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XXXII.* REACTION OF 1-METHYL-2-AMINOINDOLE WITH ALDEHYDES

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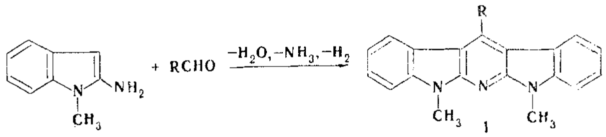
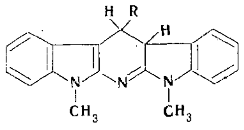
The condensation of salts of 1-methyl-2-aminoindole with aldehydes in excess alkali gives Schiff bases, while salts of 1-methyl-3-arylidene-2-iminoindolines are obtained in the absence of alkali. The latter may give 12-aryl-5,7-dimethylindolo[2,3-b]-α-carbolines (I) on reaction with excess 1-methyl-2-aminoindole. Dihydro compounds (II) are formed as intermediates.

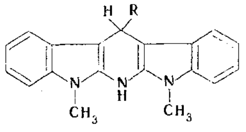
The elements of water, ammonia, and hydrogen are split out in the reaction of 1-alkyl-2-aminoindoles with aldehydes in aqueous alkali solutions, and the polycondensed indolo[2,3-b]-α-carboline or, to put it differently, diindolo[2,3-b;3',2'-e]pyridine (I) system is obtained [2]:



I



IIa



IIb

A similar transformation (the formation of dipyrazolopyridines), but under much more severe conditions, was previously noted in the reaction of 5-aminopyrazoles with aldehydes [3]. It can be assumed that dihydro derivative II is initially formed and is then aromatized on workup of the reaction mixture through oxidation or by disproportionation. However, the high yields of I, which exceed 50%, are evidence against the disproportionation. In addition, an equimolar amount of oxygen is absorbed during the reaction. It is true that the product (I) obtained in this case is more impure, apparently due to side oxidation of the starting aminoindole. (It is known that 2-aminoindoles are very readily oxidized to give 2-amino-3-hydroxyindoles [4].) In the case R = C_6H_5, we carried out an experiment without access to oxygen and isolated yellow crystals of II with the composition $C_{25}H_{21}N_3$. Recrystallization of II in the air gave indolocarboline I. Indolocarboline I was also isolated from the acylation of II with acetic anhydride. The UV spectrum of II (in chloroform) initially has absorption maxima at 263, 267, 304, 317, and 371 nm, but the spectrum of a solution of the substance changes and coincides with the spectrum of indolocarboline I (Fig. 1) after brief standing in air. The IR spectrum of II does not have absorption in the region of NH vibrations (2800-3400 cm^{-1}), which is evidence in favor of structure IIa.

The CH_3 groups in the PMR spectrum (in chloroform) are represented by two singlets at δ 3.25 and 3.64 ppm. The nonequivalence of the protons of the CH_3 groups excludes symmetrical structure IIb and is

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* See [1] for communication XXXI.

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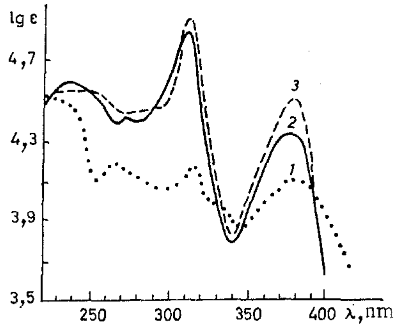
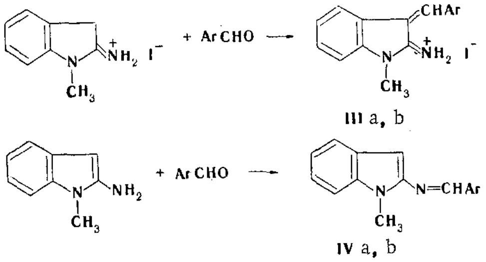


Fig. 1. UV spectra: 1) IIa immediately after dissolving in chloroform; 2) the same after standing for 4 h in air; 3) 12-phenyl-5,7-dimethyl-indolo[2,3-b]-α-carboline (I).

evidence in favor of structure IIa. The somewhat broadened signals at 3.92 and 4.08 ppm correspond to two protons of the 3,4-dihydropyridine ring. Their insignificant interaction is apparently associated with the fact that their bonds make an angle of close to 90° with the carbon atom (as confirmed by an examination of molecular models). The spectrum of the same solution recorded after 24 h shows only one signal, which corresponds to the CH_3 groups (3.79 ppm) of indolocarboline I, in the aliphatic-proton region.

The most intense peak in the mass spectrum of II is the molecular-ion peak with m/e 363. The peaks with m/e 361 ($[M-2]^+$) and 285 are also very intense. The latter corresponds to elimination of a benzene molecule from the molecular ion, as confirmed by the metastable peak. All of these data make it possible to conclude that the intermediate of the reaction has structure IIa.

By varying the reaction conditions we isolated two other types of compounds, which corresponded in elementary composition to the condensation of one aldehyde molecule with one aminoindole molecule with splitting out of a water molecule. Thus a substance with the composition $C_{18}H_{18}N_2O_2 \cdot HI$ was obtained in the reaction of 1-methyl-2-aminoindole hydriodide with veratraldehyde. Its IR spectrum contains C=N stretching vibrations (1660 cm^{-1}), while the character of the absorption at 2000-3300 cm^{-1} indicates a salt-like structure. A similar substance was obtained with p-dimethylaminobenzaldehyde. We proposed 1-methyl-3-arylidene-2-iminoindoline salt structures (III) for these compounds:



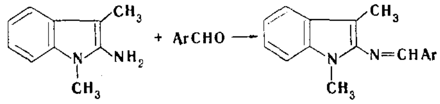
III a, b

IV a, b

a Ar = 3,4-$(CH_3O)_2C_6H_3$; b Ar = 4-$(CH_3)_2NC_6H_4$

When the reaction of 1-methyl-2-aminoindole with veratraldehyde or p-dimethylaminobenzaldehyde is carried out in the presence of excess alkali, compounds with the composition $C_{18}H_{18}N_2O_2$ and $C_{18}H_{19}N_3$, respectively, are formed; they are Schiff bases (IV), since, according to the IR spectra, they do not have NH groups. Salts III are stable on storage and are not converted to IV on alkalization but form I.

For comparison, we obtained Schiff bases V from 1,3-dimethyl-2-aminoindole:



V a-c

a Ar = 3,4-$(CH_3O)_2C_6H_3$; b Ar = 4-$(CH_3)_2NC_6H_4$; c Ar = 2-ClC_6H_4

The PMR spectrum (in CCl_4) of Vc has a singlet at δ 2.18 (3-CH_3), a singlet at 3.48 (1-CH_3), and a multiplet of aromatic ring protons at 6.50-7.10 ppm. The proton in the o position relative to the chlorine atom appears at weaker field (8.00 ppm). Finally, the azomethine proton resonates at weakest field (8.77 ppm).

The signal of the azomethine proton in the spectrum of IVb in dimethyl sulfoxide (DMSO) also appears at weakest field (8.65 ppm), but the signal of the proton in the 3 position of the indole ring (1H, 6.31 ppm) is isolated from the overall multiplet of aromatic protons (6.68-7.79 ppm). This signal of a proton in the 3 position is absent in the spectrum of salt IIIb (in DMSO). The broad signal at 9.4 ppm (2H) should be related to the NH_2^+ group, while the singlet at 8.24 ppm corresponds to the proton of the benzylidene group (=CH). The signals of the remaining eight protons of the aromatic portion of the molecule lie at 6.85-7.98 ppm. All of this corresponds to the assigned structures.

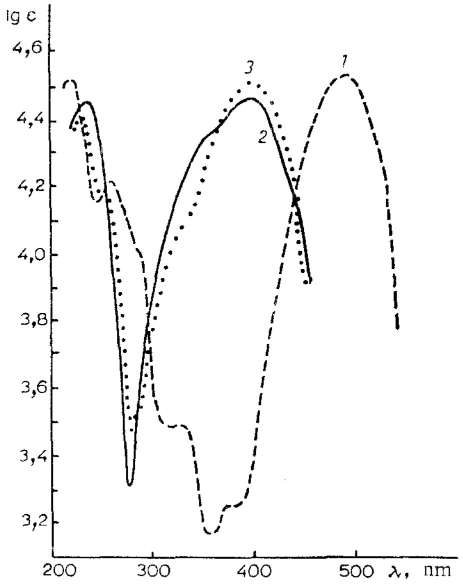


Fig. 2

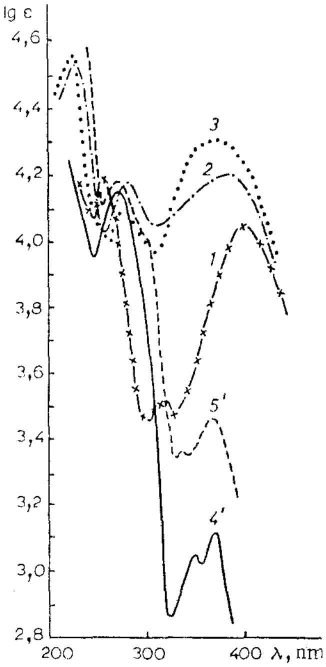


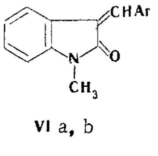
Fig. 3

Fig. 2. UV spectra: 1) IIIb; 2) Vb; 3) IVb.

Fig. 3. UV spectra: 1) IIIa; 2) Va; 3) IVa; 4) IVa after the addition of methanolic HCl; 5) the same after addition of $(C_2H_5)_3N$ to an acid solution up to the point of an alkaline reaction.

It is known that the UV spectra of aromatic azomethines have three distinctly expressed absorption bands (for example, at 210-230, 250-290, and 300-360 nm for benzalanilines [5, 6]). Most authors are inclined to believe that the long-wave K band (300-360 nm) reflects the electron transitions in the molecule as a whole.

With respect to the position of the absorption maxima and the type of curves, the UV spectra of azomethines Va, b are similar to those of azomethines IVa, b (Figs. 2 and 3). However, the spectra of 3-benzylidene derivatives III differ substantially from them. For example, the absorption maximum of the K band for 3-(p-dimethylaminobenzylidene) derivative IIIb is shifted strongly to the long-wave region (490 nm; log ε 4.53), and, in addition, the curve has two inflections. The absorption maximum of the K band is also shifted somewhat to the long-wave region (400 nm; log ε 4.03) in the case of the salt of 3-veratrylidene derivative IIIa, and the absorption intensity is considerably lower. The shift of the maxima of the K band in the case of salts III to the long-wave region as compared with Schiff bases IV or V is explained by the stronger conjugation in the system. In the case of IIIb, this shift is larger, since the donor properties of the p-dimethylamino group are greater than those of the methoxy group. The spectra of 3-arylidene derivatives of 2-ketoindolines are similar to the spectra of III (Fig. 4). While the absorption maximum of the K band is 365 nm (log ε 4.22) for VIa (in alcohol), it is 430 nm (log ε 4.53) for VIb. In this case also, the introduction of a dimethylamino group leads to a shift in the K band, although the overall effect of conjugation in model VI is less than in III because of the lower polarization of the C = O bond as compared with the $C=NH_2^+$ bond.



VI a, b

a $Ar = 3,4\text{-}(CH_3O)_2C_6H_3$; b $Ar = 4\text{-}(CH_3)_2NC_6H_4$

If hydrogen chloride is bubbled into a solution of IVa in ether, a very hygroscopic precipitate is formed. Its UV spectrum in methanol solution has three absorption maxima (Fig. 3) and differs from the spectrum of salt IIIa. Judging from the literature data (although they are contradictory), one might expect a bathochromic shift and an increase in the intensity of the long-wave band when azomethines are protonated [7-10].

In our case we observed a decrease rather than an increase in intensity; this is apparently associated with the facile solvolysis of the amidine, particularly under the influence of protonation (see [10, 11], for example, for similar facts). When this methanol solution is made alkaline (addition of triethylamine), the absorption spectrum does not return to the original spectrum of IVa, which attests to irreversible chemical transformations rather than to salt formation. If azomethine IVa is treated with an aqueous alcohol solution of hydriodic acid, it is gradually converted to salt IIIa (3 days at room temperature).

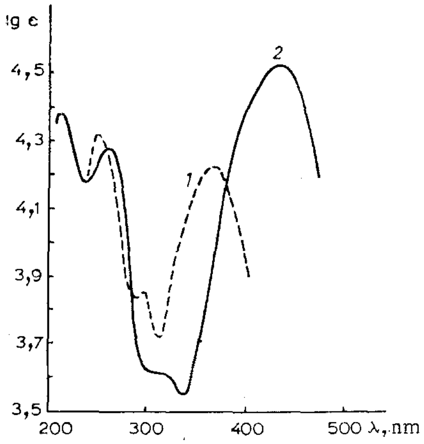


Fig. 4. UV spectra (in alcohol): 1) VIa; 2) VIb.

EXPERIMENTAL*

The IR spectra of mineral-oil suspensions were recorded with IKS-22 and UR-10 spectrometers. The UV spectra of alcohol solutions were recorded with a Cary-15 spectrophotometer. The PMR spectra were obtained with Varian T-60 and X-100 spectrometers. The mass spectrum was recorded with an MKh-1303 spectrometer.

12-Phenyl-5,7-dimethyl-12,12a-dihydroindolo[2,3-b]-α-carboline (IIa). A 0.137-g (0.5 mmole) sample of 1-methyl-2-aminoindole hydriodide was dissolved by heating in 3 ml of alcohol, and 1 ml of 0.5 N alcoholic potassium hydroxide and 0.04 ml (0.25 mmole) of freshly distilled benzaldehyde were added. The flask was filled to the top with alcohol and sealed. After 12 h the precipitated yellow crystals of IIa were removed by rapid filtration, washed with alcohol, and dried in vacuo to give a product with mp 258-260°. UV spectrum (in $CHCl_3$): λ_{max} 263, 267, 304, 317, 371 nm (log ε 4.13, 4.13, 4.13, 3.92, 4.11). PMR spectra (in $CHCl_3$): singlets at 3.25 (3H), 3.64 (3H), 3.92 (1H), 4.08 (1H) ppm. Found: C 82.6; H 5.3%. $C_{25}H_{21}N_3$. Calculated: C 82.3; H 5.5%.

1-Methyl-3-(3,4-dimethoxybenzylidene)-2-iminoindoline Hydriodide (IIIa). A 0.33-g (2 mmole) sample of veratraldehyde was added to a hot solution of 0.55 g (2 mmole) of 1-methyl-2-aminoindole hydriodide in 10 ml of alcohol, and the flask was covered with an inert gas and allowed to stand for 12 h. The precipitated crystals were separated and washed with alcohol to give 0.25 g (96%) of orange crystals of salt IIIa with mp 258-260° (from dimethylformamide containing alcohol); R_f 0.79 [paper; butanol–formic acid–water (15 : 3 : 2)]. IR spectrum (in mineral oil): 1660 cm^{-1} (C=N). UV spectrum (in alcohol): λ_{max} 255, 305, 400 nm (log ε 4.19, 3.47, 4.03). PMR spectrum (in DMSO): singlets at 8.28 (1H) and 9.68 (2H), multiplet at 6.82-7.85 (7H) ppm. Found: C 51.1; H 4.6%. $C_{18}H_{18}N_2O_2 \cdot HI$. Calculated: C 51.1; H 4.6%.

1-Methyl-3-(p-dimethylaminobenzylidene)-2-iminoindoline Hydriodide (IIIb). As in the preceding experiment, 0.27 g (1 mmole) of 1-methyl-2-aminoindole hydriodide and 0.15 g (1 mmole) of p-dimethylaminobenzaldehyde gave 0.3 g (86%) of red crystals of salt IIIb with mp 264-266° (from alcohol). IR spectrum: 1660 cm^{-1} (C=N). UV spectrum (in alcohol): λ_{max} 258, 490 nm (log ε 4.22, 4.53), inflections at 315, 275 nm (log ε 3.48, 3.25). PMR spectrum (in DMSO): singlets at 8.24 (1H), 9.4 (2H), multiplet at 6.85-7.98 (8H) ppm. Found: C 53.6; H 5.5%. $C_{18}H_{19}N_3 \cdot HI$. Calculated: C 53.3; H 5.0%.

1-Methyl-2-(3,4-dimethoxybenzylideneimino)indole (IVa). A 0.54-g (2 mmole) sample of 1-methyl-2-aminoindole was dissolved by heating in 10 ml of alcohol containing 0.145 g (30% excess) potassium hydroxide, and 0.33 g (2 mmole) of veratraldehyde was added to the hot solution while an inert gas was bubbled into it. The mixture was then refluxed for 30 min in a stream of the inert gas, and the crystals that had precipitated after 12 h were separated and washed with alcohol to give 0.3 g (60%) of yellow crystals of indole IVa with mp 148-149° (from benzene and carbon tetrachloride). UV spectrum (in alcohol): λ_{max} 225, 275, 370 nm (log ε 4.55, 4.08, 4.30). Found: C 74.0; H 6.3%. $C_{18}H_{18}N_2O_2$. Calculated: C 73.5; H 6.2%.

1-Methyl-2-(p-dimethylaminobenzylideneimino)indole (IVb). Similarly, 0.54 g (2 mmole) of 1-methyl-2-aminoindole hydriodide and 0.3 g (2 mmole) of p-dimethylaminobenzaldehyde gave 0.3 g (72%) of indole

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* E. D. Matveeva participated in the experimental work.

IVb as yellow crystals with mp 160-161° (from benzene). UV spectrum (in alcohol): λ_{max} 228, 400 nm (log ε 4.4, 4.5). PMR spectrum (in DMSO): singlets at 6.31 (1H) and 8.65 (1H) and multiplet at 6.68-7.79 (8H) ppm. Found: C 77.9; H 6.9%. $C_{18}H_{19}N_3$. Calculated: C 77.9; H 6.9%.

1,3-Dimethyl-2-(o-chlorobenzylideneimino)indole (Vc). Similarly, 0.4 g (2 mmole) of 1,3-dimethyl-2-aminoindole hydrochloride and 0.29 g (2 mmole) of o-chlorobenzaldehyde gave 0.4 g (75%) of light-yellow crystals of indole Vc with mp 82-84° (from benzene–petroleum ether). PMR spectrum (in CCl_4): singlets at 2.18 (3H), 3.48 (3H), 8.00 (1H), and 8.77 (1H) and a multiplet at 6.50-7.10 (7H) ppm. Found: C 71.2; H 5.3%. $C_{17}H_{15}ClN_2$. Calculated: C 71.2; H 5.3%.

1,3-Dimethyl-2-(3,4-dimethoxybenzylideneimino)indole (Va). Similarly, 0.4 g (2 mmole) of 1,3-dimethyl-2-aminoindole hydrochloride and 0.33 g (2 mmole) of veratraldehyde gave 0.45 g (80%) of yellow crystals of indole Va with mp 126-128° (from benzene–petroleum ether). UV spectrum (in alcohol): λ_{max} 229, 278, and 395 nm (log ε 4.51, 4.18, and 4.17). Found: C 74.0; H 6.6%. $C_{19}H_{20}N_2O_2$. Calculated: C 74.0; H 6.5%.

1,3-Dimethyl-2-(p-dimethylaminobenzylideneimino)indole (Vb). Similarly, 0.4 g (2 mmole) of 1,3-dimethyl-2-aminoindole hydrochloride and 0.3 g (2 mmole) of p-dimethylaminobenzaldehyde gave 0.4 g (70%) of yellow crystals of indole Vb with mp 132-134° (from benzene–petroleum ether). UV spectrum (in alcohol): λ_{max} 235, 400 nm (log ε 4.45, 4.45). Found: C 78.2; H 7.2%. $C_{19}H_{21}N_3$. Calculated: C 78.3; H 7.2%.

12-(p-Dimethylaminophenyl)-5,7-dimethylindolo[2,3-b]-α-carboline (I). A total of 1.8 ml of 0.2 N alcoholic potassium hydroxide was added under an inert gas to a heated mixture of 0.05 g (0.18 mmole) of 1-methyl-2-aminoindole hydriodide and 0.073 g (0.18 mmole) of 1-methyl-3-(p-dimethylaminobenzylidene)-2-iminoindoline hydriodide in 2 ml of alcohol, after which the mixture was allowed to stand for 24 h. The precipitated crystals were separated to give 0.035 g (49%) of indolocarboline I. In order to purify it, it was dissolved in benzene, and the solution was passed through a column (2 by 50) filled with activity-II aluminum oxide. The solvent was evaporated, and the residue was recrystallized from benzene to give I with mp 296-298° (mp 297-299° [2]).

LITERATURE CITED

1. V. A. Budylin, A. N. Kost, E. D. Matveeva, and V. I. Minkin, Khim. Geterotsikl. Soedin., 68 (1972).
2. R. S. Sagitullin, A. N. Kost, E. D. Matveeva, and N. I. Nemudrova, Khim. Geterotsikl. Soedin., 920 (1970).
3. A. Brack, Ann., 681, 105 (1965).
4. M. Nakagawa and T. Hino, Tetrahedron, 26, 4491 (1970).
5. B. M. Krasovitskii, B. M. Bolotin, and R. N. Murmukhametov, Zh. Obshch. Khim., 34, 3786 (1964).
6. M. S. Kisteneva, Zh. Obshch. Khim., 26, 1169 (1956).
7. P. Brocklehurst, Tetrahedron, 299 (1962).
8. V. A. Izmail'skii and Yu. A. Fedorov, Zh. Fiz. Khim., 39, 768 (1965).
9. V. A. Izmail'skii and E. E. Milliaresi, Dokl. Akad. Nauk SSSR, 141, 857 (1961).
10. R. Reeves and W. Smith, J. Am. Chem. Soc., 85, 724 (1963).
11. P. H. Gore and O. H. Wheeler, J. Org. Chem., 26, 3295 (1961).