349. *Derivatives of 4-Chloro- and 6-Nitro-quinoline.*

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The preparation of some 4-substituted quinoline derivatives, starting from 6-nitro- and 4-chloro-quinoline, is described.

The following experiments are now recorded in view of the recent appearance of other publications on similar lines.

Bachman and Cooper (*J. Org. Chem.*, 1944, **9**, 302) have described the preparation of chloronitroquinolines from 6-nitroquinoline *N*-oxide and phosphorus oxychloride. The two major products were formulated as 4- and 2-chloro-6-nitroquinoline, but the orientation was not rigidly established, and a third (and minor) product was regarded as 3-chloro-6-nitroquinoline. In repeating this work, we found, in agreement with Bachman and Cooper, that three isomers are formed; we established the constitution of the main product as 4-chloro-6-nitroquinoline by converting it into 6-*nitro*-4-*phenoxyquinoline* and thence into 6-*nitro*-4-*aminoquinoline*, identical with one of the products of the nitration of 4-aminoquinoline (Simpson and Wright, in the press). Reduction of 6-nitro-4-aminoquinoline gave a crystalline, but unstable, diamine; this formed a stable *diacetyl* derivative which reacted readily with methyl iodide and yielded 4 : 6-bisacetamidoquinoline methiodide, from which the corresponding *methochloride* was prepared. 4-Chloro-6-nitroquinoline was also converted by standard methods into 6-*nitro*-4-*anilino*- and 6-*nitro*-4-*methoxy-quinoline*; and 6-*nitro*-2-*phenoxy*- and 6-nitro-2-amino-quinoline (Tschitschibabin, Witkowsky, and Lapschin, *Ber.*, 1925, **58**, 803) were prepared from 2-chloro-6-nitroquinoline.

By the nitration of 4-chloroquinoline we obtained a crude product in high yield, from which about 27% (based on 4-chloroquinoline) of a mono-nitro-derivative, m. p. 127—129°, was readily isolated; this was converted into the corresponding 4-hydroxy-, m. p. 201°, -methoxy-, m. p. 181°, -*phenoxy*-, m. p. 116°, and -amino-derivative, m. p. 230°. After these experiments had been carried out, the publications of Riegel *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 1264), Baker *et al.* (*ibid.*, pp. 1267, 1532), and Gouley *et al.* (*ibid.*, 1947, **69**, 303) appeared, in which the same reactions are described and the products are identified as 8-nitro-derivatives. Our attempts to obtain 4-chloro-8-nitroquinoline as the sole product of the nitration of 4-chloroquinoline were unsuccessful; the experience of the American workers was essentially similar to our own, and Gouley *et al.* (*loc. cit.*) isolated 4-chloro-5-nitroquinoline as a second product from this reaction.

The foregoing 4-amino-compounds, and also 4-aminoquinoline, were prepared, like analogous cinnoline (Keneford, Schofield, and Simpson, this vol., p. 358), and quinazoline (Morley and Simpson, *ibid.*, p. 360) derivatives, by fusing the phenoxy-compounds with ammonium acetate.) The three types of heterocyclic amine differ, however, in their behaviour towards alkyl halides. Whereas quaternary salts of 4-aminoquinazolines are too reactive to be isolated (Morley and Simpson, *loc. cit.*), 4-aminoquinolines react smoothly with alcoholic methyl iodide, and thus resemble 4-aminocinnolines (Simpson, *J.*, 1947, 1653, and unpublished work). That the ring nitrogen of the quinoline molecule is attacked was shown by the conversion of 4-aminoquinoline methiodide and 6-*nitro*-4-*aminoquinoline methiodide* into *N*-methyl-4-quinolone and 6-*nitro*-N-*methyl*-4-*quinolone*, respectively, on treatment with hot aqueous alkali hydroxide; the products were authenticated by methylation of the respective hydroxy-compounds with methyl sulphate. 8-*Nitro*-4-*aminoquinoline methiodide* was also prepared; its structure was not proved, but it, too, is doubtless formed by alkylation of the ring nitrogen.

Experimental.

(Melting points are uncorrected.)

6-*Nitroquinoline* N-*Oxide*.—The procedure of Bachman and Cooper (*loc. cit.*) was modified as follows. A solution of 6-nitroquinoline (23·7 g.) in chloroform (150 c.c.) was treated with a chloroform solution (350 c.c.) of perbenzoic acid (5% excess), left at 0° for 48 hours, washed with aqueous ammonia and water,

dried, concentrated, and treated with ether, giving pure *N*-oxide, m. p. 215—217°; average yield, 43·6% [lit. m. p. 220—222° (corr.); yield unspecified].

4-, 3(?)-, *and* 2-*Chloro*-6-*nitroquinoline*.—The foregoing *N*-oxide (30 g.) was refluxed for 1 hour with phosphorus oxychloride (150 c.c.), and the clear solution was then poured on ice (750 g.). After hydrolysis of the oxychloride was complete, the suspension was filtered (filtrate *A*), and the solid (well washed and dried) was recrystallised from chloroform, yielding 2-chloro-6-nitroquinoline as amber-coloured needles, m. p. 224—226° (average yield, 5·6%). Filtrate *A* was basified (ice and ammonia), and the total solid fractionally extracted with cold 2N-hydrochloric acid (150 c.c. portions). The first 2 extracts gave a mixture (7·5 g., m. p. 120—132°) which could not be purified. Further extraction yielded 4-chloro-6-nitroquinoline, which formed colourless needles, m. p. 145—145·5°, after repeated crystallisation from chloroform–ligroin (b. p. 60—80°) (average yield, 33·2%); and finally, using 5N-acid, a substance was isolated which after crystallisation from benzene–ligroin (b. p. 60—80°) formed pale brown needles, m. p. 147—148° (105—110° when mixed with 4-chloro-6-nitroquinoline) (average yield, 2·8%), and was evidently the compound regarded by Bachman and Cooper as 3-chloro-6-nitroquinoline.

Nitration of 4-*Chloroquinoline*.—The crude mixture of 2- and 4-chloroquinoline prepared by the method of Bobranski (*Ber.*, 1938, **71**, 580) was readily separated by extracting its ethereal solution with 0·4N-hydrochloric acid; basification of the acid washings and extraction with ether gave 4-chloroquinoline (50% of mixed chloro-compounds) as an oil, b. p. 128—130°/15—17 mm., which crystallised on standing. This was nitrated as follows: (*a*) A solution of the compound (5 g.) in concentrated sulphuric acid (10 c.c.) was added during 20 minutes to nitric acid (10 c.c., *d* 1·53) at −15° with stirring; on removal of the mixture from the freezing bath, the temperature rose to 36° and then slowly fell. The solution was poured on ice (200 g.), the mixture basified, and the solid collected, dried (5·5 g., m. p. 70—90°), and repeatedly crystallised from alcohol or benzene–ligroin (b. p. 60—80°), yielding prismatic needles or irregular leaflets, respectively, of 4-chloro-8-nitroquinoline, m. p. 127—129° (lit., 126—127°, 129—130°) (average yield, 28% pure) (Found: N, 13·7; Cl, 17·6. Calc. for $C_9H_5O_2N_2Cl$: N, 13·4; Cl, 17·0%). (*b*) The chloro-compound (13·8 g.) was added during 20 minutes to a mixture of oleum (28 c.c., *d* 2·01) and nitric acid (55 c.c., *d* 1·53) at −3° to +5°. After a further 20 minutes the product was worked up as in (*a*) (crude yield, 14 g., m. p. 88—95°; average pure yield, 27%).

6-*Nitro*-4-*methoxyquinoline*.—Prepared from 4-chloro-6-nitroquinoline (0·4 g.), sodium methoxide (0·25 g.), and methanol (10 c.c.) (refluxed for ¾ hour), this *compound* (0·35 g.; 90%) crystallised from benzene–ligroin (b. p. 60—80°) in fine colourless needles, m. p. 183·5—184·5° (Found: C, 59·15; H, 3·9. $C_{10}H_8O_3N_2$ requires C, 58·8; H, 3·95%).

8-*Nitro*-4-*methoxyquinoline*.—Prepared from 4-chloro-8-nitroquinoline (0·2 g.), sodium methoxide (0·7 g.), and methanol (6 c.c.) (1 hour's reflux), 8-nitro-4-methoxyquinoline (0·12 g., 61%) crystallised from methanol in colourless prismatic needles, m. p. 180—181° (lit. m. p. 185—186°, 181—182) (Found: C, 58·3; H, 3·9; N, 13·6. Calc. for $C_{10}H_8O_3N_2$: C, 58·8; H, 3·95; N, 13·7%).

6-*Nitro*-4-*phenoxyquinoline*.—4-Chloro-6-nitroquinoline (7 g.) was heated at 120—140° (bath temp.) for 50 minutes with a solution of potassium hydroxide (1·95 g.) in phenol (70 g.). The mixture was cooled, diluted, basified with aqueous sodium hydroxide, and extracted with ether. Evaporation of the washed and dried extract gave 6-*nitro*-4-*phenoxyquinoline* (6·8 g., 76%) as cream-coloured needles, m. p. 117—118° from ligroin (b. p. 60—80°) (Found: C, 67·4; H, 4·0; N, 11·0. $C_{15}H_{10}O_3N_2$ requires C, 67·7; H, 3·8; N, 10·5%). At 90—95° the yield was 58%.

8-*Nitro*-4-*phenoxyquinoline*.—Interaction of the chloro-compound (10 g.), potassium hydroxide (2·7 g.), and phenol (100 g.) was complete in 1¾ hours at 90—95°; isolation as above gave 8-*nitro*-4-*phenoxyquinoline* (11 g., 86%) as colourless prismatic needles, m. p. 114—116° (sinters at 107°) from ligroin (b. p. 60—80°) (Found: C, 67·05; H, 3·9. $C_{15}H_{10}O_3N_2$ requires C, 67·7; H, 3·8%). Gouley *et al.* (*loc. cit.*) give m. p. 105—106° for an unanalysed specimen.

6-*Nitro*-2-*phenoxyquinoline*.—The product obtained by heating 2-chloro-6-nitroquinoline (1·5 g.), potassium hydroxide (0·41 g.), and phenol (15 g.) for 1 hour at 130—150° (lower temperatures gave a reduced yield) was isolated as above (1·3 g., 68%) and crystallised from ligroin (b. p. 60—80°) containing a little benzene; 6-*nitro*-2-*phenoxyquinoline* separated in amber-coloured needles, m. p. 151—152° (Found: C, 67·3; H, 3·4. $C_{15}H_{10}O_3N_2$ requires C, 67·7; H, 3·8%).

6-*Nitro*-4-*anilinoquinoline*.—A mixture of 4-chloro-6-nitroquinoline (0·2 g.), aniline (0·1 g.), acetone (1 c.c.), water (2 c.c.), and concentrated hydrochloric acid (1 drop) was refluxed for ½ hour. Removal of the acetone and basification with ammonia yielded 6-*nitro*-4-*anilinoquinoline* (0·25 g.; 98%), which formed orange prismatic needles, m. p. 183—184°, from alcohol (Found: N, 15·8. $C_{15}H_{11}O_2N_3$ requires N, 15·8%).

6-*Nitro*-4-*aminoquinoline*.—The phenoxy-compound (8 g.) and ammonium acetate (48 g.) were heated at 170—180° (bath temp.) for 25 minutes, cooled, diluted with water, and the solution basified. A solution of the crude product in 10% aqueous acetic acid (100 c.c.) was filtered and again basified, yielding 6-*nitro*-4-*aminoquinoline* (4·8 g., 84%), m. p. 311—312° (decomp.) after recrystallisation from alcohol, from which it formed deep orange irregular plates (Found: C, 57·1; H, 4·0; N, 22·4. $C_9H_7O_2N_3$ requires C, 57·1; H, 3·7; N, 22·2%). 6-*Nitro*-4-*acetamidoquinoline* (from the base and 5 parts of boiling acetic anhydride) crystallised from ethyl acetate in soft, almost colourless, prismatic needles, m. p. 228—229° (yield, 94%) (Found: N, 18·4. $C_{11}H_9O_3N_3$ requires N, 18·2%).

8-*Nitro*-4-*aminoquinoline*.—The temperature of a mixture of the phenoxy-compound (10 g.) and ammonium acetate (60 g.) was raised from 145° to 185° during 20 minutes, and kept at 185° for a further 10 minutes. Isolation as in the preceding example yielded 8-nitro-4-aminoquinoline (m. p. 215—222°, 6·65 g., 94%), which crystallised from ethyl acetate in irregular yellow leaflets, m. p. 229—230° [Gouley *et al.* (*loc. cit.*) give m. p. 232°] (Found: C, 57·4; H, 3·85; N, 22·2. Calc. for $C_9H_7O_2N_3$: C, 57·1; H, 3·7; N, 22·2%). 8-*Nitro*-4-*acetamidoquinoline* (yield, 80%), prepared from the base and boiling acetic anhydride, crystallised from slightly aqueous acetic acid in small colourless prisms, m. p. 290—292° (decomp.) (Found: N, 18·0. $C_{11}H_9O_3N_3$ requires N, 18·2%).

6-*Nitro*-2-*aminoquinoline*.—6-Nitro-2-phenoxyquinoline (0·3 g.) and ammonium acetate (3 g.) were kept at 210—225° for 4 hours (very little reaction was discernible after 1 hour). Extraction of the pro-

duct with 2N-hydrochloric acid yielded (acid-insoluble) unchanged phenoxy-compound (50 mg.), and (from the filtrate) 6-nitro-2-aminoquinoline (150 mg.) which formed orange prismatic needles, m. p. 256—257°, from alcohol (Found : C, 56·9; H, 4·1; N, 22·1. Calc. for $C_9H_7O_2N_3$: C, 57·1; H, 3·7; N, 22·2%). Tschitschibabin *et al.* (*loc. cit.*) give m. p. 251° and 261°. 6-*Nitro*-2-*acetamidoquinoline* separated from benzene in colourless, hair-like needles, m. p. 231—233° (Found : N, 18·4. $C_{11}H_9O_3N_3$ requires N, 18·2%).

4 : 6-*Bisacetamidoquinoline*.—A solution of 6-nitro-4-aminoquinoline (2 g.) in glacial acetic acid (12 c.c.) was added at room temperature during 10 minutes to a stirred solution of stannous chloride dihydrate (8 g.) in hydrochloric acid (16 c.c.) and water (4 c.c.). The suspension was kept at 90° for 5 minutes and then basified (sodium hydroxide); 4 : 6-diaminoquinoline rapidly crystallised in colourless needles from the clear solution [1·4 g. (83%), m. p. 208° (decomp.) after being dried in an exhausted desiccator; the base turned red in air, and after 2 days had m. p. 195° (decomp.)]. The *dihydrochloride* separated from 2N-hydrochloric acid in colourless needles, m. p. 340—342° (decomp.) (Found : Cl, 29·7. $C_9H_9N_3,2HCl$ requires Cl 30·6%). When the crude base (1·4 g., m. p. 208°) was refluxed for ¾ hour with acetic anhydride (14 c.c.), 4 : 6-*bisacetamidoquinoline* (2 g.) was formed (colourless irregular leaflets, m. p. 248·5—250°, from aqueous alcohol) (Found : C, 59·8; H, 5·8; N, 16·1. $C_{13}H_{13}O_2N_3,H_2O$ requires C, 59·7; H, 5·8; N, 16·1%). 4 : 6-Diacetamidoquinoline methiodide was prepared from the base (1·5 g.), methyl iodide (10 c.c.), and alcohol (40 c.c.) (1 hour's reflux); excess of methyl iodide was removed, the solid collected, and the filtrate again refluxed with more methyl iodide (10 c.c.) for 2 hours; total yield 78% (63% if only a single prolonged reflux was given). The salt formed yellow needles, m. p. 296—298° (decomp.), very easily soluble in water, and crystallising poorly from other solvents. The *methochloride* (from the iodide and silver chloride) crystallised well from alcohol or aqueous acetone in clusters of fine colourless needles, m. p. 318° (decomp.) (Found : C, 57·3; H, 5·5; N, 13·8. $C_{14}H_{16}O_2N_3Cl$ requires C, 57·2; H, 5·5; N, 14·3%).

6-*Nitro*-4-*aminoquinoline Methiodide*.—A suspension of 6-nitro-4-aminoquinoline (1·87 g., finely powdered) in alcohol (40 c.c.) and methyl iodide (13 c.c.) was refluxed gently for 7 hours, concentrated, and the solid collected [2·67 g. (80%), m. p. 303—304° (decomp.)]. Recrystallisation from water gave the *salt* as pale orange, lustrous, prismatic needles, m. p. 301—303° (decomp.) (Found : C, 36·6; H, 3·2; N, 12·9. $C_{10}H_{10}O_2N_3I$ requires C, 36·3; H, 3·0; N, 12·7%).

8-*Nitro*-4-*aminoquinoline Methiodide*.—A solution of 8-nitro-4-aminoquinoline (0·5 g.) in alcohol (50 c.c.) and methyl iodide (15 c.c.) was refluxed for 6 hours. Concentration and addition of ether gave 8-*nitro*-4-*aminoquinoline methiodide* [0·4 g., m. p. 247—251° (decomp.)], which separated from water in red prismatic needles, m. p. 257—258° (decomp.), apparently as a hydrate, but satisfactory analytical data could not be obtained (Found : C, 34·2, 33·8; H, 2·7, 2·6; N, 12·95. $C_{10}H_{10}O_3N_3I,H_2O$ requires C, 34·4; H, 3·45; N, 12·0%); occasionally this substance crystallised in amber needles, m. p. 242° (decomp.), which were readily convertible into the higher-melting form by crystallisation from water.

6-*Nitro*-1-*methyl*-4-*quinolone*.—(*a*) Methyl sulphate (0·22 c.c.) was added to a solution of 6-nitro-4-hydroxyquinoline (0·2 g.) in aqueous potassium hydroxide (1·9%, 4·8 c.c.) at 50°. At the end of the reaction, excess of alkali was added, and the 6-*nitro*-1-*methyl*-4-*quinolone* (0·21 g.) recrystallised from alcohol, from which it separated in yellow prismatic needles, m. p. 233—234° (Found : C, 58·9; H, 4·0. $C_{10}H_8O_3N_2$ requires C, 58·8; H, 3·95%).

(*b*) A solution of 6-nitro-4-aminoquinoline methiodide (0·3 g.) in water (8 c.c.) was refluxed for 1 hour with 10% aqueous sodium hydroxide (1 c.c.) (ammonia evolved). Recrystallisation of the product from alcohol gave pale orange prismatic needles (0·17 g.), m. p. 231—233° alone and when mixed with the sample described in (*a*).

1-*Methyl*-4-*quinolone from* 4-*Aminoquinoline Methiodide*.—The methiodide, prepared from the components in boiling ethanol, had m. p. 226—228° (Claus and Frobenius, *J. pr. Chem.*, 1897, **56**, 181, give m. p. 224°). Ammonia was evolved when it (2 g.) was refluxed in aqueous solution (10 c.c.) for ½ hour with sodium hydroxide (5 c.c. of 10%); extraction with chloroform and crystallisation of the product from benzene gave colourless prisms, m. p. 150—152°, of 1-methyl-4-quinolone (picrate, m. p. 227—229°) alone and when mixed with an authentic sample prepared from 4-hydroxyquinoline and methyl sulphate in sodium hydroxide solution.

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