INVESTIGATIONS IN THE IMIDAZOLE SERIES

LXVI.* SYNTHESIS OF 2,3-DIHYDROIMIDAZO[1,2-*a*]IMIDAZOLE DERIVATIVES

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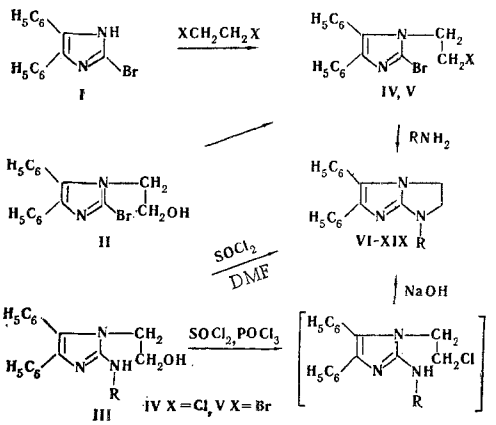
2,3-Dihydroimidazo[1,2-*a*]imidazole derivatives were synthesized by the cyclization of 1-(β-hydroxyalkyl)-2-aminoimidazoles under the influence of thionyl chloride or phosphorus oxychloride or by the reaction of 2-haloimidazoles with 1,2-dihaloethanes and subsequent treatment of the 1-(β-haloethyl)-2-haloimidazoles with ammonia or primary amines.

The synthesis of imidazo[1,2-*a*]imidazole derivatives is described in [2,3]. As a development of a brief communication [4], we have made a detailed investigation of two paths for the synthesis of previously unreported 2,3-dihydroimidazo[1,2-*a*]imidazole derivatives (VI-XIX). Thus treatment of the previously synthesized 1-(β-hydroxyethyl)-2-amino-(alkylamino, arylamino)-4,5-diphenylimidazoles (III) [1] with thionyl chloride or phosphorus oxychloride and subsequent cyclization of the intermediate 1-(β-chloroethyl)-2-amino(arylamino)-4,5-diphenylimidazoles under the influence of NaOH in ethanol gave VI, X, and XII (Table 1). This reaction can be carried out in one step by heating III with $SOCl_2$ in dimethylformamide (DMF). Compounds X and XIV were synthesized in this way.

A simpler method for the preparation of VI-XIX is the reaction of 1-(β-haloethyl)-2-bromo-4,5-diphenylimidazoles (IV and V) with ammonia or primary amines. The starting IV and V are readily obtained by the reaction of 2-bromo-4,5-diphenylimidazole (I) [5] with 1,2-dichloro(dibromo)ethanes in aqueous DMF in the presence of NaOH or by treatment of 1-(β-hydroxyethyl)-2-bromo-4,5-diphenylimidazole (II) [1] with thionyl chloride or phosphorus tribromide.

EXPERIMENTAL

1-(β-Chloroethyl)-2-bromo-4,5-diphenylimidazole (IV). A) A mixture of 3.4 g (0.01 mole) of II in 50 ml of $SOCl_2$ was refluxed for 3 h, the excess $SOCl_2$ was removed by vacuum distillation, and the residue



*See [1] for communication LXV.

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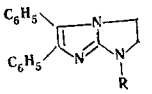
TABLE 1. 2,3-Dihydromidazo[1,2-*a*]imidazole Derivatives



Comp.	R	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
VI	H	218—220	$C_{17}H_{15}N_3 \cdot C_6H_3N_3O_7$	—	—	16,9	—	—	17,1	43—61
VII	CH_3	186—187	$C_{18}H_{17}N_3 \cdot C_6H_3N_3O_7$	57,4	4,2	16,5	57,1	4,0	16,7	71
VIII	C_6H_{11}[a]	169—170	$C_{23}H_{25}N_3$	80,1	7,0	12,5	80,4	7,3	12,2	53
IX	$C_6H_5CH_2$	185—186	$C_{24}H_{21}N_3$	82,3	6,3	11,7	82,0	6,0	12,0	74
X	C_6H_5	199—200[b]	$C_{23}H_{19}N_3$	—	—	—	—	—	—	40—74
XI	*m*-$CH_3C_6H_4$	178—179	$C_{24}H_{21}N_3$	81,7	6,0	12,2	82,0	6,0	12,0	54—57
XII	*p*-$CH_3C_6H_4$	198—199	$C_{24}H_{21}N_3$	81,5	5,9	12,4	82,0	6,0	12,0	56—68
XIII	*p*-HOC_6H_4	239—240	$C_{23}H_{19}N_3O$	78,5	5,3	11,8	78,2	5,4	11,9	68
XIV	*p*-$CH_3OC_6H_4$	203—204	$C_{24}H_{21}N_3O$	78,2	6,0	11,7	78,4	5,8	11,4	46—65
XV	*p*-$C_2H_5OC_6H_4$	200—201	$C_{25}H_{23}N_3O$	78,6	5,9	11,0	78,7	6,1	11,0	46—79
XVI	*m*-ClC_6H_4	149—150	$C_{23}H_{18}ClN_3$[c]	74,0	4,8	11,6	74,3	4,9	11,3	65
XVII	*p*-ClC_6H_4	200—201	$C_{23}H_{18}ClN_3$[d]	73,9	5,0	11,1	74,3	4,9	11,3	76
XVIII	*p*-BrC_6H_4	215—216	$C_{23}H_{18}BrN_3$[e]	66,6	4,2	10,3	66,3	4,4	10,1	72
XIX	α-$C_{10}H_7$	220—222	$C_{27}H_{21}N_3$	83,9	5,8	10,9	83,7	5,5	10,8	62

[a] C_6H_{11} is cyclohexyl.
[b] mp 199-200° [4].
[c] Found %: Cl 9.4. Calculated %: Cl 9.5.
[d] Found %: Cl 9.6. Calculated %: Cl 9.5.
[e] Found %: Br 19.5. Calculated %: Br 19.2.

was decomposed with water and neutralized with $NaHCO_3$. The mixture was extracted with chloroform, the solvent was removed by vacuum distillation, and the oily residue of base IV was dissolved in 30 ml of ethanol. Hydrogen chloride was bubbled through the ethanol solution, and the precipitated hydrochloride was removed by filtration and washed with ether to give 2.8 g (70%) of a product with mp 109-110° (ethanol). Found %: C 51.6; H 3.2; Cl + Br 37.3; N 6.9. $C_{17}H_{14}BrClN_2 \cdot HCl$. Calculated %: C 51.3; H 3.7; Cl + Br 37.9; N 7.0.

B) A mixture of 30 ml of $POCl_3$, 3.4 g (0.01 mole) of II, and three drops of concentrated hydrochloric acid was refluxed for 5 h, cooled, and the excess $POCl_3$ was removed by vacuum distillation. The residue was decomposed with water and worked up as described in experiment A to give 2.2 g (55%) of IV with mp 109-110° (ethanol).

C) A solution of 1.2 g (0.03 mole) of NaOH in 20 ml of water and 40 ml of DMF was treated with 9 g (0.03 mole) of I followed by 5.9 g (0.06 mole) of 1,2-dichloroethane. The mixture was refluxed for 8 h, cooled, poured into water, and worked up as described in experiment A to give 1.8 g (45%) of the hydrochloride of IV with mp 109-110° (ethanol).

1-(β-Bromoethyl)-2-bromo-4,5-diphenylimidazole (V). A) Phosphorus tribromide [8 g (0.03 mole)] was added gradually to a solution of 3.4 g (0.01 mole) of II in 30 ml of anhydrous DMF, and the mixture was allowed to stand for 8 h at room temperature and poured into water. The mixture was neutralized with $NaHCO_3$, and the precipitate was removed by filtration and washed with water to give 2.1 g (52%) of a product with mp 147-148° (aqueous methanol) (mp 147-148° [4]).

B) A solution of 1.2 g (0.03 mole) of NaOH in 20 ml of water and 40 ml of DMF was treated with 9 g (0.03 mole) of I followed by 11.3 g (0.06 mole) of 1,2-dibromoethane. The mixture was refluxed for 8 h and worked up as described in experiment A to give 7.5 g (61%) of a product with mp 147-148° (aqueous methanol).

2,3-Dihydroimidazo[1,2-*a*]imidazole Derivatives (VI-XIX, Table 1). A) A solution of 0.01 mole of 1-(β-hydroxyethyl)-2-amino(arylamino)-4,5-diphenylimidazole (III, R = H, C_6H_4, $C_6H_4CH_3$-p) in 30 ml of $POCl_3$ or 50 ml of $SOCl_2$ was refluxed for 2-3 h. The excess $POCl_3$ or $SOCl_2$ was removed completely by vacuum distillation, and the residue was dissolved in 30-50 ml of ethanol. The solution was filtered, 15-20 ml of 40% NaOH was added, and the mixture was refluxed for 5 h and poured into water. The precipitate was removed by filtration and washed with water to give 43, 52, and 56%, respectively, of VI, X, and XII.

B) Thionyl chloride (20-25 ml) was added to a solution of 0.01 mole of 1-(β-hydroxyethyl)-2-arylamino-4,5-diphenylimidazole (III, R = C_6H_5, $C_6H_4OCH_3$-p) in 40-50 ml of anhydrous DMF, and the mixture

was heated at 50-60° for 3 h. It was then refluxed for 5-7 h, cooled, and poured gradually into water. The mixture was neutralized with $NaHCO_3$ solution, and the precipitate was removed by filtration and washed with water and ether to give 42 and 46% of X and XIV, respectively.

C) A solution of 0.01 mole of IV or V and 0.035 mole of amine in 30 ml of methanol or ethanol was heated for 8-10 h at 170-180° (in a 150 ml autoclave) and cooled. The precipitate of X-XIX was removed by filtration and washed with water and ether. Compounds VI-IX were isolated by pouring the reaction mass into water and filtering the precipitate. In the preparation of VI, ammonia was used in excess as a 15% alcohol solution (25 ml). Compound VII was obtained by using 25% aqueous methylamine (25 ml) in a mixture with 30 ml of methanol. Compounds X and XV (58 and 46%, respectively) were also obtained by refluxing V with amines in DMF (20 ml) for 8-10 h, pouring the solution into water, and removing the precipitate by filtration.

D) A mixture of 0.01 mole of IV or V and 10 ml of amine (aniline, m-toluidine) was refluxed for 8-10 h, the unchanged amine was removed by vacuum distillation, and the residue was washed with water and ether to give 40 and 54%, respectively, of X and XI.

Compounds VI-XIX were colorless substances of basic character that were soluble in most organic solvents and insoluble in water. Solutions of X-XIX in ethanol and aqueous DMF have blue-violet fluorescences. For analysis, the compounds were purified by crystallization from aqueous acetone (VI-VIII), aqueous DMF (IX-XVII, XIX), and aqueous methanol (XVIII).

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