SYNTHESIS AND DYNAMIC STEREOCHEMISTRY OF 1,5-DISUBSTITUTED 2,3,4,5-TETRAHYDRO-1H-1,5-BENZODIAZEPIN-2-ONES

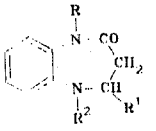
B. A. Puodzhyunaite, R. A. Yanchene,
Z. A. Stumbryavichyute, and P. P. Mikul'skis

UDC 547.892:541.63'128:543.422.25

The 1-isopropyl and 1-benzyl derivatives of 1,5-tetrahydrobenzodiazepin-2-one were synthesized by alkylation under the conditions of phase-transfer catalysis. The inversion of the heterocycle was studied by PMR spectroscopy, and the free energies of activation were determined.

The stereochemical characteristics of some 1,5-benzodiazepines and dihydro-1,5-benzodiazepin-2-ones have been studied before by a number of authors [1-3]. Here it was established that the molecules of these compounds have the boat conformation, which inverts at various rates depending on the temperature and on the structure of the substances. Tetrahydro-1H-1,5-benzodiazepin-2-ones have been studied little in this respect.

In the present work we consider aspects of the synthesis, the dynamic stereochemistry, and the conformational analysis of 1,5-disubstituted tetrahydrobenzodiazepin-2-ones, represented by the general formula I-III.



I–III

Ia-c R = $CH_2C_6H_5$, R^2 = $COCH_3$; a R^1 = H; b R^1 = CH_3; c R^1 = C_6H_5; II R = $CH(CH_3)_2$, R^1 = R^2 = H; IIIa-g R = $CH(CH_3)_2$, R^1 = H; a R^2 = $COCH_3$; b R^2 = $COCH_2Cl$; c R^2 = $CO(CH_2)_2Cl$; d R^2 = $CO(CH_2)_3Cl$; e R^2 = $CONH_2$; g R^2 = CHO

The 1-alkyltetrahydro-1,5-benzodiazepin-2-ones were obtained for the first time by alkylation under conditions of phase-transfer catalysis in the benzene–50% aqueous sodium hydroxide system in the presence of quaternary ammonium salts. Thus, the 1-alkyl derivatives Ia-c were synthesized by the reaction of the previously described 5-acetyl-4-methyl-5-acetyl, and 4-phenyl-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-ones (IV, V, VI) [5, 6] with benzyl bromide. The above-mentioned method cannot be used for the production of compounds IIIb-d, g since the initial 5-substituted derivatives containing ω-halogenoacyl or formyl groups are unstable under the conditions of phase-transfer catalysis. These compounds were obtained by the following method. From 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (VII) [7] and isopropyl bromide under the conditions of phase-transfer catalysis, the 1-isopropyl derivative (II) is formed. Its acylation by the method in [4] by the appropriate agents gave compounds IIIb-d. The formyl derivative IIIg was obtained by the reaction of II with a mixture of formic acid and acetic anhydride. The carbamoyl derivative IIIe was obtained by the reaction of the derivative II with sodium cyanate according to the method in [7].

Analysis of the data from the PMR spectra of compounds Ia and IIIa-e at the temperature of the instrument showed that the signals for the methylene protons of the ethylene fragment

Institute of Biochemistry, Academy of Sciences of the Lithuanian SSR, Vil'nyus, 232021.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 254-258, February, 1986. Original article submitted November 26, 1984; revision submitted February 12, 1985.

 0009-3122/86/2202-0206$12.50

TABLE 1. Derivatives of 2,3,4,5-Tetrahydro-1H-1,5-benzodiazepin-2-one (I-III)

Compound	mp, °C	Found, %				Molecular formula	Calculated, %				Yield, %
		C	H	Cl	N		C	H	Cl	N	
Ia	138—139	73,6	6,3	—	9,6	$C_{18}H_{18}N_2O_2$	73,5	6,2	—	9,5	92
Ib	188—190	73,6	7,0	—	9,0	$C_{19}H_{20}N_2O_2$	73,5	7,1	—	9,0	72
Ic	201—203	78,1	6,1	—	7,4	$C_{24}H_{22}N_2O_2$	77,8	6,0	—	7,6	92
II	243 dec.	59,9	6,9	14,7	11,5	$C_{12}H_{16}N_2O \cdot HCl$	59,9	7,1	14,7	11,6	48
IIIa	123—125	68,5	7,2	—	11,5	$C_{14}H_{18}N_2O_2$	68,3	7,4	—	11,4	36
IIIb	153—155	60,0	6,1	12,5	9,9	$C_{14}H_{17}ClN_2O_2$	59,9	6,1	12,6	9,9	60
IIIc	126—128	61,0	6,9	12,1	9,6	$C_{15}H_{19}ClN_2O_2$	61,1	6,5	12,0	9,5	60
IIId	110—112	62,4	7,1	11,6	9,1	$C_{16}H_{21}ClN_2O_2$	62,2	6,9	11,5	9,1	63
IIIe	217—219	63,4	6,7	—	17,0	$C_{13}H_{17}N_3O_2$	63,1	6,9	—	17,0	85
IIIg	102—104	67,4	6,7	—	12,0	$C_{13}H_{16}N_2O_2$	67,2	6,9	—	12,1	61

*Compounds Ia-c, IIIa were recrystallized from a mixture of benzene and hexane, IIIb, g from a mixture of benzene and ether, IIIc, d from ether, IIIe from benzene, and the hydrochloride of II from absolute alcohol.

TABLE 2. Spectral Characteristics and Free Energy of Activation of the Derivatives IIIa-g, Ia

Compound	Chemical shifts, δ, ppm at 34°C in $CDCl_3$				$\Delta\nu_{max}$*, Hz	T_c, K	$\Delta G^{\neq}$, kJ/mole
	$(CH_3)_2C$, d	1-N—CH, septet	3-CH_2, m	4-CH_2, m			
IIIa	1,12 1,42	4,70	2,4	3,39 4,78	28,7	373	79,0±0,4
IIIb	1,14 1,44	4,66	2,4	3,49 4,80	26,7	374	79,5±0,4
IIIc	1,13 1,42	4,63	2,5	3,40 4,72	26,4	380	80,6±0,4
IIId	1,13 1,42	4,63	1,7—2,7	3,37 4,81	25,8	377	80,1±0,4
IIIe	1,10 1,42	4,63	2,4	3,39 4,80	27,3	350	74,1±0,4
IIIg	1,20, bd	4,60	2,49, t	3,0—4,8, bs	36,4	295	61,7±0,4
Ia	—	—	—	—	83,1	383	78,0±1,0

*For compounds IIIa-g the difference between the chemical shifts of the protons of the geminal methyl groups in $CHCl_2CHCl_2$, and for (Ia) the difference between the chemical shifts of the methylene protons of the benzyl substituent in DMSO-D_6, J_{AB} = 14.9 Hz.

of the heterocycle form an ABMX spin system (Tables 2 and 3). The difference between the chemical shifts of the geminal protons at the $C_{(3)}$ atom of the heterocycle (the AB part) is small and amounts to 0.1-0.2 ppm, whereas the signals for the geminal protons of the methylene group at position 4 (the MX part) are observed in the downfield region and represent two multiplets with $\Delta\delta$ = 1.4 ppm. Such a large difference in the screening of the protons is evidently due to the steric effect of the anisotropic carbonyl group of the substituent. In compounds IIIa-e the geminal methyl groups in the 1-isopropyl substituent are then equivalent, and two doublets are observed with $\Delta\delta$ = 0.3 ppm. In compounds Ia-c the geminal protons of the 1-benzyl substituent are nonequivalent and form an AB spin system with $\Delta\delta$ = 0.7-0.9 ppm. It should be noted that for compound IIIg, which contains a formyl group at position 5, the nature of the signals for the methylene protons at positions 3 and 4 and the broadened doublet for the methyl protons show that the system is in a fairly labile state. Thus, comparison of the spectra of compounds IIIg with IIIa-e and Ia shows that the intramolecular mobility of the molecules is substantially affected by the structure and the nature of the substituent at position 5, as we have demonstrated for other 5-substituted derivatives of tetrahydro-1,5-benzodiazepin-2-ones [8].

Investigation of the temperature dependence of the spectra of compounds Ia and IIIa-g demonstrates the intramolecular mobility of the heterocycle. With increase in temperature the signals for the protons of the methylene groups at the $C_{(3)}$ and $C_{(4)}$ atoms become broader and,

TABLE 3. Parameters of the PMR Spectra of Compounds Ia-c in DMSO-D_6

Observed signals of groups	Chemical shifts, δ, ppm, and SSCC, J, Hz (in DMSO-D_6)					
	Ia		Ib		Ic	
	34°	185°	34°	185°	34°	185°
1-N—CH_2	4,62 5,51 $^2J = 14,9$	4,07, s	4,62 5,37 $^2J = 14,9$	4,71 5,14	4,68 5,43 $^2J = 14,9$	4,77 5,20
3-CH_2	2,43, m*	2,43, t	2,12 2,37 $^3J = 13,0$ $^2J = 13,0$	2,15 2,37 6,0	2,82 2,64 $^3J = 12,5$; $^2J = 12,5$	2,84 2,63 6,5
4-CH_2	3,37, m 4,71, m	4,02, t				
4-CH			5,03, m	5,00, m	6,01, m	6,03, m
4-CH_3			0,93, d	0,98, d		
CH_3CO	1,10, s	1,33, s	0,97, s	1,22, s	0,96, s	1,23, s

*Overlap with the solvent signals.

TABLE 4. Chemical Shifts and Spin—Spin Coupling Constants Calculated for the Fragment of the Heterocycle $CH^3H^4—CH^1$ (H^2 or R^1) in the Molecules of Compounds (Ia-c) in $CDCl_3$

Compound	Chemical shifts, δ, ppm				SSCC, J, Hz					
	H^1	H^2	H^3	H^4	12	13	14	23	24	34
Ia	4,93	3,41	2,57	2,48	−12,8	14,4	5,5	6,4	2,4	−13,3
Ib	5,28		2,24	2,36		12,8	5,3			−12,7
Ic	6,23		2,87	2,71		12,5	6,1			−13,0

passing through the coalescence points, are converted into triplets or broadened triplets, respectively. The behavior of the signals for the protons of the substituents at position 1 is similar; the signals for the protons of the methyl groups in compounds IIIa-g here are converted into a doublet, while the signals for the methylene protons of the benzyl substituent in the derivative (Ia) are converted into a singlet. The free energies of activation were determined at the coalescence temperature from the signals for the methylene protons at position 4 of the heterocycle and the geminal methyl groups or methylene protons of the substituents at the first nitrogen atom on the basis of the approximate equations [9]. The barriers to inversion of the seven-membered ring for compounds IIIa, g, and Ia, determined from the signals of the methylene protons in the heterocycle, have the following values: $\Delta G^{\neq}$ = 79.7 kJ/mole ($\Delta\nu$ = 129.5 Hz, T_c = 399 K), $\Delta G^{\neq}$ = 61.5 kJ/mole ($\Delta\nu$ = 100.0 Hz, T_c = 308 K), and $\Delta G^{\neq}$ = 78.6 kJ/mole ($\Delta\nu$ = 123.1 Hz, T_c = 393 K), respectively. The comparable values for the free energies of activation, obtained from the signals of the exocyclic (Table 2) and cyclic protons for these compounds, give reason to suppose that the averaging of the signals of the substituents takes place synchronously with the averaging of the signals for the protons of the heterocycle and characterize the inversion of the molecules. A similar pattern has been observed for the 1-N derivatives of dihydro-1,5-benzodiazepin-2-ones [3] and dihydro-1,4-benzodiazepin-2-ones [9, 10]. The authors of the last papers explained this by the fact that the inversion of the nitrogen is a fast process compared with the inversion of the ring [3].

The dependence of the free energy of activation $\Delta G^{\neq}$ on the nature of the substituent at the nitrogen atom at position 5 is obvious (Table 2). The increase of 17.3 kJ/mole in $\Delta G^{\neq}$ for the N-acetyl derivative (IIIa) compared with the N-formyl derivative IIIg is probably due to steric hindrances. The increase in the length of the alkyl chain of the acyl substituent in compounds IIIb-d does not lead to significant changes in the size of the inversion barrier.

The dependence of the inversion rate of the heterocycle on the nature of the substituents at position 4 was studied for the derivatives Ia-c (Table 3). The spectra of compounds Ib, c at the instrument temperature contain signals for the methylene protons at the $C_{(3)}$ atom and the methine protons at the $C_{(4)}$ atom, which form an ABX system. Whereas averaging of all the signals for the nonequivalent protons was observed in compound Ia with increase in temperature,

in compounds Ib, c containing substituents at the $C_{(4)}$ atom of the heterocycle increase in temperature to 185°C did not lead to broadening of the signals or to appreciable changes in the chemical shifts and spin–spin coupling constants. This confirms that the presence of bulky substituents (R^1 = CH_3 and C_6H_5) prevents inversion of the heterocycle. A similar effect from the methyl substituent on the inversion rate has been observed in 7-chloro-3-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepine [11].

The values of the spin–spin coupling constants provide information on the positions of the protons and the substituents at the $C_{(3)}$ and $C_{(4)}$ atoms of the heterocycle in the molecules of compounds Ia-c. From comparison of the vicinal spin–spin coupling constants (Table 4) it is seen that in compounds Ib and Ic the substituents at the $C_{(4)}$ atom are in the pseudoquatorial position [12].

EXPERIMENTAL

The reactions and the purities of the compounds were monitored on Silufol UV-254 plates in the 14:7:1.5 chloroform–ethyl acetate–methanol system. The PMR spectra were recorded on a Hitachi R-22 spectrometer at 90 MHz with HMDS as internal standard. The temperature was measured with an accuracy of ±1°C. The calculations on the ABMX (Ia) and ABX (Ib, c) spin systems were made by means of the LAOCN3 program [13].

The characteristics of compounds I-III are given in Table 1.

1-Benzyl-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (Ia). To a mixture of 3.06 g (15 mmoles) of compound IV, 100 ml of benzene, 11.25 ml of a 50% aqueous solution of sodium hydroxide, and 0.34 g (1.5 mmoles) of benzyltriethylammonium chloride we added 5.13 g (30 mmoles) of benzyl bromide. The mixture was boiled for 2 h with vigorous stirring. After cooling the benzene layer was separated, washed with water until the washing water was neutral, and evaporated. The residue was recrystallized. The derivatives Ib and Ic were obtained similarly from V and VI, and IIIa was obtained from IV and isopropyl bromide, except that the reaction mixture was boiled for 6 h.

1-Isopropyl-2,3,4-5-tetrahydro-1H-1,5-benzodiazepin-2-one (II). To a mixture of 6.4 g (40 mmoles) of compound VII, 150 ml of benzene, 60 ml of a 50% aqueous solution of sodium hydroxide, and 1.6 g (4 mmoles) of tetrabutylammonium bromide we added 19.68 g (160 mmoles) of isopropyl bromide. The reaction was then continued as for compound IIIa. After evaporating the solvent, we obtained the diazepinone II in the form of an iol, which we used in the subsequent syntheses. Compound II was identified in the form of the hydrochloride, which was isolated by saturating a solution of the base II in absolute ether with gaseous hydrogen chloride. After recrystallization we obtained 4.6 g (48%) of hydrochloride of II. PMR spectrum (DMSO-D_6): 1.12 (6H, d, CH_3); 2.28 (2H, t, 3-CH_2); 3.55 (2H, t, 4-CH_2); 4.5 (1H, m, CH); 7.3-7.7 ppm (4H, Ph).

1-Isopropyl-5-chloroacetyl-2.3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (IIIb). To a solution of 2.04 g (10 mmoles) of II and 0.79 g (10 mmoles) of dry pyridine in 20 ml of absolute benzene, while stirring and cooling to 0°C, we added a solution of 1.1 g (10 mmoles) of chloroacetyl chloride in 10 ml of absolute benzene over 20 min. The mixture was allowed to heat to room temperature, kept at 50°C for 3 h, cooled, washed with acidic water and with water, and evaporated. The residue was recrystallized.

Compounds IIIc, d were obtained similarly from the diazepinone II and β-chloropropionyl and γ-chlorobutyryl chlorides.

1-Isopropyl-5-carbamoyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (IIIe). To a mixture of 2.4 g (10 mmoles) of the hydrochloride of II and 1.3 g (20 mmoles) of sodium cyanate in 70 ml of absolute benzene, while stirring, we added 1.5 ml (20 mmoles) of trifluoroacetic acid. After 0.5 h we added a further 0.65 g (10 mmoles) of sodium cyanate and 0.75 ml (10 mmoles) of trifluoroacetic acid. The same amount of the reagents was added again after 2.5 h. The mixture was heated to 60°C and kept at this temperature for 5 h. The benzene layer was decanted, the oily precipitate was mixed with water, the mixture was neutralized with potassium carbonate, and the product was extracted with chloroform. The extract was evaporated, and the residue was recrystallized. We obtained 2.1 g of the derivative IIIg.

1-Isopropyl-5-formyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (IIIg). To 31 ml of acetic anhydride we added 1.31 ml of 98% formic acid. The mixture was kept at 50°C for 2 h. To the obtained mixture we added a solution of 6.12 g (30 mmoles) of the diazepinone II in 30 ml of absolute benzene. The mixture was kept at room temperature for 20 h, the solvent was evaporated, and the residue was recrystallized. We obtained 4.2 g of IIIg.

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HOMOLYTIC ADDITION OF 1,3-OXATHIOLANE TO UNSATURATED HYDROCARBONS

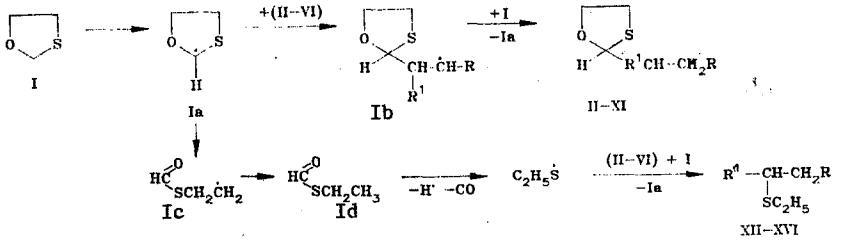
S. V. Nikolaeva, V. V. Zorin,
S. S. Zlotskii, and D. L. Rakhmankulov

UDC 543.51:541.63:547.787

The homolytic addition of 1,3-oxathiolane to olefins takes place with the formation of 2-substituted 1,3-oxathiolanes and insignificant amounts of functional derivatives of sulfides.

It is known that 1,3-dioxacycloalkanes add to olefins forming, in the general case, 2-substituted dioxacycloalkanes and functional derivatives of esters [1, 2]. The reaction with 2-methyl-1,3-oxathiolane proceeds similarly [3]. In this paper, the direction of the homolytic addition of 1,3-oxathiolane to unsaturated compounds has been studied in order to determine the effect of the nature of the olefin on the course of the reaction.

We have established that, in contrast to 2-methyl-1,3-oxathiolane, the reaction of 1,3-oxathiolane, I, with unsaturated compounds II-VI in the presence of tert-butyl peroxide at 140°C for one hour forms 2-substituted 1,3-oxathiolanes VII-XI and the corresponding sulfides XII-XVI.



II, VII, XII R=$COOCH_3$, III, VIII, XIII R=$OC(O)CH_3$, IV, IX, XIV R=CN, V, X, XV R=OC(O)H, VI, XI, XVI R=$CH_2CH_2CH_2CH_3$; II, VII, XII R^1=$COOCH_3$, III—VI, VIII—XI, XIII—XV R^1=H

Ufa Petroleum Institute, Ufa 450062.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 259-263, February, 1986. Original article submitted December 3, 1984; revision submitted March 12, 1985.

0009-3122/86/2202-0210$12.50