INVESTIGATIONS IN THE IMIDAZOLE SERIES

LXIV. SYNTHESIS OF IMIDAZO[1,2-*a*]IMIDAZOLE DERIVATIVES FROM 2-HALOIMIDAZOLES

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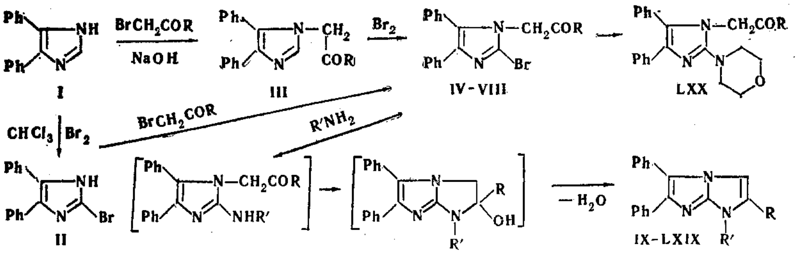
Imidazo[1,2-*a*]imidazole derivatives were synthesized by the reaction of 1-acylmethyl-2-bromo-4,5-diphenylimidazoles with ammonia and primary amines.

The synthesis of imidazo[1,2-*a*]imidazole derivatives from 2-aminoimidazoles is described in [1, 3]. In developing of our brief communication [4], it seemed of interest to make a detailed study of routes to the synthesis of imidazo[1,2-*a*]imidazole derivatives on the basis of the more accessible 2-haloimidazoles, particularly 4,5-diphenyl-2-bromoimidazole (II) [5].

1-Acetonyl-2-bromo-4,5-diphenylimidazole (IV) and 1-phenacyl-2-bromo-4,5-diphenylimidazoles (V-VII) were obtained by the reaction of II with α-bromoketones [6]. These compounds can also be synthesized by another scheme – by the reaction of 4,5-diphenylimidazoles [7] with α-bromoketones and subsequent bromination of the 1-acylmethyl-4,5-diphenylimidazoles. Thus V was obtained from I via III.

We have further investigated the reaction of IV-VIII with ammonia and primary amines of the aliphatic, alicyclic, aliphatic-aromatic, and aromatic series, including amino alcohols (aminoethanol and 2-amino-1-pentanol) and dialkylaminoalkylamines (diethylaminoethylamine), as well as with secondary amines (morpholines). It was found that the nucleophilic substitution of bromine by an amino group does not occur when the components are refluxed in alcohols (methanol, ethanol, butanol) or even in dimethylformamide. However, when IV-VIII are heated with ammonia and amines in lower alcohols (methanol and ethanol) at 165-190° (in a sealed tube or in an autoclave), simultaneous dehydration of the intermediate 1-acylmethyl-2-amino(alkylamino, arylamino)-4,5-diphenylimidazoles occurs along with replacement of the bromine atom by an amine residue. The corresponding imidazo[1,2-*a*]imidazole derivatives (IX-LXIX, Table 1) are formed. This reaction can be carried out by refluxing in excess high-boiling amines. Thus XII, XIII, XXXI, and XXXII were obtained from the reaction of IV and V with aniline and m-toluidine.

It should be noted that the reaction of V with aminoethanol at 165-170° proceeds with the formation of 1-(β-hydroxyethyl)-2,5,6-triphenylimidazoimidazole (XXVIII), while the alcohols are dehydrated to the corresponding 1-vinyl-substituted imidazo[1,2-*a*]imidazoles (XX and XXXVIII) at 180-190°.



R = Alk, Ar; R' = H, Alk, Ar

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The structures of the two-ring compounds were established from the absence of bands of the stretching vibrations of the CO and NH groups in the IR spectra. As regards the mechanism of the closing of the imidazole ring during the reaction of IV-VIII with ammonia and amines, it can be assumed that the initially formed 1-acylmethyl-2-aminoimidazoles, in analogy with 1-phenacyl-2-aryliminopyridines [8], are then converted, by means of migration of a proton from the amino (alkylamino, arylamino) group to the oxygen atom of the carbonyl group, to 2-hydroxy derivatives of imidazo[1,2-*a*]imidazoline, the dehydration of which leads to the imidazo[1,2-*a*]imidazole derivatives.

The reaction of 1-acylmethyl-2-haloimidazoles with secondary amines stops naturally at the stage involving substitution of halogen by an amine residue. Thus 1-phenacyl-2-morpholino-4,5-diphenylimidazole (LXX) was obtained by heating V with morpholine.

EXPERIMENTAL

4,5-Diphenylimidazole (I) [7] and 2-Bromo-4,5-diphenylimidazole (II) [5]. These compounds were prepared by known methods.

1-Phenacyl-4,5-diphenylimidazole (III). A solution of 6.6 g (0.03 mole) of I, 6 g (0.03 mole) of phenacyl bromide, and 1.2 g (0.03 mole) of NaOH in 150 ml of ethanol was heated at 60° with stirring for 10 h. It was then cooled and poured into water. The precipitate was removed by filtration and washed with ether to give 6 g (59%) of III with mp 167-168° (aqueous dioxane). Found %: C 82.0; H 5.2; N 8.8. $C_{23}H_{18}N_2O$. Calculated %: C 81.6; H 5.4; N 8.3.

1-Acetonyl-2-bromo-4,5-diphenylimidazole (IX). This compound was obtained in 62% yield by the reaction of II with bromoacetone under the conditions of the synthesis of the other 1-acylmethyl-2-bromo-4,5-diphenylimidazoles [6] and melted at 168-169° (aqueous methanol). IR spectrum: 1730 cm^{-1} (CO). Found %: C 60.8; H 4.2; Br 22.5; N 8.1. $C_{18}H_{15}BrN_2O$. Calculated %: C 60.9; H 4.3; Br 22.5; N 7.9.

1-Phenacyl-2-bromo-4,5-diphenylimidazole (V). Bromine [4.8 g (0.03 mole)] was added dropwise with stirring in the course of 30 min to a solution of 10.1 g (0.03 mole) of III in 100 ml of anhydrous $CHCl_3$, and the mixture was stirred for 3-4 h. The solvent was removed by vacuum distillation, the residue was dissolved in ethanol, and the solution was poured into water. The resulting mixture was neutralized with ammonium hydroxide, and the precipitate was removed by filtration and washed with ether to give 8.3 g (66%) of a product with mp 180-181° (methanol) (mp 180-181° [3]).

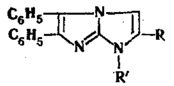
The p-methyl-, p-methoxy-, and p-bromo-substituted V (VI-VIII) were prepared as described in [6].

Imidazo[1,2-*a*]imidazole Derivatives (IX-LXIX, Table 1). A) A solution of 0.01 mole of IV-VIII and 0.02 mole of primary amine in 50 ml of methanol or ethanol was heated in an autoclave (100-150 ml) at 170-180° for 8-10 h and cooled. The solid was removed by filtration and washed with water and ether. The mother liquors were evaporated to a small volume to isolate an additional amount of compound. In the isolation of XI, XVIII, XXX, XXXVII-XLV, LII, and LVII-LXV the reaction mass at the end of the process was poured into water, and the precipitate was removed by filtration and washed with water and ether. In the synthesis of XVIII, XIX, XXI, XXXVII, and XXXIX, ammonia, methylamine, and ethylamine were used in small excess as 15-25% alcohol solutions (20-25 ml per 0.01 mole of IV-VIII), and the reaction was carried out at 180-190°. The compounds XIII-XVII, XXVIII, and XXIX were obtained at 165-170°, while XX and XXXVIII were obtained with aminoethanol at 180-190°.

B) A mixture of 0.01 mole of IV or V and 10 ml of amine (aniline, m-toluidine) was heated for 6-8 h at the boiling point of the amine, the excess was removed by vacuum distillation, and the residue was washed with ether, water, and ether to give XII, XIII, XXXI, and XXXII in yields of 52, 49, 72, and 60%, respectively. Samples of these products did not depress the melting points of the samples obtained by method A.

The imidazo[1,2-*a*]imidazole derivatives (IX-LXIX) were colorless or pale-yellow crystalline substances that were soluble in most organic solvents and insoluble in water. Alcohol or aqueous dimethyl formamide solutions of compounds with an aryl radical in the 1-position of the imidazoimidazole ring have a blue-violet fluorescence. For analysis, the compounds were purified by crystallization from aqueous methanol (IX, XII, XV, XIX-XXI, XXIII, XXVI, XXIX-XXXI, XXXVII-XXXIX, XLI, XLIII-XLV, LIII-LV, and LVII), aqueous acetone (X, XI, XIII, XXII, XXIV, XXVIII, XL, XLII, and LII), aqueous dimethylformamide (XIV, XVII, XVIII, XXXVI, L, LI, LVIII, LX, LXII, LXVIII, and LXIX), methanol (XVI, XXVI, XXXII-XXXV, XLVI-XLVIII, LVI, LVII, LXI, LXIV, LXVI, and LXVII), aqueous dioxane (XXVII, LXV), or acetone (LXVIII). IR spectrum of XXVIII: 3200 cm^{-1} (OH).

TABLE 1. Imidazo[1,2-*a*]imidazole Derivatives



Compound	R′	R	mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
					C	H	N	C	H	N	
IX	*i*-C_4H_9	CH_3	126—127	$C_{22}H_{23}N_3$	79,8	6,7	12,4	80,2	7,0	12,8	61
X	C_6H_{11}[a]	CH_3	177—178	$C_{24}H_{25}N_3$	81,4	7,3	12,3	81,1	7,1	11,8	56
XI	$C_6H_5CH_2$	CH_3	150—151	$C_{25}H_{21}N_3$	82,3	5,7	11,5	82,6	5,8	11,6	83
XII	C_6H_5	CH_3	187—188	$C_{24}H_{19}N_3$	82,1	5,6	11,9	82,5	5,5	12,0	57
XIII	*m*-$CH_3C_6H_4$	CH_3	167—168	$C_{25}H_{21}N_3$	82,5	6,2	11,8	82,6	5,8	11,6	55
XIV	*p*-$CH_3C_6H_4$	CH_3	203—204	$C_{25}H_{21}N_3$	—	—	11,4	—	—	11,6	60
XV	*p*-$CH_3OC_6H_4$	CH_3	183—184	$C_{25}H_{21}N_3O$	78,9	5,7	10,8	79,1	5,6	11,1	66
XVI	*p*-$C_2H_5OC_6H_4$	CH_3	171—172	$C_{26}H_{23}N_3O$	79,4	5.9	11,0	79,4	5,9	10,7	56
XVII	*m*-ClC_6H_4	CH_3	183—184	$C_{24}H_{18}ClN_3$[b]	75,2	4,6	10,9	75,1	4,7	10,9	75
XVIII	H	C_6H_5	239—240	$C_{23}H_{17}N_3$	81,9	5,3	12,2	82,4	5,1	12,5	90
XIX	CH_3	C_6H_5	157—158	$C_{24}H_{19}N_3$	82,3	5,5	12,0	82,5	5,5	12,0	92
XX	$CH{=}CH_2$	C_6H_5	200—202	$C_{25}H_{19}N_3$	82,8	5,8	11,4	83,1	5,3	11,6	53
XXI	C_2H_5	C_6H_5	90—91	$C_{25}H_{21}N_3$	82,7	5,8	11,7	82,6	5,5	12,0	76
XXII	C_3H_7	C_6H_5	151—152	$C_{26}H_{23}N_3$	82,3	5,9	11,2	82,7	6,1	11,1	81
XXIII	C_4H_9	C_6H_5	157—158	$C_{27}H_{25}N_3$	82,4	6,3	10,8	82,8	6,4	10,7	82
XXIV	*i*-C_4H_9	C_6H_5	140—141	$C_{27}H_{25}N_3 \cdot 1/2\ H_2O$	81,2	6,4	10,7	81,0	6,5	10,5	92
XXV	*n*-C_6H_{13}	C_6H_5	127—129	$C_{29}H_{29}N_3$	83,2	6,6	9,9	83,0	6,9	10,1	68
XXVI	C_6H_{11}[a]	C_6H_5	212—213	$C_{29}H_{27}N_3 \cdot 1/2\ H_2O$	82,2	6,5	10,2	81,8	6,6	9,8	77
XXVII	$C_6H_5CH_2$	C_6H_5	212—213	$C_{30}H_{23}N_3$	84,7	5,2	9,5	84,7	5,4	9,9	56
XXVIII	CH_2CH_2OH	C_6H_5	195—196	$C_{25}H_{21}N_3O$	79,2	5,5	11,3	79,1	5,6	11,1	53
XXIX	$CH(CH_3)(CH_2)_3OH$	C_6H_5	95—97	$C_{28}H_{27}N_3 \cdot 1/2\ H_2O$	—	—	9,4	—	—	9,8	57
XXX	$C_2H_4N(C_2H_5)_2$	C_6H_5	40—42	$C_{29}H_{30}N_4$[c]	—	—	12,8	—	—	12,9	69
XXXI	C_6H_5	C_6H_5	252—253[d]	$C_{29}H_{21}N_3$	—	—	—	—	—	—	95
XXXII	*p*-$CH_3C_6H_4$	C_6H_5	225—227	$C_{30}H_{23}N_3$	84,3	5,3	10,1	84,7	5,4	9,9	70
XXXIII	*m*-$CH_3C_6H_4$	C_6H_5	215—216	$C_{30}H_{23}N_3$	84,6	5,4	9,7	84,7	5,4	9,9	82
XXXIV	*p*-HOC_6H_4	C_6H_5	295—297	$C_{29}H_{21}N_3O \cdot 1/2\ H_2O$	79,7	5,5	9,8	79,8	5,1	9,6	83
XXXV	*p*-$CH_3OC_6H_4$	C_6H_5	172—173	$C_{30}H_{23}N_3O$	81,9	5,3	9,8	81,6	5,2	9,5	88
XXXVI	*p*-$C_2H_5OC_6H_4$	C_6H_5	249—250	$C_{31}H_{25}N_3O$	81,8	5,4	9,3	81,7	5,5	9,2	89
XXXVII	CH_3	*p*-$CH_3C_6H_4$	179—180	$C_{25}H_{21}N_3$	82,2	6,0	11,4	82,6	5,8	11,6	92

XXXVIII	CH=CH$_2$	p-CH$_3$C$_6$H$_4$	69—70	$C_{26}H_{21}N_3$	83,5	5,3	11,4	83,2	5,6	11,2	76
XXXIX	C$_2$H$_5$	p-CH$_3$C$_6$H$_4$	220—221	$C_{26}H_{23}N_3 \cdot HBr \cdot 2H_2O$	63,1	5,7	8,9	63,2	5,7	8,5	70
XL	C$_3$H$_7$	p-CH$_3$C$_6$H$_4$	161—162	$C_{27}H_{25}N_3$	83,1	6,4	10,7	82,8	6,4	10,7	61
XLI	C$_4$H$_9$	p-CH$_3$C$_6$H$_4$	130—131	$C_{28}H_{27}N_3$	82,8	6,8	10,4	82,9	6,7	10,4	84
XLII	i-C$_4$H$_9$	p-CH$_3$C$_6$H$_4$	169—170	$C_{28}H_{27}N_3$	82,5	6,5	10,3	82,9	6,7	10,4	49
XLIII	n-C$_6$H$_{13}$	p-CH$_3$C$_6$H$_4$	111—112	$C_{30}H_{31}N_3$	82,8	7,4	9,8	83,1	7,2	9,7	69
XLIV	C$_6$H$_5$CH$_2$	p-CH$_3$C$_6$H$_4$	147—149	$C_{31}H_{25}N_3$	85,1	5,8	9,9	84,7	5,7	9,6	78
XLV	C$_2$H$_4$N(C$_2$H$_5$)$_2$	p-CH$_3$C$_6$H$_4$	110—111	$C_{30}H_{32}N_4$	80,1	7,3	12,6	80,3	7,2	12,5	76
XLVI	C$_6$H$_5$	p-CH$_3$C$_6$H$_4$	230—231	$C_{30}H_{23}N_3$	84,8	5,4	9,7	84,7	5,4	9,9	47
XLVII	m-CH$_3$C$_6$H$_4$	p-CH$_3$C$_6$H$_4$	189—190	$C_{31}H_{25}N_3$	84,3	5,8	9,3	84,7	5,7	9,6	73
XLVIII	p-CH$_3$C$_6$H$_4$	p-CH$_3$C$_6$H$_4$	219—220	$C_{31}H_{25}N_3$	84,2	5,6	9,2	84,7	5,7	9,6	55
XLIX	p-HOC$_6$H$_4$	p-CH$_3$C$_6$H$_4$	295—297	$C_{30}H_{23}N_3O$	81,1	5,2	9,5	81,6	5,2	9,5	68
L	p-CH$_3$OC$_6$H$_4$	p-CH$_3$C$_6$H$_4$	224—225	$C_{31}H_{25}N_3O$	81,2	5,5	9,4	81,7	5,5	9,2	70
LI	p-C$_2$H$_5$OC$_6$H$_4$	p-CH$_3$C$_6$H$_4$	213—214	$C_{32}H_{27}N_3O$	81,6	5,9	8,7	81,8	5,8	8,9	64
LII	CH=CH$_2$	p-CH$_3$OC$_6$H$_4$	141—142	$C_{26}H_{21}N_3O$	—	—	11,0	—	—	10,7	66
LIII	C$_4$H$_9$	p-CH$_3$OC$_6$H$_4$	143—144	$C_{28}H_{27}N_3O$	—	—	10,2	—	—	10,0	67
LIV	i-C$_4$H$_9$	p-CH$_3$OC$_6$H$_4$	181—182	$C_{28}H_{27}N_3O$	79,4	6,3	10,0	79,8	6,5	10,0	57
LV	n-C$_6$H$_{13}$	p-CH$_3$OC$_6$H$_4$	132—133	$C_{30}H_{31}N_3O$	79,8	7,1	9,1	80,1	7,0	9,3	67
LVI	C$_6$H$_5$CH$_2$	p-CH$_3$OC$_6$H$_4$	142—143	$C_{31}H_{25}N_3O$	82,1	5,8	9,3	81,7	5,5	9,2	79
LVII	C$_2$H$_4$N(C$_2$H$_5$)$_2$	p-CH$_3$OC$_6$H$_4$	134—135	$C_{30}H_{32}N_4O$	77,2	7,0	11,8	77,5	6,9	12,1	95
LVIII	C$_6$H$_5$	p-CH$_3$OC$_6$H$_4$	222—223	$C_{30}H_{23}N_3O \cdot H_2O$	—	—	8,6	—	—	9,1	81
LIX	m-CH$_3$C$_6$H$_4$	p-CH$_3$OC$_6$H$_4$	196—197	$C_{31}H_{25}N_3O$	81,4	5,8	9.2	81,7	5,5	9,2	66
LX	p-CH$_3$C$_6$H$_4$	p-CH$_3$OC$_6$H$_4$	250—251	$C_{31}H_{25}N_3O$	81,5	5,6	9,0	81,7	5,5	9,2	88
LXI	p-CH$_3$OC$_6$H$_4$	p-CH$_3$OC$_6$H$_4$	231—232	$C_{31}H_{25}N_3O_2$	78,6	5,4	8,7	79,0	5,3	8,9	64
LXII	p-C$_2$H$_5$OC$_6$H$_4$	p-CH$_3$OC$_6$H$_4$	219—220	$C_{32}H_{27}N_3O_2$	78,8	5,8	8,8	79,1	5,6	8,6	83
LXIII	i-C$_4$H$_9$	p-BrC$_6$H$_4$	227—229	$C_{27}H_{24}BrN_3$ [e]	69,0	4,9	8,3	68,9	5,1	8,9	72
LXIV	n-C$_6$H$_{13}$	p-BrC$_6$H$_4$	139—140	$C_{29}H_{28}BrN_3 \cdot H_2O$	67,2	5,8	8,3	67,4	5,9	8,1	59
LXV	C$_6$H$_5$CH$_2$	p-BrC$_6$H$_4$	184—185	$C_{30}H_{22}BrN_3 \cdot H_2O$ [f]	69,6	4,5	8,2	69,0	4,6	8,0	70
LXVI	C$_6$H$_5$	p-BrC$_6$H$_4$	224—225	$C_{29}H_{20}BrN_3 \cdot H_2O$ [f]	68,3	4,3	8,8	68,5	4,4	8,2	49
LXVII	p-CH$_3$C$_6$H$_4$	p-BrC$_6$H$_4$	255—256	$C_{30}H_{22}BrN_3$ [g]	71,2	4,6	8,5	71,4	4,4	8,3	60
LXVIII	p-CH$_3$OC$_6$H$_4$	p-BrC$_6$H$_4$	247—249	$C_{30}H_{22}BrN_3O$ [h]	68,9	4,6	8,2	69,2	4,3	8,1	54
LXIX	p-C$_2$H$_5$OC$_6$H$_4$	p-BrC$_6$H$_4$	243—245	$C_{31}H_{24}BrN_3O$ [i]	69,6	4,4	7,7	69,7	4,5	7,9	56

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[a] C_6H_{11} is cyclohexyl.

[b] Found %: Cl 9.6. Calculated %: Cl 9.2.

[c] Hydrochloride with mp 114-115° (by precipitation from methanol solution by the addition of ether). Found %: Cl 12.9. $C_{29}H_{30}N_3 \cdot 2HCl \cdot 3H_2O$. Calculated %: Cl 12.6.

[d] mp 252-253° [4].

[e] Found %: Br 16.6. Calculated %: Br 17.0.

[f] Found %: Br 15.6. Calculated %: Br 15.7.

[g] Found %: Br 16.1. Calculated %: Br 15.8.

[h] Found %: Br 15.4. Calculated %: Br 15.4.

[i] Found %: Br 14.9. Calculated %: Br 14.9.

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1-Phenacyl-2-morpholino-4,5-diphenylimidazole (LXX). A solution of 4.2 g (0.01 mole) of V and 2.2 g (0.025 mole) of morpholine in 50 ml of ethanol was heated in a 150-ml autoclave at 170° for 10 h, cooled, and poured into water. The precipitate was removed by filtration and washed with ether to give 3.6 g (85%) of a product with mp 153-154° (aqueous dioxane). Found %: C 75.1; H 5.7; N 9.8. $C_{27}H_{25}N_3O_2 \cdot \frac{1}{2}H_2O$. Calculated %: C 75.0; H 6.1; N 9.7.

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