## 410. *Some* Bz-*Substituted*-3-*nitroquinolines.*

By J. S. Morley and J. C. E. Simpson.

3-Nitroquinolines are readily prepared by refluxing compounds of type (I) in acetic acid with an arylamine hydrochloride. The method has been successfully applied to compounds (I) obtained from aniline and the three toluidines, but fails with *p*-nitroaniline and with 2-nitro-*p*-toluidine.

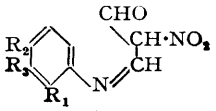
The effect of using the salt of an arylamine different from that used in the preparation of (I) has been studied, and the results are discussed in terms of the hypothesis that the ring-closure occurs *via* (VII) by loss of a proton and arylamine.

The methods to be found in the literature for the synthesis of 3-nitroquinolines do not offer attractive routes for the preparation of *Bz*-substituted homologues or analogues. Clemo and Swan (*J.*, 1945, 867) obtained 3-nitro-6 : 7-dimethoxy- and -methylenedioxy-quinoline by extending the methazonic acid–*o*-aminobenzaldehyde reaction (D.R.-P. 335,197), and 3-nitro-4-hydroxy- and thence * 4-chloro-3-nitro-quinoline have recently been prepared from anthranilic

* A compound having markedly different properties has also been described as 4-chloro-3-nitroquinoline by Gouley, Moersch, and Mosher (*J. Amer. Chem. Soc.*, 1947, **69**, 303), who prepared it by nitrating 4-hydroxyquinoline and chlorinating the product. Dr. K. Schofield informs us (private communication) that the compound of Gouley *et al.* is in reality 4-chloro-6-nitroquinoline; we have confirmed this, and have also found that the nitration produces small amounts of 8-nitro-4-hydroxyquinoline.

acid and methazonic acid (Bachman, Welton, Jenkins, and Christian, *J. Amer. Chem. Soc.*, **1947, 69**, 365), but the scope of this method, when aldehydes are used, is restricted by the fact that relatively few *o*-aminoaldehydes are known, and the preparation of new analogues would not be likely to be always a simple problem. The method recently published by Uhle and Jacobs (*J. Org. Chem.*, 1945, **10**, 76), involving condensation of nitromalonic aldehyde with an arylamine and cyclisation of the Schiff base in presence of zinc chloride at 200—300°, works well with 2-naphthylamine, but gives only a poor yield when applied to aniline. Colonna (*Chem. Abs.*, 1943, **37**, 3096) has found that 3-nitroquinoline-4-carboxylic acid is a product of the condensation of isatin with nitromethane, but this observation, although suggesting a synthesis of, possibly, general utility, has not been extended to substituted isatins.

The cyclisation of the anils of β-keto-aldehydes to quinoline derivatives has been shown by Petrow (*J.*, 1942, 693) to be greatly facilitated by the addition of a molecular proportion of the hydrochloride of the arylamine, and it seemed likely, in view of the formal similarity between such cyclisations and the reaction of Uhle and Jacobs, that an improvement of the latter might likewise result from the addition of arylamine hydrochloride. Some experiments on these lines have shown that this is in fact the case; 3-nitroquinoline derivatives are formed, sometimes in high yield, simply by refluxing the appropriate anil and arylamine hydrochloride for some hours in acetic acid without the addition of zinc chloride or other condensing agent. Thus 2-nitro-2-formylethylideneaniline (I; $R_1 = R_2 = R_3 = H$) and aniline hydrochloride gave 3-nitroquinoline (II; $R_1 = R_2 = H$) in 41% yield (Uhle and Jacobs, *loc. cit.*, report a 21%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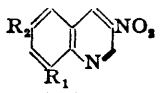
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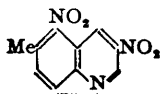
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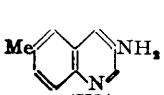
(IV.)

yield); in an experiment in which the hydrochloride was largely replaced by the free base, no quinoline derivative could be isolated. 2-Nitro-2-formylethylidene-*p*-toluidine (I; $R_1 = R_3 = H$, $R_2 = Me$) and *p*-toluidine hydrochloride gave 3-*nitro*-6-*methylquinoline* (II; $R_1 = H$, $R_2 = Me$) in 77% yield (cyclisation of the Schiff base alone by means of zinc chloride gave only a 17% yield), which on nitration gave in high yield a single product, regarded as 3 : 5-*dinitro*-6-*methylquinoline* (III), and on reduction yielded 3-*amino*-6-*methylquinoline* (IV). Similarly, 2-*nitro*-2-*formylethylidene*-m-*toluidine* (I; $R_1 = R_2 = H$, $R_3 = Me$) and *m*-toluidine hydrochloride gave 3-*nitro*-5-(or 7-)*methylquinoline* (55%); the *o*-toluidine *isomer* (I; $R_1 = Me$, $R_2 = R_3 = H$) also reacted with *o*-toluidine hydrochloride, but the yield of 3-*nitro*-8-*methylquinoline* (II; $R_1 = Me$, $R_2 = H$) was low (6·5%). No quinoline derivative was obtained from 2 : 3′-*dinitro*-2-*formylethylidene*-p-*toluidine* (I; $R_1 = H$, $R_2 = Me$, $R_3 = NO_2$) either by fusion with zinc chloride or by refluxing it with the corresponding arylamine hydrochloride in 80% acetic acid.

These results suggested that the ring-closures might occur by acid-induced intramolecular cyclisation of the anils (V) [or (VI)] formed from the arylamine and the Schiff bases, and it

(V). $Ar{\cdot}N{:}CH{\cdot}CH(NO_2){\cdot}CH{:}NHAr'$ $Ar{\cdot}N{:}CH{\cdot}C(NO_2){:}CH{\cdot}NHAr'$ (VI.)

became of interest to study cases in which Ar and Ar′ are two different aryl nuclei. We have found that 3-nitro-6-methylquinoline is formed when (I; $R_1 = R_3 = H$, $R_2 = Me$) is refluxed with either aniline hydrochloride (40% yield) or *o*-toluidine hydrochloride (22% yield), but that if *m*-toluidine hydrochloride is used the product is 3-nitro-5-(or 7-)methylquinoline (35% yield), identical with that obtained from the same hydrochloride and (I; $R_1 = R_2 = H$, $R_3 = Me$). On the other hand, interaction of (I; $R_1 = R_2 = R_3 = H$) and *p*-toluidine hydrochloride gave 3-nitro-6-methylquinoline (16%), and no 3-nitroquinoline was isolated. The reaction between (I; $R_1 = R_2 = H$, $R_3 = Me$) and *p*-toluidine hydrochloride gave a product, m. p. 135—137°, which was not identical with any of the above compounds, and is possibly a mixture of nitromethylquinolines. No quinoline derivative was isolated from the product of reaction between *p*-toluidine hydrochloride and 2 : 4′-*dinitro*-2-*formylethylideneaniline* (I; $R_1 = R_3 = H$, $R_2 = NO_2$).

Further study of this reaction is necessary before its limitations and detailed mechanism can be stated with precision. However, the existing data can be given a simple qualitative interpretation if one assumes that the entity which is cyclised is the resonating kation (VII), which

(VII.) $[Ar{\cdot}NH{:}CH{\cdot}C(NO_2){:}CH{\cdot}NHAr']^+$ $Ar{\cdot}NH{\cdot}CH{:}C(NO_2){\cdot}CH{:}NAr'$ (VIII.)

could yield the 3-nitroquinoline by loss of arylamine and a proton. The behaviour of a series of such kations, in which Ar is the same and Ar′ is varied, would depend in any given case on

the distribution of the kationic charge, which would itself change with variations in the nature of Ar′; it is thus possible to account for the formation of two different products from 2-nitro-2-formylethylidene-*p*-toluidine when it is refluxed with the hydrochlorides of aniline, *p*-toluidine, or *o*-toluidine on the one hand, and with that of *m*-toluidine on the other. Further, the resonating ion (VII) is common to each of the bases (VI) and (VIII), and hence the formation of 3-nitro-6-methylquinoline from (*a*) 2-nitro-2-formylethylideneaniline and *p*-toluidine hydrochloride and (*b*) 2-nitro-2-formylethylidene-*p*-toluidine and aniline hydrochloride is readily explained. It is to be noted, however, that the two reaction-pairs—2-nitro-2-formylethylidene-*m*-toluidine–*p*-toluidine hydrochloride and 2-nitro-2-formylethylidene *p*-toluidine–*m*-toluidine hydrochloride—do not give identical products; further investigation is needed to show whether this result is a genuine discrepancy or has arisen from manipulative difficulties.

The monoanil (I; $R_1 = R_2 = R_3 = H$) and aniline readily yielded the dianil (V or VI; Ar = Ar′ = Ph) when boiled for a short time in acetic acid in the absence of mineral acid; in dilute aqueous hydrochloric acid this compound was rapidly hydrolysed to the monoanil and aniline.

The concept of cyclisation of a resonating kation of the type (VII) derivable from two formally tautomeric anils (VI) or (VIII) is merely a particular example of the more general case (IX), where $R_1$, $R_2$, and $R_3$ are substituents or hydrogen atoms, and could equally well be applied to other quinoline syntheses in which dianils or the type in question are believed to participate (*e.g.*, König, *Ber.*, 1923, **56**, 1853; Petrow, *loc. cit.*; Johnson, Woroch, and Mathews, *J. Amer. Chem. Soc.*, 1947, **69**, 566). In the Combes synthesis, however, in which a monoanil Ar·N:CR·$CH_2$·COR′ (or Ar·NH·CR:CH·COR′) is heated in concentrated sulphuric acid, the participation of (IX) is unlikely, because it could arise only by hydrolysis of the monoanil followed by disproportionation, and Roberts and Turner (*J.*, 1927, 1832) state, and we have confirmed, that the formation of 2 : 4 : 6-trimethylquinoline from (X) is quantitative. Furthermore, we find that, in contrast to this quantitative transformation, no quinoline derivative is formed when (X) is refluxed with *p*-toluidine hydrochloride in glacial acetic acid (the products

(IX.) $[Ar{\cdot}NH{:}CR_1{\cdot}CR_2{:}CR_3{\cdot}NHAr']^+$ *p*-Me·$C_6H_4$·NH·CMe:CH·COMe (X.)

(XI.) $Ar{\cdot}\overset{\displaystyle NAr''}{C}{\cdot}CHR{\cdot}NHAr'$

from short periods of refluxing were hydrolysable to *p*-toluidine, and longer refluxing gave a neutral compound, m. p. 151°, of obscure constitution and apparent formula $C_{17}H_{20}O_2N_2$).

The Bischler indole synthesis, according to recent evidence (*Ann. Reports*, 1946, **43**, 242; see also Cowper and Stevens, *J.*, 1947, 1041), also proceeds by way of an amine-anil intermediate (XI), which, however, differs from (IX) by virtue of the fact that addition of a proton to (XI) would give an ion which, unlike (IX), is not derivable from two different base tautomers. This formal difference between the two types of synthesis might have important practical consequences should the tautomeric forms of (XI), and those of the base derivable from (IX), prove to be not readily interconvertible.

## Experimental.

(Melting points are uncorrected.)

*Schiff Bases from Nitromalondialdehyde.*—The following method, based on that of Hill and Torrey (*Amer. Chem. J.*, 1899, **22**, 95), gave consistent yields of 40% of sodionitromalondialdehyde. Mucobromic acid (20 g.) was added in one portion to a mechanically-stirred solution of sodium nitrite (20 g.) in water (50 c.c.) and alcohol (50 c.c.), and the temperature raised quickly to 50°; the spontaneous rise in temperature described by Hill and Torrey was not observed. After 10 minutes at 47—50°, the red solution was quickly cooled with vigorous stirring, and the yellow mass of sodionitromalondialdehyde collected (4·8 g.), washed with alcohol, and dried at 50°. The Schiff bases were all prepared by the same method, as illustrated by the following example. A freshly-prepared solution of sodionitromalondialdehyde (4·8 g.) in water (30 c.c.) was added in one portion to a solution of aniline hydrochloride (5 g.) in 2N-hydrochloric acid (15 c.c.). The 2-nitro-2-formylethylideneaniline which rapidly separated was collected after a few minutes (yield, 82%) and crystallised from alcohol; it then had m. p. 145—147° (Hill and Torrey give m. p. 143—144°). *2-Nitro-2-formylethylidene-o-toluidine* (80% yield), fine, pale yellow needles from alcohol, had m. p. 133—134° (Found : N, 14·1. $C_{10}H_{10}O_3N_2$ requires N, 13·6%). *2-Nitro-2-formylethylidene-m-toluidine* (81% yield) formed yellow prismatic needles, m. p. 156—157°, from alcohol or aqueous acetic acid (Found : N, 13·5%). 2-Nitro-2-formylethylidene-*p*-toluidine (yield, 80%) crystallised from alcohol or acetic acid in yellow needles, m. p. 179—180° (Hill and Torrey give m. p. 176—177°). *2 : 4′-Dinitro-2-formylethylideneaniline* (83% yield), soft yellow needles from acetic acid, had m. p. 230—231° (Found : N, 17·4. $C_9H_7O_5N_3$ requires N, 17·7%). *2 : 3′-Dinitro-2-formylethylidene-p-toluidine* (from the arylamine sulphate; yield 95%) formed soft yellow needles, m. p. 206—207° to a red liquid, from aqueous alcohol or aqueous acetic acid (Found : C, 47·8; H, 3·9; N, 16·6. $C_{10}H_9O_5N_3$ requires C, 47·8; H, 3·6; N, 16·7%); it was soluble in warm alkalis and was thereby hydrolysed to the arylamine, which separated when the solution was cooled.

*3-Nitroquinoline.*—A solution of aniline hydrochloride (0·67 g.) and 2-nitro-2-formylethylideneaniline

(1 g.) in acetic acid (10 c.c.) was refluxed for 17 hours. On cooling and dilution with water, a gum was precipitated from which the liquid (*A*) was decanted. 3-Nitroquinoline was isolated from (*A*) by basification (sodium hydroxide), and from the gum by extraction with warm 2N-hydrochloric acid followed by basification; total yield 0·37 g. (41%). The compound formed needles, m. p. 127—128°, and did not depress the m. p. of a sample prepared by the method of Uhle and Jacobs (*loc. cit.*). 2-Nitro-2-formylethylideneaniline was recovered unchanged after its solution in acetic acid had been refluxed for 24 hours, but in presence of 1 equiv. of aniline (in boiling acetic acid) the dianil was rapidly formed (brilliant yellow needles, m. p. 92—93°; Hill and Torrey give m. p. 93—94°). No quinoline derivative was isolated after equivalent amounts of the (mono)anil and aniline had been refluxed in acetic acid with 0·1 equiv. of aniline hydrochloride, but a mixture of 1 equiv. each of anil, aniline, and aniline hydrochloride gave *ca.* 10% of 3-nitroquinoline. The yield of the latter was not raised above 41% by the use of a mixture of anil and 2 equivs. of aniline hydrochloride.

3-*Nitro*-6-*methylquinoline.*—(*a*) A solution of 2-nitro-2-formylethylidene-*p*-toluidine (10 g.) and *p*-toluidine hydrochloride (7·6 g.) in acetic acid (50 c.c.) was gently refluxed for 16 hours. After dilution with an equal volume of water, 3-*nitro*-6-*methylquinoline* rapidly separated (7 g., 77%, m. p. 183—184° after being washed with a little cold acetic acid); it crystallised from absolute or aqueous ethanol in long, almost colourless prismatic needles, m. p. 185—186° (Found: C, 64·1; H, 4·3; N, 14·8. $C_{10}H_8O_2N_2$ requires C, 63·8; H, 4·3; N, 14·9%). The cyclisation was also tried in a less concentrated acetic acid solution, but the yield was smaller (0·73 g. from 2 g. of Schiff base). In both cases the reaction was incomplete after 7 hours' refluxing. 3-Nitro-6-methylquinoline and its analogues are sparingly soluble in water and fairly readily so in hot 2N-hydrochloric acid, but on cooling the free bases again separate; a mixture of a 3-nitroquinoline and an arylamine can be readily separated in this way.

(*b*) A mixture of 2-nitro-2-formyl-*p*-toluidine (0·44 g.) and powdered anhydrous zinc chloride (0·88 g.) was heated from 180° to 230° (bath temp.) during 3 minutes, and kept at 230° for 5 minutes. The cold mass was digested with hot water (50 c.c.), and the residue extracted with warm 5N-hydrochloric acid. Basification of the filtrate gave 3-nitro-6-methylquinoline (70 mg., 17·5%), m. p. 184—185° alone and mixed with authentic material.

3-*Amino*-6-*methylquinoline.*—Stannous chloride (3·9 g.) was added in portions during 20 minutes to a stirred solution of 3-nitro-6-methylquinoline (1 g.) in 10N-hydrochloric acid (6 c.c.); the temperature, which initially was not allowed to exceed 45°, was finally raised to 60° for 10 minutes with vigorous stirring. The suspension was then cooled, diluted, and made alkaline with sodium hydroxide, and the product was taken successively into ether and warm 0·5N-hydrochloric acid (charcoal). Basification of the acid solution at 0° gave 3-*amino*-6-*methylquinoline* [crude yield (m. p. 100—104°), 100%], which separated slowly from aqueous ethanol in fine white needles, m. p. 106—107° (Found: C, 75·7; H, 6·3; N, 17·9. $C_{10}H_{10}N_2$ requires C, 75·9; H, 6·4; N, 17·7%). The base, which showed a magnificent blue fluorescence in aqueous solution at pH 6, could be readily diazotised and coupled with alkaline β-naphthol.

3 : 5-*Dinitro*-6-*methylquinoline.*—3-Nitro-6-methylquinoline (8 g.) was added during 20 minutes with stirring to a mixture of nitric acid (*d* 1·53) and 65% oleum (60 c.c., 5 : 2 v/v) at −10° to −5°. After a further 10 minutes the temperature was allowed to rise to 0°, the solution poured on ice, and the solid (8·2 g., 83%, m. p. 163—164°) collected and crystallised from aqueous acetic acid and finally alcohol, from which 3 : 5-*dinitro*-6-*methylquinoline* separated in broad yellow blades, m. p. 167—168° (Found: C, 52·0; H, 3·2; N, 18·0. $C_{10}H_7O_4N_3$ requires C, 51·5; H, 3·0; N, 18·0%).

3-*Nitro*-5-(or 7-)*methylquinoline.*—A solution of 2-nitro-2-formylethylidene-*m*-toluidine (0·5 g.) and *m*-toluidine hydrochloride (0·38 g.) in acetic acid (2·5 c.c.) was refluxed for 17 hours. Dilution with water gave almost pure 3-*nitro*-5-(or 7-)*methylquinoline* (55%), which formed long, almost colourless, soft needles, m. p. 155—157°, from alcohol (Found: C, 63·85; H, 4·6; N, 14·9. $C_{10}H_8O_2N_2$ requires C, 63·8; H, 4·3; N, 14·9%).

3-*Nitro*-8-*methylquinoline.*—An exactly similar experiment to the above, but with *o*-toluidine derivatives and 15 hours' refluxing, gave a dark red solution, which was basified in the cold with 2N-sodium hydroxide. The resultant tar and suspension were extracted with ether, and the oil (0·48 g.) obtained by evaporation of the washed and dried extract was dissolved in aqueous ammoniacal alcohol; 3-*nitro*-8-*methylquinoline* (30 mg., 6·5%) separated, and formed bundles of slightly discoloured prismatic needles, m. p. 122—123° (Found: C, 64·0; H, 4·9; N, 15·3. $C_{10}H_8O_2N_2$ requires C, 63·8; H, 4·3; N, 14·9%).

*Reactions of Schiff Bases with Salts of Various Arylamines.*—The variations described in the theoretical section of this paper were all carried out using 0·4—0·5 g. of Schiff base and 1 equiv. of arylamine salt in 2·5—3 c.c. of acetic acid (15—17 hours' refluxing). The products were isolated as already described, and reaction mother-liquors were examined in cases where the total product was not extracted initially. The product from 2-nitro-2-formylethylidene-*m*-toluidine and *p*-toluidine hydrochloride formed colourless needles, m. p. 132—134°, not changed by crystallisation from aqueous alcohol or dilute hydrochloric acid; chromatography in benzene, using a 10 cm. column of alumina, was also virtually without effect, almost the whole of the material being recovered as a single fraction, m. p. 135—137° (softening at 133°) [135—144° when mixed with 3-nitro-5-(or 7-)methylquinoline].

*Condensation of* 2-p-*Toluidinopent*-2-*en*-4-*one and* p-*Toluidine Hydrochloride.*—The base, m. p. 69—70° (Roberts and Turner, *loc. cit.*, give m. p. 68—69°) (0·5 g.), and *p*-toluidine hydrochloride (0·4 g.) were refluxed for 24 hours in acetic acid (1 c.c.). The solid which slowly separated during 48 hours was crystallised from water, giving colourless needles, m. p. 150—151° (0·3 g.), of a *product* which was unchanged by crystallisation from aqueous alcohol or dilute ammonia and had no obvious basic properties (Found: C, 72·0; H, 7·47; N, 9·55, 9·9. $C_{17}H_{20}O_2N_2$ requires C, 71·8; H, 7·1; N, 9·85%). In alcoholic solution in presence of zinc chloride the condensation proceeded differently, but no single product could be isolated.

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