IMIDAZOINDOLES.

3.* ALKYLATION OF 7,8-DIMETHYLIMIDAZO[4,5-e]INDOLE

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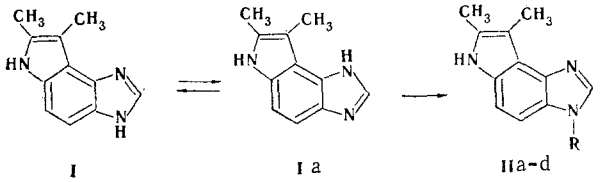
It is demonstrated that products of monoalkylation of 7,8-dimethylimidazo[4,5-e]-indole at the N_3 atom are formed in dioxane in the presence of sodium alkoxide or an aqueous solution of potassium hydroxide in the case of alkylation with alkyl halides, ethylene oxide, and acrylonitrile. The structures were proved by alternative synthesis and comparison of the UV spectra with the spectra of model structures.

The aklylation of benzimidazoles proceeds successfully when they are treated with alkyl halides, dimethyl sulfate, epoxides, and diazomethane [2, 3]. The mechanism of the alkylation of imidazole and benzimidazole has been discussed by A. M. Simonov [4]. However, the direction of the reaction in the case of unsymmetrical benzimidazoles has not yet been ascertained. Although the cyanoethylation of 5(6)-nitro- [5] and 5(6)-methylbenzimidazoles [6] and the alkylation of 5(6)-chloro- [7], 5(6)-methyl- [8], and 5(6)-nitrobenzimidazoles [9] with methyl iodide and benzyl chloride have been described, the data obtained are extremely contradictory. Thus, it has been reported that the ethylation of 5(6)-nitrobenzimidazole with diethyl sulfate gives primarily the 1,6 isomer [10], while methylation with dimethyl sulfate in alkali or without alkali gives equal amounts of the 1,5 and 1,6 isomers [11], whereas alkylation with alkyl halides gives primarily the 1,5 isomer [9].

We have studied the direction of alkylation of imidazo[4,5-e]indoles in the case of the accessible 7,8-dimethylimidazo[4,5-e]indole (I). In connection with the tautomerism of the imidazole ring (I ⇄ Ia), two isomers could be formed even in the case of selective alkylation of the system in the imidazole ring. We found that one monoalkylation product is formed in 44-80% yields in dioxane in the presence of sodium alkoxide or an aqueous solution of potassium hydroxide by the action of ethylene oxide, acrylonitrile, or aklyl halides. In addition, quaternary salts were also isolated in 5-7% yields in the case of alkylation with alkyl halides.



I Ia IIa-d

II a R = CH_3; b R = n-C_4H_9; c R = CH_2CH_2OH; d R = CH_2CH_2CN

To prove the structures of the resulting substances we synthesized samples with a fixed position of the alkyl groups at the N_1, N_3, and N_6 atoms. Starting from 2,4-dinitrochlorobenzene we obtained 1-alkyl-5-nitrobenzimidazoles, which were converted to 3-alkyl-7,8-dimethylimidazo[4,5-e]indoles (IIa, b, d) through the corresponding hydrazines [1].

Quaternization of IIe [1] gave quaternary salt III, by elimination of the benzyl group, in which (as in the synthesis of difficult-to-obtain 1,6-disubstituted benzimidazoles [12]) we obtained isomer IV with a methyl group attached to the nitrogen atom.

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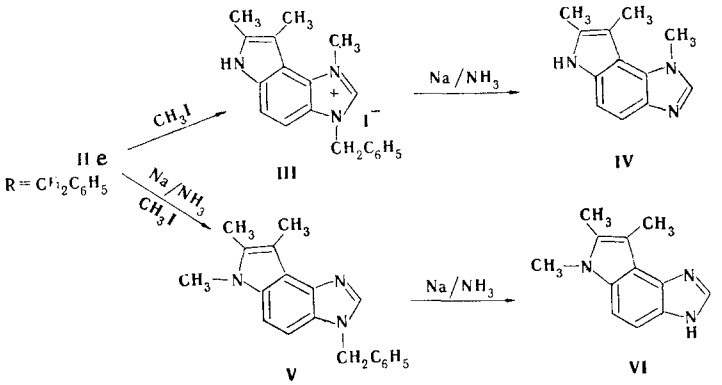
Compound V was obtained by alkylation of the sodium salt of IIe, in which the imidazole ring is protected by a benzyl group. Subsequent elimination of the benzyl group led to a third isomer, viz., VI with a methyl group attached to the N_6 group.



Compounds IIa and IV, which are substituted in the imidazole ring, have higher melting points (>300°C) and are less soluble than VI, which is substituted in the indole ring. The IR spectra of all three compounds contain an absorption band at 3475 cm^{-1}, and the stretching vibrations of the free NH group of both the indole and imidazole parts of the imidazolo[4,5-e]indole derivatives show up at the same frequency, as a result of which the spectrum of I contains only one absorption band in this region. The UV spectra of the isomers differ substantially (see Fig. 1) and can be used for identification. The UV spectrum of IIa, obtained from I by the action of methyl iodide or dimethyl sulfate, contains one long-wave absorption band, just as in the case of a sample that is known to contain a methyl group attached to N_3. In addition, IV was not detected in the reaction mixture by chromatographic monitoring of the alkylation with methyl iodide. Compounds IIb, c obtained by alkylation of I with butyl iodide and ethylene oxide did not depress the melting points of samples that were known to contain the corresponding substituents in the 3 position. Like the UV spectrum of IId obtained by alkylation of I with acrylonitrile, the UV spectra of these compounds contain one long-wave band that is characteristic for 3-alkylimidazo[4,5-e]indoles.

Thus 7,8-dimethylimidazo[4,5-e]indole undergoes alkylation at the N_3 atom in all cases.

The use of a concentrated solution of alkali, which does not mix with dioxane, in the case of alkylation with alkyl halides makes it possible to assume that the substrate, which exists in dioxane in the form of a suspension, does not form an anion but undergoes the reaction as a neutral molecule. The tautomeric equilibrium of the imidazole ring may be shifted to favor structure Ia under the influence of the NH group of indole, as observed for other unsymmetrical systems [13]. The observed alkylation in the 3 position is then understandable if one takes into account the preferableness of attack of the alkylating agent at the p pair of electrons of the "pyridine" nitrogen atom of tautomer Ia. The selectivity of the alkylation may also be a consequence of steric hindrance at the N_1 atom created by the methyl group in the 8 position. However, IIe, which has a benzyl group in the 3 position, undergoes quaternization at the N_1 atom to give the product in good yield, although prolonged heating is required, whereas a quaternary salt is formed in very low yield in the case of alkylation. Consequently, steric hindrance, while not having a decisive effect, may hinder reaction at the N_1 atom of tautomer I, which is present in lower concentrations.

The 7,8-dimethylimidazo[4,5-e]indole molecule possibly undergoes alkylation with ethylene oxide and acrylonitrile in the form of an anion, since the reaction is carried out in the presence of catalytic amounts of sodium ethoxide. The steric hindrance at the N_1 atom in this case evidently has a decisive effect in connection with the reaction with bulkier alkylating agents.

EXPERIMENTAL

The UV spectra of solutions of the compounds (~10^{-3} mole/liter) were recorded with a Hitachi EPS-3T spectrophotometer. The IR spectra of solutions of the compounds in chloroform were recorded with a UR-10 spectrometer. The course of the reaction and the individuality of the compounds obtained were monitored by thin-layer chromatography (TLC) on plates with loose Al_2O_3 (activity II) in a benzene–ethanol system (5:1) and on Silufol UV-254 plates in a cyclo-

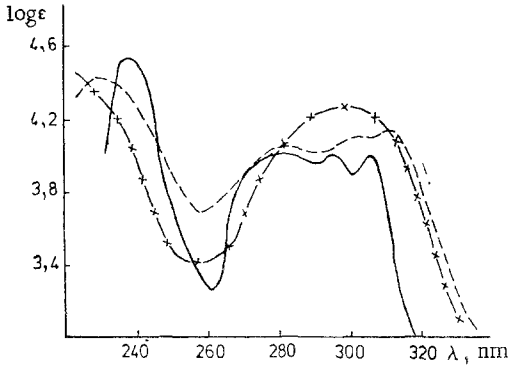


Fig. 1. UV spectra of isomeric N,7,8-trimethylimidazolo[4,5-e]indoles I (–×–×–×–) IV (———), and VI (– – –) in ethanol.

hexane–acetone–pyridine system (4:5:1) (B). The molecular weights of the compounds were measured with an MKh-1303 mass spectrometer.

7,8-Dimethylimidazo[4,5-e]indole (I) and 3-alkyl-7,8-dimethylimidazo[4,5-e]indoles (IIa-e) were obtained by cyclization of the corresponding 5-hydrazinobenzimidazoles with methyl ethyl ketone [1].

3,7,8-Trimethylimidazo[4,5-e]indole (IIa). A) A solution of 3.36 g (06 mole) of potassium hydroxide in 6 ml of water and 5.6 ml (0.09 mole) of methyl iodide was added to a suspension of 5.55 g (0.03 mole) of I in 100 ml of dioxane, and the mixture was stirred at room temperature for 3 h (until the spot of starting I vanished on the TLC chromatogram). The reaction passed through the solution stage, after which a new precipitate began to form. The precipitate was removed by filtration and washed with water and acetone to give 4.17 g of a substance that gave two spots with R_f 0.66 and 0.07 (system A) and R_f 0.27 and a spot at the start (system B). Four fractional crystallizations from alcohol yielded 2.65 g (44%) of IIa with mp 300°C (decomp.) and R_f 0.66 (system A) and 0.27 (system B). UV spectrum, λ_{max} (log ε): 301 nm (4.29). Found: C 72.4; H 6.5; N 21.0%; M^+ 199. $C_{12}H_{13}N_3$. Calculated: C 72.3; H 6.6; N 21.1%; M 199. In addition, fractional crystallization yielded 0.55 g (5.3%) of a quaternary salt with mp 285-287°C and R_f 0.07 (system A) and a spot at the start (system B). Found: C 45.7; H 4.8; N 12.3%. $C_{13}H_{16}IN_3$. Calculated: C 45.8; H 4.7; N 12.3%. The precipitates and mother liquors remaining after filtration were monitored thoroughly for the presence of isomer IV by TLC (in system B with development in air; isomer IV gave a green spot with R_f 0.13). Isomer IV was not detected in even a single case.

B) A 3.93-ml sample of an aqueous solution (66%) of potassium hydroxide was added to a suspension of 3.7 g (0.02 mole) of I in 39 ml of acetone, 3.94 ml (0.042 mole) of dimethyl sulfate was added dropwise with vigorous stirring and heating (50-60°C), and the mixture was stirred at the same temperature for 10-20 min. The precipitate was removed by filtration and washed with acetone and water to give 2.8 g (70.5%) of IIa, which was identical to the compound obtained by method A.

3-Butyl-7,8-dimethylimidazo[4,5-e]indole (IIb). A solution of 2.24 g (0.04 mole) of potassium hydroxide in 6 ml of water and 6.8 ml (0.06 mole) of butyl iodide was added to a suspension of 3.6 g (0.02 mole) of I in 50 ml of dioxane, and the mixture was heated with stirring for 2.5 h. At the end of the reaction (monitoring by TLC), the reaction mixture was evaporated to two-thirds of its original volume, and the resulting precipitate was removed by filtration and washed with a small amount of acetone and water to give 3.13 g (63%) of IIb with mp 181-182°C (from aqueous alcohol). No melting-point depression was observed for a mixture of this product with 3-butyl-7,8-dimethylimidazo[4,5-e]indole [1]. The product had R_f 0.73 (system A). UV spectrum, λ_{max} (log ε): 301 nm (4.19). Found: C 74.8; H 7.9; N 17.4%; M^+ 241. $C_{15}H_{19}N_3$. Calculated: C 74.7; H 7.9; N 17.4%; M 241. A 0.43-g (5%) sample of the quaternary salt was obtained from the dioxane mother liquor and acetone wash solutions after evaporation and chromatography with a column filled with aluminum oxide [elution with benzene–alcohol (5:1)]. UV spectrum, λ_{max} (log ε): 253 (4.19) and 301-306 nm (3.97). Found: I 30.0; N 9.5%. $C_{19}H_{22}IN_3$. Calculated: I 29.8; N 9.8%.

3-Hydroxyethyl-7,8-dimethylimidazo[4,5-e]indole (IIc). A 1-ml sample of a 3% alcohol solution of sodium ethoxide and 18 ml of ethylene oxide were added to a suspension of 3.7 g

(0.02 mole) of I in 50 ml of dioxane, and the mixture was heated in a sealed flask on a water bath for 4 h. The precipitate was removed by filtration and washed with water to give 2.91 g (63.5%) of IIc with mp 231-232°C (from alcohol). No melting-point depression was observed for a mixture of this product with 3-hydroxyethylimidazo[4,5-e]indole [1]. The product had R_f 0.39 (system A). UV spectrum, λ_{max} (log ε): 300 nm (4.22). Found: C 68.4; H 6.4; N 18.5%; M^+ 229. $C_{13}H_{15}N_3O$. Calculated: C 68.1; H 6.6; N 18.3%; M 229.

3-Cyanoethyl-7,8-dimethylimidazo[4,5-e]indole (IId). A 1-ml sample of a 3% alcohol solution of sodium ethoxide and 1.4 ml (0.02 mole) of acrylonitrile were added to a suspension of 3.7 g (0.02 mole) of I in 100 ml of dioxane, and the mixture was stirred at 50°C for 15-20 min. A few minutes after the addition of the acetonitrile, the starting solid dissolved, and a precipitate began to form. At the end of the reaction (monitoring by TLC), the precipitate was removed by filtration and washed with alcohol to give 4.05 g (85%) of IId with mp 235-236°C (from alcohol). The product had R_f 0.59 (system A). UV spectrum, λ_{max} (log ε): 300-302 nm (4.32). Found: C 70.2; H 6.1; N 23.4%; M^+ 238. $C_{14}H_{14}N_4$. Calculated: C 70.6; H 5.9; N 23.5%; M 238.

3-Benzyl-7,8-dimethylimidazo[4,5-e]indole Methiodide (III). A 5-ml (0.1 mole) sample of methyl iodide was added to a solution of 7.5 g (0.027 mole) of IIe in acetone, and the mixture was stirred at 40-45°C for 5-7 h (monitoring by TLC). The resulting precipitate was removed by filtration and washed with acetone to give 6.7 g (67.5%) of slightly yellowish needles (from alcohol) with mp 266°C (decomp.). UV spectrum, λ_{max} (log ε): 252-254 (4.18) and 310 nm (4.00). Found: C 55.0; H 4.7; N 10.2%. $C_{19}H_{20}IN_3$. Calculated: C 54.7; H 4.9; N 10.1%.

1,7,8-Trimethylimidazo[4,5-e]indole (IV). A 1.6-g (0.07 mole) sample of sodium was added in portions to a suspension of 2.09 g (0.005 mole) of III in 70 ml of liquid ammonia. After all of the sodium had been added, the mixture was stirred for 1 h, and 3.5 g (0.07 mole) of ammonium chloride was added. After evaporation of the ammonia, the residue was treated with acetone, and the precipitate was removed by filtration and washed with water to give 0.46 g (48.5%) of white crystals with mp 300°C (decomp., from alcohol). UV spectrum, λ_{max} (log ε): 238 (4.55), 281-282 (4.06), 294 (4.01), 304-305 nm (4.00). Found: C 73.2; H 6.5; N 21.3%. $C_{12}H_{13}N_3$. Calculated: C 72.9; H 6.6; N 21.1%.

3-Benzyl-6,7,8-trimethylimidazo[4,5-e]indole (V). A 0.23-g (0.01 mole) sample of sodium was dissolved in 30 ml of liquid ammonia, the solution was treated with 2.75 g (0.01 mole) of IIe, and a solution of 1.25 ml (0.02 mole) of methyl iodide in 5 ml of ether was added dropwise to the suspension. The mixture was stirred for 3 h, after which 0.54 g (0.01 mole) of ammonium chloride was added. The ammonia was evaporated, and the oily residue was treated with acetone. The precipitate was removed by filtration, washed with water, and crystallized from alcohol to give 1.94 g (67%) of V with mp 225-226°C. UV spectrum, λ_{max} (log ε): inflection at 290 (4.18), 305 (4.20), and inflection at 315 nm (4.16). The IR spectrum did not contain a band of stretching vibrations of the NH group. Found: C 79.2; H 6.8; N 14.8%. $C_{19}H_{19}N_3$. Calculated: C 78.9; H 6.5; N 14.5%.

6,7,8-Trimethylimidazo[4,5-e]indole (VI). A 0.77-g (0.033 mole) sample of sodium was added in portions to a suspension of 1.45 g (0.005 mole) of V in 60 ml of liquid ammonia, after which the mixture was stirred for 30 min, and 1.7 g (0.03 mole) of ammonium chloride was added. After evaporation of the ammonia, the residue was treated with water to give 0.7 g (70.3%) of VI with mp 240°C (decomp., from alcohol). UV spectrum, λ_{max} (log ε): 228-230 (4.14), 279-281 (4.02), inflection at 300 (4.07), and 310 nm (4.21). Found: C 72.5; H 6.4; N 21.3%. $C_{12}H_{13}N_3$. Calculated: C 72.3; H 6.6; N 21.1%.

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REDUCTION OF 4-ARYLAZOINDOLES

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It was established that 4-acetamido-5-hydroxyindole derivatives are formed in the reduction of 4-phenylazo-5-hydroxyindole derivatives with zinc dust in acetic acid in the presence of acetic anhydride and sodium acetate. However, p-semidine rearrangement of the intermediate hydrazo derivatives is observed in the analogous reduction of 4-arylazo-5-methoxyindoles, and 4-acetamido-5-methoxy-7-arylaminoindoles are formed. The latter are oxidized by oxygen and nitric acid to 4-oxo-7-arylimino-4,7-dihydroindoles; nitration of the arylimino ring occurs in some cases under the influence of nitric acid.

We have previously observed rearrangements of the o-benzidine and o-semidine type in the reduction of 3-arylazoindoles with zinc dust in acetic acid in the presence of acetic anhydride and sodium acetate [1-3]; it was established that the direction of the rearrangement depends on the character of the substituent attached to the nitrogen atom of the indole ring but is independent of the character and position of the substituents in the aryl ring of the arylazo group.

We have now found that rearrangement does not occur in the reduction of 1,2-dimethyl-3-carbethoxy-4-phenylazo-5-hydroxyindole (Ia) by the same method and that the only product is 1,2-dimethyl-3-carbethoxy-4-acetamido-5-hydroxyindole (II), which is converted to 1,2,5-trimethyl-3-carbethoxyoxazolo[4,5-e]indole (III) if the process is carried out under more severe conditions. However, p-semidine rearrangement of the intermediate hydrazo derivatives A is observed in the analogous reduction of 1,2-dimethyl-3-carbethoxy-4-arylazo-5-methoxyindoles (Ie-h) obtained from Ia-d by the action of dimethyl sulfate in an alkaline medium, and 1,2-dimethyl-3-carbethoxy-4-acetamido-5-methoxy-7-arylaminoindoles (IVa-d) are formed.

The direction of the rearrangement in the case of IVa was confirmed by the PMR spectrum. Two doublet signals at 6.92 and 7.2 ppm ($J \sim 9$ Hz), which are related to 6-H and 7-H of the indole ring, are observed in the PMR spectrum of the starting 4-phenylazo-5-methoxyindole derivative (Ie). The character of the signal of the proton of the indole ring (singlet at 6.64 ppm) in the PMR spectrum of rearrangement product IVa indicates replacement of one of the two ortho protons of the indole ring. This substituting group is a phenylamino residue, as evidenced by the signals of the remaining aromatic protons in the spectrum, viz., a doublet at 6.60 ppm (2H), a triplet at 7.13 ppm (2H), and a triplet at 6.72 ppm (1H), which correspond, respectively, to the ortho, meta, and para protons of the monosubstituted phenyl ring. Since the rearrangement cannot take place in the meta position relative to the amino group, 7-phenylamino-5-methoxyindole derivative IVa is formed.

If 1,2-dimethyl-3-carbethoxy-4-phenylazo-5-acetoxyindole (Ii), obtained by the action of acetic anhydride on Ia, is used in the investigated reaction, 1,2,5-trimethyl-3-carbethoxy-8-phenylaminooxazolo[4,5-e]indole (V) is formed. In this case the reaction evidently proceeds through a step involving the formation of a product (B) of semidine rearrangement, after which an oxazole ring is formed.

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