INVESTIGATIONS IN THE IMIDAZOLE SERIES

LXV.* SYNTHESIS OF 2-AMINOIMIDAZOLE DERIVATIVES FROM 2-HALOIMIDAZOLES

B. A. Priimenko and P. M. Kochergin

UDC 547.781:542.944.1'958.3

The reaction of 1-alkyl(hydroxyalkyl)-2-bromo-4,5-diphenylimidazoles with ammonia and primary and secondary amines was studied, and a new synthesis of 2-aminoimidazole derivatives was realized on the basis of 2-haloimidazoles. The starting compounds were obtained by the bromination of 1-alkyl(hydroxyalkyl)-4,5-diphenylimidazoles with bromine or by alkylation of 2-bromo-4,5-diphenylimidazole with alkyl halides, β-halo alcohols, and olefin oxides.

Several methods for obtaining 2-aminoimidazoles [2-6], 1-alkyl(aryl)-2-aminoimidazoles [2-4, 7], and 1-aryl-2-arylaminoimidazoles [3] are known. However, such a simple reaction as nucleophilic substitution of 2-haloimidazoles with an amino group was not reported until a brief communication [8] appeared.

In developing the research in [8], we have investigated the bromination of 1-methyl(β-hydroxyethyl, β-hydroxypropyl)-4,5-diphenylimidazoles (I-III) [9-12] with bromine and the alkylation of 2-bromo-4,5-diphenylimidazole (IV) [13] with alkyl halides, β-halo alcohols, and olefin oxides. The corresponding 1-alkyl(β-hydroxyalkyl, β-hydroxyaralkyl)-2-bromo-4,5-diphenylimidazoles (V-IX, Table 1) were obtained. It should be noted that the same compound (VIII) is formed by the reaction of IV with both styrene chlorohydrin and styrene oxide.

The structures of V-IX were confirmed by IR spectra (the presence of an absorption band of the OH group at 3270-3280 cm^{-1}) and by alternative synthesis, in the case of VII, from the known 1-(β-hydroxypropyl)-4,5-diphenylimidazole (II) [12].

There are indications in the literature that the hydroxyalkylation of 4,5-diphenylimidazole [12], 2-chloronaphth[1,2-d]imidazole [14], and 8-chlorotheophylline [15] by unsymmetrical olefin oxides also proceeds unambiguously to form the corresponding secondary alcohols with alkyl (aryl) groups in the β-position of the ethyl group bonded to the nitrogen atom of the imidazole ring.

We further made a detailed investigation of the reaction of V-VIII with ammonia and primary and secondary amines. It was noted that this reaction does not occur at 66-120° (refluxing in methanol, ethanol, or butanol). However, at 155-185° [refluxing in dimethylformamide (DMF), excess high-boiling amine, or heating in a low-boiling solvent in an autoclave] the bromine atom is nucleophilically substituted by an amino (alkylamino, arylamino, cycloalkylamino) group to form the corresponding 1-alkyl(β-hydroxyalkyl, β-hydroxyaralkyl)-2-amino(alkylamino, arylamino, cycloalkylamino)-4,5-diphenylimidazoles (X-XXXV, Table 1). The structures of X-XXXV were confirmed by the IR spectra, in which bands of the stretching vibrations of NH and OH groups are present at 3050-3450 cm^{-1}.

Thus, as a result of this investigation, we have realized a comparatively simple synthesis of substituted 2-aminoimidazoles on the basis of 2-haloimidazoles, particularly 2-bromoimidazoles.

*See [1] for communication LXIV.

Zaporozhe State Medical Institute. S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1248-1251, September, 1971. Original article submitted July 20, 1970.

TABLE 1. 2-Bromo- and 2-Aminoimidazole Derivatives

Comp.	R	R′	mp, °C (dec.)	Empirical formula	Found, %			Calc., %			Yield, %	ν_{NH}, ν_{OH}[a], cm^{-1}
					C	H	N	C	H	N		
V	H	—	149—150	$C_{16}H_{13}BrN_2$ [b]	61,2	4,2	8,7	61,3	4,2	8,9	57—78	—
VI	CH_2OH	—	165—166[c]	$C_{17}H_{15}BrN_2O$	—	—	—	—	—	—	44—71	3280
VII	$CH(OH)CH_3$	—	160—161	$C_{18}H_{17}BrN_2O$ [d]	—	—	7,8	—	—	7,8	60—67	3270
VIII	$CH(OH)C_6H_5$	—	200—201	$C_{23}H_{19}BrN_2$ [e]	65,5	4,5	6,5	65,9	4,6	6,7	60—71	3280
IX	$CH(OH)C_6H_4NO_2$-*p*	—	215—216	$C_{23}H_{18}BrN_3O_3$	59,7	4,2	9,3	59,5	4,0	9,1	75	—
X	CH_3	C_6H_5	219—220	$C_{22}H_{19}N_3$	80,9	5,9	12,9	81,2	5,6	12,9	92	—
XI	CH_3	*p*-$CH_3C_6H_4$	174—175	$C_{23}H_{21}N_3$	81,4	6,4	12,2	81,4	6,2	12,4	85	—
XII	CH_2OH	H	215—217	$C_{17}H_{17}N_3O \cdot C_6H_3N_3O_7$	54,3	3,7	16,6	54,3	4,0	16,5	72	—
XIII	CH_2OH	CH_3	206—208	$C_{18}H_{19}N_3O \cdot C_6H_3N_3O_7$	—	—	16,6	—	—	16,1	62	
XIV	$CH(OH)C_6H_5$	C_2H_5	160—161	$C_{25}H_{25}N_3O$	78,6	6,4	10,3	78,3	6,6	10,8	78	
XV	$CH(OH)C_6H_5$	C_3H_7	192—193	$C_{26}H_{27}N_3O$	78,2	6,9	10,8	78,6	6,8	10,6	71	3070, 3310
XVI	$CH(OH)C_6H_5$	C_4H_9	197—198	$C_{27}H_{29}N_3O$	78,2	7,0	10,1	78,8	7,1	10,2	73	3070, 3300
XVII	$CH(OH)C_6H_5$	*i*-C_4H_9	215—216	$C_{27}H_{29}N_3O$	78,5	7,1	10,1	78,8	7,1	10,2	63	3070, 3280
XVIII	$CH(OH)C_6H_5$	$C_6H_5CH_2$	218—219[f]	$C_{30}H_{27}N_3O$	80,7	6,3	9,8	80,9	6,1	9,4	76	3050, 3270
XIX	CH_2OH	C_6H_5	219—220[f]	$C_{28}H_{21}N_3O$	—	—	—	—	—	—	58	3160, 3440
XX	$CH(OH)CH_3$	C_6H_5	152—153	$C_{24}H_{23}N_3O \cdot 1/2\,H_2O$	76,5	6,7	11,0	76,2	6,4	11,1	87	3240, 3350
XXI	$CH(OH)C_6H_5$	C_6H_5	215—216	$C_{29}H_{25}N_3O$	80,4	6,2	10,2	80,7	5,8	9,7	56	
XXII	CH_2OH	*m*-$CH_3C_6H_4$	215—216	$C_{24}H_{23}N_3O$	77,8	6,5	11,6	78,0	6,3	11,4	43	3100, 3290
XXIII	$CH(OH)CH_3$	*m*-$CH_3C_6H_4$	193—194	$C_{25}H_{25}N_3O$	77,8	6,3	11,0	78,3	6,6	11,0	74	
XXIV	CH_2OH	*p*-$CH_3C_6H_4$	203—204	$C_{24}H_{23}N_3O$	78,0	6,4	11,2	78,0	6,3	11,4	68	3080, 3170
XXV	$CH(OH)C_6H_5$	*p*-$CH_3C_6H_4$	214—215	$C_{30}H_{27}N_3O$	80,6	6,2	9,4	80,9	6,1	9,4	72	
XXVI	CH_2OH	*p*-$CH_3OC_6H_4$	164—165	$C_{24}H_{23}N_3O_2$	74,4	6,2	10,9	74,8	6,0	10,9	52	3070, 3150
XXVII	$CH(OH)C_6H_5$	*p*-$CH_3OC_6H_4$	187—188	$C_{30}H_{27}N_3O_2$	78,4	5,9	9,20	78,1	5,9	9,1	78	3200, 3360
XXVIII	CH_2OH	*p*-$C_6H_5OC_6H_4$	210—212	$C_{29}H_{25}N_3O_2$	75,7	6,2	10,2	75,2	6,3	10,5	73	3080, 3170
XXIX	CH_2OH	*m*-ClC_6H_4	182—183	$C_{23}H_{20}ClN_3O$ [g]	70,7	5,3	10,3	70,8	5,2	10,8	51	
XXX	CH_2OH	*p*-ClC_6H_4	210—212	$C_{23}H_{20}ClN_3O$ [h]	70,5	4,9	10,6	70,8	5,2	10,8	74	3160, 3440
XXXI	CH_2OH	*p*-BrC_6H_4	203—204	$C_{23}H_{20}BrN_3O$ [i]	63,0	4,3	9,3	63,5	4,6	9,8	69	3160, 3450
XXXII	CH_2OH	α-$C_{10}H_7$	255—256	$C_{27}H_{23}N_3O$	79,7	5,7	10,0	80,0	5,7	10,4	49	3160, 3400
XXXIII	CH_3	$C_5H_{10}N$ [j]	123—124	$C_{21}H_{23}N_3 \cdot 1/2\,H_2O$	77,6	6,9	13,2	77,3	7,4	12,9	79	—
XXXIV	CH_3	C_4H_8NO [k]	126—127	$C_{20}H_{21}N_3O \cdot H_2O$	71,5	6,7	12,7	71,2	6,9	12,4	94	—
XXXV	CH_2OH	$C_5H_{10}N$ [j]	210—212	$C_{21}H_{23}N_3O_2 \cdot H_2O$	68,7	7,3	11,8	68,6	6,9	11,4	69	—

[a] The IR spectra of mineral oil suspensions were recorded with a UR-10 spectrometer.

[b] Found %: Br 25.2. Calculated %: Br 25.5.

[c] mp 165-166° [8].

[d] Found %: Br 22.8. Calculated %: Br 22.4.

[e] Found %: Br 19.3. Calculated %: Br 19.1.

[f] mp 219-220° [8].

[g] Found %: Cl 9.0. Calculated %: Cl 9.1.

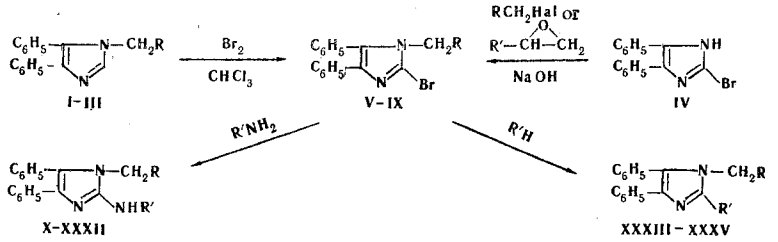
[h] Found %: Cl 9.1. Calculated %: Cl 9.1.

[i] Found %: Br 18.6. Calculated %: Br 18.4.

[j] $C_5H_{10}N$ is piperidino.

[k] C_4H_8NO is morpholino.

We thank V. V. Kolpakova, Yu. N. Sheinker, and their co-workers for performing the microanalyses and recording the IR spectra.



EXPERIMENTAL

1-Methyl-4,5-diphenylimidazole (I) [9], 1-(β-hydroxyethyl)-4,5-diphenylimidazole (II) [10, 11], 1-(β-hydroxypropyl)-4,5-diphenylimidazole (III) [12], and 2-bromo-4,5-diphenylimidazole (IV) [13]. These compounds were prepared by methods described in the literature.

1-Alkyl(β-hydroxyalkyl, β-hydroxyaralkyl)-2-bromo-4,5-diphenylimidazoles (V-IX, Table 1). A) Bromine (0.031 mole) was added with stirring in the course of 30 min to a solution of 0.03 mole of I-III in 100 ml of chloroform, and the mixture was stirred at 18-20° for 4 h. The solvent was removed by vacuum distillation, the residue was dissolved in ethanol, and the solution was neutralized with ammonium hydroxide and poured into water. The precipitate was removed by filtration and washed with ether to give 57-60% of V-VII.

B) A solution of 0.02 mole of IV, 0.02 mole of NaOH, and 0.04 mole of ethylene chlorohydrin (or ethylene bromohydrin) or 0.021 mole of styrene chlorohydrin in 50 ml of 70% DMF was stirred for 12 h at 50-60° and poured into water. The precipitate was removed by filtration and washed with ether to give 70-71 and 60%, respectively, of VI and VIII. Under similar conditions, V was obtained by the methylation of IV with methyl iodide (0.21 mole per 0.1 mole of IV) in ethanol in the presence of 0.1 mole of NaOH at 50-60° for 5 h.

C) Pyridine (0.01-0.02 mole) and 0.06 mole of olefin oxide were added to a solution of 0.03 mole of IV in 30-40 ml of DMF, and the mixture was stirred at 60-65° for 6-8 h and worked up as described in experiment B to give 67, 70, and 75%, respectively, of VII-IX. Compound IX was similarly obtained in 44% yield, with the difference that the reaction was carried out at 15-20° in ethanol in the presence of NaOH (1 mole per 1 mole of IV). Mixtures of samples of V-VIII obtained by methods A-C melted without depression.

Compounds V-IX were colorless or pale yellow (IX) crystalline substances that were soluble in most organic solvents and insoluble in water. For analysis, the compounds were purified by crystallization from aqueous dioxane (V-VII, IX) or aqueous acetone (VIII).

1-Alkyl(β-hydroxyalkyl, β-hydroxyaralkyl)-2-amino(alkylamino, arylamino, cycloalkylamino)-4,5-diphenylimidazoles (X-XXXV, Table 1). A) A mixture of 0.01 mole of V-VIII, 0.025 mole of amine, and 50 ml of ethanol or 20-25 ml of alcoholic ammonia, methylamine, or ethylamine and 20-25 ml of ethanol was heated at 160-180° (in a 150 ml autoclave) for 8-10 h and cooled. The precipitate was removed by filtration and washed with water and ether. Evaporation of the alcohol mother liquor gave an additional amount of compound. Compounds XII-XVIII and XXXII-XXXV were isolated by pouring the reaction mixture into water.

B) A mixture of 3.4 g of VII and 10 ml of aniline or m-toluidine was refluxed for 6-8 h, the unchanged amine was removed by vacuum distillation, and the residue was washed with water and ether to give 87 and 71%, respectively, of XX and XXIII. These samples did not depress the melting points of the compounds obtained by method A.

Compounds X-XXXV were colorless or pale-yellow crystalline substances that were soluble in most organic solvents and insoluble in water. For analysis, the compounds were purified by crystallization from aqueous dioxane (X, XI, XXXIII-XXXV), aqueous acetone (XII-XVII), aqueous DMF (XVIII, XXI, XXV, XXVII, XXIX, and XXXI), aqueous ethanol (XIX, XXII, XXIV, XXVI, XXX, and (XXXII), or aqueous methanol (XX).

LITERATURE CITED

1. B. A. Priimenko and P. M. Kochergin, Khim. Geterotsikl. Soedin., 1243 (1971).
2. K. Hofmann, Imidazole and Its Derivatives, New York (1953).

3. Z. N. Nazarova (editor), Outline of the Chemistry of Azoles [in Russian], Izd. Rostovsk. Univ. (1965).
4. A. F. Pozharskii, A. D. Garnovskii, and A. M. Simonov, Usp. Khim., 35, 261 (1966).
5. J. Iwai and J. Jura, Japanese Patent No. 24,885; Chem. Abstr., 60, 4154 (1964).
6. S. Nakamura, Pharm. Bull. Japan, 3, 379 (1955); Chem. Abstr., 50, 15897 (1956).
7. B. A. Tertov and V. V. Burykin, Khim. Geterotsikl. Soedin., 180 (1969).
8. P. M. Kochergin, M. V. Povstyanoi, B. A. Priimenko, and V. S. Ponomar', Khim. Geterotsikl. Soedin., 129 (1970).
9. A. Pinner, Ber., 35, 4131 (1902).
10. N. Yamada and Y. Takahashi, Japanese Patent No. 263; Chem. Abstr., 66, 85,793 (1967).
11. J. Kawakami, French Patent No. 1,551,851; Referativnyi Zh. Khim., 7N382 (1970).
12. J. Kawakami, British Patent No. 1,134,580; Chem. Abstr., 70, 57,853 (1969).
13. J. D. Lamb and F. L. Pyman, J. Chem. Soc., 125, 706 (1924).
14. M. V. Povstyanoi and P. M. Kochergin, Khim. Geterotsikl. Soedin., 1121 (1971).
15. J. Zajaczkowska and M. Eckstein, Diss. Pharm. Pharmacol., 20(3), 287 (1968); Chem. Abstr., 70, 381 (1969).