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

VIII.* 1H- AND 1-METHYL-2-PHENYLIMIDAZO[1,2-a]BENZIMIDAZOLES AND THEIR REACTIVITIES

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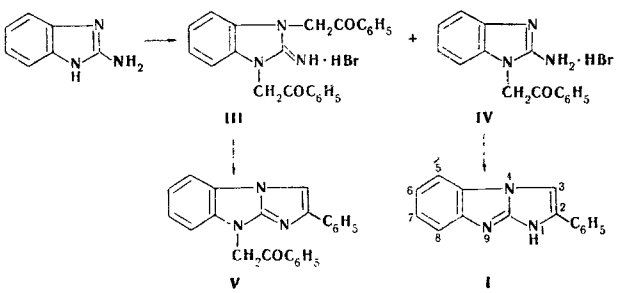
UDC 547.785.5.1:541.67

1H-2-Phenyl- and 1-methyl-2-phenylimidazo[1,2-a]benzimidazoles were synthesized by the action of phenacyl bromide on 2-amino- and 2-methylaminobenzimidazoles and subsequent cyclization of the resulting 1-phenacyl derivatives. The reactivities of the compounds obtained with respect to electrophilic substitution reactions were studied. It is shown that bromination proceeds in the 3 position of the imidazole ring, while hydroxymethylation proceeds in the benzene ring of the heterocycle. Calculations by the LCAO MO method within the π-electron approximation for the 1H and 9H tautomers of 2-phenylimidazo[1,2-a]-benzimidazole, which are in complete agreement with the experimental data, are presented.

The reactivities of 9-substituted imidazo[1,2-a]benzimidazoles have been quite well studied [2-5], but there is no information in the literature regarding the behavior of the tautomeric 1-substituted compounds. The aim of the present research was the preparation of 1-substituted imidazo[1,2-a]benzimidazoles and a study of their behavior with respect to electrophilic agents.

Since 2-phenylimidazo[1,2-a]benzimidazoles with an unsubstituted NH group (I) could not be obtained in good yield by debenzylation of 9-benzyl-substituted I with sodium metal in liquid ammonia [1], we worked out a method for its preparation from 2-aminobenzimidazole. Similarly, we synthesized 1-methyl-2-phenylimidazo[1,2-a]benzimidazole (II) from 2-methylaminobenzimidazole.

The reaction of phenacyl bromide with 2-aminobenzimidazole in acetone in the cold gives a mixture of 1,3-diphenacyl-2-iminobenzimidazoline hydrobromide (III) and 1-phenacyl-2-aminobenzimidazole hydrobromide (IV).



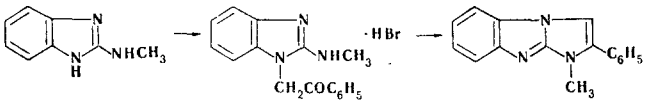
When a twofold excess of phenacyl bromide is used, the yield of III increases to 85-90%. Both of the compounds are readily cyclized on refluxing with hydrochloric acid to give 9-phenacyl-2-phenylimidazo[1,2-a]benzimidazole (V) and I, respectively.

*See [1] for communication VII.

Scientific-Research Institute of Physical and Organic Chemistry. Rostov State University, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 797-802, June, 1973. Original article submitted June 9, 1972.

Alkylation of I with methyl iodide in liquid ammonia in the presence of sodium amide to give II gives unsatisfactory yields because of the poor solubility of the starting compound in this solvent.

The reaction of methylamine with 1-benzyl-2-chlorobenzimidazole in alcohol (in an autoclave at 150°C for 18 h) gave 1-benzyl-2-methylaminobenzimidazole, the debenzylation of which with sodium in liquid ammonia leads to 2-methylaminobenzimidazole (VI), which could not be obtained directly [6] from 2-chlorobenzimidazole and methylamine (only benzimidazolone was isolated). Refluxing VI with phenacyl bromide in alcohol gives a quantitative yield of 2-methylamino-1-phenacylbenzimidazole (VIII) hydrobromide, which is cyclized to II on refluxing in concentrated hydrochloric acid [7].

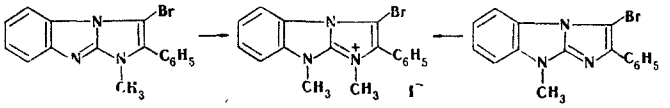


VII II

Compound II can also be obtained by dehydrogenation [8] of 1-methyl-2-phenyl-2,3-dihydroimidazo-[1,2-a]benzimidazole [1] with active manganese dioxide in chloroform at 50-70° for 15-20 h.

In contrast to 9-methyl-2-phenylimidazo[1,2-a]benzimidazole [3, 4], II does not undergo such electrophilic substitution reactions as nitrosation, azo coupling, formylation, and acylation. Hydroxymethylation proceeds with much more difficulty (refluxing in 40% formaldehyde solution) than for the 9H tautomer [5]. The resulting hydroxymethyl derivative is quite readily oxidized to the aldehyde by active manganese dioxide. The position of the formyl group can be established on the basis of the chemical transformations of the compound obtained. The methiodide, which is not identical to 9-methyl-2-phenyl-3-formylimidazo-[1,2-a]benzimidazole methiodide [3], is formed quite readily by the action of methyl iodide. Since benzoic acid was obtained in the oxidation of the aldehyde with alkaline potassium permanganate solution, it can be assumed that hydroxymethylation proceeds in the benzene ring entering into the heterocyclic system.

The action of bromine on II in chloroform readily gives 1-methyl-3-bromo-2-phenylimidazo[1,2-a]-benzimidazole (VIII), the benzenesulfonate and methiodide of which are identical to the benzenesulfonate and methiodide of 9-methylimidazo[1,2-a]benzimidazole [2].



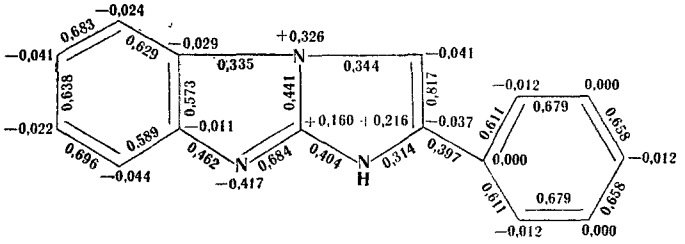
VIII IX

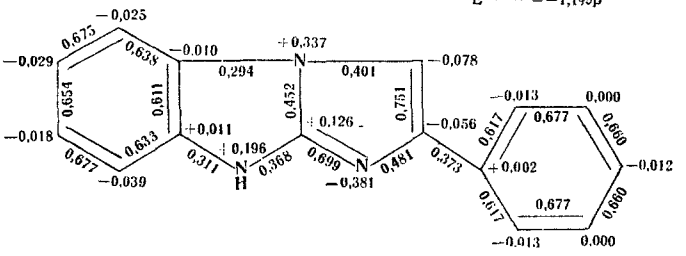
The bromine in the compound obtained proved to be of low reactivity in nucleophilic substitution reactions. It could not be replaced by nitro and amino groups by heating with sodium nitrite and, respectively, diethylamine in dimethylformamide (DMF).

Calculation of both tautomeric forms of imidazo[1,2-a]benzimidazole by the Hückel LCAO MO method within the π-electron approximation showed that the greatest π-electron density is in the 2 and 3 position of 9H-2-phenylimidazo[1,2-a]benzimidazole. This result is in agreement with our previous experimental data [2-5], which attest to the high reactivity of the 3 position of 9-alkylimidazo[1,2-a]benzimidazoles in electrophilic substitution reactions.

The middle imidazole ring in the 9H tautomer is a π-surplus ring and, consequently, should have a tendency to eject the superfluous π electron into the condensed outer imidazole ring, which is also the most π-electron-enriched ring (see [9]). In the case of the 1H tautomer, the outer imidazole ring is a π-surplus ring, and ejection of the superfluous π electron into the benzimidazole fragment of the molecule should occur. As a result of this, the electron density in the 3 position decreases as compared with the electron density of the 9H derivative by a factor of almost two. This causes a decrease in the reactivity of the 1H tautomer with respect to electrophilic substitution reactions; this is in complete agreement with the experimental data presented above.

When our study had been completed, there appeared a patent communication [10] regarding the reaction of 2-aminobenzimidazole with phenacyl bromide and the production of I and V. However, the reaction conditions described in the patent are completely different from those proposed by us.





EXPERIMENTAL

The IR spectra were recorded with a UR-20 spectrophotometer. The quantum-mechanical calculations were made with the Streitwieser parameters via the method described in [9].

Reaction of 2-Aminobenzimidazole with Phenacyl Bromide. A 0.8-g (4 mmole) sample of phenacyl bromide was added to a warm solution of 0.52 g (4 mmole) of 2-aminobenzimidazole in 15 ml of acetone, and the mixture was stirred thoroughly until the bromide had dissolved completely. The solution was then allowed to stand. The next day, the resulting precipitate (1.12 g) was removed by filtration and washed with acetone. It proved to be a mixture of two substances, which were separated by treatment with boiling alcohol. The insoluble portion of the precipitate [0.37 g (41% based on phenacyl bromide)], with mp 295° (dec., from aqueous alcohol), was 1,3-diphenacyl-2-iminobenzimidazoline hydrobromide (III). Found: C 61.2; H 4.5; Br 17.4; N 9.3%. $C_{23}H_{19}N_3O_2 \cdot HBr$. Calculated: C 61.3; H 4.5; Br 17.7; N 9.3%.

The alcohol solution on cooling and on addition of ether yielded 0.74 g (56% based on phenacyl bromide) of a white fibrous precipitate of 2-amino-1-phenacylbenzimidazole hydrobromide (IV) with mp 250° (on introduction into the hot melting-point apparatus; from alcohol). Found: C 54.3; H 4.2; Br 23.9; N 12.5%. $C_{15}H_{13}N_3O \cdot HBr$. Calculated: C 54.2; H 4.2; Br 24.0; N 12.6%.

Compound III was also formed in 85-90% yield on reaction of 2-aminobenzimidazole with 2 moles of phenacyl bromide and in quantiative yield on refluxing 2-amino-1-phenacylbenzimidazole with an equivalent amount of phenacyl bromide.

1,3-Diphenacyl-2-iminobenzimidazoline. This compound was obtained by treatment of III with ammonia. The large silky needles had mp 213° (from alcohol). IR spectrum (in chloroform), cm^{-1}: ν 1650 (C=O), 1712, 1620 (C=N), 3363 (CNH). Found: C 74.5; H 5.1; N 11.6%. $C_{23}H_{19}N_3O_2$. Calculated: C 74.8; H 5.2; N 11.4%.

9-Phenacyl-2-phenylimidazo[1,2-a]benzimidazole (V). A 0.9-g sample of III (the base form) was refluxed in 30 ml of concentrated HCl for 2 h. The mixture was cooled, and the voluminous fibrous precipitate was removed by filtration and washed with water and acetone to give 0.95 g (quantitative) of white silky needles with mp 265° (from alcohol–water). Found: C 71.3; H 4.8; Cl 9.0; N 10.8%. $C_{25}H_{17}N_3O \cdot HCl$. Calculated: C 71.2; H 4.7; Cl 9.1; N 10.8%.

Treatment of the resulting hydrochloride with ammonia in the cold for 1 h gave V, which was obtained as white needles (which yellowed slightly on heating in a desiccator) with mp 207-208° (dec., from aqueous alcohol). Found: C 78.6; H 5.1; N 12.1%. $C_{23}H_{17}N_3O$. Calculated: C 78.6; H 4.9; N 12.0%. IR spectrum (in chloroform), cm^{-1}: ν 1712 (C=O), 1620 (C=N).

2-Amino-1-phenacylbenzimidazole. An excess amount of 22% ammonium hydroxide was added to a hot aqueous alcohol solution of IV, and the solution was heated to the boiling point and allowed to stand. The precipitate that formed on cooling was removed by filtration and washed with water to give a quantita-

tive yield of large slightly cream-colored needles (from alcohol). When a capillary containing the substance was introduced into the hot melting-point apparatus to determine its melting point, it melted at 225° without decomposition, after which the melt began to crystallize and melted again only at ~300°. Cyclization apparently occurred during melting. When a capillary containing the substance was introduced into the cold apparatus and heated slowly, the substance gradually decomposed without melting (200-275°). Found: C 72.0; H 5.5; N 17.0%. $C_{15}H_{13}N_3O$. Calculated: C 71.7; H 5.2; N 16.7%. IR spectrum (in mineral oil), cm^{-1}: ν 1695 (C=O), 3425 and 3325 (NH), 1555 (C=N).

1H-2-Phenylimidazo[1,2-a]benzimidazole (I). A 0.3-g sample of IV was refluxed for 2 h with 10 ml of concentrated HCl, during which the solid changed but did not dissolve. The mixture was cooled, and the solid was removed by filtration and washed with water. It was then heated in alcohol in the presence of excess ammonia for 5 min to give 0.21 g (91.3%) of large colorless crystals with mp 310° (from DMF) [1]. In determination of the melting point, the capillary containing the substance was introduced into the hot device at a temperature ~20-30° below the melting point.

1-Benzyl-2-methylaminobenzimidazole. An 80-ml sample of a saturated (in the cold) methanol solution of methylamine, which was obtained from 50 g of methylamine hydrochloride and 50 ml of methanol, was added to 10 g of 1-benzyl-2-chlorobenzimidazole [11]. The mixture was stirred and heated in an autoclave at 150° for 18 h. The solvent was removed, and the residue was triturated with water. The white crystals of 1-benzyl-2-methylaminobenzimidazole were removed by filtration and washed twice on the filter with water to give 9.6 g (98.5%) of a product with mp 175° (from aqueous alcohol). Found: C 75.7; H 6.4; N 17.7%. $C_{15}H_{15}N_3$. Calculated: C 75.9; H 6.4; N 17.7%.

2-Methylaminobenzimidazole (IV). A 1.15-g (~50 mmole) sample of sodium metal was added in portions in the course of 1 h to a suspension of 3.6 g (15 mmole) of 1-benzyl-2-methylaminobenzimidazole in 100-125 ml of liquid ammonia, and the dark-blue solution was stirred and held on a cooling bath for another 1-1.5 h, after which 3 g of ammonium chloride was added carefully. The ammonia was evaporated, and the residue was treated with chloroform. The solid was treated with cold water, removed by filtration, and washed twice on the filter with water to give 1.6 g (71%) of large colorless plates with mp 193° (from water). Found: C 65.2; H 6.4; N 28.6%. $C_8H_9N_3$. Calculated: C 65.3; H 6.2; N 28.5%.

It is significant that a smaller amount of sodium and a stirring time less than 1 h lead to unsatisfactory results, since in this case debenzylation proceeds with lower yields, and a large amount of starting compound is recovered.

2-Methylamino-1-phenacylbenzimidazole. A solution of 0.45 g (3 mmole) of VI and 0.6 g (3 mmole) of phenacyl bromide in 5 ml of alcohol was refluxed for 2.5 h. The mixture was then cooled, ether was added, and the precipitated hydrobromide (VIII) was removed by filtration. The yield was quantitative. The compound was isolated as a crystal hydrate with one molecule of water. The snow-white silky needles had mp 164° (dec., from alcohol–ether). Found: Br 21.9; N 11.3%. $C_{16}H_{15}N_3O \cdot HBr \cdot H_2O$. Calculated: Br 21.9; N 11.5%.

Treatment of VII [sic] with ammonia gave snow-white needles of the base with mp 169-170° (from aqueous alcohol). Found: C 72.5; H 5.4; N 16.0%. $C_{16}H_{15}N_3O$. Calculated: C 72.4; H 5.7; N 15.8%.

1-Methyl-2-phenylimidazo[1,2-a]benzimidazole (II). A. A mixture of 0.4 g of VII (in the base form) and 10 ml of concentrated HCl was refluxed for 2 h. The solution was cooled, neutralized with 22% ammonium hydroxide, and extracted with chloroform. The extract was evaporated to give 0.37 g of II as white crystals with mp 127° (from aqueous alcohol). The yield was quantitative. Found: C 77.8; H 5.4; N 16.8%. $C_{16}H_{13}N_3$. Calculated: C 77.7; H 5.3; N 17.0%.

B. This compound was also obtained by the method in [7]. A 7-g sample of 2-chloro-1-phenacylbenzimidazole in a methanol solution of methylamine, obtained by saturation of 50 ml of methanol with methylamine (from 50 g of $CH_3NH_2 \cdot HCl$), was heated in an autoclave at 150° for 7 h. The solution was cooled and evaporated, and the II was purified by chromatography with a column filled with Al_2O_3 (elution with chloroform) to give 5.5 g (88%) of white crystals, identical to those obtained by method A. The hydrochloride was obtained as shiny snow-white prisms with mp 243° (dec., from alcohol–ether). (mp 238-240° [7]).

3-Bromo-1-methyl-2-phenylimidazo[1,2-a]benzimidazole (VIII). This compound was formed as the hydrobromide in quantitative yield by the action of an equivalent amount of bromine on a solution of II in chloroform at room temperature. The shiny white plates had mp 259° (dec., from alcohol). Found: C 47.4; H 3.4; Br 39.1; N 10.4%. $C_{16}H_{12}BrN_3 \cdot HBr$. Calculated: C 47.2; H 3.2; Br 39.3; N 10.3%. The base of the bromo derivarive was isolated by treatment of the hydrobromide with ammonia to give colorless needles

with mp 205° (from alcohol). Found: C 59.2; H 4.0; Br 24.2; N 12.9%. $C_{16}H_{12}BrN_3$. Calculated: C 58.9; H 3.7; Br 24.5; N 12.9%.

3-Bromo-1,9-dimethyl-2-phenylimidazo[1,2-a]benzimidazolium Benzenesulfonate. This compound was obtained in 87% yield by fusing VIII with a twofold amount of methyl benzenesulfonate at 80° for 5 min. The melt was triturated with acetone to give a white solid with mp 227°. No melting-point depression was observed for a mixture of this product with the benzenesulfonate obtained from the 9-methyl derivative [5].

3-Bromo-1,9-dimethyl-2-phenylimidazo[1,2-a]benzimidazolium Methiodide. This compound was obtained by the action of a saturated aqueous solution of potassium iodide on a hot alcohol solution of IX. The strongly electrically charged silky needles had mp 265° (dec., from 90% aqueous alcohol). This compound was also identical to that obtained from the 9-methyl derivative. Found: C 43.7; H 3.5; Br, I 44.4; N 9.0%. $C_{17}H_{15}BrIN_3$. Calculated: C 43.6; H 3.2; Br, I 44.2; N 9.0%.

Hydroxymethyl-1-methyl-2-phenylimidazo[1,2-a]benzimidazole. A suspension of 0.5 g (2 mmole) of II in 7 ml of 40% formaldehyde solution was refluxed for 2 h. The starting compound was converted to an oil, which gradually began to crystallize. The mixture was cooled, and the solid was removed by filtration, washed with water, and dried in a desiccator at 110° to give 0.53 g (95.7%) of white needles with mp 211° (from alcohol). IR spectrum (in mineral oil), cm^{-1}: ν 3135 (OH, broad), 1055, 1380 (δ_{OH} C—O). IR spectrum (in chloroform), cm^{-1}: ν 3610 (OH), 1045, 1270 (δ_{OH} C—O) [12]. Found: C 73.3; H 5.4; N 15.1%. $C_{17}H_{15}N_3O$. Calculated: C 73.6; H 5.4; N 15.1%.

Formyl-1-methyl-2-phenylimidazo[1,2-a]benzimidazole. A 6-g sample of activated manganese dioxide [13] was added to a stirred solution of 0.6 g of the hydroxymethyl derivative in 25 ml of dry chloroform, and stirring was then continued until oxidation was complete (as followed by chromatography). After 20-30 min, a distinct yellow spot (Al_2O_3, elution with $CHCl_3$, development with iodine, R_f 0.78), which emerges above the starting compound (R_f 0.44), appeared on the chromatogram. At the end of the reaction, the manganese dioxide was removed by filtration and washed on the filter with chloroform. The chloroform solution was evaporated to give a quantitative yield (0.58 g) of the aldehyde. The compound was isolated as the crystal hydrate with mp 133°. On drying at 70-80°, the crystals lost water and were converted from large colorless needles to a slightly yellowish finely crystalline material with mp 160° (from alcohol). IR spectrum (in chloroform), cm^{-1}: ν 1665 (C=O), 1638 (C=N). Found: C 74.2; H 4.8; N 15.5%. $C_{17}H_{13}N_3O$. Calculated: C 74.2; H 4.8; N 15.3%.

2,4-Dinitrophenylhydrazone. This was obtained as dark-red silky needles with mp 274° (from DMF). Found: N 21.5%. $C_{23}H_{17}N_7O_4$. Calculated: N 21.5%.

The methiodide was formed in 87% yield by refluxing (for 4 h) an alcohol solution of the formyl derivative with excess methyl iodide. The snow-white needles had 233° (dec., from alcohol). Melting-point depression (210-212°) was observed for a mixture of this product with 9-methyl-2-phenyl-3-formylimidazo-[1,2-a]benzimidazole methiodide. Found: N 10.1%. $C_{18}H_{16}IN_3O$. Calculated: N 10.1%.

Oxidation of the formyl derivative with potassium permanganate in alkaline media proceeded readily and gave benzoic acid with mp 122° in 66% yield.

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