# INVESTIGATIONS IN THE IMIDAZOLE SERIES

## LXXVIII.* REACTION OF 2-AMINOBENZOTHIAZOLES WITH α-HALO KETONES

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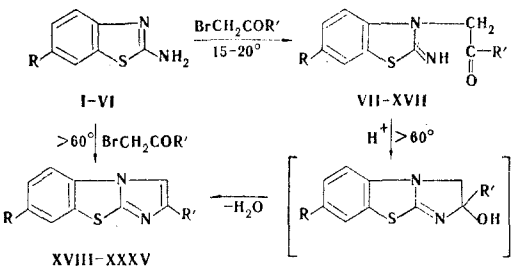
The reaction of 2-aminobenzothiazole and its 6-substituted derivatives with α-bromomethyl alkyl (aryl, heteryl) ketones was investigated in detail. Under mild conditions, 3-acylmethyl-2-iminobenzothiazolines were isolated. Their structures were established, and their properties and the conditions for cyclization to imidazo[2,1-b]benzothiazole derivatives were studied.

The reaction of 2-aminobenzothiazole and some of its derivatives with α-bromo ketones, which leads to imidazo[2,1-b]benzothiazole derivatives, was described in [2-9]. However, this reaction, particularly its stepwise character and the properties of the intermediates, has not been adequately studied.

As briefly reported in [10], in order to search for biologically active substances in condensed imidazole systems with a common nitrogen atom, we made a detailed investigation of the reaction of 2-aminobenzothiazole (I) and its 6-substituted derivatives (II-VI) having both electron-donor and electron-acceptor groups with α-bromomethyl ketones of the aliphatic, aromatic, and heterocyclic series. It was established that 3-acylmethyl-2-iminobenzothiazolines (VII-XVII, Table 1) are formed when this reaction is carried out under mild conditions – in acetone at 15-20°C; the structures of the products were confirmed by qualitative reactions for a carbonyl group and by the IR spectra, which contain distinct absorption bands of CO and NH groups at 1680-1707 and 3320-3345 $cm^{-1}$, respectively.

Compounds VII-XVII (both the hydrobromides and the free bases) proved to be stable crystalline substances and withstood brief heating in low-boiling neutral organic solvents. They are less stable in alkaline and acidic media, and readily split out a molecule of water to give imidazo[2,1-b]benzothiazole derivatives (XVIII-XXXV, Table 1) on heating in HCOOH, $CH_3COOH$, HCl, HBr, and $H_3PO_4$, as well as under the influence of dehydrating agents ($POCl_3$ and concentrated $H_2SO_4$).




*See [1] for communication LXXVII.

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TABLE 1. 3-Acylmethyl-2-iminobenzothiazolines (VII-XVII) and Imidazo[2,1-b]benzothiazole Derivatives (XVIII-XXXII)

| Compound | R | R′ | mp, °C | Empirical formula | Found, % | | | | Calculated, % | | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | S | C | H | N | S | |
| VII | H | $C_6H_5$ | 174—175[a] | $C_{15}H_{12}N_2OS$ | 66,8 | 4,9 | 10,4 | 11,8 | 67,1 | 4,5 | 10,4 | 11,9 | 75 |
| VIII | H | $p$-$CH_3C_6H_4$ | 138—140 | $C_{16}H_{14}N_2OS$ | 68,1 | 5,0 | 10,0 | 11,7 | 68,0 | 5,0 | 9,9 | 11,4 | 53 |
| IX | H | $p$-$CH_3OC_6H_4$ | 160—162 | $C_{16}H_{14}N_2O_2S$ | 64,0 | 4,6 | 9,6 | 10,7 | 64,4 | 4,7 | 9,4 | 10,7 | 32 |
| X | H | $p$-$O_2NC_6H_4$ | 264—267 | $C_{15}H_{11}N_3O_3S$ | 57,6 | 3,5 | 13,4 | 10,1 | 57,5 | 3,5 | 13,4 | 10,2 | 68 |
| XI | H | $p$-$C_6H_5C_6H_4$ | 165—167 | $C_{21}H_{16}N_2OS$ | 73,0 | 4,7 | 8,1 | 9,0 | 73,2 | 4,7 | 8,1 | 9,3 | 34 |
| XII | H | β-$C_{10}H_7$ | 162—164 | $C_{19}H_{14}N_2OS$ | 72,0 | 4,5 | 8,7 | 10,3 | 71,6 | 4,4 | 8,8 | 10,0 | 64 |
| XIII | H | α-$C_4H_3S$ | 164—166 | $C_{13}H_{10}N_2OS_2$ | 57,0 | 3,7 | 10,0 | 23,0 | 56,9 | 3,7 | 10,2 | 23,3 | 84 |
| XIV | $CH_3$ | $p$-$CH_3C_6H_4$ | 130—131 | $C_{17}H_{16}N_2OS$ | 69,2 | 5,6 | 9,9 | 10,9 | 68,9 | 5,4 | 9,5 | 10,8 | 71 |
| XV | $CH_3$ | $p$-$CH_3OC_6H_4$ | 158—160 | $C_{17}H_{16}N_2O_2S$ | 65,0 | 5,1 | 9,3 | 10,4 | 65,3 | 5,2 | 9,0 | 10,3 | 39 |
| XVI | $CH_3O$ | $p$-$O_2NC_6H_4$ | 243—244 | $C_{16}H_{13}N_3O_4S$ | 56,1 | 3,5 | 12,3 | 9,3 | 56,0 | 3,2 | 12,2 | 9,3 | 95 |
| XVII | $C_2H_5O$ | $p$-$CH_3OC_6H_4$ | 138—139 | $C_{18}H_{18}N_2O_3S$ | 63,4 | 5,2 | 8,0 | 9,1 | 63,1 | 5,3 | 8,2 | 9,4 | 44 |
| *XVIII* | *H* | $C(CH_3)_3$ | 298—300 | $C_{13}H_{14}N_2S \cdot HBr$[b] | 50,0 | 4,6 | 8,9 | 10,2 | 50,1 | 4,8 | 9,0 | 10,3 | 56 |
| XIX | H | $p$-$CH_3C_6H_4$ | 122—123 | $C_{16}H_{12}N_2S$ | 72,4 | 4,5 | 10,4 | 12,0 | 72,7 | 4,5 | 10,6 | 12,1 | 81 |
| XX | H | $p$-$CH_3OC_6H_4$ | 174—176 | $C_{16}H_{12}N_2OS$ | 68,5 | 4,3 | 9,7 | 11,7 | 65,8 | 4,3 | 10,0 | 11,4 | 76 |
| XXI | H | $p$-$C_6H_5C_6H_4$ | 165—167 | $C_{21}H_{14}N_2S$ | 77,1 | 4,7 | 8,5 | 9,8 | 77,3 | 4,3 | 8,6 | 9,8 | 71 |
| XXII | H | α-$C_4H_3S$ | 142—143 | $C_{13}H_8N_2S_2$ | 60,5 | 2,9 | 10,9 | 25,2 | 60,9 | 3,1 | 10,9 | 25,0 | 79 |
| XXIII | $CH_3$ | $p$-$CH_3C_6H_4$ | 149—151 | $C_{17}H_{14}N_2S$ | 73,3 | 5,1 | 9,9 | 11,5 | 73,3 | 5,1 | 10,0 | 11,5 | 76 |
| XXIV | $CH_3$ | $p$-$CH_3OC_6H_4$ | 195—197 | $C_{17}H_{14}N_2OS$ | 69,3 | 4,6 | 9,5 | 11,0 | 69,3 | 4,8 | 9,5 | 10,9 | 82 |
| XXV | $CH_3O$ | $p$-$CH_3OC_6H_4$ | 193—194 | $C_{17}H_{14}N_2OS$ | 65,4 | 4,6 | 8,7 | 10,4 | 65,8 | 4,5 | 9,0 | 10,3 | 85 |
| XXVI | $C_2H_5O$ | $C_6H_5$ | 145—147 | $C_{17}H_{14}N_2OS$ | 69,6 | 4,9 | 9,3 | 10,8 | 69,3 | 4,8 | 9,5 | 10,9 | 83 |
| XXVII | $C_2H_5O$ | $p$-$CH_3OC_6H_4$ | 216—217 | $C_{18}H_{16}N_2O_2S$ | 66,8 | 5,0 | 8,6 | 10,0 | 66,6 | 5,0 | 8,6 | 9,9 | 77 |
| XXVIII | $C_2H_5O$ | $p$-$O_2NC_6H_4$ | 231—232 | $C_{17}H_{13}N_3O_3S$ | 59,9 | 3,9 | 12,5 | 9,3 | 60,1 | 3,9 | 12,4 | 9,4 | 84 |
| XXIX | Br | $C_6H_5$ | 211—212 | $C_{15}H_9BrN_2S$[c] | 54,9 | 2,4 | 8,5 | 9,9 | 54,7 | 2,7 | 8,5 | 9,7 | 58 |
| XXX | Br | $p$-$CH_3OC_6H_4$ | 243—244 | $C_{16}H_{11}BrN_2O$[d] | 53,2 | 3,2 | 7,5 | 8,8 | 53,5 | 3,1 | 7,8 | 8,9 | 47 |
| XXXI | Br | $p$-$O_2NC_6H_4$ | 286—287 | $C_{15}H_8BrN_3O_2S$[e] | 48,4 | 2,2 | 11,5 | 8,4 | 48,1 | 2,1 | 11,2 | 8,5 | 64 |
| XXXII | $O_2N$ | $C_6H_5$ | 272—273 | $C_{15}H_9N_2O_2S$ | 61,2 | 2,8 | 14,0 | 10,8 | 61,0 | 3,0 | 14,2 | 10,8 | 32 |

[a] According to [9], mp 145-146.5°.
[b] Found: Br 25.8%. Calculated: Br 25.7%.
[c] Found: Br 24.1%. Calculated: Br 24.3%.
[d] Found: Br 22.2%. Calculated: Br 22.2%.
[e] Found: Br 21.4%. Calculated: Br 21.3%.

The conversion of VII-XVII to XVIII-XXXV, like the conversion of 2-acylmethylthiobenzimidazoles to thiazolo[3,2-a]benzimidazole derivatives [11], probably proceeds by migration of a proton from the NH group to the oxygen atom of the CO group of the ketone residue with subsequent dehydration of the intermediate 2-hydroxyimidazolino[2,1-b]benzothiazoles. The imidazole-ring-closing reaction is catalyzed by acids, as attested to by the following fact: XV does not undergo change on heating in ethanol for 1 h, while it is converted to an almost quantitative yield of XXIV in the presence of HCl under the same conditions. The reaction of I-VI with $\alpha$-bromo ketones while refluxing in alcohols (methanol, ethanol, etc.) leads immediately to three-ring compounds XVIII-XXXV, regardless of the structure of the halo ketones and the character of the substituent in the 6 position of the benzothiazole ring.

## EXPERIMENTAL

2-Aminobenzothiazole (I) and its 6-substituted derivatives (II-VI) were prepared by known methods.

3-Acylmethyl-2-iminobenzothiazolines (VII-XVII, Table 1). A solution of 0.01-0.011 mole of $\alpha$-bromo ketone in 20-30 ml of acetone was added to a solution of 0.01 mole of I-IV in 20-30 ml of acetone, and the mixture was allowed to stand at 18-20° for 24-48 h. The precipitated hydrobromides of VII-XVII were removed by filtration and dissolved in water. The aqueous solutions were neutralized with sodium carbonate or ammonia, and bases VII-XVII were removed by filtration. The colorless, yellow (X, XVI), or cream-colored (XIII) crystalline substances were purified for analysis by crystallization from methanol (IX, XIII, XV), aqueous methanol (XIV), ethanol (VII, XVII), aqueous acetone (VIII), aqueous dioxane (XI), dimethylformamide (DMF)–ethanol (1 : 1) (X), or by reprecipitation from acetone solution by the addition of water (XII). The $\nu_{CO}$ and $\nu_{NH}$ values in the IR spectra of mineral oil suspensions were recorded with a UR-10 spectrophotometer and were as follows ($cm^{-1}$)*. VII 1695, 3325; VIII 1696, 3320; IX 1690, 3340; X 1707, 3320; XI 1695, 3345; XII 1705, 3360; XIII 1680, 3320; XIV 1698, 3320; XV 1685, 3330; XVII 1690, 3320.

Imidazo[2,1-b]benzothiazole Derivatives (XVIII-XXXV, Table 1). A. A solution of 0.01 mole of I-VI and 0.01 mole of $\alpha$-bromo ketone in 20-30 ml of ethanol was refluxed for 18 h (in the preparation of XVIII, XX, XXI, XXIII-XXVIII, XXX, and XXXI) or for 30 h (XXIX, XXXII). The solutions were cooled, and the precipitated hydrobromides were removed by filtration, washed with ether, and dissolved in aqueous ethanol or DMF. The solutions were neutralized with ammonium hydroxide, and the precipitates were removed by filtration.

B. A mixture of 0.01 mole of VIII or XIII in 15 ml of 36% HCl or 46% HBr was refluxed for 4 h, cooled, and worked up as described in experiment A to give XIX and XXII. Similarly, XXXIII {R = H, R' = $C_6H_5$, mp 99-100° (from ethanol), mp 98-100° [2,7], mp 110° [9]}; XXXIV {R = H, R' = $C_6H_4NO_2$-p, mp 271-273° [dec., from DMF–ethanol (3 : 1)] (mp 284-286° [7])}, and XXXV {R = $CH_3O$, R' = $C_6H_4NO_2$-p, mp 263-265° [dec., from DMF–ethanol (1 : 1)] (mp 263-265° [8])} were obtained from VII, X, and XVI in 96, 64, and 70% yields, respectively.

C. A solution of 3.2 g of XV in 5 ml of 85% HCOOH, 98% $CH_3COOH$, 85% $H_3PO_4$, 96% $H_2SO_4$, or $POCl_3$ was refluxed for 4 h, heated at 95-100° for 4 h, and allowed to stand at 18-20° for 2 h or at 18-20° for 1 h, respectively. The reaction mass was poured into water and neutralized with ammonia, and the precipitate was removed by filtration to give 99, 95, 98, 86, and 90% yields of XXIV, respectively.

D. Two drops of concentrated HCl were added to a solution of 1.6 g of XV in 20 ml of ethanol, and the mixture was refluxed for 1 h and worked up as described in experiment A to give 98% XXIV.

Compounds XVIII-XXXV were colorless, cream-colored (XVIII, XXII), or yellow (XXVIII, XXXI, XXXII, XXXIV, XXXV) crystalline substances and were purified for analysis by crystallization from methanol (XX, XXI, XXIII), ethanol (XXIV, XXVI), aqueous ethanol (XVIII, XIX, XXII), DMF–ethanol (1 : 1) (XXV, XXVII), DMF (XXIII, XXX-XXXII), or DMF–water (1 : 2) (XXIX).

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