# RESEARCH IN THE IMIDAZOLE SERIES

## LXVII.* SYNTHESIS OF NAPHTH[1',2' : 4,5]IMIDAZO[2,1-b]THIAZOLE DERIVATIVES FROM 2-MERCAPTONAPHTH[1,2-d]IMIDAZOLE

E. G. Knysh, A. N. Krasovskii,
and P. M. Kochergin

UDC 547.785.5'789.07

Alkyl(aryl)-substituted naphth[1',2' : 4,5]imidazo[2,1-b]thiazoles were synthesized by the reaction of 2-mercaptonaphth[1,2-d]imidazole with $\alpha$-halo ketones. The intermediate 2-acylalkylthionaphth[1,2-d]imidazoles were isolated, and the conditions for their cyclization to naphth[1',2' : 4,5]imidazo[2,1-b]thiazole derivatives were studied.

Continuing our earlier research [2, 3], we have established that 2-mercaptonaphth[1,2-d]imidazole (I) reacts readily with $\alpha$-halo ketones. Depending on the conditions used to carry out the reaction and the structure of the halo ketone, 2-acylalkylthionapthth[1,2-d]imidazoles (II-XIV, Table 1) or their dehydration products – naphth[1',2' : 4,5]imidazo[2,1-b]thiazole† derivatives (XV-XXVII, Table 2) – are formed. Thus four-ring compounds (XV, XVI, XX, and XXI) were obtained when I was refluxed with aliphatic halo ketones in ethanol or dimethylformamide (DMF), while in contrast to the reaction of 2-mercaptobenzimidazole with the indicated halo ketones [4], with aliphatic-aromatic halo ketones and bromopinacolone under the same conditions the process stops at the 2-acylalkylthionaphth [1,2-d]imidazole (IV, IX, and XI) stage. In the case of aliphatic halo ketones, the intermediate compounds (for example, II) can be isolated only when I is heated no higher than 50°.

The case of closing the thiazole ring in the reaction of I with halo ketones of the aliphatic series is explained, as in the synthesis of imidazo[2,1-b]thiazole [5] and thiazolo[3,2-a]benzimadazole derivatives [4], by the catalytic effect of the hydrogen ions due to the hydrogen halide liberated in the reaction. Thus II is not changed when refluxed in ethanol, while when this compound is heated under the same conditions in the presence of HCl, it is almost quantitatively converted to XV. Further evidence of the catalytic effect of acids on the closing of the diazole ring is the fact that only 2-acylalkylthionaphth[1,2-d]imidazoles (II-IV, VII, VIII, XIII, and XIV) are formed when I is heated with $\alpha$-halo ketones, regardless of their structure, in ethanol in the presence of sodium ethoxide or alkali.

A study of the IR spectra of II-XIV showed that the absorption band of a CO group at 1650-1780 cm$^{-1}$ is practically absent for some of the compounds in this series (II, V, VI, VIII, and XIII), while there is a band at 3070-3270 cm$^{-1}$, which is probably related to the stretching vibrations of the OH group. Like 2-formylalkylthionaphth[1,2-d]imidazoles [2], these compounds in the solid state can apparently exist as tautomeric forms – 8-hydroxy derivatives of naphth[1',2' : 4,5]imidazo[2,1-b]thiazoline.

In order to obtain naphth[1',2' : 4,5]imidazo[2,1-b]thiazole derivatives that contain various substituents in the 8 and 9 positions of the compounds, we made a detailed study of the cyclization of II-XIV. It

---

*See [1] for communication LXVI.

†The numbering of the atoms of the four-ring system in this paper is given in conformity with the IUPAC rules. The numbering of the four-ring system in [2, 3] started with the sulfur atom and proceeded counterclockwise.

---

Zaporozhe State Medical Institute. S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 25-29, January, 1972. Original article submitted August 13, 1970.

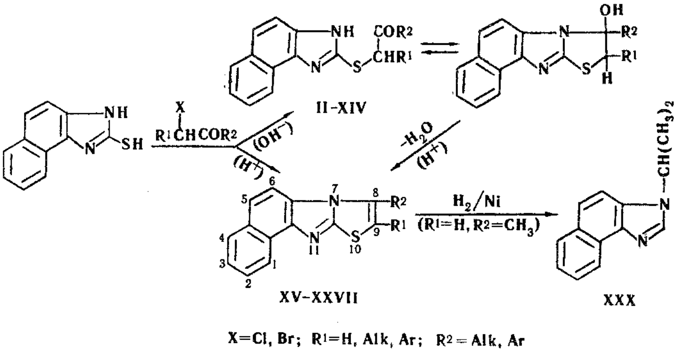
TABLE 1. 2-Acylalkylthionaphth[1,2-d]imidazoles (II-XIV)

| Compound | $R^1$ | $R^2$ | Mp, °C (dec) | IR spectrum,[a] cm⁻¹ |  | Empirical formula | Found, % |  |  |  | Calculated, % |  |  |  | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  | $\nu_{CO}$ | $\nu_{OH}$ or $\nu_{NH}$ |  | C | H | N | S | C | H | N | S |  |
| II | H | $CH_3$ | 123—124 | 1640 w | 3080 | $C_{14}H_{12}N_2OS$ | 65,7 | 4,7 | 10,8 | 12,4 | 65,6 | 4,7 | 10,9 | 12,5 | 80 |
| III | H | $C_4H_9$ | 200—201 | 1720 | 3080, 3350 | $C_{17}H_{18}N_2OS \cdot HCl$[b] | 61,3 | 5,8 | 8,2 | 9,8 | 61,0 | 5,7 | 8,4 | 9,6 | 84 |
| IV | H | $C(CH_3)_3$ | 111—112 | 1720 | 3050, 3100 | $C_{17}H_{18}N_2OS$ | 68,8 | 6,4 | 9,2 | 10,6 | 68,4 | 6,1 | 9,4 | 10,7 | 92 |
| V | $CH_3$ | $CH_3$ | 155—156 | 1630 w | 3070 | $C_{15}H_{14}N_2OS$ | 66,7 | 5,3 | 10,3 | 11,6 | 66,6 | 5,2 | 10,4 | 11,9 | 95 |
| VI | $CH_3$ | $C_2H_5$ | 109—110 | 1635 w | 3070, 3140 | $C_{16}H_{16}N_2OS$ | 67,4 | 5,5 | 9,5 | 11,5 | 67,5 | 5,7 | 9,8 | 11,3 | 97 |
| VII | $C_2H_5$ | $CH_3$ | 185—186 | 1715 | 3080, 3140 | $C_{16}H_{16}N_2OS \cdot HCl$[c] | 60,2 | 5,2 | 8,6 | 9,6 | 58,9 | 5,3 | 8,7 | 10,0 | 98 |
| VIII | $C_3H_7$ | $CH_3$ | 138—139 | 1640 w | 3070, 3270 | $C_{17}H_{18}N_2OS$ | 68,8 | 5,9 | 9,4 | 10,9 | 68,4 | 6,1 | 9,4 | 10,7 | 74 |
| IX | H | $C_6H_5$ | 175—176 | — | — | $C_{19}H_{14}N_2OS \cdot H_2O$[d] | 68,1 | 4,7 | 8,8 | 9,2 | 67,8 | 4,8 | 8,3 | 9,5 | 93 |
| X | H | $p$-$BrC_6H_4$ | 176—177 | 1665 | 3070, 3270 | $C_{19}H_{13}BrN_2OS$[e] | 57,2 | 3,5 | 6,8 | 7,8 | 57,4 | 3,3 | 7,0 | 8,1 | 99 |
| XI | H | $p$-$O_2NC_6H_4$ | 184—185 | — | — | $C_{19}H_{13}N_3O_3S \cdot H_2O$ | 60,7 | 4,1 | 11,3 | 8,6 | 61,2 | 3,8 | 11,3 | 8,6 | 95 |
| XII | $CH_3$ | $C_6H_5$ | 175—176 | 1680 | 3070, 3300 | $C_{20}H_{16}N_2OS$ | 72,4 | 4,7 | 8,2 | 9,9 | 72,3 | 4,8 | 8,4 | 9,7 | 74 |
| XIII | $C_6H_5$ | $CH_3$ | 140—141 | 1645 w | 3070 | $C_{20}H_{16}N_2OS$ | 72,7 | 4,8 | 8,7 | 9,7 | 72,3 | 4,8 | 8,4 | 9,6 | 89 |
| XIV | $C_6H_5$ | $C_6H_5$ | 249—250 | 1685 | 3080, 3340 | $C_{25}H_{18}N_2OS \cdot HBr$[f] | 63,3 | 4,0 | 6,3 | 6,8 | 63,2 | 4,0 | 5,9 | 6,7 | 76 |

---

a) The IR spectra of mineral oil suspensions were recorded with a UR-10 spectrometer. b) Found: Cl 10.3%. Calculated: Cl 10.6%. c) Found: Cl 11.0%. Calculated: Cl 11.0%. d) The 2,4-dinitrophenylhydrazone of IX had mp 194-196° (dec., from aqueous dioxane). Found: C 59.7; H 3.6; N 16.8; S 6.4%. Calculated for $C_{25}H_{18}N_6O_4S$: C 60.2; H 3.6; N 16.9; S 6.4%. e) Found: Br 20.2%. Calculated: Br 20.1%. f) Found: Br 16.6%. Calculated: Br 16.8%. We thank Yu. N. Sheinker, V. V. Kolpakova, and their co-workers for recording the IR spectra and performing the microanalyses of the compounds.

was established that compounds of this series that contain aliphatic ketone residues (excpet for pinacolone) are readily converted to alkyl-substituted naphth[1',2' : 4,5]imidazo[2,1-b]thiazoles (XV, XVI, and XVIII-XXI) when they are heated in organic or mineral acids (HCOOH, $CH_3COOH$, HCl, and $H_3PO_4$) and also under the influence of dehydrating agents ($POCl_3$ and $H_2SO_4$). 2-Pinacolonylthio- and 2-acylalkylthionaphth[1,2-d]imidazoles that contain aliphatic-aromatic ketone residues (IV and IX-XIV) cyclize to tert-butyl(aryl)-substituted naphth[1', 2' : 4,5]imidazo[2,1-b]thiazoles (XVII and XXII-XXVII) only on refluxing in $POCl_3$ or 85-89% $H_3PO_4$. In conformity with the known data regarding the stepwise character of the mechanism of the closing of the thiazole ring [4, 5], we assume that, in this case, II-XIV are initially converted to 8-hydroxynaphth[1',2' : 4,5]imidazo[2,1-b]thiazolines, which are then dehydrated to form XV-XXVII.



The purity of the naphth[1',2' : 4,5]imidazo[2,1-b]thiazole derivatives was confirmed in a number of cases by chromatography, and their structures were confirmed by IR spectroscopy (absence of absorption bands of CO and NH groups) and by reductive desulfuration of 8-methylnaphth[1',2' : 4,5]imidazo[2,1-b]thiazole (XV) under the influence of Raney nickel [2] to 3-isopropylnaphth-[1,2-d]imidazole (XXX).

## EXPERIMENTAL

2-Acylalkylthionaphth[1,2-d]imidazoles (II-XIV, Table 1). A) A solution of 0.01 mole of I [6], 0.01 mole of α-halo ketone (chloroketones were used to synthesize II and XIV, while the corresponding bromo ketones were used in the remaining cases), and 0.01 mole of sodium ethoxide in 30-50 ml of ethanol was stirred at 60-65° for 1 h (at 50° for 1 h in the preparation of XII). The mixture was cooled, and the precipitate (V, XIII) was removed by filtration and washed with water. An additional amount of substance was isolated by evaporation of the alcohol mother liquor to a small volume. Compounds II-IV, VII, VIII, XIII, and XIV were isolated by pouring the reaction mass into water, and the precipitate (II, VI, VIII, XIII) was removed by filtration or extracted with chloroform (III, VII, and XIV). Compounds X and XI

TABLE 2. Naphth[1',2' : 4,5]imidazo[2,1-b]thiazole Derivatives (XV-XXVII)

| Compound | $R^1$ | $R^2$ | Mp, °C (dec.) | Empirical formula | Found, % |  |  |  | Calc, % |  |  |  | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  | C | H | N | S | C | H | N | S |  |
| XV | H | $CH_3$ | 179—180 | $C_{14}H_{10}N_2S^a$ | 70,8 | 4,3 | 11,4 | 13,9 | 70,6 | 4,2 | 11,9 | 13,5 | 92 |
| XVI | H | $C_4H_9$ | 155—156 | $C_{17}H_{16}N_2S$ | 72,6 | 5,7 | 9,7 | 11,6 | 72,8 | 5,7 | 10,0 | 11,4 | 75 |
| XVII | H | $C(CH_3)_3$ | 154—155 | $C_{17}H_{16}N_2S$ | 72,5 | 5,5 | 10,0 | 11,6 | 72,8 | 5,7 | 10,0 | 11,4 | 90 |
| XVIII | $CH_3$ | $CH_3$ | 220—221 | $C_{15}H_{12}N_2S^b$ | 71,2 | 4,8 | 11,4 | 13,0 | 71,4 | 4,8 | 11,1 | 12,7 | 92<br>99 |
| XIX | $CH_3$ | $C_2H_5$ | 201—202 | $C_{16}H_{14}N_2S^c$ | 72,1 | 5,4 | 10,2 | 12,2 | 72,1 | 5,3 | 10,5 | 12,0 | 98 |
| XX | $C_2H_5$ | $CH_3$ | 137—138 | $C_{16}H_{14}N_2S \times \times H_2O$ | 67,8 | 5,7 | 9,5 | 10,8 | 67,6 | 5,7 | 9,8 | 11,2 | 88 |
| XXI | $C_3H_7$ | $CH_3$ | 148—149 | $C_{17}H_{16}N_2S$ | 73,0 | 5,9 | 9,6 | 11,5 | 72,8 | 5,8 | 10,0 | 11,4 | 71 |
| XXII | H | $C_6H_5$ | 201—203 | $C_{19}H_{12}N_2S \times \times 1/2\ H_2O$ | 69,8 | 5,2 | 8,4 | 9,6 | 69,7 | 4,8 | 8,5 | 9,8 | 63 |
| XXIII | H | $p$-$BrC_6H_4$ | 199—200 | $C_{19}H_{11}BrN_2S^d$ | 60,0 | 3,0 | 7,1 | 8,1 | 60,2 | 2,9 | 7,4 | 8,4 | 84 |
| XXIV | H | $p$-$O_2NC_6H_4$ | 242—243 | $C_{19}H_{11}N_3O_2S$ | 66,2 | 3,3 | 12,6 | 9,2 | 66,1 | 3,2 | 12,2 | 9,3 | 80 |
| XXV | $CH_3$ | $C_6H_5$ | 225—227 | $C_{20}H_{14}N_2S$ | 76,2 | 4,3 | 8,5 | 10,1 | 76,4 | 4,5 | 8,9 | 10,2 | 94 |
| XXVI | $C_6H_5$ | $CH_3$ | 214—215 | $C_{20}H_{14}N_2S$ | 76,4 | 4,5 | 8,5 | 9,9 | 76,4 | 4,5 | 8,9 | 10,2 | 84 |
| XXVII | $C_6H_5$ | $C_6H_5$ | 201—202 | $C_{25}H_{16}N_2S$ | 79,3 | 4,4 | 7,7 | 8,5 | 79,7 | 4,3 | 7,4 | 8,5 | 74 |

---

a) The hydrochloride of XV had mp 225-227° (dec., from ethanol). Found: Cl 12.7%. Calculated: Cl 12.9%. b) $R_f$ 0.90 [dioxane–dichloroethane (2.5 : 1)]; 0.92 [$CCl_4$–$CHCl_3$–dichloroethane (2.5 : 1 : 1)]. c) $R_f$ 0.93 [dioxane–dichloroethane (2.5 : 1)]; 0.92 [$CCl_4$–$CHCl_3$–dichloroethane (2.5 : 1 : 1)]. d) Found: Br 20.9%. Calculated: Br 21.1%.

were similarly obtained, with the difference that the reaction was carried out in alcohol in the presence of KOH or NaOH, the reaction mass was poured into water, and the precipitate was removed by filtration.

B) A solution of 0.01 mole of I and 0.01 mole of α-bromo ketone in 50-100 ml of ethanol was heated at 45-50° for 4 h (in the preparation of II) or refluxed for 2 h (in the preparation of IV, IX, and XI). The mixture was cooled, poured into water, and neutralized with sodium carbonate. The precipitate was removed by filtration and washed with water. The yields of II, IV, IX, and XI were 73, 92, 93, and 94%, respectively. Compounds IX and XI (91% and 96% yields, respectively) were also isolated when the reaction was carried out in refluxing DMF (4 h).

Compounds II-XV are colorless or yellow (XI) crystalline substances of basic character that give qualitative reactions for the carbonyl group. In UV light they have a blue-violet fluorescence. The compounds were purified for analysis by crystallization from methanol (III), ethanol (V, IX, and XIV), aqueous ethanol (II, IV, VI, and VIII), propyl alcohol (X), butyl alcohol (XI), or aqueous acetone (XII and XIII).

Napth[1',2' : 4,5]imidazo[2,1-b]thiazole Derivatives (XV-XXVII, Table 2). A) A solution of 0.01 mole of I and 0.01-0.011 mole of α-bromo ketone in 30 ml of DMF was refluxed for 4 h and cooled. The mixture was neutralized with ammonium hydroxide and poured into water. The precipitate was removed by filtration to give 90, 88, and 71% yields of XVI, XX, and XXI, respectively. Compound XV (82% yield) was obtained by refluxing I with chloroacetone in ethanol (4 h).

B) A mixture of 0.01 mole of 2-acylalkylthionaphth[1,2-d]imidazole (IV, VI, IX, X, XII, and XIII) and 30-50 ml of $POCl_3$ was refluxed for 2 h (VI), 10 h (IV, IX, XII, and XIII), or 25 h (X). The $POCl_3$ was removed by vacuum distillation, and the residue was decomposed with water. The mixture was neutralized with ammonium hydroxide, and the precipitate was removed by filtration and washed with water to give XVII, XIX, XXII, XXIII, and XV.

C) A solution of 0.01 mole of XI or XIV in 20 ml of 85% $H_3PO_4$ was refluxed for 1 h and cooled. The cold mixture was poured into water and worked up as described above to give 80 and 74% yields of XXIV and XXVII, respectively. Compound XVIII (99% yield) was obtained in the same way, with the difference that the reaction was carried out at 95-100°.

D) A solution of 0.01 mole of V in 10 ml of concentrated $H_2SO_4$ was allowed to stand at 18-20° for 24 h. It was then poured into water and worked up as described in experiment B to give 97% of XVIII.

E) A solution of 0.005 mole of II and three drops of concentrated HCl in 200 ml of ethanol was refluxed for 4 h and worked up as in experiment B to give 96% of XV. Compound XVIII (95% yield) was similarly obtained by refluxing V in concentrated HCl.

F) A solution of 0.01 mole of V in 20 ml of 85% HCOOH was refluxed for 4 h and worked up as described in experiment B to give 95% of XVIII. Compound XV (92% yield) was similarly obtained, but the reaction was carried out in glacial $CH_3COOH$.

Compounds XV-XXVII are colorless or yellow (XXIV) crystalline substances of basic character that have a blue-violet fluorescence in UV light. The compounds were purified for analysis by crystallization from aqueous methanol (XVI), ethanol (XV, XVIII, and XIX), aqueous ethanol (XVII, XX, XXI, XXII, and XXIII), ethanol–dioxane (1 : 1) (XXVI), ethanol–DMF (1 : 1) (XXVII), or aqueous dioxane (XXIV and XXV).

2-Isopropylaminonaphthalene (XXVIII). A solution of 40 g (0.28 mole) of $\beta$-naphthylamine and 49 g (0.29 mole) of isopropyl iodide in 100 g of anhydrous ethanol was refluxed for 2 h, cooled, and poured into water. The mixture was neutralized with sodium carbonate and then acidified to pH 3 with dilute $H_2SO_4$. The precipitated $\beta$-naphthylamine sulfate was removed by filtration. The filtrate was made alkaline with NaOH and extracted with $CHCl_3$. The extract was washed with water and dried over $CaCl_2$. The solvent was removed by vacuum distillation to give 32 g (58%) of technical XXVIII as a viscous, oily substance that was soluble in organic solvents and insoluble in water. The hydrochloride of XXVIII had mp 205-206° (from aqueous dioxane). Found: C 70.5; H 8.5; Cl 16.3; N 6.3%. $C_{13}H_{15}N \cdot HCl$. Calculated: C 70.5; H 8.5; Cl 15.8; N 6.2%.

1-Phenylazo-2-isopropylaminonaphthalene (XXIX). A solution of benzenediazonium chloride [prepared from 13.5 g (0.145 mole) of aniline, 10.4 g (0.15 mole) of $NaNO_2$, and 40 ml of concentrated HCl] was added gradually with stirring to a cooled (to 5°) solution of 27.6 g (0.124 mole) of the hydrochloride of XXVIII in 300 ml of ethanol. The precipitate was removed by filtration and washed with water to give 27 g (60%) of red prisms of XXIX with mp 94-95° (from ethanol). Found: C 78.6; H 6.2; N 14.2%. $C_{19}H_{19}N_3$. Calculated: C 78.9; H 6.6; N 14.5%.

3-Isopropylnaphth[1,2-d]imidazole (XXX). A) An alcohol paste of Raney nickel (10 g) was added to a solution of 0.5 g of XV in 10 ml of ethanol, and the mixture was refluxed for 8 h. The catalyst was removed by filtration, and the solvent was removed by distillation to dryness to give 0.1 g (23%) of XXX with mp 105-106° (from aqueous dioxane). Found: C 80.1; H 6.6; N 13.3%. $C_{14}H_{13}N_2$. Calculated: C 80.3; H 6.3; N 13.4%.

B) Zinc dust was added in small portions to a refluxing solution of 15 g of XXIX in 100 ml of 30% acetic acid until the dark-red color of the solution changed to light-yellow. The hot solution was filtered, cooled, and neutralized with ammonium hydroxide. The mixture was extracted with chloroform, and the extract was washed with water and dried over $CaCl_2$. The solvent was removed by vacuum distillation, and 90 ml of 85% HCOOH was added to the residue (9 g) of crude 1-amino-2-isopropylaminonaphthalene. The solution was then refluxed for 2 h (with charcoal near the end), filtered, and neutralized with KOH. The precipitate was removed by filtration and washed with water to give 8 g (73%) of XXX with mp 105-106° (from aqueous dioxane). This product did not depress the melting point of the substance obtained via experiment A.

## LITERATURE CITED

1. B. A. Priimenko and P. M. Kochergin, Khim. Geterotsikl. Soedin., 1252 (1971).
2. E. G. Knysh, A. N. Krasovskii, and P. M. Kochergin, Khim. Geterotsikl. Soedin., 1128 (1971).
3. P. M. Kochergin, A. N. Krasovskii, and E. G. Knysh, USSR Author's Certificate No. 232,976; Byull. Izobr., No. 2, 30 (1969).
4. A. N. Krasovskii and P. M. Kochergin, Khim. Geterotsikl. Soedin., 321 (1969).
5. P. M. Kochergin and M. N. Shchukina, Zh. Obshch. Khim., 26, 458 (1956).
6. J. G. Farbenindustrie, German Patent No. 557,138; Chem. Abstr., 27, 1233 (1933).