were extracted with ethyl acetate and subsequently isolated and purified by chromatography by the method used for Ib, c, and e.

Nitroso-α, ε-Diureidocaproic Acid (Ih). We dissolved 4 g (0.014 mole) of IIIf in 25 ml of water and 15 ml of concentrated hydrochloric acid. The reaction mixture was cooled to 5°C, and to it we promptly added 8 g (0.95 mole) of sodium citrate while maintaining the temperature at 10°C during the addition. The solution was then maintained at 4 - 6°C for 2 h. The yellowish precipitate that formed was filtered, washed with cold water, and dried under vacuum.

LITERATURE CITED

1. F. M. Schabel, T. P. Johnston, and J. A. Montgomery, Cancer Res., 23, 727 (1963).
2. N. M. Émanuél' and E. M. Vermel', Dokl. Akad. Nauk SSSR, 163, 483 (1976).
3. N. M. Émanuél' and E. M. Vermel', Cancer Chemother. Rep., 58, 135 (1974).
4. T. Machinami, K. Kobajanki, G. Hajakaw, et al., Bull. Chem. Soc. Jpn., 48, 3761 (1975).
5. J. A. Montgomery, R. James, G. S. McCaleb, et al., J. Med. Chem., 10, 668 (1967).
6. I. A. D'yakonov, Aliphatic Diazocompounds [in Russian], Leningrad (1958).
7. K. Veigand and G. Khilgetag, Experimental Methods in Organic Chemistry [in Russian], Moscow, p. 549 (1968).
8. L. P. Ivanitskaya and L. V. Makukhol, Antibiotiki, 1972, No. 2, 117.

SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2-MERCAPTOIMIDAZOLE DERIVATIVES

M. V. Povstyanoi, B. A. Priimenko, and P. M. Kochergin

UDC 615.31:547.784.6

Substituted 2-mercaptoimidazoles are of definite interest in the planned search of new biologically active substances and as intermediates for the synthesis of condensed heterocyclic systems based upon them.

It is the purpose of this work to synthesize new derivatives of the 2-mercaptoimidazole series and to investigate their biological activity.

We studied the reaction of 2-substituted mercaptoimidazoles (I, II) with alkyl halides, β-halogenated alcohols, α-epoxides, α-halo ketones, and esters of haloacetic acids. It was established that, in contrast with 2-methylmercapto-benzimidazole [1] and 2-methylmercaptonaphth[1,2-d]-imidazole [2], compounds I and II react only with alkyl halides and α-epoxides. That reaction takes place on heating of the starting materials in an alcohol medium in the presence of alkaline reagents (sodium alcoholate or alkali hydroxides), and leads to the formation of corresponding N-substituted 2-methyl(benzyl)mercapto-4,5-diphenylimidazoles (III, V - IX) (See Table 1).

However, under the conditions investigated, we failed to react I with ethylene oxide, and 1-(β-hydroxyethyl)-2-methylmercapto-4,5-diphenylimidazole (IV) was obtained by the methylation of 1-(β-hydroxyethyl)-2-mercapto-4,5-diphenylimidazole (XVI) by using methyl iodide in low-molecular-weight alcohols in the presence of an equivalent amount of an alkaline reagent. Compound XVI was synthesized by substituting bromine in 1-(β-hydroxyethyl)-2-bromo-4,5-diphenylimidazole [3] by a mercapto group, using the method previously reported [4].

From the reaction of I and II with unsymmetrical derivatives of ethylene oxide we isolated only one isomer which, in accordance with Krassuski's rule and our data [1, 2], has the structure of a secondary alcohol.

We obtained 1-acetylmethyl-2-mercaptoimidazole (X) by methylating 1-phenacyl-2-mercapto-4,5-diphenylimidazole which had been previously described [4].

Khersonsk Branch of the Odessa Technological Institute. Zaporozhye Medical Institute.

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 12, No. 5, pp. 59-62, May, 1978. Original article submitted September 23, 1977.

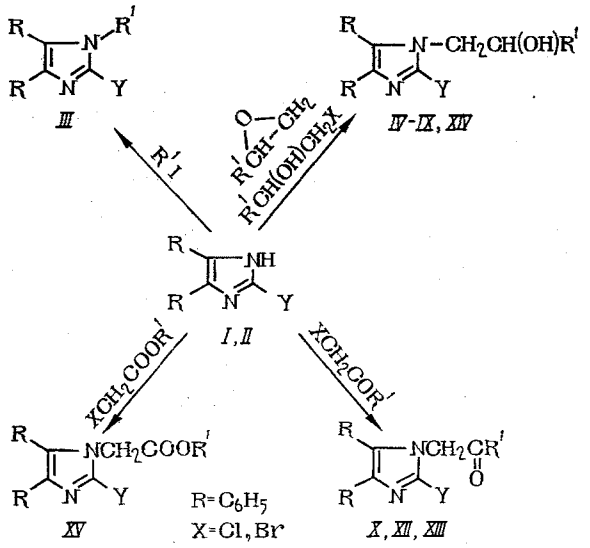
0091-150X/78/1205-0606$07.50

TABLE 1. 2,3-Disubstituted 4,5-Diphenylimidazoles

Compound	Y	R*	Yield, %	Melting point, °C	Found, %				Molecular formula	Calculated, %			
					C	H	N	S		C	H	N	S
II	$SCH_2C_6H_5$	—	90	187—8	77,1	5,0	8,3	9,4	$C_{22}H_{18}N_2S$	77,2	5,3	8,2	9,4
III	SCH_3	CH_3	37	117,5—8,5	73,0	5,80	—	11,52	$C_{17}H_{16}N_2S$	72,82	5,75	—	11,42
IV	SCH_3	H	74	142—3	69,3	5,6	9,3	10,5	$C_{18}H_{18}N_2OS$	69,6	5,8	9,0	10,3
V	SCH_3	CH_3	62	126—7	70,7	6,1	8,9	9,9	$C_{19}H_{20}N_2OS$	70,3	6,2	8,6	9,9
VI	SCH_3	C_6H_5	63	206—7	74,3	5,9	7,2	8,4	$C_{24}H_{22}N_2OS$	74,6	5,7	7,2	8,3
VII	SCH_3	$4\text{-}NO_2C_6H_4$	64	212—3	66,6	4,9	9,9	7,4	$C_{24}H_{21}N_3O_3S$	66,8	4,9	9,7	7,4
VIII	$SCH_2C_6H_5$	C_6H_5	74	169—70	77,9	5,7	6,2	7,1	$C_{30}H_{26}N_2OS$	77,9	5,7	6,1	6,9
IX	$SCH_2C_6H_5$	$4\text{-}NO_2C_6H_4$	97	202—4	70,6	5,0	8,2	6,4	$C_{30}H_{25}N_3O_3S$	70,9	5,0	8,3	6,3
X	SCH_3	C_6H_5	83	167—8	75,1	4,9	7,1	8,2	$C_{24}H_{20}N_2OS$	74,9	5,2	7,3	8,3
XI	SO_2CH_3	—	92	222—4	64,8	4,7	9,0	10,2	$C_{16}H_{14}N_2O_2S$	64,4	4,7	9,4	10,7
XII	SO_2CH_3	C_6H_5	42	199—200	68,9	4,8	6,9	7,6	$C_{24}H_{20}N_2O_3S$	69,2	4,8	6,7	7,7
XIII	SO_2CH_3	$4\text{-}BrC_6H_4$	53	181—2	58,6	4,0	5,5	6,4	$C_{24}H_{19}BrN_2O_3S$	58,2	3,9	5,7	6,5
XIV	SO_2CH_3	H	76	158—60	63,3	5,2	8,2	9,1	$C_{18}H_{18}N_2O_2S$	63,1	5,3	8,2	9,4
XV	SO_2CH_3	C_2H_5	53	134—5	62,7	5,4	7,4	8,4	$C_{20}H_{20}N_2O_4S$	62,5	5,2	7,3	8,3

*Compounds were purified by recrystallization from aqueous dioxane (II, XIV, VI, VIII, IX, VII), from methanol (III, X, XII), aqueous ethanol (IV, V), aqueous dimethylformamide (VII, XIII), and ethanol (XV).

We further established that the oxidation of the methyl mercapto-group in I to a methylsulfoxy group in compound XI leads to a considerably greater reactivity of the latter with β-halogenated alcohols and α-epoxides.



By the reaction of 4,5-diphenylimidazolyl-2-methylsulfone (XI) with ethylene bromo(chloro)hydrin, α-bromoketone or ethyl ester of bromoacetic acid in absolute ethanol and in the presence of sodium ethoxide, we synthesized the corresponding disubstituted 4,5-diphenylimidazoles (XII - XV), with various active functional groups in positions 1 and 2.

The structure of all the compounds synthesized was confirmed by IR-spectral data. In the IR spectra of compounds IV - IX and XIV we noted absorption bands around 3350 - 3210 cm^{-1}, which are characteristic of the vibrations of the OH group. In the IR spectra of compounds X, XII, and XIII there were well-defined vibrations of the carbonyl group around 1700-1670 cm^{-1}, and in compound XV, vibrations of the complex ester carbonyl around 1750 cm^{-1}.

All of the sulfones XI - XV showed two characteristic intense absorption bands around 1150 - 1120 and 1320 - 1300 cm^{-1}. The assignment of those to the vibrations of the S=O of the sulfones is confirmed by the fact that in the majority of the investigated compounds XI - XV, thecoupling effect has no substantial role in changing the frequency [5].

The synthesized compounds were investigated in relation to their cardiovascular, antimicrobial, and antifungal activity. Compounds III, IV, and XIV showed a moderate hypotensive effect. All of the compounds investigated have a weak or moderate antifungal and antibacterial activity against gram-positive test microbes. Compounds III, IV, and XIV showed no significant effect on oxidative phosphorylating system of liver and brain mitochondria.

In spite of the fact that the substances synthesized show a moderate hypotensive effect, our data is interesting for the further search formore effective water-soluble analogs.

EXPERIMENTAL

The IR spectra were obtained on the UR-10 instrument, with paraffin oil mullsor potassium bromide pellets. The compound 2-methylmercapto-4,5-diphenylimidazole (I) was obtained by the method previously described [6].

2-Benzylmercapto-4,5-diphenylimidazole (II). To a solution of 1.2 g (0.03 mole) of sodium hydroxide in 150 ml of ethanol we added 7.56 g (0.03 mole) of 4,5-diphenylimidazolone-2-thione [7] and 3.78 g (0.03 mole) of benzyl chloride. The mixture was sitrred at 60 - 65°C for 30 - 40 min, chilled, and the precipitate filtered, washed with water, and dried. The technical (or crude) product of II was suitable for further synthesis without additional purification.

1-Methyl(β-hydroxyalkyl, β-hydroxyaralkyl, acylmethyl)-2-alkylmercapto-4,5-diphenylimidazoles (III - VIII). A. To a solution of 0.01- 0.05 mole of sodium hydroxide or sodium metal in 50 to 100 ml of ethanol we added 0.01 mole of compound I or II and 0.02 - 0.03 mole of methyl iodide or the α-oxide (of propylene, styrene, p-nitrostyrene). The mixture was warmed for

5 - 6 h at 60 - 80°C or, in the case of propylene oxide, at 30 - 35°C. It was then chilled and allowed to stand till a precipitate formed, which was filtered and recrystallized to obtain compounds V, VII, and VIII. Compounds III, IV, and VII were isolated by diluting the reaction mixture with water.

B. To a solution of sodium ethoxide prepared from 0.23 g (0.01 g-atom) of sodium and 20 - 30 ml of ethanol, we added 0.01 mole of 1-β-hydroxyethyl-4,5-diphenylimidazolone-2-thione or 1-phenacyl-4,5-diphenylimidazolone-2-thione and 1.7 g (0.012 mole) of methyl iodide. The mixture was warmed in a boiling water to a pH of 7.0. The reaction mixture was cooled, the water decanted, and the precipitate of IV and X was filtered and recrystallized.

4,5-Diphenylimidazolyl-2-methylsulfone (XI). We dissolved 5.32 g (0.02 mole) of I in 50 ml of glacial acetic acid, and to the solution added 10 ml of 27.4% hydrogen peroxide. The mixture was allowed to stand at 20 - 24°C for 6 days, then the precipitate was filtered and washed with ether.

N-substituted and 4,5-Diphenylimidazolyl-2-methylsulfones (XII - XV). To a solution of sodium ethoxide prepared from 0.23 g (0.01 mole) of sodium in 100 ml of absolute ethanol, we added 0.01 mole of α-bromoketone or the ethyl ester of bromo-(chloro)-acetic acid, or 0.02 mole ethylene bromohydrin (chlorohydrin). The reaction mixture was heated to boiling for 10 - 15 h, or for 2 - 3 h (in the case of the ester of halogen-substituted acetic acid). The mixture was chilled, and the precipitate filtered and recrystallized.

LITERATURE CITED

1. E. V. Logachev, M. B. Povstyanoi, P. M. Kochergin, et al., Izv. Vyssh, Uchebn. Zaved. SSSR, Khim. Khim. Technol., 19, 1039 - 1042 (1976).
2. M. V. Povstyanoi and P. M. Kochergin, Khim. Geterotsikl. Soedin., No. 6, 816-820 (1972).
3. B. A. Primenko and P. M. Kochergin, Khim. Geterotsikl. Soedin., No. 9, 1252-1254 (1971).
4. I. A. Mazur, P. M. Kochergin, and G. S. Tkachenko, Khim. Geterotsikl. Soedin., No. 6, 824-826 (1970).
5. L. Bellamy, Infrared Spectra of Complex Molecules [Russian translation], Moscow (1963) p. 512.
6. A. Anschutz and K. Schwickerath, Ann.,* 1895, p. 284.
7. P. M. Kochergin, Zh. Obshch. Khim., 31, 1093 - 1096 (1961).

*As in Russian Original — Consultants Bureau.