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HETEROCYCLIZATION OF 2-ALLYLTHIOBENZIMIDAZOLES INTO DERIVATIVES OF BENZIMIDAZO[2,1-b]-1,3-THIAZINES

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It was found that bromination of 2-allylthiobenzimidazoles in organic solvents forms products of addition of bromine to the olefin bond – 2,3-dibromopropylthiobenzimidazoles, which spontaneously or on heating cyclize into 3-bromobenzimidazo[2,1-b]-1,3-thiazines or cyclodehydrobromination products — 2H- or 4H-benzimidazo[2,1-b]-1,3-thiazines.

Continuing the study of heterocyclization paths in azole systems, we have here investigated the transformations of 2-allylthiobenzimidazoles Ia, b with bromine in various solvents and temperature conditions. Bromination of azole Ia in DMFA or pyridine forms a mixture of compounds consisting of thiazine II and thiazines IIIa and IVa. Azole Ib under the same conditions together with thiazines IIIb and IVb also forms about 10% of thiazoline V.

The formation of thiazines IIIa and IVa could be represented as resulting from dehydrobromination of thiazine II. However, control experiments on the conversion of thiazide II or its salt II·HBr into thiazines IIIa and IVa, both by allowing the reaction mixture to stand for a long time (about one month) at room temperature and by boiling in acetonitrile, demonstrate their sufficient stability, and only by heating under more drastic conditions ($\geq$ 100°C in DMFA) can a small amount of thiazines IIIa and IVa be obtained. Hence, the mechanism of their formation is different. Apparently, the overall process of heterocyclization, which leads to the indicated mixture of the compounds, consists of at least four parallel reactions which have some common intermediate.

As is well known [1], heterocyclizations in unsaturated systems are treated as electrophilic intramolecular reactions of olefin bonds, where the rate-determining stage involves the formation of a carbenium center or a transition state with the participation of a halide π-complex and a ring-forming nucleophilic atom. If the latter is sufficiently basic (as in the case of azole systems), the protoactivity of the solvent can appreciably affect the course of the process, up to the point of suppressing a given direction; this should be observed even when a synthetic method of study is used.

Indeed, bromination of azoles Ia, b in acetic acid forms products of addition of bromide to the olefin bond — 2,3-dibromopropylthiobenzimidazoles VIa, b. The latter are partially (10-30%) isolated directed from the reaction mixture in the form of dihydrobromides VIa, b·HBr, and partially by treatment of the reaction mixture with hydrobromic acid, so that the indicated salts are obtained in good yields (56-63%) (see Scheme and Table 1).

The action of weak alkaline agents (sodium hydrocarbonate or acetate) converts the salts VIa, b·HBr into bases VIa, b. The 2-unsubstituted dibromide VIa was found to be a very labile compound; even at room temperature in acetone, acetonitrile, or in the melt, it slowly cyclizes into 3-bromothiazine hydrobromide II·HBr and into 2H- and 4H-thiazines IIIa and IVa. The hydrobromide II·HBr is readily converted into base II by weak alkaline agents (NaOAc, $NaHCO_3$).

A crystalline mixture of thiazines IIIa and IVa (molar ratio of isomers ~1:1) is formed in a high yield (90%) also by boiling 3-bromothiazane II with methanol solutions of alkalis, similarly to the conversion of the 3-chloro analog of thiazane III, described in [2].

The 2-methyl-substituted dibromide IVb is more stable than its analog VIa; it is purified by recrystallization from alcohols and does not change appreciably after prolonged boiling in acetonitrile. It forms cyclization products — 2H- and 4H-thiazines IIIb and IVb — only after being heated in DMFA a 100-120°C. Under action of diazabicyclo[2,2,2]octane, the dibromide IIb is converted into bisammonium salt VII, while its analog VIa under the same conditions yields thiazanes II, II·HBr and thiazines IIIa and IVa.

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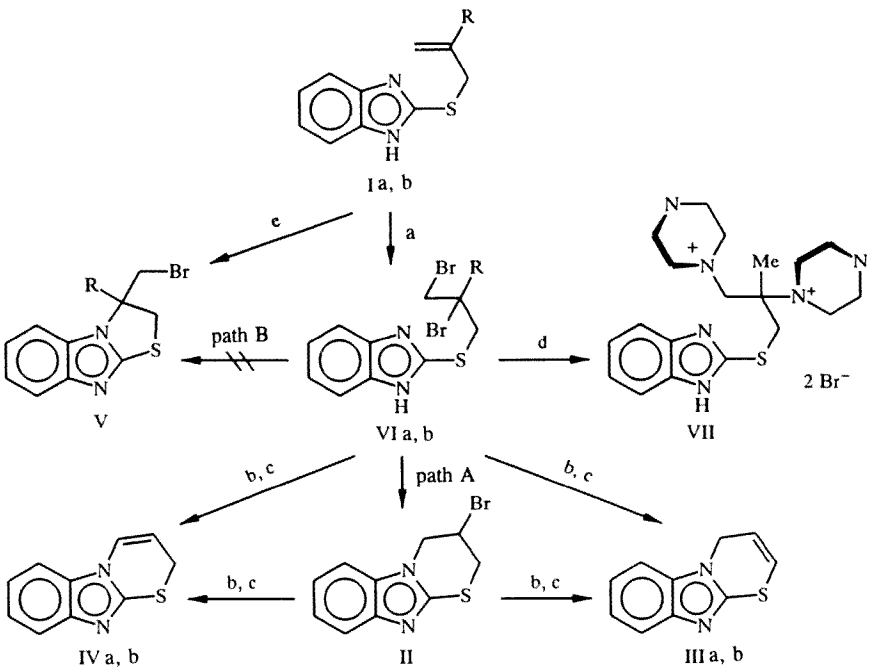
Scheme



Reactants: a Br_2, AcOH; b Δ; c NaOH or KOH; d DABCO; e Br_2, Py
I—IVa, VIa R = H; I—IVb, VIb, VII R = CH_3

The ESR spectra of compounds IIa, b, IIa, b·HBr lack the signals of olefin protons, and the chemical shift of the signal of the CH_2Br fragment approximately corresponds to the shift of the analogous protons in the spectrum of dibromoethane (3.7 ppm). The saltlike structure of compounds VIa, b·HBr is confirmed by the presence of signals of the protons of the NH group at 9.1-11.2 ppm. The spectra of compounds VIa, b and VIa, b·HBr (CH_2S 3.7-4.0, CH_2Br 3.9-4.1, CHBr 4.5-4.9 ppm) differ appreciably from the spectra of thiazanes II, II·HBr, in which the signals of the CH_2N and CHBr groups are manifested at 4.52-4.89 ppm and 5.24-5.42 ppm, respectively.

Compound VIb and the alternative 3-methyl-3-bromomethylbenzimidazole [2,1-b]thiazoline (V), obtained by brominating compound Ib in pyridine, are observed in a sample of the mixture through a lowering of the melting point and a difference between the spectral and chromatographic characteristics (Tables 1 and 2). Nonidentical with each other were found to be compounds VIb and 2-methyl-2-bromomethylbenzimidazo[2,1-b]thiazoline (VIII), which is obtained by brominating N-methallylbenzimidazole-2-thione.

Compounds VIa, b do not contain a saltlike-bound hydrogen bromide in the molecule, as indicated by their stability under action of weak alkaline agents ($NaHCO_3$, NaOAc) for several hours at room temperature. We obtained the hydrobromides VIa, b·HBr also by an independent synthesis from benzimidazole-2-thione and 1,2,3-tribromopropane without hydrogen bromide acceptors in DMFA.

These facts make it possible definitely to refer the structure of compounds VIa, b, VIa, b·HBr to acyclic dibromides — products of addition of bromine to the olefin bond of allylthioazoles Ia, b.

A characteristic feature of the ESR spectra of thiazines IIIa, b and IVa, b is the fact that they contain signals of the 2-H and 4-H groups (6.00-7.00 ppm), and in the case of 3-unsubstituted thiazines IIIa and IVa, these signals are manifested in the form of doublets with an SSCC of 6.8 Hz and 10.2 Hz, respectively. The signals of the protons of the 3-H central groups in the spectra of compounds IIIa and IVa are multiplet signals (5.54 and 6.00 ppm), as expected.

The IR spectra of compounds II II·HBr, VIa, b, VIa, b·HBr show bands of stretching vibrations of C−Br bonds (740-750 c^{-1}) and CH groups (3080-3135 cm^{-1}). The spectra of thiazines IIIa, b and IVa, b show absorption bands of the C=C bonds (ν 1650-1655) of olefin fragments, C=C aromatic bonds (ν 1500-1520 cm^{-1} and 1575-1640 cm^{-1}), and C−H bonds (ν 3080-3120 cm^{-1}).

TABLE 1. Yields and Principal Constants of Synthesized Thiazanes II, II·HBr, Thiazines IIIa, b, IVa, 2,3-Dibromopropylbenzimidazoles VIa, b, VIa, b·HBr, and Bisammonium Salt VII

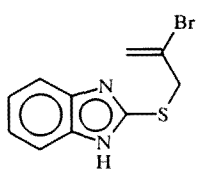
Compound	Empirical formula	mp, °C (solvent for crystallization)	R_f*	Yield, %
II	$C_{10}H_9BrN_2S$	165...166 (acetonitrile)	0,49*2	76
II · HBr	$C_{10}H_{10}Br_2N_2S$	242...244 (acetic acid)	0,09	50
IIIa, IVa	$C_{10}H_8N_2S$	136...137*3 (isopropyl alcohol–water, 2:1)	0,60*2; 0,67*2	90
IIIb	$C_{11}H_{10}N_2S$	153...154 (isopropyl alcohol)	0,76; 0,67*2	14
V	$C_{10}H_{11}BrN_2S$	101...102 (hexane)	0,75	11
VIa	$C_{10}H_9Br_2N_2S$	Resinlike product, unstable	0,79	100
IVb	$C_{11}H_{11}Br_2N_2S$	139...140 (isopropyl alcohol)	0,79	100
VIa · HBr	$C_{10}H_{10}Br_3N_2S$	158,5...160 (acetic acid)	0,13	63
VIb · HBr	$C_{11}H_{12}Br_3N_2S$	164...166 (acetic acid)	0,12	56
VII	$C_{23}H_{35}Br_2N_6S$	203 (dec.) (water)	0,02	94

*Eluent) 10:1 mixture of chloroform and methanol.

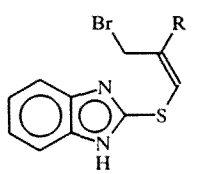
*2Eluent) ether.

*3Melting point of 1:1 mixture of isomers IIIa and IVa.

Thus, in the bromination of azole derivatives of type I in the aprotic and protoactive solvent, formation of cyclic compounds II-V or dibromo-substituted compounds VI is substantially determined by the state of the ring-forming nitrogen atom of the azole nucleus. In the aprotic solvent, cyclization takes place to an appreciable extent and its direction is substantially determined by the basicity of the heteroatom. Thus, for the most basic benzimidazole system (pK_a of the heteronucleus is 5.5), formation of thiazolines V is observed, and for the less basic benzothiazoles (pK_a ~3), formation of thiazanium salts is observed [3]. In acetic acid, however, the nucleophilic nitrogen atom of the heteronucleus, responsible for the intramolecular process, is blocked by hydrogen bonds (or even by salt formation) with the solvent, and the reaction takes place in the direction of formation of dibromo derivatives VIa, b, which can be isolated as intermediate products of heterocyclizations. Further in the process of cyclodehydrobromination, the nitrogen atom of the heteronucleus may play the role of the main center in elimination, which results in the formation of brominated ethylene bromides or allyl bromides (intermediates of types IX, X), or it may be the ring-forming atom replacing the bromine in the indicated intermediates via an appropriate mechanism (for example, S_N1, S_N2 or Ad_NE), so that bromothiazane II or thiazines III, IV are obtained.



IX



X

EXPERIMENTAL

The ESR spectra were recorded with a Varian Gemini 200 instrument, internal standard TMS or HMDS, and the IR spectra were measured with a UR-20 spectrometer slit program 4, recording speed 160 cm^{-1}/min. Thin layer chromatography was carried out on Silufol plates in a 10:1 chloroform–methanol system and ether; developer, iodine vapor.

The ultimate analysis data for C, H, Br, N, S of compounds II-VII are consistent with the calculated data.

TABLE 2. Chemical Shifts of Proton Signals in the ESR Spectra and Fundamental Absorption Bands in the IR Spectra of the Synthesized Compounds II, II·HBr, IIIa, b, IVa, VIa, b, VIa, b·HBr, VII*

Compound	ESR spectrum, δ, ppm	IR spectrum, cm^{-1}
II	3,65 (1H, m, CH_2S), 3,80 (1H, m, CH_2S), 4,52 (1H, m, CH_2N), 4,63 (1H, m, CH_2N), 5,24 (1H, m, CHBr), 7,17...7,47 (4H, m, H_{arom})	3055 (CH_{arom}), 1610, 1575 ($C=C_{arom}$), 740 (CBr)
II·HBr	3,90 (1H, m, CH_2S), 4,10 (1H, m, CH_2S), 4,89 (2H, m, CH_2N), 5,42 (1H, m, CHBr)	3430 (N^+H), 3080, 3020 (CH_{arom}), 1605, 1520 ($C=C_{arom}$), 750 (CBr)
IIIa	4,80 (2H, s, CH_2N), 5,54 (1H, m, CH=C), 6,33 (1H, d, CH=C), 7,22...7,64 (H_{arom})	3050, 3020 (CH_{arom}), 1650, 1620, 1595, 1570 ($C=C_{thiaz.arom}$)
IIIb	1,98 (3H, s, CH_3C), 4,63 (2H, s, CH_2N), 6,00 (1H, s, CH=C), 7,23...7,72 (4H, m, H_{arom})	3045 (CH_{arom}), 1655 ($C=C_{thiaz}$), 1605 ($C=C_{arom}$)
IVa	3,63 (2H, s, CH_2S), 6,00 (1H, m, CH=C), 7,00 (1H, d, CH=C)*2, 7,22...7,64 (4H, m, H_{arom})	—
VIa·HBr	4,10 (4H, m, CH_2S, CH_2Br), 4,95 (1H, m, CHBr), 7,49...7,74 (4H, m, H_{arom})	3135 (CH), 3060, 3020 (CH_{arom}), 1640, 1520 ($C=C_{arom}$), 746 (CBr)
VIb·HBr	1,94 (3H, s, CH_3C), 4,17 (4H, m, CH_2S, CH_2Br), 7,50...7,73 (4H, m, H_{arom})	3060, 3020 (CH_{arom}), 1620, 1520 ($C=C_{arom}$), 746 (CBr)
VIa	3,82 (2H, m, CH_2S), 4,10 (2H, m, CH_2Br), 4,57 (1H, m, CHBr), 7,38...7,77 (4H, m, H_{arom})	3132 (CH), 3065, 3015 (CH_{arom}), 1625, 1595, 1508 ($C=C_{arom}$), 760 (CBr)
VIb	1,93 (3H, s, CH_3C), 3,97 (2H, d, CH_2S), 4,07 (2H, d, CH_2Br)*3, 7,12...7,45 (4H, m, H_{arom})	3070, 3050 (CH_{arom}), 1610, 1580 ($C=C_{arom}$), 745 (CBr)
VII	2,15 (3H, s, CH_3C), 3,05 (1H, m, CH_2C), 3,42 (3H, m, CH_2C, CH_2S), 4,06 (2H, m, CH_2N^+), 7,18...7,50 (4H, m, H_{arom})	3080, 3030 (CH_{arom}), 1605 ($C=C_{arom}$)

*The ESR spectra of compounds II·HBr VIa, b·HBR and VII were recorded in DMSO-D_6, the rest in $CDCl_3$; NH δ for compounds II·HBr, 9.50 ppm, VIa·HBr, 11.20 ppm, VIb·HBr, 9.10 ppm. Their position is highly unstable. The IR spectra of compounds II-VII were recorded in Nujol, and the spectrum of compound IIIa is given for its mixture with isomeric thiazine VIa (1:1).

*2J 6.8 Hz.

*3J 10.2 Hz.

Reactions of 2-Allylthiobenzimidazoles Ia, b with Bromide in DMFA. To a solution of 10 mmoles of one of the 2-allylbenzimidazoles Ia, b in 10 ml of DMFA is added dropwise a room temperature 0.52 ml (10 mmoles) of bromine. To the solution obtained is added in one portion 0.82 g (10 mmoles) of anhydrous sodium acetate, then the mixture is agitated for 15 min and analyzed by TLC. In the conversion products of azoles Ia, b, one finds 2-(2,3-dibromopropylthio)benzimidazoles VIa, b, as well as small amounts of 3-bromobenzimidazo[2,1-b]-1,3-thiazane (II) (conversion of azole Ia) or 3-methyl-3-bromobenzimidazo[2,1-b]thioazoline (V) (conversion of azole Ib). The reaction mixture is heated for 5 h at 80°C, a mixture of thiazane II and thiazines IIIa and IVa is obtained from azole Ia, and thiazines IIIb, IVb, thiazoline V, and unreacted dibromide VIb are obtained from the methyl analog. Subsequent heating for 8 h a 120°C yields only thiazines IIIa, IVa in the case of conversion of azole Ia, and as a result of the reaction of azole Ib—thiazoline V, and chiefly, a mixture of thiazines IIIb, IVb.

Hydrobromides of 2,3-Dibromopropylthiobenzimidazoles (VIa, b·HBr). To a solution of 0.1 mole of the one of the 2-allylthiobenzimidazoles Ia, b in 300 ml of acetic acid is added dropwise with stirring 5.68 ml (0.11 mole) of bromide. The mixing is continued for another 2 h, and the mixture is left standing overnight. The precipitate of the corresponding hydrobromide IVa, b·HBr is filtered off and dried. To the mother liquor is added 20 ml of concentrated hydrobromic acid, and the solution is evaporated down to 1/5 of its volume and left standing, 6 to 8 h at 5-10°C. The precipitate is filtered off, dried, combined with the first portion of the substance, and recrystallized. Compounds VIa, b·HBr consist of colorless platelike crystals that are stable in storage and partially lose hydrogen bromide only in a vacuum at 100°C.

To isolate the free bases VIa, b, it is preferable to use weak alkaline agents (sodium acetate or hydrocarbonate) up to 20°C, since under these conditions, the dibromides IIa, b obtained react no further with the indicated proton acceptors.

To a suspension of 0.1 mole of thoroughly crushed salt VIb·HBr in water is added 16.4 g (0.2 mole) of sodium acetate, and the mixture is agitated for 2 to 3 h. The precipitate of base VIb is filtered off and recrystallized.

In the case of the less stable dibromide VIa, the reaction of the salt VIa·HBr with sodium acetate or hydrocarbonate is carried out in the two-phase system choroform–water or benzene–water with a hydrobromide to acetate ratio of 1:2.

3-Bromobenzimidazo[2,1-b]-1,3-thiazane Hydrobromide (II·HBr). To a suspension of 15.3 g (35.5 mmoles) of hydrobromide VIa·HBr are added 2.91 g (43.7 mmoles) of sodium acetate ad 20 ml of acetonitrile. The mixture is heated at 80°C until the reaction product crystallizes (about 1 to 1.5 h), then 15 ml of acetonitrile is added, and the heating is continued for 1 h. After cooling, the precipitate if filtered off, washed with water, alcohol, and ether, and dried. Yield 7.65 g (62%).

3-Bromobenzimidazo[2,1-b]-1,3-thiazane (II). A mixture of 0.7 g (1.62 mmoles) of hydrobromide VIa·HBr, 6 ml of acetonitrile, 2 ml of water, and 0.17 g (2 mmoles) of sodium hydrocarbonate is agitated to complete homogenization and left standing for 7 days at room temperature (to completeness of the reaction of dibromide VIa, checked with TLC. To the solution obtained is added another 0.17 g (2 mmoles) of sodium hydrocarbonate and after agitation for 1 h the solution is evaporated to dryness in a vacuum. The residue is washed with water and the precipitate is filtered off and dried. Yield of thiazane II, 0.41 g (94%).

Reaction with Thiazane II with Alkalis. To a solution of 7 g (26 mmoles) of thiazane II in 20 ml of methanol is added a solution of 7.84 g (0.14 mmoles) of thiazane II in 20 ml of methanol, and the mixture is boiled for 6 h. The precipitate formed is filtered off and washed with water until the wash waters show a neutral reaction, then dried. A colorless, crystalline substance is obtained in the amount of 2.3 g. The mother liquor is evaporated to dryness in a vacuum, 50 ml of water is added to the crystalline residue obtained, and the mixture is thoroughly agitated. The precipitate is filtered off and washed in water until the reaction of the wash waters is neutral, dried, and an additional 2.1 g of substance is obtained which in composition is the same as the first batch; total yield, 4.4 g (90%). The reaction producer consists of an approximately equimolar mixture of the two thiazines IIIa and IVa, which crystallize jointly from alcohols or their mixtures with water; m.p. of mixture, 136-137°C (isopropyl alcohol–water, 2:1). R_f 0.60; 0.67 (eluent, ether).

3-Methyl-4H-benzimidazo[2,1-b]-1,3-triazine (IVb). A solution of 2 g (5.49 mmoles) of dibromide VIb in 25 ml of DMFA is heated for 6 h at 120°C. The solution is diluted with 100 ml of chloroform, a solution of 0.82 g (10 mmoles) of sodium acetate in 30 ml of water is added, and the mixture is agitated for 1 h at room temperature. The chloroform layer is separated, washed with water (4 × 30 ml), and dried with anhydrous sodium sulfate. The solution is distilled under vacuum, and from the oily residue obtained, after treatment with hexane and cooling to 0°C, is isolated 0.2 g (18%) of crystalline thiazine IVb, which is purified by recrystallization. The mother liquor contains a equimolar mixture of 4H- and 2H-thiazines IVb and Vb (according to the data of TLC and ESR spectra).

2-Methyl-2,3-bis(1,4-diazabicyclo[2,2,2]-1-ammonio)propylthiobenzimidazole (VII). To a solution of 3.5 g (9.6 mmoles) of dibromide VIb in 8 ml of acetronitrile is added 2.15 g (19.2 mmoles) of 1,4-diazabicyclo[2,2,2]octane, and the mixture is boiled for 30 min. After 3 to 5 min, an abundant colorless precipitate of bisammonium salt VII is formed, which after cooling of the suspension is filtered off. Compound VII is soluble in DMSO, DMFA, and moderately in water, and on heating in alcohols and acetic acid.

REFERENCES

1. Yu. I. Gevaza, V. I. Staninets, and N. S. Zefirov, Electrophilic Intramolecular Cyclization of Olefins [in Russian], Naukova Dumka, Kiev (1990).
2. J. Sawlewicz and M. Grzybowski, Acta Pol. Pharm., **35**, 7 (1978).
3. N. I. Korotkikh, A. F. Aslanov, and O. P. Shvaika, Khim. Geterotsikl. Soedin., No. 6, 855 (1990).