C_{11}H_{12}ON_2 \cdot 3H_2O$ requires gain, 28.7%). Exposure of this to a dry atmosphere for about 48 hours regenerated the anhydrous nitroso-compound.

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