INVESTIGATIONS IN THE IMIDAZOLE SERIES

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

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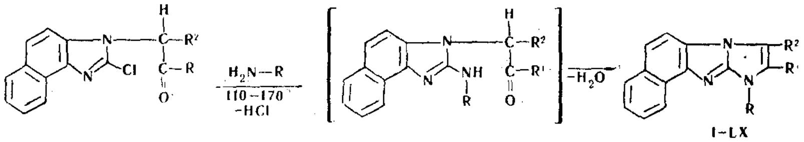
1-H-Naphth[1,2-d]imidazo[3,2-b]imidazole derivatives were synthesized by the reaction of 2-chloro-3-acylalkylnaphth[1,2-d]imidazoles with ammonia, primary amines, amino alcohols, dialkylaminoalkylamines, and α-amino acid esters.

1-H-Naphth[1,2-d]imidazo[3,2-b]imidazoles have not yet been described in the literature. We previously [2] reported the synthesis of one compound of this series. Since naphth[1,2-d]imidazo[3,2-b]imidazole derivatives may be of interest as biologically active substances or intermediates in the synthesis of new dyes, we made a detailed investigation of the reaction of 2-chloro-3-acylalkylnaphth[1,2-d]imidazoles [1] with ammonia and primary amines. It was established that nucleophilic substitution of the chloride atom by an amino (alkylamino or arylamino) group occurs simultaneously with cyclization of 2-amino(alkylamino, arylamino)-3-acylalkylnaphth[1,2-d]imidazoles to form naphth[1,2-d]imidazo[3,2-b]imidazole derivatives (I-LX, Table 1) on heating 2-chloro-3-acylalkylnaphth[1,2-d]imidazoles with ammonia, primary aliphatic, aliphatic-aromatic, and aromatic amines, amino alcohols, dialkylaminoalkylamines, and amino esters in alcohol solutions, dimethylformamide, or without a solvent at 110-185°. 1-Carbethoxymethyl-2-phenylnaphth[1,2-d]imidazo[3,2-b]imidazole and 1-carbethoxymethyl-2-(p-bromophenyl)naphth[1,2-d]imidazo[3,2-b]imidazole were saponified, without isolation in pure form, to the corresponding acids (X and LIII).



I-LX

Some peculiarities were encountered only in the reaction of 2-chloro-3-(p-methylphenacyl)- and 2-chloro-3-(p-methoxyphenacyl)naphth[1,2-d]imidazoles with monoethanolamine. When the reaction was carried out above 160° C, the corresponding 1-vinyl-substituted XXVI and XXXIX, whose formation is apparently explained by the ease of dehydration of XXV and XXXVIII at high temperatures, were isolated instead of 1-(β-hydroxyethyl)2-(p-methylphenyl)- and 1-(β-hydroxyethyl)-2-(p-methoxyphenyl)naphth[1,2-d]-imidazo[3,2-b]imidazoles (XXV and XXXVIII).

The structures of I-LX were established on the basis of the results of elemental analysis and were also confirmed by the IR spectra, in which, except for X and LIII, whose IR spectra contained distinct absorption bands of a CO group at 1670 and 1690 cm^{-1}, respectively, bands of the stretching vibrations of a CO group were absent.

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*See [1] for communication LIX.

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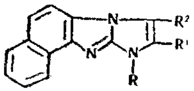
TABLE 1. 1H-Naphth[1,2-d]imidazo[3,2-b]imidazoles



Compound	R	R′	R″	Mp (dec.), °C	Empirical formula	Found, %				Calculated, %				Yield, %
						C	H	hal-ogen	N	C	H	hal-ogen	N	
I	H	$C(CH_3)_3$	H	210—212	$C_{17}H_{17}N_3$	77,7	4,8	—	16,2	77,5	4,5	—	16,0	62
II	H	C_6H_5	H	260—262	$C_{19}H_{13}N_3$	81,0	4,5	—	14,5	80,5	4,6	—	14,8	70
III	H	C_6H_5	CH_3	280—282	$C_{20}H_{15}N_3$	80,5	5,1	—	14,5	80,8	5,1	—	14,1	67
IV	C_6H_5	CH_3	H	132—133	$C_{20}H_{15}N_3$	80,4	5,1	—	13,8	80,8	5,1	—	14,1	50—60
V	m-$CH_3C_6H_4$	CH_3	H	140—141	$C_{21}H_{17}N_3$	81,1	5,5	—	13,6	81,0	5,5	—	13,5	62
VI	p-$CH_3C_6H_4$	CH_3	H	147—148	$C_{21}H_{17}N_3$	80,8	5,8	—	13,3	81,0	5,5	—	13,5	52—64
VII	CH_3	C_6H_5	H	142—143	$C_{20}H_{15}N_3$	80,7	5,0	—	13,8	80,8	5,1	—	14,1	60
VIII	C_2H_5	C_6H_5	H	218—220	$C_{21}H_{17}N_3 \cdot C_6H_3N_3O_7$	59,5	4,0	—	15,7	60,0	3,7	—	15,5	53
IX	CH_2CH_2OH	C_6H_5	H	192—193	$C_{21}H_{17}N_3O$	77,3	5,2	—	13,2	77,0	5,2	—	12,8	61
X	CH_2COOH	C_6H_5	H	265—267	$C_{21}H_{15}N_3O_2$	73,4	4,6	—	12,2	73,9	4,4	—	12,3	47
XI	$CH_2CH{=}CH_2$	C_6H_5	H	185—187	$C_{22}H_{17}N_3 \cdot C_6H_3N_3O_7$	61,2	3,7	—	15,3	60,9	3,6	—	15,2	61
XII	C_4H_9	C_6H_5	H	78—80	$C_{23}H_{21}N_3$ [a]	80,9	6,7	—	12,5	81,4	6,2	—	12,4	40
XIII	i-C_4H_9	C_6H_5	H	240—242	$C_{23}H_{21}N_3 \cdot C_6H_3N_3O_7$	61,3	3,9	—	14,5	61,3	4,2	—	14,8	64
XIV	C_6H_{11}	C_6H_5	H	176—177	$C_{25}H_{23}N_3$	82,2	6,6	—	11,4	82,2	6,3	—	11,5	50
XV	C_6H_6	C_6H_5	H	237—238	$C_{25}H_{17}N_3$ [b]	83,9	5,1	—	11,9	83,5	4,8	—	11,9	78—82
XVI	m-$CH_3C_6H_4$	C_6H_5	H	228—229	$C_{26}H_{19}N_3$	83,4	5,0	—	11,3	83,6	5,1	—	11,2	86
XVII	p-$C_2H_5OC_6H_4$	C_6H_5	H	249—250	$C_{27}H_{21}N_3O$	80,3	5,2	—	10,4	80,4	5,2	—	10,4	80—84
XVIII	m-ClC_6H_4	C_6H_5	H	232—234	$C_{25}H_{16}ClN_3$	76,2	4,3	9,3	10,6	76,2	4,1	9,0	10,7	83
XIX	p-BrC_6H_4	C_6H_5	H	290—292	$C_{25}H_{16}BrN_3$	68,8	3,7	17,9	9,9	68,5	3,7	18,2	9,6	70—78
XX	$C_{10}H_7$	C_6H_5	H	221—222	$C_{29}H_{19}N_3$	85,3	4,9	—	10,0	85,1	4,7	—	10,3	61
XXI	C_6H_5	C_6H_5	CH_3	284—286	$C_{26}H_{19}N_3$	83,6	4,8	—	11,7	83,6	5,1	—	11,2	82—85
XXII	p-ClC_6H_4	C_6H_5	CH_3	274—276	$C_{26}H_{18}ClN_3$	76,7	4,6	8,7	10,0	76,6	4,5	8,7	10,3	87
XXIII	CH_3	p-$CH_3C_6H_4$	H	166—167	$C_{21}H_{17}N_3$	81,0	5,8	—	13,2	81,0	5,5	—	14,5	43
XXIV	C_2H_5	p-$CH_3C_6H_4$	H	144—145	$C_{22}H_{19}N_3$	81,1	6,0	—	12,9	81,2	5,9	—	12,9	47
XXV	CH_2CH_2OH	p-$CH_3C_6H_4$	H	187—188	$C_{22}H_{19}N_3O \cdot H_2O$	73,9	6,2	—	12,0	73,5	6,0	—	11,7	52
XXVI	$CH{=}CH_2$	p-$CH_3C_6H_4$	H	146—148	$C_{22}H_{17}N_3$	81,3	5,6	—	13,1	81,7	5,3	—	12,3	37
XXVII	C_3H_7	p-$CH_3C_6H_4$	H	115—116	$C_{23}H_{21}N_3$	81,1	6,1	—	12,3	81,4	6,2	—	12,4	42
XXVIII	C_4H_9	p-$CH_3C_6H_4$	H	279—280	$C_{24}H_{23}N_3 \cdot HBr$	65,9	5,6	18,8	10,1	66,4	5,6	18,4	9,7	63

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[a] The picrate had mp 211-213°. Found: C 61.0; H 4.3; N 15.2%. Calculated: C 61.3; H 4.2; N 14.8%.

[b] The picrate had mp 266-268°. Found: C 63.1; H 3.5; N 14.2%. Calculated: C 63.3; H 3.4; N 14.3%.

Table 1 (continued)

Compound	R	R′	R″	Mp (dec.), °C	Empirical formula	Found, %				Calculated, %				Yield, %
						C	H	halogen	N	C	H	halogen	N	
XXIX	*iso*-C_4H_9	*p*-$CH_3C_6H_4$	H	284—285	$C_{24}H_{23}N_3 \cdot HBr$	66,1	5,7	18,3	9,7	66,4	5,6	18,4	9,7	58
XXX	$CH_2CH_2N(C_2H_5)_2$	*p*-$CH_3C_6H_4$	H	220—222	$C_{26}H_{28}N_4 \cdot 2HBr \cdot H_2O$	54,6	5,9	27,5	9,5	54,2	5,6	27,7	9,7	59
XXXI	C_6H_5	*p*-$CH_3C_6H_4$	H	235—236	$C_{26}H_{19}N_3$	83,1	5,2	—	11,6	83,6	5,1	—	11,2	75
XXXII	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	H	243—244	$C_{27}H_{21}N_3$	84,0	5,8	—	10,6	83,7	5,5	—	10,8	80—83
XXXIII	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	H	250—251	$C_{26}H_{18}ClN_3$	76,9	4,7	8,4	10,6	76,6	4,4	8,7	10,3	80
XXXIV	*p*-BrC_6H_4	*p*-$CH_3C_6H_4$	H	262—264	$C_{26}H_{18}BrN_3$	68,8	4,1	17,4	9,0	69,0	4,0	17,7	9,3	76
XXXV	$CH_2C_6H_5$	*p*-$CH_3C_6H_4$	H	202—203	$C_{27}H_{21}N_3$	83,4	5,5	—	10,6	83,7	5,5	—	10,8	59
XXXVI	CH_3	*p*-$CH_3OC_6H_4$	H	143—144	$C_{21}H_{17}N_3O$	76,5	5,3	—	12,6	77,0	5,2	—	12,8	58
XXXVII	C_2H_5	*p*-$CH_3OC_6H_4$	H	142—143	$C_{22}H_{19}N_3O$	77,1	5,7	—	12,1	77,4	5,6	—	12,3	55
XXXVIII	CH_2CH_2OH	*p*-$CH_3OC_6H_4$	H	213—215	$C_{22}H_{19}N_3O_2$	74,3	5,4	—	12,0	73,9	5,4	—	11,8	66
XXXIX	$CH{=}CH_2$	*p*-$CH_3OC_6H_4$	H	137—138	$C_{22}H_{17}N_3O$	77,6	5,5	—	12,0	77,8	5,0	—	12,4	45
XL	C_3H_7	*p*-$CH_3OC_6H_4$	H	126—127	$C_{23}H_{21}N_3O$	78,0	6,0	—	11,6	77,7	6,0	—	11,8	43
XLI	C_4H_9	*p*-$CH_3OC_6H_4$	H	113—114	$C_{24}H_{23}N_3O$	78,0	6,0	—	11,3	78,0	6,3	—	11,4	51
XLII	*iso*-C_4H_9	*p*-$CH_3OC_6H_4$	H	169—170	$C_{24}H_{23}N_3O$	77,9	6,5	—	11,3	78,0	6,3	—	11,4	62
XLIII	C_5H_{11}	*p*-$CH_3OC_6H_4$	H	113—114	$C_{25}H_{25}N_3O$	78,6	6,5	—	11,0	78,3	6,6	—	11,0	42
XLIV	$CH_3CH(CH_2)_3OH$	*p*-$CH_3OC_6H_4$	H	245—246	$C_{25}H_{25}N_3O_2$	74,9	6,3	—	10,6	75,2	6,3	—	10,5	62
XLV	$CH_2CH_2N(C_2H_5)_2$	*p*-$CH_3OC_6H_4$	H	248—250	$C_{26}H_{28}N_4O \cdot 2HBr$	54,1	5,5	27,5	9,4	54,4	5,3	27,8	9,7	43
XLVI	C_6H_5	*p*-$CH_3OC_6H_4$	H	218—219	$C_{26}H_{19}N_3O \cdot 1/2H_2O$	78,6	5,1	—	10,6	78,4	5,1	—	10,5	73
XLVII	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	H	258—260	$C_{27}H_{21}N_3O_2$	76,8	5,3	—	10,2	77,3	5,0	—	10,0	83
XLVIII	*p*-ClC_6H_4	*p*-$CH_3OC_6H_4$	H	227—228	$C_{26}H_{18}ClN_3O$	73,3	4,2	8,7	9,6	73,7	4,3	8,3	9,9	85
XLIX	*p*-BrC_6H_4	*p*-$CH_3OC_6H_4$	H	253—254	$C_{26}H_{18}BrN_3O$	66,5	4,1	17,4	9,1	66,7	3,9	17,1	9,0	69
L	C_6H_5	*p*-ClC_6H_4	H	265—267	$C_{25}H_{16}ClN_3$	76,5	4,2	9,0	10,4	76,2	4,1	9,0	10,7	84
LI	*p*-ClC_6H_4	*p*-ClC_6H_4	H	280—282	$C_{25}H_{15}Cl_2N_3$	69,9	3,3	16,3	9,9	70,1	3,5	16,6	9,8	91
LII	*p*-BrC_6H_4	*p*-ClC_6H_4	H	286—288	$C_{25}H_{15}BrClN_3$	63,7	3,3	24,7	8,6	63,5	3,2	24,4	8,9	88
LIII	CH_2COOH	*p*-BrC_6H_4	H	278—280	$C_{21}H_{14}BrN_3O_2$	60,3	3,5	19,3	9,8	60,0	3,4	19,0	10,0	40
LIV	CH_2CH_2OH	*p*-BrC_6H_4	H	207—208	$C_{21}H_{16}BrN_3O$	62,4	4,2	19,9	10,3	62,1	4,0	19,7	10,3	70—75
LV	C_6H_5	*p*-BrC_6H_4	H	284—285	$C_{25}H_{16}BrN_3$	68,1	4,0	18,5	9,7	68,5	3,7	18,2	9,6	80—85
LVI	*m*-$CH_3C_6H_4$	*p*-BrC_6H_4	H	226—227	$C_{26}H_{18}BrN_3$	69,4	4,0	17,8	9,7	69,0	4,0	17,7	9,3	83
LVII	*p*-$CH_3OC_6H_4$	*p*-BrC_6H_4	H	267—268	$C_{26}H_{18}BrN_3O$	66,4	4,1	17,0	9,0	66,7	3,9	17,0	8,9	75—80
LVIII	*m*-ClC_6H_4	*p*-BrC_6H_4	H	253—254	$C_{25}H_{15}BrClN_3$	63,8	3,2	24,6	8,9	63,5	3,2	24,4	8,9	82
LIX	*p*-ClC_6H_4	*p*-BrC_6H_4	H	283—284	$C_{25}H_{15}BrClN_3$	63,7	3,3	24,1	8,7	63,5	3,2	24,4	8,9	85—90
LX	*p*-BrC_6H_4	*p*-BrC_6H_4	H	287—288	$C_{25}H_{15}Br_2N_3$	58,0	2,8	31,1	8,3	58,0	2,9	31,0	8,1	82—90

EXPERIMENTAL

Naphth[1,2-d]imidazo[3,2-b]imidazole Derivatives (I-LX). A) A solution of 0.01 mole of 2-chloro-3-acylalkylnaphth[1,2-d]imidazole [1] and 0.025 mole of primary amine in 10-20 ml of methanol or ethanol was heated in an autoclave (0.05-0.1 liter) at 130-170° (preferably at 140-160°) for 6-10 h. The mixture was cooled, and the precipitate was removed by filtration and washed first with water and then with cold methanol. The mother liquors were evaporated to a small volume to isolate additional amounts of product. Ammonia, methylamine, and ethylamine were used in large excess in the form of 15-25% alcohol solutions (15-20 ml per 0.01 mole of 2-chloro-3-acylalkylnaphth[1,2-d]imidazole). This method was used to obtain I-III, V, VII-IX, XI-XIV, XXIII-XXX, and XXXV-XLV.

B) A mixture of 0.01 mole of 2-chloro-3-acylalkylnaphth[1,2-d]imidazole and 0.025 mole of amine in 20-30 ml of butanol, isobutanol, or dimethylformamide was refluxed for 3-5 h, cooled, and 30 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 IV, VI, X, XV-XXII, XXXI-XXXIV, and XLVI-LX.

In the preparation of X and LIII, the reaction mass was cooled and poured into 2 N sodium hydroxide. The mixture was refluxed for 10-20 min, cooled, and neutralized with 2 N HCl or acetic acid. The precipitate was removed by filtration and washed with water.

C) A mixture of 0.01 mole of 2-chloro-3-phenacylnaphth[1,2-d]imidazole or 2-chloro-3-(p-methylphenacyl)naphth[1,2-d]imidazole and 0.025 mole of aniline was heated for 10-15 min at 180-185° and cooled. The precipitate was washed with water and methanol to give 67 and 70%, respectively, of XV and XXXI.

Compounds I-LX were colorless, crystalline, basic substances that were soluble in most organic solvents and insoluble in water. Analytically pure compounds were obtained by crystallization from aqueous dimethylformamide (I-III, X, XIX-XXII, XXXI-XXXV, XLIV, XLVI-LIII, LV-LX), aqueous ethanol (IV-IX, XI-XIII, XVIII, XXIII-XXVII, XXXVI-XLIII), aqueous acetone (XII), aqueous dioxane (XIV, XV), and ethanol (XVI, XVII, LIV).

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