RESEARCH ON BENZIMIDAZOLE DERIVATIVES.

XXXII*. SYNTHESIS AND TRANSFORMATIONS OF 2-AMINO-3-ACYL-1-METHYLBENZIMIDAZOLIUM SALTS

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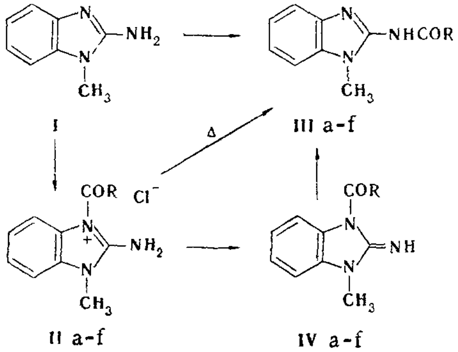
The acylation of 2-amino-1-methylbenzimidazole in acetone proceeds with the formation of 2-amino-3-acyl-1-methylbenzimidazolium salts. When these salts are heated, they rearrange to 2-acylamino derivatives, but they react with bases to give 2-imino-3-acyl-1-methylbenzimidazolines, which are also readily rearranged to 2-acylamino derivatives. The rearrangement of the aroyl derivatives is facilitated when there are acceptor substituents in the aroyl residue.

It has been shown that, as in the case of other amino derivatives of nitrogen heterocycles, acylamino-substituted compounds (III) are formed in the reaction of acid chlorides and anhydrides with 2-amino-1-methyl benzimidazole (I) [2]. We recently established that the reaction of 2-amino-1-methylbenzimidazole (I) with excess benzoyl chloride in acetone solution gives 2-amino-3-benzoyl-1-methylbenzimidazolium chloride (IIb) [3]. Continuing this research, we synthesized a number of compounds of the II type with various acyl residues (Table 1). All of these compounds are characterized by intense absorption of a carbonyl group at 1700-1740 cm^{-1}, which indicates that the acyl group is attached to the ring N atom, inasmuch as the absorption frequency of the carbonyl group in genuine 2-acylamino derivatives (III) [4] is 1620-1700 cm^{-1}. The absorption frequency of the CO group in 1-methyl-2-benzamido-



II-IV a $R=CH_3$; b $R=C_6H_5$; c $R=p\text{-}CH_3OC_6H_4$; d $R=3,4\text{-}(CH_3O)_2C_6H_3$; e $R=p\text{-}BrC_6H_4$; f $R=p\text{-}NO_2C_6H_4$

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*See [1] for communication XXXI.

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benzimidazole hydrochloride (1690 cm^{-1}) also differs substantially from that of salt IIb.

The attachment of the acyl group to the cyclic N atom is confirmed by the presence in the IR spectra of II of a band of deformation vibrations of an unsubstituted amino group (1665-1680 cm^{-1}) [5].

Evidence in favor of the correctness of this assignment is the absence of the indicated band in the spectrum of quaternary salt IIb, which we obtained by acylation of amino-group-deuterated 2-amino-1-methyl-benzimidazole in deuteroacetone. It is remarkable that the ν_{CO} and δ_{NH_2} frequencies for II in mineral oil have the same values as in chloroform solution: this indicates the presence of an intramolecular hydrogen bond.

The physical properties of the compounds obtained (the low melting points and solubility in water and chloroform) correspond to the structure of II. In fact, 2-benzamido-1-methylbenzimidazole hydrochloride has a high melting point (226°) and is not soluble in water or chloroform.

A distinctive feature of IIa-f is their relatively low stability. In aqueous solutions they are almost completely hydrolyzed in 1 h at 20° to 2-amino-1-methylbenzimidazole and the carboxylic acid, and they are hydrolyzed considerably more rapidly in sunlight or on irradiation with UV light. When salts IIa-f are heated in an ampul they are rearranged to 2-acylamino derivates (IIIa-f, Table 2). The rate of this reaction depends markedly on the nature of the substituent in the benzene ring of the aryl group. p-Nitrobenzoyl derivative IIf undergoes rearrangement most readily. Salt IIc, which contains a p-methoxybenzoyl grouping, is rearranged with considerably greater difficulty.

The ease of the rearrangement described here is evidently due to aromatic stabilization of the imdazole ring on passing from II to III, inasmuch as the aromatic character of the imidazole ring in salts IIa-f is sharply reduced. The mechanism of this rearrangement will be considered later.

Despite the ease of hydrolysis of salts IIa-f we were able to convert them to 2-iminobenzimidazolines (IV). The latter are isolated as oils immediately after the addition of sodium carbonate solution to freshly prepared solutions of IIa-f at room temperature. The liberated oil is extracted rapidly with anhydrous benzene. The IR spectra of freshly prepared solutions satisfactorily confirms structures IVa-f. All three fragments characteristic for an imine — C=N, C=O, and N—H groups — appear in their spectra (Table 1). When solutions of the imines are allowed to stand, their IR spectra change substantially, and their absorption ultimately coincides with the absorption of 2-acylamino-1-ethylbenzimidazoles. The introduction of a methoxy group into the para position of the benzoyl group inhibits the rearrangement: the IR spectrum of a benzene solution of IVc remains practically unchanged after 24 h, while the benzoyl derivative (IVb) is completely rearranged to IIIb after the same time. On the other hand, imine IVf is distinguished by the maximum instability: a precipitate of the rearrangement product (IIIf) is formed from its freshly obtained benzene solution after 20-30 min. The introduction of a bromine atom into the benzene ring of the acyl group (IVe) also accelerates the rearrangement of the imine, but to a lesser extent than the introduction of a nitro group. The instability of imines IV is apparently due to the same reason as in the case of quaternary salts II. The rearrangement of imines IV is sharply inhibited in the presence of triethylamine: the IR spectrum of a solution of the imine obtained by the action of triethylamine on a solution of IIb in chloroform does not change after 24 h; this is probably associated with blocking of the carbonyl carbon atom by triethylamine.

By precipitation with petroleum ether we were able to isolate imines IVb and IVc from their benzene solutions and obtain their picrates. The IR spectra very

TABLE 1. IR Spectra of 2-Amino-3-acyl-1-methylbenzimidazolium Chlorides (II) and 3-Acyl-2-imino-1-methylbenzimidazolines (IV)

Compound	In mineral oil		In chloroform			Compound	In benzene		
	ν_{CO}	δ_{NH_2}	ν_{CO}	δ_{NH_2}	ν_{NH_2}		ν_{CO}	ν_{CN}	ν_{NH}
IIa	1720	1675	1740	1675	3370	IVa	1695	1645	3345
IIb	1720	1670	1720	1670	3380	IVb	1700	1660	3360
IIc	1710	1665	1713	1665	3390	IVc	1700	1660	3360
IId	1700	1665	—*	—	—	IVd	1690	1645	3350
IIe	1715	1675	1722	1675	3390	IVe	1695	1650	3360
IIf	1720	1670	1725	1680	3300	IVf	1710	1660	3375

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*Salt IId is only slightly soluble in chloroform.

†A broad, low-intensity band.

TABLE 2. Properties of 2-Amino-3-acyl-1-methylbenzimidazolium Chlorides

Compound	mp, °C	Empirical formula	Found, %		Calc., %		Yield of II, %	Rearrangement conditions		Yield, of III, %
			Cl	N	Cl	N		temp., °C	time, h	
IIa	123	$C_{10}H_{12}ClN_3O$	16	18,9	15,7	18,6	70	85	2,5	70
IIb	125	$C_{15}H_{14}ClN_3O$	12,6	14,9	12,3	14,6	85	170	3,5	68
IIc	140	$C_{16}H_{16}ClN_3O_2$	11,4	13,5	11,2	13,2	82	180	5	65
IId	158	$C_{17}H_{18}ClN_3O_3$	10,5	12,3	10,2	12,1	65	180	5	67
IIe	176	$C_{15}H_{13}BrClN_3O$	9,9	11,7	9,7	11,5	73	120	1	67
IIf	130	$C_{15}H_{13}ClN_4O_3$	10,9	17,1	10,6	16,8	80	100	0,5	84

clearly indicate an imine structure. It should be noted that the stability of the imines increases markedly in the crystalline state. Thus, amine IVb, which rearranges completely in 24 h, remains virtually unchanged in a week in the crystalline form, judging from the IR spectrum.

EXPERIMENTAL

The IR spectra were recorded with a UR-20 spectrometer.

3-Acyl-1-methyl-2-aminobenzimidazolium Chlorides (IIa-f). A solution of 0.5 g (3.4 mmole) of amine I in 20 ml of absolute acetone was added with stirring to a solution of 10.2 mmole of the acid chloride in 20 ml of acetone. A colorless precipitate formed immediately; it was removed by filtration after 1.5 h. The experiments were carried out in a dry box with dry nitrogen.

3-Acyl-1-methyl-2-iminobenzimidazolines (IVb,c). A solution of 7 mmole of sodium carbonate in 1 ml of water was added to a freshly prepared solution of 6 mmole of IIb,c in 4 ml of water, and the imine was extracted rapidly with one 15-ml portion of benzene. The extract was dried by passing through a Schott funnel filled with anhydrous potassium carbonate. Imines IVb,c were precipitated by the action of petroleum ether on the benzene solution. The precipitates were removed by filtration in a dry nitrogen atmosphere to give 1-methyl-3-benzoyl-2-iminobenzimidazoline (IVb) with mp 131-132° in 62% yield. Found: C 71.9; H 5.4; N 16.9%. $C_{15}H_{13}N_3O$. Calculated: C 71.7; H 5.2; N 16.7%. The picrate had mp 279-280°. Found: C 52.4; H 3.2; N 17.3%. $C_{15}H_{13}N_3O \cdot C_6H_3N_3O_7$. Calculated: C 52.5; H 3.4; N 17.4%. 1-Methyl-3-(p-methoxybenzoyl)-2-iminobenzimidazoline (IVc), with mp 160°, was obtained in 65% yield. Found: C 68.5; H 5.7; N 15.3%. $C_{16}H_{15}N_3O_2$. Calculated: C 68.3; H 5.4; N 14.9%. The picrate had mp 250-251°. Found: C 51.6; H 3.4; N 16.3%. $C_{16}H_{15}N_3O_2 \cdot C_6H_3N_3O_7$. Calculated: C 51.8; H 3.6; N 16.5%.

Methylation of Imines IVb,c. A 0.25-g (1 mmole) sample of IIb was dissolved in 2 ml of water, and a solution of 2 mmole of sodium carbonate and 2 ml of water was added. The liberated imine was extracted with 50 ml (500 mmole) of methyl iodide, and the solution was passed through a column filled with anhydrous potassium carbonate and refluxed for ~1 h. The methyl iodide was removed by vacuum distillation, 2 ml of 3% hydrochloric acid was added to the residue, and the mixture was refluxed for 30 min. It was then cooled, made alkaline with sodium carbonate solution, and extracted with chloroform. The chloroform extract was passed through a column filled with aluminum oxide. Compounds IVb and IVc yielded, respectively, 0.14 (47%) and 0.17 g (53%) of 2-methylaminobenzimidazole, with mp 178°, which was identical to the compound described in [7].

2-Acylamino-1-methylbenzimidazoles (IIIa-f). A) the compounds were obtained by Schotten—Baumann acylation of I. Compound IIIc had mp 211-212° (from benzene). Found: C 68.3; H 5.4; N 14.6%. $C_{16}H_{15}N_3O_2$. Calculated: C 68.3; H 5.4; N 14.9%. Compound IIId had mp 169-170° (from benzene and petroleum ether). Found: C 65.5; H 5.4; N 13.3%. $C_{17}H_{17}N_3O_3$. Calculated C 65.7; H 5.5; N 13.4%. Compound IIIe had mp 237-238° (from dioxane). Found: C 54.5; H 3.5; Br 24.1; N 12.7%. $C_{15}H_{12}BrN_3O$. Calculated: C 54.6; H 3.6; Br 24.2; N 12.7%. Compound IIIa,b,f were described in [2, 6].

B) Chloroform solutions of imines IVb,c were evaporated to dryness while protecting them from air moisture. The residual oil was heated at 100-110° for 10-15 min until it solidified, and the solid was dissolved in chloroform and purified with a column containing Al_2O_3. The yields of IIIa-f were 50-60% based on quaternary salts IIa-f.

C) Compounds III were obtained in the form of the hydrochlorides by rearrangement of salts IIa-f by heating in sealed ampuls (Table 2). The bases were isolated by the usual methods.

Compounds IIIa-f obtained by methods A, B, and C were identical.

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