

POLYCONDENSED NITROGEN HETEROCYCLES. PART 18¹. INFLUENCE OF
pH IN THE INTRAMOLECULAR COUPLING REACTION OF DIAZOTIZED 2-
(2-AMINOPHENYL)-PYRROLES

Girolamo Cirrincione, Gaetano Dattolo, Anna Maria Almerico,
and Enrico Aiello

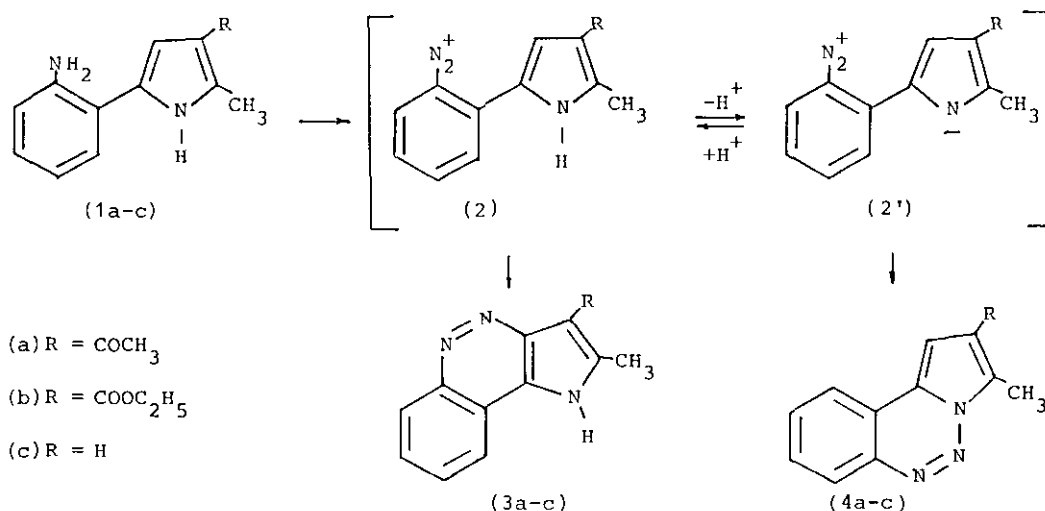
Istituto di Chimica Farmaceutica e Tossicologica dell'Uni-
versità di Palermo, Via Archirafi 32, 90123 Palermo, Italy

Abstract- 1H-pyrrolocinnolines (3) or pyrrolobenzotriazines (4)
are obtained for amines (1) depending on the pH of the medium.
The reaction course was explained on the basis of the position
of the equilibrium $2 \rightleftharpoons 2'$ affected by the substituents.

1-Substituted pyrrolo [3,2-c] cinnoline derivatives showed antigerminative
properties on seeds of *Echinochloa crus-galli*^{2a}. In order to search structu-
re-activity relationship we attempted to synthesize 1H-pyrrolo [3,2-c] cinn-
olines using as starting material amine derivatives (1a,b). Diazotization of
these compounds carried out in acetic acid was immediately followed by the
electrophilic attack of the diazonium group on the pyrrole nitrogen and led
to pyrrolo [1,2-c] benzo [1,2,3] triazines (4a,b)².

It is well known that substitutions on the pyrrole ring by weak electrophi-
les are affected by the variation of the acidity of the medium³ and that in-
tramolecular acylations with possibility of ring closure at the nitrogen or
at the 3-carbon, if performed in polyphosphoric acid, give mainly the C-ring
closure⁴. Considering that increase in the acidity of the medium led to a
higher yield of C-substitution, we thought to undertake a different approach
to 1H-pyrrolocinnolines performing the diazotization of the amino derivatives
(1) in strong acid conditions.

Diazotization of the compounds (1a,b) in concentrate hydrochloric acid gave the expected 1H-pyrrolo[3,2-c]cinnolines (3a,b) in high yield (87%).



The different course of the ring closure in acetic acid and in hydrochloric acid can be explained considering the position of the equilibrium $2 \rightleftharpoons 2'$.

When hydrochloric acid is used as medium, the concentration of the pyrrole anion, which is the reactive species for the N-substitution⁵, is virtually nil. On the other hand, in acetic acid the pyrrole anion is in concentration still low but sufficient to promote the N-ring closure reaction shifting the equilibrium to the right. Of course the position of the equilibrium is depending also on the effects that the substituents on the 2- and 4-position in the intermediate (2) exert on the ring: they both are concord in making the pyrrole NH more acidic and the 3-position less reactive, because of their electronwithdrawing effects.

Moreover the presence of both of them is necessary to make the N-ring closure possible (at pH=5). In fact the diazotization of the amine (1c) (R=H), even when performed in acetic acid, exclusively led to 1H-pyrrolocinnoline (3c).

EXPERIMENTAL

All melting points were taken on a Büchi-Tottoli capillary melting point apparatus and are uncorrected; ir spectra were determined in bromoform with a Perkin-Elmer 299 spectrophotometer; ¹H and ¹³C nmr spectra were obtained with a JEOL FX-100 spectrometer (TMS as an internal reference); mass spectra were obtain-

ed 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.

Diazotization in hydrochloric acid of compounds (1a,b).

A solution of amines (1a,b)² (10 mmoles) in 88 ml of 6N HCl was diazotized with 4 ml of 18% aqueous sodium nitrite at 0-5°C. After 1 h the mixture was allowed to r.t. and adjusted to pH 7 with 10% aqueous sodium hydroxide. The precipitate was filtered off, air dried and recrystallized to give in 87% yield 3-substituted 1H-pyrrolo[3,2-c]cinnolines (3a,b) identical (ir and mass spectra) with those reported by us previously.⁶

Preparation of 2-(2-aminophenyl)-5-methylpyrrole (1c).

Ethyl 5-methyl-2-(2-nitrophenyl)-pyrrole 4-carboxylate^{2b} (10 mmoles) were dissolved in 20 ml of 50% ethanol and refluxed with potassium hydroxide (30 mmoles) in 15 ml of water for 2 h. The cooled solution was poured onto crushed ice and extracted with diethyl ether. The aqueous solution was acidified with 4N HCl and the solid was collected and recrystallized from ethanol to give 5-methyl-2-(2-nitrophenyl)-pyrrole-4-carboxylic acid (yield 70%), mp 210°C; ir: 3315 (NH), 2860 (br OH), 1645 (CO) cm^{-1} ; nmr (DMSO- d_6) δ : 2.48 (3H,s,CH₃), 6.46 (1H,d,J=2.4 Hz,CH), 7.32-7.95 (4H,m,C₆H₄), 11.64 (1H,br OH), 11.76 (1H,br NH); ms M^+ 246 m/z. Anal. Calcd. for C₁₂H₁₀N₂O₄: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.39; H, 3.87; N, 11.21. The acid derivative was kept at 220°C for 5 min.. The residue was chromatographed on column of silica gel (eluant DCM) to give 5-methyl-2-(2-nitrophenyl)-pyrrole (yield 83%), mp 54°C; ir: 3440 (NH) cm^{-1} ; nmr (CDCl₃) δ : 2.34 (3H,s,CH₃), 5.98 (1H,dd,J=2.4Hz,J=3.6Hz,CH), 6.36 (1H,dd J=2.4Hz,J=3.6Hz,CH), 7.08-7.76 (4H,m,C₆H₄), 8.50 (1H,br NH); ms M^+ 202 m/z. Anal. Calcd. for C₁₁H₁₀N₂O₂: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.26; H, 4.91; N, 13.78. The nitro derivative was reduced over 10% Pd-C in ethanol in a Parr apparatus at 45 psi. After 12 h at r.t., the catalyst was filtered off and the solvent was evaporated under reduced pressure to give (1c) which was recrystallized from ethanol (yield 100%), mp 93°C; ir: 3440 (NH), 3340 and 3200 (NH₂) cm^{-1} ; nmr (CDCl₃) δ : 2.26 (3H,s,CH₃), 3.70 (2H,br NH₂), 5.92 (1H,dd J=2.4Hz,J=3.6Hz,CH), 6.23

(1H, dd, J=2.4Hz, J=3.6Hz, CH), 6.58-7.24 (4H, m, C₆H₄), 8.20 (1H, br NH); ms M⁺ 172 m/z. Anal. Calcd. for C₁₁H₁₂N₂: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.51; H, 7.19; N, 16.20.

Diazotization of compound (1c).

Compound (1c) was diazotized in acetic acid according to the procedure described previously.² 2-Methyl-1H-pyrrole [3,2-c]cinnoline (3c) was recrystallized from ethanol (yield 80%), mp 340°C; ir: 3110 (br NH) cm⁻¹; nmr (DMSO-d₆) δ_H: 2.59 (3H, s, CH₃), 6.88 (1H, d, J=2.4Hz, CH), 7.78-8.50 (4H, m, C₆H₄), 12.54 (1H, br NH); δ_C: 143.26 (s), 141.70 (s), 135.88 (s), 127.17 (d, 2C), 124.35 (d), 119.85 (s), 118.29 (d), 111.89 (s), 98.74 (d), 13.21 (q), all assignments of which were confirmed by off-resonance experiments; ms M⁺ 183 m/z. Anal. Calcd. for C₁₁H₉N₃: C, 72.11; H, 4.95; N, 22.94. Found: C, 71.97; H, 4.66; N, 22.74.

ACKNOWLEDGEMENT

This work was supported by a Grant from C.N.R. and from the Ministero P.I.

REFERENCES AND NOTES

- ° An account of this work was presented at "IV Convegno Nazionale Divisione Chimica Farmaceutica della Società Chimica Italiana", Palermo Oct. 1983.
- 1) Part 17: A.M. Almerico, G. Dattolo, G. Cirrincione, G. Presti and E. Aiello, communicated at "IV Convegno Nazionale Divisione Chimica Farmaceutica della Società Chimica Italiana", Palermo Oct. 1983.
- 2) a) G. Dattolo, G. Cirrincione, A.M. Almerico, I. D'Asdia and E. Aiello, Heterocycles, 1982, 19, 681; b) E. Aiello, Atti Accad. Sci. Lettere Arti Palermo, 1970, 30, 237.
- 3) R.A. Jones and G.P. Bean, "The Chemistry of Pyrroles", Academic Press, London 1977, p. 157 and references cited therein.
- 4) H. Votz and R. Draese, Tetrahedron Letters, 1970, 56, 4917.
- 5) A. Treibs and G. Fritz, Annalen, 1958, 611, 162.
- 6) G. Dattolo, G. Cirrincione, A.M. Almerico, L. Lamartina and E. Aiello, J. Chem. Res. (S), 1985, 164.

Received, 13th June, 1985