CYCLIZATION OF N-ALKYLAZINIUM CATIONS WITH BIFUNCTIONAL NUCLEOPHILES.
22.* CRYSTAL AND MOLECULAR STRUCTURE OF TETRAHYDROQUINOXALINE CONDENSED WITH THE SIX-MEMBERED 1,3,4-THIADIAZINE RING

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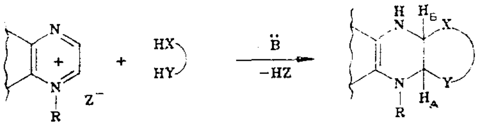
X-ray diffraction examination of 4-acetyl-10-methyl-2-phenyl-1,4,4a,5,10,10a-hexahydro-1,3,4-thiadiazino[5,6-b]quinoxaline has shown that the 4a-H and 10a-H hydrogens attached to the carbon atoms common to both heterocycles are cis-oriented, as in the annelation of five-membered heterocycles to the tetrahydropyrazine ring, but in this case the torsion angle $H_{(4a)}C_{(4a)}C_{(10a)}H_{(10a)}$ is much greater, having a value of 60°.

The ability of 1,4-diazinium salts to add bifunctional nucleophiles at the carbon atoms of both C=N bonds to give cyclization products constitutes a route to quite a wide range of condensed heterocyclic systems in which the tetrahydropyrazine ring is coupled with various carbo- and heterocycles [2, 3]. This is accomplished by varying the structure of the binucleophiles using different combinations of the reactive centers NH, SH, OH, or CH, changing the size of the connecting chain, and introducing substituents into the pyrazine ring, including annelation of benzene, pyridine, and pyrimidine rings.



$R = CH_3, C_2H_5$; X, Y = N, S, O, C

Previously-studied cyclizations of N-alkylpyrazinium [2-4], quinoxalinium [2-5], pyrido[2,3-b]pyrazinium [5], and pteridinium [6] cations with 1,3- and 1,4-binucleophiles have established the general features of the annelation of five- and six-membered heterocycles to pyrazines and the regio- and stereostructures of the cycloadducts, and studies have been made of the possibility and course of their isomerization and other features of the reaction [2-8]. Examination of the ^1H and ^{13}C NMR spectra of a large number of condensed tetrahydroquinoxalines has also shown that the spatial structure of the cycloadducts is dependent on the size of the annelated ring [7, 8]. For instance, when tetrahydroquinoxalines are coupled with five-membered heterocycles, the coupling constants between protons H_A and H_B have values between 7 and 9 Hz [7]. Similar values of $^3J_{AB}$ = 7-8 Hz were also found in the PMR spectra of tetrahydropyrazines and tetrahydropteridines condensed with pyrrole and imidazole rings [4, 6]. From the Karplus relationship [9], these values for the vicinal constant $^3J_{AB}$ correspond to dihedral angles between the planes $H_A{-}C_A{-}C_B$ and $C_A{-}C_B{-}H_B$ from 0 to 23°. Indeed, x-ray diffraction analysis of tetrahydroquinoxalines condensed with five-membered heterocycles confirmed the pronounced cis-orientation of hydrogen atoms H_A and H_B [10-12]. It was shown that the tetrahydropyrazine ring in these condensed systems has an asymmetric boat conformation, but the torsion angles $H_A{-}C_A{-}C_B{-}H_B$ do not exceed 23° [10-12]. In the case of tetrahydroquinoxalines condensed with six-membered heterocycles, much lower values of the vicinal constant $^3J_{AB}$ (2-4 Hz) were typically found [8], indicating a change in the mutual spatial orientations of hydrogen atoms H_A and H_B at the carbon atoms common to both rings. According to the Karplus relationship [9], these values for $^3J_{AB}$ should corre-

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[*] For Communication 21, see [1].

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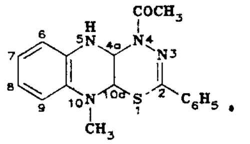
TABLE 1. Bond Lengths d (Å) in (I)

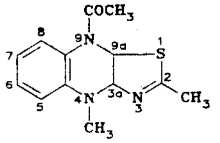
Bond	d	Bond	d	Bond	d
$S_{(1)}—C_{(2)}$	1,74(1)	$N_{(10)}—C_{(9a)}$	1,39(2)	$C_{(8)}—C_{(9)}$	1,39(2)
$S_{(1)}—C_{(10a)}$	1,85(1)	$N_{(10)}—C_{(10a)}$	1,41(1)	$C_{(9)}—C_{(9a)}$	1,40(2)
$O_{(1)}—C_{(11)}$	1,22(2)	$N_{(10)}—C_{(13)}$	1,44(1)	$C_{(11)}—C_{(12)}$	1,49(2)
$N_{(3)}—N_{(4)}$	1,39(1)	$C_{(2)}—C_{(14)}$	1,50(2)	$C_{(14)}—C_{(15)}$	1,38(2)
$N_{(3)}—C_{(2)}$	1,29(1)	$C_{(4a)}—C_{(10a)}$	1,50(1)	$C_{(14)}—C_{(19)}$	1,42(2)
$N_{(4)}—C_{(4a)}$	1,45(1)	$C_{(5a)}—C_{(6)}$	1,38(2)	$C_{(15)}—C_{(16)}$	1,44(2)
$N_{(4)}—C_{(11)}$	1,38(1)	$C_{(5a)}—C_{(9a)}$	1,39(2)	$C_{(16)}—C_{(17)}$	1,36(2)
$N_{(5)}—C_{(4a)}$	1,44(1)	$C_{(6)}—C_{(7)}$	1,39(2)	$C_{(17)}—C_{(18)}$	1,38(2)
$N_{(5)}—C_{(5a)}$	1,40(1)	$C_{(7)}—C_{(8)}$	1,40(2)	$C_{(18)}—C_{(19)}$	1,36(2)

spond to higher values of the torsion angles $H_A—C_A—C_B—H_B$ in the range 45-59°, but no reliable experimental data on the spatial structure of tetrahydropyrazines with a [b]-annelated six-membered ring have yet been obtained.

The object of the present investigation was to determine the crystal and molecular structure of the tetrahydroquinoxaline (I), condensed with the six-membered thiadiazine ring, and to compare the results with those obtained in an x-ray examination of the tetrahydroquinoxaline (II), condensed with the five-membered thiazole ring [11]. The common feature of the structures of (I) and (II) is the presence of the same set of heteroatoms adjacent to the nodal carbon atoms, thus making it possible to establish how replacement of the five-membered thiazole ring by the six-membered thiadiazole ring affects the geometry and conformation of the tetrahydroquinoxaline system.



I



II

The results of the x-ray diffraction study of 4-acetyl-10-methyl-2-phenyl-1,4,4a,5,10,-10a-hexahydro-1,3,4-thiadiazino[5,6-b]quinoxaline (I) are given in Fig. 1 and Tables 1 and 2.

The greater conformational flexibility of the thiadiazine ring as compared with the thiazole ring enables the molecule of (I) to adopt the most favored skew conformation relative to the $C_{(4a)}—C_{(10a)}$ bond, which is common to both heterocycles. The torsion angle $S_{(1)}C_{(10a)}$-$C_{(4a)}N_{(4)}$ in (I) is equal to −53.6°, whereas in (II) the corresponding angle $S_{(1)}C_{(9a)}C_{(3a)}N_{(3)}$ has a value of −11.5° [11]. The consequent decrease in strain in (I) results primarily in a shortening of the $C_{(4a)}$-$C_{(10a)}$ bond to 1.50 Å, as compared with a $C_{(3a)}$-$C_{(9a)}$ bond length in (II) of 1.56 Å, which is considerably longer [11]. In addition, the conformation of the tetrahydropyrazine ring changes from distorted boat in (II) to unsymmetrical semichair in (I), atoms $C_{(4a)}$ and $C_{(10a)}$ being located on opposite sides of the plane $N_{(5)}C_{(5a)}C_{(9a)}N_{(10)}$, which is complied with to within 0.02 Å, at distances of 0.42 and −0.23 Å respectively. According to Aguilera et al. [13], this conformation is prefered in 1,2,3,4-tetrahydroquinoxalines. Hydrogen atoms $H_{(4a)}$ and $H_{(10a)}$ are located in the pseudoequatorial and pseudoaxial positions relative to the tetrahydropyrazine ring. Their mutual orientation may be regarded, as before, as being of the cis-type, as in the thiazolo[4,5-b]quinoxalines (II), so that the thiadiazine ring may be regarded as being cis-coupled to the tetrahydropyrazine ring (Fig. 1), but the torsion angle $H_{(4a)}C_{(4a)}C_{(10a)}H_{(10a)}$ in (I) is much larger (60.4°). The change in the conformation of the tetrahydropyrazine ring in (I) as compared with (II) is apparently not only due to replacement of the thiazole by the thiadiazine ring, but also to the absence of an acetyl group in the central pyrazine ring, since in the product of the reaction of N-methylquinoxalinium with acetylacetone [14], the N-acetylated tetrahydropyrazine nucleus is not condensed with any rings. The absence of an acetyl group at $N_{(5)}$ of the central heterocycle in (I) results in the equalization therein of the lengths of the N—C bonds with the benzene ring (1.40 and 1.39 Å), a value equal to that of the shorter of such bonds in the tetrahydroquinoxaline (II). This equalization is apparently due to the participation of the unshared electron pairs of atoms $N_{(5)}$ and $N_{(10)}$ in conjugation with the π-system of the benzene ring, which is seen for only one atom, $N_{(4)}$, in (II) [11]. The

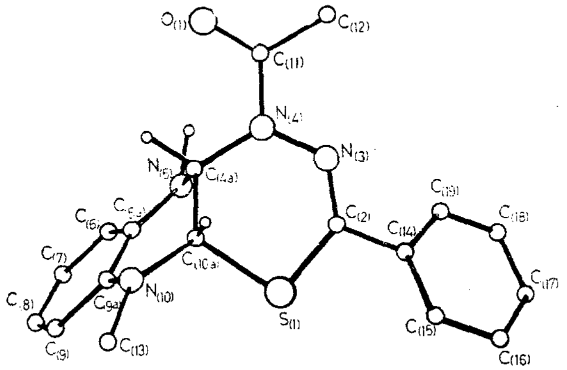


Fig. 1. General view of the molecule of 1,3,4-thiadiazino[5,6-b]quinoxaline (I).

TABLE 2. Principal Valence Angles, ω, deg.

Angle	ω	Angle	ω	Angle	ω
$C_{(2)}S_{(1)}C_{(10a)}$	101,9(5)	$N_{(4)}C_{(4a)}C_{(10a)}$	113,0(8)	$S_{(1)}C_{(10a)}C_{(4a)}$	110,2(7)
$N_{(4)}N_{(3)}C_{(2)}$	119,2(9)	$N_{(5)}C_{(4a)}C_{(10a)}$	110,0(8)	$N_{(10)}C_{(10a)}C_{(4a)}$	111,8(8)
$N_{(3)}N_{(4)}C_{(4a)}$	121,8(8)	$N_{(5)}C_{(5a)}C_{(6)}$	119,4(9)	$O_{(1)}C_{(11)}N_{(4)}$	119(1)
$N_{(3)}N_{(4)}C_{(11)}$	116,0(9)	$N_{(5)}C_{(5a)}C_{(9a)}$	121,2(9)	$O_{(1)}C_{(11)}C_{(12)}$	123(1)
$C_{(4a)}N_{(4)}C_{(11)}$	120,7(9)	$C_{(6)}C_{(5a)}C_{(9a)}$	119(1)	$N_{(4)}C_{(11)}C_{(12)}$	118(1)
$C_{(4a)}N_{(5)}C_{(5a)}$	115,4(8)	$C_{(5a)}C_{(6)}C_{(7)}$	121(1)	$C_{(2)}C_{(14)}C_{(15)}$	121(1)
$C_{(9a)}N_{(10)}C_{(10a)}$	118,4(9)	$C_{(6)}C_{(7)}C_{(8)}$	119(1)	$C_{(2)}C_{(14)}C_{(19)}$	120(1)
$C_{(9a)}N_{(10)}C_{(13)}$	121,7(9)	$C_{(7)}C_{(8)}C_{(9)}$	120(1)	$C_{(15)}C_{(14)}C_{(19)}$	119(1)
$C_{(10a)}N_{(10)}C_{(13)}$	117,4(9)	$C_{(8)}C_{(9)}C_{(9a)}$	120(1)	$C_{(14)}C_{(15)}C_{(16)}$	120(1)
$S_{(1)}C_{(2)}N_{(3)}$	129,0(8)	$N_{(10)}C_{(9a)}C_{(5a)}$	120(1)	$C_{(15)}C_{(16)}C_{(17)}$	119(1)
$S_{(1)}C_{(2)}C_{(14)}$	114,7(7)	$N_{(10)}C_{(9a)}C_{(9)}$	120(1)	$C_{(16)}C_{(17)}C_{(18)}$	122(1)
$N_{(3)}C_{(2)}C_{(14)}$	116,3(9)	$C_{(5a)}C_{(9a)}C_{(9)}$	120(1)	$C_{(17)}C_{(18)}C_{(19)}$	120(1)
$N_{(4)}C_{(4a)}N_{(5)}$	108,8(8)	$S_{(1)}C_{(10a)}N_{(10)}$	110,1(7)	$C_{(14)}C_{(19)}C_{(18)}$	121(1)

departures of atoms $N_{(5)}$ and $N_{(10)}$ from the plane of the benzene ring in (I) are −0.038 and 0.032 Å respectively.

The thiadiazine ring in (I) has the distorted boat conformation, atoms $N_{(4)}$ and $C_{(4a)}$ departing from the plane of the remaining four ring atoms (complied with to within 0.02 Å) by 0.039 and 0.63 Å. The Kremer–Pople parameters for this ring, modified according to [15], had the following values: $Q = 0.796$ Å, $\theta = 37.06°$, $\psi = 149.1°$, $\sigma = 1.39°$. The $C_{(2)} = N_{(3)}$ double bond in this ring (1.29 Å) is localized, and has the same value as that found in 2-phenylazo-4H-1,3,4-benzothiadiazine [16], but the $N_{(3)}$–$N_{(4)}$ bond in (I) (1.39 Å) is longer than that in the benzothiadiazine (1.335 Å). The increased length of the $N_{(3)}$–$N_{(4)}$ bond is probably due to the participation of the unshared electron pair at $N_{(4)}$ in conjugation with the $C_{(11)} = O_{(1)}$ double bond of the acetyl group. The $N_{(4)}$–$C_{(11)}$ bond length, 1.38 Å, is the same as that of the corresponding bond in (II), and the torsion angle $N_{(3)}N_{(4)}C_{(11)}O_{(1)}$ is −179.4°. The increase in the endocyclic valence angle at $C_{(2)}$ to 129.0°, also reported in [16], is usual for 1,3-thiazines [17, 18], as is the difference in the lengths of bonds $S_{(1)}$–$C_{(2)}$ (1.74 Å) and $S_{(1)}$–$C_{(10a)}$ (1.85 Å), due to the differing hybridization of atoms $C_{(2)}$ and $C_{(10a)}$. The plane of the phenyl substituent $C_{(14)}$–$C_{(19)}$ makes a dihedral angle of 24.5° with the planar portion of the thiadiazine ring.

In the crystal, the molecules of (I) are combined in centrosymmetric dimers (Fig. 2) by pairs of hydrogen bonds $N_{(5)}$–$H_{(5)} \cdots O_{(1)}$ of length 2.97 Å.

X-ray structural examination has thus provided information on the crystal structure of a tetrahydroquinoxaline condensed with a six-membered thiadiazine ring. The value found for the torsion angle $H_{(4a)}C_{(4a)}C_{(10a)}H_{(10a)}$ (60.4 ± 0.8°) is in good agreement with the PMR spectroscopic findings for the compound in solution, which correspond to the average state of the conformational equilibrium. Bearing in mind the similarities of the vicinal constants between $H_{(4a)}$ and $H_{(10a)}$ in the PMR spectra of (I) and tetrahydroquinoxalines condensed with other six-membered heterocycles (2-4 Hz, [8]), it may be regarded as highly

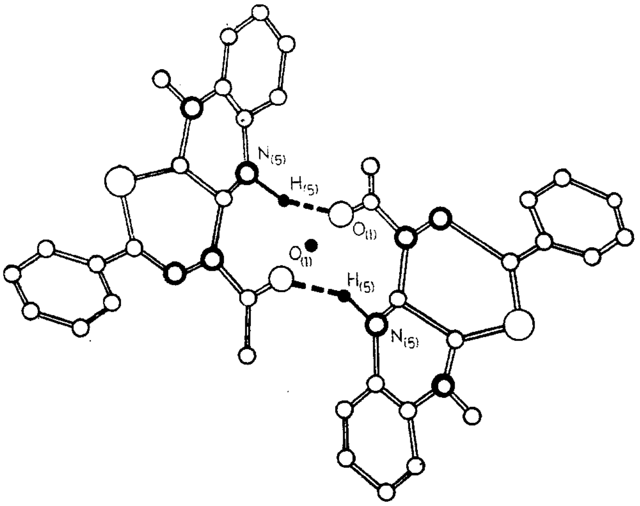


Fig. 2. Projection of the hydrogen-bonded dimer on plane XOZ.

TABLE 3. Coordinates of Nonhydrogen Atoms ($\times 10^4$) and Their Isotropic Equivalent Temperature Factors

Atom	x	y	z	B_{iso}^{eq}, Å^2
$S_{(1)}$	−379(1)	900(6)	6622(1)	4,09(9)
$O_{(1)}$	−2054(3)	4735(16)	4980(3)	5,8(3)
$N_{(3)}$	−857(3)	379(18)	5595(3)	4,1(3)
$N_{(4)}$	−1315(3)	2149(18)	5537(3)	4,1(3)
$N_{(5)}$	−1790(3)	2(16)	5966(3)	3,7(3)
$N_{(10)}$	−1225(4)	3375(17)	6800(3)	4,3(4)
$C_{(2)}$	−448(4)	−197(20)	6043(4)	3,5(4)
$C_{(4a)}$	−1520(4)	2456(21)	5921(4)	3,8(4)
$C_{(5a)}$	−1924(4)	−147(23)	6376(4)	3,4(4)
$C_{(6)}$	−2329(4)	−2043(21)	6374(4)	4,0(4)
$C_{(7)}$	−2466(5)	−2298(23)	6776(5)	5,2(5)
$C_{(8)}$	−2170(6)	−672(29)	7199(4)	5,7(5)
$C_{(9)}$	−1754(5)	1209(23)	7210(4)	4,4(4)
$C_{(9a)}$	−1628(4)	1452(22)	6799(4)	3,8(4)
$C_{(10a)}$	−1021(4)	3247(19)	6426(3)	3,7(4)
$C_{(11)}$	−1650(5)	3158(24)	5056(4)	4,6(5)
$C_{(12)}$	−1499(5)	2237(26)	4649(4)	5,9(5)
$C_{(13)}$	−880(4)	4976(22)	7239(4)	5,2(4)
$C_{(14)}$	23(4)	−2158(22)	6077(4)	3,8(4)
$C_{(15)}$	585(5)	−2214(23)	6489(4)	4,5(4)
$C_{(16)}$	1036(5)	−4050(27)	6504(4)	5,6(5)
$C_{(17)}$	895(5)	−5743(24)	6111(5)	5,1(5)
$C_{(18)}$	336(5)	−5683(25)	5693(4)	5,2(5)
$C_{(19)}$	−97(5)	−3954(26)	5674(4)	4,8(4)

likely that this structure is present in other compounds of this series, and is due to annelation of six-membered heterocycles to tetrahydropyrazines.

EXPERIMENTAL

4-Acetyl-10-methyl-2-phenyl-1,4,4a,5,10,10a-hexahydro-1,3,4-thiadiazino-[5,6-b]-quinoxaline (I) was obtained by acetylating the product of the cyclization of N-methylquinoxalinium iodide with thiobenzohydrazide [1].

The transparent acicular crystals of (I) were monoclinic. At 20°C, $a = 24.760(4)$, $b = 5.0433(6)$, $c = 29.686(2)$ Å, $\beta = 116.889(9)°$, $d_{calc} = 1.36$ g/cm^3, Z = 8, space group C2/c. The cell parameters and the intensities of 2705 independent reflexions, 999 of which had $I \geq 2\sigma$ and were used in calculating and refining the structure, were measured on a Hilger-Watts four-circle automatic diffractometer (λ_{MoK_α}, graphite monochromator, $\theta/2\theta$ scanning, $\theta \leq 30°$). The structure was calculated by the direct method using the MULTAN program, and refined by full-matrix least squares in anisotropic approximation for all the non-

TABLE 4. Coordinates of Hydrogen Atoms ($\times 10^3$)

Atom	x	y	z	Atom	x	y	z
$H_{(4a)}$	−186	402	583	$H_{(12.3)}$	−132	33	470
$H_{(5)}$	−219	−89	553	$H_{(13.1)}$	−113	552	734
$H_{(6)}$	−254	−335	604	$H_{(13.2)}$	−62	430	763
$H_{(7)}$	−278	−376	677	$H_{(13.3)}$	−51	604	731
$H_{(8)}$	−227	−81	751	$H_{(15)}$	68	−97	679
$H_{(9)}$	−153	239	753	$H_{(16)}$	146	−337	686
$H_{(10a)}$	−85	517	638	$H_{(17)}$	121	−707	611
$H_{(12.1)}$	−115	375	469	$H_{(18)}$	24	−698	539
$H_{(12.2)}$	−185	223	429	$H_{(19)}$	−52	−400	536

hydrogen atoms. All the hydrogen atoms were located by the difference series, but were not refined, and their contributions with $B_{iso} = 6$ Å^2 taken into account in calculating F_{calc}. The final stage of refinement was carried out using 915 reflections with $I \geq 5\sigma$, to divergence factors $R = 0.066$ and $R_w = 0.052$. All calculations were carried out on an Eclipse S/200 computer using the INEXTL program [19].

The coordinates of the nonhydrogen atoms are given in Table 3, and those of the hydrogen atoms in Table 4.

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