RESEARCHES ON IMIDAZOLES

XXXII. Pyrrolo[1,2-a]Imidazoles*

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A number of pyrrol[1,2-a]imidazole derivatives are synthesized by heating 1,2-dialkyl-3-[β-ketoalkyl(aralkyl)]imidazolinium halides with aqueous sodium bicarbonate, or by heating the corresponding imidazolinium hydroxides with water.

In the last decade, particularly in connection with the discovery of the valuable biological properties of alkaloids of the pyrrolizidine group, pyrrolizidine being a reduced derivative of pyrrolo[1,2-a]pyrrole [1, 2], condensed heterocyclic systems with a nitrogen atom in common and containing a pyrrole ring, have attracted the attention of research workers. A. E. Chichibabin [3, 4], when studying the action of sodium bicarbonate on 1-phenacyl-2-methylpyridinium bromide, effected a building up of the pyrrole ring, for the first time from 2-alkyl heterocyclic compounds, thus synthesizing derivatives of pyrrole [1, 2-a]-pyridine (indolizine, pyrrocoline). Other authors have used this method to synthesize derivatives of indolizine [5–8], pyrrolo[1,2-b]thiazole [9–14], pyrrolo[1,2-a]pyrimidine [15], pyrrolo [1,2-a]quinoxaline [16], and other heterocyclic compounds [17]. However, up to the present the 1H-pyrrol[1,2-a]imidazole had not been investigated. Only a few compounds which are di-, tetra-, and hexa derivatives of this bicyclic system [18–23], have been described. A substituted 5H-pyrrol[1,2-a] imidazole [20] is also known.

A previous paper [24] dealt with the preparation of derivatives of 1H-pyrrol[1,2-a]imidazole. The present paper is devoted to a more detailed study of the synthesis of these compounds. The starting compounds used are 1,2-dialkyl-3-[β-ketoalkyl(aralkyl)] imidazolinium halides [25]. A study is made of the cyclization of these quaternary salts on heating in water, alcohols, dimethylformamide, and acetic anhydride, in the presence of various bases i. e., sodium bicarbonate and carbonate, sodium acetate, sodium hydroxide, etc. The reaction is found to proceed best in aqueous solution in the presence of a slight excess (about 10%) sodium bicarbonate. Pyrrolimidazole derivatives I–X (table) are obtained in that way.

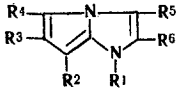
Formation of pyrrolimidazoles depends both on the cyclization conditions, and on the structure of the starting imidazolinium halide. According to our observations, cyclization of quaternary salts of 1,2-dialkylimidazoles with aliphatic aromatic ketones, viz. phenacyl bromide and its substitution products, proceeds best.

As a result of the presence of a pyrrole ring, pyrrolimidazole derivatives are less stable than compounds of the imidazole series. To a large extent the stability of the pyrrolimidazole bicyclic system depends on the nature of the substituents in both the pyrrole and imidazole parts of the molecule. In a series of experiments where 1, 2-dialkyl-3-β-ketoalkyl(aralkyl)imidazolinium halides were heated in aqueous solution in the presence on the bases mentioned above, marked tar formation was observed, and so far it has not proved possible to obtain the corresponding pyrrolimidazoles. In some cases scission products of the starting imidazolinium halides were isolated. Thus when 1-ethyl-2-methyl-3-acetonyl-5-chloroimidazolinium chloride was heated with aqueous sodium bicarbonate, 1-ethyl-2-methyl-5-chloroimidazole was detected, being isolated as its picrate (XVI). Refluxing 1-ethyl-2-methyl-3-p-bromophenacyl-5-chloroimidazolinium bromide with acetic anhydride containing sodium acetate gave p-bromobenzoic acid (XVII). The literature describes a similar scission of N-phenacyl derivatives of pyridine and pyrimidazole in alkaline solution [17, 26]. 1-Ethyl-2-methyl-3-desyl-5-chloroimidazolinium chloride is not cyclized by boiling with water in the presence of an equivalent quantity of sodium bicarbonate, probably because of steric hindrance. At higher temperatures, in boiling dimethylformamide containing sodium acetate, there is pyrrole ring closure and hydrolysis of the halogen, to give 1-ethyl-5, 6-diphenylpyrrol[1,2-a]imidazol-2-one (XVIII). The structure of XVIII was confirmed by its IR spectrum, which showed an absorption band characteristic of the CO group.

When investigating the cyclization of imidazolinium halides to pyrrolimidazole derivatives, it proved possible to isolate some intermediate products of the reaction. Thus addition of picric acid to an aqueous solution of the reaction products after removing pyrrolimidazoles (II, III, VII and VII, table) gave picrates of imidazolinium bases (XI–XIV). Heating 1-ethyl-2-methyl-3-desyl-5-chloroimidazolinium chloride with aqueous sodium bicarbonate gave, instead of the expected bicyclic compound, the corresponding imidazolinium hydroxide (XV). Thus hydroxides of quaternary imidazolinium bases are

*For Part XXXI see [25].

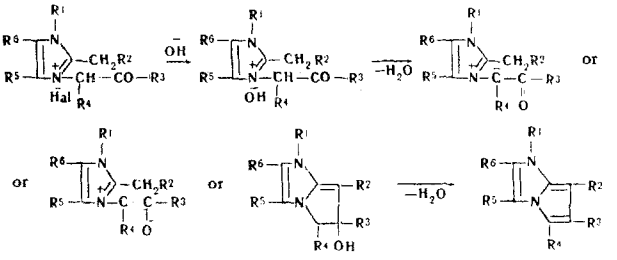
Pyrrol[1,2-a]imidazoles*



Compound	R¹	R²	R³	R⁴	R⁵	R⁶	Mp, °C	Formula	Found, %				Calculated, %				Yield, %
									C	H	Hal	N	C	H	Hal	N	
I	CH_3	H	*p*-BrC_6H_4	H	H	H	135—136 (decomp)	$C_{13}H_{11}BrN_2$	56.50	4.05	29.15	9.52	56.75	4.03	29.04	10.18	46
Ia	CH_3	H	*p*-BrC_6H_4	H	H	H	238—240 (decomp)	$C_{13}H_{11}BrN_2 \cdot C_6H_3N_3O_7$	45.28	3.00	15.87	13.64	45.25	2.79	15.85	13.87	—
II	C_2H_5	H	C_6H_5	H	H	Cl	84—85	$C_{14}H_{13}ClN_2$	68.29	5.45	14.96	11.54	68.71	5.35	14.49	11.44	84
IIa	C_2H_5	H	C_6H_5	H	H	Cl	236—238 (decomp)	$C_{14}H_{13}ClN_2 \cdot C_6H_3N_3O_7$	50.71	3.30	7.34	14.72	50.69	3.40	7.48	14.78	—
III	C_2H_5	H	*p*-BrC_6H_4	H	H	Cl	148—150 (decomp)	$C_{14}H_{12}BrClN_2$	51.74	3.74	—	8.53	51.95	3.74	—	8.66	74
IV	C_2H_5	H	C_6H_5	CH_3	H	Cl	162—164	$C_{15}H_{15}ClN_2 \cdot C_6H_3N_3O_7$	51.75	3.74	7.30	14.16	51.70	3.72	7.27	14.35	—
V	C_2H_5	H	*p*-$C_6H_5C_6H_4$	CH_3	H	Cl	128—130	$C_{21}H_{19}ClN_2$	75.36	5.82	10.44	8.44	75.32	5.72	10.59	8.37	91
VI	C_3H_7	CH_3	C_6H_5	H	H	Cl	167—168	$C_{16}H_{17}ClN_2 \cdot C_6H_3N_3O_7$	52.83	4.30	7.08		52.65	4.52	7.06	13.95	—
VII	C_3H_7	CH_3	*p*-BrC_6H_4	H	H	Cl	99—100	$C_{16}H_{16}BrClN_2$	54.19	4.60	—	8.09	54.64	4.58	—	7.97	23
VIII	C_3H_7	CH_3	*p*-BrC_6H_4	H	Cl	H	186—188 (decomp)	$C_{16}H_{16}BrClN_2 \cdot C_6H_3N_3O_7$	45.53	3.16	—	11.94	45.49	3.29	—	12.06	—
IX	C_2H_5	H	*p*-BrC_6H_4	H	C_6H_5	C_6H_5	182—184	$C_{26}H_{21}Br_2N_2$	70.44	4.89	17.50	6.47	70.75	4.79	18.10	6.35	92
X	C_6H_5	H	*p*-BrC_6H_4	H	C_6H_5	C_6H_5	199—201	$C_{30}H_{21}BrN_2$	73.73	4.31	16.06	5.77	73.62	4.32	16.33	5.72	90
Xa	C_6H_5	H	*p*-BrC_6H_5	H	C_6H_5	C_6H_5	204—205	$C_{30}H_{21}BrN_2 \cdot C_6H_3N_3O_7$	—	—	—	9.60	—	—	—	9.75	—

*For analysis the compounds were purified by recrystallization: I and VII ex iso-PrOH; **Ia** ex 50% aqueous HCOOH; IIa ex glacial AcOH; II, III, VIII, and **Xa** ex EtOH; IV, VI ex water; V ex petrol ether (60°–80° C); **IX** ex AcOEt; **X** ex benzene.

to be regarded as primary intermediate products of cyclization of 1, 2-dialkyl-3-β-ketoalkyl(aralkyl) imidazolinium halides to pyrrol[1,2-a]imidazole derivatives. Actually, boiling 1-ethyl-2-methyl-3-p-bromophenacyl-5-chloroimidazolinium hydroxide with water gives 1-ethyl-2-chloro-6-p-bromophenylpyrrol[1,2-a]imidazole (**III**, table). The next intermediate products in closure of the pyrrole ring are probably betaines or 6-hydroxypyrrolin[1, 2-a] imidazoles.



EXPERIMENTAL

Pyrrol[1, 2-a]imidazoles (I–X, Table). 0.0105 Mole $NaHCO_3$ was added to a hot solution of 0.01 mole 1,2-dialkyl-3-[β-ketoalkyl(aralkyl)]imidazolinium halide [25] in water (30–100 ml), and the whole refluxed for 2–5 hr, when a precipitate soon formed; after cooling the solid was filtered off, washed with water and dried. The I–III, V, VII, IX, X prepared were colorless or slightly colored crystalline compounds, which darkened on keeping, were readily soluble in most organic solvents, insoluble in water, slightly soluble in petrol ether, which formed salts with mineral acids and gave picrates. Where there was considerable tar in the reaction products, the pyrrolimidazole was extracted with ether, the solution washed with water, dried over Na_2SO_4, the solvent distilled off, the residue boiled with petrol ether (40°–60° C), the solution decanted, and mixed with an ether solution of picric acid, and in that way pyrrolimidazoles were obtained as picrates **IV**, **VI**, and **VIII** (table). After filtering off the precipitate of pyrrolimidazole, the mother liquor was extracted with more ether, the aqueous solution acidified to pH 5–6 with AcOH, then mixed with an aqueous solution of picric acid. Picrates of the following hydroxides were isolated in small amounts: 1-ethyl-2-methyl-3-phenacyl-5-chloroimidazolinium (XI, mp 153–154° C, ex water); 1-ethyl-2-methyl-3-p-bromophenacyl-5-chloroimidazolinium (XII) mp 177–179 (ex EtOH); 1-propyl-2-ethyl-3-(p-bromophenacyl)-5-chloroimidazolinium (XIII, mp 109°–110° C, ex EtOH); 1-propyl-2-ethyl-3-(p-bromophenzcyl)-4-chloroimidazolinium (XIV, mp 157–158° C, ex EtOH). Refluxing 1-ethyl-2-methyl-3-desyl-5-chloroimidazolinium chloride (2 g, 0.0053 mole) with water (30 ml) containing $NaHCO_3$ (0.5 g) for 3 hr, led to the isolation of 1.1 g (58%) 1-ethyl-2-methyl-3-desyl-5-chloroimidazolinium hydroxide (XV, mp 157°–158° C, picrate (XVa) mp 200°–201°. Picrates XI–XVa and hydroxide XV proved to be identical with the previously prepared analogous compounds [25]. Heating 1-ethyl-2-methyl-3-acetonyl-5-chloroimidazolinium chloride with aqueous $NaHCO_3$ in the way previously described, followed by extraction with ether, and treatment of the ether extract with picric acid, gave 1-ethyl-2-methyl-5-chloroimidazole picrate (XVI) mp 154°–155° C. Undepressed mixed mp with an authentic specimen [27]. Refluxing (2 hr) 1-ethyl-2-methyl-3-(p-bromophenacyl)-5-chloroimidazolinium bromide with Ac_2O in the presence of AcOHa · $3H_2O$ (30% excess), followed by pouring the reaction products into water, and extracting with $CHCl_3$ gave p-bromobenzoic acid (XVII), mp 252°–254° C. Undepressed mixed mp with an authentic specimen.

b) 1 g 1-Ethyl-2-methyl-3-(p-bromophenacyl)-5-chloroimidazolinium hydroxide [25] in 10 ml water, was boiled for 3 hr, the products cooled, the solid filtered off, and then washed with water. Yield 0.6 g (66%) III mp 148°–150° C (ex EtOH). Mixed mp with III prepared by method a, undepressed.

1-Ethyl-5, 6-diphenylpyrrol[1, 2-a]imidazol-2-one (XVIII). A mixture of 1 g (0.0027 mole) 1-ethyl-2-methyl-3-desyl-5-chloroimidazolinium chloride [25] and 0.4 g (0.003 mole) AcONa · $3H_2O$ in 25 ml dimethylformamide, was refluxed for 2 hr, then poured into 150–200 ml water, and the solid filtered off, to give XVIII, mp 135°–136° C (ex EtOH). Found: C 79.40; H 6.12; N 9.32%. Calculated for $C_{20}H_{18}N_2O$; C 79.44; H 6.00; N 9.26%. IR spectrum (in vaseline): 1728 cm^{-1} (ν_{CO}).

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