SYNTHESIS OF BENZAZOLES, 1,3,4-OXADIAZOLES, AND 1,3,4-THIADIAZOLES CONTAINING β -ALKYLTHIOETHYL RADICALS

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By the condensation of hydrochlorides of iminoesters of β -alkylthiopropionic acids with o-phenylenediamine, o-aminophenols, hydrazides of acids, and thiosemicarbazide, we have synthesized 2-substituted benzimidazoles and benzoxazoles, 2,5-disubstituted 1,3,4-oxadiazoles, and 2-amino-5-substituted 1,3,4-thiadiazoles containing β -alkylthioethyl fragments.

Among the derivatives of benzazoles and 1,3,4-oxa- and 1,3,4-thiadiazoles, various substances have been isolated with a broad spectrum of pharmacological activity [1, 2], and also effective herbicides, fungicides, and plant growth regulators [3, 4]. At the same time, it is known [5] that the introduction of thioalkyl groupings into the molecules of biologically active substances will frequently lead to substantial modifications of their biological activity.

With the aim of searching for new potentially biologically active substances, we have synthesized benzimidazoles, benzoxazoles, 1,3,4-oxadiazoles, and 1,3,4-thiadiazoles containing β -alkylthioethyl radicals.

It is known [6-8] that the hydrochlorides of iminoesters of carboxylic acids may serve as key substances in the synthesis of 2-substituted benzazoles, 2,5-disubstituted 1,3,4-oxadiazoles, and 2-amino-5-substituted 1,3,4-thiadiazoles. In the present work, we used as the starting substances the hydrochlorides of methyl aminoesters of β -alkylthiopropionic acids (Ia,b). These compounds were obtained with yields of 88-92% by the Pinner reaction, passing a stream of dry HCl into a mixture of corresponding nitrile and methanol in anhydrous ether, at 0°C.





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In the IR spectra of the iminoester hydrochlorides Ia,b, there are characteristic absorption bands at 1675-1670 cm⁻¹ pertaining to stretching vibrations of the C=N bond [9]. The medium-intensity bands in the 1025-1015 cm⁻¹ interval should be assigned to stretching vibrations of the C-O bond in the iminoester group [6]. In the high-frequency region of the spectrum, stretching vibrations of the C=N⁺H group are represented by absorption maxima at 3130-3120 cm⁻¹, characteristic for salts of imines [7].

As a result of condensation of the iminoester hydrochlorides Ia,b with o-phenylenediamine, $4-R^{1}-5-R^{2}-2$ -aminophenols, N-acylhydrazines, and thiosemicarbazide, we have obtained (respectively) 2-substituted benzimidazoles (IIa,b), 2-substituted $5-R^{1}-6-R^{2}$ -benzoxazoles (IIIa-d), 2,5-disubstituted 1,3,4-oxadiazoles (IVa-f), and 5-substituted 2-amino-1,3,4-thiadiazoles (Va,b) containing β -alkylthioethyl fragments.

All of the condensation reactions were performed by boiling equimolar quantities of the reagents for several hours. Under these conditions, the yields of the benzimidazoles IIa,b, benzoxazoles IIIa-d, and 1,3,4-oxadiazoles IVa-f were in the 78-89% range (see Table 1). However, in carrying out reactions of the iminoester hydrochlorides Ia,b with thiosemicarbazide, we observed considerable tar formation in the reaction mixture, from which the desired 1,3,4-thiadiazoles Va,b were recovered with yields of only 48-52%.

In the IR spectra of the benzimidazoles IIa,b and the benzoxazoles IIIa-d, we observe intense absorption bands in the 1640-1625 cm⁻¹ region, characteristic for vibrations of C=N in 2-substituted benzazoles [10]. In the spectra of compounds IIa,b there are also variable-intensity bands pertaining to stretching vibrations (1550, 1485-1480, 1465-1460, and 1330 cm⁻¹), breathing vibrations (1065-1060 cm⁻¹), and in-plane bending vibrations of the benzimidazole ring [10, 11]. The structure of the benzoxazoles IIIa-d is confirmed by the presence of intense absorption bands at 1590-1580 and 935-930 cm⁻¹, characteristic for the benzoxazole ring, and also absorption maxima at 1255-1250 and 1020-1010 cm⁻¹ pertaining to asymmetric and symmetric stretching vibrations of the =C-O-C= fragment of benzoxazoles [10, 12].

In the spectra of the 1,3,4-oxadiazoles IVa-f, intense absorption maxima are observed in the 1615-1595 and 1490-1470 cm⁻¹ intervals, characteristic for stretching vibrations of the oxadiazole ring [10]. The presence of this ring is also supported by the absorption bands at 1245-1225 and 1045-1030 cm⁻¹ pertaining to stretching vibrations of the =C-O-C= fragment in 1,3,4-oxadiazoles [13].

In the spectra of compounds Va,b there are absorption bands in the regions 1525-1520, 1490-1480, 1385, 1235-1230, 1040-1030, and 865 cm⁻¹, characteristic for vibrations of the 1,3,4-thiadiazole ring [10].

In the PMR spectra of the synthesized compounds II-V (see Table 1), signals of the ethylene fragment protons are manifested in the form of symmetric triplets at 2.52-2.85 ppm ($-SCH_2-$) and 2.95-3.12 ppm ($-CH_2Het$).

EXPERIMENTAL

IR spectra were taken in a Bruker IFS-48 instrument in tablets with KBr or in white mineral oil. PMR spectra were obtained in a Bruker WP-100 SY spectrometer, internal standard TMS. The course of the reaction and the purity of the products were monitored by means of TLC on Al_2O_3 (Brockman activity grade III) in a solvent system consisting of 30:1 benzene-methanol (A) or 2.15:1 CCl₄-propanol (B), with development by iodine vapor. The characteristics of the synthesized compounds are listed in Table 1.

The results of elemental analysis of the compounds for C, H, and N matched the calculated values.

Hydrochloride of Methyl Iminoester of β -Isobutylthiopropionic Acid (Ia, C₈H₁₇NOS·HCl). A solution of 7.15 g (50 mmoles) of β -isobutylpropionitrile and 3.2 g (100 mmoles) of absolute methanol in 75 ml of dry ether was stirred at 0°C for 1.5 h while passing in a stream of dry HCl. The reaction mixture was held for 24 h at 20°C; the precipitate was filtered off, washed on the filter with dry ether, and vacuum-dried over KOH: mp 112-113.5°C (decomp.). Yield 9.3 g (88%).

Hydrochloride of Methyl Iminoester of β -Benzylthiopropionic Acid (Ib, C₁₁H₁₅NOS·HCl) was obtained analogously, from β -benzylthiopropionitrile. Product mp 137-139°C (decomp.). Yield 93%.

General Procedure for Obtaining 2-(β -Alkylthioethyl)benzimidazoles (IIa,b), 2-(β -Alkylthioethyl)-5-R¹-6-R²benzoxazoles (IIIa-d), and 2-(β -Alkylthioethyl)-5-substituted 1,3,4-Oxadiazoles (IVa-f). A mixture of 20 mmoles of the iminoester hydrochloride Ia or Ib and 20 mmoles of o-phenylenediamine, 4-R¹-5-R²-2-aminophenol or N-acylhydrazine in 50 ml of absolute ethanol was refluxed while stirring for 3-4 h. The reaction mixture was cooled to 20°C and poured into 150 ml of cold water containing 1.48 g (15 mmoles) of NaHCO₃. The precipitate was filtered off, vacuum-dried over P₂O₅, and crystallized from suitable solvents (see Table 1).

	Yield,	82	85	78	89	83	85	61	87	80	82	84	88	48	52	
	PMR spectrum: chemical shifts δ , ppm ^{*3} and SSCC J, Hz	1,10 (6H, d, 2Me), 1,52 (1H, m, CHMe ₂), 2,32 (2H, d, SCH ₂ CH), 2,52 (2H, t, SCH ₂), 2,98 (2H, t, CH ₂ He),	2.64 (2H, t, SCH2), 2.95 (2H, t, CH2)(t, CH2)(t), 3.38 (2H, s, SCH2)(t), 6.977, 12 (5H, m, Ph), 7,627,86 (4H, m, H _{arom}), 8.14 (1H, bc. wh)	1 10.06 (H) d. d. 20.06 (H) d. 1, 63 (1H, m, CHMe ₂), 2,45 (2H, d, S <u>CH₂</u> CH), 2,72 (2H, t, <u>CH₂S</u>), 3,08 (2H, t, <u>CH₂He</u>), 7,307,48 (4H, m, H)	2,71 (2H, t, SCH2), 3,12 (2H, t, CH2Het), 3,52 (2H, s, SCH2Ph), 7,087,16 (5H,m, Ph), 7,387,50 (4H,m, H _{aron})) 2,78 (2H, t, SCH ₂), 3,04 (2H, t, CH ₂ Hei), 3,44 (2H, s, S <u>CH</u> ₂ Ph), 6,907,12 (5H, m, Ph), 7,26 (1H, dd, 4-H, J ₄₅ = -8,3), 7,64 (1H, dd, 5-H, J ₅₇ = 2,3), 7,88 (1H, q 7-H)	2.68 (2H, t, SCH ₂), 2.96 (2H, t, CH ₂ Het), 3.65 (2H, s, SCH ₂ Ph), 7,107,18 (5H, m, Ph), 7,32 (1H, dd, 7-H, J ₆₇ 7,5), 7,68 (1H, q, 4-H, J ₄₆ - 2,5), 7,83 (1H, dd, 6-H), 8,36 (2H, br.s NH ₂)	1,08 (6H, d, 2Me ⁵), 1,45 (1H, m, CHMe ₂), 2,37 (2H, d, SCH ₂ CH), 2,35 (2H, t, SCH ₂), 3,10 (2H, t, CH ₂ He), 7,357,50 (5H, m,Ph)) 1,1,1,4 (6H,d, 2Me), 1,55 (1H, m, CHMe ₂), 2,42 (2H, d, SCH ₂ H), 2,67 (2H, t, SCH ₂), 2,96 (2H, t, CH ₂ Het), 3,95 (2H, s, 1,05,17,18,7,34 (4H, m, H,, 7,56 (1H, d, 2-H indole J = 2,7), 8,08 (1H, br.s NH)	1,07 (6H, d, 2Me), 1,49 (1H, m, CHMe ₂), 2,50 (2H, d, SCH ₂ CH), 2,84 (2H, t, SCH ₂), 3,12 (2H, t, CH ₂ He), 7,647,78 (4H, m, H ₂ ,)	2,72 (2H, t, S <u>CH2</u>), 3,04 (2H, t, <u>CH2</u> Het), 3,65 (2H, s, S <u>CH2</u> Ph),6,937,18 (10H, m, H _{arom})) 2,85 (2H, t, S <u>CH</u> ₂), 3,10 (2H, t, <u>CH</u> ₂ Hei), 3,72 (2H, s, S <u>CH</u> ₂ Ph), 4,12 (2H, s, Ind <u>CH</u> ₂), 7,107,35 (9H, m, H _{arom}), 7,66 (1H, d, 2-H indole, <i>J</i> = 2,5), 8,15 (1H, br.s, NH)	2.63 (2H, t, SCH ₂), 2.97 (2H, t, CH ₂ HeU), 3.52 (2H, s, SCH ₂ Ph), 7,087,23 (5H, m, Ph), 7,707,83 (4H, m, H _{arom})	[1] 1,05 (6H, d, 2Me), 1,63 (1H, m, CHMe ₂), 2,37 (2H, d, SCH ₂ CH), 2,78 (2H, t, SCH ₂), 3,03 (2H, t, CH ₂ Het), 5,78 (2H, br.s, NH ₂)	2,78 (2H, t, S <u>CH2</u>), 3,08 (2H, t, <u>CH2</u> He0), 3,80 (2H, s, S <u>CH2</u> Ph), 5,56 (2H, br.s NH2), 6,937,14 (5H, m,Ph)	ystallized from 2:1 hexane – benzene mixture; IIb from benzene; IIIa from petroleum
	R _r *2	0,54(A)	0,44(A)	0,38(B)	0,50(B)	0,30(B)	0,40(A)	0,64(A)	0,30(B)	0,28(A)	0,72(B)	0,35(B)	0,56(B)	0,20(B)	0,32(B)	re recry
•	mp, °C*	9293	131132	8890	135136 (decomp.)	182184 (decomp.)	156157	155 (subl.)	182184	140141,5	8890	110111	8687,5	170171	160162	and IVf we
	Empirical formula	C ₁₆ H ₁₈ N ₂ S	C ₁₆ H ₁₆ N ₂ S	C ₁₃ H ₁₇ NOS	C ₁₆ H ₁₅ NOS	C ₁₆ H ₁₄ N ₂ O ₃ S	C ₁₆ H ₁₆ N ₂ O ₃ S ₂	C ₁₄ H ₁₈ N ₂ OS	C ₁₇ H ₁₆ N ₃ OS	C ₁₃ H _{17N3} OS	C ₁₇ H ₁₆ N ₂ OS	C ₂₀ H ₁₉ N ₃ OS	C ₁₆ H ₁₆ N ₃ OS	C ₈ H ₁₅ N ₃ S ₂	C ₁₁ H ₁₃ N ₃ S ₂	nds IIa, IIIb,
	Compound	lļa	цb	III.a	qIII	IIIc	PIII	IV.a	qvi	IVc	DVI	IVe	IVf	۲a ۲	vb	*Compou

TABLE 1. Characteristics of Synthesized Benzazoles, 1,3,4- Oxadiazoles, and 1,3,4-Thiadiazoles

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ether; IIIc and IVb,c,d from aqueous ethanol; IVa,e from 10:1 petroleum ether-methanol mixture; Va,b from toluene. *2Solvent system is indicated in parentheses.

*³Spectra of compounds IIa,b, IIIa-c, and IVa,c,d,f were recorded in acetone-d₆; compounds IIId, IVb,e, and Va,b in DMSOч^{6.} 2-Amino-5-(β -isobutylthioethyl)-1,3,4-thiadiazole (Va). A mixture of 1.48 g (7 mmoles) of the iminoester hydrochloride Ia and 0.64 g (7 mmoles) of thiosemicarbazide in 20 ml of absolute ethanol was refluxed while stirring for 4 h. The reaction mixture was evaporated to dryness under reduced pressure; the residue was chromatographed in a column with Al₂O₃ (80 × 4.5 cm), eluted by a 15:1 benzene-methanol mixture. Yield 0.73 g (48%).

2-Amino-5-(β -benzylthioethyl)-1,3,4-thiadiazole (Vb) was obtained analogously, from the iminoester hydrochloride Ib.

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