INVESTIGATION OF IMIDAZO[1,2-a]BENZIMIDAZOLE DERIVATIVES

VI.* PREPARATION OF IMIDAZO[1,2-a]BENZIMIDAZOLE DERIVATIVES FROM 1-ALKYL- AND 1-ARALKYL-2-IMINOBENZIMIDAZOLINE-3-ACETIC ACIDS AND THEIR ESTERS

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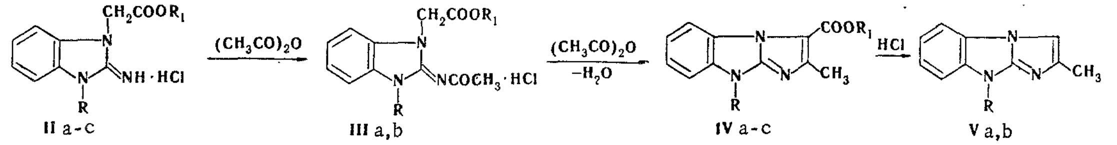
Esters of 1-alkyl- and 1-aralkyl-2-iminobenzimidazoline-3-acetic acids are converted to esters of 2,9-dimethylimidazo[1,2,-a]benzimidazole-3-carboxylic acid on heating with acetic anhydride. The brief action of acetic anhydride on the free iminobenzimidazolineacetic acids gives 2-oxo-2,3-dihydroimidazo[1,2-a]benzimidazoles, which are converted to 2,9-substituted 3-acetylimidazo[1,2-a]benzimidazoles on prolonged heating with acetic anhydride.

In order to obtain new compounds of the imidazo[1,2-a]benzimidazole series, we studied the action of acetic anydride on 1-alkyl- and 1-aralkyl-2-iminobenzimidazoline-3-acetic acids (Ia, b) and their esters (IIa-c); the latter are readily formed by mixing 1-alkyl- and 1-aralkyl-2-amino-benzimidazoles with esters of chloroacetic acid [2]. N-Acetyl derivatives (IIIa, b) are obtained in 80-85% yield by brief heating of IIa, b in acetic anhydride. Bands of an ester carbonyl group at 1780 cm^{-1}, a strong band of a single bond (ν_{C-O}) at 1240 cm^{-1}, and the carbonyl absorption of an acetyl group at 1730 cm^{-1} appear distinctly in the IR spectrum of IIIa. The entry of an acetyl group into the imino group is confirmed by the conversion of IIIa to 1-methyl-3-carboxymethylbenzimidazolone [3] by the action of alkali. Acid hydrolysis of IIIa gives the hydrochloride of Ia [2].

While the reaction with acetic anhydride in the series of esters of imidazolyl-2-mercaptoacetic acids terminates in the formation of N-acetyl derivatives [4, 5], when IIIa, b are heated for a long time in acetic anhydride, they undergo cyclization to give esters of imidazo[1,2-a]benzimidazole-3-carboxylic acid (IVa, b). The new imidazole ring is formed by splitting out of water through the acetyl and methylene groups.



II-V a $R=R_1=CH_3$; b $R=CH_2C_6H_5$, $R_1=CH_3$; c $R=CH_3$, $R_1=C_7H_{15}$

After 4-5 h, the yield of cyclization product is 47-50%, but it increases to 85-89% in the presence of sodium acetate.

The structure of IVa-c was confirmed by the IR spectra, in which strong bands are observed at 1710 and 1100-1110 cm^{-1} ($\nu_{C=O}$) and 1600 cm^{-1} ($\nu_{C=N}$), and also by the conversion of IVc to IVa by transesterification.

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*See [1] for communication V.

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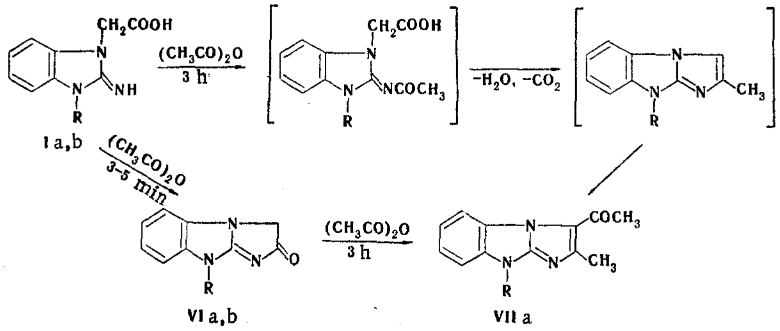
The hydrolysis of IVa, b by hydrochloric acid is accompanied by decarboxylation and leads to 9-alkyl- and 9-aralkyl-2-methylimidazo[1,2-a]benzimidazoles (Va, b) [6]; this is apparently due to the high instability of the initially formed acid IV ($R_1 = H$). In fact, the similarly constructed 3-lithio-9-methyl-2-phenylimidazo[1,2-a]benzimidazole [6] rapidly decomposed to 9-methyl-2-phenylimidazo[1,2-a]benzimidazole on treatment with solid carbon dioxide. The corresponding organolithium compound of Va was not obtained because of the insufficient lability of the halogen in the 3-bromo derivative of Va.

Esters IIIa, b are readily saponified with concentrated hydrochloric acid to the hydrochlorides of the corresponding acids (Ia, b). When Ia, b are heated in acetic anhydride for 3-5 min, they cyclize with splitting out of water to give 9-alkyl- and 9-aralkyl-2-oxo-2,3-dihydroimidazo[1,2-a]benzimidazoles (VIa, b) in 85-90% yield. The latter are also obtained by heating Ia, b in pyridine with acetic anhydride, but the yields are lower (55-60%). The IR spectra of VIa, b show strong absorption bands of the CO group at 1720-1725 cm^{-1}. The spectrum of VIa differs markedly from the IR spectrum of Ia, in which there are bands of the stretching vibrations of hydroxyl and imino groups (3270 and 3360 cm^{-1}, respectively) in addition to the absorption band of the CO group at 1768 cm^{-1}. Subsequent heating (for 3 h) of Ia or VIa in acetic anhydride leads to an unexpected result. In this case, two compounds are formed. The major reaction product (in 50-52% yield) is 3-acetyl-2,9-dimethylimidazo[1,2-a]benzimidazole (VIIa), the structure of which was proved by alternative synthesis by direct acetylation of Va. This compound is resistant to the action of acids and alkalis and forms a 2,4-dinitrophenylhydrazone; the band of a carboxyl group is present in its IR spectrum at 1630 cm^{-1}.

The indicated reaction direction is apparently determined by the ease of opening of the imidazolinone ring. The N-acetyl derivative (Ia) formed in this case cyclizes to 2,9-dimethylimidazo[1,2-a]benzimidazole-3-carboxylic acid under the reaction conditions; the latter is immediately decarboxylated, and the resulting 2,9-dimethylimidazo[1,2-a]benzimidazole undergoes C-acetylation to give VIIa.



I, VI a $R = CH_3$; b $R = CH_2C_6H_5$; VII a $R = CH_3$

The second compound (VIIIa), obtained in low yield (10-12%) by heating Ia or VIa in acetic anhydride, is bright yellow and only slightly soluble in the usual organic solvents; its IR spectrum is almost completely identical to the spectrum of VIa. These data make it possible to propose that VIIIa is the product of condensation of acetic anhydride with two molecules of VIa.

EXPERIMENTAL

1-Benzyl-2-imino-3-carbomethoxymethylbenzimidazoline Hydrochloride (Ib). This compound was obtained in 94% yield by the method used to prepare IIa [2]. The colorless prisms had mp 235° (from alcohol containing ether). Found: C 61.9; H 5.6; Cl 10.2%. $C_{17}HN_3O_2 \cdot HCl$. Calculated: C 61.6; H 5.5; Cl 10.7%.

1-Benzyl-2-imino-3-carboxymethylbenzimidazoline Hydrochloride (IIb · HCl). A solution of 1 g of Ib in 20 ml of concentrated HCl was refluxed for 3 h, and the resulting precipitate was removed by filtration and washed with acetone to give 0.82 g (86%) of colorless needles with mp 239-240° (from alcohol). Found: C 60.2; H 5.5; Cl 11.2%. $C_{16}H_{15}N_3O_2 \cdot HCl$. Calculated: C 60.5; H 5.1; Cl 11.1%.

1-Benzyl-2-imino-3-carboxymethylbenzimidazoline (IIb). This compound was isolated by treatment of IIb · HCl with concentrated ammonium hydroxide solution in the cold. The ammonia was evaporated to give white fibrous needles (93%) with mp 271° (from alcohol containing ether) that were insoluble in water. Found: N 15.2%. $C_{16}H_{15}N_3O_2$. Calculated: N 14.9%.

TABLE 1. Products of the Reaction of 1-Alkyl- and 1-Aralkyl-2-imino-3-carbomethoxymethylbenzimidazolines with Acetic Anhydride

Compound	R	R_1	mp, °C (crystallization solvent)	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
IIIa	CH_3	CH_3	198 (alcohol)	$C_{13}H_{15}N_3O_3 \cdot HCl$*	52	5,5	—	52,4	5,4	—	81,9
IIIb	$CH_2C_6H_5$	CH_3	226 (alcohol)	$C_{19}H_{19}N_3O_3 \cdot HCl$†	61	5,7	—	61	5,4	—	85,7
IVa	CH_3	CH_3	138 (aqueous alcohol)	$C_{13}H_{13}N_3O_2$	63,9	5,3	17,2	64,1	5,4	17,3	89,2
IVb	$CH_2C_6H_5$	CH_3	112 (petroleum ether)	$C_{19}H_{17}N_3O_2$	71,3	5,8	13,0	71,4	5,4	13,1	85,4
IVc	CH_3	C_7H_{15}	79—80 (petroleum ether)	$C_{19}H_{25}N_3O_2$	69,5	7,9	12,8	69,7	7,7	12,9	76

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*Found: Cl 11.4%. Calculated: Cl 11.9%

†Found: Cl 9.8%. Calculated: Cl 9.5%.

2-Acetamido-1-methyl-3-carbomethoxymethylbenzimidazoline Hydrochloride (IIIa). A suspension of 1.02 g (4 mmole) of Ia in 12 ml of acetic anhydride was refluxed until the solid had dissolved completely (1 h). The solution was cooled, 35-40 ml of ether was added, and the resulting precipitate was removed by filtration.

Hydrolysis of IIIa. A. A 0.3-g (1 mmole) sample of IIIa was heated with 5 ml of 20% aqueous KOH solution for 4 h. The solution was acidified with concentrated HCl to give 0.2 g (91%) of 1-methyl-3-carboxymethylbenzimidazolone with mp 208-209° (mp 218-219° [3]). No melting-point depression was observed for a mixture of this product with 1-methyl-3-carboxymethylbenzimidazolone obtained via the method in [3].

B. Heating of IIIa with concentrated HCl for 2 h gave a compound with mp 275° in 85% yield. This compound was identical to a known sample of the hydrochloride of Ia [2].

2,9-Dimethyl-3-carbomethoxyimidazo[1,2-a]benzimidazole (IVa). A. A suspension of 1 g (4 mmole) of IIa in 10 ml of acetic anhydride containing 0.8 g of freshly calcined sodium acetate was refluxed for 5 h. It was then cooled and poured over ice. After the acetic anhydride had decomposed completely, the solution was neutralized with sodium bicarbonate. The resulting precipitate was removed by filtration and washed repeatedly with water. The compound was quite soluble in alcohol, chloroform, and benzene.

Compounds IVb and IVc were similarly obtained (see Table 1).

B. Preparation by transesterification of IVc. A solution of 0.33 g of IVc in 10 ml of methanol was refluxed for 6 h in the presence of catalytic amounts of sodium methoxide. The methanol was removed by distillation, and the residue was treated with water. The solid was removed by filtration and crystallized from aqueous alcohol to give 0.19 g (79%) of product. The product was identical to the compound obtained via method A with respect to chromatography (Al_2O_3, chloroform, development with iodine) and melting point.

9-Benzyl-2-methylimidazo[1,2-a]benzimidazole (Vb). A solution of 0.96 g (3 mmole) of IVb in 15 ml of dilute hydrochloric acid (1:1) was refluxed for 6 h, after which it was cooled and neutralized with 22% ammonium hydroxide. The oily precipitate was extracted with 30-35 ml of chloroform, and the solvent was evaporated to give 0.78 g (95%) of Vb as an oil, which began to crystallize in a vacuum desiccator over P_2O_5 to give colorless prisms with mp 111° (from aqueous alcohol) that were soluble in chloroform, benzene, ether, and alcohol. Found: C 77.8; H 5.8; N 15.7%. $C_{17}H_{15}N_3$. Calculated: C 78.1; H 5.8; N 16.1%. The picrate had mp 192° (alcohol). Found: C 56.2; H 3.8%. $C_{23}H_{18}N_6O$. Calculated: C 56.3; H 3.7%.

9-Methyl-2-oxo-2,3-dihydroimidazo[1,2.-a]benzimidazole (VIa). A solution of 2 g of Ia in 4 ml of acetic anhydride was refluxed for 3-5 min, after which it was cooled, and the precipitate was removed by filtration and washed with ether to give 1.6 g (85%) of product. The product was crystallized from dimethylformamide to give shiny colorless prisms with mp 265-266°. Found: C 64.3; H 5.0 N 22.8%. $C_{10}H_9N_3O$. Calculated C 64.1; H 4.8; N 22.4%. Compound VIb was similarly obtained in 90% yield as colorless prisms with mp 198° (alcohol). Found: C 72.7; H 4.8; N 16.0%. $C_{16}H_{13}N_3O$. Calculated: C 73.0 H 5.0; N 15.9%.

3-Acetyl-2,9-dimethylimidazo[1,2-a]benzimidazole (VIIa). A. A solution of 0.37 g (2 mmole) of Va in 5 ml of acetic anhydride was heated for 3 h, after which it was cooled and poured over ice. The aqueous mixture was neutralized with sodium bicarbonate, and the precipitate was removed by filtration and washed repeatedly with water to give 0.39 g (87%) of colorless needles with mp 178° (from aqueous alcohol) that were soluble in alcohol, chloroform, and benzene. Found: C 68.7; H 5.7; N 18.6%. $C_{12}H_{13}N_3O$. Calculated: C 68.7; H 5.8; N 18.5%. The 2,4-dinitrophenylhydrazone of VIIa was obtained as dark-brown needles with mp 260-261° (from DMF). Found: N 23.7%. $C_{19}H_{17}N_7O_4$. Calculated: N 24.0%.

B. A solution of 1 g of Ia in 10 ml of acetic anhydride was refluxed for 3 h. After 10-12 h, 0.12 g (12%) of VIIIa precipitated from the solution. The precipitate was removed by filtration and washed with water to give yellow prisms with mp 315° (from DMF). The compound was insoluble in the usual organic solvents. Found: C 66.0; H 4.7; N 21.1%. $C_{22}H_{18}N_6O_2$. Calculated: C 66.3; H 4.5; N 21.1%. IR spectrum: ν_{CO} 1710 cm^{-1}. The filtrate was poured over ice and, after the acetic anhydride had decomposed, neutralized with 22% ammonium hydroxide solution. The precipitate was removed by filtration and washed with water. Chromatography of a chloroform solution of the precipitate with a column filled with aluminum oxide gave 0.57 g (50%) colorless crystals with mp 178°. The compound was identical to the product obtained by method A with respect to melting point and chromatography.

3-Acetyl-2,9-dimethylimidazo[1,2-a]benzimidazole Hydrochloride (VIIa · HCl). A 0.23-g (1 mmole) sample of VIIa was treated in the cold with concentrated HCl. The solid was removed by filtration and washed with alcohol to give 0.26 g (quantitative) of colorless needles with mp 276° (from alcohol) that were soluble in water. Found: C 59.5; H 5.6; Cl 12.9%. $C_{13}H_{13}N_3O \cdot HCl$. Calculated C 59.2; H 5.3; Cl 13.4%.

The IR spectra of mineral oil suspensions were recorded with a UR-20 spectrophotometer (the spectra of IVa, b were obtained from chloroform solutions).

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