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SUBSTITUTED AND SPIRO-ANNELATED PERHYDRO-1,2,3-OXATHIAZINE 2,2-DIOXIDES AND 1-BENZYL-4-METHYLAZETIDINES

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We obtained perhydro-1,2,3-oxathiazine 2,2-dioxides by cyclization of 4-N-benzylamino-4-tetramethylene(phenyl-, methylphenyl-, dimethyl)but-1-enes in conc. H_2SO_4 at 25°C. When treated with an alcoholic solution of base, the oxathiazines are converted to 2-substituted and spiro-annelated 1-benzyl-4-methylazetidines.

Keywords: azetidines, homoallyl amines, 1,2,3-oxathiazine 2,2-dioxides.

The chemistry of completely hydrogenated 1,2,3-oxathiazine 2,2-dioxides has been virtually unstudied [1, 2]. This is because of the lack of simple methods for synthesis of such heterocyclic systems, difficulties encountered in their isolation, and also their high chemical lability.

Cyclization of *gem*-benzylaminoallylcyclohexane and -cyclooctane when treated with conc. H_2SO_4 in boiling chloroform was used earlier to obtain spiro[1,2,3-oxathiazine-4,1'-cyclohexane(-cyclooctane)], and they were subsequently cleaved to form the corresponding spiro[azetidine-2,1'-cycloalkanes] [3, 4].

With the aim of studying the limits of applicability for the method and the stereochemistry of the process, we studied cyclization of a series of homoallylamines **1a-d** when treated with sulfuric acid. The starting allylamines **1a-d** are readily formed by reaction of the corresponding Schiff's bases with allyl magnesium bromide [5, 6].

When amines **1a-d** are treated with excess conc. H_2SO_4 at 25°C, the 1,2,3-oxathiazine 2,2-dioxides **2a-d** are formed in 43%-83% yield. Formation of the oxathiazines **2** probably occurs through a cyclic ammonium salt, the subsequent dehydration of which when treated with excess H_2SO_4 yields the target compounds.

Oxathiazines **2** are finely crystalline white powders that are high-melting and poorly soluble in most organic solvents. Their structure has been proven by the totality of spectral data (Tables 1 and 2). The IR spectra of compounds **2a-d** are characterized by the presence of intense stretching vibration bands for the SO_2 group at 1370-1190 cm^{-1}. In the mass spectra of compounds **2**, there are no molecular ion peaks but we observe peaks for fragmentary ions $[M-80]^+$, corresponding to ejection of an SO_3 molecule from M^+. As we might expect, the maximum intensity in all cases is observed for ions with *m*/*z* 91, due to elimination of a benzyl radical from the nitrogen atom.

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TABLE 1. Physicochemical and Spectral Characteristics of Oxathiazines **2a-d** and Azetidines **3a-d**

Compound*	Empirical formula	Found, % / Calculated, %			*M*		mp, °C	R_f*[2]	IR spectrum, cm^{-1}, ν_{SO2}	Yield, %
		C	H	N	Found $[M]^+$	Calculated				
2a	$C_{15}H_{21}NO_3S$	60.89 / 60.81	7.23 / 7.09	4.98 / 4.73	215 $[M–SO_3]^+$	295	214-215.5	—	1298, 1190	43
2b	$C_{17}H_{19}NO_3S$	64.35	5.99	4.09 / 4.42	237 $[M–SO_3]^+$	317	87-100 (with decomp.)	—	1282, 1231	83
2c	$C_{18}H_{21}NO_3S$	65.26	6.34	4.03 / 4.23	—	331	185-190 (with decomp.	—	1370, 1215	69
2d	$C_{13}H_{19}NO_3S$	57.99	7.06	5.12 / 5.20	189 $[M–SO_3]^+$	296	225-227	—	1233, 1187	51
3a	$C_{15}H_{21}N$	83.89 / 83.72	10.01 / 9.77	6.48 / 6.51	215	215	—	0.50	—	31
3b	$C_{17}H_{19}N$	86.08	8.02	5.70 / 5.91	237	237	—	0.30	—	40
3c	$C_{18}H_{21}N$	86.06	8.37	5.55 / 5.56	251	251	—	0.47 0.55	—	30
3d	$C_{13}H_{19}N$	82.54	10.05	7.21 / 7.41	189	189		0.62	—	48

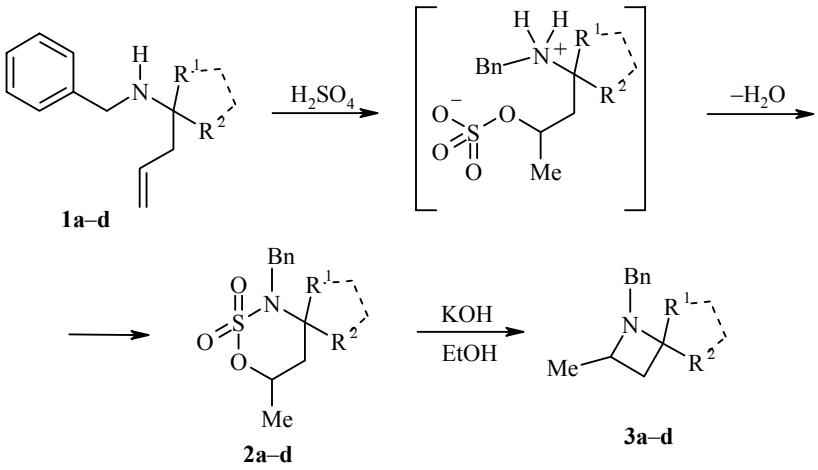
* For compounds **2b,c** and **3b,c**, data are given for isomer mixtures.

*[2] The R_f values were obtained in a mixture of ethyl acetate–hexane, 1:3 (compounds **3a,d**), 1:4 (compound **3b**), and 1:5 (compound **3c**).

TABLE 2. ^{1}H NMR Spectra of 1,2,3-Oxathiazine 2,2-Dioxides **2a-d**

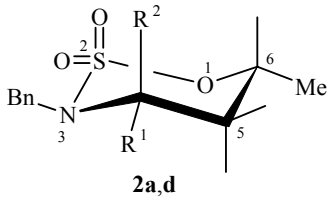
Compound*	Chemical shifts, δ, ppm								SSCC, *J*, Hz						
	4 dd	5*a*	5*e*	6	6-CH_3 d	NCH_2 AB	H–Ar m	R^1 R^2	4, 5*a*	4, 5*e*	5*a*, 5*e*	5*a*, 6	5*e*, 6	6, CH_3	CH_2N AB
2a	—	2.20 dd	1.67 dd	4.59 ddq	1.27	4.35 3.97	7.67-7.27	2.00-1.51 m	—	—	16.2	10.7	1.2	6.1	12.2
2b maj	4.11	2.71-2.48 m		4.64 dq	1.26	3.98 3.63	7.46-7.09 m		10.4	3.1	12.0	9.5	0	6.4	13.7
2b min	4.42	2.47 ddd	2.04 ddd	4.93 ddq	1.31	3.79 3.64			11.0	4.0	15.0	11.8	3.1	6.1	—
2c maj	—	2.75 dd	1.75 d	4.85 dq	1.36	3.95 3.47	7.75-7.15	1.49 s	—	—	15.8	10.4	0	5.2	13.1
2c min	—	2.45 dd	1.84 d	4.70 dq	0.97	4.04 3.83		1.99 s	—	—	15.6	10.1	0	5.8	—
2d	—	2.11 dd	1.65 dd	4.59 m	1.24	4.21 4.04	7.65-7.35	1.46 s 1.39 s	—	—	15.6	10.7	1.2	6.4	12.8

* The ^{1}H NMR spectra were taken in DMSO-d_6 (compound **2a**) and $CDCl_3$ (compound **2b-d**).



1, **2 a** $R^1+R^2=(CH_2)_4$; **b** $R^1=H$, $R^2=Ph$; **c** $R^1=Me$, $R^2=Ph$; **d** $R^1=R^2=Me$

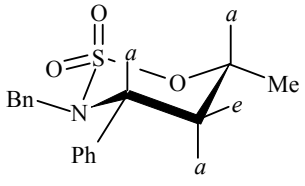
According to the ^1H NMR data (Table 2), the oxathiazines **2a** and **2d**, symmetrically substituted at $C_{(4)}$, are formed as a single geometric isomer which exists in the *chair* conformation with an equatorial 6-Me group. The ^1H NMR spectra of these compounds are characterized by the presence of a multiplet for the H-6 proton at 4.59 ppm. The spin–spin coupling constant J_{5a6a} = 10.7 Hz is clear evidence for an axial position for the H-6 proton.



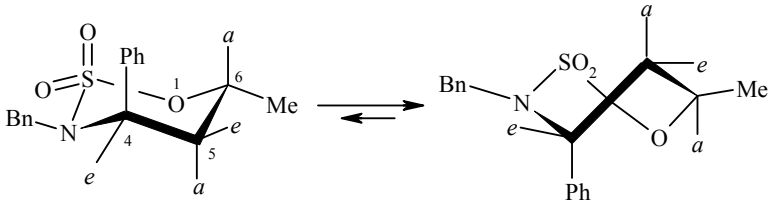
2a,**d**

Cyclization of the homoallylamines **1b** and **1c**, which are asymmetrically substituted at the position 4, occurs stereoselectively. Compounds **2b** and **2c** are formed as mixtures of two isomers with respect to the position of the substituents at $C_{(4)}$ and the methyl group at $C_{(6)}$ of the oxathiazine ring, in a ratio of ~1:1.7 and 1:1.8 respectively. This is indicated by the presence of a double set of signals for each group of protons in their ^1H NMR spectra (see Table 2). Detailed analysis of the spectra for mixtures of the **2b** and **2c** isomers allowed us to draw a conclusion concerning their structure. The spectrum of the minor **2b** isomer is characterized by the presence of large (11.0 and 11.8 Hz) and small (4.0 and 3.1 Hz) vicinal spin–spin coupling constants for the H-4 and H-6 protons, with chemical shifts of respectively 4.42 ppm and 4.93 ppm. Consequently, for this isomer we may hypothesize a *chair* conformation with an axial position for the H-4 and H-6 protons and an equatorial position for the 4-Ph and 6-Me groups.

In the ^1H NMR spectrum of the major **2b** isomer, for the H-6 proton with chemical shift 4.64 ppm we observe only one large spin–spin coupling constant J_{56} = 9.5 Hz; the second constant is equal to zero. For the H-4 proton with chemical shift 4.11 ppm, we observe two spin–spin coupling constants J_{45} = 10.4 Hz and 3.1 Hz. The values of these constants allow us to hypothesize a *twist* conformation for the major isomer. Thus in analogy with cyclization of 4-N-phenylamino- and 4-N-benzylamino-1-butenes to form 2-substituted 4-methyltetrahydroquinolines and 3-substituted 5-methyltetrahydrobenz-2-azepines [5-8], we may hypothesize that the isomers formed upon cyclization of homoallylamine **1b** have an equatorial position for the 6-Me groups and differ only in the orientation of the 4-Ph substituent.

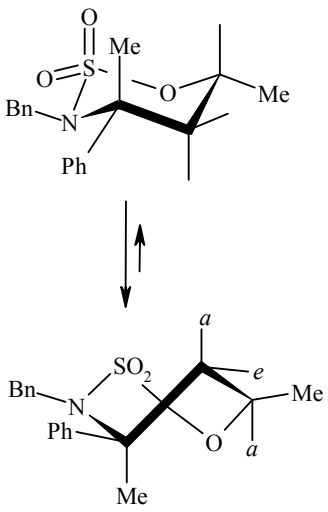


2b minor

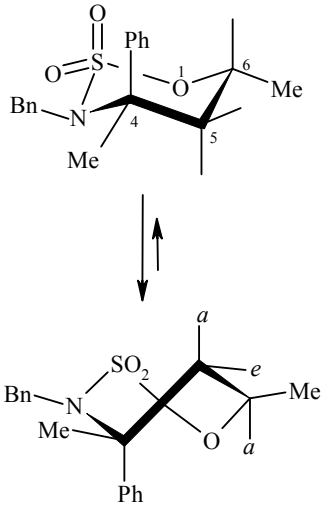


2b major

The minor isomer with an equatorial position of the substituents at $C_{(4)}$ and $C_{(6)}$ is energetically favorable, while the major isomer, due to steric 1,3-diaxial interaction, goes to the *twist* conformation, where these interactions are smaller. Evidence in favor of the indicated hypotheses comes from the results of cyclization of homoallylamine **1c** to form oxathiazine **2c**. In this case, we might also expect formation of two isomers with an equatorial 6-Me group and accordingly an equatorial and axial phenyl substituent at $C_{(4)}$.



2c minor



2c major

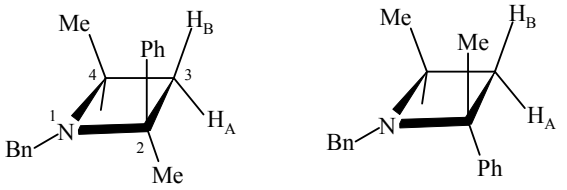
In both isomers, the 1,3-diaxial interaction of the substituents at $C_{(4)}$ is responsible for their existence in the *twist* form. In the ^{1}H NMR spectra of the **2c** isomers (Table 2), we observe only one spin–spin coupling constant J_{56} = 10.1 Hz for the minor isomer and 10.4 Hz for the major isomer. The second spin–spin coupling constant is J_{56} = 0.

Perhydrooxathiazine 2,2-dioxides **2a-d**, when treated with a 15% alcoholic solution of potassium hydroxide, are converted in 30-61% yield to azetidines **3a-d**, which are fluid oils. Based on literature data [9], we may suggest that in the first step, as a result of attack on the sulfur atom by the ethoxy dianion, cleavage of the N–S bond of the oxathiazine ring occurs. Subsequent nucleophilic attack on the amide anion formed at the carbon atom bearing the sulfo group leads to the final azetidine.

The structure of azetidines **3a-d** has been proven by spectral methods. In their IR spectra, we see no absorption bands for the NH and OH bonds. In the mass spectra, there are molecular ion peaks of medium intensity, corresponding to their empirical formulas. The main direction of decomposition of the molecular ion is associated with abstraction of a benzyl radical. In the mass spectra, we also observe ions that are characteristic for fragmentation of azetidines, due to the ring "breaking in half" at the $C_{(1)}$–$C_{(4)}$ and $C_{(2)}$–$C_{(3)}$ bonds.

Azetidines **3b** and **3c**, which are asymmetrically substituted at the 2 position, are formed as a mixture of isomers with respect to the position of the substituents at $C_{(2)}$ and $C_{(4)}$, in a ratio of ~1:1. In the starting oxathiazines **2b** and **2c**, the isomer ratio was 1:1.7 and 1:1.8; consequently, the reaction is not stereoselective.

In contrast to the **3b** isomers, the stereoisomers of azetidine **3c** have different chromatographic mobilities and were isolated using column chromatography.



3cA **3cB**

Their stereochemistry was established using the proton–proton nuclear Overhauser effect (NOE) (Table 3). The most pronounced NOE appears on protons of the methyl groups at $C_{(2)}$ and $C_{(4)}$. Thus in the spectrum of the chromatographically more mobile isomer **3cA** (R_f 0.55), there is no NOE for protons in the methyl groups, while in the spectrum of the less mobile **3cB** (R_f 0.47) we observe the NOE. Thus in isomer **3cA**, the methyl groups are *trans* to each other while in **3cB** they are *cis*.

The ^{1}H NMR spectra of azetidines **3a-d** (Table 4) are characterized by the presence of a doublet signal from the protons of the 4-Me group at 1.1-0.9 ppm (J_{4Me} = 5.8-6.2 Hz), two doublet-of-doublet signals from the methylene protons at $C_{(3)}$ with chemical shift 2.7-1.6 ppm, and a multiplet from the H-4 proton at 3.6-3.2 ppm. The methylene protons of the N-benzyl group are chemically nonequivalent, and are detected at 3.9-3.2 ppm (AB system, J_{AB} = 12.8-14.0 Hz).

TABLE 3. Assessment of the Nuclear Overhauser Effect (NOE) from the 1H NMR Spectra of Compounds **3cA** and **3cB**

C	NOE on protons*	Irradiated protons				
		{2-Me}	{3A-H}	{3B-H}	{4-H}	{4-Me}
3cA	2-Me		+			
	3A-H	+		+	+	
	3B-H		+			+
	4-H	+	+			+
	4-Me			+	+	
3cB	2-Me					+
	3A-H			+		
	3B-H	+	+			+
	4-H		+			+
	4-Me	+		+	+	

* The plus sign (+) marks NOE's exceeding 3%.

TABLE 4. ^{1}H and ^{13}C NMR Spectra of Azetidines **3a-d***

Compound	Chemical shifts, δ, ppm								SSCC, *J*, Hz						
	2 dd	3A	3B	4	4-Me d	NCH_2 AB	H–Ar m	R^1 R^2	2,3A	2,3B	3A,3B	3A,4	3B,4	4,Me	CH_2N AB
3a	—	1.96 dd	1.64 dd	3.19 ddk	0.90	3.69 3.46	7.45-7.10	1.25-2.00 m	—	—	9.8	7.3	8.2	6.1	12.8
3bA	3.23	1.83 m	2.21 m	3.40 m	0.85	3.87 3.51	7.50-7.10	—	8.2	6.9	10.0	8.2	7.3	6.1	12.8
3bB	3.00	~1.90*[2] m	2.80 m	~3.50*[2] m	1.05	3.48 3.15	7.50-7.10	—	7.0	8.0	10.0	7.2	7.2	6.1	12.8
3cA	—	1.81 dd	2.23 dd	3.37 m	0.83	3.91 3.53	7.50-7.10	1.60s	—	—	10.1	8.2	7.3	5.8	13.1
3cB	—	1.92 dd	2.75 dd	3.56 m	1.09	3.44 3.21	7.50-7.10	1.64s	—	—	11.0	7.0	7.6	6.1	14.0
3d	—	1.90 dd	2.20 dd	3.22 ddk	0.90	3.70 3.40	7.45-7.15	0.85s 0.89s	—	—	9.7	7.0	8.0	6.1	13.0

* The chemical shifts in the ^{13}C NMR spectra were measured relative to the signal for the solvent $CDCl_3$, δ 77.0 ppm. ^{13}C NMR spectrum, δ, ppm for **3cA**: 150.31 and 140.17 (s, quaternary-Ph), 128.93, 127.89, 127.88, 124.67 (d, m, *o*-Ph), 126.57 and 125.81 (d, *p*-Ph), 63.65 (s, $C_{(2)}$), 57.64 (d, $C_{(4)}$), 55.49 (t, CH_2N), 41.96 (t, $C_{(3)}$), 20.43 (q, 2-Me), 22.85 (q, 4-Me). For compound **3cB**: 144.27 and 140.27 (s, quaternary-Ph), 128.53, 127.85, 127.78, 126.53 (d, m, *o*-Ph), 126.49 and 126.32 (d, *p*-Ph), 63.09 (s, $C_{(2)}$), 55.99 (d, $C_{(4)}$), 53.44 (t, CH_2N), 40.41 (t, $C_{(3)}$), 29.14 (q, 2-Me), 21.74 (q, 4-Me).

*[2] An exact determination was difficult due to the mutual overlap of the proton signals.

In the ^{13}C NMR spectra (Table 4) for the **3cA** and **3cB** isomers, we observe signals from all the carbon atoms in the molecule; their multiplicity and spin–spin coupling constants also correlate well with the structure. In particular, at 53.44-65.09 ppm we see signals from the N–CH_2 carbon atoms, $C_{(2)}$ and $C_{(4)}$, bonded to the electronegative nitrogen atom.

EXPERIMENTAL

The IR spectra were recorded on UR-20 or Specord IR-75 spectrometers in KBr disks (for the crystalline compounds) or in a film (for the oils). The mass spectra were recorded on Finnigan MAT 95 XL and HP MS 5988 mass spectrometers with direct injection of the sample into the ion source. Ionizing potential 70 eV. The ^1H and ^{13}C NMR spectra were obtained at 20°C on a Bruker WP-200 (200 MHz) or a Bruker WH-400 (400 MHz and 100 MHz for ^1H and ^{13}C respectively), internal standard TMS. For the TLC, we used Silufol UV-254 plates (visualization by iodine vapor).

The physicochemical and spectral characteristics are given in Tables 1, 2, and 4.

3-Benzyl-6-methyl-3,4,5,6-tetrahydrospiro[1,2,3-oxathiazine-2,2-dioxide-4,1'-cyclopentane] (2a), 6-Methyl-3,4,5,6-tetrahydro-4-phenyl- (2b), [-4,6-Dimethyl-4-phenyl- (2c), -4,4,6-Trimethyl- (2d)]-3-benzyl-1,2,3-oxathiazine-2,2-dioxides (General Procedure). Homoallyl amine **1a-d** (0.015 mol) were added carefully to 96% H_2SO_4 (25 ml) that had been cooled down to ~0°C. The reaction mixture was stirred until completely homogenized, and then allowed to stand at room temperature for 24 hours. The next day, the reaction mass was poured over ice (~100 cm^3), neutralized with a 25% aqueous solution of ammonia while cooled with ice water, and the pH was brought up to pH ~8-9. The reaction products were extracted with chloroform (5 × 40 ml), and the extract was dried with Na_2SO_4. After the solvent was removed, the crystals that precipitated were washed several times with ethyl acetate. Oxathiazines **2** were obtained as finely crystalline white powders.

1-Benzyl-4-methylspiro[azetidine-2,1'-cyclopentane] (3a), 1-Benzyl-4-methyl-2-phenylazetidine (3b), 2,4-Dimethyl-2-phenyl- (3c), 1-Benzyl[2,2,4-trimethyl- (3d)]azetidines (General Procedure). Oxathiazine **3a-d** (7.00 mmol) was boiled in a 15% ethanol solution of KOH (25 ml) for 20 h. Then the reaction mass was poured into water (100 mL) and extracted with ether (3 × 50 ml), and then the extract was dried with $MgSO_4$. After the solvent was driven off, the residue was purified on aluminum oxide (2 × 2 cm), with ether as the eluent. Azetidines **3a-d** were obtained as yellow fluid oils. The mixture of isomers of compound **3c** was chromatographed on a column (25 × 0.7 cm) with aluminum oxide; the eluent was 1:30 ethyl acetate–hexane. We individually isolated azetidines **3cA** (11%, R_f 0.55) and **3cB** (7%, R_f 0.47)

The yields, physicochemical characteristics, and elemental analysis data for azetidines **3a-d** are given in Table 1; the ^1H and ^{13}C NMR spectroscopy data are given in Table 4.

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