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

VII.* DEBENZYLATION OF 9-BENZYL-2-PHENYL(METHYL)IMIDAZO-[1,2-a]BENZIMIDAZOLE

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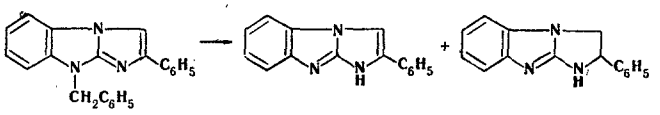
The debenzylation of N-benzylimidazo[1,2-a]benzimidazoles with sodium in liquid ammonia was studied. The debenzylation of the 2-phenyl-substituted derivative is accompanied by hydrogenation of the outer imidazole ring to give 2-phenyl-2,3-dihydro-1H-imidazo[1,2-a]benzimidazole, the alkylation of which in alkaline media and neutral media, respectively, gives the 1-methyl derivative and the 9-methyl derivative. The 1-methyl derivative was subjected to quaternization and bromination; the latter proceeds in the condensed benzene ring. Debenzylation of the 2-methyl derivative of imidazo[1,2-a]benzimidazole is not accompanied by hydrogenation but gives 2-methyl-1(9)H-imidazo[1,2-a]benzimidazole.

In order to obtain imidazo[1,2-a]benzimidazole derivatives without substituents attached to the NH group and in order to further investigate the biological activity of compounds of this series [2], we undertook the debenzylation of 9-benzylimidazo[1,2-a]benzimidazoles by the action of sodium metal in liquid ammonia under the conditions described for imidazole [3] and condensed imidazole systems [4-6].

The action of 2 g-atom of sodium metal on 9-benzyl-2-phenylimidazo[1,2-a]benzimidazole (I) leads to a mixture of three substances: the starting compounds (44%), a substance with mp 221°C (III) (26%), and 2-phenylimidazo[1,2-a]benzimidazole (II) with mp 310° (30%), which is identical to the compound synthesized from 2-aminobenzimidazole and phenacyl bromide (see the following communication) and from 2-chlorobenzimidazole by the method in [7] (in [7] its melting point is too low, viz., 287°).



I II III

When 4-5 g-atom of sodium is used, primarily III (90%) and a small amount (~9%) of II are formed. The debenzylation is accompanied by hydrogenation of the outer imidazole ring and the formation of 2-phenyl-2,3-dihydro-1H-imidazo[1,2-a]benzimidazole (III) (the debenzylation of 2,3-disubstituted 4-benzylpyrrolo[1,2-a]benzimidazoles proceeds similarly [5, 8]); this is confirmed by the results of elementary analysis and the IR, UV, and PMR spectra and also by the chemical transformations of the compound obtained.

The IR spectrum of III contains a band of NH stretching vibrations at 3435 cm^{-1} and a band at 1640 cm^{-1}, which can be ascribed to the C=N bond. The same bands appear in the IR spectrum of 2,3-dihydroimidazo[1,2-a]benzimidazole, which does not have a substituent in the 2 position [9].

The 2,3-dihydro derivative could not be dehydrogenated with chloranil in benzene [10] or even by the action of N-bromosuccinimide [11].

* See [1] for communication VI.

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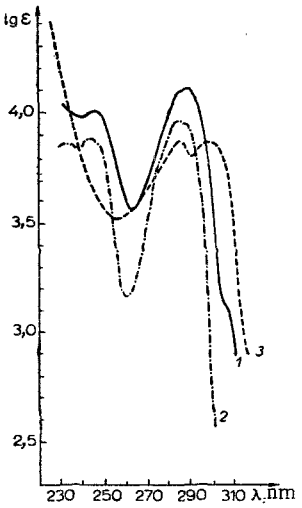


Fig. 1

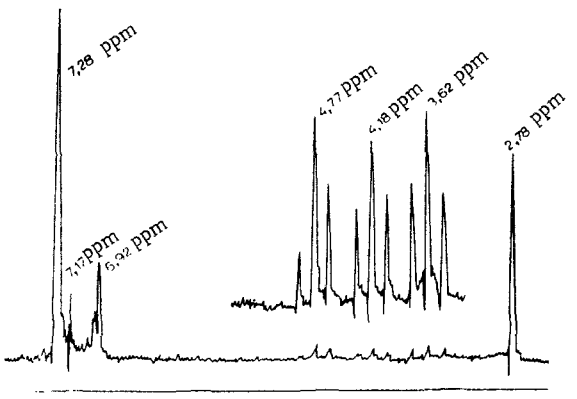
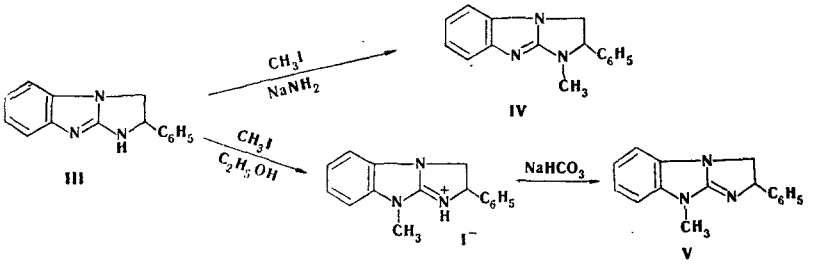


Fig. 2

Fig. 1. UV spectra (in methanol): 1) 2-phenyl-2,3-dihydro-1H-imidazo[1,2-a]benzimidazoles; 2) 1-methyl-2-phenyl-2,3-dihydroimidazo[1,2-a]benzimidazole; 3) 9-methyl-2-phenyl-2,3-dihydroimidazo[1,2-a]benzimidazole.

Fig. 2. PMR spectrum of 1-methyl-2-phenyl-2,3-dihydroimidazo[1,2-a]-benzimidazole (in $CDCl_3$).

Compound III is readily methylated with methyl iodide in liquid ammonia in the presence of sodium amide to give 1-methyl-substituted IV in good yield. The action of methyl iodide in neutral media and decomposition of the resulting hydriodide leads to 9-methyl derivative V. The band of stretching vibrations of the NH group vanishes in the IR spectra of the resulting 1- and 9-methyl derivatives.



A comparison of the UV spectra of III, IV, and V with the spectra of the 1H-, 1-alkyl-, and 9-alkyl-2,3-dihydro derivatives of imidazo[1,2-a]benzimidazoles [9] confirms the proposed structures. The electronic spectra of all of these compounds have absorption bands at 285-300 nm, but, in addition, an absorption maximum at 244-246 nm is characteristic for the 1-methyl and 1-H derivatives of imidazo[1,2-a]benzimidazole, while the 9-methyl derivative does not have a maximum in this region (Fig. 1).

Compounds IV and V are readily quaternized with methyl iodide to give a quaternary salt, which is readily cleaved in alkaline media.

Monobromo derivative VI is formed in quantitative yield by the action of an equimolecular amount of bromine on IV in chloroform. In the PMR spectra of IV and its bromo derivative (VI), the signals from the three protons in the 2 and 3 positions appear as a complex multiplet consisting of 9 lines at 3.5-4.92 ppm, which arise as a result of coupling of the two nonequivalent geminal protons in the 3 position with one another and of each of them with the proton in the 2 position (an ABC system). The overall intensity of all of the peaks in this region is three proton units, which attests to the fact that bromination proceeds in one of the aromatic rings. The signals of the protons of the phenyl groups of the three-ring system appear as a poorly resolved multiplet at 6.92-7.28 ppm (Fig. 2). Oxidation of VI with alkaline potassium permanganate solution leads to benzoic acid; this excludes the entry of bromine into the phenyl ring in the 2 position. Thus bromination proceeds in the condensed benzene ring, but it was found to be dificult to determine more precisely the position of the bromine. In contrast to 3-bromo-2-phenylimidazo[1,2-a]benzimidazole [12], the bromine in VI does not undergo exchange with sodium nitrite and with amines in dimethylformamide.

In an attempt to obtain V by hydrogenation of 9-methyl-2-phenylimidazo[1,2-a]benzimidazole by the Birch method [13, 14] or by refluxing in a protic solvent with sodium metal [14], we isolated, in addition to the starting compound, 1-methyl-2-aminobenzimidazole, which is apparently formed as a result of cleavage of the initially obtained 9-methyl-2,3-dihydro derivative, which is unstable to the action of alkaline agents.

In order to study the nature of the group in the 2 position of 9-benzylimidazo[1,2-a]benzimidazole on debenzylation and hydrogenation, we synthesized 9-benzyl-2-methylimidazol[1,2-a]benzimidazole (VIII) by the usual method [15] starting from 2-amino-1-benzylbenzimidzole (VII) and bromoacetone. Compound VIII can also be prepared directly from VII and acetone by using the method in [16] for the preparation of quaternary salts and cyclization of the resulting imine in concentrated hydrochloric acid without isolation of it (see [17]).

2-Methyl-1(9)H-imidazol[1,2-a]benzimidazole (IX) was isolated in quantitative yield by the action of sodium metal in liquid ammonia on VIII. Thus the outer imidazole ring (at the C_2-C_3 bond) is not hydrogenated in this case. The stretching vibrations of the NH group appear as a distinct band at 3480 cm^{-1} [18] in the IR spectrum of the compound obtained. The PMR spectrum is characterized by the presence of signals of the protons of the CH_3 group at 2.05 ppm and by signals of the protons of the entire aromatic system at 6.9-7.1 ppm.

A difficult-to-separate mixture of isomeric 1-methyl and 9-methyl derivatives is formed in the alkylation of 2-methylimidazo[1,2-a]benzimidazole in alkaline and neutral media.

EXPERIMENTAL

The IR spectra of mineral oil suspensions or chloroform solutions of the compounds were measured with a UR-20 spectrophotometer. The UV spectra of methanol solutions were recorded with an SF-4A spectrophotometer. The PMR spectra of 12% solutions of the substances in $CDCl_3$ and CF_3COOH were obtained with a PE-2305 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard.

Debenzylation of 9-Benzyl-2-phenylimidazo[1,2-a]benzimidazole (I). A. A 0.5-g (0.02 g-atom) sample of sodium was added in small portions in the course of 1 h to a suspension of 3.2 g (0.01 mole) of I in 50-70 ml of liquid ammonia, after which the mixture was stirred for another 10-15 min. It was then added carefully to a solution of 1.2 g (~ 0.02 mole) of ammonium chloride. The ammonia was evaporated, the residue was treated with chloroform, and the precipitate was removed by filtration and washed twice with chloroform. The chloroform solution was evaporated to a small volume and chromatographed with a column filled with Al_2O_3. 9-Benzyl derivative I moved with the front. 2-Phenyl-2,3-dihydro-1H-imidazo[1,2-a]-benzimidazole (III) was eluted with alcohol. Evaporation of the solvents gave 1.4 g (44%) of I and 0.7 g (30%) of III. Compound III was soluble in benzene, acetone, and hot alcohol, but insoluble in water. The snow-white needles had mp 221° (from alcohol). IR spectrum ($CHCl_3$); ν_{NH} 3435, $\nu_{C=N}$ 1643 cm^{-1}. Found: C 76.8; H 5.6; N 18.1%. $C_{15}H_{13}N_3$. Calculated: C 76.6; H 5.5; N 17.9%. The product formed stable picrates and salts with mineral acids.

The chloroform-insoluble residue was treated with hot water to remove the inorganic salts. Drying yielded 0.6 g (26%) of 2-phenyl-1H-imidazo[1,2-a]benzimidazole (II) as large colorless needles with mp 310° (from DMF). The compound was only slightly soluble in most organic solvents. No melting-point depression was observed for a mixture of this product with an authentic sample obtained from 2-aminobenzimidazole. IR spectrum (mineral oil): ν_{NH} 3225, $\nu_{C=N}$ 1683 cm^{-1}. Found: C 77.3; H 4.7; N 18.0%. $C_{15}H_{11}N_3$. Calculated: C 77.3; H 4.7; N 18.0%.

B. The reaction was carried out as in part A, but the amount of sodium was increased to 0.05 g-atom per 0.01 mole of I. After evaporation of the ammonia, the dry residue was treated with chloroform and removed by filtration. Evaporation of the chloroform gave 2.1 g (90%) of III. The ($CHCl_3$-insoluble residue yielded 0.22 g (9.1%) of II.

1-Methyl-2-phenyl-2,3-dihydroimidazo[1,2-a]benzimidazole (IV). A. A 0.46-g (2 mmole) sample of III was added with stirring to a solution of sodium amide obtained from 0.05 g (2 g-atom) of sodium in 50 ml of liquid ammonia containing a few crystals of $Fe(NO_3)_3$. After 30 min, 0.28 g (2 mmole) of cold methyl iodide was added, and the mixture was stirred for another 20 min. The ammonia was then evaporated, and the dry residue was treated with chloroform. The chloroform solution was filtered to remove the inorganic salts, and the filtrate was evaporated. The yield of IV was 0.49 g (~ 100%). Recrystallization from aqueous alcohol gave snow-white needles of the monohydrate with mp 112°. Found: N 16.1%. $C_{16}H_{15}N_3 \cdot H_2O$. Calculated: N 15.7%. The crystal hydrate readily lost water on drying at 100-105° to give the anhydrous com-

pound with mp 146°. IR spectrum ($CHCl_3$): $\nu_{C=N}$ 1643 cm^{-1}. Found: C 77.2; H 5.9; N 17.0%. $C_{16}H_{15}N_3$. Calculated: C 77.1; H 6.0; N 16.9%. The hydrochloride was obtained as fine snow-white needles with mp 234° (from alcohol–ether). Found: C 67.3; H 5.6; Cl 12.3; N 14.8%. $C_{16}H_{15}N_3 \cdot HCl$. Calculated: C 67.3; H 5.6; Cl 12.4; N 14.7%.

B. This same compound was obtained by the action of sodium in liquid ammonia on 9-benzyl-2-phenylimidazo[1,2-a]benzimidazole methiodide, but in this case the compound was more impure, and the yield was 60%.

9-Benzyl-2-phenylimidazo[1,2-a]benzimidazole Methiodide. An alcohol solution of I was refluxed with excess methyl iodide for 12 h to give colorless needles (70%) with mp 257° (dec., from alcohol). Found: C 59.4; H 4.5; I 27.0; N 9.1%. $C_{23}H_{20}IN_3$. Calculated: C 59.3; H 4.4; I 27.3; N 9.0%.

9-Methyl-2-phenyl-2,3-dihydroimidazo[1,2-a]benzimidazole Hydriodide (X). A solution of 0.46 g (2 mmole) of III and 0.5 ml of CH_3I in 10 ml of ethanol was refluxed for 4 h. The next day, the resulting precipitate (0.59 g) was removed by filtration, and the mother liquor was treated with ether to give an additional 0.12 g of substance for an overall yield of 95% of snow-white needles with mp 236° (from alcohol). Found: C 51.2; H 4.4; I 34.1; N 11.2%. $C_{16}H_{15}N_3 \cdot HI$. Calculated: C 50.9; H 4.3; I 33.7; N 11.1%.

9-Methyl-2-phenyl-2,3-dihydroimidazo[1,2-a]benzimidazole (V). A sample of X was heated on a water bath with excess 10% ammonium hydroxide or with sodium carbonate solution until the solid was converted to a colorless oil, which was separated (or extracted with $CHCl_3$), washed with water, and vacuum-dried over P_2O_5 to give a difficult-to-crystallize, hygroscopic, caramel-like substance (in 60% yield) with mp 65°. The hydrochloride was obtained as fine snow-white needles with mp 258° (from alcohol–ether). Found: C 67.5; H 5.8; Cl 12.4; N 14.9%. $C_{16}H_{15}N_3 \cdot HCl$. Calculated: C 67.3; H 5.6; Cl 12.4; N 14.7%.

1(9)-Methyl-2-phenyl-2,3-dihydroimidazo[1,2-a]benzimidazole Methiodide. This compound was obtained in quantitative yield by refluxing an alcohol solution of IV or V with methyl iodide for 3 h. The large colorless needles had mp 234° (dec., from alcohol). Found: C 52.5; H 4.7; I 32.6; N 10.7%. $C_{17}H_{18}IN_3$. Calculated: C 52.2; H 4.6; I 32.4; N 10.8%.

x-Bromo-1-methyl-2-phenyl-2,3-dihydroimidazo[1,2-a]benzimidazole (VI). A solution of 0.2 ml (4 mmole) of bromine in 5 ml of $CHCl_3$ was added slowly with vigorous stirring to a solution of 1 g (4 mmole) of IV in 10 ml of dry $CHCl_3$. After all of the bromine had been added, stirring was continued for another 30-40 min, and the chloroform was then evaporated. The residue was a colorless transparent oil that crystallized rapidly on trituration with ether to give 1.56 g (95%) of fine snow-white needles with mp 268° (from alcohol–ether). Found: C 47.2; H 3.6; Br 39.2; N 10.5%. $C_{16}H_{14}BrN_3 \cdot HBr$. Calculated: C 47.0; H 3.7; Br 39.0; N 10.3%. Base VI was isolated by treatment of the hydrobromide with 10% sodium hydroxide solution. The resulting large colorless needles had mp 195° (from alcohol). Found: C 58.7; H 4.0; Br 24.2; N 12.6%. $C_{16}H_{14}BrN_3$. Calculated: C 58.6; H 4.3; Br 24.3; N 12.8%.

Oxidation of Bromo Derivative VI. A 1-g sample of water-moistened VI was added to a solution of 2.5 g of KOH and 1.5 g of $KMnO_4$ in 20 ml of water, and the mixture was refluxed for 1.5 h, after which 1.5 g of $KMnO_4$ was added, and the mixture was refluxed for another 1 h. Two to three drops of alcohol were then added to the suspension until the solution was completely decolorized. The MnO_2 was removed from the hot solution by filtration, and the filtrate was acidified with acetic acid and extracted with ether. Evaporation of the ether gave 0.24 g (67%) of benzoic acid with mp 122° (from water). No melting-point depression was observed for a mixture with an authentic sample of the acid.

Action of Sodium on 9-Methyl-2-phenylimidazo[1,2-a]benzimidazole in Liquid Ammonia. A stable blue coloration was not formed by the action of a fivefold amount of sodium on the 9-methyl-2-phenyl derivative under the conditions described above for the debenzylation of I. The ammonia was evaporated, and the dry residue was treated with $CHCl_3$. The chloroform was evaporated, and the viscous mass, which had the strong odor of ethylbenzene, was triturated with ether. The resulting crystalline solid was removed by filtration to give 0.9 g (61%) of 2-amino-1-methylbenzimidazole as shiny white plates with mp 201° (from alcohol). No melting-point depression was observed for a mixture with an authentic sample of the compound. The ether solution yielded 0.95 g (38%) of the starting compound.

3-Acetonyl-1-benzyl-2-iminobenzimidazoline (XI). A 6.6-ml (0.08 mole) sample of bromoacetone was added to a hot solution of 17.8 g (0.08 mole) of VII in 150 ml of ethanol, and the mixture was stirred thoroughly while cooling the flask with cold water. After 10-15 min, the precipitated hydrobromide of XI was removed by filtration, washed with ether, and dried at 110° to give 23.5 g (82%) of a product with mp

213° (from alcohol–ether). Found: C 57.0; H 5.1; Br 22.6; N 11.8%. $C_{17}H_{17}N_3O \cdot HBr$. Calculated: C 56.7; H 5.0; Br 22.2; N 11.7%.

Base XI was isolated by treating the hydrobromide with ammonia. The fine snow-white needles had mp 158-159° (from alcohol). IR spectrum ($CHCl_3$): ν_{CO} 1745, $\nu_{C=N}$ 1650, ν_{NH} 3360, δ_{NH} 1620 cm^{-1}. Found: C 72.9; H 6.2; N 15.0%. $C_{17}H_{17}N_3O$. Calculated: C 73.1; H 6.1; N 15.0%.

9-Benzyl-2-methylimidazo[1,2-a]benzimidazole (VIII). A. A 5-g sample of the hydrobromide of XI was refluxed in 150 ml of concentrated hydrochloric acid for 2 h, after which the mixture was cooled, and the hydrochloride of VIII (4.18 g) was removed by filtration, washed with water, and dissolved by heating in alcohol in the presence of ammonia. The solution was then cooled, and the VIII was precipitated with cold water to give 3.45 g (95%) of white fibrous crystals with mp 111° (from aqueous alcohol) after vacuum drying over P_2O_5. The compound was hygroscopic and readily formed a crystal hydrate with mp 80°. The product was identical to the compound previously obtained [1] by saponification of 9-benzyl-2-methyl-3-carbomethoxyimidazo[1,2-a]benzimidazole with hydrochloric acid.

B. A 0.64-g (2.5 mmole) sample of finely ground iodine was added in portions to a stirred solution of 1.12 g (5 mmole) of VII in 10 ml of acetone, and the mixture was refluxed for 1 h. The next day, the acetone was removed by distillation, and 15 ml of concentrated hydrochloric acid was added to the residue. The acid mixture was refluxed for 1.5 h, and the solution was cooled, made alkaline with ammonia, and extracted with chloroform. The chloroform layer was separted, and the crystals of VII (0.55 g; 50% of the amine introduced into the reaction) were removed by filtration and washed with chloroform. The filtrate was evaporated to a small volume and chromatographed on Al_2O_3 (with $CHCl_3$ as the eluent). The yield of VIII with mp 111° (after drying) was 0.54 g (87% based on the amount of amine that underwent reaction).

2-Methyl-1(9)H-imidazo[1,2-a]benzimidazole (IX). A 10-mmole sample of VIII was debenzylated with 25 g-atom of sodium. The ammonia was evaporated, the residue was treated rapidly with dry chloroform, the inorganic salts were removed by filtration, and the chloroform was evaporated to give a quantitative yield of brownish crystals of IX. The reaction product was quite unstable and decomposed on storage in air and light. The yellowish prisms had mp 194° (dec., from benzene). The compound was soluble in acetone and alcohol, but insoluble in water and petroleum ether. IR spectrum ($CHCl_3$): ν_{NH} 3480, δ_{NH} 1615, $\nu_{C=N}$ 1650 cm^{-1} [19]. Found: C 70.4; H 5.5; N 24.3%. $C_{10}H_9N_3$. Calculated: C 70.2; H 5.3; N 24.5%.

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