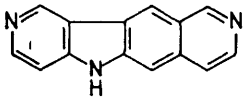
N-1 Substitution of 4-Arylamino-3-nitropyridines by a Heterocyclic Ring-opening Reaction

By **Claire Ducrocq, Emile Bisagni,* Christian Rivalle, and Joel Mispelter,** Laboratoire de Synthèse Organique de l'Institut Curie, Section de Biologie, Bâtiment 110, 15 rue Georges Clémenceau, 91405 Orsay, France

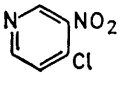
The normal substitution of 4-chloro-3-nitropyridine by primary aromatic amines is accompanied by the unexpected formation of 1-aryl-4-arylimino-3-nitropyridines. These products are formed *via* intermediate 4-arylamino-3-nitro-1-(3-nitro-4-pyridyl)pyridinium chlorides that are substituted by the primary amines by a mechanism involving addition–heterocyclic ring opening, closure, and elimination.

DURING our investigations on the synthesis of pyrido-[3′,4′:4,5]pyrrolo[2,3-*g*]isoquinolines (1) which have been found to be DNA intercalating agents and which displayed antitumour activity, we have prepared intermediate compounds by the substitution of 4-chloro-3-nitropyridine (2) with aniline, *p*-xylidine, and 3-cyano-2-methylaniline. In addition to the expected 4-arylamino-3-nitropyridines (3a—c), side products (4a—c) are also formed in each. Such derivatives have not been reported in previous studies of the reactions of 4-chloro-3-nitropyridine with various primary amines.[1,2] The formation of these side products implies that a secondary reaction is taking place involving opening and closing of the pyridine nucleus.

In order to investigate this side reaction we have examined the possible reactions of 4-chloro-3-nitropyridine with anilines and with other intermediate products formed in the reaction. The first reaction



(1)



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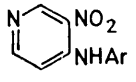
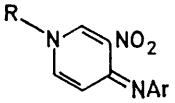


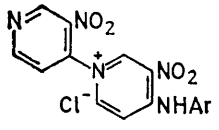
(3)

a; Ar=Ph
b; Ar=$C_6H_3Me_2$-2,5
c; Ar=C_6H_3Me-2,CN-3



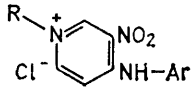
(4)

a; R=Ar=Ph
b; R=Ar=$C_6H_3Me_2$-2,5
c; R=Ar=C_6H_3Me-2,CN-3
d; R=C_6H_4OMe-*p*; Ar=Ph
e; R=Me; Ar=Ph
f; R=cyclohexyl; Ar=Ph
g; R=3-nitro-4-pyridyl; Ar=$C_6H_3Me_2$-2,5



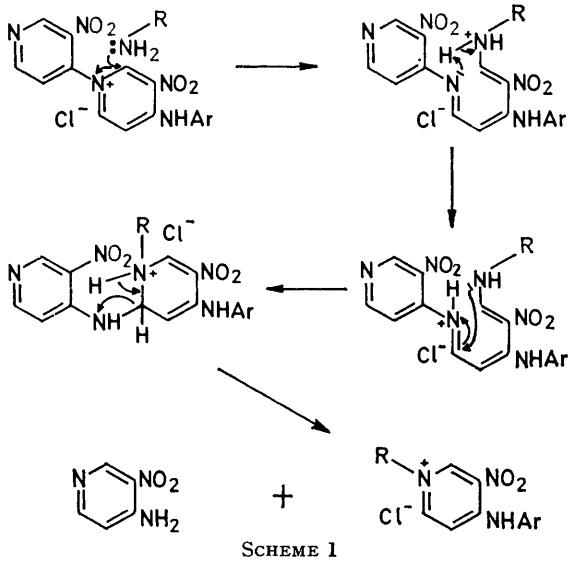
(5)

a; Ar=C_6H_5Ph
b; Ar=$C_6H_3Me_2$-2,5



(6)

observed is the normal substitution which leads to compounds (3). The isolated free bases (3) react with 4-chloro-3-nitropyridine (2) to yield quantitatively the 4-arylamino-3-nitro-*N*-(3-nitro-4-pyridyl)pyridinium chlorides (5), which react with various aromatic or aliphatic amines to give the 1-substituted 4-arylimino-3-nitro-1,4-dihydropyridines (4), *via* the hydrochloride intermediates (6).

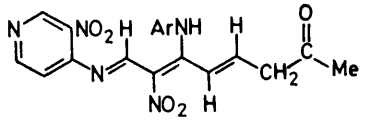


SCHEME 1

The opening of the pyridine nucleus with various *N*-(2,4-dinitrophenyl)pyridinium chlorides has already been described.[3-6] However, we could find no example where the leaving group was itself a pyridine derivative. Moreover, 3-nitropyridines have been reported to be inert with regard to 2,4-dinitrochlorobenzene.[6] The electron-donating effect of the 4-arylamino group in the intermediates (3) is probably sufficient to account for this apparent contradiction. Substitution at N-1 of the 4-chloro-3-nitro pyridines *via* the intermediates (5) which can be isolated can be interpreted by the mechanism in Scheme 1.

The ring opening could take place by a 1,2- or a 1,6-cleavage mechanism, and we believe it takes place by the former, since the 2,5-dimethyl compound (5b) reacts with acetone to give a new compound, elemental analyses and the i.r. spectrum of which are compatible with the isomeric (7) and (8). A referee suggested that structure (9) was also possible. Structure (8) is excluded by the n.m.r. spectrum in deuteriochloroform which shows two nonequivalent protons at δ 2.7 and 3.42 (*J* 18 Hz), two coupled vinyl protons at δ 6.36 and 5.26 (*J* 8.1 Hz), and

a third proton at δ 6.3 which shows three couplings: with each of the CH_2 protons (J 8.9 and 2.6 Hz) and with the proton at δ 6.36 (J 1 Hz). Although the non-equivalence of the CH_2 protons could be explained by structure (9), the small long-range coupling constant of 1 Hz could more easily be explained by structure (7) [H(4)–H(7) coupling]. Moreover, the formation of (9) is difficult to explain from the chemical point of view, whereas addition of water, opening of the pyridine 1,2 bond, and aldol condensation with acetone followed by



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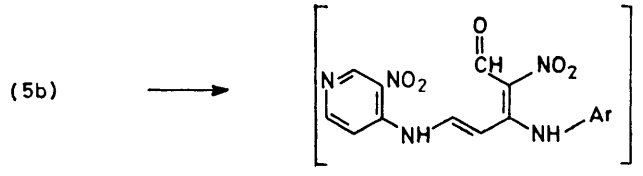

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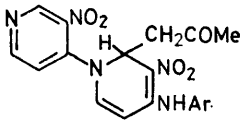

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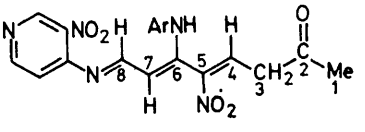

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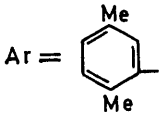

dehydration, would account for the formation of (7), *via* the intermediate (10). This interpretation is in agreement with the results reported by Tamura *et al.*[5] who obtained 5-(2,4-dinitroanilino)penta-2,4-dienal by opening of 2,4-dinitrophenylpyridinium chloride.

In conclusion, on the one hand during the reactions of 4-chloro-3-nitropyridine with arylamines to prepare (3), it is not possible to prevent completely the formation of the imines (4). It is only possible to limit the quantity produced by performing the reaction with an excess of the amine. On the other hand, the quaternary salts (5) can be obtained quantitatively, and these salts react with primary aromatic or aliphatic amines to yield 1-substituted 4-arylimino-3-nitro-1,4-dihydropyridines (4).

EXPERIMENTAL

M.p.s were determined with a Reichert hot-stage apparatus. I.r. spectra were obtained for KBr pellets with a Perkin-Elmer model 21 double-beam spectrometer. Unless otherwise stated, n.m.r. spectra were recorded with a Hitachi–Perkin-Elmer 60 MHz apparatus [solvent $(CD_3)_2SO$; Me_4Si as internal standard].

Preparation of 4-*Anilino*-3-*nitropyridine* (3a).—A solution of 4-chloro-3-nitropyridine (6.34 g, 40 mmol) and aniline (3.72 g, 40 mmol) in ethanol (30 ml) was left overnight at room temperature. Solvent was removed under reduced pressure, a solution of the residue in water was made alkaline, and the precipitate obtained was recrystallized (from ethanol) to give the *anilino-pyridine* (3a) as orange-yellow needles, m.p. 118 °C (5.6 g, 65%) (Found: C, 61.4; H, 4.2; N, 19.8. $C_{11}H_9N_3O_2$ requires C, 61.4; H, 4.2; N, 19.5%); ν(N–H) 3 360; ν(NO_2) 1 570 (*as*) and 1 315 (*s*) cm^{-1}; δ($CDCl_3$) 6.95 (d, $J_{5,6}$ 6 Hz, 5-H), 8.25 (6-H), 9.3 (2-H), and 9.7 (NH).

4-(2,5-*Dimethylanilino*)-3-*nitropyridine* (3b) *and* 1-(2,5-*Dimethylphenyl*)-4-(2,5-*dimethylphenylimino*)-3-*nitro*-1,4-*dihydropyridine* (4b).—A solution of 4-chloro-3-nitropyridine (4.75 g, 30 mmol) in commercial absolute alcohol (25 ml) and *p*-xylidine (3.63 g, 30 mmol) were mixed and left at room temperature overnight. A yellow compound, insoluble in ethanol was formed, which was filtered off, dried, and recrystallized from benzene, and identified as 4-(2,5-*dimethylphenylimino*)-3-*nitro*-1-(3-*nitro*-4-*pyridyl*)-1,4-*dihydropyridine* (4g) (30 mg, 0.26% with respect to *p*-xylidine), m.p. 220 °C (Found: C, 56.4; H, 4.5; N, 18.2. $C_{18}H_{15}N_5O_4,H_2O$ requires C, 56.4; H, 4.5; N, 18.3%); ν(C=N) 1 650 cm^{-1}; δ 2.15 and 2.3 (Me), 8.5 (d, $J_{2,6}$ 2 Hz, 2-H), 6.1 (5-H), and 7.25 (d, $J_{5,6}$ 8 Hz, 6-H).

The ethanolic solution was evaporated under reduced pressure, the residue was dissolved in water, and the pH adjusted to 8. Extraction with chloroform and evaporation of the extracts left a yellow oil which crystallized on addition of hexane. The solid obtained was treated with boiling cyclohexane (100 ml), and the insoluble fraction recrystallized from ethanol to afford the red *imino-nitro-compound* (4b), m.p. 201—207° (300 mg, 3%) (Found: C 72.6; H, 5.9; N, 12.0. $C_{21}H_{21}N_3O_2$ requires C, 72.6; H, 6.1; N, 12.1%); ν(C=N) 1 650; ν(NO_2) 1 570 (*as*) and 1 305 (*s*) cm^{-1}; δ 2.0 and 2.3 (Me), 8.5 (d, $J_{2,6}$ 2 Hz, 2-H), 6.1 (d, $J_{5,6}$ 8 Hz, 5-H), and 7.25 (6-H). The volume of the cyclohexane solution was reduced to 50 ml and the desired *nitro-compound* (3b) crystallized out, as yellow prisms, m.p. 65—66 °C (4 g, 55%) (Found: C, 64.2; H, 5.3; N, 17.3. $C_{13}H_{13}N_3O_2$ requires C, 64.2; H, 5.4; N, 17.3%); ν(N–H) 3 240; ν(NO_2) 1 505 (*as*) and 1 305 (*s*) cm^{-1}; δ($CDCl_3$): 2.1 and 2.3 (Me); other signals comparable to those of (3a).

4-(3-*Cyano*-2-*methylanilino*)-3-*nitropyridine* (3c) *and* 1-(3-*Cyano*-2-*methylphenyl*)-4-(3-*cyano*-2-*methylphenylimino*)-3-*nitro*-1,4-*dihydropyridine* (4c).—A solution of 3-cyano-2-methylaniline (2.6 g, 20 mmol) and 4-chloro-3-nitropyridine (3.1 g, 20 mmol) in ethanol (500 ml) was left overnight at room temperature. Solvent was then removed under reduced pressure, and the residue was taken up in water and extracted with chloroform. Evaporation of the organic phase left a residue which recrystallized from ethanol to afford the *cyano-compound* (3c) as yellow prisms, m.p. 158 °C (1.25 g, 25%) (Found: C, 61.4; H, 4.2; N, 21.8. $C_{13}H_{10}N_4O_2$ requires C, 61.4; H, 4.0; N, 22.0%); ν(N–H) 3 320; ν(C≡N) 2 220; ν(NO_2) 1 520 (*as*) and 1 360 (*s*) cm^{-1}; δ 2.4 (Me), 6.5 (d, $J_{5,6}$ 6 Hz, 5-H), 8.25 (6-H), 9.15 (2-H), and 9.95 (NH).

Treatment of the aqueous phase with 1M-sodium hydroxide yielded the *imino-compound* (4c) as red plates (from ethanol or xylene), m.p. 240 °C (1.4 g, 36%) (Found: C,

65.2; H, 4.6; N, 17.9. $C_{21}H_{15}N_5O_2,H_2O$ requires C, 65.1; H, 4.4; N, 18.1%); ν(C≡N) 2 240; ν(C=N) 1 665; ν(NO_2) 1 575 (*as*) and 1 315 (*s*) cm^{-1}; δ 2.25 and 2.45 (Me), 6.2 (d, $J_{5,6}$ 8 Hz, 5-H), 7.4 (d, $J_{6,2}$ 2 Hz, 6-H), and 8.7 (2-H).

The yield of compound (3c) is improved by increasing the amount of 3-cyano-2-methylaniline with respect to the chloro-pyridine, or by maintaining the reaction mixture for a longer time at a lower temperature, *e.g.* 6 °C for 72 h.

4-*Anilino*-3-*nitro*-1-(3-*nitro*-4-*pyridyl*)*pyridinium Chloride* (5a).—A solution of 4-anilino-3-nitropyridine (3a) (5.6 g, 26 mmol) and 4-chloro-3-nitropyridine (4.12 g, 26 mmol) in dry acetonitrile (100 ml) was left at room temperature for 30 days. Solvent was then removed under reduced pressure, and a solution of the residue in acetone was dried and treated with acetone to give the *pyridinium chloride* (5a) as beige crystals, m.p. 177—185 °C (9.5 g, 98%) (Found: C, 51.2; H, 3.3; Cl, 9.3; N, 18.7. $C_{16}H_{12}ClN_5O_4$ requires C, 51.45; H, 3.2; Cl, 9.5; N, 18.7%); ν(N–H) 2 700—3 100; ν(NO_2) 1 560 (*as*) and 1 350 (*s*) cm^{-1}; δ (D_2O): 7.4 (d, $J_{5,6}$ 8 Hz, 5-H), 8.05 (d, $J_{5',6'}$ 5 Hz, 5′-H), 8.35 (d, $J_{6,2}$ 2 Hz, 6-H), 9.2 (6′-H), 9.55 (2-H), and 9.75 (2-H) (primed numbers refer to the pyridyl ring).

4-(2,5-*Dimethylanilino*)-3-*nitro*-1-(3-*nitro*-4-*pyridyl*)-*pyridinium Chloride* (5b).—A similar procedure as for the preparation of compound (5a), but with 2,5-dimethylaniline replacing aniline, gave the *dimethyl compound* (5b) as beige crystals, m.p. 168—170 °C (Found: C, 51.7; H, 3.9; Cl, 8.04; N, 16.9. $C_{18}H_{16}ClN_5O_4,H_2O$ requires C, 51.45; H, 4.3; Cl, 8.4; N, 16.7%), the n.m.r. spectrum (D_2O) of which is comparable to that of compound (5a).

1-*Phenyl*-4-(*phenylimino*)-3-*nitro*-1,4-*dihydropyridine* (4a).—To a solution of the chloride (5a) (1.12 g, 3 mmol) in the minimum volume of ethanol (300 ml) was added aniline (300 mg, 3 mmol). The solution immediately turned red, and after a few minutes solvent was removed under reduced pressure. The residue was dissolved in water and the solution made alkaline. Extraction with chloroform, followed by evaporation of the dried chloroform extracts, gave the *imino-compound* (4a) as orange-red plates, m.p. 208—210 °C (from ethanol) (0.7 g, 80%) (Found: C, 70.1; H, 4.6; N, 14.31. $C_{17}H_{13}N_3O_2$ requires C, 70.1; H, 4.5; N, 14.4%) ν (C=N)1 670; ν(NO_2) 1 580 (*as*) and 1 310 (*s*) cm^{-1}; δ 6.4 (d, $J_{5,6}$ 8 Hz, 5-H), 7.5 (d, $J_{6,2}$ 2 Hz, 6-H), and 8.7 (2-H).

1-(4-*Methoxyphenyl*)-3-*nitro*-4-*phenylimino*-1,4-*dihydropyridine* (4d).—The foregoing technique, with *p*-anisidine instead of aniline, gave the expected *methoxy-compound* (4d) as red plates, m.p. 157—158 °C (81%) (Found: C, 67.3; H, 4.7; N, 12.8. $C_{18}H_{15}N_2O_3$ requires C, 67.3; H, 4.7; N, 13.1%), ν(C=N) 1 665; ν(NO_2) 1 520 (*as*) and 1 300 (*s*) cm^{-1}; δ($CDCl_3$) 3.9 (Me), and other signals similar to those of (4a).

1-*Methyl*-3-*nitro*-4-*phenylimino*-1,4-*dihydropyridine* (4e).—A similar technique as for (4a) and (4d), using methylamine, afforded the *methyl compound* (4e) as red crystals (from methanol), m.p. 218 °C (58%) (Found: C, 62.9; H, 4.9; N, 18.2. $C_{12}H_{11}N_3O_2$ requires C, 62.9; H, 4.8; N, 18.4%); δ 3.6 (Me); aromatic resonances analogous to those of the preceding compound (4d).

1-*Cyclohexyl*-3-*nitro*-4-*phenylimino*-1,4-*dihydropyridine* (4f).—The foregoing technique with cyclohexylamine gave the *cyclohexyl compound* (4f) as red plates (from ethanol), m.p. 196—198 °C (67%) (Found: C, 68.4; H, 6.6; N, 14.1. $C_{17}H_{19}N_3O_2$ requires C, 68.7; H, 6.4; N, 14.1%); δ 1—2 (cyclohexyl protons); other signals comparable to those of the preceding compounds.

6-(2,5-*Dimethylanilino*)-5-*nitro*-8-(3-*nitro*-4-*pyridylimino*)-*octa*-4,6-*dien*-2-*one* (7).—The pyridinium chloride (5b) (1.2 g, 3 mmol) was dissolved in acetone (2 l) under reflux; evaporation under reduced pressure and recrystallization of the residue from ethanol gave the *ketone* (7) as red needles, m.p. 149 °C (Found: C, 57.6; H, 5.0; N, 15.8. $C_{21}H_{23}N_5O_6$ requires C, 57.1; H, 5.25; N, 15.9%); ν(N–H) 3 100—2 850; ν(C=O) 1 710; ν(C=C) 1 625; ν(NO_2) 1 550 (*as*) and 1 360 (*s*); δ(O–H) 1 340 and 1 250; ν(C–O) 1 105 cm^{-1}; n.m.r. spectrum (XL 100 apparatus) as described in the Discussion section.

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REFERENCES

[1] J. Delarge and C. L. Lapiere, *Pharm. Acta Helv.*, 1975, **50**, 188.

[2] R. R. Bishop, E. A. S. Cavell, and N. B. Chapman, *J. Chem. Soc.*, 1952, 437.

[3] A. F. Vompe, N. F. Turitsyna, and I. I. Levkoev, *Doklady Akad. Nauk. S.S.S.R.*, 1949, **65**, 839 (*Chem. Abs.*, 1949, **43**, 6626).

[4] A. F. Vompe and N. F. Turitsyna, *Zhur. obshchei Khim.*, 1957, **27**, 3282 (*Chem. Abs.*, 1958, **52**, 9112d).

[5] Y. Tamura, N. Tsujimoto, and M. Mano, *Chem. Pharm. Bull.* (Japan), 1971, **19**, 130; Y. Tamura, N. Tsujimoto, and M. Uchimura, *ibid.*, p. 143.

[6] Y. Tamura, Y. Miki, T. Honda, and M. Ikeda, *J. Heterocyclic Chem.*, 1972, **9**, 865.