Polycondensed Nitrogen Heterocycles. Part 23. Pyrrolo[3,2-*c*]cinnolines by a Japp-Klingemann Type Reaction

Girolamo Cirrincione, Anna Maria Almerico and Enrico Aiello

Istituto Farmacochimico dell'Università di Palermo,
Via Archirafi 32, 90123 Palermo Italy

Gaetano Dattolo

Istituto di Chimica Farmaceutica dell'Università di Milano,
Viale Abruzzi 42, 20131 Milano Italy

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Pyrrolo[3,2-*c*]cinnoline derivatives were obtained by an unusual Japp-Klingemann reaction involving an intramolecular azadehalogenation on the pyrrole nucleus. Such an azadehalogenation represents the first example of Japp-Klingemann reaction in which the extrusion of positive chlorine ion is verified.

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In connection with our studies on polycondensed nitrogen heterocycles with potential antineoplastic activity [1-4], we became interested in the preparation of compounds of type **2**, structural analogues of ethidium bromide **3** and of the reactive species **4**, generated from Mitomycin C, that are well known anticancer drugs which intercalate with DNA [5,6].

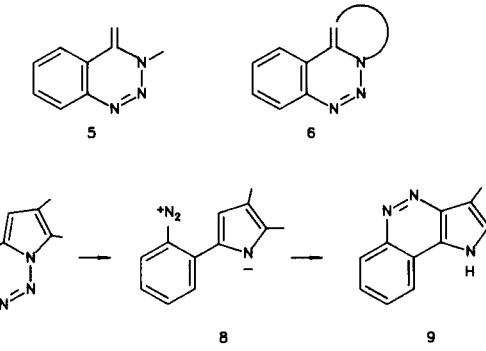
We have already synthesized pyrrolo[3,2-*b*]indole derivatives of type **2** (X = NH), using derivatives of type **1** (X = NH_2, Y = NH_2, Hal) as starting material, through an intramolecular nucleophilic substitution reaction, acid catalysed, in pyrrole series [7,8], and one of these derivatives, namely 3-acetyl-2-methyl-1-phenylpyrrolo[3,2-*b*]indole, resulted to be toxic at the dosage of 30 mg/Kg when tested against Leukemia 3PS31.

With the aim of preparing less toxic and more active derivatives and in an attempt to generalize the pattern of the nucleophilic substitution by varing the attacking group, we are now interested in the synthesis of compounds of type **1** (X = OH, Y = Hal), as key intermediates to prepare pyrrolo[3,2-*b*]benzofurane of type **2** (X = O).

1 2

3 4

An entry to 2-(2-hydroxyphenyl)-1*H*-pyrroles of type **1** could be provided by the opportune pyrrolobenzotriazines. In fact benzotriazines **5** and annelated benzotriazines of type **6** behaved as masked diazonium salts during thermal or base assisted decomposition [9,10]. Also pyrrolo[1,2-*c*]benzo-1,2,3-triazines **7** upon thermolysis gave rise to an intermediate diazonium species **8** that immediately led to pyrrolo[3,2-*c*]cinnolines **9**, by a sequence of 1,5-sigmatropic shifts [11].



5 6

7 8 9

Therefore, thermolysis of derivatives of type **7** in an aprotic dipolar solvent in the presence of alkaline hydroxydes might allow the decomposition of the diazonium group in the intermediate of type **8**, followed by nucleophilic substitution by a hydroxide ion to give **1** (X = OH, Y = Hal), providing that the 3-position of the pyrrole moiety is substituted to avoid the intramolecular coupling reaction. The halogens were chosen as substituents because of the easy halogenation of the pyrrole nucleus [12] and since the same halogens become suitable leaving groups for the intramolecular nucleophilic substitution leading to pyrrolobenzofuran **2** (X = O).

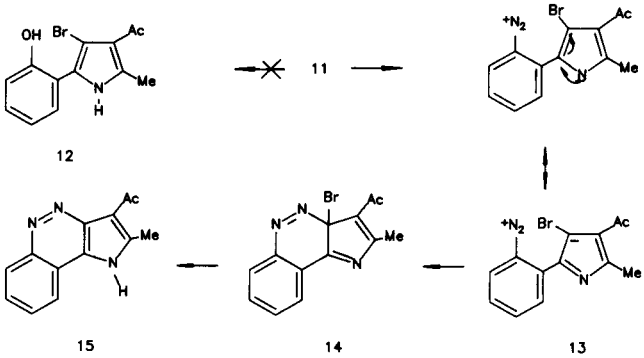
To this purpose, 2-acetyl-1-bromo-3-methylpyrrolo[1,2-*c*]benzo-1,2,3-triazine **11** was prepared in excellent yield by bromination with NBS in DMF of the corresponding pyrrolobenzotriazine **10**. The bromination site in the compound **11** was assigned on the basis of nmr spectra; in fact in the ^1H nmr spectrum the signal at 7.11 ppm due to the pyrrole CH in derivative **10** [11] disappeared and the signal due to the proton bonded to C-10 shifted to 8.86 ppm because of the anisotropic effect of the bromine. In the ^{13}C nmr a signal at 87.83 ppm confirmed the presence

of a pyrrole β-carbon bonded to a bromine. The corresponding signal in the derivative **10** appeared at 98.67 ppm [11].

10 11

Derivative **11** was then refluxed in DMSO in the presence of potassium hydroxide. The reaction did not lead to the hydroxy derivative **12**, but pyrrolocinnoline **15** was only isolated in good yield (65%).

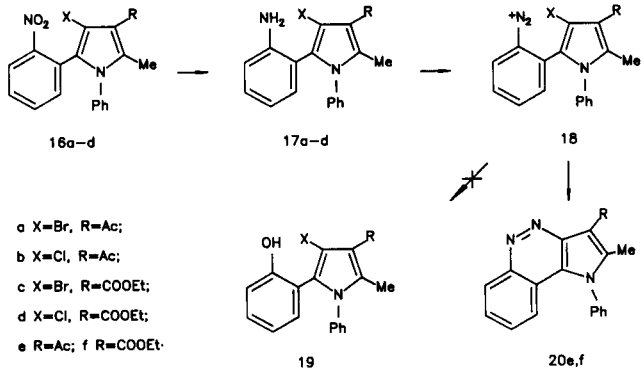
This reaction can be envisaged as occurring by heterolytic rupture of the N-1 N-2 bond of the benzotriazine, leading to the zwitterion **13**. Electrophilic attack of the diazonium group to the negative charged carbon and subsequent base assisted elimination of bromonium ion gave the pyrrolocinnoline **15**. The proposed mechanism closely resembles the Japp-Klingemann reaction in which the primary azo compound rearranges, usually with loss of acetyl or carboxyl residues, through a nucleophilic attack by the base on the potential leaving group. However our reaction is an unusual Japp-Klingemann since it is the first example in a five membered heterocycle and although the bromine can serve as activating substituent, the bromonium ion is rarely a leaving group. In fact the sole example of a Japp-Klingemann reaction in heterocyclic series with bromonium ion as leaving group is verified in the case of 3-bromotriacetic lactone [13].



12 15 14 13

Another route to 2-(2-hydroxyphenyl)pyrroles could then involve the diazotization of derivatives of type **17** followed by the thermal decomposition of the diazonium salts in aqueous medium. At the same time, it could be possible to verify if the above Japp-Klingemann reaction also occurs in *N*-substituted pyrroles of type **17**. Such derivatives lead to the less prone intermediates **18** in which the electronic effects make the azadehalogenation more difficult than in the case of intermediate **13**. In fact the pyrrole β-carbon does not bear a full negative charge and the presence of the phenyl substituent in the 1 position lowers the electron density of the pyrrole ring. Moreover, under the employed experimental conditions (acetic acid/water), the nucleophilic assistance is provided by the less efficient nucleophile water.

To this purpose compounds **17a-d** were obtained by reduction with titanium trichloride in acetic acid of the corresponding nitro-halo derivatives **16a-d**.



16a–d 17a–d 18 19 20e,f

a X=Br, R=Ac;
b X=Cl, R=Ac;
c X=Br, R=COOEt;
d X=Cl, R=COOEt;
e R=Ac; f R=COOEt

The amines **17** were diazotized in acetic acid/water with sodium nitrite and the reaction mixture was heated at 60°. Under such experimental conditions the 2-(2-hydroxyphenyl)pyrroles of type **19** could not be isolated, but the azadehalogenation again took place and pyrrolocinnolines **20e,f** were obtained.

This reaction represents an unusual Japp-Klingemann reaction in that it is the first example of such a reactivity in the azole series and the sole case in which extrusion of a positive chlorine ion is verified. The driving force that makes this reaction very easy is the remarkable stability of the final products as it is verified in every Japp-Klingemann rearrangement.

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.

Preparation of 2-Acetyl-1-bromo-3-methylpyrrolo[1,2-*c*]benzo-1,2,3-triazine (**11**).

To a solution of compound **10** [11] (10 mmoles) in dry DMF (50 ml), *N*-bromosuccinimide (10 mmoles) in dry DMF (20 ml) was added with stirring at room temperature. After stirring for 24 hours the reaction mixture was poured onto crushed ice and the solid precipitated was collected, air dried and recrystallized from ethanol (yield 95%), mp 140°; ir: 1620 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.75 (3H, s, CH_3), 2.97 (3H, s, CH_3), 7.61-7.81 (2H, t, H-8 and H-9), 8.24 (1H, d, H-7), 8.86 (1H, d, H-10); ^{13}C nmr (DMSO-d_6): δ

10.80 (q), 32.00 (q), 87.83 (s), 114.96 (s), 118.48 (s), 120.65 (d), 123.17 (s), 128.16 (d), 130.28 (d), 130.57 (s), 133.39 (d), 134.68 (s), 196.03 (s); ms: M^+ = 303.

Anal. Calcd. for $C_{13}H_{10}N_3OBr$: C, 51.50; H, 3.33; N, 13.86. Found: C, 51.32; H, 3.31; N, 13.79.

Thermolysis of 2-Acetyl-1-bromo-3-methylpyrrolo[1,2-*c*]benzo-1,2,3-triazine (**11**) in Dimethyl Sulfoxide and Potassium Hydroxide.

To a solution of compound **11** (5 mmoles) in DMSO (30 ml) potassium hydroxide (6 mmoles) in DMSO (10 ml) was added. After being refluxed for 2 hours the tlc did not show any starting material. The reaction mixture was poured onto crushed ice. The residue was collected and purified by refluxing in ethanol (yield 65%), mp >320°. The analytical and spectral data (ir, nmr, mass) were in agreement with those of an authentic sample of 1-acetyl-2-methyl-1*H*-pyrrolo[3,2-*c*]cinnoline (**15**) [14].

Preparation of 3-Halo-5-methyl-2-(2-nitrophenyl)-1-phenyl-4-R-pyrroles **16a-d**.

4-Acetyl- and 4-ethoxycarbonyl-5-methyl-2-(2-nitrophenyl)-1-phenylpyrroles were halogenated with *N*-halosuccinimides in DMF as described previously for **16a** (X = Br, R = Ac) and **16b** (X = Cl, R = Ac) [12].

Compound **16c** (X = Br, R = $COOC_2H_5$) was recrystallized from ethanol (yield 93%), mp 114-115°; ir: 1695 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.35 (3H, t, CH_2-C*H*$_3$), 2.34 (3H, s, CH_3), 4.32 (2H, q, CH_2), 7.03-7.82 (9H, m, C_6H_5 and C_6H_4); ms: M^+ = 428.

Anal. Calcd. for $C_{20}H_{17}N_2O_4Br$: C, 55.96; H, 3.99; N, 6.53. Found: C, 56.06; H, 3.91; N, 6.49.

Compound **16d** (X = Cl, R = $COOC_2H_5$) was recrystallized from ethanol (yield 68%), mp 119-120°; ir: 1690 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.30 (3H, t, CH_2-C*H*$_3$), 2.30 (3H, s, CH_3), 4.22 (2H, q, CH_2), 7.26 (5H, s, C_6H_5), 7.33-7.93 (4H, m, C_6H_4); ms: M^+ = 384.

Anal. Calcd. for $C_{20}H_{17}N_2O_4Cl$: C, 62.42; H, 4.45; N, 7.28. Found: C, 62.31; H, 4.50; N, 7.33.

Preparation of 2-(2-Aminophenyl)-3-halo-5-methyl-1-phenyl-4-R-pyrroles **17a-d**.

The preparation of these compounds was carried out according to the procedure described previously for **17a-c** [1].

Compound **17d** (X = Cl, R = $COOC_2H_5$) was recrystallized from ethanol (yield 88%), mp 141-142°; ir: 3460 and 3360 (NH_2), 1690 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.30 (3H, t, CH_2-C*H*$_3$), 2.23 (3H, s, CH_3), 4.23 (2H, q, CH_2), 4.79 (2H, s, exchangeable NH_2), 6.17-7.00 (4H, m, C_6H_4), 7.23 (5H, s, C_6H_5); ms: M^+ = 354.

Anal. Calcd. for $C_{20}H_{19}N_2O_2Cl$: C, 67.69; H, 5.40; N, 7.90. Found: C, 67.74; H, 5.44; N, 7.85.

Diazotization of 2-(2-aminophenyl)-3-halo-5-methyl-1-phenyl-4-R-pyrroles **17a-d**.

Amino compounds **17a-d** (10 mmoles) were dissolved in acetic acid-water (1:1, 100 ml). The mixture was cooled to 0° and diazotized with sodium nitrite (10 mmoles) in water (10 ml). After 15 minutes the mixture was heated at 60° for 30 minutes, then cooled to room temperature and poured onto crushed ice. The precipitate was collected, dried and purified by column of silica gel using dichloromethane as eluant.

Compounds **17a,b** yielded 1-acetyl-2-methyl-3-phenylpyrrolo-[3,2-*c*]cinnoline (**20e**) which had analytical and spectral data (ir, nmr, mass) identical to an authentic sample [14] (yield 55-58%). Compounds **17c,d** yielded 1-ethoxycarbonyl-2-methyl-3-phenylpyrrolo[3,2-*c*]cinnoline (**20f**) which had analytical and spectral data (ir, nmr, mass) identical to an authentic sample [14] (yield 50-60%).

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REFERENCES AND NOTES

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