POLYCONDENSED NITROGEN HETEROCYCLES. PART 18. INFLUENCE OF pH IN THE INTRAMOLECULAR COUPLING REACTION OF DIAZOTIZED 2-(2-AMINOPHENYL)-PYRROLES

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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≠2' affected by the substituents.

1-Substituted pyrrolo[3,2-c]cinnoline derivatives showed antigerminative properties on seeds of Echinochloa crus-galli2a. In order to search structure-reactivity relationship we attempted to synthetize 1H-pyrrolo[2,3-c]cinnolines 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-a]benzo[1,2,3]triazines (4a,b)2.

It is well known that substitutions on the pyrrole ring by weak electrophiles are affected by the variation of the acidity of the medium3 and that intramolecular 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\%).

\[
\begin{align*}
(1a-c) & \\
& \xrightarrow{\text{Diazotization}} (2) \quad \xleftrightharpoons{\text{H}^+} \quad (2') \\
& \xrightarrow{\text{N-ring closure}} (3a-c) \quad (4a-c)
\end{align*}
\]

(a) \(R = \text{COCH}_3\)  
(b) \(R = \text{COOCH}_2\text{H}_5\)  
(c) \(R = \text{H}\)

The different course of the ring closure in acetic acid and in hydrochloric acid can be explained considering the position of the equilibrium \(2 \equiv 2'\). When hydrochloric acid is used as medium, the concentration of the pyrrole anion, which is the reactive species for the N-substitution, 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) \((R=\text{H})\), 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; \(^1\)H and \(^13\)C nmr spectra were obtained with a JEOL FX-100 spectrometer (TMS as an internal reference); mass spectra were obtain-
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\(_6\)) \(\delta\) : 2.48 (3H, s, CH\(_3\)), 6.46 (1H, d, J=2.4 Hz, CH), 7.32-7.95 (4H, m, C\(_6\)H\(_4\)), 11.64 (1H, br OH), 11.76 (1H, br NH); ms M\(^+\) 246 m/z. Anal. Calcd. for C\(_{12}\)H\(_{10}\)N\(_2\)O\(_4\) : 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 85%), mp 54°C; ir: 3440 (NH) cm\(^{-1}\); nmr (CDCl\(_3\)) \(\delta\) : 2.34 (3H, s, CH\(_3\)), 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, C\(_6\)H\(_4\)), 8.50 (1H, br NH); ms M\(^+\) 202 m/z. Anal. Calcd. for C\(_{11}\)H\(_{10}\)N\(_2\)O\(_2\) : 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 (NH\(_2\)) cm\(^{-1}\); nmr (CDCl\(_3\)) \(\delta\) : 2.26 (3H, s, CH\(_3\)), 3.70 (2H, br NH\(_2\)) , 5.92 (1H, dd J=2.4Hz, J=3.6Hz, CH), 6.23


\[ \text{Anal. Calcd. for } C_{11}H_{12}N_2: \text{ C, 76.71; H, 7.02; N, 16.27. Found: C, 76.51; H, 7.19; N, 16.20.} \]

**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-\(d_6\)) \(\delta_H\): 2.59 (3H, s, CH\(_3\)), 6.88 (1H, d, \(J=2.4\) Hz, CH), 7.78-8.50 (4H, m, C\(_6\)H\(_4\)), 12.54 (1H, br NH); \(\delta_C\): 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 \(C_{11}H_9N_3\): C, 72.11; H, 4.95; N, 22.94. Found: C, 71.97; H, 4.66; N, 22.74.

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