A NEW METHOD FOR THE SYNTHESIS OF PYRROLO[1,2-a]PYRAZINES AND PYRROLO[1,2-a]QUINOXALINES

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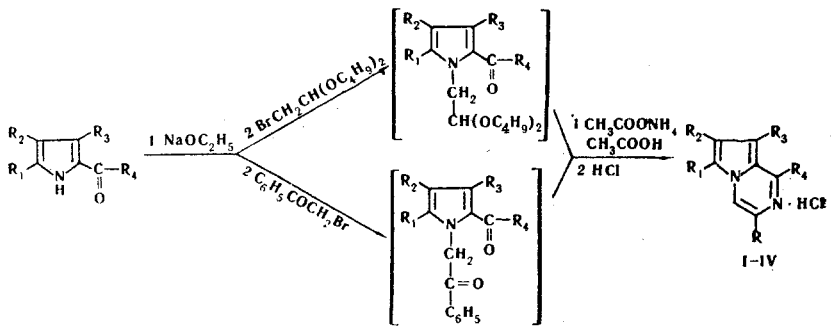
A new method is proposed for the synthesis of pyrrolo[1,2-a]pyrazines and pyrrolo[1,2-a]-quinoxalines. By the alkylation of sodium derivatives of 2-acylpyrroles with α-bromo carbonyl compounds or their acetals and subsequent treatment of the reaction products with ammonium acetate in acetic acid, a number of derivatives of pyrrolo[1,2-a]pyrazine, including the first member of the class, pyrrolo[1,2-a]pyrazine itself, have been obtained. Similarly, from 2-benzoylpyrrole and the dimethyl ketal of α-bromocyclohexanone was obtained 4-phenyltetrahydropyrrolo[1,2-a]quinoxaline, which readily dehydrogenates in the presence of Raney nickel to form 4-phenylpyrrolo[1,2-a]quinoxaline.

Previously, pyrrolo[1,2-a]pyrazine and 4-methylpyrrolo[1,2-a]pyrazine were obtained in admixture with derivatives of pyrrolo[2,3-c]pyridine by the cyclization of substituted acylpyrrole imines [1,2]. The necessity of using difficultly accessible starting materials for the reaction and the difficulties connected with the separation of the pyrrolo[1,2-a]pyrazines and the pyrrolo[2,3-c]pyridines, which have similar properties, limited the possibilities of this method.

We have proposed a new method for the synthesis of derivatives of pyrrolo[1,2-a]pyrazine which is free from these defects. Various representatives of this class of condensed heterocycles, both those containing substituents in any positions of the molecules and also the first member of the class – pyrrolo[1,2-a]pyrazine (I) itself – have been obtained.

2-Acylpyrroles were used as the starting materials for the synthesis of the pyrrolo[1,2-a]pyrazines. By the action of sodium alkoxides they were converted into their sodium derivatives, which were alkylated with the dibutyl acetal of α-bromoacetaldehyde or with ω-bromoacetophenone. The dicarbonyl derivatives so formed were not isolated but were converted by boiling with ammonium acetate in acetic acid solution into the pyrrolo[1,2-a]pyrazines (I-IV), which were isolated in the form of the hydrochlorides.



I R = R1 = R2 = R3 = R4 = H; II R = H, R1 = R3 = R4 = CH3, R2 = COOC2H5; III R = R1 = R2 = R3 = H, R4 = C6H5; IV R = R4 = C6H5, R1 = R2 = R3 = H

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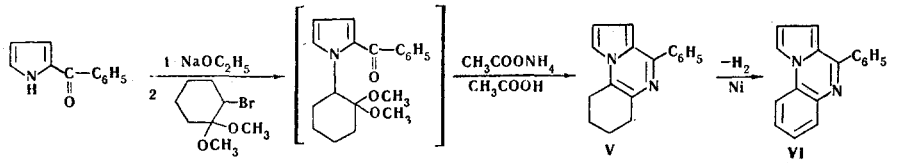
Analogously, the sodium derivatives of 2-benzoylpyrrole and the dimethyl ketal of α-bromocyclohexanone gave the hydrochloride of 4-phenyltetrahydropyrrolo[1,2-a]quinoxaline (V). The dehydrogenation of the base V over Raney nickel catalyst in boiling toluene gave an almost quantitative yield of 4-phenylpyrrolo[1,2-a]quinoxaline (VI). Some substituted pyrrolo[1,2-a]quinoxalines have been obtained recently by a multistage synthesis from quinoxaline derivatives [3].



The UV spectrum of pyrrolo[1,2-a]pyrazine (I) taken in ethanolic solution has several absorption bands with λ_{max} 226, 285, 294, 303 and 340-360 nm, (log ε 4.39, 3.45, 3.53, 3.37, and 3.41). The strongest band with λ_{max} 226 nm (log ε 4.39) is connected with the absorption of the pyrrole ring, which generally appears at 210 nm (log ε 4.0) [4]. The conjugation of the pyrrole ring with the double bonds of the pyrazine ring leads to a displacement of the peak into the longer-wave region of the spectrum and to an increase in the intensity of absorption. In the spectrum of the pyrrolo[1,2-a]pyrazine (III), in which there is a phenyl radical in position 4, the absorption of the pyrrole ring is shifted to 230 nm (log ε 4.27) and a broad high-intensity band appears in the spectrum with λ_{max} 250 nm (log ε 4.2) which is connected with the absorption of the benzene chromophore conjugated with the pyrrolo[1,2-a]pyrazine molecule.

In the UV spectrum of 4-phenyltetrahydropyrrolo[1,2-a]quinoxaline (V) there are absorption bands with λ_{max} 230, 252, 317 and 365 nm (log ε 4.29, 4.29, 3.97 and 3.6). The first two maxima are also found in the spectrum of 4-phenylpyrrolo[1,2-a]pyrazine (III) and are due to the absorption of the pyrrole and benzene rings of the molecule.

The UV spectrum of 4-phenylpyrrolo[1,2-a]quinoxaline (VI) in ethanol differs considerably from that of 4-phenyltetrahydropyrrolo[1,2-a]quinoxaline (V) and has the shape characteristic for complex condensed systems with high-intensity absorption maxima at 227, 243, 248, 268 and 340 nm (log ε 4.36, 4.38, 4.40, 4.20 and 3.86).

EXPERIMENTAL

Hydrochloride of Pyrrolo[1,2-a]pyrazine (I). An ethanolic solution of sodium ethoxide prepared from 4.6 g (0.2 g-at) of sodium was added to a solution of 19 g (0.2 mole) of 2-formylpyrrole in 50 ml of dioxane. The solvent was distilled off from the solution formed, the last traces in vacuum. To the solid sodium derivative of 2-formylpyrrole so produced a solution of 50.6 g (0.2 mole) of the dibutyl acetal of bromoacetaldehyde in 100 ml of dry dimethylformamide was added, and the reaction mixture was boiled for 1 hr and was then poured into water. The oil that separated out was extracted with benzene and the benzene extract was dried with a Dean–Stark attachment. The solvent was distilled off in vacuum, the residual oily substance was dissolved in 250 ml of acetic acid, and the solution was treated with 150 g of ammonium acetate and boiled for 2 hr. Then the acetic acid was distilled off in vacuum, the residue was dissolved in water, the resin that deposited was separated off, and the mother solution was made alkaline with concentrated caustic soda solution. The emulsion formed was extracted with ether. The ethereal extract was shaken

TABLE 1. Pyrrolo[1,2-a]pyrazine Hydrochlorides

Compound	mp °C	Empirical formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
II	180—182 (decomp.)	$C_{13}H_{17}N_2O_2Cl$	57,75 58,07	6,35 6,39	—	58,09	6,33	—	37,5
III	185—187 (decomp.)	$C_{13}H_{11}N_2Cl$	67,30 67,52	4,82 4,89	12,50 12,46	67,68	4,80	12,14	50
IV	115—116	$C_{19}H_{15}N_2Cl$	—	—	9,15 9,39	—	—	9,13	25

with 10 g of activated carbon, filtered, dried with magnesium sulfate, and then treated with an equivalent amount of ethereal hydrogen chloride. Yield 8 g (26%), mp 160-161°C (from acetone). Found, %: C 54.44; H 4.86; N 18.16. Calculated for $C_7H_7N_2Cl$, %: C 54.38; H 4.56; N 18.12.

For information on the other pyrrolo[1,2-a]pyrazines (II-IV), see Table 1.

Hydrochloride of 4-Phenyltetrahydropyrrolo[1,2-a]quinoxaline (V). The experiment was carried out with 8.5 g (0.05 mole) of 2-benzoylpyrrole, 20 ml of dioxane, the sodium ethoxide prepared from 1.15 g (0.05 g-at) of sodium, 11.2 g (0.05 mole) of the dimethyl ketal of α-bromocyclohexanone, 30 ml of dry dimethylformamide, 60 ml of acetic acid, and 40 g of ammonium acetate. The reaction and the isolation of the product were performed under the conditions for the preparation of I. The yield of V was 7 g (56.4%), mp 202-204°C (decomp.) Found, %: C 71.36; H 6.37; N 10.04. Calculated for $C_{17}H_{17}N_2Cl$, %: C 71.69; H 6.01; N 9.83.

4-Phenylpyrrolo[1,2-a]quinoxaline (VI). A flask fitted with a Dean-Stark attachment was charged with 2.4 g (0.01 mole) of the base V, 6 ml of a suspension of Raney nickel in water, and 60 ml of xylene. The reaction mixture was boiled with the elimination of water for 4 hr and was filtered hot, and then the catalyst was washed repeatedly with xylene and the filtrate was evaporated in vacuum. This gave a viscous oily substance which crystallized on standing. Yield 2.3 g (96%), mp 94-95°C (from petroleum ether). Found, %: C 84.43; H 4.82; N 11.49. Calculated for $C_{17}H_{12}N_2$, %: C 83.58; H 4.95; N 11.46.

LITERATURE CITED

1. W. Herz and S. Tocker, J. Am. Chem. Soc., 77, 6355 (1955).
2. W. Paudler and D. Dunham, J. Het. Chem. 2, 410 (1965).
3. E. Taylor and G. Cheeseman, J. Am. Chem. Soc., 86, 1830 (1964).
4. J. Brand and G. Eglinton, Applications of Spectroscopy to Organic Chemistry [Russian translation], Moscow, p. 215 (1967).