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

XVI.* SYNTHESIS OF 3-ALKOXYCARBONYL-2-ARYLIMIDAZO[1,2-a]BENZIMIDAZOLES

T. A. Kuz'menko, V. A. Anisimova,
N. I. Avdyunina, and A. M. Simonov

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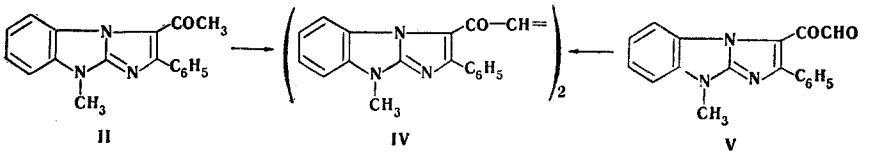
3-Alkoxycarbonyl-2-arylimidazo[1,2-a]benzimidazoles were synthesized by alkaline cleavage of 3-trichloromethyl ketones of the imidazo[1,2-a]benzimidazole series, which are formed by acylation of this three-ring system with trichloroacetyl chloride. The same compounds were also obtained by esterification of the corresponding 3-carboxylic acid. The haloform reaction with 3-acetyl-2-phenylimidazo[1,2-a]benzimidazole proceeds anomalously and leads to bis(9-methyl-2-phenylimidazo[1,2-a]-benzimidazol-3-yl)-2-buten-1,4-dione, the structure of which was confirmed by independent synthesis.

Compounds that surpass dibasol with respect to their degree of lowering of arterial pressure and the duration of their action have been found among 3-alkoxycarbonyl derivatives of 2-methylimidazo[1,2-a]benzimidazole [2]; however, their activity is lower than that of some other derivatives of this heterocycle. It is known that replacement of the methyl group in the 2 position of imidazo[1,2-a]benzimidazole by a phenyl group leads to intensification of the activity and a decrease in the toxicity of the compounds [2, 3]. The task of the present research was to work out the synthesis of 3-alkoxycarbonyl-2-arylimidazo[1,2-a]benzimidazoles (I).

An attempt to obtain them via the scheme proposed for the corresponding 2-methyl-substituted compounds [4] was unsuccessful, since the starting 2-benzimido-1-methyl-3-methoxycarbonylmethylbenzimidazoline is not formed either by fusion of 2-benzamido-1-methylbenzimidazole with α-haloacetic esters or by benzoylation of 3-methoxycarbonylmethyl-2-imino-1-methylbenzimidazoline with benzoyl chloride in alkaline media (because of the instability of 2-imino-3-benzimidazolinylacetic acid esters with respect to the action of basic reagents [5]).

We therefore selected stable derivatives of 2-arylimidazo[1,2-a]benzimidazoles themselves as the starting compounds. However, unsaturated diketone IV was obtained instead of the expected 2-phenylimidazo[1,2-a]benzimidazole-3-carboxylic acid (III) in the haloform reaction with the readily accessible 3-acetyl-2-phenylimidazo[1,2-a]benzimidazole (II).

To prove its structure via the scheme proposed for the synthesis of phenylglyoxal [6], we synthesized the corresponding glyoxal V from (9-methyl-2-phenylimidazo[1,2-a]benzimidazol-3-oyl)methylpyridinium iodide (VI) through nitrone VII. Diketone IV was obtained by condensation of glyoxal V with 3-acetyl derivative II under the conditions in [7].



II IV V

The peculiar course of the haloform reaction in the imidazo[1,2-a]benzimidazole series made us decide to study the possibility of the synthesis of the necessary trihalo ketones by acylation of 2-arylimidazo[1,2-a]benzimidazoles with trichloroacetyl chloride. We found

*See [1] for communication XV.

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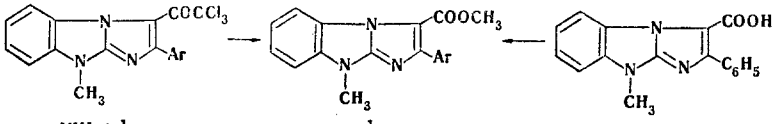
that this reaction proceeds under mild conditions, but the yields of 3-trichloro ketones VIII do not exceed 40%, since half the starting imidazo[1,2-a]benzimidazole is tied up by the hydrogen chloride liberated in the reaction. The use of pyridine, triethylamine, or sodium bicarbonate as the hydrogen-chloride acceptor does not raise the yields of ketones.

When trichloro ketones VIII are heated briefly with sodium methoxide, they are converted to 3-methoxycarbonyl-9-methyl-2-arylimidazo[1,2-a]benzimidazoles (I). In addition to the bands peculiar to the imidazobenzimidazole ring, characteristic bands of an ester grouping appear in their IR spectra at 1680 (C=O) and 1140 cm^{-1} (C–O–C).



I, VIII a Ar = C_6H_5; b Ar = $C_{10}H_7$-α

The esters are readily hydrolyzed in acidic and alkaline media. The acid hydrolysis of Ia is accompanied by decarboxylation of acid III; this is probably due to a decrease in the electron density in the 3 position owing to protonation of the 1-N atom. The salt of acid III is formed under alkaline conditions; the free acid was isolated from a solution of the salt by careful acidification. The free acid is stable under ordinary conditions and can also be synthesized in almost quantitative yield by carboxylation of the 3-lithio derivative of imidazo[1,2-a]benzimidazole [8].

Taking into account the unsatisfactory yields of trichloro ketones VIII, we attempted to obtain ester Ia starting from the acid described above. Only traces of the ester were obtained by heating its lithium salt with an alkyl halide. 3-methoxycarbonyl derivative Ia was obtained in 50-55% yield in the case of esterification with diazomethane. We were able to raise the yield of ester Ia to 86% by treatment of acid III with thionyl chloride and refluxing the resulting acid chloride with alcohol.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer.

1,4-Bis(9-methyl-2-phenylimidazo[1,2-a]benzimidazol-3-yl)-2-butene-1,4-dione (IV). A) A total of 10 ml of 10% NaOH solution was added to a solution of 1.17 g (4 mmole) of ketone II in 50 ml of dioxane, and a solution of 3.04 g of iodine and 6 g of potassium iodide in 30 ml of water was then added dropwise with stirring, initially at room temperature until a persistent dark color developed, after which the temperature was raised to 60°C; the iodine solution was added as the color vanished. The mixture was then cooled, and diluted to twice its original volume with water, and the precipitate was removed by filtration and washed with water and a small amount of alcohol to give 0.59 g (52%) of greenish-yellow fibrous needles with mp 328°C (from DMF). Found: C 7.49; H 4.4; N 14.3%. $C_{36}H_{26}N_6O_2$. Calculated: C 75.2; H 4.6; N 14.6%. IR spectrum: 1595, 1620 (C=C and C=N); 1625 cm^{-1} (C=O).

B) A solution of 0.29 g (1 mmole) of ketone II and 0.3 g (1 mmole) of glyoxal V in butanol was heated in the presence of catalytic amounts of 20% NaOH for 2 min, and the resulting precipitate was removed by filtration and washed with water to give 0.56 g (98%) of a compound that was identical to the compound obtained in experiment A.

3-Glyoxyloyl-9-methyl-2-phenylimidazo[1,2-a]benzimidazole (V). A solution of 0.29 g (1 mmole) of 3-acetyl-9-methyl-2-phenylimidazo[1,2-a]benzimidazole (II) and 0.25 g (1 mmole) of finely ground iodine in 3 ml of pyridine was refluxed with stirring for 30 h, after which it was cooled, and the precipitated iodide VI was removed by filtration and washed with water, a small amount of alcohol, and ether to give 0.28 g (57%) of a product with mp 244-246°C (dec., from alcohol). Found: C 55.4; H 4.2; I 25.9; N 11.2%. $C_{23}H_{19}IN_4O$. Calculated: C 55.9; H 3.9; I 25.7; N 11.3%. A total of 2 ml of 5% NaOH was added dropwise with stirring to a cooled (with an ice bath) suspension of 0.49 g (1 mmole) of pyridinium salt VI and 0.15 g (1 mmole) of p-nitrosodimethylaniline in 7 ml of alcohol. After 1 h, the brick-red precipitate was removed by filtration and washed with water to give 0.35 g (80%) of nitrone VII

as orange prisms with mp 196-198°C (dec., from alcohol). Found: C 71.4; H 5.2; N 16.1%. $C_{26}H_{23}N_5O_2$. Calculated: C 71.4; H 5.3; N 16.0%. Glyoxal V was formed by acidification of a cooled (to 0-5°C) suspension of 0.87 g (2 mmole) of nitrone VII in 10 ml of water to pH 1 with concentrated HCl. The yield of colorless crystals with mp 156-157°C (from butanol) was 0.47 g (77%). IR spectrum: 1620 and 1640 cm^{-1} (C=O). Found: C 71.7; H 4.3; N 13.6%. $C_{18}H_{13}N_3O_2$. Calculated: C 71.3; H 4.3; N 13.9%.

9-Methyl-3-trichloroacetyl-2-phenylimidazo[1,2-a]benzimidazole (VIIIa). A 0.12-ml (1 mmole) sample of trichloroacetyl chloride was added to a solution of 0.48 g (2 mmole) of 9-methyl-2-phenylimidazo[1,2-a]benzimidazole in 20 ml of dry benzene, and the precipitated hydrochloride of the starting compound was removed by filtration (after 2 h) and washed on the filter with chloroform until the wash liquid became colorless. The filtrate was evaporated to give 0.32 g (41%) of bright-yellow fibrous crystals with mp 230°C (dec., from alcohol). IR spectrum: 1640 cm^{-1} (C=O). Found: C 55.0; H 3.3; Cl 27.3%. $C_{18}H_{12}Cl_3N_3O$. Calculated: C 55.0; H 3.1; Cl 27.1%.

9-Methyl-3-trichloroacetyl-2-naphthylimidazo[1,2-a]benzimidazole (VIIIb). This compound was similarly obtained from 9-methyl-2-naphthylimidazo[1,2-a]benzimidazole [9]. The yield of yellow crystals with mp 245°C (from alcohol) was 43%. Found: C 59.7; H 3.4; Cl 23.6%. $C_{22}H_{14}Cl_3N_3O$. Calculated: C 59.7; H 3.2; Cl 24.0%.

3-Methoxycarbonyl-9-methyl-2-phenylimidazo[1,2-a]benzimidazole (Ia). A) A 0.39-g (1 mmole) sample of trichloro ketone VIIIa was heated for 3 min in a solution of sodium methoxide prepared from 0.1 g of sodium and 5 ml of methanol. The reaction mixture was then cooled, and the precipitate (0.2 g) was removed by filtration and washed with water. Dilution of the mother liquor with water gave an additional 0.07 g of ester Ia. The yield of colorless needles with mp 147°C (from ethyl acetate) was 0.27 g (93%). The product was readily soluble in chloroform, benzene, and acetone. Found: C 70.8; H 5.0; N 13.7%. $C_{18}H_{15}N_3O_2$. Calculated: C 70.8; H 5.0; N 13.8%.

B) A suspension of 0.7 g (2.5 mmole) of 3-carboxy-9-methyl-2-phenylimidazo[1,2-a]benzimidazole (III) in an ether solution of diazomethane (a tenfold excess) was allowed to stand at 5°C for 24 h, after which the precipitate of unchanged acid was removed by filtration, and the mother liquor was evaporated to dryness to give 0.4 g (55%) of a product that was identical to the compound obtained in experiment A.

C) A mixture of 0.29 g (1 mmole) of acid III and 0.12 g (1 mmole) of thionyl chloride in 5 ml of dry benzene was refluxed until the solid had dissolved completely (2 h). Absolute methanol (0.5 ml) was then added, and the mixture was refluxed for another 35 min. The solvent was then removed by evaporation, and the residue was treated with 10% NH_4OH and purified by chromatography with a column filled with Al_2O_3 (elution with chloroform) to give 0.26 g (86%) of product. No melting-point depression was observed for a mixture of this product with an authentic sample of ester Ia.

3-Methoxycarbonyl-9-methyl-2-naphthylimidazo[1,2-a]benzimidazole (Ib). This compound was obtained in 95% yield from trichloroacetyl derivative VIIIb under conditions similar to those described above in experiment A. The colorless prisms had mp 172°C (from alcohol). Found: C 74.2; H 4.9; N 11.6%. $C_{22}H_{17}N_3O_2$. Calculated: C 74.3; H 4.8; N 11.8%.

3-Carboxy-9-methyl-2-phenylimidazo[1,2-a]benzimidazole (III). A) A 0.3-g (1 mmole) sample of ester Ia was refluxed in 20% NaOH solution for 3 h, after which the mixture was cooled, and the precipitate was removed by filtration and washed with aqueous acetone. A solution of the salt of acid III in 5 ml of water was acidified carefully to pH 4-5 with acetic acid, and the resulting precipitate was removed by filtration, washed with water, and dried at 80°C to give colorless crystals with mp 171-172°C (dec., from butanol). Found: C 69.8; H 4.7; N 14.3%. $C_{17}H_{13}N_3O_2$. Calculated: C 70.1; H 4.5; N 14.4%.

B) A toluene solution of 3-lithio-9-methyl-2-phenylimidazo[1,2-a]benzimidazole [8], obtained from 1.65 g of 3-bromo-9-methyl-2-phenylimidazo[1,2-a]benzimidazole, was poured over dry ice, after which the excess CO_2 was allowed to vaporize, and the residue was treated with 50 ml of water. The aqueous layer was separated and acidified to pH 4-5 with acetic acid,

and the precipitate was removed by filtration and washed with water to give 1.3 g (94%) of a product that was identical to the compound obtained in experiment A.

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NMR SPECTRA OF PYRIMIDINES.

EFFECT OF SUBSTITUENTS ON THE CHEMICAL SHIFT OF THE PARA PROTONS IN 2- AND 5-SUBSTITUTED PYRIMIDINES

O. P. Shkurko and V. P. Mamaev

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The chemical shifts of the protons of the pyrimidine ring in the 2 position for a series of 5-substituted pyrimidines and in the 5 position for a series of 2-substituted pyrimidines in solutions in dimethyl sulfoxide were determined. The correlation equations that link the relative chemical shifts with the F and R substituent constants were calculated. The correlation equations were analyzed by comparison with the corresponding correlation equation for a series of monosubstituted benzenes. The reasons for the change in the conductivity of the electronic effects of the substituents via inductive and conjugation mechanisms in the pyrimidine ring as compared with the conductivity in the benzene ring are discussed.

Gronowitz and co-workers [1] in a study of the PMR spectra of 2- and 5-substituted pyrimidines pointed out the nonequivalence of the effect of substituents on the chemical shifts of the protons in the para positions relative to the substituent. However, the insufficiently extensive set of investigated compounds and the small differences in the chemical shifts have made it impossible to draw an unambiguous conclusion regarding the nature of this effect.

Continuing our research on the transmission of the effects of substituents in the pyrimidine ring [2, 3] we determined the chemical shifts of the protons of the pyrimidine ring in the 2 position ($\delta_{2\text{-H}}$) for 5-substituted pyrimidines and in the 5 position ($\delta_{5\text{-H}}$) for 2-substituted pyrimidines (Table 1). The relative chemical shifts presented in [1] for acetone solutions were found to be close to the values that we found for solutions of the same compounds in dimethyl sulfoxide (DMSO). A qualitative comparison of the values presented in both columns of Table 1 confirms the conclusion [1] regarding the different effects of substituents in each of the series presented. This difference is displayed most distinctly for strong electron-donor or strong electron-acceptor substituents. For example, the presence

Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Academy of Sciences of the USSR, Novosibirsk 630090.

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