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1,3-THIAZEPINES.
1. SYNTHESIS AND SPECTRAL PROPERTIES OF 2-IMINOHEXAHYDRO-1,3-THIAZEPINES

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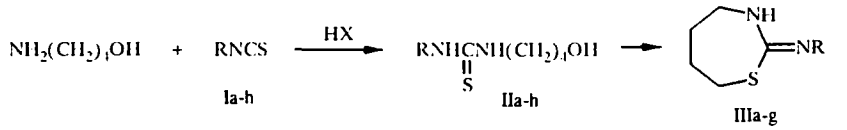
By reaction of 4-amino-1-butanol with isothiocyanates RNCS, we have synthesized N-(4-hydroxybutyl)-N'-R-thioureas, which by cyclization when treated with hydrohalic acids are converted to the corresponding 2-(R)-imino)hexahydro-1,3-thiazepines. The structure of the compounds obtained has been confirmed by PMR, IR, and mass spectra.

2-Amino-1,3-thiazepines and their hydrogenated derivatives are a little studied class of heterocyclic amines [1, 2] which contain an ambifunctional system of atoms N–C=N, making it possible to expect formation of both substituted amines and imines in nucleophilic substitution and addition reactions. Moreover, they are certainly of interest as compounds exhibiting biological activity [3-5].

With the goal of synthesizing new derivatives of aminothiazepine and studying their physicochemical properties, we have reacted 4-amino-1-butanol with isothiocyanates (Ia-h). The N-(4-hydroxybutyl)-N'-substituted thioureas formed in this case (IIa-h) without additional purification were subjected to dehydration and cyclization by boiling with concentrated hydrohalic acids.



Ia-h IIa-h IIIa-g

X = Br, Cl; a R = CH_2Ph, b R = Ph, c R = $C_{10}H_7$-α; d R = $C_6H_4NMe_2$-4, e R = $C_6H_3Me_2$-2,6, f R = $C_6H_2Me_3$-2,4,6, g R = $C_6H_4CF_3$-3, h R = $CH_2=CHCH_2$

For purposes of identification, the products IIa-h were isolated in pure form and characterized (Table 1). Compounds IIa, b have been described previously in [6]. From all the isothiocyanates except Ih, we obtained the corresponding target hexahydrothiazepines (IIIa-g). In the case of the allylisothiocyanate Ih, in an attempt to isolate product IIIh from acid solution by neutralization we observed its rapid decomposition with liberation of sulfur. This also occurred in synthesis of compound IIIh from purified thiourea IIh. Apparently it is as unstable as 2-aminotetrahydrothiazepine [7].

The structure of the synthesized thioureas IIc-h and the thiazepine derivatives IIIa-g was confirmed by PMR, IR, and mass spectra (Tables 2 and 3). Earlier, in analogy to 1,3-thiazepines, the structure of a substituted amine was assigned to compound IIIa and an imine structure was assigned to compound IIIb [6].

In the IR spectra of compounds IIc-h, there are absorption bands for NH and OH groups connected by a hydrogen bond. In the spectra of hexahydrothiazepines IIIa-g, these bands (due to the absence of OH groups) are shifted toward lower frequencies. The absorption of the C=N bond in these compounds is observed in the range 1617-1630 cm^{-1}, which is characteristic for the imine structure we propose (see the scheme) but contradicts the amine structure assigned earlier [6] to product IIIa.

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TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
IIc	$C_{15}H_{18}N_2OS$	65,71 / 65,66	6,59 / 6,61	10,17 / 10,21	117,5 - 118	66
IId	$C_{13}H_{21}N_3OS$	58,24 / 58,39	7,88 / 7,92	15,64 / 15,71	112,5 - 113,5	87
IIe	$C_{13}H_{20}N_2OS$	61,95 / 61,87	7,88, / 7,98	10,97 / 11,10	86 - 87	99
IIf	$C_{14}H_{22}N_2OS$	63,00 / 63,12	8,41 / 8,32	10,49 / 10,52	56 - 57	42
IIg	$C_{12}H_{15}F_3N_2OS$	49,17 / 49,31	4,89 / 5,17	9,71 / 9,58	59 - 60	86
IIh	$C_8H_{16}N_2OS$	50,92 / 51,03	8,28 / 8,56	14,59 / 14,88	Oil	63
IIIa	$C_{12}H_{16}N_2S$				70,5 - 71,5	30
IIIb	$C_{11}H_{14}N_2S$				127 - 128	57
IIIc	$C_{15}H_{16}N_2S$	70,22 / 70,27	6,17 / 6,29	10,87 / 10,93	154 - 155	45
IIId	$C_{13}H_{19}N_3S$	62,54 / 62,61	7,69 / 7,68	16,81 / 16,85	143 - 144	50
IIIe	$C_{13}H_{18}N_2S$	66,69 / 66,62	7,63 / 7,74	11,77 / 11,95	127 - 127,5	77
IIIf	$C_{14}H_{20}N_2S$	67,76 / 67,70	8,15 / 8,12	11,05 / 11,28	130 - 131	78
IIIg	$C_{12}H_{13}F_3N_2S$	52,39 / 52,54	4,62 / 4,78	10,13 / 10,21	130 - 131	56

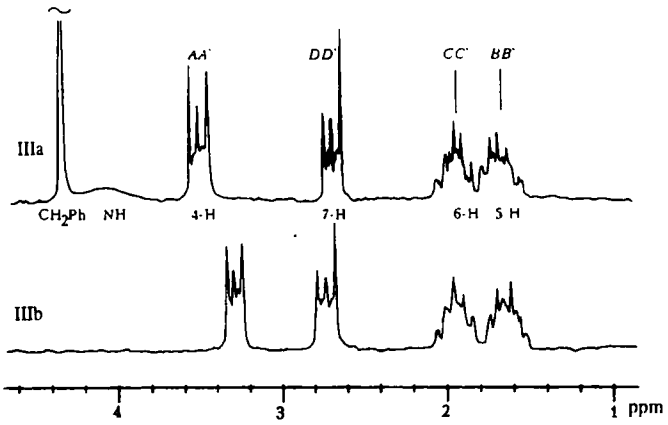

Fig. 1. Signals from protons of methylene groups on the heterocycle in PMR spectra of compounds IIIa and IIIb.

In the mass spectra of thioureas IIc-h, there are intense peaks for molecular ions and also the fragments $RNCS^+$ and RNH_2^+. There are important differences in the behavior of hexahydrothiazepines IIIa-g under electron impact. Compound IIIa is characterized by low probability of formation of the fragment RN = C = NH^+ (*m/z* 132; $C_8H_8N_2$; 132.06950) and pronounced decomposition with formation of fragmentary ions RNH^+ and R^+ (*m/z* 106 and 91 respectively). In the spectra of compounds IIIb-g, on the other hand, there is an intense signal from the indicated fragment and there is no peak from the RNH ion (except for compound Id) (Table 3).

In the PMR spectra of substituted thioureas IIa-h, the methylene protons are represented by two complex four-proton multiplets in the ranges 1.4-1.7 and 3.4-3.7 ppm. In the spectra of compounds IId-g, the signal from the hydroxyl proton has the form of a broadened singlet in the region 1.75-1.90 ppm, while in the spectra of compounds IIc and IIh it overlaps with the signals from the methylene protons. The protons of the NH groups of thioureas IIc-g appear as two broadened singlets in the region 5.67-6.85 and 7.50-8.18 ppm (in the case of naphthylthiourea IIc, the downfield signal overlaps with the signals from

TABLE 2. Spectral Characteristics of Compounds IIc-h

Compound	IR spectrum ν, cm^{-1}		Mass spectrum m/z (I, %)			PMR spectrum, δ, ppm						
	NHC=S	NH, OH	M^+	$RNCS^+$	Other fragments	$-CH_2CH_2-$ (4H, m)	CH_2O, CH_2N (m)	H_{arom}	NHAr (1H, br.s)	NHAlk (br. s)	OH (1H)	Other signals
IIc	1560	3440, 3270, 3187	274(89)	185(100)	187(46), 186(91), 169(34), 168(51), 160(56), 153(61), 143(96), 127(90), 126(56)	1.20 - 1.70	3.30 - 3.67 (4H)	7.30 - 8.06 (7H, m)	7.80 - 7.90*	5.98 (1H)	*[2]	–
IId	1555	3370, 3250	267(30)	178(100)	233(13), 177(61), 162(26), 161(18), 153(27), 136(85), 135(39), 121(27)	1.40 - 1.70	3.35 - 3.75 (4H)	6.65 (2H, d[3]), 7.05 (2H, d[3])	7.70	6.08 (1H)	1.80 (br.s)	2.90 (6H, s, 2Me)
IIe	1555	3350, 3270, 3160	252(52)	163 (48)	237(95), 219(46), 218(29), 165(27), 164(22), 147(39), 146(37), 130(42), 121(100)	1.34 - 1.66	3.40 - 3.84 (4H)	7.20 (3H, br.s)	7.76	5.87 1H)	1.90 (br. s)	2.20 (6H, s, 2Me)
IIf	1548	3376, 3247	266(100)	177(30)	251(50), 233(36), 161(30), 160(27), 152(36), 135(95), 134(28), 120(31)	1.42 - 1.70	3.45 - 3.62 (4H)	6.90 (2H, s)	7.35	5.67 (1H)	1.80 (br.s)	2.15 (6H, s, 2Me), 2.23 (3H, s, Me)
IIg	1554	3253, 3063	292(58)	203(57)	259(32), 187(34), 186(36), 161(100), 149(29), 145(46)	1.40 - 1.75	3.45 - 3.70 (4H)	7.45 (4H, s)	8.18	6.52 (1H)	1.75 (s)	–
IIh	1570	3350, 3100	188(100)	–	173(73), 129(14), 115(18), 57(48)	1.29 - 1.90	3.00 - 3.80 (4H), 3.80 - 4.20[4] (2H)	–	–	6.85 (2H)		5.10[5] (1H, m, CH_2), 5.18[6] (1H, m, CH_2), 5.90[7] (1H, m, CH)

*Signal overlaps with the signal from the naphthyl substituent.

*[2]Signal overlaps with the multiplet from the methylene protons.

*[3]Spin–spin coupling constant (J = 9 Hz).

*[4]Broadened quintet.

*[5]J = 9.8, 3.0, 3.0 Hz.

*[6]J = 15.0, 3.0, 3.0 Hz.

*[7]J = 15.0, 9.8, 4.0, 4.0 Hz.

TABLE 3. Spectral Characteristics of Compounds IIIa-g

Compound	IR spectrum ν, cm^{-1}		Mass spectrum m/z (I, %)						PMR spectrum, δ, ppm, spin–spin coupling constant, J, Hz						
	C=N	NH	M^+	$[M-1]^+$	$[M-SH]^+$	$RN{=}C{-}NH^{+\cdot}$	R^+	Other fragments	4-H (2H, m)	5-H (m)	6-H (m)	7-H (2H, m)	H_{arom}	(1H, br. s)	Other signals
IIIa	1630	3220 - 3040	220 (64)	219 (7)	187 (9)	132 (5)	91 (100)	106 (90), 87 (18), 65 (16)	3,52	1,69 (2H)	1,94 (2H)	2,69	7,24 (5H, s)	4,13	4,34 (2H, s, CH_2Ph)
IIIb	1620	3225	206 (80)	205 (100)	173 (19)	118 (32)	77 (22)	131 (10), 130 (14), 119 (16)	3,33	1,64 (2H)	1,96 (2H)	2,77	6,80 - 7,38 (5H, m)	5,30	–
IIIc	1622	3238, 3170, 3130, 3050	256 (100)	255 (70)	223 (14)	168 (88)	127 (19)	185 (13), 154 (13), 153 (18), 141 (18), 140 (18)	3,39	1,54 (2H)	1,96 (2H)	2,69	6,75 - 8,00 (7H, m)	5,80	–
IIId	1620	3220, 3145, 3110	249 (100)	248 (16)	216 (1)	161 (63)	120 (2)	160 (23), 145 (10), 135 (22)	3,28	1,40 - 2,10 (4H)		2,70	6,73 (2H, d, J = 9,00), 6,76 (2H, d, J = 9,00)	5,50	2,82 (6H, s, 2NMe)
IIIe	1625	3220 - 3100	234 (100)	233 (4)	201 (37)	146 (64)	105 (11)	219 (55), 158 (18), 145 (35), 130 (19), 103 (11), 77 (12)	3,28	1,40 - 2,10 (4H)		2,78	6,80 - 7,35 (3H, m)	6,40	2,13 (6H, s, 2MeAr)
IIIf	1630	3220 - 3100	248 (100)	247 (4)	215 (35)	160 (84)	119 (9)	233 (77), 173 (11), 172 (19), 159 (45), 145 (39)	3,28	1,40 - 2,10 (4H)		2,77	6,90 (2H, s)	6,25	2,03(6H, s, 2MeAr), 2,22 (3H, s, MeAr)
IIIg	1617	3230	274 (97)	273 (100)	241 (53)	186 (71)	145 (55)	203 (14), 174 (10), 171 (11)	3,29	1,40 - 2,10 (4H)		2,76	6,93 - 7,40 (4H, m)	6,50	–

the protons of the naphthalene ring). In the spectrum of allylthiourea IIh, the practically equivalent protons of the two NH groups are represented by a two-proton broad singlet at 6.85 ppm.

In the PMR spectra of imines IIIa-h, there are also several characteristic groups of signals. The signals from the methylene protons on the ring adjacent to the nitrogen and sulfur atoms are always well separated. The methylene protons in the 5 and 6 positions appear as two complex multiplets, partially overlapping each other. From the nature of the multiplicity of the signals, we can conclude that all the geminal protons of the ring are magnetically equivalent and form a spectrum of the AA'BB'CC'DD' type (A – $H_{(4)}$ protons, D – $H_{(7)}$ protons). The signals from the AA' and DD' parts are well separated in the spectrum and have identical width and characteristic structure but are somewhat differently skewed toward their vicinal partners (see Fig. 1). From the distance between their extreme intense lines, we can conclude that in both cases the multiplet is determined by the two vicinal spin–spin coupling constants with sum about 10.0 Hz. The signal from the proton of the NH group in all compounds III are strongly broadened (up to 80 Hz) and are found in the region 4.13-6.5 ppm.

The difference between the values of the chemical shifts for the protons of the heterocycle in thiazepine derivatives IIIa and IIIb-g is very small. The greatest deviation is displayed by the signal from the methylene protons at $C_{(4)}$ (about 0.24 ppm). This was initially explained by the difference in the structure of the indicated compounds, which was consistent with the assignment of derivative IIIa to 2-aminotetrahydrothiazapine [6]. However, in the spectrum of compound IIIa, as in the spectra of compounds IIIb-g, there is no interaction between the protons of the NH and CH_2 groups (Fig. 1), although such interaction should occur in the linear chain $=C-NH-CH_2-Ph$, i.e., in the case of an exocyclic amino group [8]. We know that in compounds with an endocyclic NH group, such an interaction is not apparent [9, 10]. Consequently, product IIIa most likely is 2-benzyliminohexahydrothiazepine. The differences in the mass spectra of imines IIIa and IIIb-g, like the chemical shifts of the protons of the 4-CH_2 groups, are due to the nature of the substituents: benzyl in compound IIIa and aromatic in compounds IIIb-g. A definitive conclusion will make it possible to carry out an x-ray diffraction study of the structure of compound IIIa.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer in KBr pellets. The mass spectra were taken on MKh 1310 and MKh 1321 instruments. The full-range electron impact spectra were obtained using direct injection of the sample (SVP-5) for an ionization chamber temperature of 150-170°C, heater ampul temperature 80-120°C, ionizing potential 70 eV, collector current 60 mA. The PMR spectra were recorded on a Tesla BS-667 spectrometer with operating frequency 100 MHz in deuterochloroform solution, internal standard HMDS.

In this work we used the following reagents: 4-amino-1-butanol and isothiocyanates Ib, c, h, purified by distillation under vacuum. Compound Ia was obtained by thermal decomposition of benzylthiocyanate at 200°C [11], compounds Id-f were synthesized according to the method in [12], while isothiocyanate Ig was synthesized by the familiar technique [13].

N-(4-Hydroxybutyl)-N'-R-thioureas (IIa-h) and 2-R-Iminohexahydro-1,3-thiazepines (IIIa-g). A solution of 0.2 moles isothiocyanate Ia-g in 15 ml acetone was added dropwise with stirring at a temperature of 15-20°C to a solution of 17.8 g (0.2 moles) 4-amino-1-butanol in 35 ml dry acetone. The reaction mixture was allowed to stand for a day at room temperature and then boiled for 1-3 h. After driving off the acetone under reduced pressure, the thiourea IIa-h was obtained. The products IIa-g were purified by recrystallization from benzene or aqueous ethanol; IIh was purified by column chromatography on silica gel L100/160 (hexane, benzene as the eluent). In order to obtain compound IIIa-g, 200 ml conc. HCl or HBr was added to the reaction mass after driving off the acetone and this was boiled for 5 h. Water (100 ml) was added to the reaction mixture (evaporated down to half volume), and on cooling it was neutralized with a solution of base. The product IIIa-g was filtered off, washed with water, dried, and recrystallized from hexane or acetone.

REFERENCES

1. K.-H. Wunsch and A. Ehlers, Z. Chem., **10**, 361 (1970).
2. A. Levai, Khim. Geterotsikl. Soedin., No. 11, 1443 (1986).
3. D. L. Garmaise, G. J. Paris, and G. Efthymaidis, Can. J. Chem., **49**, 971 (1971).

4. L. Toldy, J. Reiter, Mrs. G. Szilagyi, I. Toth, J. Borsy, J. Szekely, and I. Schafer, Hungarian Pat. 7487; Chem. Abstr., **80**, 95928 (1974).
5. K. Hideg, O. Hankovsky, E. Palosi, G. Hajos, and L. Szporny, German Pat. 2429290; Chem. Abstr., **82**, 156307 (1975).
6. Z. Olszenko-Piontkowa and T. Urbanski, Org. Prep. Proc. Int., **3**, 27 (1971); Chem. Abstr., **74**, 125665 (1974).
7. T. Kato, N. Katagiri, U. Izumi, J. Miura, T. Jamazaki, and Y. Hirai, Heterocycles, **15**, 399 (1981).
8. N. E. Alexandrou and D. N. Nikolaides, Org. Magn. Res., **4**, 591 (1972).
9. E. Cherbuliez, Br. Baehler, O. Espejo, H. Jindra, B. Willhalm, and J. Rabinowitz, Helv. Chim. Acta, **50**, 331 (1967).
10. L. Toldy, P. Sohar, K. Farago, I. Toth, and L. Bartalits, Tetrahedron Lett., **25**, 2167 (1970).
11. E. Cherbuliez, G. Weber, G. Wyss, and J. Rabinowitz, Helv. Chim. Acta, **48**, 1031 (1965).
12. N. I. Volynkin, Zh. Org. Khim., **27**, 485 (1957).
13. F. Kurzer and I. Canelle, Tetrahedron, **19**, 1603 (1963).