SYNTHESIS OF PYRROLOQUINOLINES

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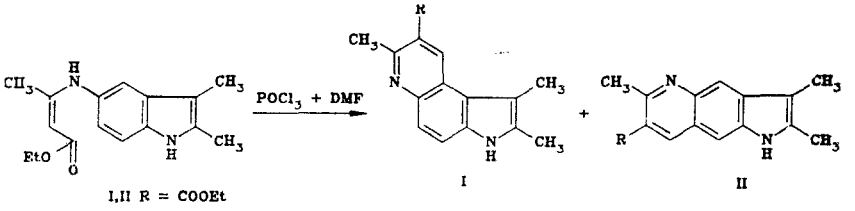
The ethyl ester of β-(2,3-dimethylindolyl-5)aminocrotonic acid under Vilsmeier reaction conditions is converted into isomeric linear and bent pyrroloquinolines with predominant formation of the latter. The enaminoketone which is obtained from the same aminoindole and dibenzoylmethane under the same conditions underoges the usual Comb cyclization with a change in the ratio for the yield of isomeric pyrroloquinolines.

The thermal cyclization of indolylaminocrotonates which was found earlier by us and proceeds regiospecifically is a useful method for production of pyrroloquinolines with bent ring junctions [1]. Continuing studies in this direction, we studied the behavior of indolyl-5-aminocrotonate under Vilsmeier reaction conditions. It is known that crotonates of anilines in this reaction are converted into derivatives of quinoline [2]. Cyclization at the 4 or 6 position of the indole subsequent to initial electrophilic attack on the Vilsmeier complex at the second carbon atom of the aminocrotonate should be expected for derivatives of 2,3-dimethyl-5-aminoindole.

Refluxing an equimolar quantity of (2,3-dimethylindolyl-5-)-aminocrotonate and Vilsmeier reagent in chloroform for 6 h leads to formation in good yield of the two isomeric pyrroloquinolines I and II with predominant formation of the bent one (ratio 7:1).



The pyrroloquinolines which were obtained were separated preparatively on thick layer aluminum oxide using ethylacetate.

Signals for the protons of the three methyl groups, the ethoxy group, singlets for the γ-H protons of pyridine, and N—H were observed in the PMR spectrum of I. Two protons of the benzene ring appear as two doublets of an AB-system with spin—spin coupling constant of 9 Hz. In contrast to compound I, the two benzene protons give two singlets in the PMR of the linear pyrroloquinoline II. The signals of the remaining protons in the spectrum of II are not significantly different in chemical shift from those of pyrroloquinoline I.

The electronic spectra of pyrroloquinolines I and II are characterized by four well defined absorption maxima. The difference in the spectrum of the bent pyrroloquinoline I from the linear II consists in the different intensities of the short wavelength band. The band at 288 nm which is more intense than for the bent isomer can be assigned to the π-π^* transition for the linear isomer. A bathochromic shift by 30 nm of the short wavelength band in the spectrum of II also indicates the large conjugation in the linear isomer by comparison with the bent isomer I.

Pyrroloquinolines I and II have high stability to electron impact. The most intense signal in the mass spectra is the peak of the molecular ion. All spectral data agree well with those in the literature for isomeric pyrroloquinolines with analogously joined rings [3].

The use of the enaminoketone formed form the same aminoindole and dibenzoylmethane instead of the aminocrotonate was interesting. Two isomeric pyrroloquinolines which are described in agreement with the literature by the structures III and IV were separated from the

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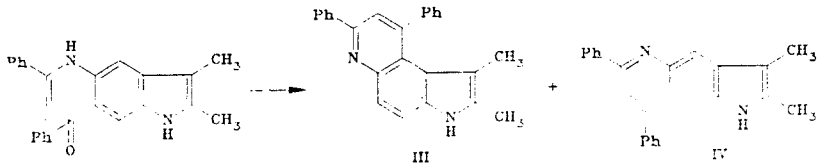
reaction mixture obtained upon heating the indolylenaminoketone in chloroform with the Vilsmeier reagent.



In contrast to the aminocrotonates, the enaminoketones under these conditions undergo the usual Comb cyclization with a small change in the dirction toward formation of the bent pyrroloquinoline (ratio 1:1). $POCl_3$ probably acts as a cyclizing agent in this case. Refluxing the enamine in the $POCl_3$ gives analogous results, only with a higher yield of pyrroloquinolines.

Thus, (2,3-dimethylindolyl-5)enaminocrotonate under Vilsmeier reaction conditions is heteroaromatized into a mixture of two pyrroloquinolines with predominant formation of the bent isomer. Such electrophilic attack agrees with previously obtained results [3]. The dependence of the direction of cyclization in the case of (2,3-dimethylindolyl-6)enaminoketone on the character of the acidic agent is observed for the first time. Earlier studies showed that indolylaminovinylketone gives only the linear pyrroloquinoline using sulfuric, trifluoroacetic, or phosphoric acids, which is explained by steric demands of the perisubstituents upon formation of the bent system [3]. The anomaly when using $POCl_3$ as the cyclizing agent is probably explained by some changes in the cyclization reaction mechanism which leads to minimal influence of steric factors.

EXPERIMENTAL

UV spectra were measured on a Cary-219 instrument in ethanol. PMR spectra were taken on Varian S-100XL and Tesla BS-467C (60 MHz) instrments in DMSO-D_6 relative to TMS. Mass spectra were obtained on a Varian MAT-112 mass spectrometer. The reaction was monitored using TLC. Elemental analysis for C and H corresponded to those calculated.

The ethyl ester of β-(2,3-dimethylindolyl-5)aminocrotonic acid and 3-(indolylamino) vinylketone were synthesized as described earlier [1, 3].

1,2,7-Trimethyl-8-carbethoxypyrrolo[3,2-f]quinoline (I, $C_{17}H_{18}N_2O_2$) and 2,3,6-trimethyl-7-carbethoxypyrrolo[2,3-g]quinoline (II, $C_{17}H_{18}N_2O_2$). To a solution of 1 g (3.68 mmole) of 2,3-dimethylindole aminocrotonate in 50 ml chloroform was added Vilsmeier reagent prepared from 1 ml $POCl_3$ (10.6 mmole) and 1 ml DMF (10.9 mmole). The mixture was refluxed for 6 h, cooled, diluted with 200 ml chloroform, and treated with 50 ml 12% aqueous ammonia. The organic layer was separated, washed with water 3-4 times, and dried with Na_2SO_4. After removing chloroform, 900 mg of a mixture of I and II was obtained. The two isomeric pyrroloquinolines were separated preparatively on thick layer Al_2O_3 (neutral to Brockman II) using ethylacetate. Compound I, yield 350 mg (34%), mp 214-215°C. UV spectrum, λ_{max} (log ε): 240 (4.61), 284 (4.12), 360 (3.75), 388 nm (3.92). PMR spectrum: 1.37 (3H, t, CH_2CH_3; J = 7 Hz); 2.27 (3H, s, 2-CH_3); 2.28 (3H, s, 1-CH_3); 2.65 (3H, s, 7-CH_3); 4.23 (2H, q, CH_2CH_3; J = 7 Hz); 7.22 (1H, d, 4-H; J_{45} = 9 Hz); 7.50 (1H, d, 5-H; J_{54} = 9 Hz); 8.80 (1H, s, 9-H); 10.93 ppm (s, NH). Compound II, yield 50 mg (5%), mp 204-205°C. UV spectrum, λ_{max} (log ε): 235 (4.42), 2.86 (4.71), 352 (3.89), 416 nm (3.75). PMR spectrum: 1.39 (3H, t, CH_2CH_3; J = 7 Hz); 2.28 (3H, s, 3-CH_3); 2.42 (3H, s, 2-CH_3); 2.84 (3H, s, 6-CH_3); 4.36 (2H, q, CH_2CH_3; J = 7 Hz); 7.83 (1H, s, 9-H); 7.89 (1H, s, 4-H); 8.85 (1H, s, 8-H); 11.08 ppm (s, NH).

7,9-Diphenyl-1,2-dimethylpyrrolo[3,2-f]quinoline (III) and 6,8-diphenyl-2,3-dimethylpyrrolo[2,3-g]quinoline (IV). These were obtained analogously from 1,3-diphenyl-3-[(2,3-dimethylindolyl-5)amino]propen-2-one-1. The isomers were separated preparatively on thick layer Al_2O_3 (neutral to Brockman II) using benzene–ethylacetate (10:1). Yield of III 14%, mp 258-260°C (mp 259-262°C [3]). Yield of IV 15%, mp 208-210°C (mp 210-212°C [3]). Refluxing of this same enaminoketone in $POCl_3$ for 8 h with subsequent treatment of the reaction mixture with aqueous ammonia and proceeding as above gave III (25% yield) and IV (30% yield).

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SYNTHESIS OF 4-METHYL-1H-IMIDAZO[4,5-c]QUINOLINE

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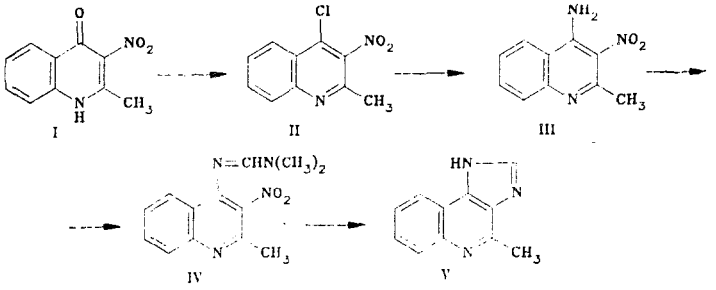
A four-step synthesis of 4-methyl-1H-imidazo[4,5-c]quinoline from 2-methyl-3-nitro-4-oxo-1,4-dihydroquinoline is developed.

Synthesis of imidazo[4,5-c]quinolines based on the reaction of N-substituted 3,4-diaminoquinolines with formic acid or orthoesters [1, 2] is known.

We developed a new synthetic method for 4-methyl-1H-imidazo[4,5-c]quinoline V from 2-methyl-3-nitro-4-oxo-1,4-dihydroquinoline I [3]. Chloroquinoline II, which upon reaction with an alcoholic solution of ammonia forms the aminoquinoline III with quantitative yield, is obtained by treatment of quinoline I with $POCl_3$ in the presence of triethylamine. Condensation of III with the diethylacetal of dimethylformamide gives the formamidine IV, reductive cyclization of which with zinc in acetic acid leads to imidazo[4,5-c]quinoline V.



EXPERIMENTAL

Melting points were determined on a Kofler block (GDR). IR spectra were recorded on a Perkin-Elmer 599 instrument in vaseline, UV spectra were recorded on Perkin-Elmer 575 and Specord M-40 instruments in ethanol. PMR spectra were recorded on Varian XL-100 and XL-200 instruments with working frequencies of 100 and 200 MHz, respectively, and an internal standard of TMS. Mass spectra were taken on a Varian MAT-112 spectrometer with ionization energy of 70 eV and a source temperature of 180°C.

Elemental analysis for C, H, N, and Cl corresponded to those calculated.

2-Methyl-3-nitro-4-chloroquinoline (II, $C_{10}H_7ClN_2O_2$). To a suspension of 6.7 g (33 mmole) quinoline I in 6.7 g (9.2 ml, 66 mmole) triethylamine at room temperature were added dropwise with stirring 58.6 g (35 ml, 383 mmole) $POCl_3$. The reaction mixture was heated at 110°C for 1 h and cooled to room temperature. Excess $POCl_3$ was removed in vacuum. To the residue were added 100 ml chloroform and the solution was poured onto ice with ammonia. The mixture was extracted with chloroform (4 × 50 ml), the chloroform extract was washed with water (2 × 35 ml), dried over Na_2SO_4 and evaporated. The solid residue was dried in vacuum. Yield 6.3 g (86%), mp 79-82°C (from ethanol). IR spectrum: 1610, 1600, 1550, 1535 (C=C, C=N, NO_2), 1330 cm^{-1} (NO_2). UV spectrum, λ_{max} (log ε): 210 (4.41), 232 nm (4.47). PMR spectrum (DMSO-D_6): 2.69 (3H, s, CH_3); 7.85-8.26 ppm (m, 4H arom.). Mass spectrum, m/z: 222 (M^+), 176 $[M - NO_2]^+$.

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