1-[p-(3'-Oxobutyl)aminophenyl]-3-(p-dimethylaminophenyl)benzo[f]quinoline (XII). An alcohol–toluene solution (1:2) of 1.95 g (5 mmole) of amine VIII, 7.5 mmole of methyl vinyl ketone, and five drops of concentrated HCl was heated on a boiling-water bath for 4 h, after which it was cooled and the resulting precipitate was removed by filtration, neutralized with an aqueous-alcohol solution of ammonia, and recrystallized from alcohol or toluene to give 0.9 g (39%) of product.

Amino Ketones IX-XI. These compounds were similarly obtained; the reaction time was 10-15 min.

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RESEARCH ON IMIDAZO[1,2-a]BENZIMIDAZOLE DERIVATIVES

XII.* 3-ACYL-SUBSTITUTED IMIDAZO[1,2-a]BENZIMIDAZOLES

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UDC 547.785.5

Stable 3-acetyl derivatives of imidazo[1,2-a]benzimidazole were synthesized by the action of acetic anhydride on 2,9-disubstituted imidazo[1,2-a]benzimidazole. The former were also obtained by cyclization of 1-alkyl(aralkyl)-3-acylmethyl-2-iminobenzimidazoline hydrobromides in acetic anhydride in the presence of anhydrous sodium acetate. 3-Benzoyl-substituted imidazo[1,2-a]benzimidazoles, which are unstable in acidic media, were synthesized by the action of benzoyl chloride in the presence of pyridine or excess starting imidazo[1,2-a]benzimidazole.

Imidazo[1,2-a]benzimidazoles (Ia-e), like many similarly constructed systems with a nitrogen atom in common [2-4], are readily acetylated in the 3 position on brief heating with acetic anhydride.

*See [1] for communication XI.

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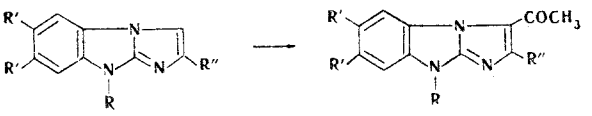


I a-e II a-e

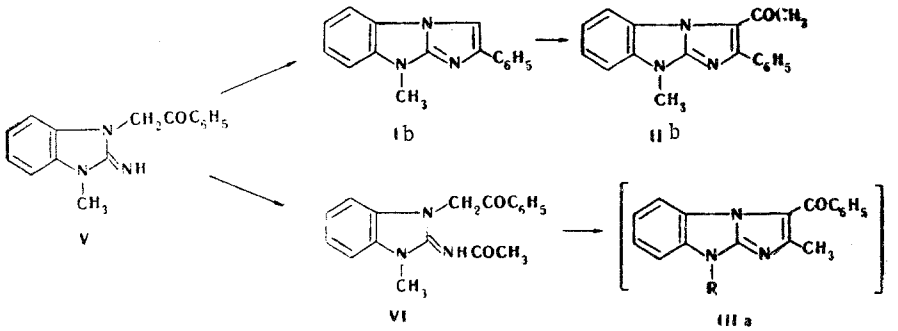
R = CH_3, C_2H_5, $CH_2C_6H_5$; R′ = H, CH_3; R″ = CH_3, C_6H_5, C_6H_4Br

The facile splitting out of an acetyl group on heating in acidic media is characteristic for compounds with an acetyl group attached to a carbon atom with increased electron density. Acetyl-substituted naphtho[2,1-d]pyrrolo[1,2-a]imidazoles [5] and pyrrolo[1,2-a]benzimidazoles [2] are particularly unstable. Imidazo[1,2-a]benzimidazole is the aza analog of the latter, and inasmuch as introduction of an —N = group in place of a —CH= group in the ring usually reduces the π-surplus character of the ring, one might have expected higher stability of acetyl derivatives II with respect to hydrolysis. In fact, 3-acetyl-2,9-dimethylimidazo[1,-2-a]benzimidazole is not hydrolyzed by the action of acids and alkalis [6]. 2-Phenyl derivative IIb readily undergoes acid hydrolysis: Refluxing in dilute hydrochloric acid (1:1) for 5 h leads to complete detachment of the acetyl group. 3-Benzoylimidazo[1,2-a]benzimidazoles (IIIa, b), obtained by the action of benzoyl chloride on Ia, b in the presence of pyridine or excess starting imidazo[1,2-a]benzimidazole, are even less stable: They lose their benzoyl group even when they are dissolved in hydrochloric acid at room temperature.

Acetyl-substituted II readily undergo the usual reactions characteristic for ketones of this type, for example [7], in contrast to 1(3)-acetyl derivatives of pyrrolo[1,2-a]benzimidazole. The latter do not give reaction for a carbonyl group; this is explained [8] by conjugation of the carbonyl group with the nitrogen atom and, as a result of this, polarization of the molecule similar to that observed for carboxylic acid amides.

The band of carbonyl absorption in the spectra of 3-acyl-substituted imidazo[1,2-a] benzimidazoles is shifted to the low-frequency region (1620-1640 cm^{-1}), and this confirms the pronounced electron-donor character of the system [9].

3-Acetyl-2-methylimidazo[1,2-a]benzimidazoles can be obtained by a simpler method — by the action of acetic anhydride on 1-alkyl(aralkyl)-3-acetonyl-2-iminobenzimidazoline hydrobromides (IV) in the presence of anhydrous sodium acetate. The reaction proceeds in one step, and acetyl derivatives are formed in high yields. However, when this reaction is carried out with imine 3-phenacyl derivative V, we were able to isolate two different acetyl derivatives. This is due to reaction via two pathways: cyclization of the imine to imidazo-[1,2-a]benzimidazoles and acylation of the resulting three-ring compound, acylation of the imino group, and cyclization of the resulting 3-acetimidobenzimidazoline derivative VI through the oxygen of the acetyl group and methylene hydrogen atoms of the 3-ketoalkyl grouping.



V Ib IIb VI IIIa

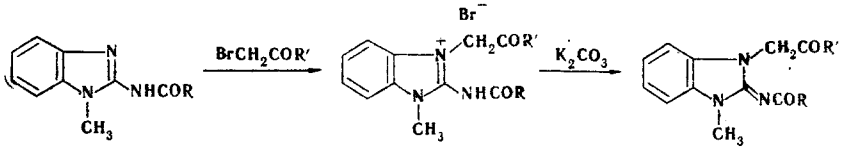
In the case of 3-acetonyl derivatives of 2-iminobenzimidazoline both reaction paths lead to a single reaction product — 3-acetyl-2-methyl-substituted imidazo[1,2-a]benzimidazole. In the case of imine V the desired compound (IIb) is formed via the first pathway. The result of the second transformation is the form of 3-acetyl-2-methylimidazo[1,2-a]benzimidazole (IIa) instead of the expected benzoyl derivative (IIIa). This fact can be explained by the ease of hydrolysis of the latter in acidic media, as noted above, and by acetylation of the resulting 2,9-dimethylimidazo[1,2-a]benzimidazole to give IIa.

TABLE 1. 3-Acyl-Substituted Imidazo[1,2-a]benzimidazoles (IIa-e)

Compound[a]	R	R″	mp, °C[b]	Empirical formula	Found, %			Calc., %			Method	Yield, %
					C	H	N	C	H	N		
IIa	CH_3	CH_3	178	$C_{13}H_{13}N_3O$	68,7	6,0	18.5	68,7	5,8	18,5	A	89
											B	100
IIb	CH_3	C_6H_5	212	$C_{18}H_{15}N_3O$	74,5	5,4	14,3	74,7	5,2	14,5	A	92
											C	56[c]
IIb(H)	CH_3	C_6H_5	240	$C_{24}H_{19}N_7O_4$	51,4	4.2	21,4	61,4	4,1	21,4		
IIbHCl	CH_3	C_6H_5	217	$C_{18}H_{15}N_3O \cdot HCl$[d]	66,2	5,1	12.8	66,4	5,0	12.9		
IIc	$CH_2C_6H_5$	CH_3	170	$C_{19}H_{17}N_3O$	75,2	5,6	13,9	75,2	5,6	13,9	B	95
IIc(H)	$CH_2C_6H_5$	CH_3	218	$C_{25}H_{21}N_7O_4$	62,3	4,6	20.2	62,1	4,4	20,3		
IId[e]	C_2H_5	CH_3	176	$C_{16}H_{19}N_3O$	71,2	7,1	15,6	71,4	7,1	15,6	B	96
IId(H)	C_2H_5	CH_3	216	$C_{22}H_{23}N_7O_4$	58,7	5.0	21,8	58,8	5,2	21,8		
IIe	CH_3	p-C_6H_4Br	197	$C_{18}H_{14}BrN_3O$[f]	58,5	3,8	11,3	58,7	3.8	11,4	A	85
IIe(H)	CH_3	p-C_6H_4Br	267	$C_{24}H_{18}BrN_7O_4$[g]	52,3	3,2	18,0	52,6	3,3	17,9		

[a]The letter "H" designates the 2,4-dinitrophenylhydrazones of II. [b]Compounds IIa-e and IId(H) were crystallized from alcohol, IIb(H), IIc(H), and IIe(H) were crystallized from alcohol—DMF, and IIb·HCl was crystallized from alcohol—ether. [c]Acetyl derivative IIa was also isolated from this reaction in 42% yield. [d]Found: Cl 10.5%. Calculated: Cl 10.9%. [e]In all of the compounds described, R' = H, whereas R' = CH_3 in the case of IId. [f]Found: Br 21.4%. Calculated: Br 21.7%. [g]Found: Br 14.4%. Calculated: Br 14.6%.

We made an attempt to obtain acyl-substituted imidazo[1,2-a]benzimidazole from 2-acylaminobenzimidazoles (VII), as in [10]. Inasmuch as the basicity of the ring nitrogen atom of acylamines VII is lower than the basicities of 2-aminobenzimidazoles, their quaternization by bromo ketones proceeds with much greater difficulty. As in the case of 2-acetimidopyridine [10] and 2-acetimidothiazole [11] derivatives, the cyclization of the hydrobromides VIII in acidic media leads to splitting out of an acyl group and formation of Ia, b.



VII a, b VIII a, b IX a, b

VII–IX a R = CH_3, R′ = C_6H_5; b R = R′ = C_6H_5

Cyclization does not occur in alkaline media, but, as in [11], the bases of acylimines IX are liberated.

The phenacyl group ν_{CO} band appears at 1700 cm^{-1} in the IR spectra of 2-acetimido- and 2-benzimido-1-methyl-3-phenacylbenzimidazolines, whereas the band of carbonyl absorption of the acyl group in the 2 position is shifted to a considerable degree to the low-frequency side (1550 cm^{-1}, in chloroform) [12].

We were able to cyclize VIIIa only by refluxing it in dimethylformamide (DMF) in the presence of triethylamine.

EXPERIMENTAL

The IR spectra of chloroform solutions of the compounds were recorded with a UR-20 spectrometer. Thin-layer chromatography (TLC) was carried out on Al_2O_3 with elution by chloroform and development with iodine vapors.

3-Acetyl-2,9-disubstituted Imidazo[1,2-a]benzimidazoles (IIa-e, Table 1). A) A solution of 2 mmole of 2,9-disubstituted imidazo[1,2-a]benzimidazole in 5 ml of acetic anhydride was

refluxed for 1-2 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed thoroughly with water. In those cases where the acetyl derivative did not precipitate readily, the reaction mixture was poured over ice, and the mixture was neutralized with sodium bicarbonate after decomposition of the acetic anhydride. The precipitate was removed by filtration or extracted with chloroform.

The hydrochlorides of the starting compounds can be used in the reaction, but it is then necessary to carry it out in the presence of anhydrous sodium acetate. The R_f values of the compounds ranged from 0.87 to 0.92.

B) A solution of 1 g of the hydrobromide of 1-alkyl-3-β-ketoalkyl(aralkyl)-2-iminobenzimidazoline in 10 ml of acetic anhydride was refluxed for 30-60 min in the presence of 1 g of anhydrous sodium acetate. The reaction mixture was then poured over ice, and the aqueous mixture was neutralized with 22% ammonium hydroxide. The resulting precipitate was removed by filtration and washed with water. When 3-phenacyl derivative V was subjected to this reaction, the precipitate was a mixture of 3-acetyl derivatives of 2-phenyl- and 2-methylimidazo[1,2-a]benzimidazoles. The latter were separated by recrystallization from alcohol on the basis of the lower solubility of 2-phenyl derivative IIb.

2-Acetimido-1-methyl-3-phenacylbenzimidazoline Hydrobromide (VIIIa). A solution of 1.43 g (7.5 mmole) of 2-acetamido-1-methylbenzimidazole [13] and 1.5 g (7.5 mmole) of phenacyl bromide in 15 ml of ethanol was refluxed for 10 h, after which it was cooled, and the resulting precipitate (1.8 g) was removed by filtration and washed with alcohol and ether. Dilution of the mother liquor with ether yielded another 0.53 g of the hydrobromide for an overall yield of 2.33 g (80%). The product was soluble in hot alcohol and water. The shiny, snowy-white plates had mp 218° (from alcohol). Found: C 55.5; H 4.8; Br 20.3; N 10.5%. $C_{28}H_{17}N_3O_2 \cdot HBr$. Calculated: C 55.7; H 4.7; Br 20.6; N 10.8%.

2-Acetimido-1-methyl-3-phenacylbenzimidazoline (IXa). A 2.5-ml sample of a 2 N solution of K_2CO_3 was added to a hot solution of 0.39 g (1 mmole) of hydrobromide VIII in 6 ml of 50% ethanol, and the solution was cooled gradually to precipitate the product, which was separated and washed with water to give 0.3 g (98%) of small, silky, snowy-white needles with mp 186° (from alcohol) and R_f 0.5 (yellow spot). Found: C 70.3; H 5.8; N 13.4%. $C_{18}H_{17}N_3O_2$. Calculated: C 70.3; H 5.6; N 13.7%. The same compound was obtained by treatment of the hydrobromide with ammonia.

2-Benzimido-1-methyl-3-phenacylbenzimidazoline Hydrobromide (VIIIb). This compound was obtained in 62% yield by refluxing an alcohol solution of equimolecular amounts of 2-benzamido-1-methylbenzimidazole [12] and phenacyl bromide for 12 h. The snowy-white needles had mp 222° (dec.). Found: C 61.6; H 4.7; Br 17.5; N 9.2%. $C_{23}H_{19}N_3O_2 \cdot HBr$. Calculated: C 61.3; H 4.5; Br 17.8; N 9.3%.

3-Benzoyl-9-methyl-2-phenylimidazo[1,2-a]benzimidazole (IIIb). A thoroughly ground mixture of 0.5 g (2 mmole) of 9-methyl-2-phenylimidazo[1,2-a]benzimidazole and 0.5 ml of benzoyl chloride was heated on a glycerol bath at 80° for 2-3 min. As soon as the mixture began to thicken, 1 ml of dry pyridine was added, and the mixture was heated to the boiling point. It was then cooled and diluted with 5 ml of water, and the resulting oily precipitate was separated from the water and treated with ether. The resulting crystals were removed by filtration and washed with ether to give 0.49 g (70%) of slightly yellowish shiny plates with mp 215° (from alcohol). The product was soluble in acetone and chloroform but insoluble in water and ether and had R_f 0.88 (slightly yellowish spot). Found: C 78.7; H 4.8; N 12.4%. $C_{23}H_{17}N_3O$. Calculated: C 78.6; H 4.9; N 12.2%.

3-Benzoyl-2,9-dimethylimidazo[1,2-a]benzimidazole (IIIa). A) A 0.3-ml sample [0.35 g (2.5 mmole)] of freshly distilled benzoyl chloride was added to a solution of 0.93 g (5 mmole) of 2,9-dimethylimidazo[1,2-a]benzimidazole in 15 ml of absolute benzene, and the hydrochloride of the starting compound that precipitated after 1 h was removed by filtration. The mother liquor was evaporated, and the oily residue was treated with ammonia. The resulting precipitate was removed by filtration, washed with water, and air dried. It was then treated with ether to remove traces of the starting compound. The insoluble portion was dissolved in chloroform and chromatographed with a small column filled with aluminum oxide (elution with chloroform) to separate benzoyl derivative IIIa from the $C_6H_5CONH_2$. The yield was 0.36 g (50% based on the converted imidazo[1,2-a]benzimidazole). The slightly yellowish fibrous needles had mp 156° (from benzene) and R_f 0.87 (bright-blue spot that took

on a violet tint on standing). The product was soluble in chloroform and acetone and hot benzene and isooctane, but insoluble in petroleum ether and diethyl ether. Found: C 74.5; H 5.2; N 14.4%. $C_{18}H_{15}N_3O$. Calculated: C 74.7; H 5.2; N 14.5%. The yield of IIIa was much lower under the conditions of benzoylation of 2-phenyl derivative **Ib**, and the reaction was accompanied by the formation of side products.

B) A 0.25-ml sample of dry triethylamine was added to a solution of 0.39 g (1 mmole) of hydrobromide VIIIa in 5 ml of DMF, and the mixture was refluxed for 5 h. It was then cooled, and 10 ml of water was gradually added to it. The resulting precipitate was removed by filtration and purified successively by chromatography and recrystallization from benzene to give 0.14 g (48%) of a product that was identical to the compound isolated via method A.

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RESEARCH ON IMIDAZO[1,2-a]BENZIMIDAZOLE DERIVATIVES

XIII.* SYNTHESIS AND PROPERTIES OF ALCOHOLS OF THE IMIDAZO[1,2-a]BENZIMIDAZOLE SERIES

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A. M. Simonov, G. V. Kovalev,
and S. M. Gofman

UDC 547.785.5.07

Various hydroxy derivatives of imidazo[1,2-a]benzimidazole were synthesized from its 3-bromo, 3-formyl, and 3-acetyl derivatives. The properties and pharmacological activity of the products were studied.

It is well known [2-5] that carbinols in the benzimidazole series display a rather broad spectrum of physiological activity; thus they have antivirus, hypotensive, and local anesthetic properties. The hydroxy-benzyl grouping is primarily responsible, for example,

*See [1] for communication XII.

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