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

IX.* COMPOUNDS OF THE 2-OXO-2,3-DIHYDROIMIDAZO[1,2-a]BENZIMIDAZOLE SERIES AND THEIR TRANSFORMATIONS

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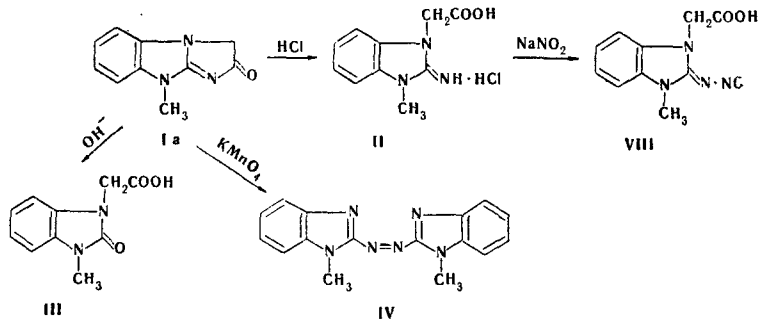
The hydrolysis of the 1,2-amide bond by the action of acids and alkalis, monobromination, and condensation with aldehydes at the methylene group were investigated for 9-methyl-(benzyl)-2-oxo-2,3-dihydroimidazo[1,2-a]benzimidazoles (I). After reduction of the 3-(o-nitro)benzylidene derivative obtained by this condensation, the amino group reacts with the 2-oxo group to give a five-ring system. The synthesis of 1-methyl-2-oxo-2,3-dihydro-imidazo[1,2-a]benzimidazole is described.

In a study of the chemical properties of the previously described [2] 9-R-2-oxo-2,3-dihydroimidazo-[1,2-a]benzimidazoles (Ia, b), we have established that Ia is readily hydrolyzed at the amide 1,2 bond by the action of acid and alkali solutions to give 2-imino-1-methyl-3-carboxymethylbenzimidazoline hydrochloride (II) [3] and 1-methyl-3-carboxymethylbenzimidazolone [4], respectively.

As in the case of imidazo[1,2-a]benzimidazole [5], the oxidation of Ia with potassium permanganate in neutral media leads to opening of the outer imidazole ring to give 1,1'-dimethyl-2,2'-azobenzimidazole (IV).



As compared with the already well-known systems of this type [6-9], the activity of the methylene group in Ia, b is lower. Thus they form condensation products (Va, b, c and VIa, b) (see Table 1) only with the most reactive aldehydes (o- and p-nitrobenzaldehydes, 5-nitrofurfural), while Ia, b do not react with benzaldehyde and nitroso compounds.

Azo coupling with benzenediazonium fluoborates leads to a complex mixture of transformation products from which we were unable to isolate dyes.

A monobromo derivative (VII) is formed in the bromination of Ia in glacial acetic acid. According to the PMR data, bromination proceeds in the benzene ring rather than at the methylene group, since the singlet from two methylene protons at 4.75 ppm, which is in the spectrum of the starting compound, is retained in the spectrum of VII.

*See [1] for communication VIII.

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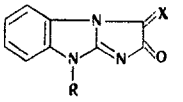
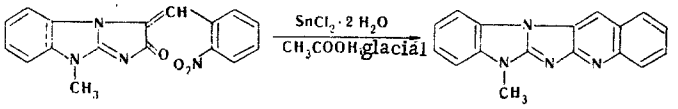
TABLE 1. 3-Arylidene(heterylidene)-9-methyl(benzyl)-2-oxo-2,3-dihydroimidazo[1,2-a]benzimidazoles



Compound	R	X	mp, °C (crystallization solvent)	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
Va	CH_3	p-$NO_2C_6H_4$	317 DMF	$C_{17}H_{12}N_4O_3$	63,9	3,8	17,3	63,7	3,8	17,5	74
Vb	CH_3	5-NO_2-Fur-furylidene	314 Alcohol-DMF	$C_{15}H_{10}N_4O_4$	58,2	3,5	18,1	58,1	3,2	18,1	75
Vc	CH_3	o-$NO_2C_2H_4$	262 DMF	$C_{17}H_{12}N_4O_3$	63,4	3,9	17,2	63,7	3,8	17,5	62
VIa	$CH_2C_6H_5$	p-$NO_2C_6H_4$	300—301 DMF	$C_{23}H_{16}N_4O_3$	69,8	4,3	14,0	69,7	4,1	14,1	70
VIb	$CH_2C_6H_5$	5-NO_2-Fur-furylidene	276 Alcohol-DMF	$C_{21}H_{14}N_4O_4$	65,3	3,8	14,4	65,3	3,7	14,5	76

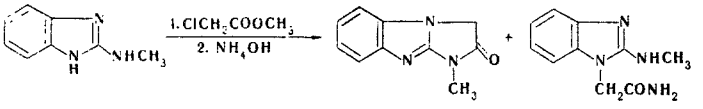
Opening of the imidazoline ring to give (N-nitroso)-2-imino-1-methyl-3-carboxymethylbenzimidazoline (VIII) occurs during the action of excess sodium nitrite on Ia in dilute acetic acid. The structure of VIII was proved by alternative synthesis by nitrosation of II.

Reduction of the 3-(p-nitro)benzylidene derivative (Va) with stannous chloride in glacial acetic acid leads to the corresponding amine (IX). For the o-nitro isomer (Vc), the reaction is accompanied by cyclization through the amino and carbonyl groups. The formation of a five-ring system (X) is confirmed by the IR spectrum, in which bands corresponding to absorption of carbonyl and amino groups are not observed.



Vc X

It seemed of interest to compare the properties of Ia with those of the 1-methyl isomer (XI). To obtain XI, 2-methylaminobenzimidazole (XII) [1] was refluxed with excess methyl chloroacetate for 1 h, after which the reaction mixture was treated with 22% ammonium hydroxide. In this case, two compounds were obtained: one of them proved to be the desired XI (in 23% yield), while the other was 1-carbamylmethyl-2-methylaminobenzimidazole (XIII) (in 64% yield). The structure of the latter was confirmed by alternative synthesis – by fusing 2-methylaminobenzimidazole with chloroacetamide – and by the IR spectrum, which contains absorption bands of a CO group at 1685 cm^{-1} and an NH_2 group at 3310 and 3405 cm^{-1}.



XII XI XIII

Heating of XIII in acetic anhydride gives XI, the structure of which is in agreement with the IR (ν_{CO} 1760 cm^{-1}) and PMR (two distinct singlets at δ 3.22 and 4.73 ppm, related, respectively, to the methyl and methylene protons) spectra. Compound XI condenses with active aldehydes of aromatic character, but, like Ia, does not react with benzaldehyde.

In conclusion, we note that attempts to synthesize 1-benzyl-2-oxo-2,3-dihydroimidazo[1,2-a]benzimidazole (Ib) from 1-benzyl-2-chloroacetamidobenzimidazole (XIV) by splitting out of hydrogen halide [10-12] did not lead to the desired result. When XIV is heated in benzene solution with piperidine, only substitution of the chlorine atom by a piperidine residue occurs. Pyridinium salt XV is formed with pyridine. The action of triethylamine in refluxing benzene and of liquid ammonia (for 30 h) leads to splitting out of a chloroacetyl group and isolation of 1-benzyl-2-aminobenzimidazole. Attempts to accomplish thermal cyclization of XIV were also unsuccessful: when the compound is heated briefly (at 200° for 30-40 min), it remains unchanged, but it resinifies on longer heating.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were measured with a UR-20 spectrophotometer. The PMR spectra were recorded with a PE-2305 spectrometer with an operating frequency of 60 MHz with hexamethyldisiloxane as the internal standard. The chemical shifts are given on the δ

scale and are converted with respect to tetramethylsilane. The spectra of 10% solutions in trifluoroacetic acid solutions at 25° were recorded.

Hydrolysis of 9-Methyl-2-oxo-2,3-dihydroimidazo[1,2-a]benzimidazole (Ia). A. A compound with mp 275° was formed in 92% yield when Ia was heated with concentrated HCl for 5-10 min. No melting-point depression was observed for a mixture of this product with II.

B. A 0.19-g (1 mmole) sample of Ia was refluxed in 4 ml of 10% NaOH solution for 2 h. Acidification of the mixture gave 0.14 g (70%) of a substance with mp 208-209°, which was identical to a genuine sample of III.

Action of Potassium Permanganate on Ia. A 3.6-g sample of potassium permanganate was added to 0.6 g of Ia in 5 ml of water, and the mixture was heated on a water bath for 3 h. It was then cooled, and the precipitate was removed by filtration; the product was extracted with hot acetone. Evaporation of the acetone left 0.32 g of a dark-orange material, which was purified by column chromatography (Al_2O_3 and chloroform) to give bright-orange needles with mp 283-284°. No melting-point depression was observed for a mixture of this product with a genuine sample of IV.

Ylidene Derivatives of 9-R-2-Oxo-2,3-dihydroimidazo[1,2-a]benzimidazoles (Va, b, c and VIa, b). These compounds were obtained by heating equimolecular amounts of Ia (Ib) and the appropriate aldehydes in glacial acetic acid or acetic anhydride for 15-20 min. The resulting precipitates were removed by filtration and washed with ether. In the reaction of Ia with p-nitrobenzaldehyde in glacial acetic acid, we observed the formation of a pale-yellow compound with mp 272° (from alcohol–DMF), which was identified as the hydrate of Va. Found: C 60.7; H 4.2%. $C_{17}H_{12}N_4O_3 \cdot H_2O$. Calculated: C 60.4; H 4.2%. On heating in acetic anhydride, it lost water and was converted to Va.

Bromination of Ia. A solution of 2 mmole of bromine in glacial acetic acid was added with stirring and heating (50-60°) in the course of 30 min to a solution of 0.38 g (2 mmole) of Ia in glacial acetic acid. The precipitated bromo derivative (VII) that formed on cooling the mixture was removed by filtration and washed with ether to give 0.4 g (76%) of slightly yellowish needles with mp 263° (from alcohol–ether). Found: C 44.8; H 3.4; Br 30.4; N 15.9%. $C_{10}H_8BrN_3O$. Calculated: C 45.1; H 3.0; Br 30.0; N 15.8%.

(N-Nitroso)-2-imino-1-methyl-3-carboxymethylbenzimidazoline (VIII). A. A 0.42-g (6 mmole) sample of sodium nitrite was added gradually at room temperature to a suspension of 0.38 g (2 mmole) of Ia in 2 ml of water acidified with acetic acid. The precipitate that formed after 2 days was removed by filtration to give 0.07 g (15%) of dark-yellow prisms with mp 152° (from ethanol). Found: N 23.8%. $C_{10}H_{10}N_4O_3$. Calculated: N 23.9%.

B. A compound identical to that obtained by method A was formed in 76% yield by the action of excess sodium nitrite on II under the conditions of experiment A after 20 min.

3-(p-Aminobenzylidene)-9-methyl-2-oxo-2,3-dihydroimidazo[1,2-a]benzimidazole (IX). A suspension of 1 g of Va in 10 ml of a solution of 3 g $SnCl_2 \cdot 2H_2O$ in glacial acetic acid saturated with hydrogen chloride was heated on a boiling-water bath for 5 h. The resulting tin complex was removed by filtration and decomposed by refluxing for 3-5 min with 10% sodium hydroxide solution. The solid material was removed by filtration and washed with water to give 0.72 g (80%) of pale-orange needles with mp 287° (DMF). Found: C 70.1; H 5.1; N 19.0%. $C_{17}H_{14}N_4O$. Calculated: C 70.3; H 4.9; N 19.3%. IR spectrum (in mineral oil): ν_{CO} 1720, ν_{NH} 3235, 3340 cm^{-1}.

7-Methylquinolino[4,5-b]imidazo[1,2-a]benzimidazole (X). This compound was obtained in 85% yield from Va under conditions similar to those described above. The pale-yellow crystals had mp 321-322° (DMF). Found: C 74.9; H 4.4; N 20.3%. $C_{17}H_{12}N_4$. Calculated: C 75.0; H 4.4; N 20.6%.

Reaction of 2-Methylaminobenzimidazole with Methyl Chloroacetate. A solution of 1.02 g (7 mmole) of XII in 3 ml of methyl chloroacetate was refluxed for 1 h, after which the excess ester was removed by distillation at reduced pressure. The residue was treated with 5 ml of concentrated ammonium hydroxide and extracted with chloroform. The resulting colorless solid amide (XIII) was removed by filtration and washed with chloroform to give 0.85 g (64%) of product. The chloroform layer was separated and evaporated to give 0.32 g (23%) of XI.

1-Carbamylmethyl-2-methylaminobenzimidazole (XIII). Equimolecular amounts of 2-methylaminobenzimidazole and chloroacetamide were fused at 120-125° for 30 min. The mixture was cooled, and the melt was triturated with ether. The solid was removed by filtration and treated with 22% ammonium hydrox-

ide to give an almost quantitative yield of shiny colorless plates with mp 215-216° (from water). Found: C 58.6; H 5.8; N 27.6%. $C_{10}H_{12}N_4O$. Calculated: C 58.8; H 5.9; N 27.4%.

1-Methyl-2-oxo-2,3-dihydroimidazo[1,2-a]benzimidazole (XI). A 0.2 g sample of XIII was heated with 0.8 ml of acetic anhydride for 15-20 min. The precipitate that formed when the mixture was cooled was removed by filtration and washed with ether to give 0.15 g (78%) of colorless fibrous needles with mp 214° (alcohol) that were soluble in hot water, chloroform, and benzene. Found: C 64.3; H 5.0; N 22.7%. $C_{10}N_9N_3O$. Calculated: C 64.1; H 4.8; N 22.5%.

3-(p-Nitrobenzylidene)-1-methyl-2-oxo-2,3-dihydroimidazo[1,2-a]benzimidazole. A 0.19-g (1 mmole) sample of XI was heated in 2 ml of acetic anhydride with 1 mmole of p-nitrobenzaldehyde for 1 h. The precipitate that formed on cooling was removed by filtration to give (in 70% yield) bright-yellow shiny needles with mp 284°. Found: N 17.8%. $C_{17}H_{12}N_4O_3$. Calculated: N 17.5%.

3-(5-Nitrofurfurylidene)-1-methyl-2-oxo-2,3-dihydroimidazo[1,2-a]benzimidazole. This compound was similarly obtained in 82% yield as yellow prisms with mp 278°. Found: C 58.1; H 3.4%. $C_{15}H_{10}N_4O_4$. Calculated: C 58.1; H 3.2%.

1-Benzyl-2-chloroacetamidobenzimidazole (XIV). A solution of 1.36 g (0.012 mole) of chloroacetyl chloride in 5 ml of benzene was added with stirring to a refluxing solution of 2.23 g (0.01 mole) of 1-benzyl-2-aminobenzimidazole in 100 ml of absolute benzene and 1-2 ml of pyridine, and the mixture was refluxed for 3 h. The precipitate that formed after 12 h was removed by filtration and washed thoroughly with water to give 2.25 g (75%) of colorless fibrous needles with mp 210° (benzene). Found: C 64.0; H 4.9; Cl 12.0%. $C_{16}H_{14}ClN_3O$. Calculated: C 64.1; H 4.7; Cl 11.8%. IR spectrum (in mineral oil): ν_{CO} 1632, ν_{NH} 3318 cm^{-1}.

1-Benzyl-2N-piperidinoacetamidobenzimidazole. A solution of 0.3 g (1 mmole) of XIV and 0.2 g (2 mmole) of piperidine in 5 ml of absolute benzene was refluxed for 6 h, after which the solvent was removed by distillation, and the residue was treated with boiling water. The aqueous mixture was filtered to give 0.35 g (quantitative yield) of colorless needles with mp 151° (from aqueous alcohol). Found: C 72.1; H 6.9; N 16.3%. $C_{21}H_{24}N_4O$. Calculated: C 72.4; H 6.9; N 16.1%.

N-(1-Benzyl-2-benzimidazolylaminoacetyl)pyridinium Chloride (XV). A solution of 0.3 g (1 mmole) of XIV in 5 ml of absolute pyridine was refluxed for 4 h. The precipitate that formed on cooling the mixture was removed by filtration and washed with ether to give 0.32 g (84%) of colorless needles with mp 152° (pyridine) that were soluble in water and alcohol. Found: N 14.8%. $C_{21}H_{19}ClN_4O$. Calculated: N 14.8%. IR spectrum (in mineral oil): ν_{CO} 1635, ν_{NH} 3370 cm^{-1}.

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