RESEARCH IN THE IMIDAZOLE SERIES. 94.* SYNTHESIS OF DERIVATIVES OF PYRROLO[1,2-a]BENZIMIDAZOLYL-4-ACETIC ACID

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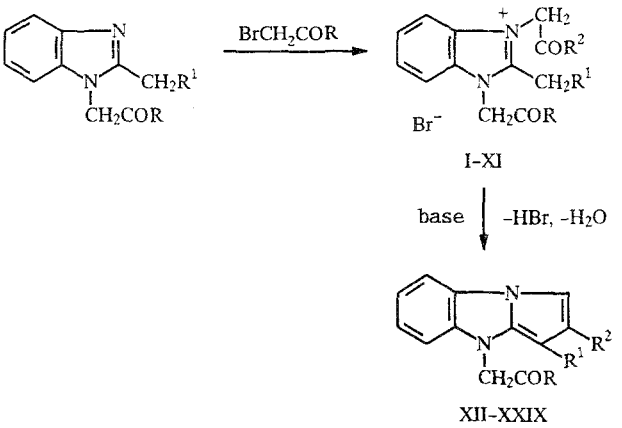
Derivatives of pyrrolo[1,2-a]benzimidazolyl-4-acetic acid have been synthesized by quaternization of 2-alkyl(aralkyl)benzimidazolyl-1-acetic acids and their esters and amides by α-bromoketones, followed by cyclization of the resulting 1,2,3-substituted benzimidazolium bromides by the action of sodium alcoholate, ammonia, amines (primary, secondary, or tertiary), or hydrazine hydrate.

We had previously reported the synthesis and certain properties of various derivatives of pyrrolo[1,2-a]benzimidazole [2-13]; however, compounds having a carboxymethyl group or its derivatives in position 4 had not yet been investigated.

With the aim of searching for biologically active substances, we carried out the synthesis of a series of 2- and 2,3-substituted pyrrolo[1,2-a]benzimidazolyl-4-acetic acids and their derivatives obtained by reactions at the carboxyl group – namely, esters, amides, and hydrazides. This work was reported briefly at a conference [4].

As starting substances we used 2-alkyl(aralkyl)benzimidazolyl-1-acetic acids and their esters and amides [1], which were quaternized by α-bromoketones. The resulting bromides of 2-alkyl(aralkyl)-3-acylmethylbenzimidazolium-1-acetic acids and their esters and amides I-XI (Table 1) were cyclized by the action of bases: sodium alcoholates, ammonia, amines (primary, secondary, or tertiary), or hydrazine hydrate. Thus, upon heating the bromide of 2-benzyl-3-phenacylbenzimidazolyl-1-acetic acid (I) with triethylamine in ethanol, we obtained 2,3-diphenyl-pyrrolo[1,2-a]benzimidazolyl-4-acetic acid (XII, Table 2). This same acid is readily formed by hydrolysis of its ethyl ester XXI in water in the presence of sodium bicarbonate.



In the case of the quaternary salts of the methyl and ethyl esters of benzimidazolyl-1-acetic acids II-X, in order to avoid hydrolysis of the ester groups during the closure of the pyrrole ring, the reaction was performed in the corresponding anhydrous

*For Communication 93, see [1].

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TABLE 1. 1,3-Disubstituted 2-Alkyl(aralkyl)benzimidazolium Bromides I-XI

Compound	R	R^1	R^2	Empirical formula	mp, °C	Yield, %
I	OH	Ph	Ph	$C_{24}H_{21}BrN_2O_3$	175...176	62
II	OMe	H	Me	$C_{14}H_{17}BrN_2O_3$	230...232	84
III	OMe	H	Ph	$C_{19}H_{19}BrN_2O_3$	204...206	89
IV	OMe	H	C_6H_4Me-*p*	$C_{20}H_{21}BrN_2O_3$	216...218	90
V	OMe	H	C_6H_4OMe-*p*	$C_{20}H_{21}BrN_2O_4$	214...215	84
VI	OMe	H	C_6H_4Br-*p*	$C_{19}H_{18}Br_2N_2O_3$	210...212	56
VII	OMe	H	$C_6H_4NO_2$-*p*	$C_{19}H_{18}BrN_3O_5$	227...228	94
VIII	OEt	H	Ph	$C_{20}H_{21}BrN_2O_3$	214...216	86
IX	OEt	Me	Ph	$C_{21}H_{23}BrN_2O_3$	234...235	58
X	OEt	Ph	Ph	$C_{26}H_{25}BrN_2O_3$	211...213	55
XI	NHBu	H	Ph	$C_{22}H_{26}BrN_3O_2$	216...217	95

TABLE 2. Derivatives of Pyrrolo[1,2-a]benzimidazolyl-4-acetic Acid

Compound	R	R^1	R^2	Empirical formula	mp, °C	Yield, %
XII	OH	Ph	Ph	$C_{24}H_{18}N_2O_2 \cdot H_2O$	156...157	87
XIII	OMe	H	Me	$C_{14}H_{14}N_2O_2$	103...105 (decomp.)	70
XIIIa	OMe	H	Ph	$C_{14}H_{14}N_2O_2 \cdot HCl$	185...186	
XIV	OMe	H	Ph	$C_{19}H_{16}N_2O_2$	130...132 (decomp.)	45
XV	OMe	H	C_6H_4Me-*p*	$C_{20}H_{18}N_2O_2$	105...107	60
XVI	OMe	H	C_6H_4OMe-*p*	$C_{20}H_{18}N_2O_3$	146..148	70
XVII	OMe	H	C_6H_4Br-*p*	$C_{19}H_{15}BrN_2O_2$	147...148	74
XVIII	OMe	H	$C_6H_4NO_2$-*p*	$C_{19}H_{15}N_3O_4$	195...196	73
XIX	OEt	H	Ph	$C_{20}H_{18}N_2O_2$	113...115	44
XIXa	OEt	H	Ph	$C_{20}H_{18}N_2O_2 \cdot HCl \cdot H_2O$	215...217	
XX	OEt	Me	Ph	$C_{21}H_{20}N_2O_2$	94...95	56
XXI	OEt	Ph	Ph	$C_{26}H_{22}N_2O_2 \cdot HCl$	241...242	42
XXII	NH_2	H	Ph	$C_{18}H_{15}N_3O$	230...231	75
XXIII	NH_2	Me	Ph	$C_{19}H_{17}N_3O$	220...222	70
XXIV	NHBu	H	Ph	$C_{22}H_{23}N_3O$	200...201	84
XXV	$NHCH_2CH_2OH$	H	Ph	$C_{20}H_{19}N_3O_2$	204...206 (decomp.)	51
XXVI	$NH(CH_2)_3OH$	H	Ph	$C_{21}H_{21}N_3O_2$	195...196	85
XXVII	$NH(CH_2)_2NEt_2$	H	Ph	$C_{24}H_{28}N_4O$	139...140	67
XXVIII	N-Cyclobutyl	H	Ph	$C_{22}H_{21}N_3O$	178...180 (decomp.)	54
XXIX	$NHNH_2$	H	Ph	$C_{18}H_{16}N_4O$	228...230	46

alcohol in the presence of equimolar quantities of sodium alcoholate. This was the technique used in synthesizing the esters of pyrrolo[1,2-a]benzimidazolyl-4-acetic acids XIII-XXI (see Table 2).

The amides of pyrrolo[1,2-a]benzimidazolyl-4-acetic acid XXII and XXIII were obtained by two methods: by cyclization of bromides of the esters of 2-methyl(ethyl)-3-phenacylbenzimidazolyl-1-acetic acids VIII and IX in an aqueous ammonia solution, and by aminolysis of the esters of pyrrolo[1,2-a]benzimidazolyl-4-acetic acids XIV and XX in an alcoholic solution of ammonia.

For the synthesis of N-substituted amides of pyrrolo[1,2-a]benzimidazolyl-4-acetic acids XXIV-XXVIII, three methods were used. In the first method, quaternary salts of N-substituted amides of benzimidazolyl-1-acetic acid in a lower alcohol were cyclized in the presence of sodium alcoholate. Thus, from the bromide of the butylamide of 2-methyl-3-phenacylbenzimidazolyl-1-acetic acid (XI) and sodium methylate in methanol, we obtained the butylamide of 2-phenylpyrrolo[1,2-a]benzimidazolyl-4-acetic acid (XXIV).

In the second method, we used the more readily available bromides of esters of 2,3-disubstituted benzimidazolyl-1-acetic acid; when these are heated with primary or secondary amines, not only is the pyrrole ring closed, but this is followed

by amination of the ester group. Thus, from the bromide VIII together with either n-butylamine, aminoethanol, 3-aminopropanol, diethylaminoethylamine, or cyclobutylamine, we synthesized N-substituted amides of 2-phenylpyrrolo[1,2-a]benzimidazolyl-4-acetic acid XXIV-XXVIII.

The third method of obtaining N-substituted amides of pyrrolo[1,2-a]benzimidazolyl-4-acetic acid consists of reacting the esters of the corresponding tricyclic acids with amines in alcohol, with heating. Thus, from the ethyl ester of 2-phenylpyrrolo[1,2-a]benzimidazolyl-4-acetic acid (XIX) and n-butylamine, we synthesized the amide XXIV. All of these are convenient preparative methods.

The hydrazide of 2-phenylpyrrolo[1,2-a]benzimidazolyl-4-acetic acid (XXIX) was synthesized by two methods: by treatment, with hydrazine hydrate, of the bromide of the ethyl ester of 2-methyl-3-phenacylbenzimidazolyl-1-acetic acid (VIII) and the methyl ester of 2-phenylpyrrolobenzimidazolyl-4-acetic acid (XIV).

In the IR spectra of the 1,3-disubstituted 2-alkyl(aralkyl)benzimidazolium bromides III-X, distinct bands are observed corresponding to stretching vibrations of the CO group in the 1685-1700 cm^{-1} region, and of the COOAlk group in the 1740-1765 cm^{-1} region.

In the IR spectra of the tricyclic esters XIII-XX, the absorption bands of the ester group occur in the same region (1730-1760 cm^{-1}), whereas the bands for the amides and hydrazides of the corresponding acids XXII-XXIX are shifted to 1660-1670 cm^{-1}. For the amides and hydrazides, we also observe an absorption band of the NH group in the 3300-3420 cm^{-1} region.

EXPERIMENTAL

The characteristics of the synthesized compounds are listed in Tables 1 and 2.

The results of elemental analyses of compounds I-XXIX for C, H, and N were in agreement with the calculated values.

The IR spectra of the compounds were taken in a UR-10 instrument, in white mineral oil. The TLC of the compounds was performed on Silufol UV-254 plates, developed by iodine vapor.

1-Carboxymethyl(carbalkoxymethyl)-2-alkyl(aralkyl)-3-acylmethylbenzimidazolium Bromides I-XI. To a solution of 0.01 mole of 2-alkyl(aralkyl)benzimidazolyl-1-acetic acid, or its ester, amide, or hydrazide, in 15-20 ml of acetone, 0.01 mole of an α-bromoketone was added. The mixture was refluxed 5 h (2 h for compound XI) and then cooled; the precipitate was filtered off, washed with acetone, and dried. For compound I — refluxing in methanol for 8 h; after removal of the solvent, the product was washed with ether. For analysis, the compounds were purified by crystallization from methanol (II-VII) or ethanol (VIII-XI), or by precipitation by ether from acetone (I).

2,3-Diphenylpyrrolo[1,2-a]benzimidazolyl-4-acetic Acid (XII). A. A solution of 1.94 g (0.005 mole) of compound I and 0.52 g (0.005 mole) of triethylamine in 10 ml of ethanol was refluxed 2 h, cooled, and poured into water (40 ml); the precipitate was filtered off, washed with water, and dried. Yield 1.0 g (69%).

B. A solution of 1.97 g of compound XXI in 20 ml of a saturated sodium bicarbonate solution was refluxed 3 h, filtered, cooled, and acidified with acetic acid to an acid reaction; the precipitate was filtered off, washed with water, and dried. Yield 1.60 g (87%). A test on mixed samples obtained by methods A and B did not give any melting point depression.

Esters of Pyrrolo[1,2-a]benzimidazolyl-4-acetic Acid (XIII-XXI). To a solution of 0.01 mole of compounds II-X (see Table 1) in 40-50 ml of anhydrous methanol (for the methyl esters) or anhydrous ethanol (for the ethyl esters), a solution of 0.01 mole of sodium methylate or ethylate was added. The mixture was refluxed 2-3 h, cooled, and poured into water; the precipitate was filtered off, washed with water, and dried.

Amides of pyrrolo[1,2-a]benzimidazolyl-4-acetic Acid (XXII, XXIII). A. A mixture of 2.08 g of compound VIII and 30 ml of a 25% aqueous ammonia solution was refluxed 1 h and then cooled; the precipitate was filtered off, washed with water, and dried. Yield of amide XXII 0.9 g. Analogously, from compound IX, obtained the amide XXIII upon heating for 5 h.

B. A solution of 0.1 mole of the ester XIV or XX in 50 ml of a 12% alcoholic ammonia solution was refluxed 3 h; the solvent was driven off down to a small volume; the remaining liquid was cooled; and the precipitate was filtered off, washed with alcohol, and dried. Yields of XXII and XXIII 75% and 70%, respectively. A test on mixed samples obtained by methods A and B did not indicate any melting point depression.

Butylamide of 2-phenylpyrrolo[1,2-a]benzimidazolyl-4-acetic acid (XXIV). A. A solution of 2.22 g (0.005 mole) of compound XI and 0.27 g (0.005 mole) of sodium methylate in 20 ml of anhydrous methanol was refluxed 1 h and then cooled; the precipitate was filtered off, washed with water, and dried. Yield of compound XXIV 1.45 g (84%).

B. A solution of 4.17 g of VIII and 10 ml of n-butylamine in 40 ml of ethanol was refluxed 2 h and then cooled; the precipitate was filtered off, washed with alcohol, and dried. Yield of compound XXIV 2.2 g (64%).

C. A solution of 3.18 g of compound XIX and 5 ml of n-butylamine in 20 ml of ethanol was refluxed 3.5 h and then treated as described above. Yield of compound XXIV 2.3 g (62%). A mixed melting point test on samples of XXIV obtained by methods A, B, and C did not show any melting point depression.

N-Substituted Amides of 2-phenylpyrrolo[1,2-a]benzimidazolyl-4-acetic Acid (XXV-XXVIII). Obtained from compound VIII in the same manner as for compound XXIV (method B), with the reaction solution refluxed for 5 h (XXV), 3 h (XXVI), or 4 h (XXVII, XXVIII).

Hydrazide of 2-phenylpyrrolo[1,2-a]benzimidazolyl-4-acetic Acid (XXIX). A. A 2.08-g quantity of compound VIII in 20 ml of 25% hydrazine hydrate was refluxed 4 h and then cooled; the residue was filtered off, washed with water, and dried. Yield of compound XXIX 0.75 g (46%).

B. A mixture of 1.52 g of compound XIV and 3 ml of 25% hydrazine hydrate in 15 ml of methanol was refluxed 3 h and then cooled; the precipitate was filtered off and dried. Yield of compound XXIX 1.2 g (73%). A mixed melting point test on samples of XXIX obtained by methods A and B did not indicate any melting point depression.

For analysis, compounds XII-XXIX (see Table 2) were purified by crystallization from ethanol (XII, XIX, XIXa, XX, XXI, XXIV, XXVI), crystallization from methanol (XIII, XIV, XVI, XXV, XXVII), precipitation by ether from methanol (XIIIa) or from a methanol–DMF mixture (XV, XVII, XVIII, XXII), or from an ethanol–DMF mixture (XXIII, XXVIII, XXIX).

Values of R_f: XIII 0.77 (benzene); XIV 0.57 (ether); XV 0.53 (ether); XVI 0.54 (benzene); XVII 0.59 (10:1 ether–benzene); XVIII 0.80 (ether); XIX 0.49 (10:1 ether–benzene); XXIV 0.32 (methanol).

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