INVESTIGATIONS IN THE IMIDAZOLE SERIES

LXXV.* SYNTHESIS OF 2-METHYLMERCAPTO-3-ACYLMETHYL(β-HYDROXYALKYL)NAPHTH[1,2-d]IMIDAZOLES AND THEIR CONVERSION TO NAPHTH[1,2-d]IMIDAZO[3,2-b]IMIDAZOLE AND NAPHTH[1,2-d]-IMIDAZO[3,2-b]IMIDAZOLINE DERIVATIVES

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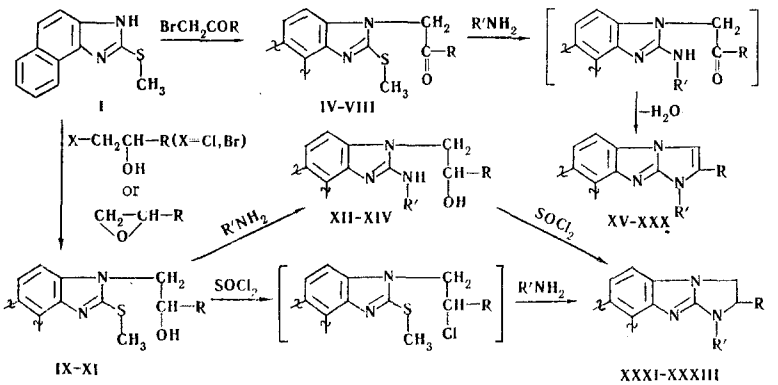
The reaction of 2-methylmercaptonaphth[1,2-d]imidazole with α-halo ketones, β-halo alcohols, and olefin oxides gave 2-methylmercapto-3-acylmethyl(β-hydroxyalkyl)naphth-[1,2-d]imidazoles. Their conversion to naphth[1,2-d]imidazo[3,2-b]imidazole and naphth-[1,2-d]imidazo[3,2-b]imidazoline derivatives was studied.

In developing the research in [2] in order to obtain biologically active substances, we made a detailed investigation of the reaction of 2-methylmercaptonaphth[1,2-d]imidazole (I) with α-bromomethyl aryl ketones, ethylene chloro(bromo)hydrins, styrene chlorohydrin, and the oxides of ethylene, styrene and p-nitrostyrene. It was found that I reacts with the above compounds in aqueous alcoholic NaOH to give the corresponding 3-substituted I (IV-XI, Table 1). We also observed a similar course for these reactions in the case of 2-chloronaphth[1,2-d]imidazole [3].

The structure of IV-XI was confirmed by means of the IR spectra (the presence of absorption of CO or OH groups) and also by alternative synthesis of some compounds of this series from the corresponding 3-substituted 2-chloronaphth[1,2-d]imidazoles. Thus IV and X, which proved to be identical to the compounds obtained by the reaction of I with phenacyl bromide, styrene chlorohydrin, or styrene oxide, were synthesized by the reaction of 2-chloro-3-phenacyl(β-hydroxyphenylethyl)naphth[1,2-d]imidazoles [3] with thiourea via the method in [4] with subsequent methylation of the 2-mercapto-3-phenacyl(β-hydroxyphenylethyl)naphth-[1,2-d]imidazoles (II, III) with methyl iodide.



*See [1] for communication LXXIV.

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TABLE 1. 2,3-Disubstituted Naphth[1,2-d]imidazoles (IV-XIV)

Compound	R	R′	mp, (dec.), °C	Empirical formula	Found, %				Calc., %				Yield, %
					C	H	N	S	C	H	N	S	
IV	C_6H_5	—	185—186	$C_{20}H_{16}N_2OS$	—	—	—	—	—	—	—	—	20
V	p-$CH_3C_6H_4$	—	187—188	$C_{21}H_{18}N_2OS$	72,6	5,2	8,1	9,1	72,8	5,2	8,1	9,3	20
VI	p-$CH_3OC_6H_4$	—	190—191	$C_{21}H_{18}N_2O_2S$	69,2	5,0	7,5	8,8	69,6	5,0	7,7	8,8	20
VII	p-ClC_6H_4	—	188—190	$C_{20}H_{15}ClN_2OS$ [a]	65,3	3,9	7,2	8,7	65,5	4,1	7,6	8,7	33
VIII	p-BrC_6H_4	—	196—198	$C_{20}H_{15}BrN_2OS$ [b]	57,3	3,5	6,9	8,3	57,1	3,8	7,0	8,0	35
IX	$HOCH_2CH_2$	—	143—144	$C_{14}H_{14}N_2OS$	—	—	—	—	—	—	—	—	22—30
X	$C_6H_5CH(OH)CH_2$	—	164—165	$C_{20}H_{18}N_2OS$	71,8	5,3	8,2	9,2	71,8	5,4	8,4	9,6	20—50
XI	p-$NO_2C_6H_4CH(OH)CH_2$	—	200—202	$C_{20}H_{17}N_3O_3S$	63,0	4,5	11,1	8,3	63,3	4,5	11,1	8,4	47—53
XII	H	m-$CH_3OC_6H_4$	214—215	$C_{20}H_{19}N_3O_2$	72,2	5,6	12,3	—	72,1	5,7	12,6	—	78
XIII	H	3,4-$(CH_3)_2C_6H_3$	218—219	$C_{21}H_{21}N_3O$	75,9	6,6	12,6	—	76,1	6,4	12,7	—	80
XIV	C_6H_5	C_6H_5	273—275 [c]	$C_{25}H_{21}N_3O$	—	—	—	—	—	—	—	—	26

[a] Found: Cl 9.6%. Calculated: Cl 9.7%. [b] Found: Br 20.4%. Calculated: Br 20.0%. [c] According to [7], mp 273-275°.

TABLE 2. Naphth[1,2-d]imidazo[3,2-b]imidazole (XV-XXX) and Naphth[1,2-d]imidazo[3,2-b]imidazoline (XXXI-XXXIII) Derivatives

Compound	R	R′	mp (dec.), °C	Empirical formula	Found, %				Calc., %				Yield, %
					C	H	halogen	N	C	H	halogen	N	
XV	C_6H_5	p-$CH_3C_6H_4$	271—273	$C_{26}H_{19}N_3$	83,5	5,1	—	11,5	83,6	5,1	—	11,2	76
XVI	C_6H_5	p-$CH_3OC_6H_4$	266—268	$C_{26}H_{19}N_3O$	80,3	5,0	—	10,6	80,2	4,9	—	10,8	71
XVII	C_6H_5	p-ClC_6H_4	261—262	$C_{25}H_{16}ClN_3$	76,4	4,2	9,2	10,8	76,2	4,1	9,0	10,7	81
XVIII	C_6H_5	$CH_2C_6H_5$	198—199	$C_{26}H_{19}N_3$	83,3	5,2	—	10,9	83,6	5,1	—	11,2	63
XIX	p-$CH_3C_6H_4$	C_6H_5	235—237 [a]	$C_{26}H_{19}N_3$	—	—	—	—	—	—	—	—	81
XX	p-$CH_3C_6H_4$	m-$CH_3C_6H_4$	240—242	$C_{27}H_{21}N_3$	84,0	5,5	—	10,6	83,7	5,5	—	10,8	85
XXI	p-$CH_3C_6H_4$	p-$CH_3OC_6H_4$	251—252	$C_{27}H_{21}N_3O$	80,0	5,4	—	10,6	80,4	5,2	—	10,4	83
XXII	p-$CH_3C_6H_4$	p-$C_2H_5OC_6H_4$	239—240	$C_{28}H_{23}N_3O$	80,7	5,4	—	9,9	80,5	5,5	—	10,1	77
XXIII	p-$CH_3C_6H_4$	m-ClC_6H_4	229—230	$C_{26}H_{18}ClN_3$	76,5	4,6	8,3	10,1	76,6	4,4	8,6	10,3	72
XXIV	p-$CH_3OC_6H_4$	m-$CH_3C_6H_4$	219—220	$C_{27}H_{21}N_3O$	80,8	5,2	—	10,0	80,4	5,2	—	10,4	80
XXV	p-$CH_3OC_6H_4$	p-$CH_3C_6H_4$	228—230	$C_{27}H_{21}N_3O$	80,5	5,0	—	10,7	80,4	5,2	—	10,4	84
XXVI	p-$CH_3OC_6H_4$	p-$C_2H_5OC_6H_4$	218—220	$C_{28}H_{23}N_3O_2$	77,2	5,2	—	9,5	77,6	5,3	—	9,7	76
XXVII	p-$CH_3OC_6H_4$	m-ClC_6H_4	202—204	$C_{26}H_{18}ClN_3O$	73,2	4,3	8,2	9,7	73,7	4,3	8,6	9,9	70
XXVIII	p-BrC_6H_4	p-$CH_3C_6H_4$	271—272	$C_{26}H_{18}BrN_3$	69,4	4,2	17,4	9,7	69,0	4,0	17,7	9,3	87
XXIX	p-BrC_6H_4	p-$C_2H_5OC_6H_4$	263—264	$C_{27}H_{20}BrN_3$	67,5	4,1	16,2	8,5	67,2	4,2	16,5	8,7	76
XXX	p-BrC_6H_4	$CH_2C_6H_5$	215—217	$C_{26}H_{18}BrN_3$	69,3	4,2	7,4	9,7	69,0	4,0	17,7	9,3	59
XXXI	H	m-$CH_3OC_6H_4$	232—234	$C_{20}H_{17}N_3O$	76,2	5,6	—	13,1	76,2	5,4	—	13,3	43—60
XXXII	H	3,4-$(CH_3)_2C_6H_3$	241—243	$C_{21}H_{19}N_3$	80,4	6,3	—	13,1	80,5	6,1	—	13,4	56—63
XXXIII	C_6H_5	C_6H_5	220—222 [b]	$C_{25}H_{18}N_3$	—	—	—	—	—	—	—	—	23

[a] According to [8], this compound has mp 235-237°. [b] According to [7], this compound has mp 220-222°.

In connection with the capacity of the methylmercapto group in the 2 position of the naphthimidazole ring to undergo nucleophilic substitution reactions [5], it seemed of interest to study the reaction of IV-XI with primary amines, since this opened up a new route to the synthesis of naphth[1,2-d]imidazo[3,2-b]imidazole and naphth[1,2-d]imidazo[3,2-b]imidazoline derivatives from the accessible 2-mercaptonaphth[1,2-d]imidazole [6].

It was found that simultaneous dehydration of the intermediate 2-arylamino-3-acylmethylnaphth[1,2-d]imidazoles to form XV-XXX occurs along with substitution of the SCH_3 group by an amino group when IV-VI and VIII are heated with aromatic amines in lower alcohols at 170-175° (in an autoclave).

In contrast to IV-VI and VIII, when IX or X are heated with arylamines under the same conditions, the reaction stops at the step involving the formation of 2-arylamino-3-(β-hydroxyalkyl)naphth[1,2-d]imidazoles (XII-XIV). As was previously established [7], these compounds readily cyclize to XXXI-XXXIII on reaction with $SOCl_2$. Another variant of the synthesis of XXXI and XXXII is the treatment of IX with thionyl chloride with subsequent heating of the intermediate 2-methylmercapto-3-(β-chloroethyl)naphth[1,2-d]imidazole with primary amines.

The structure of the four-ringed compounds was established by means of the IR spectra (the absence of absorption bands of the CO, OH, and NH groups) and by the identical character of some of the compounds (XIX and XXXIII) and the corresponding samples previously obtained from 2-chloro-3-phenacyl(β-hydroxyphenylethyl)naphth[1,2-d]imidazoles [7, 8].

EXPERIMENTAL

2-Methylmercaptonaphth[1,2-d]imidazole (I). A 0.1-mole sample of 2-mercaptonaphth[1,2-d]imidazole [6] and 0.11 mole of CH_3I were added to a solution of 0.1 mole of sodium ethoxide in 120 ml of ethanol, and the mixture was heated at 60-65° for 3 h and refluxed for 30 min. The solvent was removed by vacuum distillation, and the base (I) was extracted with ether to give 22 g (86%) of a sticky, viscous liquid. The hydrochloride had mp 220-222° (from ethanol). Found: C 57.2; H 4.1; Cl 14.0; N 11.3; S 12.7%. $C_{12}H_{10}N_2S \cdot HCl$. Calculated: C 57.5; H 4.2; Cl 14.1; N 11.2; S 12.8%. Base I was mentioned in [5] without any indication of the synthetic method or physical constants and results of analysis.

2-Mercapto-3-phenacylnaphth[1,2-d]imidazole (II). This compound was obtained by the method in [4].

2-Mercapto-3-(β-hydroxyphenylethyl)naphth[1,2-d]imidazole (III). This compound was obtained in 80% yield in the same way as II from 2-chloro-3-(β-hydroxyphenylethyl)naphth[1,2-d]imidazole [3] and thiourea and had mp 170-172° (from ethanol). Found: C 70.9; H 5.1; N 8.8; S 9.9%. $C_{19}H_{16}N_2OS$. Calculated: C 71.2; H 5.0; N 8.7; S 10.0%.

2-Methylmercapto-3-acylmethylnaphth[1,2-d]imidazoles (IV-VIII). A. A solution of 0.01 mole of the hydrochloride of I, 0.02 mole of NaOH, and 0.02 mole of α-bromo ketone in 50 ml of 50% ethanol was heated at 50-55° for 48 h and cooled. The precipitate was removed by filtration and washed with water and ether.

B. A 0.01-mole sample of II and 0.012 mole of CH_3I were added to a solution of 0.01 mole of sodium ethoxide in 25 ml of ethanol, and the mixture was heated at 50-60° for 1 h, and refluxed for 30 min, cooled, and poured into water. The precipitated IV was removed by filtration and washed with water and methanol. The product did not depress the melting point of a sample obtained by method A.

2-Methylmercapto-3-(β-hydroxyalkyl)naphth[1,2-d]imidazoles (IX-XI). A. This compound was obtained in the same way as IV-VIII (method A) with the difference that β-halo alcohols (ethylene chlorohydrin, ethylene bromohydrin, and styrene chlorohydrin) were used instead of α-bromo ketones.

B. A solution of 0.01 mole of the hydrochloride of I, 0.02 mole of NaOH, and 0.03 mole of styrene oxide or p-nitrostyrene oxide was heated and worked up as in experiment A. In the case of ethylene oxide (0.07 mole), the reaction was carried out at 15-20°. Samples of IX and X prepared by this method did not depress the melting points of samples prepared by method A.

C. A 0.01-mole sample of III and 0.012 mole of CH_3I were added to a solution of 0.01 mole of sodium ethoxide in 20 ml of ethanol, and the mixture was heated and worked up as described for the synthesis of IV (method B) to give X, which did not depress the melting point of a sample obtained by method A.

2-Arylamino-3-(β-hydroxyalkyl)naphth[1,2-d]imidazoles (XII-XIV, Table 1). A solution of 0.01 mole of IX or X and 0.02 mole of amine in 30 ml of methanol was heated at 170-175° for 9 h, cooled, and poured into water. The precipitate was removed by filtration and washed with water and cold methanol.

Naphth[1,2-d]imidazo[3,2-b]imidazole Derivatives (XV-XXX). A mixture of 0.01 mole of IV-VI or VIII, 0.012-0.015 mole of amine, and 20-30 ml of methanol was heated at 170-175° for 7 h and cooled. The precipitate was removed by filtration and washed with ethanol and water. Dilution of the alcohol mother liquors with water gave an additional amount of product. Compounds XVIII, XX, XXIII, and XXIV were isolated by dilution of the reaction mixture with water and removal of the precipitate by filtration.

Naphth[1,2-d]imidazo[3,2-b]imidazoline Derivatives (XXXI-XXXIII). A. Thionyl chloride (20 ml) was added to a solution of 0.01 mole of XII-XIV in 50 ml of anhydrous DMF, and the mixture was heated at 65-70° for 3 h, refluxed for 5 h, cooled, and poured into water. The aqueous mixture was made alkaline with ammonium hydroxide or sodium bicarbonate, and the precipitate was removed by filtration and washed with water and methanol.

B. A mixture of 0.01 mole of IX and 20 ml of thionyl chloride was refluxed for 3 h. The $SOCl_2$ was removed by vacuum distillation, and the residual 2-methylmercapto-3-(β-chloroethyl)naphth[1,2-d]imidazole hydrochloride was dissolved in 20 ml of methanol. A 0.02-0.025-mole sample of an amine was added to the methanol solution, and the mixture was heated at 170-180° for 8 h and cooled. The precipitate was removed by filtration and washed with water and methanol. Evaporation of the mother liquor gave an additional amount of compound.

The compounds were purified for analysis by crystallization from ethanol (IV, XV, XVI, XVIII, and XXIII), aqueous ethanol (IX, X), aqueous acetone (V, VI, XII, and XIII), dioxane (VIII, XI), or aqueous DMF (VII, XIV, XVII, XIX-XXII, and XXIV-XXXIII).

IR Spectra. The IR spectra of mineral-oil suspensions of the compounds contained the following bands (cm^{-1}): IV 1690 (CO), V 1700 (CO), VI 1695 (CO), VII 1700 (CO), IX 3250 (OH), X 3220 (OH), XII 3100, 3200 (OH, NH), XIII 3130, 3230 (OH, NH).

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