Chemistry of Heterocyclic Compounds, Vol. 32, No. 9, 1996

REACTION OF 2-IMINOBENZOTHIAZOLINES WITH PROPYLENE OXIDE

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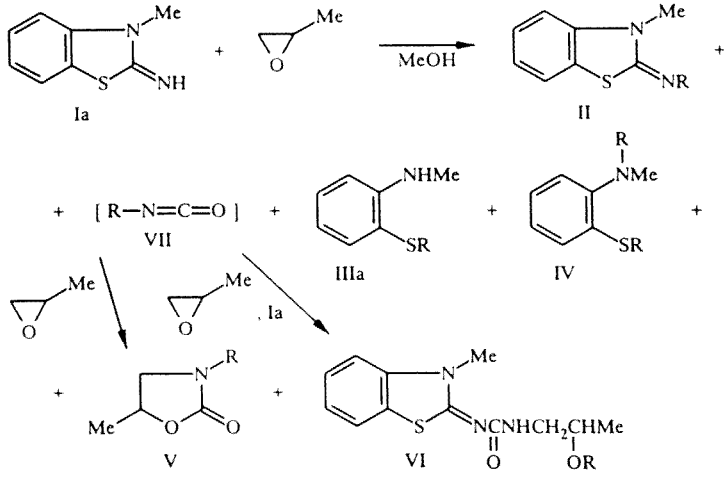
The reaction of 2-iminobenzothiazolines with propylene oxide in methanol involves splitting of the thiazoline ring and formation of derivatives of o-aminothiophenol, urea, and oxazolidinone. It is shown that dialkylaminobenzothiazoles, in contrast to their imino isomers, do not react with oxiranes.

Continuing the study [1, 2] of a new reaction which we observed in a series of heterocyclic amines, i.e., splitting of the heteroring under action of oxiranes, we carried out the reaction of 2-iminobenzothiazolines Ia, b with propylene oxide.

2-Imino-3-methylbenzothiazoline (Ia) kept with propylene oxide in methanol at 20-30°C forms, in addition to the expected product of normal alkylation (II), o-[N-methyl-S-(2-hydroxypropyl)]aminothiophenols (III and IV), as well as 3-(2-hydroxypropyl)-5-methyloxazolidin-2-one (V) and N-(3-methylbenzothiazolyl-2-idene)-N'-(2'-hydroxypropoxypropyl)urea (VI).



R = $CH_2CH(OH)Me$

Such a composition of the reaction mixture enabled us to propose the following scheme of the process: propylene oxide causes formation of product II and splitting of the benzothiazoline ring at the C_2-S and C_2-N bonds with ejection of the $=C=N-R$ fragment, which in the presence of methanol is evidently converted into 2-hydroxypropyl isocyanate (VII). The latter reacts with the initial oxide and imine, forming oxazolidinone V and urea VI, respectively. It could be postulated that the reaction forms, not isocyanate VII, but immediately oxazolidinone V, which may also be an acylating agent [3]. In this case, however, in urea VI the oxypropyl groups should add, not successively, but both to a single nitrogen atom not bound to the ring. However, the mass-spectral data for compound VI do not permit such a structure. The presence of a signal with m/z 279 $[M-CHOHCH_3]^+$ and absence of the peak with m/z 235 $[M-2(CHOHCH_3)]^+$ provide evidence in favor of successive addition of the oxypropyl groups. In the ESR spectrum, the values of the chemical shifts of the two methine protons differ (4.15 and 5.25 ppm), thus also confirming the structure VI.

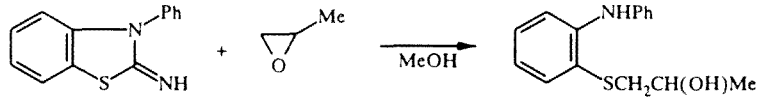
Phytochemistry Institute, Academy of Sciences of Uzbekistan Republic, Tashkent 700170. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1279-1283, September, 1996. Original article submitted July 11, 1996.

 0009-3122/96/3209-1100$15.00

Under action of propylene oxide, product II may undergo splitting, as well as alkylation at the hydroxyl group, and therefore, we were unable to isolate it in pure form. The composition of the reaction mixtures was determined from the results of mass spectroscopy of secondary ions using liquid matrices (LSIMS) and analysis by means of AELC. The LSIMS spectra of the reaction mixtures (Table 1) recorded the peaks of protonated molecular ions – alkylation products of type II, where R = $CH_2CH(OH)CH_3$, $CH_2CH(CH_3)O-CH_2CH(OH)CH_3$ and $CH_2CH(CH_3)OCH_2CH(CH_3)OCH_2CH(OH)CH_3$ (m/z 223, 281 and 339, respectively), $[M + H]^+$ peaks of o-aminothiophenols IIa and IV (m/z 198 and 256), urea VI (m/z 324), products of the reaction of methanol with propylene oxide (m/z 322 and 380), as well as unidentified substances (m/z 248, 326, 327 and 343).

Analysis of the dynamics of accumulation of o-aminothiophenols IIIa, IV and urea VI (Table 1) showed that when equimolar amounts of the initial reactants are allowed to stand for 1-2 months, only an insignificant splitting of the benzothiazoline ring is observed. When propylene oxide was present in fivefold excess, products IIIa, IV and VI were seen to form in only 7 days. As the duration of the reaction increased, the yield of compound IIIa was found to increase slightly, apparently as a result of its further alkylation by propylene oxide. In our view, the low yield of compound VI is due to a greater participation of amine Ia and isocyanate VII in the competitive processes. We were unable to study the dynamics of oxazolidinone accumulation, since this compound is not recorded under the conditions of analysis by the AELC method and does not form a molecular ion in LSIMS.

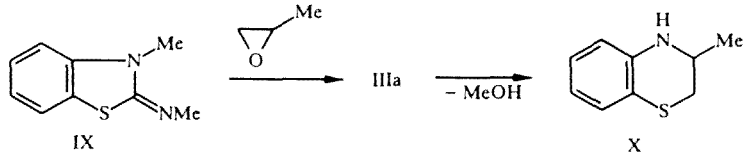
Judging from the data of mass-spectrometric analysis, in the reaction of 2-imino-3-phenylbenzothiazoline Ib with propylene oxide, a set of compounds analogous to those obtained in the case of amine Ia are formed. However, because of their low yields, we were able to isolate only N-phenyl-S-(2-hydroxypropyl)-o-aminothiophenol (IIIb) from the reaction mixture.



Ib IIIb

In connection with the results obtained, it was of interest to explain whether splitting occurs in the case of the aminobenzothiazole derivatives having no labile hydrogen atom and hence, not participating in the reaction of "normal" alkylation. On the other hand, it was necessary to evaluate the influence of the substrate structure (amino or imino form) on the splitting process. To answer these questions, two isomeric compounds — 2-dimethylaminobenzothiazole (VIII) and 2-methylimino-3-methylbenzothiazoline (IX) — with a fivefold excess of propylene oxide in methanol were kept at 20-30°C for 1-5 months. It was found that aminobenzothiazole VIII does not undergo cleavage: in the reaction mixture, the corresponding o-aminothiophenols are absent. The mass spectrum recorded peaks of the protonated ion of the initial 2-dimethylaminobenzothiazole (m/z 179) and products of the reaction of methanol with propylene oxide (m/z 147, 162, 220, 266, 278 and 311).

Under the same conditions, iminobenzothiazoline IX forms substituted o-aminothiophenols IIIa and IV in yields of 7% and 9%, respectively (Table 1). In the spectrum of LSIMS, in addition to the peaks of protonated ions of the initial benzothiazoline IX (m/z 179), as well as o-aminothiophenols IIIa and IV (m/z 198 and 256, respectively), we observed a series of peaks of ions with m/z 166, 224, 282 and 340, differing from each other by 58 amu, i.e., by the propylene oxide molecule. The precursor of the series with $[M + H]^+$ 166 is most likely 3-methyl-2,3-dihydro-1,4-benzothiazine (X) — the cyclization product of o-aminothiophenol IIIa with the splitting off of a methanol molecule.



IX X

The formation of benzothiazines apparently decreases the total yield of o-aminothiophenols IIIa and IV in the reaction of propylene oxide with benzothiazoline IX.

It should be noted that the results of this study are analogous to those obtained previously in a study of the reaction of 2-aminobenzothiazole with propylene oxide [2].

TABLE 1. Conditions of Reaction of Compounds Ia, VIII, IX with Propylene Oxide and Results of Analysis of the Reaction Mixtures by AELC and LSIMS Methods

Initial amine	Amine to oxirane ratio, moles	Duration of reaction, days	Yield of products, % (AELC data)			Values of m/z (rate, %) $[M + H]^+$ and other ions (LSIMS data)					
			IIIa	IV	VI	initial imine	II	IIIa	IV	VI	other ions
Ia	1 : 1	7	–	–	–	165 (19)	223 (100)	–	–	–	281 (2), 326 (5), 327 (4), 339 (1)
Ia	1 : 1	60	Traces	Traces	Traces	165 (33)	223 (100)	–	–	324 (2)	248 (12), 281 (3), 326 (5), 339 (4), 343 (5)
Ia	1 : 5	7	2	2	3	165 (17)	223 (100)	–	256 (2)	324 (1)	281 (15), 339 (2)
Ia	1 : 5	30	9	16	4	*	–	–	–	–	
Ia	1 : 5	60	9	45	6	165 (20)	223 (100)	198 (20)	256 (80)	324 (7)	281 (83), 322 (95), 339 (2), 380 (10)
VIII	1 : 5	150	–	–	–	179 (3)	–	–	–	–	147 (100), 162 (31), 220 (31), 266 (13), 278 (6), 311 (35)
IX	1 : 5	150	7	9	–	179 (17)	–	198 (24)	256 (30)	–	166 (100), 224 (39), 282 (30), 340 (4), 313 (15), 371 (24)

*No analysis was performed.

The structure of the synthesized compounds was demonstrated by means of data of ESR, mass, IR and UV spectra, and was also confirmed by ultimate analysis. The IR spectra show bands of stretching vibrations of O–H and N–H bonds in the 3400-3220 cm^{-1} region. In addition, the spectrum of urea VI has the absorption band of the =N–C=O group at 1610 cm^{-1}. The UV spectra of the synthesized compounds yield little information. The spectra of compounds IIIa and IV contain three types of absorption bands at 206-208, 241-242 and 293-296 nm. Characteristic of o-aminothiophenol IIIb are two absorption peaks at 260 nm and 285 nm. The UV spectrum of urea VI has a finer structure. In the mass spectra of the synthesized compounds, the most stable fragments are those obtained by elimination of the ethoxy radical or acetone molecule from the molecular ions. The low intensity of the molecular ion of urea VI (around 1%) evidently indicates a low stability of this compound.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer in KBr pellets, the UV spectra were recorded on an EPS-3T Hitachi spectrometer in ethanol, and the ESR spectra were recorded on a Jeol C-60-HL instrument, with HMDS as the internal standard. The recording conditions of the correlated electron-impact mass spectra and LSIMS are described in [2]. The analysis using the AELC method was carried out on a Milikhrom chromatograph, the column was 64 × 2 mm, the sorbent was Silasorb 600, and the eluent was 80:15:5 hexane–chloroform–isopropanol, at λ = 250 nm. The reaction was monitored by thin-layer chromatography on Silufol UV-254 plates, the eluent being 2:1:1 acetone–benzene–chloroform. The initial amines Ia, b, VIII and IX were synthesized in accordance with the methods described in [4-6].

Reaction of Benzothiazolines Ia, b, VIII, IX with Propylene Oxide (general method). To a solution of 10 mmole of benzothiazoline in 10 ml of methanol is added 2.9 g (50 mmole) of propylene oxide, and the mixture obtained is kept at room temperature with periodic agitation. The duration of the reaction is given in Table 1. Methanol and excess propylene oxide are driven off, the residue is analyzed by AELC and mass-spectrometrically, the products are separated by column chromatography with L 100/160 silica gel, the eluent being hexane, and with a benzene–hexane mixture and benzene. The physicochemical properties of oxazolidinone V are the same as those indicated in [2].

o-[N-Methyl-S-(2-hydroxypropyl)]aminothiophenol (IIIa). Oil, R_f 0.86. IR spectrum: 3380 cm^{-1} (NH, OH). UV spectrum, λ_{max}: 208, 242 and 293 nm. Mass spectrum, m/z (I, %): 197 (M^+, 60), 150 (48), 140 (12), 139 (100), 138 (46), 137 (24), 136 (32), 124 (14), 109 (14), 107 (12), 106 (14), 94 (48), 77 (16). Found, %: C 60.90; H 7.57; N 7.16. $C_{10}H_{15}NOS$. Calculated, %: C 60.88; H 7.66; N 7.10.

o-[N-Phenyl-S-(2-hydroxypropyl)]aminothiophenol (IIIb). Oil, R_f 0.83. IR spectrum: 3350 cm^{-1} (NH, OH). UV spectrum, λ_{max}: 260 sh., 285 nm. ESR spectrum ($CDCl_3$): 1.1 (3H, d, CH_3); 2.7 (2H, d, CH_2); 3.65 (1H, m, CH); 4.5 (1H, s, OH); 6.65-7.5 ppm (9H, m, Ar). Mass spectrum, m/z (I, 1%): 259 (M^+, 100), 212 (31), 202 (16), 201 (90), 200 (49), 199 (44), 198 (12), 180 (25), 169 (11), 168 (18), 167 (34). Found, %: C 69.52; H 6.48; N 5.32. $C_{15}H_{17}NOS$. Calculated, %: C 69.46; H 6.61; N 5.40.

o-[N-Methyl-N,S-bis(2-hydroxypropyl)]aminothiophenol (IV). Oil, R_f 0.75. IR spectrum: 3400 cm^{-1} (OH). UV spectrum, λ_{max}: 206, 241 and 290 sh. nm. ESR spectrum ($CDCl_3$): 1.15 (6H, q, $2CH_3$); 2.65 (3H, s, CH_3); 2.8 (4H, m, $2CH_2$); 3.7 (4H, m, 2CH, 20H); 7.1 ppm (4H, m, Ar). Mass spectrum, m/z (I, %): 255 (M^+, 18), 211 (16), 210 (100), 153 (10), 152 (62), 151 (43), 150 (59), 145 (14), 138 (18), 137 (24), 136 (15), 121 (17), 109 (14), 91 (12). Found, %: C 61.20; H 8.18; N 5.53. $C_{13}H_{21}NO_2S$. Calculated, %: C 61.14; H 8.29; N 5.49.

N-(3-Methylbenzothiazolyl-2-idene)-N′-(2′-hydroxypropoxypropyl)urea (VI). Mp 194-196°C (ethanol). R_f 0.36. IR spectrum: 3300-3220 (NH, OH), 1610 cm^{-1} (=N–C=O). UV spectrum, λ_{max}: 218, 229, 269 sh., 278, 300 sh., 310 nm. ESR spectrum (CF_3COOH): 1.03 (3H, d, CH_3); 1.1 (3H, d, CH_3); 3.1-3.8 (4H, m, $2CH_2$); 3.7 (3H, s, CH_3); 4.15 (1H, m, CH); 5.25 (1H, m, CH); 7.35-7.6 ppm (4H, m, Ar). Mass spectrum, m/z (I, %): 323 (M^+, 1), 279 (10), 192 (14), 191 (100), 176 (7), 164 (8), 149 (5), 136 (12). Found, %: C 55.78; H 6.63; N 13.12. $C_{15}H_{21}N_3O_3S$. Calculated, %: C 55.71; H 6.55; N 12.99.

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