STUDIES IN THE IMIDAZOLE SERIES

XXXVIII. The Arylpyrrolo[1, 2-a]imidazoles*

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By quaternization of 1-alkyl(aryl, aralkyl)-2-methyl-4, 5-diarylimidazoles with α-bromo ketones and by subsequent cyclization of the quaternary salts of imidazole, a number of arylpyrrolo[1, 2-a]imidazoles were obtained. A study was made of the effect of different bases on the process of cyclization and the yield of pyrroloimidazole derivatives. The structure was established of certain intermediate products of the reaction involving the closure of the pyrrole ring.

In the course of previous investigations [1, 2] we synthesized a number of arylpyrrolo[1, 2-a]imidazoles. By means of the reaction between 1, 2-disubstituted imidazoles (XXXVI–XLII) and α-bromoketones, the bromides of 1-alkyl(aryl, aralkyl)-2-alkyl-3-β-ketoalkyl(aralkyl)imidazole (I–XIII), Table 1) were obtained. Heating of the bromides of compounds III, VI, VIII, X, XI, and XIII in an aqueous solution of sodium bicarbonate led to the formation of the arylpyrroloimidazoles of compounds XVII, XXII, XXVI, XXVIII, XXIX, and XXXII (Table 2), with satisfactory yields. However, under these conditions, the reaction required prolonged boiling (6 hr) and large volumes of solvent because of the poor solubility of the quaternary salts of imidazole in water (1 g in 200–300 ml). The bromide of compound VII did not undergo cyclization under the above-mentioned conditions.

By conducting the cyclization reaction of the quaternary salts of imidazole in ethanol in the presence of a stronger base, sodium ethoxide, it was possible to reduce the reaction volumes by a factor of ten and to shorten the duration of the process to 15–60 min. Thus, the pyrroloimidazoles of compounds XVIII, XIX, XX, XXI, XXIII, XXIV, XXV, XXVII, XXX, and XXXI (Table 2) were obtained.

In the case of the bromide of 1-ethyl-2-methyl-3-phenacyl-5-chloroimidazole (XXXIV) a more detailed study was conducted of the different bases in the process of its intramolecular cyclization (Table 3). It was established that only strong bases, sodium alcoholate, caustic alkalis, carbonates, and bicarbonates of the alkali metals and secondary amines, lead to the formation of high yields of 1-ethyl-2-chloro-6-phenylpyrrolo[1, 2-a]-imidazole (XXXIII). With weak bases, the cyclization reaction of compound XXXIV does not proceed to completion or does not proceed in general. The process ceases on the formation of intermediate products of closure of the pyrrole ring, or the anhydrobase of imidazole, during the action (with picric acid) the picrate of 1-ethyl-2-methyl-3-phenacyl-chlorimidazole (XXXV) was formed.

Not only the base used but also substitutes in the imidazole ring of the quaternary salt affect the formation of pyrroloimidazoles. Thus, the quaternary salts based on the 1, 2-disubstituted derivatives of 4, 5-diphenylimidazole readily undergo cyclization even with the residues of aliphatic ketones in position 3 with the formation of the corresponding pyrroloimidazoles. Substitution in position 1 of the imidazole nucleus apparently has no important effect on the course of the reaction.

Unsuccessful attempts were made to induce cyclization of the quaternary salts of imidazole containing the NO_2 group in position 5 or the CH_2OH group in position 2 of the imidazole nucleus (I, II, IV, V). In the case of the nitro compounds of IV and V, both on heating in aqueous $NaHCO_3$ and also in an alcoholic solution of sodium ethoxylate, there was intensive saponification of the reaction mass. From the products of the reaction of compound IV, 1, 2-dimethyl-5-nitroimidazole (XLI) was isolated as a result of cleavage of the original quaternary salt, as this occured in case of certain halogenides of 5-chloroimidazole [2].

On boiling the bromide of 1-methyl-2-oxymethyl-5-chloro-3-n-bromophenacylimidazole (II) in an alcoholic solution of sodium ethoxide the anhydrobase of compound XV (the enol-betain according to the terminology of Kröhnke [3]) was obtained.

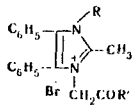
Compound XV and also the anhydrobases of compounds XIV and XVI are formed during the action of NaOH on salts of compounds I, II, and XI in the cold, as had been previously observed by us in other cases [2]. The anhydrobase of compound XVI, in contrast to compounds XIV and XV, on heating in water in the absence of an alkaline agent is almost quantitatively converted into the pyrroloimidazole of compound XXIX.

The structure of the enol-betaines of compounds XIV–XVI was confirmed by data of the elementary analysis and by a study of IR and UV spectra. In the IR spectra of these compounds there is not absorption band of the CO group (Fig. 1.) which indicates that their structure resembles that of the O-betaines. Certain anhydrobases of the pyridine series have a similar structure [4]. In the UV spectra of the O-betaines there is one distinct absorption maximum or a shoulder in the 240–265 nm region. In the UV spectra of the pyrroloimidazoles, for example compounds XXVIII, XXIX, and XXXI (Table 2), there are two absorption maxima in the 245–280 and 360 nm regions (Fig. 2).

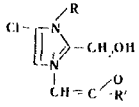
*For Part XXXVI, see [11].

Table 1

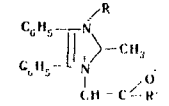
Bromides (I–XIII) and Anhydrobases (XIV–XVI) of 1-Alkyl(aryl)2-alkyl-3-β-ketoalkyl(aralkyl)imidazole



I–XIII



XIV, XV



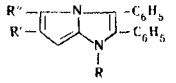
XVI

Compound	R	R′	mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
					C	H	Br	N	C	H	Br	N	
I	CH_3	C_6H_5	191—192[a]	$C_{13}H_{14}BrClN_2O_2$[b]	45.16	4.16	23.10	7.83	45.17	4.08	23.12	8.10	93
II	CH_3	p-BrC_6H_4	185—187	$C_{13}H_{13}Br_2ClN_2O_2$	36.73	3.08	18.95	6.53	36.78	3.08	18.82	6.59	82
III	C_2H_5	p-$CH_3OC_6H_4$	212—214	$C_{15}H_{18}BrClN_2O_2$[c]	48.03	4.76	—	7.57	48.24	4.85	—	7.49	88
IV	CH_3	p-BrC_6H_4	266—268 (decomp.)	$C_{13}H_{13}Br_2N_3O_3$[c]	37.50	3.11	38.40	9.93	37.25	3.13	38.14	10.02	80
V	CH_2CH_2OH	C_6H_5	192—194	$C_{14}H_{16}BrN_3O_4$[c]	45.29	4.29	21.57	11.20	45.42	4.36	21.58	11.35	51
VI	C_2H_5	C_6H_5	204—205,5	$C_{26}H_{25}BrN_2O$	67.19	5.78	17.42	5.83	67.68	5.46	17.32	6.07	81
VII	C_6H_5	CH_3	157—158,5	$C_{25}H_{23}BrN_2O$	—	—	17.67	6.19	—	—	17.86	6.26	74
VIII	C_6H_5	C_6H_5	109—110	$C_{30}H_{25}BrN_2O$	70.50	5.0	15.40	5.27	70.73	4.95	15.69	5.49	82
IX	C_6H_5	p-$CH_3OC_6H_4$	129—131	$C_{31}H_{27}BrN_2O_2$	69.32	5.28	14.94	4.80	69.01	5.04	14.81	5.19	31
X	C_6H_5	m-$O_2NC_6H_4$	257—259	$C_{30}H_{24}BrN_3O_3$	64.66	4.19	15.14	7.60	64.99	4.36	14.41	7.58	67
XI	C_6H_5	p-$O_2NC_6H_4$	265 (decomp.)	$C_{30}H_{24}BrN_3O_3$	64.51	4.33	14.69	7.58	64.99	4.36	14.41	7.58	81
XII	$C_6H_5CH_2$	C_6H_5	216—218	$C_{31}H_{27}BrN_2O$	71.20	4.90	15.13	5.16	71.12	5.20	15.27	5.35	81
XIII	$C_6H_5CH_2$	p-BrC_6H_4	203—204	$C_{31}H_{26}BrN_2O$	61.62	4.35	26.99	4.64	61.81	4.35	26.53	4.65	61
XIV	CH_3	C_6H_5	128—129	$C_{13}H_{13}ClN_2O_2$[d]	59.03	4.80	13.41	10.32	58.98	4.95	13.39	10.59	87
XV	CH_3	p-BrC_6H_4	129—131	$C_{13}H_{12}BrClN_2O_2$	44.98	3.34	—	7.82	45.44	3.52	—	8.15	65
XVI	C_6H_5[e]	p-$O_2NC_6H_4$	84—86 (decomp.)	$C_{30}H_{23}N_3O_3 \cdot H_2O$[f]	72.72	5.16	—	8.68	73.30	5.13	—	8.55	85

[a] For the analysis the compounds were purified by crystallization: I-V, VII, X-XV, from anydrous ethanol; VI and VIII by precipitation with ether from anhydrous ethanol; IX by precipitation with ether from acetone; XVI the technical product was subjected to analysis. [b] Bromides of compounds I and II in place of C_6H_5 in position 4 and 5 of the imidazole nucleus contain Cl in position 5, and in place of the CH_3 group in position 2 contain group CH_2 OH. [c] Bromides of compounds III, IV, and V in place of C_6H_5 in positions 4 and 5 of the imidazole nucleus contain in position 5 the Cl, and NO_2 groups respectively. [d] Found: Cl, 13.41. Calculated %: Cl, 13.39. [e] UV spectra: N compounds, λ_{max}, nm (lg ε): XIV 245 (4.182); XV 263 (4.174); XVI shoulder 240 (4.46). [f] The anhydrobase of compound XVI crystallized with a molecule of water which is not lost on drying in a vacuum desicator above P_2O_5. On desication above 100° C it is converted into compound XXIX. Determination of water according to Fisher is hindered on account of the bright orange color of the compound.

Table 2

The Pyrrolo[1,2-a]imidazoles



Compound	R	R′	R″	Mp, ° C	Empirical formula	Found, %			Calculated, %			Yield, %
						C	H	N	C	H	N	
XVII	C_2H_5[a]	p-$CH_3OC_6H_4$	H	165—167	$C_{15}H_{15}ClN_2O$	65.43	5.29	10.06	65.57	5.50	10.19	54
XVIII	CH_3[b]	C_6H_5	H	118—150	$C_{25}H_{20}N_2$	85.95	5.65	7.79	86.17	5.76	8.05	36
XIX	CH_3[c]	p-BrC_6H_4	H	173—175	$C_{25}H_{19}BrN_2$	69.94	4.30	6.27	70.26	4.48	6.55	39
XX	C_2H_5	CH_3	H	95—96	$C_{21}H_{20}N_2$	84.20	6.78	9.43	83.96	6.71	9.33	35
XXI	C_2H_5	CH_3	CH_3	99—100	$C_{22}H_{22}N_2$	84.43	7.06	8.61	84.04	7.05	8.90	26
XXII	C_2H_5	C_6H_5	H	158—159	$C_{26}H_{22}N_2$	86.23	5.97	8.0	86.15	6.12	7.73	53
XXIII	C_2H_5	C_6H_5	CH_3	162—165	$C_{27}H_{24}N_2$	85.74	6.65	7.36	86.13	6.42	7.44	33
XXIV	C_6H_5	CH_3	H	186—188	$C_{25}H_{20}N_2$	86.53	6.08	7.93	86.17	5.79	8.04	40
XXV	C_6H_5	CH_3	CH_3	177—179	$C_{26}H_{22}N_2$	85.95	6.33	7.85	86.15	6.12	7.73	36
XXVI	C_6H_5	C_6H_5	H	218—220	$C_{30}H_{22}N_2$	87.40	5.40	6.97	87.78	5.40	6.83	84
XXVII	C_6H_5	p-$CH_3OC_6H_4$	H	235—237	$C_{31}H_{24}N_2O$	84.03	5.24	6.27	84.51	5.49	6.36	81
XXVIII	C_6H_5[d]	m-$O_2NC_6H_4$	H	182—184	$C_{30}H_{21}N_3O_2$	79.40	4.66	9.36	79.10	4.65	9.22	91
XXIX	C_6H_5	p-$O_2NC_6H_4$	H	235—237 (decomp.)	$C_{30}H_{21}N_3O_2$	79.40	4.82	8.95	79.10	4.65	9.22	61
XXX	$C_6H_5CH_2$	CH_3	H	124.5—126	$C_{26}H_{22}N_2$	86.25	6.06	7.41	86.15	6.12	7.73	53
XXXI	$C_6H_5CH_2$	C_6H_5	H	174—176.5 (decomp.)	$C_{31}H_{24}N_2$	87.32	5.57	6.44	87.70	5.70	6.60	89
XXXII	$C_6H_5CH_2$	p-BrC_6H_4	H	180—181 (decomp.)	$C_{31}H_{23}BrN_2$	73.91	4.89	5.72	73.95	4.60	5.56	92

[a] In compound **XVII** in place of C_6H_5 in position 2 and 3 Cl is found in position 2.[b] For analysis the compounds were purified by crystallization: **XVIII, XX** and **XXX**, from anhydrous ethanol; **XIX, XXII, XXIV, XXVI, XXVII, XXXI,** and **XXXII** from benzene; **XXI, XXV,** from ethanol; **XXIII,** from ethyl acetate; **XXVIII, XXIX,** from a mixture of ethanol and dimethyl formamide.[c] For compounds **XVII, XXIV, XXVI–XXIX, XXXI,** and **XXII** the yields are indicated by the quaternary salts of imidazole; for the remaining compounds the yields are indicated for the original 1,2-disubstituted derivatives of imidazole, as the quaternary salts were not isolated.[d] UV spectra: compound, λ_{max}, nm (lg ϵ): **XXXI** 245 (4.288) and 360(4.243); **XXVIII,** 295 (4.514) and 360(4.041); **XXIX,** 285(4.245) and 365 (4.431).

Table 3

Effect of the Nature of the Base on Cyclization of the Salts of Imidazole of **XXXIV**

Base	Duration of boiling, hr	Yield of **XXXIII**, %	**XXXV** isolated, %
C_2H_5ONa	5	79	—
NaOH	2	79	—
$Ca(OH)_2$	10	79	—
$Ba(OH)_2$	5	47	39
Na_2CO_3	5	63	20
$NaHCO_3$	5	63—84	5—16
$CaCO_3$	10	Traces	79
CH_3COONa	20	Traces	75
NH_4OH	20	Traces	90
Isobutylamine	10	15	—
Piperidine	10	55	—
Pyridine	10	8	—

EXPERIMENTAL

The bromide of 1-ethyl-2-methyl-3-phenacyl-5-chloroimidazole (XXXIV) [1], 1-ethyl-2-methyl-4,5-diphenylimidazole (XXXVI) [1],

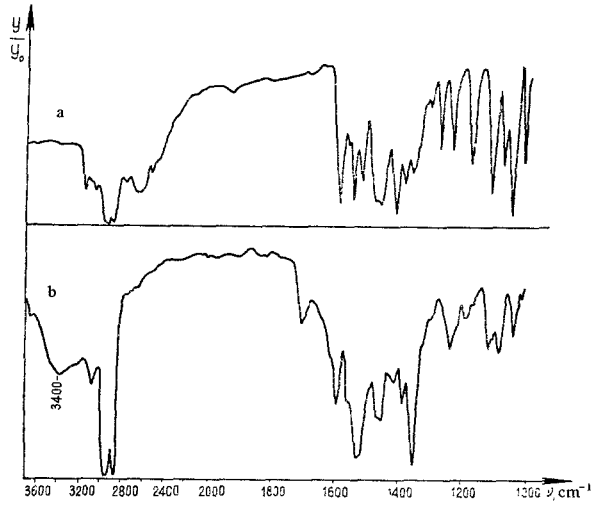


Fig. 1. IR spectra. a) anhydrobase of 1-methyl-2-oxymethyl-3-n-bromophenacyl-5-chloroimidazole (XV); b) anhydrobase of 1,4,5-triphenyl-2-methyl-3-n-nitrophenacylimidazole (XVI).

1-phenyl-2-methyl-4,5-diphenylimidazole (XXXVII) [1] and 1-β-oxyphenyl-2-methyl-5-nitroimidazole (XLII) [5] were previously prepared.

1-Methyl-2-oxymethyl-5-chloroimidazole (XXXVII) was obtained by heating 1-methyl-5-chlorimidazole [6] with a 40% aqueous solution of CH_2O in a sealed tube for 18 hr at 145-150° C. When the reaction was conducted for 4 hr at 120° C [7], a mixture of the original and final products was formed which was difficult to separate.

1-Dimethyl-4,5-diphenylimidazole (XXXIX) was obtained by methylation of the previously prepared 2-methyl-4,5-diphenylimidazole [1] by methyl iodide, as described for 1,2-dimethylbenzimidazole [8]. Picrate. mp 198-199° C (from ethanol). Found, %: C 57.74; H 3.91; N 14.12. Calculated for $C_{17}H_{16}N_2 \cdot C_6H_3N_3O_7$, %: 57.86; H 4.01; N 14.67.

1-Benzyl-2-methyl-4,5-diphenylimidazole (XL) [9] and **1,2-dimethyl-5-nitroimidazole (XLI)** [10] were obtained according to well known methods.

1-Ethyl-2-chloro-6-phenylpyrrolo(1,2-a)imidazole (XXXIII). A 0.055 mole quantity of the base was added to a solution of 0.05 mole of the bromide of compound **XXXIV** in 10 ml of water (in 10 ml ethanol in the case of sodium ethoxide), the mixture was boiled, cooled, and the precipitate was removed by filtration. Compound **XXXIII** was obtained with a mp of 82-84° C (from ethanol). According to data in the literature [1], mp is 84-85° C. After removal of **XXXIII** the aqueous filtrate was washed with ether from resin-like substances, acidified with CH_3COOH, an aqueous solution of picric acid was added, and the precipitate of the picrate of 1-ethyl-2-methyl-3-phenacyl-5-chloroimidazole (**XXXV**) was removed by filtration, and washed with ether, mp, 153-154° C (from ethanol). According to data in the literature [1], the mp is 153-154° C. In the case of isobutylamine, piperidine, and pyridine it was impossible to isolate the picrate of compound XXXV because of the mixture of picrates of the corresponding amines.

Bromides of 1-alkyl(aryl)-2-alkyl-3-ketoalkyl(aryl)imidazole (I-XIII, Table 1). These compounds were obtained by boiling 1,2-dialkylimidazoles of compounds **XXXVI-XLII** with the α-bromo ketones in acetone (5 hrs for **I-V**, and **IX-XIII**, and 20 hrs for **VI-VIII**) as described by us previously [1]. Compounds **VI**, **VII**, and **IX** are soluble in acetone and are isolated by precipitation with ether.

Anhydrobases of 1-alkyl(aryl)-2-alkyl-3-phenacylimidazole (XIV-XVI, Table 1). These compounds were obtained by adding 40% NaOH to an aqueous solution of bromides of compounds **I**, **II** and **XI**, and the resulting precipitates were removed by filtration and washed with water.

Pyrrolo[1,2-a]imidazoles (XVII-XXXII, Table 2). Compounds **XVII**, **XXII**, **XXVI**, **XXVIII**, **XXIX**, and **XXXII** were obtained by boiling the bromides of compounds **III**, **VI**, **VIII**, **X**, **XI**, and **XIII** in an aqueous solution in the presence of $NaHCO_3$ (10% excess of the theoretical amounts) according to a previously described method [2]. For the synthesis of compounds **XVIII-XXII**, **XXIII-XXV**, **XXVII**, **XXX**, and **XXXI** the corresponding bromides of inidazole were prepared in the manner described for compound **VI** (the aliphatic bromoketones were used with 100% excess and the reaction was conducted at room temperature for 48-72 hr). The thick caramel-like substances which formed were extracted by decanting from the solvent and were dissolved in anhydrous ethanol (5 ml/g bromide), a solution of sodium ethoxide was added (an equimolecular quantity calculated for a 100% yield of bromide), the mixture was boiled for 15 min (**XXIII**), 30 min (**XX**, **XXIV** and **XXVII**), or 60 min (**XVIII**, **XIX**, **XXI**, **XXV**, **XXX**, and **XXI**), cooled, and the precipitate was removed by filtration and washed with ethanol. The anhydrobase of compound **XV** separated out on boiling the bromide of compound **II** in ethanol in the presence of sodium ethoxide for 30 min. On boiling the bromide of compound **IV** in an aqueous solution of $NaHCO_3$ as described above and with subsequent chromatography of the resinified mass in a column containing aluminum oxide, 1,2-dimethyl-5-nitroimidazole (**XLI**) with a mp of 135-137° C was isolated. A sample of a mixture with pure XLI (mp 138-139° C) [10] did not depress the melting point. The picrate had a mp of 160-162° C. According to data in the literature [10] the mp of picrate was 162-163° C.

A) A 0.5 g quantity of compound **XVI** in 50 ml water was boiled for 5 hrs, cooled, and the precipitate was removed by filtration. A 0.45 g (97.3%) quantity of a compound with a mp of 235-237° C was obtained (from a mixture of ethanol and dimethyl-formamide) which did not cause depression of the melting point on mixing with compound **XXIX**.

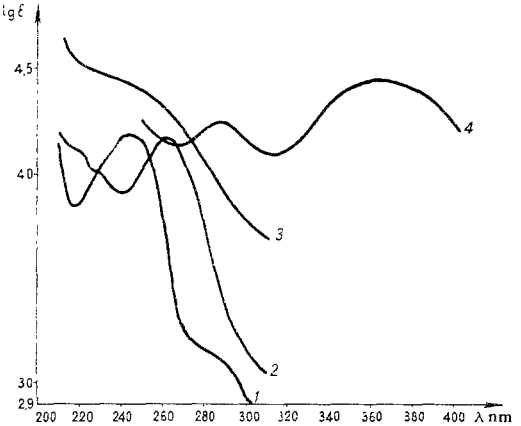


Fig. 2. UV spectra: 1) anhydrobase of 1-methyl-2-oxymethyl-3-phenacyl-5-chloroimidazole (**XIV**); 2) anhydrobase of 1-methyl-2-oxymethyl-3-n-bromophenacylimidazole (**XV**); 3) anhydrobase of 1,4,5-triphenyl-2-methyl-3-n-nitrophenylimidazole (**XVI**); 4) 1,2,3-triphenyl-6-6-n-nitrophenylpyrrolo 1,2-a imidazole (**XXIX**).

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