REACTIONS OF 2-AMINOBENZOTHIAZOLES WITH PHENYL GLYCIDYL ETHER

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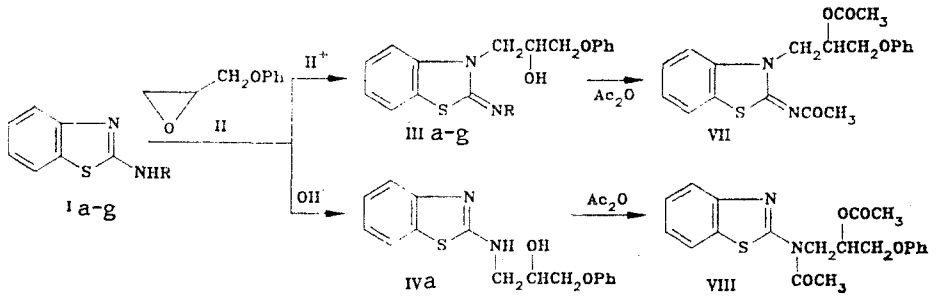
In acidic media 2-aminobenzothiazole and its derivatives react with phenyl glycidyl ether at the ring nitrogen atom, while in alkaline media they react at the exocyclic nitrogen atom. The structures of the compounds were proved by spectral methods and alternative synthesis.

It is known that the alkylation of 2-aminobenzothiazoles with various reagents in neutral media is most often realized at the ring nitrogen atom [1]. An alkaline medium, on the other hand, promotes reaction at the exocyclic amino group [2]. The available information regarding the effect of an acidic medium are contradictory [3, 4]. However, alkylation in neutral media that takes place at the amino group has been described in a number of reports [5-10]. In an investigation of the reaction of 2-aminobenzothiazoles with acrylic acid [11] we have previously shown that the result of the reaction is a product of alkylation at the exocyclic amino group. In a continuation of our research in the aminobenzothiazole series we have studied the reaction of unsubstituted 2-aminobenzothiazole (Ia) and its derivatives (Ib-g) with phenyl glycidyl ether (II). It should be noted that virtually no study has been devoted to the reactions of 2-aminobenzothiazoles with alkene oxides: the synthesis of oligomeric products with an amino structure in the case of treatment of Ia with ethylene oxide was reported in a single publication [12]. In addition, a paper [13] in which an imino structure was assigned to the product of the reaction of 2-aminothiazole with phenyl glycidyl ether only in analogy with aminopyridine has been published.

We have shown that both mono- and disubstituted derivatives are formed as a result of the reaction of unsubstituted heterylamine Ia with oxirane II; opening of the oxirane ring occurs in accordance with Krasuskii's rule [14]. A product with an imino structure, viz., 2-imino-3-(γ-phenoxy-β-hydroxypropyl)benzothiazoline (IIIa) was obtained in both acidic and neutral media (Table 1). Its low yield (up to 30%) is explained by the fact that, in addition to the principal reaction products, side products, viz., 1-ethoxy-2-hydroxyphenoxypropane (5-13%) in alcohol and 1-acetoxy-2-hydroxy-3-phenoxypropane (37-60%) and 2-acetamidobenzothiazole (1.5-4%) in acetic acid, are formed as a result of the reaction of the starting substances with the solvent; we confirmed this in special experiments. As a rule, a significant amount (20-30%) of 2-aminobenzothiazole (Ia) is detected in these reaction mixtures.



I, III a R=H; b R=CH_3; c R=C_2H_5; d R=C_6H_5; e R=$CH_2C_6H_5$; f R=C_6H_{11}; g R=$COCH_3$

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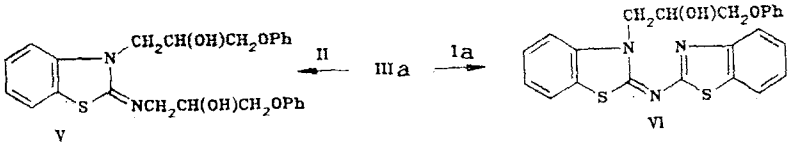
TABLE 1. Yields of the Products and Conditions for Carrying Out the Reaction of 2-Aminobenzothiazole (I) with Phenyl Glycidyl Ether (II)

Ia:II ratio, moles	Solvent	T_r, °C	Time, h	Yields of product, % (HPLC data)			
				IIIa	IVa	V	VI
1:1	—	90	10	4	—	53	—
1:3	—	90	10	—	—	67	—
1:1	Benzene	Refluxing	10	21	—	59	5
1:1	Xylene	Refluxing	10	27	—	27	21
1:1	Xylene	Refluxing	36	28	—	24	46
1:2	Xylene	Refluxing	10	14	—	42	30
1:1	Alcohol	Refluxing	10	—	—	57	—
1:1	Alcohol	Refluxing	10	—	43	10	—
1:1	Chloroform	20...25	2	—	11	—	—
1:1	CH_3COOH	65	10	14	—	—	—
1:1,5	CH_3COOH	65	5	26	—	—	—
1:1,5	CH_3COOH	65	10	28	—	—	—
1:2	CH_3COOH	65	5	18	—	—	—
1:2	CH_3COOH	65	10	24	—	—	—

*The reaction was carried out in the presence of an equimolar amount of NaOH.

On the other hand, IIIa may react with the starting reagents to give diaddition products of the V and VI type.

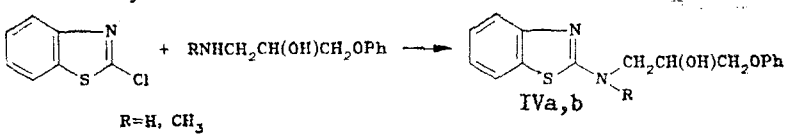
A mixture of products IIIa, V, and VI is formed in the case of refluxing the mixture in aprotic solvents (benzene, xylene); the yield of VI increases with an increase in the reaction temperature and time. Primarily V is formed in the absence of a solvent and in the case of refluxing in alcohol.



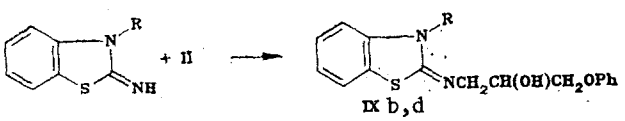
The reactions of heterylamines Ib-g carried out in excess oxirane II, as well as in benzene in the presence of boron trifluoride etherate, lead to IIIb-g.

In an alkaline medium oxirane II reacts at the exocyclic nitrogen atom of substrate Ia to give 2-γ-phenoxy-β-hydroxypropylaminobenzothiazole (IVa).

The structures of the synthesized compounds were established by means of IR, UV, and PMR spectroscopy and mass spectrometry (Tables 2 and 3). The structure of VI was confirmed by additionally determining the elementary composition of the molecular ion with m/z 433 as $C_{23}H_{19}N_3O_2S_2$. To prove the structures we also resorted to alternative synthesis and the synthesis of derivatives or isomeric compounds. Diacetyl products VII and VIII were obtained by treatment of heterylamino alcohols IIIa and IVa with acetic anhydride. The corresponding alkylaminobenzothiazoles IVa, b were synthesized by the reaction of 2-chlorobenzothiazole with γ-phenoxy-β-hydroxypropylamines.



The isomeric (with respect to IIIb, d) IXb, d were obtained by the reaction of the corresponding iminobenzothiazolines with oxirane II:



EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions in ethanol were obtained with a Hitachi EPS-3T spectrophotometer. The PMR spectra were recorded with a Jeol C-60 HL spectrometer with tetramethylsilane (TMS) as the internal standard. The mass spectra of IIIa, b-IV and IXb were recorded with an MKh-1303 spectrometer (with direct introduction of the samples); the input temperature was 20-100°C, and the ionizing voltage was 40 eV. The mass spectra of IIIc-g, V-VIII, and IXd and the elementary composition were determined with an MKh-1310 spectrometer; the temperature of the system for the direct

TABLE 2. Characteristics of the Synthesized Compounds

Compound	Empirical formula	mp,* °C	R_f**	IR spectrum, ν, cm⁻¹ C=N,	IR spectrum, ν, cm⁻¹ NH, OH	UV spectrum, λ_{max}, (log ε)	PMR spectrum, δ, ppm ($CDCl_3$)	Yield, % (method of synthesis)
IIIa	$C_{16}H_{16}N_2O_2S$	85...86	0,63	1610	3310	225 (4,56), 265,5 (4,2), 271 (4,21), 276 sh (4,13), 296,5 (3,66)	4,0 (2H, d, CH_2O); 4,2...4,4 (3H, m, CH_2N, CH); 6,07 (2H, s OH, NH); 6,9...7,5 (9H, Ar)	23
IIIb	$C_{17}H_{18}N_2O_2S$	94,5...96	0,42	1630	3180	223 (4,47), 266 (3,96), 278 sh (3,70), 303 (3,80)	3,0 (3H, s, CH_3); 3,95 (2H, d, CH_2O); 4,1...4,4 (3H, m, CH_2N, CH); 6,5 (1H, s, OH); 6,8...7,35 (9H, m, Ar)	42 (A)
IIIc	$C_{18}H_{20}N_2O_2S$	54...55	0,61	1635	3400	223 (4,54), 266 (4,03), 278 sh (3,85), 304 (3,80)	1,25 (3H, t, CH_3); 2,95...3,37 (2H, q, CH_2); 3,95 (2H, d, CH_2O); 4,1...4,4 (3H, m, CH_2N, CH); 6,8...7,35 (10H, m, OH, Ar)	32 (A) 29 (B)
IIId	$C_{22}H_{20}N_2O_2S$	123...124	0,75	1625	3340	223 (4,60), 270 sh (3,94), 278 sh (3,98), 305 (3,80)	3,98 (2H, d, CH_2O); 4,27...4,44 (3H, m, CH, CH_2N); 5,45 (1H, s, OH); 6,76...7,25 (14H, m, Ar)	45 (B)
IIIe	$C_{23}H_{22}N_2O_2S$	98...101	0,63	1630	3255	223 (4,38), 245 sh (3,73), 268 (3,91), 278 sh (3,68), 304 (3,61)	3,95 (2H, d, CH_2O); 4,25...4,35 (5H, m, $2CH_2N$, CH); 6,75... 7,25 (15H, m, OH, Ar)	24 (A) 13 (B)
IIIf	$C_{22}H_{26}N_2O_2S$	59...60	0,77	1620	3260	223 (4,53), 267 (3,99), 277 sh (3,84), 304 (3,71)	1,2...1,72 (10H, m, C_6H_{10}); 2,87 (1H, m, H—C_6H_{10}); 3,95 (2H, d, CH_2O); 4,15...4,3 (3H, m, CH, CH_2N); 6,8...7,4 (10H, m, OH, Ar)	47 (A) 27 (B)
IIIg	$C_{18}H_{18}N_2O_3S$	103...104	0,48	1600 (NCO)	3400	218 (4,32), 259 (3,64), 272 (3,74), 278 (3,76), 314 (4,18)	2,23 (3H, s, CH_3); 3,95 (2H, d, CH_2O); 4,24 (1H, m, CH); 4,55 (2H, d, CH_2N), 5,68 (1H, s, OH); 6,78...7,5 (9H, m, Ar)	30 (A)
IVa	$C_{16}H_{16}N_2O_2S$	142...144	0,79	1560	3295	221 (4,52), 265 (3,96), 277 sh (3,74), 295,5 (3,66)	3,6 (2H, d, CH_2N); 3,95 (2H, d, CH_2O); 4,2...4,4 (1H, m, CH); 6,73...7,58 (9H, m, Ar)***	11 (A) 93 (B)
IVb	$C_{17}H_{18}N_2O_2S$	134...135	0,48	1550	3220	225 (4,57), 272 (4,27), 277 sh (4,21), 300 sh (3,61)	3,12 (3H, s, CH_3); 3,88 (2H, d, CH_2N); 4,0 (2H, d, CH_2O); 4,15...4,3 (1H, m, CH); 6,85...7,66 (10H, m, OH, Ar)	30 (B)
V	$C_{25}H_{26}N_2O_4S$	107...108	0,80	1630	3380	223 (4,58), 266 (4,06), 271 sh (4,05), 278 sh (3,91), 305 (3,76)	3,3 (2H, d CH_2N); 3,9...4,35 (9H, m, $2CH_2O$, CH_2N, OH, 2CH); 6,75...7,35 (14H, m, Ar)	54 (A) 89 (B)
VI	$C_{23}H_{19}N_3O_2S_2$	127...128	0,90	1520	3420	222 (4,79), 267 (4,27), 279 (4,27), 290 (4,25), 340 sh (4,57), 349 (4,62)	4,0 (2H, d, CH_2O); 4,4...4,65 (4H, m, CH_2N, CH, OH); 6,85...7,93 (13H, m, Ar)	14
VII	$C_{20}H_{20}N_2O_4S$	151...152	0,82	1500	1620 (NCO), 1745 (OCO)	218 (3,41), 258 (2,67), 271,5 (2,77), 278 (2,79), 314,5 (3,23)	1,85 (3H, s, CH_3OCO); 2,2 (3H, s, CH_3CON); 4,15 (2H, d, CH_2O); 4,5...4,75 (2H, q, CH_2N); 5,4...5,75 (1H, s, CH); 6,75...7,65 (9H, m, Ar)	58
VIII	$C_{20}H_{20}N_2O_4S$	160...162	0,85	1504	1670 (NCO), 1740 (OCO)	220 sh (4,37), 246 (3,79), 271,5 (4,06), 277,5 (4,06), 288 (3,93), 299 (3,89)	1,9 (3H, s, CH_3COO); 2,5 (3H, s, CH_3CON); 4,2 (2H, d, CH_2O); 4,4...4,65 (2H, q, CH_2N); 5,5...5,8 (1H, m, CH); 6,8...7,8 (9H, m, Ar)	30
IXb	$C_{17}H_{18}N_2O_2S$	73...74	0,73	1630	3340	224 (4,60), 266 (4,0), 278 sh (3,77), 306 (3,72)	2,83 (1H, s, OH); 3,35 (5H, d, CH_3, CH_2N); 4,0...4,28 (3H, m, CH_2O, CH); 6,78...7,34 (9H, m, Ar)	27 (A)
IXd	$C_{22}H_{20}N_2O_2S$	96...97	0,44	1650	3590	224 (4,49), 267 (3,97), 278 sh (3,77), 305 (3,64)	2,93 (1H, s, OH); 3,4 (2H, d, CH_2N); 3,93...4,2 (3H, m, CH_2O, CH); 6,55...7,5 (14H, m, Ar)	47 (A)

*The compounds were recrystallized: IIIa, c, f from hexane, IIIb, IVa, V, and VI from benzene, IIId, g and IXb, d from ethanol, VII and VIII from ethyl acetate, IIIe from hexane—ethanol (1:1), and IVb from benzene—ethanol (1:1).

**In a benzene—chloroform—acetone system (1:1:2) for IIIa, IVa, and V-VIII and in an acetone—benzene system (1:5) for remaining compounds.

***The spectrum was recorded with the addition of CF_3COOH.

TABLE 3. Characteristic Ions in the Mass Spectra of III-IX*

Compound	m/z (I_{rel}, %)
IIIa	300 (22), 283 (3), 207 (16), 194 (16), 193 (100), 189 (13), 164 (32), 163 (15), 150 (46), 136 (18), 133 (11)
IIIb	314 (24), 221 (55), 207 (100), 178 (29), 164 (100), 163 (37), 149 (24), 136 (94), 135 (24), 109 (34), 77 (28)
IIIc	328 (10), 235 (51), 221 (78), 178 (61), 177 (24), 163 (39), 150 (54), 149 (100), 136 (40), 133 (17), 109 (24)
IIId	376 (35), 284 (26), 283 (91), 269 (32), 240 (13), 239 (21), 227 (25), 226 (100), 225 (47), 136 (15), 109 (14)
IIIe	390 (7), 389 (25), 298 (20), 297 (88), 284 (20), 283 (100), 254 (24), 241 (20), 240 (76), 239 (26), 91 (72)
IIIf	382 (30), 339 (16), 290 (25), 289 (93), 276 (25), 275 (100), 232 (55), 189 (20), 175 (20), 164 (24), 150 (64)
IIIg	342 (4), 235 (100), 193 (43), 192 (21), 164 (19), 163 (23), 150 (100), 149 (56), 136 (20), 94 (20), 77 (20)
IVa	300 (17), 283 (1), 207 (21), 193 (100), 189 (44), 164 (17), 163 (63), 150 (23), 136 (39)
IVb	314 (100), 221 (53), 207 (29), 203 (15), 178 (15), 177 (57), 136 (24), 97 (15), 83 (15), 71 (18), 44 (58)
V	450 (7), 358 (12), 357 (55), 344 (13), 343 (58), 314 (22), 313 (100), 300 (11), 207 (16), 203 (13), 193 (28), 189 (20), 175 (18), 164 (20), 163 (85), 150 (13), 149 (13), 136 (33), 133 (16)
VI	433 (70), 342 (11), 341 (19), 340 (59), 326 (41), 322 (22), 297 (22), 296 (15), 285 (30), 284 (85), 283 (100), 163 (7), 150 (7), 149 (26), 148 (19), 136 (17)
VII	384 (3), 291 (32), 249 (15), 205 (4), 189 (18), 163 (14), 150 (29), 149 (16), 133 (100)
VIII	384 (52), 342 (53), 325 (48), 291 (65), 283 (46), 249 (34), 231 (56), 207 (10), 190 (17), 189 (100), 163 (68), 164 (10), 150 (9), 136 (16), 133 (22)
IXb	314 (6), 207 (22), 178 (40), 177 (100), 164 (30), 150 (22), 149 (84), 136 (83), 129 (24), 111 (24), 109 (32)
IXd	376 (9), 359 (4), 270 (3), 269 (16), 240 (19), 239 (100), 226 (6), 136 (2), 133 (2), 91 (4), 77 (4)

*The M^+ values and the 10 most intense peaks are presented.

introduction of the samples was 100-130°C, the ionizing voltage was 50 eV, and the reference substance was perfluorinated kerosene. The determination of the compositions of the reaction mixtures by high-performance liquid chromatography (HPLC) was carried out with a Milikhrom chromatograph with a 6.2 × 2 mm column; the sorbent was Silasorb 300, and the mobile phase was hexane–chloroform–isopropyl alcohol (70:20:10). The course of the reactions and the purity of the compounds were monitored on Silufol UV-254 plates. The separation and purification of the substances were carried out with columns packed with silica gel 100/160 μ with successive elution with hexane, benzene, and acetone. The yields of the compounds are presented for chromatographically pure samples. The melting points were determined with a Boetius microblock.

The results of elementary analysis for C, H, and N of all of the compounds were in agreement with the calculated values.

2-Imino-3-(γ-phenoxy-β-hydroxypropyl)benzothiazoline (IIIa). A solution of 1.5 g (10 mmole) of 2-aminobenzothiazole and 2.3 g (15 mmole) of oxirane II in 15 ml of acetic acid was stirred for 5 h at 65-70°C, after which the acetic acid was removed by distillation in vacuo, and the residue was chromatographed with a column. The resulting acetic acid salt of IIIa was treated with $NaHCO_3$ solution, and the product was recrystallized.

2-R-Imino-3-(γ-phenoxy-β-hydroxypropyl)benzothiazolines IIIb-g and 2-(γ-Phenoxy-β-hydroxypropyl)imino-3-R-benzothiazolines IXb, d. A. A solution of 10 mmole of the corresponding heterylamine in 20 mmole of oxirane II was stirred for 10 h at 90°C, after which the reaction mixture was chromatographed with a column. The product was recrystallized from a suitable solvent.

B. A 10-mmole sample of oxirane II and 0.2 ml of boron trifluoride etherate were added to a solution of 10 mmole of Ib-e in absolute benzene, and the mixture was stirred for 10 h at 60°C. It was then poured into 20 ml of water, and the benzene layer was separated and dried with Na_2SO_4. The solvent was evaporated, and the residue was chromatographed with a column.

2-(γ-Phenoxy-β-hydroxypropyl)aminobenzothiazole (IVa). A. A 0.6-ml sample of 50% NaOH solution was added to a solution of 1.5 g (10 mmole) of I and 1.5 g (10 mmole) of oxirane II in 25 ml of chloroform, and the mixture was stirred for 2 h at room temperature. It was then filtered, and the chloroform layer was separated, washed with water

until the wash water was neutral, and dried with anhydrous Na_2SO_4. The solvent was evaporated, and the residue was recrystallized.

B. A mixture of 0.85 g (5 mmole) of 2-chlorobenzothiazole and 1.67 g (10 mmole) of γ-phenoxy-β-hydroxypropylamine was stirred for 2.5 h on an oil bath at 120-130°C, after which it was cooled and washed with benzene and water, and the residue was recrystallized. No melting-point depression was observed for a mixture of samples obtained by the two methods.

A similar procedure was used to synthesize 2-[N-methyl-N-(γ-phenoxy-β-hydroxypropyl)amino]benzothiazole (IVb).

2-(γ-Phenoxy-β-hydroxypropyl)imino-3-(γ-phenoxy-β-hydroxypropyl)benzothiazoline (V). A. A mixture of 1.5 g (10 mmole) of Ia and 4.5 g (30 mmole) of oxirane II was stirred for 10 h at 90°C, after which it was cooled, and the precipitated crystals were separated and recrystallized.

B. A mixture of 0.03 g (0.1 mmole) of IIIa and 0.9 g (6 mmole) of oxirane II was stirred for 10 h at 90°C, after which the excess oxirane II was removed by distillation in vacuo, and the residue was recrystallized.

2-(2-Benzothiazolyl)imino-3-(γ-phenoxy-β-hydroxypropyl)benzothiazoline (VI). A solution of 0.75 g (5 mmole) of amine Ia and 0.75 g (5 mmole) of oxirane II in 15 ml of m-xylene was refluxed for 36 h, after which the solvent was removed, and the residue was chromatographed with a column.

2-Acetylimino-3-(γ-phenoxy-β-acetoxypropyl)benzothiazoline (VII). A solution of 0.28 g (0.9 mmole) of IIIa and 0.51 g (5 mmole) of acetic anhydride in 10 ml of benzene was stirred for 20 h at 35°C, after which the benzene was removed by distillation, and the residue was washed with water and recrystallized.

2-[N-Acetyl-N-(γ-phenoxy-β-acetoxypropyl)]aminobenzothiazole (VIII). A solution of 0.5 g (1.7 mmole) of heterylamine IVa and 1.9 g (18 mmole) of acetic anhydride in 15 ml of benzene was refluxed for 5 h, after which it was poured into 30 ml of water. The benzene layer was separated and dried with $CaCl_2$, and the solvent was removed by distillation. The dry residue was chromatographed with a column.

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