INVESTIGATIONS IN THE IMIDAZOLE FIELD

XLI. Cyclization of 1,2-Dialkyl-3-(β-oxoalkyl[aralkyl])benzimidazolium Halides into Pyrrolo [1,2-a]benzimidazoles and the Intermediates in Pyrrole Ring Closure*

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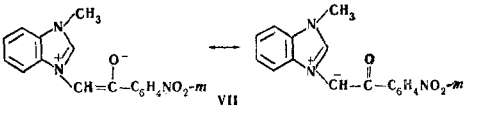
It has been established that various inorganic and organic bases can be used for the cyclization of 1,2-dialkyl-3-(β-oxoalkyl[aralkyl])benzimidazolium halides into derivatives of pyrrolo[1,2-a]benzimidazole. The action of strong bases on quaternary benzimidazolium salts gives O-betaines—intermediates in the closure of the pyrrole ring.

Continuing previous work [1, 2], it appeared of interest to study in more detail the cyclization of 1,2-dialkyl-3-(β-oxoalkyl[aralkyl])benzimidazolium halides into pyrrolo[1,2-a]benzimidazole derivatives under comparable conditions in the presence of inorganic and organic bases and also to isolate the intermediates in this reaction. Using 1,2-dimethyl-3-phenacylbenzimidazolium bromide (XI) as an example, it has been established that the closure of the pyrrole ring with the formation of 4-methyl-2-phenylpyrrolo[1,2-a]benzimidazole (XIV) takes place when this bromide is heated in the presence of almost all the bases we have studied—alkoxides, hydroxides, carbonates, and bicarbonates of the alkali metals, trisodium phosphate, ammonium carbonate, ammonium hydroxide, benzyltrialkyl ammonium hydroxides, and tertiary, secondary, and primary amines. The cyclization of 3-(β-oxoalkyl[aralkyl]) benzimidazolium halides into pyrrolo[1,2-a]benzimidazoles takes place more readily than the cyclization of 3-(β-oxoalkyl[aralkyl])imidazolium halides, where the use of weak bases leads to pyrrolo[1,2-a]imidazoles in very low yields [3].

The action of the calculated amount of NaOH or NH_4OH on the bromides I and II (table) and the 1,2-dimethyl-3-nitrophenacylbenzimidazolium bromides XII and XIII in aqueous solution in the cold gave the crystalline compounds VII–X*, which, judging from the results of elementary analysis, are the anhydrobases (enol betaines) of the corresponding benzimidazolium salts and are apparently formed in each case as the result of the splitting out of a molecule of water from the corresponding quaternary benzimidazolium base. These compounds, like the analogous pyridinium [4], quinolinium, and isoquinolinium [5] bases, give characteristic color reactions with picryl chloride and chloranil, which shows the similarity of their structures.

On treatment with HBr, the anhydrobases VII–X are converted into the initial benzimidazolium bromides I, II, XII, and XIII, and under the action of picric acid they are converted into the picrates of the corresponding quaternary benzimidazolium bases III–VI. The anhydrobases IX and X, like the anhydrobases of the imidazole series [3] are intermediates in the closure of the pyrrole ring in the synthesis of the pyrrolo[1,2-a]benzimidazoles from the 1,2-dialkyl-3-(β-oxoalkyl [aralkyl])benzimidazolium halides, since on being heated in water without the addition of an alkaline agent they are rapidly converted in almost quantitative yield into the 4-methyl-2-nitrophenylpyrrolo[1,2-a]benzimidazoles XV and XVI, which we have obtained previously in one stage by the cyclization of the bromides XII and XIII by heating them in aqueous $NaHCO_3$ solution.

The structure of the anhydrobases was established by physicochemical methods. The PMR spectrum of compound IX (Fig. 1) has clear signals of a proton attached to a carbon atom of a double bond and of the protons of two methyl groups. The IR spectrum of this compound lacks the absorption band of a CO group (Fig. 2). These facts show that the anhydrobase IX has the structure of an O-betaine. Compound X has an analogous structure. The IR spectrum of the anhydrobase VII (Fig. 3) which has no alkyl group in position 2 of the imidazole nucleus, taken in solution (dimethyl sulfoxide) has a strong band of the stretching vibrations of a CO group, but in the crystalline state (mull in paraffin oil) the absorption band of the CO group becomes very weak. This shows that the anhydrobase VII can apparently exist in two forms—as an O-betaine (predominating in the crystalline state) and as a C-betaine (predominating in solution).



VII

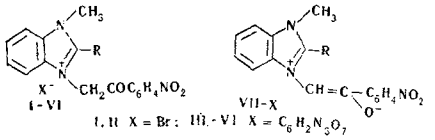
The UV spectra of VII–X are fairly similar. The spectra of IX and X have sharper absorption maxima in the region around 270 nm than the spectra of VII and VIII*.

The investigations performed permit the conclusion that the cyclization of the 1,2-dialkyl-3(β-oxoalkyl [aralkyl])benzimidazolium halides under the action of bases into pyrrolo[1,2-a]benzimidazoles takes place in the following way:

*For part XL, see [1].

*The UV, IR, and PMR spectra were taken by Yu. N. Sheinker and his colleagues.

1-Methyl-3-nitrophenacyl-2-R-benzimidazolium Bromides (I, II), Picrates (III–VI), and Anhydrobases (VII–X)



I-VI VII-X

I, II X = Br; III-VI X = $C_6H_2N_3O_7$

Compound	R	Mp, °C (decomp.)	Empirical formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
I	H	221—222	$C_{16}H_{13}BrN_3O_3$**	51.02	3.70	11.10	51.08	3.75	11.17	90
II	H	228—230	$C_{16}H_{13}BrN_3O_3$***	50.95	3.96	11.29	51.08	3.75	11.17	77
III	H	216—218	$C_{16}H_{14}N_3O_3 \cdot C_6H_2N_3O_7$	50.56	3.32	15.68	50.39	3.08	16.03	96
IV	H	183—184	$C_{16}H_{14}N_3O_3 \cdot C_6H_2N_3O_7$	50.58	3.04	15.99	50.39	3.08	16.03	93
V	CH_3	188—189	$C_{17}H_{16}N_3O_3 \cdot C_6H_2N_3O_7$	51.39	3.58	15.23	51.31	3.37	15.61	94
VI	CH_3	177—178	$C_{17}H_{16}N_3O_3 \cdot C_6H_2N_3O_7$	51.45	3.29	15.41	51.31	3.37	15.61	90
VII	H	112—113	$C_{16}H_{13}N_3O_3 \cdot H_2O$	61.45	4.48	13.31	61.33	4.82	13.41	95
VIII	H	90—92	$C_{16}H_{13}N_3O_3$	64.78	4.60	14.50	65.07	4.44	14.23	91
IX	CH_3	112—113	$C_{17}H_{15}N_3O_3$	65.71	4.91	13.78	66.00	4.88	13.58	63
X	CH_3	119—120	$C_{17}H_{15}N_3O_3$	65.63	4.86	13.44	66.00	4.88	13.58	47

*Compounds I, III, V, and IX contained the NO_2 group in the m-position and compounds II, IV, VI, VIII, and X contained the NO_2 group in the p-position. For analysis the compounds were purified by crystallization from anhydrous ethanol (I) from methanol (II, VIII), from dimethylformamide-water (4 : 1) (III), from acetone-water (1 : 1) (IV,V), from water (VI), or from ethanol (VII); compounds IX and X were analyzed in the form of the technical products, since attempts to crystallize them from organic solvents led to their cyclization into the corresponding pyrrolobenzimidazoles XV and XVI. The values of ν_{CO}, cm^{-1}, in the IR spectra (taken in paraffin oil on a UR-10 instrument) as follows: 1701 (I), 1717 (II), 1713 (IV), 1710 (V), 1711 (VII, in dimethyl sulfoxide); the UR spectra (taken in ethanolic solutions on a EPS-3 instrument), compound, λ_{max}, nm (log ε): VII, 270 (4.06), 276 (3.99), 355 (3.58); VIII, 270 (4.27), 400 (3.63); IX, 235 (4.20), 263 (4.09), 271 (4.11), 278 (4.08); X, 264 (4.27), 275 (4.27), 277 (4.20), 374 (3.62).

**Found, %: Br 20.95. Calculated, %: Br 21.14.

***Found, %: Br 21.19. Calculated, %: Br 21.24.

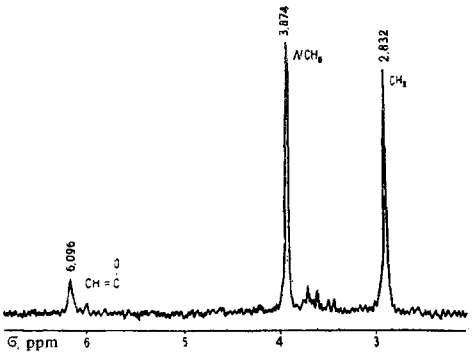


Fig. 1. PMR Spectrum in $CDCl_3$ of the 1,2-dimethyl-3-m-nitrophenacyl-benzimidazolium anhydrobase IX.

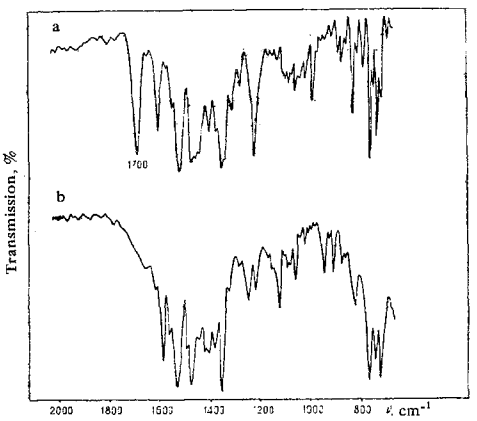
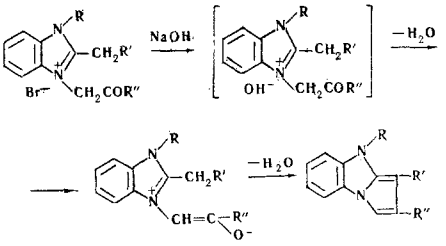


Fig. 2. IR spectra in crystals: a) 1,2-dimethyl-3-m-nitrophenacylbenzimidazolium bromide (XII); b) 1,2-dimethyl-3-nitrophenacylbenzimidazolium anhydrobase (IX).



The closure of the pyrrole ring is a specific reaction taking place only under the action of bases and not taking place when the quaternary benzimidazolium salts are simply heated or when they are treated with water-abstracting agents. When the bromide XI was heated with concentrated H_2SO_4 at 100° C, judging from the evolution of HBr, only an exchange reaction, replacement of Br by SO_4H, took place. When picric acid was added to the reaction mixture, 1,2-dimethyl-3-phenacylbenzimidazolium picrate (XVII) was obtained in almost quantitative yield. The heating of XI to its melting point led to its thermal decomposition with the formation of 1,2-dimethylbenzimidazole (XVIII), as takes place when 1,3-dialkylbenzimidazolium halides are heated [6].

EXPERIMENTAL

The 1-methyl-3-(m- and p-nitrophenacyl)benzimidazolium bromides I and II were obtained by the reaction of 1-methylbenzimidazole [7] with the corresponding nitrophenacyl bromides as described previously [2].

The 1,2-dimethyl-3-phenacyl- and 1,2-dimethyl-3-(m-and p-nitrophenacyl)benzimidazolium bromides XI–XIII were also obtained as described previously [2].

The 1-methyl-3-nitrophenacyl-2-R-benzimidazolium picrates III–VI were obtained by the addition of picric acid to aqueous solutions of the bromides I, II, XII, and XIII.

The 1-methyl-3-nitrophenacyl-2-R-benzimidazolium anhydrobases (VII–X). A solution of 1 mM of one of the bromides, I, XII, and XIII in the pure state and 15 ml of distilled water was treated with 1.1 mM of NaOH, chemically pure (in the form of a 40% aqueous solution), and the precipitate of VII, IX, or X, respectively, was filtered off and washed with water. Compound VIII was isolated by the addition of 25% aqueous NH_3 to a solution of II in dimethylformamide. They formed red (VII), brown (VIII, X), or orange (IX) crystals. Compounds VII and VIII are sparingly soluble in organic solvents and insoluble in water, and IX and X are soluble in organic solvents and sparingly soluble in cold water.

Compounds I–X are characterized in the table.

Reactions of the benzimidazolium anhydrobases. A) A few drops of 40% HBr was added to a solution or a finely-ground suspension of 1mM of one of compounds VII–X in methanol, ethanol, or acetone, and the precipitate was filtered off. The bromides obtained in this way were identical with respect to mp and IR spectra with the benzimidazolium bromides I, II, XII, and XIII, respectively.

B) To a solution of 1 mM of one of compounds VII, IX, and X in ethanol or of VIII in dimethylformamide was added an aqueous solution of picric acid. The benzimidazolium picrates obtained in this way were identical with the picrates III–VI in respect of mps and IR spectra.

C) A mixture of 1 mM of IX or X and 20–30 ml of water was boiled for 15–30 min and cooled, and the precipitate was filtered off. This gave with yields of 96–98% 4-methyl-2-(m-nitrophenyl)pyrrolo[1,2-a]-benzimidazole (XV, mp 170.5–171.5° C, from dimethylformamide) and 4-methyl-2-(p-nitrophenyl)pyrrolo[1,2-a]benzimidazole (XVI), mp 180–182° C (from a mixture of ethanol and dimethylformamide), identical with the corresponding pyrrolobenzimidazoles prepared by the cyclization of the bromides XII and XIII by heating them in aqueous $NaHCO_3$ solution as described previously [2].

4-Methyl-2-phenylpyrrolo[1,2-a]benzimidazole (XIV). A solution of 1 g (2.9 mM) of XI in 50 ml of water (or, when a sodium alkoxide was used, in the corresponding alcohol) was treated with 3 mM of a base (in the case of NH_4OH a slight excess), and the mixture was boiled for 5 hr (in the case of pyridine and sodium acetate, 20 hr), after which the precipitate of XIV was filtered off. When calcium carbonate, sodium acetate, dibutylamine, and pyridine were used, the XIV was extracted with ether and isolated in the form of the picrate. The bases used and the yields of XIV obtained, % were: C_2H_5ONa (93); CH_3ONa (86); NaOH (91); $Ca(OH)_2$ (95); K_2CO_3 (86); Na_2CO_3 (91); $NaHCO_3$ (95); $(NH_4)_2CO_3$ (35); $CaCO_3$ (18); Na_3PO_4 (70); CH_3COONa (7); and $(C_2H_5)_3N-CH_2C_6H_5OH-$ (43); NH_4OH (91); $(C_2H_5)_3N$ (50); $(C_4H_9)_2NH$ (36); $C_4H_9NH_2$ (70); pyridine (19).

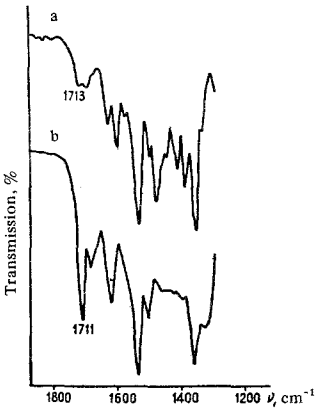


Fig. 3. IR spectra of 1-methyl-3-m-nitrophenacylbenzimidazolium anhydrobase (VII): a) in crystals; b) in dimethyl sulfoxide.

Action of sulfuric acid on 1,2-dimethyl-3-phenacylbenzimidazolium bromide (XI). A mixture of 0.5 g (1.2 mM) of XI and 1 ml of 96% H_2SO_4 was heated at 100–110° C for 1 hr, cooled, and poured into water (30 ml), and the resulting solution was treated with an aqueous solution of picric acid. The yellow precipitate was filtered off to give 0.65 g (91%) of 1,2-dimethyl-3-phenacylbenzimidazolium picrate (XVII) with mp 166–168° C, showing no depression of the melting point in admixture with an authentic sample of this picrate [2].

Thermal decomposition of 1,2-dimethyl-3-phenacylbenzimidazolium bromide (XI). Compound XI (0.5 g; 1.4 mM) was heated to its mp of 242–244° C (bath temperature 270–280° C), and the melt was kept at this temperature for 15 min and was then cooled and poured into water, after which the solution was filtered from resinified products and treated with an aqueous solution of picric acid, the precipitate being filtered off. This gave 0.25 g (46%) of 1,2-dimenthyl benzimidazole picrate (XVIII) with mp 231–234° C, giving no depression of the melting point in a mixture with an authentic sample of the picrate of this compound [2].

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