INVESTIGATIONS IN THE IMIDAZOLE SERIES

LXI.* SYNTHESIS OF 2,3-DIHYDRO DERIVATIVES OF NAPHTH[1,2-d]IMIDAZO[3,2-b]IMIDAZOLE

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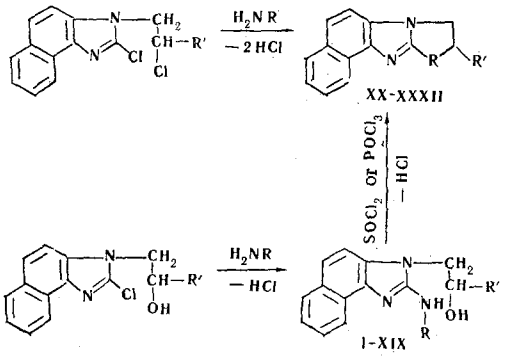
2,3-Dihydro derivatives of naphth[1,2-d]imidazo[3,2-b]imidazole were synthesized by the reaction of 2-chloro-3-(β-haloalkyl)naphth[1,2-d]imidazole with ammonia and primary amines and by the reaction of 2-chloro-3-(β-hydroxyalkyl)naphth[1,2-d]imidazole with ammonia and amines with subsequent cyclization of the resulting 2-amino(alkylamino, arylamino)-3-(β-hydroxyalkyl)naphth[1,2-d]imidazoles under the influence of thionyl chloride or phosphorus oxychloride. Dihydro derivatives of the condensed naphth[1,2-d]imidazo[3,2-b]imidazole system have not been described in the literature.

In a continuation of our earlier investigation [2], we have studied the action of ammonia and primary amines on the previously [3] prepared 2-chloro-3-(β-haloalkyl)naphth[1,2-d]imidazoles and 2-chloro-3-(β-hydroxyalkyl)naphth[1,2-d]imidazoles. It was established that simultaneous splitting out of hydrogen halide to form 2,3-dihydro derivatives of naphth[1,2-d]imidazo[3,2-b]imidazole (XX-XXXII) occurs along with substitution of one of the halogen atoms by an amino (alkylamino, arylamino) group when 2-chloro-3-(β-haloalkyl)naphth[1,2-d]imidazoles are heated with ammonia and primary amines in alcohol solutions or in dimethylformamide at 120-180° C.

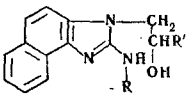
The corresponding 2-amino(alkylamino, arylamino)-3-(β-hydroxyalkyl)naphth[1,2-d]imidazoles (I-XIX) were obtained by the reaction of 2-chloro-3-(β-hydroxyalkyl)naphth[1,2-d]imidazoles with ammonia and amines. Like 1-(β-hydroxyethyl)-2-aminoimidazoline [4] and 1-(β-hydroxyethyl)-3-ethyl-2-iminobenzimidazoline [5], when I-XIX are treated with $SOCl_2$ or $POCl_3$ with subsequent heating of the intermediate 2-amino(alkylamino, arylamino)-3-(β-chloroalkyl)naphth[1,2-d]imidazoles under the influence of NaOH and, in some cases (for example, in the preparation of XXIII and XXVIII), also in the absence of alkali, they undergo imidazole ring closure to form 2,3-dihydro derivatives of naphth[1,2-d]imidazo[3,2-b]imidazole.



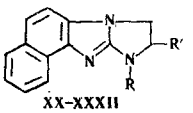
*See [1] for communication LX.

Zaporozhe Medical Institute. S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1125-1127, August, 1971. Original article submitted February 9, 1970.

TABLE 1



I-XIX



XX-XXXII

Compound	R	R′	mp(dec.), °C	Empirical formula	Found, %			Calculated, %			Yield, %
					C	H	N	C	H	N	
I	H	H	240—242	$C_{13}H_{13}N_3O \cdot C_6H_3N_3O_7$	50,3	3,6	18,4	50,0	3,5	18,4	65
II	CH_3	H	216—218	$C_{14}H_{15}N_3O \cdot C_6H_3N_3O_7$	51,4	4,1	17,7	51,1	3,9	17,9	48
III	C_2H_5	C_6H_5	167—168	$C_{21}H_{21}N_3O$	75,7	6,4	12,9	76,1	6,4	12,7	70
IV	C_3H_7	C_6H_5	178—179	$C_{22}H_{23}N_3O$	76,6	6,7	12,1	76,5	6,7	12,2	40
V	C_4H_9	C_6H_5	200—201	$C_{23}H_{25}N_3O$	76,4	7,4	11,4	76,8	7,0	11,7	50
VI	*iso*-C_4H_9	C_6H_5	203—205	$C_{23}H_{25}N_3O$	76,7	6,9	11,3	76,8	7,0	11,7	65
VII	C_6H_5	H	255—257	$C_{19}H_{17}N_3O$	74,8	5,7	13,7	75,2	5,7	13,8	70—73
VIII	C_6H_5	C_6H_5	273—275	$C_{25}H_{21}N_3O$	79,5	5,8	11,0	79,1	5,6	11,1	28
IX	m-$CH_3C_6H_4$	H	220—221	$C_{20}H_{19}N_3O$	75,9	5,9	13,1	75,7	6,0	13,2	62
X	*p*-$CH_3C_6H_4$	H	234—236	$C_{20}H_{19}N_3O$	75,9	6,1	13,0	75,7	6,0	13,2	60
XI	*p*-$CH_3OC_6H_4$	H	195—196	$C_{20}H_{19}N_3O_2$	71,7	5,5	12,8	72,0	5,7	12,6	64
XII	*p*-$CH_3OC_6H_4$	C_6H_5	248—250	$C_{26}H_{23}N_3O_2$	76,4	6,0	10,1	76,3	5,7	10,3	30
XIII	*p*-$C_2H_5OC_6H_4$	H	231—232	$C_{21}H_{21}N_3O_2$	72,8	6,3	12,2	72,6	6,1	12,1	60
XIV	*m*-ClC_6H_4	H	226—227	$C_{19}H_{16}ClN_3O$[a]	67,5	5,0	12,6	67,5	4,8	12,4	55
XV	*p*-ClC_6H_4	H	198—199	$C_{19}H_{16}ClN_3O$[b]	68,0	4,8	12,5	67,5	4,8	12,4	55—60
XVI	*m*-BrC_6H_4	H	230—232	$C_{19}H_{16}BrN_3O$[c]	59,7	4,3	10,6	59,7	4,2	11,0	53
XVII	*p*-BrC_6H_4	H	237—238	$C_{19}H_{16}BrN_3O$[d]	60,1	4,3	10,9	59,7	4,2	11,0	50
XVIII	$C_6H_5CH_2$	H	173—175	$C_{20}H_{19}N_3O$	75,3	5,9	13,4	75,7	6,0	13,2	30
XIX	$C_{10}H_7$	H	288—290	$C_{23}H_{19}N_3O$	77,9	5,3	11,8	78,2	5,4	11,9	50—85
XX	H	H	162—163	$C_{13}H_{11}N_3 \cdot C_6H_3N_3O_7$	52,4	3,3	19,4	52,1	3,2	19,2	40—53
XXI	H	C_6H_5	208—210	$C_{19}H_{14}N_3 \cdot C_6H_3N_3O_7$	60,4	3,7	14,2	60.1	3,4	14,0	56
XXII	CH_3	H	173—174	$C_{14}H_{13}N_3 \cdot C_6H_3N_3O_7$	53,3	3,7	18,4	53,1	3,6	18,6	47
XXIII	C_6H_5	H	258—259	$C_{19}H_{15}N_3$	79,9	5,3	15,0	80,0	5,3	14,7	50—70
XXIV	C_6H_5	C_6H_5	220—222	$C_{25}H_{18}N_3$	83,5	5,2	11,8	83,3	5,0	11,7	21
XXV	m-$CH_3C_6H_4$	H	245—246	$C_{20}H_{17}N_3$	80,0	5,8	14,0	80,2	5,7	14,0	50
XXVI	*p*-$CH_3C_6H_4$	H	203—204	$C_{20}H_{17}N_3$	80,2	5,7	14,4	80,2	5,7	14,0	45—60
XXVII	*p*-$CH_3OC_6H_4$	H	182—183	$C_{20}H_{17}N_3O$	75,8	5,3	13,2	76,2	5,4	13,3	60
XXVIII	*p*-$C_2H_5OC_6H_4$	H	210—211	$C_{21}H_{19}N_3O$	76,4	5,7	12,3	76,6	5,8	12,7	48—56
XXIX	*m*-ClC_6H_4	H	247—248	$C_{19}H_{14}ClN_3$[f]	71,2	4,3	13,4	71,4	4,4	13,1	50—55
XXX	*p*-ClC_6H_4	H	236—237	$C_{19}H_{14}ClN_3$[g]	71,6	4,4	12,9	71,4	4,4	13,1	56
XXXI	3,4-$Cl_2C_6H_3$	H	266—267	$C_{19}H_{13}Cl_2N_3$[h]	64,5	3,7	11,9	64,4	3,7	11,9	75
XXXII	$C_6H_5CH_2$	H	186—187	$C_{20}H_{17}N_3$	80,5	5,8	14,4	80,2	5,7	14,0	50

[a] Found: Cl 10.2%. Calculated: Cl 10.5%.
[b] Found: Cl 10.4%. Calculated: Cl 10.5%.
[c] Found: Br 20.8%. Calculated: Br 20.9%.
[d] Found: Br 21.2%. Calculated: Br 20.9%.
[e] α-Naphthyl.
[f] Found: Cl 10.8%. Calculated: Cl 11.1%.
[g] Found: Cl 11.4%. Calculated: Cl 11.1%.
[h] Found: Cl 19.8%. Calculated: Cl 20.0%.

The structure of four-ring compounds XX-XXXII was established on the basis of the results of elemental analysis (Table 1) and also by the IR spectra, in which bands of the valence vibrations of OH or NH groups at 2700-3200 cm^{-1}, which are present in the IR spectra of the starting imidazoles, are absent.

EXPERIMENTAL

2-Amino(alkylamino, arylamino)-3-(β-hydroxyalkyl)naphth[1,2-d]imidazoles (I-XIX). A) A solution of 0.01 mole of 2-chloro-3-(β-hydroxyalkyl)naphth[1,2-d]imidazole [3] and 0.025 mole of primary amine in 15-20 ml of methanol or ethanol was heated in a 0.05-0.1 liter autoclave at 150-170° for 8-10 h and cooled. The precipitate was removed by filtration and washed with water and then with cold methanol. The mother liquors were evaporated to a small volume to isolate an additional amount of product. Ammonia and methylamine were used in large excesses as 15-20% alcohol solutions [15-20 ml per 0.01 mole of 2-chloro-3-(β-hydroxyethyl)naphth[1,2-d]imidazole]. This method was used to obtain I-XVI and XVIII.

B) A mixture of 0.01 mole of 2-chloro-3-(β-hydroxyalkyl)naphth[1,2-d]imidazole and 0.025 mole of amine in 20-30 ml of dimethylformamide was refluxed for 6-8 h, cooled, and 30-50 ml of methanol was added. The mixture was poured into water, and the precipitate was removed by filtration and washed with cold methanol. This method was used to obtain VII, XV, XVII, and XIX. Samples of VII and XV did not depress the melting points of the corresponding samples obtained via method A.

2,3-Dihydronaphth[1,2-d]imidazo[3,2-b]imidazoles (XX-XXXII). A) A solution of 0.01 mole of 2-chloro-3-(β-haloalkyl)naphth[1,2-d]imidazole [3] and 0.035 mole of primary amine in 10-20 ml of methanol or ethanol was heated in a 0.05-0.1 liter autoclave at 150-180° for 6-8 h and cooled. The precipitate was removed by filtration and washed with water and then methanol. Evaporation of the mother liquors to a small volume gave an additional amount of product. As in the preparation of I and II, ammonia and methylamine were used in large excesses. This method was used to obtain XX-XXV, XXIX, XXXI, and XXXII.

B) A solution of 0.01 mole of 2-chloro-3-(β-haloethyl)naphth[1,2-d]imidazole [3] and 0.035 mole of amine in 10-20 ml of butanol or dimethylformamide was refluxed for 4-6 h and cooled. The precipitate was removed by filtration and washed with water and methanol. This method was used to obtain XXIII and XXVI-XXX.

C) A solution of 0.01 mole of I, VII, or X in 30 ml of $POCl_3$ or in 50 ml of $SOCl_2$ was refluxed for 2-3 h, the excess $POCl_3$ or $SOCl_2$ was removed by vacuum distillation, 20-30 ml of $CHCl_3$ was added, and the mixture was vacuum evaporated to dryness. The residue was dissolved in 30-50 ml of methanol, and the solution was filtered. The filtrate was treated with 40% NaOH solution until it was strongly alkaline, and the mixture was refluxed for 3-5 h and poured into water. The mixture was neutralized with 2 N HCl, and the precipitate was removed by filtration to give 40, 56, and 45% yields, respectively, of XX, XXIII, and XXVI.

D) A total of 15-20 ml of $SOCl_2$ was added to a solution of 0.01 mole of VII or XIII in 30-50 ml of dimethylformamide, and the mixture was heated at 65-70° for 3 h and then refluxed for 5 h, cooled, and poured into water. The mixture was neutralized with NH_3 or Na_2CO_3, and the precipitate was removed by filtration to give 52 and 48%, respectively, of XXIII and XXVIII. A sample of XXIII obtained by this method did not depress the melting points of those obtained by methods A-C.

Compounds I-XXXII were basic, colorless, crystalline substances that were soluble in most organic solvents and mineral acids and insoluble in water. Analytically pure substances were obtained by crystallization from aqueous alcohol (I, II, XIV, XVII, XVIII, and XX-XXII), aqueous acetone (III-VI, IX, X, and XVI), ethanol (VII, XI, and XIII), and aqueous dimethylformamide (VIII, XII, XV, XIX, and XXIII-XXXII).

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