Polycondensed Nitrogen Heterocycles. Part 19 [1]. Pyrrolo[1,2-*f*]phenanthridines by Pschorr-Type Cyclization Brought about by Hypophosphorous Acid

Gaetano Dattolo, Girolamo Cirrincione, Anna Maria Almerico, Enrico Aiello* and Isabella D'Asdia

Istituto di Chimica Farmaceutica e Tossicologica dell'Università, Via Archirafi 32, 90123 Palermo, Italy

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Pyrrolo[1,2-*f*]phenanthridines were prepared in good yields by the diazotization in acetic acid of the amines **1a,b** and subsequent treatment with hypophosphorous acid. The necessity for hypophosphorous acid in the reaction was demonstrated.

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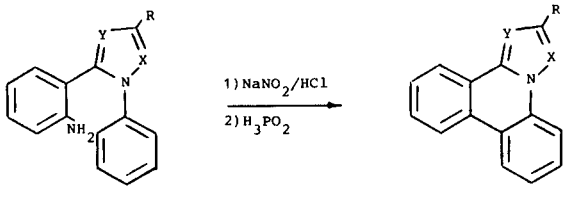
Pyrrolophenanthridine derivative, obtained from Amaryllidaceae, have shown anticancer activity [2-5], but virtually nothing is known about the pharmacological properties of pyrrolo[1,2-*f*]phenanthridines, since the reports on this ring system are limited only to the synthesis. Routes leading to the title compounds reported so far have involved the annelation of a pyrrole ring to the phenanthridine nucleus [6]. In connection with our studies on polycondensed nitrogen heterocycles with potential biological activity, we undertook a different approach to pyrrolo-[1,2-*f*]phenanthridines. Our projected synthesis involved the diazotization of aminophenylpyrroles of type **1** and subsequent cyclization by action of hypophosphorous acid. The same reaction sequence had successfully led to pyrazolo- [7] and triazolophenanthridines [8] **5** and **6** from the corresponding amines **2** and **3**.

Scheme 1

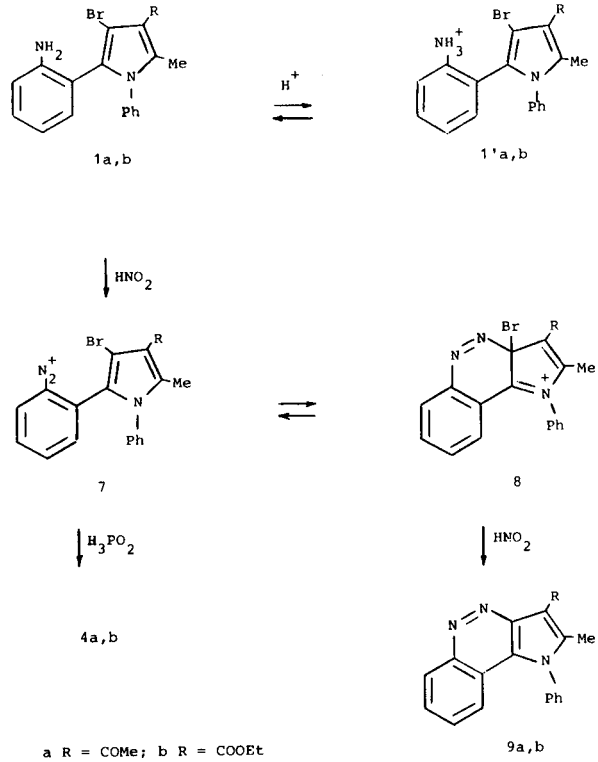


1 a X = C-Me; Y = C-Br; R = COMe
b X = C-Me; Y = C-Br; R = COOEt
2 X = N; Y = C-Br; R = Me
3 a X = Y = N; R = COMe
b X = Y = N; R = COOEt
c X = Y = N; R = Ph

4
5
6

In fact it is quite unusual to use hypophosphorous acid in the Pschorr reaction, as it is generally acknowledged to be a good dediazoniating agent [9], and the Pschorr stoichiometry, assuming dinitrogen formation, does not require reduction. The starting compounds **1a,b** were prepared in good yield by reduction of the corresponding nitro-derivatives with titanium trichloride in acetic acid. The first attempt to prepare pyrrolo-phenanthridine was carried out using the same experimental conditions reported in the synthesis of the ring systems **5** and **6**, *i.e.* diazotising the amines **1a,b** in 6*N* hydrochloric acid with sodium nitrite in seven fold excess. Unfortunately, under these experimental conditions we were able to isolate only pyrrolocinnolines **9a,b** in 70-80% yields. In this case the excess of nitrous acid may be responsible for debromination of the intermediate **8** (Scheme 2). Therefore we repeated the reaction with stoichiometric amount of sodium nitrite. Pyrrolo[1,2-*f*]phenanthridines **4a,b** were isolated but in low yields (5-13%), together with pyrrolocinnolines **9a,b** (40%) and unreacted starting material (41-45%).

Scheme 2



These findings suggested that it was necessary to involve the nitrite as much as possible in the diazotization reaction, to limit its reducing action that gives rise to pyrrolo-cinnolines. Then to accelerate the diazotization it was necessary to shift the equilibrium **1** ⇌ **1′** to the free amino derivative and acetic acid as medium was chosen. In this reaction, although we still found some pyrrolocinnolines, we indeed obtained the expected pyrrolo[1,2-*f*]-phenanthridines **4a,b** in good yield (55-60%).

At this stage it seemed interesting to us to check whether the hypophosphorous acid was necessary for the ring closure. Therefore the diazotization of the amines **1a,b** was carried out in acetic acid without the addition of hypophosphorous acid. In this case only traces of pyrrolophenanthridines were obtained.

These results demonstrate that hypophosphorous acid can be used to bring about a Pschorr reaction and that hypophosphite dediazoniations should not be tried if Pschorr cyclisation are possible. A closer look at the literature revealed further examples in which hypophosphite when used for the dediazoniation resulted in Pschorr-type cyclisation [11].

The pyrrolophenanthridines **4a,b** were screened for inhibitory activity against mouse P-388 lymphocytic leukemia. Compound **4b** was inactive whilst **4a** showed to be toxic at 60 mg/Kg. These data are the results of screening performed under the auspices of the Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, Mariland.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting-point apparatus. The ir spectra were determined for nujol mulls with a Perkin-Elmer 299 spectrophotometer; ^1H and ^{13}C nmr specra were obtained with a Varian FT-80A pulsed Fourier transform spectrometer (TMS as internal reference); all ^{13}C nmr spectral assignments were confirmed by off-resonance irradiation experiments (SFORD); mass spectra were run on a JEOL JMS-01 SG-2 double focusing mass spectrometer operating with an electron beam energy of 75 eV and 10 KV accelerating voltage. All the known compounds were identified by comparison of their melting points and ir spectra with those of authentic samples. The chromatography was performed on silica gel columns.

Preparation of the 2-(2-Aminophenyl)pyrroles (**1a,b**).

4-Substituted 3-bromo-5-methyl-2-(2-nitrophenyl)pyrroles [12] (15 mmoles) were dissolved in acetic acid (120 ml). Aqueous titanium trichloride (15%, 88 ml) was added. The solution was stirred overnight at room temperature. It was then poured into cooled aqueous sodium hydroxide (20%, 700 ml). The reaction mixture was extracted with dichloromethane-methanol (95:5). The organic layer was dried over sodium sulphate and evaporated under reduced pressure. The residue was recrystallized from ethanol to give compounds **1a,b** (80%). Compound **1a** (R = COMe), the mp and ir were identical to those reported [13]. Compound **1b** (R = CO_2Et), mp 148°; ir: 3460 and 3360 (NH_2), 1690 cm^{-1} (CO); ^1H nmr (deuteriochloroform): δ 1.37 (3H, t, CH_2CH_3), 2.35 (3H, s, CH_3), 3.71 (2H, s, exchangeable NH_2), 4.33 (2H, q, CH_2), 6.47-7.28 (9H, m, C_6H_5 and C_6H_4); ms: m/e 398, 400 (M^+).

Anal. Calcd. for $C_{20}H_{19}BrN_2O_2$: C, 60.2; H, 4.8; N, 7.0. Found: C, 59.9; H, 4.9; N, 6.9.

Diazotization in Hydrochloric Acid of **1a,b** with Sodium Nitrite.

(a) Ratio (amine:nitrite)1:8.

Compounds **1a,b** (5 mmoles) in hydrochloric acid (6*N*, 44 ml), were diazotized with aqueous sodium nitrite (10%, 28 ml) at 0-5°. After 30 minutes hypophosphorous acid (50%, 11 ml) was added and the reactants were allowed to stir at rt overnight. The reaction mixture was neutralized with sodium hydroxide (3*N*). The crude product was collected and chromatographed (eluant dicloromethane-ethyl acetate 8:2) to give pyrrolo-[3,2-*c*]cinnoline derivatives [14] **9a** (70%) and **9b** (80%).

(b) Ratio (amine:nitrile) 1:1.

Compounds **1a,b** (5 mmoles) were diazotized with aqueous sodium nitrite (10%, 3.5 ml) and the reaction was carried out and worked up as above. The crude product was chromatographed (eluant dichloromethane) to give 2-acetyl and 2-ethoxycarbonyl-1-bromo-3-methylpyrrole-[1,2-*f*]phenanthridines **4a,b**. Compound **4a** (R = COMe) (5%), mp 131° (from ethanol); ir: 1660 cm^{-1} (CO); ^1H nmr (deuteriochloroform): δ 2.75 (3H, s, CH_3), 2.96 (3H, s, CH_3), 7.25-9.28 (8H, m, Ar-H); ^{13}C nmr (deuteriochloroform): δ 17.38 (q), 32.35 (q), 90.80 (s), 118.64 (d), 118.88 (s), 122.33 (d), 123.32 (d), 124.14 (d), 124.38 (s), 125.19 (d), 126.28 (s), 126.42 (s), 126.77 (s), 126.89 (d), 127.59 (d), 128.00 (d), 130.58 (s), 133.79 (s), 198.03 (s); ms: m/e 351, 353 (M^+).

Anal. Calcd. for $C_{19}H_{14}BrNO$: C, 64.8; H, 4.0; N, 4.0. Found: C, 64.9; H, 3.8; N, 3.9.

Compound **4b** (R = CO_2Et) (13%) had mp 144° (from ethanol); ir: 1700 cm^{-1} (CO); ^1H nmr (deuteriodimethylsulfoxide): δ 1.41 (3H, t, CH_2CH_3), 3.0 (3H, s, CH_3), 4.39 (2H, q, CH_2), 7.47-9.24 (8H, m, Ar-H); ^{13}C nmr (deuteriodimethylsulfoxide): δ 14.15 (q), 16.73 (q), 60.24 (t), 91.29 (s), 117.77 (s), 118.71 (d), 122.24 (d), 122.88 (d), 123.11 (s), 123.93 (s), 124.23 (d), 124.94 (s), 125.46 (d), 125.64 (s), 127.11 (d), 127.99 (d), 128.11 (d), 131.86 (s), 132.74 (s), 163.62 (s); ms: m/e 381, 383 (M^+).

Anal. Calcd. for $C_{20}H_{16}BrNO_2$: C, 62.8; H, 4.2; N, 3.7. Found: C, 62.6; H, 4.0; N, 3.6.

Further elution with dichloromethane-ethyl acetate (8:2) gave unreacted starting material **1a** (41%) and **1b** (45%) and pyrrolo[3,2-*c*]cinnolines **9a,b** (40%).

Diazotization in Acetic Acid of **1a,b** with Sodium Nitrite.

Ratio (amine:nitrite) 1:1.

To compounds **1a,b** (5 mmoles) dissolved in the minimum volume of acetone, acetic acid (25 ml) was added. The mixture was cooled at 0-5° and diazotized with aqueous sodium nitrite (10%, 3.5 ml). The reaction was carried out and worked up as above. Chromatography of the crude product gave compounds **4a** (55%) and **4b** (60%); **1a** (9%) and **1b** (25%); **9a** (12%) and **9b** (10%).

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