Chemistry of Heterocyclic Compounds, Vol. 31, No. 4, 1995

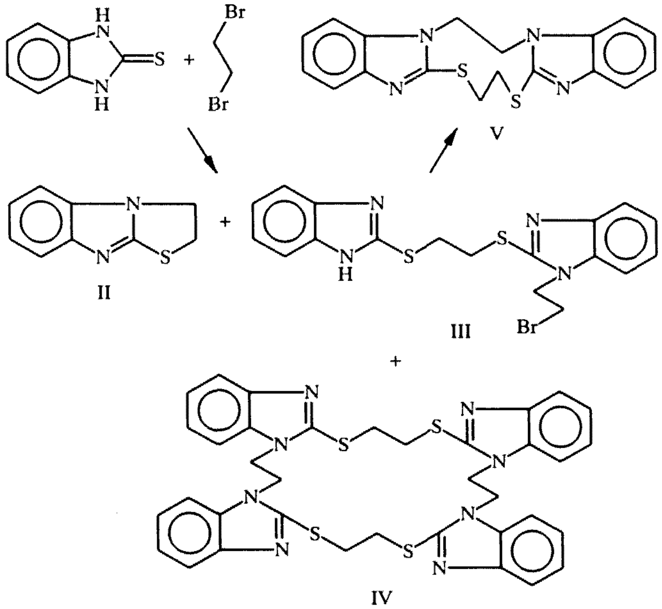
RESEARCH IN THE FIELD OF UNSATURATED DERIVATIVES OF AZOLES.

12.* REACTION OF BENZIMIDAZOLE-2-THIONE WITH 1,2-DIBROMOETHANE; TEMPLATE SYNTHESIS OF CORONANDS

I. I. Popov

Benzimidazole-2-thione and 2-(mercaptomethyl)benzimidazole react with 1,2-dibromoethane in the presence of caustic under conditions of interfacial catalysis, forming macrocyclic compounds along with linear compounds.

The reaction of benzimidazole with 1,2-dibromoethane in the presence of alcoholic KOH gives a mixture of 1-vinylbenzimidazole and 1,2-bis(1-benzimidazolyl)ethane [2]. Benzimidazole-2-thione (I) reacts with haloalkanes in stages, initially forming S-alkyl derivatives and then S, N-dialkyl derivatives [3]. Such a sequence of forming C–S and C–N bonds for the thione I has been used in the synthesis of macrocyclic ligands and podands. Upon alkylation of the thione I by 1,2-dibromoethane in aprotic dipolar solvents at room temperature under conditions of interfacial catalysis, following a procedure given in [4], with the reaction mixture containing barium cation, the reaction products contained, along with the bis-sulfide III and a small quantity of compound II, a cycloeicosane derivative, coronand-20 (IV). The relative amounts of compounds II, III, and IV depend on the polarity of the organic phase. Thus, partial replacement of DMSO by a mixture of dioxane and THF results in the formation of III as very nearly the sole product, with a minute amounts of byproducts. In an attempt to synthesize the coronand IV by the action of KOH in DMSO on the bromide III, as a result of intramolecular alkylation, compound V was obtained. We were not successful in methylating compound III by methyl iodide upon heating in a DMF/K_2CO_3 mixture; here also, the process of intramolecular cyclization predominated, with formation of the coronand V.



---

*For communication 11, see [1].

Rostov State University, Rostov-on-Don 344090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 571-574, April, 1995. Original article submitted March 11, 1995.

TABLE 1. Characteristics of Compounds II-V, VII, and VIII

Compound	mp, °C	PMR spectrum, δ, ppm	Yield, %
II	90	7,1 (4H, s, Ar), 4,3 (2H, t, CH_2), 3,9 (2H, t, CH_2)	5,7
III	215	7,0 (8H, s, Ar), 3,8 (4H, s, CH_2CH_2), 3,5 (4H, s, CH_2CH_2)	61
IV	108	7,1 (16H, s, Ar), 4,3 t and 4,0 t (16H, CH_2CH_2)	20
V	110	7,1 (8H, s, Ar), 4,3 t and 3.95 t (8H, CH_2CH_2)	91
VII	267	7,2 (8H, s, Ar), 4,2 (4H, t, $—CH_2CH_2Br$), 2,95 (4H, t, $—SCH_2CH_2S—$), 3,9 (4H, s, CH_2)	40
VIII	148	7,3 (8H, s, Ar), 4,2 s and 3,0 s (8H, CH_2CH_2), 3,8 (4H, s, CH_2)	84

TABLE 2. Mass Spectra of Compounds II-IV and VIII

Compound	m/z (and I_{rel}, %)
II	178 (15), 176 (100), 161 (13), 148 (19), 147 (6), 143 (10), 134 (21), 132 (7), 131 (23), 130 (24), 129 (7), 118 (13), 116 (23), 107 (5), 103 (27), 102 (15), 91 (7), 90 (34), 88 (13), 77 (12), 76 (18), 75 (10), 64 (15), 63 (20), 62 (7), 51 (12), 50 (13)
III	329 (8), 328 (11), 327 (71), 267 (11), 219 (6), 178 (11), 176 (100), 151 (91)
IV	233 (6), 219 (21), 217 (15), 179 (18), 178 (32), 177 (100)
V	179 (6), 178 (12), 177 (49), 176 (100), 39 (5)
VIII	192 (16), 191 (51), 190 (100), 189 (28), 162 (13), 157 (27), 145 (13), 144 (69), 143 (20), 131 (10), 118 (22), 117 (33), 103 (9), 102 (12), 90 (16), 89 (11), 77 (22), 76 (19), 75 (10), 67 (7), 64 (11), 63 (15), 59 (8), 58(10), 51 (22), 50 (13), 46 (18)

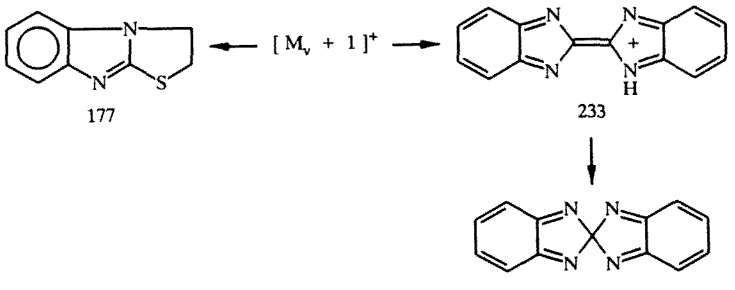
---

*Values listed for ion peaks are those with intensity greater than 5% of the maximum.

In the IR spectrum of compound III there is an absorption band of an associated NH group at 3200-3400 cm^{-1}; this band does not appear in the spectra of compound II, IV, or V. In the PMR spectrum of the cyclic compounds II, IV, and V, a downfield shift of the ethylene-group signals is observed (triplets at 3.9 and 4.3 ppm), in comparison with the signals of these groups in the PMR spectrum of their linear analog III (3.5 and 3.6 ppm).

In the mass spectrum of compound II there is a base peak of the molecular ion M^+ with m/z 176, and also intense peaks of fragment ions with m/z 161 $[M-CH_3]^+$, 148 $[M-CH_2{=}CH_2]^+$, 132 $[M-C{=}S]^+$, 118 $[M-CH_2{=}CHSH]^+$.

In the mass spectrum of the macrocyclic compound IV there is a signal of an unstable ion with m/z 353 (1.4) corresponding to the molecular mass of the protonated coronand V, formed as a result of decomposition of the cation radical of the macromolecular coronand IV; further fragmentation of the ion with m/z 353 leads to fragment ions 233 and 219 and a base ion 177 $[M_{II} + 1]$



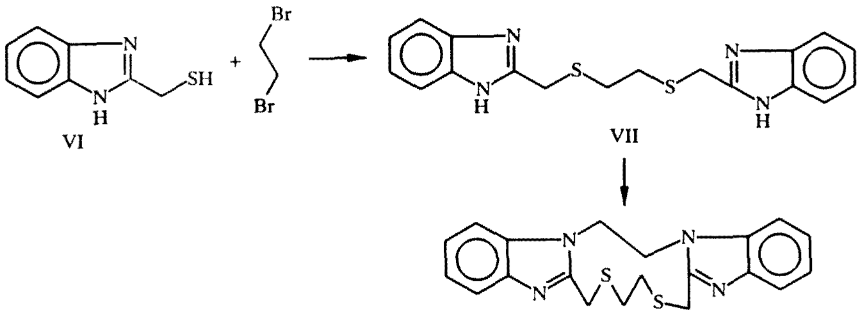
177

233

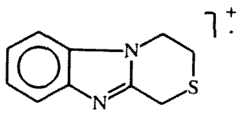
219

In the mass spectrum of the coronand V there are signals of the base ion with m/z 176 and low-intensity ions 353 $[M + 1]^+$ and 324 (2) $[M-CH_2{=}CH_2]^+$. The cation radical of compound III, under conditions of electron impact, loses a bromine atom, forming an unstable cation with m/z 353 (0.5) $[M_V + 1]$, further fragmentation of which leads to fragment ions with rather high intensities 327, 267, and 151, and also a base ion with m/z 177 $[M_{II} + 1]^+$. It should be noted that the 353 and 267 ions are detected only in the mass spectrum obtained by chemical ionization.

The reaction of 2-(mercaptomethyl)benzimidazole (VI) with 1,2-dibromoethane under conditions analogous to those in the synthesis of compound III results in the formation of the podand VII.



In the IR spectrum of compound VII there is a broad absorption band of the NH group at 3300-3500 cm^{-1}, which is not present in the IR spectrum of the coronand VIII that is formed by the interaction of the podand VII with KOH in DMSO in the presence of lithium hydroxide. In the PMR spectra of compounds VII and VIII, the singlets of the protons at 3.9 (4H) and 3.8 (4H) pertain to 2-benzimidazolylmethylene groups (compare [5]). The broadened signal of protons of the coronand VIII at 4.2 ppm pertains to the bromoethyl group and the N,N-ethylene group, since in the PMR spectrum of 1,2-bis(1-benzimidazolyl)ethane the signal of the ethylene protons is manifested in the form of a broad signal at 4.4 ppm. The other triplet of protons of compound VII and the broad signal of protons of the coronand VIII at 2.95 and 3.0 ppm apparently pertain to signals of the ethylene disulfide bridge group. Fragmentation of the cation radical of the macrocyclic compound VIII under electron impact leads to the base ion *m/z* 190, further fragmentation of which forms fragment ions of benzimidazole derivatives *m/z* 157, 144, and 118.



190

EXPERIMENTAL

The IR spectra were recorded in an IR-20 instrument in white mineral oil, PMR spectra in a Tesla 487 C instrument (80 MHz) in CF_3COOH. Mass spectra were obtained in a Finnigan 4021 spectrometer with an ionizing voltage of 70 eV, ionization chamber temperature 200-250°C. The chromatography was performed on Al_2O_3 (Grade III Brockman activity). The physicochemical characteristics and PMR spectrometric data are presented in Table 1, and the mass spectra in Table 2.

Elemental analyses for C, H, N, and S matched the calculated values.

Interaction of Benzimidazole-2-thione (I) with 1,2-Dibromoethane. A mixture of 6 g (KOH, 2 g KCl, and 1.7 g $Ba(OH)_2$ was ground together into a powder. Then, 0.1 g of triethylbenzylammonium chloride (TBAC), 3 g (0.02 mole) of the thione I, and 9 ml of DMSO were added, after which 4 g (0.021 mole) of dibromoethane was added dropwise with vigorous stirring. After the exothermic reaction had ended, another 4 g (0.042 mole) of dibromoethane was added, and the reaction mixture was allowed to stand overnight. Then it was diluted with three volumes of water, and the precipitated compound III was filtered off, dissolved with heating in dilute HCl, filtered, and precipitated with ammonia. Yield of compound III 2.4 g (55%). The mother liquor after removing compound III from the reaction mixture was evaporated down, and the residue was dissolved in dilute HCl, refluxed with activated carbon, and filtered; from the filtrate, a mixture of compounds II, III, and IV was precipitated with ammonia. Compound II, which is readily soluble in cold dilute HCl, was separated from the mixture of crystals of the hydrochlorides of compounds III and IV; the filtrate was neutralized with ammonia, and the resulting crystals of compound II were dissolved in ether and purified with in a column with aluminum oxide. Yield of 2,3-dihydrothiazolo[3,2-a]benzimidazole (II, $C_9H_8N_2S$) 0.2 g (5.7%). The mixture of hydrochlorides of compounds III and IV was dissolved with heating in dilute HCl and then cooled, after which the precipitated hydrochloride of the podand III was separated. From the mother liquor, recovered 0.7 g (20%) of 1,8,11,18-tetrathia-3,6,13,16-tetrazatetrabenzylimidazole[2,1-b, 1,2-f, 2,1-k 1,2-o]cycloeicosane (IV, $C_{36}H_{32}N_8S_4$).

1-(2-Benzimidazolylthio)-2-[1-(2-bromoethyl)-2-benzimidazolylthio]ethane (III, $C_{18}H_{17}BrN_4S_2$). A. To a mixture of 6 g KOH and 6 g NaCl, ground into a powder, 3 g (0.02 mole) of the thione I, 0.1 g of TEBAC, 10 ml of dioxane, 5 ml of THF, and 5 ml of DMSO were added, after which 8 g (0.042 mole) of dibromoethane was added dropwise with stirring. The reaction mixture was left overnight, after which it was acidified with dilute HCl to pH 4, refluxed with activated carbon, and filtered; the filtrate was neutralized with ammonia, and the precipitate was transferred to a filter, dried, and chromatographed in chloroform in a column with Al_2O_3. Yield of compound III 2.1 g (60%).

B. To a powdered mixture of 60 g KOH and 60 g NaCl, 30 g (0.2 mole) of the thione I, 1 g of TEBAC, 50 ml of dioxane, 50 ml of THF, and 50 ml of DMSO were added, after which 20 ml (43.6 g, 0.23 mole) of 1,2-dibromoethane was added dropwise with stirring. After adding the first 10 ml of the 1,2-dibromoethane, strong heating of the reaction mixture was observed; it was then left overnight, after which it was refluxed for 1 h while stirring and then allowed to cool to room temperature. Next, 5 ml (10.9 g, 0.058 mole) of 1,2-dibromoethane was added, and the mixture was again refluxed for 1 h. Upon cooling, a precipitate formed; this was suspended in warm water and neutralized with dilute HCl, after which the precipitate was filtered off. Obtained 4.1 g of colorless crystals with a slight yellow tinge. The mother liquor, after removing the first precipitate, was evaporated down and neutralized with dilute HCl, and the snow-white crystals that precipitated were filtered off. Yield 22.5 g. Total yield 26.6 g (61%). Compound III is difficulty soluble in chloroform; it crystallizes from alcohol, DMSO, or dioxane. IR spectrum: 3200-3400 cm^{-1} (NH_{ass}).

1,2-Bis(2-benzimidazolylmethylthio)ethane (VII, $C_{20}H_{21}BrN_4S_2$). Obtained in the same manner as compound III by method B, from a mixture of 24.6 g (0.15 mole) of the mercapto derivative VI, 40 g of powdered KOH and 50 g of NaCl, 40 ml of THF, 10 ml of DMSO, and 1.5 g of TEBAC, with the addition of 60 g (0.32 mole) of dibromoethane. When the reaction was completed, the mixture was diluted with water; the oil that separated out was chilled with ice and filtered. Obtained 26.5 g of a viscous oil, which was treated with dilute HCl and heated until it dissolved; alcohol was added, and the mixture was refluxed with activated carbon and filtered. After cooling, obtained the yellow hydrochloride of compound VII in amount of 16.5 g (44%); this was crystallized from an alcohol–acetone mixture and converted to the base by treatment with aqueous ammonia. The product was crystallized from a mixture of alcohol and CCl_4. IR spectrum: 3300-3500 cm^{-1} (NH_{ass}).

1,8-Dithia-3,6-diazabisbenzimidazo[2,1-b, 1,2-f]cyclododecane (VIII, $C_{20}H_{20}N_4S_2$). To 4.6 g (0.01 mole) of compound VII, added 5 ml of DMSO and 3 ml of THF, 0.1 g of TEBAC, 1 g (0.02 mole) of $LiOH \cdot H_2O$, and 2.2 g (0.04 mole) of KOH powder; the mixture was heated on a boiling water bath while stirring and refluxing; compound VII gradually passed into solution during this operation. The reaction mixture was left overnight, after which it was diluted with ice water; the precipitate was filtered off and purified in chloroform in a column with Al_2O_3. Yield 3.2 g. Crystallized from CCl_4 with the addition of several drops of $CHCl_3$.

REFERENCES

1. I. I. Popov, Khim. Geterotsikl. Soedin., No. 4, 567 (1995).
2. A. M. Simonov and A. F. Pozharskii, Zh. Obshch. Khim., **31**, 3970 (1961).
3. P. N. Preston, Chem. Rev., **74**, 166 (1974).
4. I. I. Popov, USSR Inventor's Certificate 1,183,503, Byull. Izobret., No. 37 (1985).
5. I. I. Popov, Khim. Geterotsikl. Soedin., No. 5, 664 (1993).