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CYCLIZATION OF N-ALKYLAZINIUM CATIONS WITH BIFUNCTIONAL NUCLEOPHILES. 24.* SYNTHESIS OF CONDENSED 1,2,4-TRIAZINO- AND 1,2,4-OXADIAZINO[5,6-b]QUINOXALINE SYSTEMS

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UDC 547.863.19'872.3.07:542.953:543.422.25

Cyclization of quinoxalinium salts with amidoximes and amidhydrazones yields partially hydrogenated derivatives of new 1,2,4-oxadiazino- and 1,2,4-triazino[5,6-b]quinoxaline heterocyclic systems.

Condensed tricyclic systems containing the quinoxaline bicycle are of considerable interest. A special place is occupied by the alloxazine heterocyclic system, viz., the pyrimido-[4,5-b]annellated quinoxaline. This is the structural basis of flavin adenyl dinucleotide, riboflavin, and other flavins that play an important role in biochemical processes [2].

Between flavins and quinoxalines there is not only a formal structural similarity, but also a definite resemblance in chemical behavior. It is known that flavin thioanalogs [3, 4] and 1,3,10-trimethylalloxazinium salts [5] can add two alcohol or thioalcohol molecules, just as in the reactions of quaternary quinoxalinium salts [6]. The structural and chemical resemblance of flavins to quinoxalines, and the possibility of annelation of six-membered heterocycles to quinoxalines suggests the use of the reactions of quinoxalinium salts to synthesize structural analogs of flavins. The present work was an attempt to annelate six-membered rings containing a 1,3-diazino segment to quinoxalines. For this purpose we studied the reactions of quinoxalinium salts I with amidohydrazones II and amidoximes III; the latter are aminoazomethynes that potentially might play the role of 1,4-bifunctional nucleophile and annelate a 1,2,4-triazine or 1,2,4-oxadiazine segment to a quinoxaline framework.

*For Communication 23, see [1].

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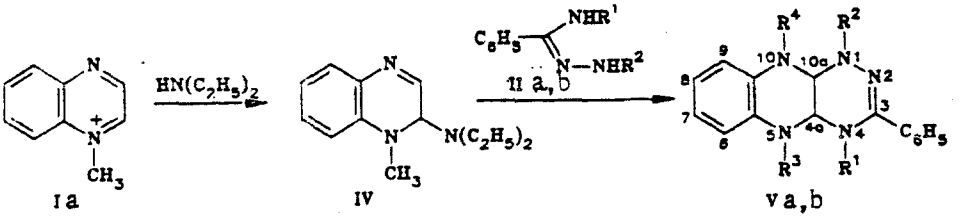
0009-3122/87/2308-0895$12.50

TABLE 1. Properties of 1,2,4-Triazino[5,6-b]quinoxalines Va, b and 1,2,4-Oxadiazino[5,6-b]quinoxalines VIa-e

Compound	T_{mp}, °C	UV spectrum, λ_{max}, nm (log ε)	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
Va	171—173		74,6	6,0	19,5	$C_{22}H_{21}N_5$	74,3	6,0	19,7	71
Vb	194—196		72,2	5,4	18,1	$C_{23}H_{21}N_5O$	72,0	5,5	18,3	86
VIa	168—170	221 (4,58), 261 (3,59), 307 (3,63)	60,8	6,4	25,4	$C_{11}H_{14}N_4O$	60,5	6,5	25,7	75
VIb	151—153	223 (4,37), 265 (3,36), 312 (3,43)	62,1	7,0	24,0	$C_{12}H_{16}N_4O$	62,1	6,9	24,1	49
VIc	162—164	222 (4,59), 260 (3,60), 305 (3,65)	69,7	6,2	18,7	$C_{17}H_{18}N_4O$	69,4	6,2	19,0	77
VId	168—169	223 (4,61), 255 (3,97), 307 (3,66)	68,8	5,8	20,2	$C_{16}H_{16}N_4O$	68,6	5,8	20,0	89
VIe	157—159		53,7	4,5	16,0	$C_{16}H_{15}BrN_4O$	53,5	4,2	15,6	61

It is known that in alkaline medium in the presence of an oxidant, amidohydrazones form tetrazines [7]. To avoid their formation as byproducts the reaction of amidohydrazones IIa, b was carried out not with N-methylquinoxalinium iodide (Ia) in the presence of an organic base, but with the previously prepared and isolated adduct of salt Ia with diethylamine (IV) [8]. In this case the 1,4,4a,5,10,10a-hexahydro-1,2,4-triazino[5,6-b]quinoxalines Va, b were isolated (Table 1).



II, V a $R^1=C_6H_5$, $R^2=R^3=H$, $R^4=CH_3$; b $R^1=R^4=H$, $R^2=COC_6H_5$, $R^3=CH_3$

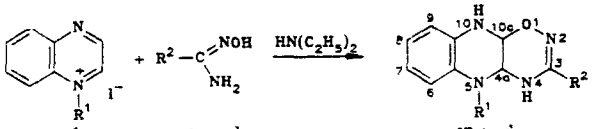
Compounds Va, b must be distinguished from imidazo[4,5-b]quinoxalines; the formation of the latter is quite likely if we consider that N-monosubstituted benzamidines, which are close analogs of reagents IIa, b, react with quinoxalines to form specifically imidazo[4,5-b]-quinoxalines [9].

The conclusion that the 1,2,4-triazine ring is annelated, but not the imidazole ring, was based on comparison of the ^1H and ^{13}C NMR spectra of compounds Va, b with those of the previously described 3a,4,9,9a-tetrahydroimidazo[4,5-b]quinoxalines [9]. The spectra of these groups of compounds differ substantially both in the chemical shifts of the carbons that are common to the two condensed rings, and in the SSCC values between protons at nodal atoms. In the ^{13}C NMR spectra the nodal carbons of imidazo[4,5-b]quinoxalines resonate in the 75-84 ppm region, whereas in the spectrum of compound Vb the chemical shifts of $C_{(4a)}$ and $C_{(10a)}$ are 63.5 and 53.3 ppm, respectively. The vicinal SSCC between the 4a-H and 10a-H protons in the PMR spectra of compounds Va, b are 3.3-3.4 Hz, whereas imidazo[4,5-b]quinoxalines are characterized by significantly higher values, 8.8-9.8 Hz [9]. The upfield shift of the carbon signals, along with the sharp decrease in SSCC between the protons at the nodal atoms, are characteristic of the transition from tetrahydropyrazines, which are joined in a five-membered heterocycle, to their six-membered analogs with the same set of heteroatoms in the nodal segment [10]. The regioorientation of the triazine ring when it is joined to pyrazine was established from the ^1H NMR spectra; the proton signals of both nodal atoms show splitting at the protons of the adjacent NH groups, which disappears upon deuteration.

TABLE 2. ^{1}H NMR Spectra of 1,2,4-Oxadiazino[5,6-b]quinoxalines VI

Compound	Proton chemical shifts, ppm							SSCC, Hz		
	N–CH_3 (s)	4a-H (dd)	10a-H (dd)	N_4–H (d)	N_{10}–H (d)	R^2	benzene ring (s)	$^3J_{4a,10a}$	$^3J_{4a,4}$	$^3J_{10a,10}$
VIa	2,79	4,36	4,66	7,37	6,66	1,75 (s, 3H, CH_3)	6,52	2,4	4,4	3,9
VIc	2,70	4,39	4,72	7,45	6,73	3,39 (s, 2H, CH_2), 7,28 (s, 5H, C_6H_5)	6,53	2,2	4,3	3,8
VId	2,97	4,70	4,99	8,29	7,19	7,6—8,2 (m, 5H, C_6H_5)	6,84	2,2	5,2	4,0
VIe	2,88	4,57	4,85	7,88	6,83	7,4—7,7 (m, 4H, p-BrC_6H_4)	6,59	2,8	4,4	3,8

The reaction of amidoximes IIIa-d with quinoxalinium iodides Ia, b goes smoothly in ethanol medium in the presence of a base (di- or triethylamine), also exclusively by 1,4-diaddition, and gives 1,4,4a,5,10,10a-hexahydro-4H,1,2,4-oxadiazino[5,6-b]quinoxalines VIa-e* (Table 1).



Ia,b IIIa-d VIa-e

I, VIa, c-e $R^1=CH_3$, b $R^1=C_2H_5$; IIIa, VIa,b $R^2=CH_3$; IIIb, VIc $R^2=CH_2C_6H_5$; IIIc, VId $R^2=C_6H_5$; IIId VIe $R^2=C_6H_4Br$-p

The conclusion concerning the relative orientation of the oxadiazine and pyrazine rings in compounds VIa-e follows from a consideration of the ^{1}H (Table 2) and ^{13}C NMR spectra of compound VIa. In the ^{1}H NMR spectra the 4a-H and 10a-H protons appear as double doublets, since in addition to the vicinal constants $^3J_{4a,10a}$ = 2.2-2.8 Hz the interaction with the protons of the adjacent NH groups appears distinctly. The ^{13}C NMR spectrum of compound VIa in DMSO-D_6 is in good agreement with that of the model compound 11-methyl-5,5a,6,11,11a,12-hexahydrobenzoxazino[1,4][2,3-b]quinoxaline VII, which has the same set of heteroatoms at the nodal carbons [12].

Thus the signal of $C_{(4a)}$ appears at 63.05 ppm, while that of $C_{(10a)}$, which is located between nitrogen and oxygen, appears at 76.52 ppm. For the model compound the chemical shifts of the respective carbons are 62.2 ($^1J_{CH}$ = 154.9, $^3J_{C_{(11a)}H\text{-}NCH_3}$ = 3 Hz) and 77.2 ppm ($^1J_{CH}$ = 166 Hz). Recording of the ^{13}C NMR spectrum of compound VIa with retention of SSC with protons gives additional evidence in favor of the regioorientation of the oxadiazine ring proposed above. The stronger-field $C_{(4a)}$ signal, besides the direct SSCC through one bond ($^1J_{C_{(4a)}H_{(4a)}}$ = 153 Hz), has a vicinal constant, $^3J_{C_{(4a)},H\text{-}NCH_3}$ = 3 Hz, with the N-methyl protons. The assignment of the 4a-H and 10a-H signals is also confirmed by experiments on the selective decoupling of the SSC of the 4a-H and 10a-H protons with $C_{(4a)}$ and $C_{(10a)}$, respectively.

Compounds VIa-e are representatives of a new heterocyclic system, 1,2,4-oxadiazino[5,6-b]-quinoxaline. No information has been published on any heterocyclic system that contains condensed pyrazine and 1,2,4-oxadiazine rings. The closest analogs of compounds VI are the 1,3,4-oxadiazino[5,6-b]quinoxaline derivatives obtained by cyclization of 2,3-dichloro- and 2-chloro-3-nitroquinoxaline with benzhydrazides [13].

These cyclizations of quinoxalinium salts with amidoximes and amidohydrazones enable us to obtain, in one step, substances that can be considered the hydrogenated oxa- and aza analogs of alloxazines.

*For previous communication, see [11].

EXPERIMENTAL

^{1}N NMR spectra in DMSO-D_6 were recorded with a Perkin–Elmer spectrometer (60 MHz), with HMDS internal standard. ^{13}C NMR spectra were recorded with Brucker WH-90 (22.62 MHz) and WP-80 (20 MHz) instruments in DMSO-D_6. ^{13}C chemical shifts were measured relative to the solvent signal (δ 39.7 ppm) and adjusted to the δ scale. UV spectra were obtained in ethanol with a Specord UV-vis spectrophotometer.

N-methyl- and N-ethylquinoxalinium iodides (Ia, b) were synthesized by the procedure of [9]. N^3-Phenylbenzamidohydrazone IIa [14], N^1-benzoylbenzamidohydrazone IIb [15], acetamidoxime IIIa [16], benzyl amidoxime IIIb [17], benzamidoxime IIIc [18], and p-bromobenzamidoxime IIId [19] were synthesized by published procedures.

10-Methyl-3,4-diphenyl-1,4,4a,5,10,10a-hexahydro-1,2,4-triazino[5,6-b]quinoxaline (Va). To a solution of 0.8 g (3.7 mmole) of the adduct of N-methylquinoxaline with diethylamine IV, obtained from 3.7 mmole of salt Ia according to [8], in 5 ml of ethanol was added 0.78 g (3.7 mmole) of N^3-phenylbenzamidohydrazone (IIa). The precipitate was filtered off and recrystallized from ethanol. Yield 0.92 g (71%), cream-colored prisms, mp 171-173°. ^{1}H NMR spectrum (DMSO-D_6): 2.95 (s, 3H, N-CH_3); 4.48 (br.d, 10a-H, $^3J_{4a,10a}$ = 3.3 Hz); 4.97 (br.d, 4a-H); 6.25 (br.s, NH); 6.52 (s, 4H, benzene ring protons); 6.7-7.5 ppm (m, 11H, NH and 10 CH of two phenyl rings).

1-Benzoyl-5-methyl-3-phenyl-1,4,4a,5,10,10a-hexahydro-1,2,4-triazino[5,6-b]quinoxaline (Vb). To a solution of 0.8 g (3.7 mmole) of 1-methyl-2-N,N-diethyl-1,2-dihydroquinoxaline IV in 2 ml of DMSO was added a solution of 0.83 g (3.7 mmole) of N^1-benzoylbenzamidohydrazone IIb in 3 ml of DMSO. The orange solution was poured with stirring into 200 ml of water. The precipitate was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 1.2 g (86%), colorless prisms, mp 194-196°. ^{1}H NMR spectrum (DMSO-D_6): 3.1 (s, 3H, N-CH_3); 5.05 (br.d, 4a-H, $^3J_{4a,10a}$ = 3.4 Hz); 6.03 (br.d, 10a-H); 6.16 (br.s, NH); 6.58 (s, 4H, benzene ring protons); 7.2-8.0 ppm (m, 11H, NH and 10 CH of two phenyl rings). ^{13}C NMR spectrum (DMSO-D_6): 37.3 (NCH_3); 53.3 ($C_{(4a)}$); 63.5 ($C_{(10a)}$); 112.1; 112.7; 117.5; 118.9 (4 CH of benzene ring); 126.6, 127.5, 128.1, 129.7, 130.2 (10 aromatic CH); 130.4, 133.1, 133.3, 135.6 (4 quaternary C); 144.5 (N–C=N); 167.8 (N–C=O).

3,5-Dimethyl-4,4a,5,10,10a-hexahydro-4H-1,2,4-oxadiazino]5,6-b]quinoxaline (VIa). To a suspension of 3 g (11 mmole) of compound Ia and 0.82 g (11 mmole) of acetamidoxime IIIa in 8 ml of ethanol at 20° was added 3 ml of diethylamine with stirring. A colorless solution formed, from which crystals of compound VIa began to precipitate practically at once. The reaction mixture was let stand for 20 h for complete crystallization, after which the precipitate was filtered off and recrystallized from ethanol. Yield 1.8 g (75%), mp 168-170° (Tables 1 and 2). ^{13}C NMR spectrum (DMSO-D_6): 17.55 (3-CH_3, $^1J_{CH}$ = 128.8 Hz); 34.23 (N-CH_3, $^1J_{CH}$ = 135.9 Hz); 63.05 ($C_{(4a)}$, $^1J_{CH}$ = 153 Hz, $^3J_{4a\text{-}C,N\text{–}CH_3}$ = 3 Hz); 76.52 ($C_{(10a)}$, $^1J_{CH}$ = 163.1 Hz); 112.50, 113.35, 119.04, 119.40 (4 arom. CH); 132.20, 133.12 (2 quaternary C); 149.90 ppm (N–C=N).

Compounds VIb-e were synthesized analogously from the respective amidoximes and N-alkylquinoxalinium salts (Tables 1 and 2).

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CHEMICAL PROPERTIES OF 2,2,4-TRISUBSTITUTED 2,3-DIHYDRO-1H-1,5-BENZODIAZEPINES

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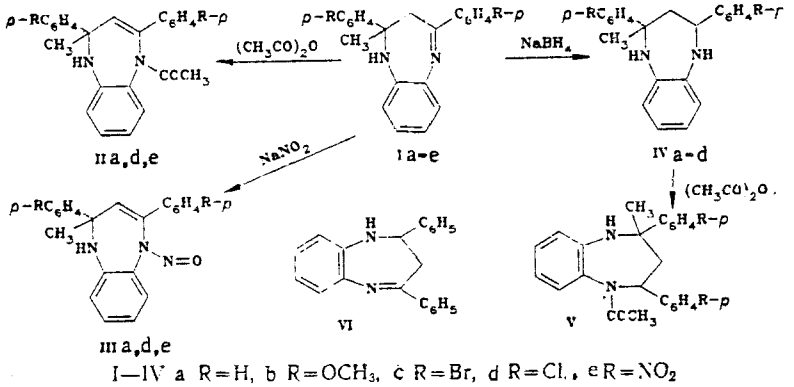
UDC 547.892.04:542.951'958.2:543.422.25:541.63

Acetylation and nitrosation of 2,4-diaryl-2-methyl-2,3-dihydro-1H-1,5-benzodiazepines take place at the azomethyne nitrogen. Reduction is stereoselective.

2,4-Diaryl-2,3-dihydro-1H-1,5-benzodiazepines are not stable in acid medium [1]. On the other hand their 2,2,4-trisubstituted derivatives are resistant to acid, as evidenced by the use of an acid catalyst ($BF_3 \cdot Et_2O$ or HCl) [2, 3] in their synthesis. Thus the presence of the second substituent at position 2 of the heterocycle causes a drastic change in the chemical stability of the dihydrobenzodiazepine system. The present work presents a broader investigation of the effect of this substituent on dihydrobenzodiazepine properties. For this purpose acetylation, nitrosation, and reduction of 2,4-diaryl-2-methyl-2,3-dihydro-1H-1,5-benzodiazepines (Ia-e) were carried out, and methylation and oxidation were attempted.

Scheme 1



I—IV a R=H, b R=OCH_3, c R=Br, d R=Cl, e R=NO_2

Acetylation of compounds Ia, d, e could be carried out by brief boiling of their solution in acetic anhydride. Previous attempts to acetylate compound Ia [3] under milder conditions (in methanol, pyridine, dioxane) were unsuccessful. In the present case 5-acetyl-2,4-diaryl-2-methyl-1,2-dihydro-5H-benzodiazepines (IIa, d, e) were obtained in good yield (Table 1). Data from the IR and UV spectroscopes are proof of the formation of 5-acetyl derivatives (Table 1). Thus in the IR spectrum of compounds IIa, d, e the C=N valence vibration band (1608-1612

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