POLYCONDENSED NITROGEN HETEROCYCLES. PART 20.[1] REACTIVITY OF DIAZOTIZED 1-(2-AMINOPHENYL)-PYRROLES. PYRROLO[1,2-f]PHENANTHRIDINES

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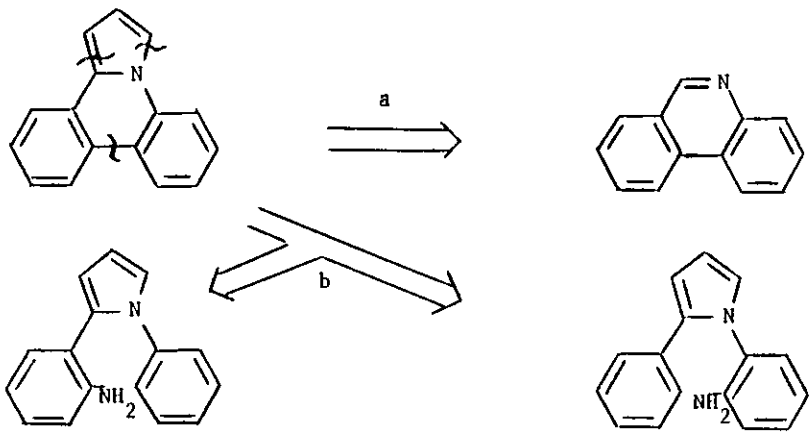
Abstract- Compounds (2) were diazotized under several conditions to prepare pyrrolo[1,2-f]phenanthridines (5). However, together with the Pschorr type cyclization, decomposition and intermolecular coupling reactions were observed.

To synthetize the pyrrolo[1,2-f]phenanthridine ring system, structurally related to pseudolicorine which have shown anticancer activity,[2-5] two possible disconnections could be considered.

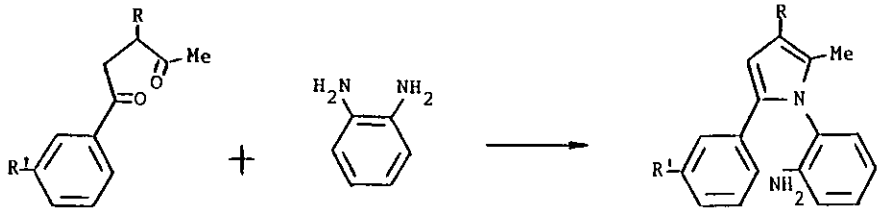


(1) (2)

The disconnection a, involving the annelation of a phenanthridine nucleus with a pyrrole ring, was the only one reported.[6,7] The strategy b could be achieved by using either the aminophenylpyrrole (1) or (2) as starting material.
We recently reported the synthesis of pyrrolo[1,2-f]phenanthridine derivatives by diazotization in acetic acid of the amino derivatives of type (1) followed by Pschorr type cyclization brought about by hypophosphorous acid.[1]

Despite the satisfactory results obtained, we started the synthesis of pyrrolo-phenanthridine from compound (2) to get derivatives functionalized at the phenanthridine moiety.

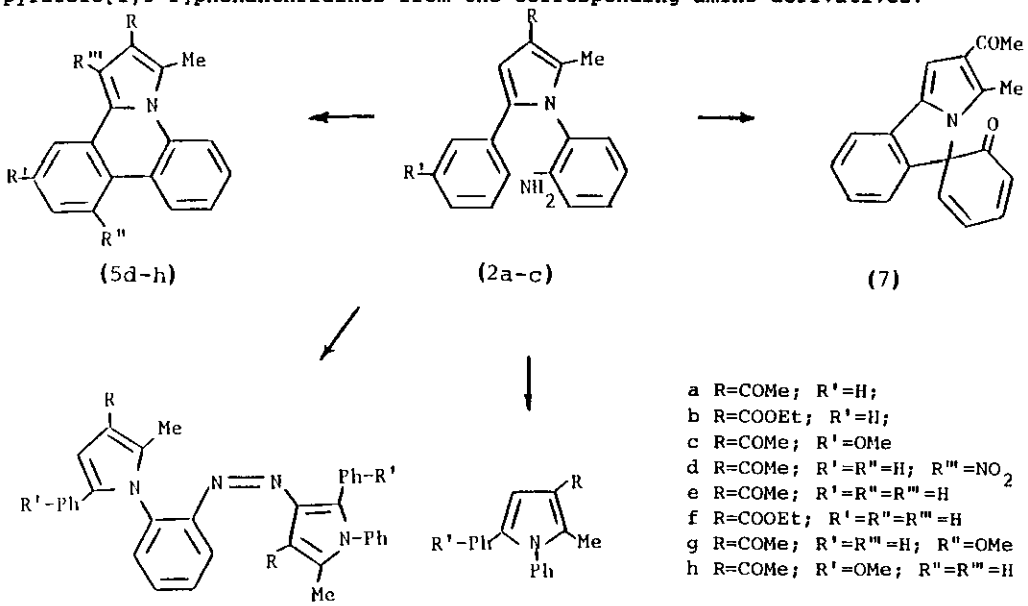
The 1-(2-aminophenyl)-pyrroles (2) were prepared in good yields by reaction of 1,2-phenylendiamine with the suitable 1,4-diketones (3a-c).



(3a-c) (2a-c)

Compounds (2a,b) diazotized in acetic acid as reported previously[1] led only to the azo derivatives (4a,b) because of the high reactivity of the 3 position of the pyrrole ring.

Therefore hydrochloric acid was chosen as medium so that the protonation of the pyrrole could reduce the formation of the azo derivatives (4).The diazotization of the amine (2a) was carried out using the procedure which successfully led to pyrazolo[1,5-f]phenanthridines from the corresponding amino derivatives.[8,9]



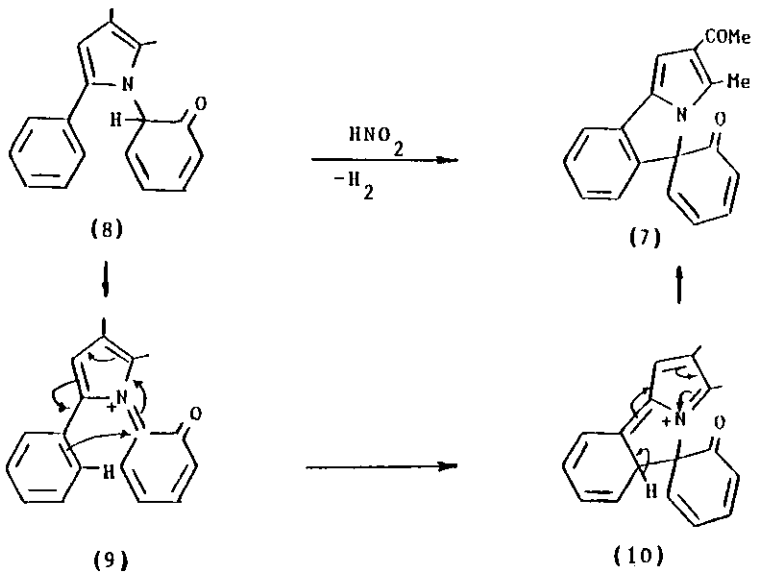
(5d-h) (2a-c) (7)

(4a-c) (6a-c)

a R=COMe; R'=H;
b R=COOEt; R'=H;
c R=COMe; R'=OMe
d R=COMe; R'=R"=H; R"'=NO_2
e R=COMe; R'=R"=R"'=H
f R=COOEt; R'=R"=R"'=H
g R=COMe; R'=R"'=H; R"=OMe
h R=COMe; R'=OMe; R"=R"'=H

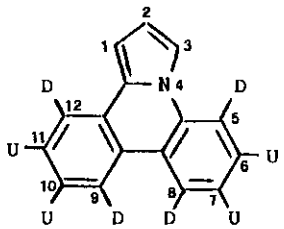
While the yield of azo derivative (4) was actually limited, the large excess of sodium nitrite gave rise to a very complex reaction mixture from which it was

possible to isolate also compounds (6), (7) and a little amount of pyrrolophenanthridine (5d) nitrated in the 1 position (yield 8%). To the major product of the reaction (28%) was assigned the spiro-type structure (7) on the basis of elemental analysis (in agreement with $C_{19}H_{15}NO_2$), ms (M^+=289), as well as the spectroscopic evidence. The ir spectrum showed two strong absorption bands at 1700 and 1650 cm^{-1} due to the cyclic ketone and to the acetyl respectively. The ^1H nmr spectrum, besides the substituent signals and pyrrole CH, showed two separate multiplets for four protons each attributable to the ring protons; the ^{13}C nmr spectrum exhibited, together with the methyl signals, nine doublets, six singlets for the ring C atoms and two downfield singlets at 197.9 and 202.8 ppm due to the acetyl and the cyclic ketone respectively. The formation of (7) can be explained assuming that the decomposition of the diazonium salt gave rise to the hydroxy derivative (8) which, because of the excess of nitrite, was oxidized to the final structure probably through the mechanism shown below.



To avoid the problems due to the excess of nitrite, the diazotization of the amines (2a,b) was carried out in hydrochloric acid with equimolecular amount of nitrite. In these experimental conditions, compounds (4), (5) and (6) were obtained. The dediazoniation and subsequent Pschorr type closure gave rise indeed to pyrrolo[1,2-f]phenanthridines (5e,f) (yield 8-11 %) but at the same time a simple loss of nitrogen led to pyrroles (6), suggesting that the phenyl in the 2 position is not sufficiently activated to the cyclization reaction. Therefore we repeated the diazotization using as starting compound the amino

derivative (2c) in which the benzene ring in the 2 position was activated with a methoxy group in the opportune position. In this case compounds (4c), (5g), (5h) and (6c) were isolated in similar yields to those obtained in the preceding attempt. The structure of (5g) and (5h) were assigned on the basis of the ^1H nmr spectrum: in fact compounds of type (5) unsubstituted at the phenanthridine moiety show two different sets of signals for four protons each as shown in the figure.[10]



U = Upfield; D = Downfield

The introdution of a methoxy group in the 9 or 11 position modifies in different way the pattern of the signals since it replaces a downfield proton in the case of (5g) and an upfield proton in the case of (5h). Moreover the across-space anisotropic effect of the methoxy group upon a close proton[11] causes a further downfield shift of the 8-H in the structure (5g).

In conclusion these findings suggest that the electronic effects do not influence this type of ring closure which occurs by a radical pathway.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary apparatus; ir spectra were determined in bromoform with a Perkin-Elmer 299 spectrophotometer; nmr spectra were obtained with a Varian FT-80 spectrometer (TMS as internal reference); mass spectra were obtained with a JEOL JMS-01 SG-2 double focusing mass spectrometer operating with an electron beam energy of 75 eV and 10 Kv accelerating voltage.

General method for the preparation of 1-(2-aminophenyl)-5-methyl-2-(3-R'-phenyl)-4-R-pyrroles (2a-c).

The diketones (3a)[12], (3b)[13], (3c)[14] (20 mmoles), 1,2-phenylendiamine (20 mmoles) and acetic acid (100 ml) was refluxed for 20 min. After cooling, the resultant solution was poured onto crushed ice. The solid precipitate was filtered off, air dried and in the case of (2a) was recrystallized; in the case of (2b,c) it was purified by chromatography (eluant; dichloromethane).

Compound (2a) (R'=H, R=COMe) was recrystallized from benzene, (yield 51%), mp 87°C; ir: 3450 and 3350 (NH_2), 1650 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.25 (3H,s,CH_3), 2.42 (3H,s,CH_3), 4.98 (2H,s,exchangeable NH_2), 6.77-7.19 (10H,m, ArH); ms M^+ 290 m/z. Anal. Calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.77; H, 6.25; N, 9.49.

Compound (2b) (R'=H, R=COOEt) was recrystallized from benzene, (yield 63%), mp 108°C (lit.[15] mp 109°C); ir: 3450 and 3360 (NH_2), 1685 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.40 (3H,t,CH_3), 2.36 (3H,s,CH_3), 3.60 (2H,s,exchangeable NH_2), 4.40 (2H,q, CH_2), 6.76-7.35 (10H,m,ArH); ms M^+ 320 m/z.

Compound (2c) (R'=OMe, R=COMe) was recrystallized from benzene, (yield 65%), mp 101°C; ir: 3430 and 3330 (NH_2), 1650 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ: 2.40 (3H,s, CH_3), 2.50 (3H,s,CH_3), 3.60 (5H,s,CH_3 and exchangeable NH_2), 6.75-7.40 (9H,m, ArH); ms M^+ 320 m/z. Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 75.11; H, 6.43; N, 8.71.

Diazotization in acetic acid of compounds (2a,b)

To compounds (2a,b) (5 mmoles) dissolved in the minimum volume of acetone, acetic acid (25 ml) was added. The mixture was cooled at 0-5°C and diazotized with 10% aqueous sodium nitrite (3.5 ml). After 0.5 h 50% hypophosphorous acid (11 ml) was added and the reactants were allowed to stir at r.t. overnight. The reaction mixture was neutralized with 3N sodium hydroxide. The crude product was collected and recrystallized from ethanol to give 3-{2-[4-R-5-methyl-2-(3-R'-phenyl)-pyrrole-1-yl]-phenyl-1-azo}-4-R-5-methyl-2-(3-R'-phenyl)-1-phenyl-pyrroles (4a,b).

Compound (4a) (R=COMe, R'=H): (yield 85%), mp 235°C; ir: 1680 (CO), 1650 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 1.80 (3H,s,CH_3), 2.20 (3H,s,CH_3), 2.71 (3H,s,CH_3), 2.97 (3H,s,CH_3), 6.89-9.15 (20H,m,ArH); ms M^+ 576 m/z. Anal. Calcd. for $C_{38}H_{32}N_4O_2$: C, 79.14; H, 5.59; N, 9.72. Found: C, 78.96; H, 5.40; N, 9.57.

Compound (4b) (R=COOEt, R'=H): (yield 85%), mp 195°C; ir: 1720 (CO), 1700 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 1.00 (3H,t,CH_3), 1.28 (3H,t,CH_3), 2.22 (3H,s,CH_3), 2.82 (3H,s,CH_3), 3.81 (2H,q,CH_2), 4.21 (2H,q,CH_2), 6.67-9.02 (20H,m,ArH); ms M^+ 636 m/z. Anal. Calcd. for $C_{40}H_{36}N_4O_4$: C, 74.45; H, 5.70; N, 8.80. Found: C, 75.19; H, 5.46; N,8.69.

Diazotization in hydrochloric acid of compound (2a) with sodium nitrite with ratio of amine to nitrite (1:8)

Compound (2a) (5 mmoles) in 6N hydrochloric acid (44 ml), was diazotized with 10% aqueous sodium nitrite (28 ml) at 0-5°C. After 0.5 h 50% hypophosphorous acid (11 ml) was added and the reactants were alloved to stir at r.t. overnight. The reaction mixture was neutralized with 3N sodium hydroxide. The crude product was collected and chromatographed. Elution with dichloromethane gave at first 2-acetyl-3-methyl-1-nitropyrrolo[1,2-f]phenanthridine (5d),

(yield 8%), mp 160°C (from ethanol); ir: 1680 (CO), 1330 (NO_2) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.94 (3H,s, CH_3), 3.27 (3H,s,CH_3), 7.55-7.75 (4H,m,H_6,H_7,H_{10},H_{11}) 8.11-8.75 (4H,m,H_5,H_8,H_9, H_{12}); ms M^+ 318 m/z. Anal. Calcd. for $C_{19}H_{14}N_2O_3$: C, 71.69; H, 4.43; N, 8.80. Found: C, 71.50; H, 4.49; N, 8.82.

The second product to be eluted was 3-acetyl-1,5-diphenyl-2-methylpyrrole (6a), (yield 18%), mp 100°C (from ethanol) (lit.[12] mp 101°C); ir: 1650 (CO) cm^{-1}, ^1H nmr (DMSO-d_6) δ: 2.30 (3H,s,CH_3), 2.42 (3H,s,CH_3), 6.88 (1H,s,CH), 7.00-7.50 (10H,m,ArH); ms M^+ 275 m/z.

The third product to be eluted was spiro{2-acetyl-3-methylpyrrolo[1,2-a]isoindole-5,2'-cyclohexandien-1'-one} (7), (yield 28%), mp 150°C (from ethanol); ir: 1700 (CO), 1650 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.47 (3H,s,CH_3), 2.66 (3H,s, CH_3),7.71-8.04 (4H,m,ArH), 8.47 (1H,s,CH), 8.66-8.98 (4H,m,ArH), ^{13}C nmr (DMSO-d_6) δ: 26.95 (q), 31.41 (q), 122.70 (2d), 123.58 (s), 124.52 (s), 125.88 (d), 128.05 (d), 128.22 (d), 129.05 (d), 129.28 (d), 131.45 (d), 132.22 (s), 133.51 (d), 142.25 (s), 147.36 (s), 151.65 (s), 197.91 (s), 202.84 (s); ms M^+ 289 m/z. Anal. Calcd. for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.82; H, 4.98; N, 4.70.

Further elution with dichloromethane:ethyl acetate (9:1) gave (4a) (yield 9%).

Diazotization in hydrochloric acid of compounds (2a-c) with sodium nitrite with ratio of amine to nitrite (1:1)

Compounds (2a-c) (5 mmoles) were diazotized with aqueous sodium nitrite (3.5 ml) and the reaction was carried out and worked up as above. The crude product was collected and chromatographed.

In the case of (2a) elution with dichloromathane gave at first 2-acetyl-3-methylpyrrolo[1,2-f]phenanthridine (5e), (yield 11%), mp 146°C (from ethanol); ir: 1660 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.55 (3H,s,CH_3), 3.15 (3H,s,CH_3), 7.43-7.61 (4H,m,H_6,H_7,H_{10},H_{11}), 7.69 (1H,s,H_1), 8.34-8.80 (4H,m,H_5,H_8,H_9,H_{12}); ms M^+ 273 m/z. Anal. Calcd. for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.13. Found: C, 83.50; H, 5.47; N, 4.96.

The second product to be eluted was compound (6a) (yield 5%). The third product to be eluted was unreacted starting compound (2a) (yield 21%). Further elution with dichloromethane:ethyl acetate (9:1) gave the azo compound (4a) (yield 25%). In the case of (2b), elution with dichloromethane gave at first 2-carbethoxy-3-methylpyrrolo[1,2-f]phenanthridine (5f), (yield 8%), mp 138°C (from ethanol); ir: 1700 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 1.35 (3H,t,CH_3), 3.17

(3H,s,CH_3), 4.30 (2H,q,CH_2), 7.44 (1H,s,H_1), 7.49-7.84 (4H,m,H_6,H_7,H_{10},H_{11}), 8.09-8.74 (4H,m,H_5,H_8,H_9,H_{12}); ms M^+ 303 m/z. Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62. Found: C, 79.92; H, 5.72; N, 4.56.

The second product to be eluted was 3-carbethoxy-1,5-diphenyl-2-methylpyrrole (6b), (yield 5%), mp 99°C (from ethanol) (lit.[16] mp 100°C); ir: 1690 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 1.29 (3H,t,CH_3), 2.32 (3H,s,CH_3), 4.24 (2H,q,CH_2), 6.70 (1H,s,CH), 7.05-7.49 (10H,m,ArH); ms M^+ 305 m/z.

The third product to be eluted was unreacted starting material (2b) (yield 23%). Further elution with dichloromethane:ethyl acetate (9:1) gave the azo compound (4b) (yield 42%).

In the case of (2c) elution with dichloromethane gave 2-acetyl-3-methyl-9-methoxypyrrolo[1,2-f]phenanthridine (5g), (yield 3%), mp 150°C (from ethanol); ir: 1665 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.54 (3H,s,CH_3), 3.10 (3H,s,CH_3), 4.03 (3H,s,CH_3), 7.04 (1H,dd($J_{10,11}$=7.2 Hz,$J_{10,12}$=2.4 Hz),H_{10}), 7.26-7.58 (3H,m,H_6, H_7,H_{11}), 7.54 (1H,s,H_1), 7.76 (1H,dd($J_{12,11}$=7.2 Hz,$J_{12,10}$=2.4 Hz),H_{12}), 8.22 (1H,dd($J_{5,6}$=9.6 Hz,$J_{5,7}$=2.4 Hz),H_5), 9.24 (1H,dd($J_{8,7}$=9.6 Hz,$J_{8,6}$=2.4 Hz),H_8); ms M^+ 303 m/z. Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62. Found: C, 79.47; H,5.43; N, 4.58.

The second product to be eluted was 2-acetyl-3-methyl-11-methoxypyrrolo[1,2-f]-phenanthridine (5h), (yield 3%), mp 136°C (from ethanol); ir: 1665 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.60 (3H,s,CH_3), 3.18 (3H,s,CH_3), 3.96 (3H,s,CH_3), 7.04 (1H,dd($J_{10,9}$=9.6 Hz,$J_{10,12}$=2.4 Hz),H_{10}), 7.40-7.70 (3H,m,H_6,H_7,H_{12}), 7.76 (1H,s,H_1), 8.20-8.52 (3H,m,H_5,H_8,H_9); ms M^+ 303 m/z. Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62. Found: C, 79.31; H, 5.78; N, 4.52.

The third product to be eluted was 3-acetyl-2-methyl-5-(3-methoxyphenyl)-1-phenylpyrrole (6c), (yield 10%), mp 86°C (from ethanol); ir: 1655 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.48 (3H,s,CH_3), 2.52 (3H,s,CH_3), 3.60 (3H,s,CH_3), 6.52-7.56 (9H,m,ArH), 6.78 (1H,s,CH); ms M^+ 305 m/z. Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.82; H, 6.07; N, 4.48.

The fourth product to be eluted was unreacted starting material (2c) (yield 21%). Further elution with dichloromethane:ethyl acetate (9:1) gave 3-{2-[4-acetyl-5-methyl-2-(3-methoxyphenyl)-pyrrole-1-yl]-phenyl-1-azo}-4-acetyl-5-methyl-2-(3-methoxyphenyl)-1-phenylpyrrole (4c), (yield 53%), mp 198°C (from ethanol); ir: 1690 (CO), 1650 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 1.79 (3H,s,CH_3), 2.21 (3H,s,CH_3), 2.51 (3H,s,CH_3), 2.67 (3H,s,CH_3), 3.40 (3H,s,CH_3), 3.44 (3H,s,

CH_3), 6.53-9.35 (18H,m,ArH); ms M^+ 636 m/z. Anal. Calcd. for $C_{40}H_{36}N_4O_4$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.32; H, 5.61; N, 8.88.

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