DIRECT ANNELATION OF SIX-MEMBERED HETEROCYCLES WITH A QUINOXALINE RING*

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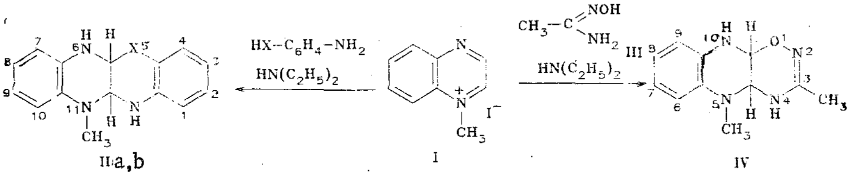
A series of papers in which derivatives of pyrazine and quinoxaline condensed with five- and six-membered heterorings were obtained by reactions of 2,3-dichloropyrazines and 2,3-dichloroquinoxalines with bisnucleophilic reagents were recently published. It was noted that 2,3-dichloro-1,4-diazines are ideal starting compounds for such annelations [2, 3].

In previous communications we have shown that N-alkylpyrazinium and quinoxalinium cations as such, without introduction of any substituents, are also applicable for the synthesis of condensed pyrazines and quinoxalines with annelated furan, pyrrole, imidazole, thiazole, and other five-membered rings [4]. These cyclizations are based on the diaddition of 1,3-bisnucleophiles and lead to hydrogenated analogs of those pyrazines and quinoxalines that can be obtained in cyclizations with replacement of chlorine atoms in the 2 and 3 positions of the pyrazine ring.

In the present research we have established for the first time that 1,4-bisnucleophilic reagents such as o-phenylenediamine and o-aminophenol also undergo cyclization with N-methylquinoxalinium iodide (I) to give quinoxalino[2,3-b]quinoxaline (IIa) and benzoxazino[1,4]-[2,3-b]quinoxaline (IIb) derivatives, respectively. 1,2,4-Oxadiazino[5,6-b]quinoxaline (IV) — a representative of a new heterocyclic system — was obtained in the reaction of cation I with amidoxime III. This compound can be regarded as the oxa analog of hydrogenated flavines.



IIa,b I IV

a X=NH; b X=O

The structures of IIa,b and IV were established on the basis of ^1H and ^{13}C NMR and mass-spectral data. In the ^{13}C NMR spectrum of IIb without proton decoupling in d_6-DMSO the signal of the nodal 11a-C atom at 62.2 ppm has, in addition to $^1J_{CH} = 154.9$ Hz, a long-range $^3J_{CH}$ constant with the protons of the methyl group (∿3 Hz), whereas the signal at 77.2 ppm, which belongs to the 5a-C atom between the nitrogen and oxygen atoms, has only a direct $^1J_{CH}$ constant of 165.9 Hz. The nodal 4a-C (62.1 ppm) and 10a-C (75.6 ppm) atoms have close chemical shifts in the ^{13}C NMR spectrum of IV. These data, as well as the existence of spin–spin coupling with the protons of the NH group for both nodal hydrogen atoms in the ^1H NMR spectra, unambiguously prove the relative orientation of the heterorings in IIb and IV.

In contrast to the cyclizations with 1,3-bisnucleophiles, in which the reaction products have a cis orientation of the nodal protons ($^3J_{H,H} = 7$-10 Hz), low values of the vicinal constants in the pyrazine ring ($^3J_{H,H} = 2$-3 Hz), which are close to the values observed for trans-2,3-disubstituted tetrahydroquinoxalines [5], are characteristic for six-membered heterocycles annelated with tetrahydroquinoxalines.

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*Communication 12 from the series "Cyclizations of N-alkylazinium cations with bisnucleophiles." See [1] for communication 11.

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The reactions were carried out in ethanol at room temperature with diethylamine as the base; the reagent ratio was 1:1:1. All of the synthesized substances had satisfactory results of elementary analysis. The following compounds were obtained (melting points and yields given): IIa, 129-130°C, 70%; IIb, 101-102°C, 53%; IV, 158-159°C, 75%.

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NEW REACTION INVOLVING THE DETRITYLATION OF N-TRITYL-SUBSTITUTED CYCLIC AMINO ACIDS

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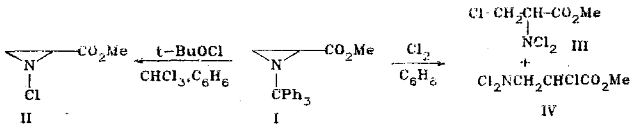
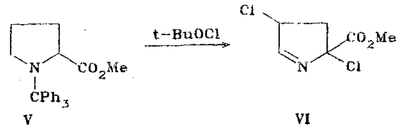
The removal of an N-trityl protective group can be accomplished by acidic hydrolysis or catalytic hydrogenation [1]. For the first time we have observed the detritylation of methyl esters of N-tritylazine (I) and N-tritylproline (V) under the influence of chlorinating reagents. The reaction of ester I with tert-butyl hypochlorite leads to trans-1-chloro-2-methoxycarbonylaziridine (II), which, according to the PMR and mass spectra, is identical to the compound previously obtained in [2]. The reaction with chlorine is accompanied by opening of the aziridine ring and the formation of an equimolar mixture of methyl esters of N,N-dichloro-β-chloro-α-alanine [III, PMR spectrum (360 MHz, $CDCl_3 + C_6D_6$): 3.49 (s, 3H, OMe); 3.64 and 3.73 (two AB quartets, 2H, CH_2); 4.08 ppm (AB quartet, 1H, CH); ^2J = 11.2, ^3J = 4.6 and 7.8 Hz] and N,N-dichloro-α-chloro-β-alanine [IV, PMR spectrum (360 MHz, $CDCl_3 + C_6D_6$): 3.49 (s, 3H, OMe); 3.72 and 4.00 (two AB quartets, 2H, CH_2); 4.36 ppm (t, 1H, CH); ^2J = 13.5, ^3J = 6.3 and 6.3 Hz]. Ester I does not react with N-chlorosuccinimide or sodium hypochlorite (according to TLC data).





Detritylation to give 2-methoxycarbonyl-2,4-dichloro-5-pyrroline (VI) also occurs in the reaction of ester V with tert-butyl hypochlorite. IR spectrum of VI (film): 1683 (C=N) and 1700 cm^{-1} (C=O). PMR spectrum (90 MHz, $CDCl_3$): 2.99 and 3.07 (two AB quartets, 2H, CH_2; ^2J = 14.4, ^3J = 7.0 Hz); 3.82 (s, 3H, OMe); 4.91 (two t, 1H, 4-H; ^3J = 3.0 and 7.0 Hz); 7.65 ppm (d, 1H, 5-H; ^3J = 3.0 Hz).

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