SYNTHESIS AND ALKYLATION OF 9-ETHOXY-1H-PYRROLO[3,2-b]QUINOLINE

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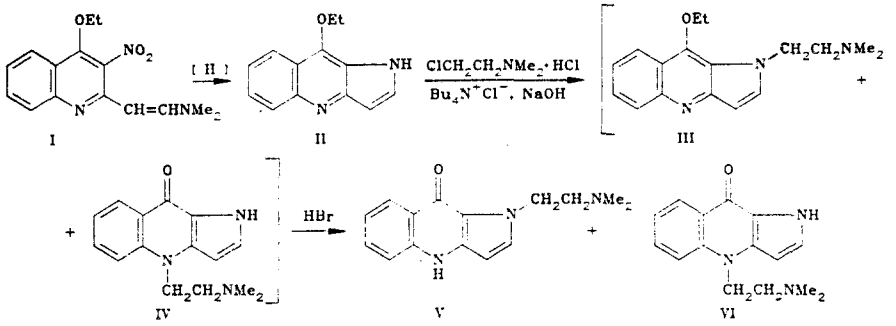
9-Ethoxy-1H-pyrrolo[3,2-b]quinoline has been synthesized by the hydrogenation of 2-[2-(N,N-dimethylamino)vinyl]-3-nitro-4-ethoxyquinoline using Raney nickel. Alkylation using N,N-dimethylchloroethylamine and hydrolysis with HBr gave two isomers whose structures were established using PMR and mass spectrometry.

This report describes the synthesis and properties of the 1H-pyrrolo[3,2-b]quinoline system.

Hydrogenation of 2-[2-(N,N-dimethylamino)vinyl]-3-nitro-4-ethoxyquinoline (I) [1] with Raney nickel caused reduction of the nitro group, transamination, and cyclization to form 9-ethoxy-1H-pyrrolo[3,2-b]-quinoline (II).

We have studied the alkylation of 1H-pyrrolo[3,2-b]quinoline II by N,N-dimethylchloroethylamine under phase transfer catalytic conditions. Chromatographic and spectroscopic data show that more than one product is formed and the mixture (III + IV) could be hydrolyzed with hydrobromic acid and separated by preparative chromatography to give two isomers (V and VI).



The PMR spectra of V and VI contain the same series of signals but the chemical shift values of analogous groups were different (see Experimental) which is typical of isomeric structures. The structures of V and VI were established by NMR spectroscopy using nuclear Overhauser experiments. Irradiation of the NH proton at 11.90 ppm in compound V led to an intensity increase of 12% for the 3-H proton doublet at 6.16 ppm and a 9% increase for the 5- and 6-H multiplet at 7.54 ppm proving the steric proximity of the NH to 3-H and 5-H. In the same way, irradiation of the methylene group attached to the cyclic nitrogen (a triplet at 4.61 ppm) caused a 36% increase in the doublet signal for 2-H at 7.43 ppm. Both of these results agreed with the structure V in which the dimethylaminoethyl group is at ring position 1.

When compound VI was subjected to the same experiment different proton groups were found to respond. Thus irradiation of the NH proton increased the intensity of the 2-H doublet at 7.46 ppm by 25%. Similarly, irradiation of the side chain methylene increased the 3-H proton at 6.43 ppm by 24% and the 5-H and 6-H multiplet at 7.70 ppm by 30%. These results are in good agreement with VI in which the side chain is at the ring N-4.

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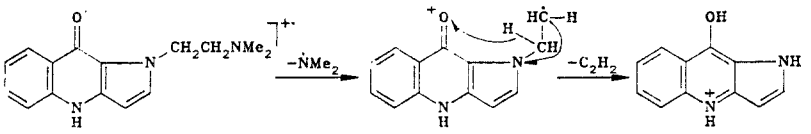
TABLE 1. Mass Spectra of V and VI

Compound	m/z (Irelative, %)									
	M^+	$[M-N(CH_3)_2]^+$	$[M-HN(CH_3)_2]^+$	$[M-CH_2N(CH_3)_2]^+$	$[M-N(CH_3)_2-C_2H_2]^+$	$[M-HN(CH_3)_2-C_2H_2]^+$	$[CH_2CH_2N(CH_3)_2]^+$	$[CH_2CHN(CH_3)_2]^+$	$[CH_2N(CH_3)_2]^+$	W_M
V	255 (2,8)	211 (1,2)	210 (0,9)	197 (2,4)	185 (30)	184 (33)	72 (46)	71 (52)	58 (100)	1,7
VI	255 (7)	211 (0,7)	210 (0,8)	197 (1,7)					58 (100)	5,5

The mass spectra of isomers V and VI showed ions for $[M-N(CH_3)_2]^+$, $[M-HN(CH_3)_2]^+$, $[M-CH_2N(CH_3)_2]^+$, and $H_2C{=}\overset{+}{N}(CH_3)_2$ due to dissociation in the side chain. Because the latter ion was of maximum abundance, the charge is basically located on the exocyclic nitrogen atom.

Significant differences are seen in the mass spectra of V and VI (see Table 1). Thus the molecular ion peak intensity ($I_{relative}$) and the stability to electron impact (W_M) are significantly lower in V than in VI because there are additional fragmentation routes occurring in V. The mass spectrum of V showed intense fragment peaks at m/z 185, 184, 72, and 71 which are absent in VI. Their formation is in agreement with DADI spectra arising through stepwise elimination of C_2H_2 from the ions $[M-N(CH_3)_2]^+$ and $[M-HN(CH_3)_2]^+$. In agreement with published data ([2], p. 81) double hydrogen migration results from the promixity of the radical center to the oxygen atom in V:



These features can be used to determine the position of the aminoalkyl substituents in pyrroloquinolines.

EXPERIMENTAL

Melting points were determined on a Köffler block and IR spectra on a Perkin-Elmer 599 instrument as Vaseline mulls. UV spectra were recorded on a Perkin-Elmer 575 instrument and mass spectra on a Varian MAT-112 (ionization energy 70 eV, ion source 180°C). PMR spectra were obtained on a Varian XL-200 (200 MHz) spectrometer referred to internal TMS. Elemental analytical data for C, H, and N agreed with that calculated.

9-Ethoxy-1H-pyrrolo[3,2-b]quinoline (II) ($C_{13}H_{12}N_2O$). A suspension of quinoline I (3 g, 10.5 mmole) in absolute ethanol (300 ml) was hydrogenated over Raney nickel (3 g, 51.1 mmole) at atmospheric pressure and 20°C until absorption of hydrogen ceased. The catalyst was filtered off, washed with absolute ethanol (100 ml), and the filtrate evaporated to give a dark green solid residue. Drying in vacuo gave 2.1 g (95.5%) with mp 165-168°C (from ethyl acetate). IR spectrum: 3130 (NH), 1615, 1555, 1530 cm^{-1} (C=N, CH=CH). UV spectrum (in alcohol, λ_{max}, log ε): 245 (4.77), 318 (3.90), 355 (3.78), 370 nm (3.78). Mass spectrum, m/z (%): 212 (100) M^+, 184 (98), 183 (61), 156 (17), 155 (28). PMR spectrum (DMSO-d_6); 1.49 (3H, t, CH_3), 4.62 (2H, q, CH_2); 6.65 (1H, d, J_{32} = 3.4 Hz, 3-H); 7.94 (1H, d, 2-H); 7.40 (1H, t), 7.59 (1H, t), 7.96 (1H, d), (5-H, 6-H, 7-H); 8.24 (1H, d, 8-H); 11.42 ppm (1H, br. s, NH).

1-[2-(N,N-Dimethylamino)ethyl]- and 4-[2-(N,N-Dimethylamino)ethyl]-9-oxo-4,9-dihydropyrrolo[3,2-b]quinoline (V, VI). Benzene (10 ml), tetrabutylammonium chloride (0.07 g, 0.24 mole), and N,N-dimethylchloroethylamine hydrochloride (0.4 g, 2.9 mmole) were added with intensive stirring to a suspension of II (0.5 g, 2.4 mmole) in 40% NaOH (10 ml). The mixture was stirred for 3 h at 50°C, cooled to 20°C, and water (10 ml) was added. The benzene layer was separated, washed with water (30 ml) and dried (Na_2SO_4). The drying agent was filtered off and washed with benzene (50 ml) and the filtrate was evaporated to dryness to give an oily residue. The residue was dissolved in absolute ether (30 ml), acidified to pH 1

with HCl solution in C_2H_5OH, and the precipitated solid rapidly filtered off and dried in vacuo (over H_2SO_4) to give a mixture of the hydrochlorides of III and IV (0.2 g). The mixture was dissolved in 48% HBr (6 ml), refluxed for 4.5 h, cooled to 20°C, and the solution basified with 2N NaOH to pH 9. It was extracted with $CHCl_3$ (5 × 35 ml), washed with water (2 × 25 ml), dried (Na_2SO_4), evaporated to dryness and further dried in vacuo (H_2SO_4) to give a mixture of V and VI (0.1 g). The mixture was separated by preparative chromatography on bonded layer silica gel (DC-Fertigplatten Kieselgel 60 F_{254} Merck) using chloroform—methanol (3:1) as eluent to give V and VI. Isomer V (0.05 g, 50%) had mp 178-180°C and PMR spectrum (DMSO-d_6): 2.18 (6H, s, CH_3); 2.64 (2H, t, CH_2—NMe_2); 4.61 (2H, t, CH_2); 6.16 (1H, d, J_{32} = 2.9 Hz, 3-H); 7.43 (1H, d, 2-H); 7.16 (1H, m, 7-H); 7.54 (2H, m, 5-H, 6-H); 8.25 (1H, d, 8-H); 11.90 ppm (1H, br s, NH). Isomer VI (0.02 g, 20%) had mp 220-222°C and PMR spectrum (DMSO-d_6); 2.26 (6H, s, CH_3); 2.61 (2H, t, CH_2—NMe_2); 4.47 (t, 2H, CH_2); 6.43 (1H, d, $^3J_{32}$ = 2.9 Hz, 3-H); 7.46 (1H, d, 2-H); 7.26 (1H, m, 7-H); 7.70 (2H, m, 5-H, 6-H); 8.39 (1H, d, 8-H); 12.02 ppm (1H, br. s, NH).

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4-METHYL-5-HYDROXYPYRIMIDINE AND ITS N-OXIDES: SYNTHESIS AND INVESTIGATION OF THE REACTIVITIES IN ELECTROPHILIC SUBSTITUTION

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A new more accessible method for the synthesis of 4-methyl-5-hydroxypyrimidine is proposed; its 1- and 3-oxides were obtained. An attempt was made to evaluate the reactivities of the individual positions of the heterocyclic ring of pyrimidine and its 3-oxide in aminomethylation.

5-Hydroxypyrimidines, which have a symmetrical (relative to the two heteroatoms) meta position that is the only one capable of electrophilic substitution in the unactivated molecule, but is occupied by an electron donor in this case,* occupy a special place among diazines. Therefore, only the remaining three even-numbered positions (2, 4, and 6), two of which are symmetrical (4 and 6), can also be the subject of the resultative attack by electrophiles. We have previously [1, 2] demonstrated for the first time the possibility of the aminomethylation, diazo coupling, and iodination of the even-numbered positions of the ring in the case of 5-hydroxypyrimidine (I), 4,6-dimethyl-5-hydroxypyramidine (II), 4-phenyl-5-hydroxypyrimidine, and the 1-oxide of II.

The aims of the present research were to compare the relative activities of the unsymmetrical 2 and 6 positions of the pyrimidine ring vis-a-vis an occupied 4 position and, chiefly, to ascertain the effect on them of N-oxidation of each of the nitrogen atoms (as a result of which significant redistribution of the electron density of the heterocyclic ring occurs) under competitive conditions of electrophilic substitution. We also attempted to evaluate this relationship previously when we carried out hydrogen-isotope exchange of the 1-oxides of I and II [3, 4].

*5-Amino and other substituted pyrimidines that have an electron-donor substituent in the 5 position can be assigned to this classification.

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