INDOLE DERIVATIVES.

CXIII.* SYNTHESIS AND SOME PROPERTIES OF 3-AMINOINDOLE

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3-Aminoindole was obtained by the action of alkali on its hydrochloride in a reductive medium. Acylation of 3-aminoindole with acetic anhydride gave its mono-, di-, and triacetyl derivatives, whereas reaction with p-substituted benzenesulfonyl chlorides gave the corresponding N-3-indolylsulfonamides. The reaction of 3-aminoindole with aromatic aldehydes gives Schiff bases.

Little study has been devoted to 3-aminoindole (I), although it was first obtained in 1914 [2]. This is probably associated with the prevailing opinion that 2- [3,4] and 3-aminoindoles [2] are unstable.

We have established that dry crystalline amine I is stable and can be stored without appreciable signs of decomposition for a long time. We synthesized I by two methods: 1) from its hydrochloride (II) by the action of alkali in a reductive medium [we have previously obtained hydrochloride II from 3-indolyl isocyanate [5] (III)] and 2) by reduction of isonitrosoindole by the Madelung method [2]. To avoid the decomposition of free amine I it is recommended that it be dried rapidly in vacuo after its preparation in the crystalline state.

Structure I is confirmed by the IR, UV, and PMR spectral data, as well as by the mass spectrometric data. The IR spectrum of I (in mineral oil) contains several absorption bands of an NH_2 group at 3080-3310 cm^{-1} and of an indole NH bond at 3380 cm^{-1}. The band of an indole NH bond appears at 3500 cm^{-1} in the spectrum of a chloroform solution of the compound, and the band of an amino group appears at 3480 and 3260 cm^{-1}. In the UV spectrum of I the absorption bands are shifted bathochromically as compared with the spectrum of indole [6] (λ_{max} 219, 261, and 288 nm) and appear at 230, 284, and 291 nm. For example, the larger bathochromic shift of the short-wave absorption band ($\Delta\lambda$ 11 nm) in this case as compared with the value (6 nm) observed in the UV spectra of aniline and benzene is possibly associated with the lower (than in the case of aniline) degree of charge transfer from the amino group to the indole ring [7]. This is in agreement with the higher basicity of amine I determined by potentiometric titration in dimethyl sulfoxide (DMS)—water (1:20) (pK_{BH^+} 6.42), as compared with the basicity of aniline (4.58).

It should be noted that the basicity of amine I is also lower than that of 2-aminoindole (pK_{BH^+} 8.85), which, on the basis of the spectral data and the chemical properties [4], actually has 2-aminoindolenine and 1-methyl-2-aminoindole structures (pK_{BH^+} 9.6). This difference may be associated with the decrease in stabilization during the formation of a bond through the unshared pair of the nitrogen atom of amine I and the consequent exclusion of the possibility of its delocalization in the indole ring. As a result of blocking of the unshared pair of electrons on the nitrogen atom in hydrochloride II, the UV spectrum of the latter becomes similar to the spectrum of indole.

The multiplet at 6.74-7.56 ppm in the PMR spectrum of amine I in $DCON(CD_3)_2$ corresponds to aromatic protons. The protons of the NH_2 and NH groups of indole are represented by broad singlets at 10.15 and 10.28 ppm, respectively, and the proton attached to the C_2 atom of the indole ring is represented by a doublet at 6.74 ppm, which is converted to a singlet when CD_3OD is added.

The maximum peak in the mass spectrum of I is the molecular ion peak with mass 132. The molecular

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*See [1] for communication CXII.

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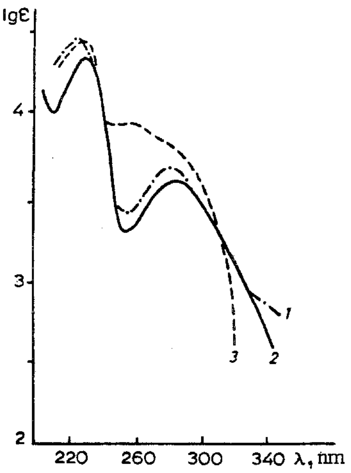


Fig. 1

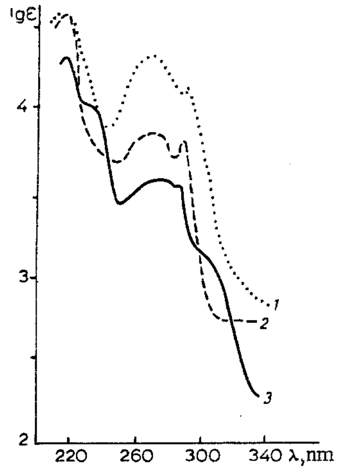


Fig. 2

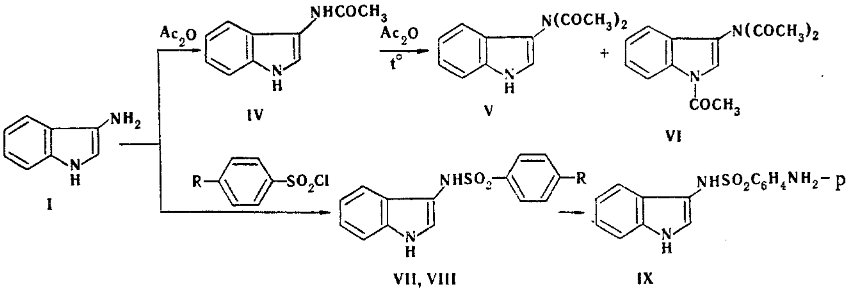
Fig. 1. UV spectra of alcohol solutions of: 1) methyl 3-indolylcarbamate; 2) 3-aminoindole; 3) 3-acetamidoindole.

Fig. 2. UV spectra of alcohol solutions of: 1) 3-(p-aminobenzenesulfamido)indole; 2) 3-diacetamidoindole; 3) 3-aminoindole hydrochloride.

ion undergoes sucessive fragmentation with the ejection of H_2CN and HCN particles to give ions with m/e 104 and 77; this is confirmed by metastable transformations.

3-Aminoindole reacts with acetic anhydride to give exclusively N-acetylation products – mono-, di-, and triacetyl-3-aminoindoles (IV-VI). The analogous reactions of 2-aminoindole lead to both N- and C-acetylation products [4]; in the latter case the C_3 atom of indole is acetylated. The reaction of I with acetic anhydride proceeds even in the cold, and 3-acetamidoindole (IV) is obtained in 96% yield. A mixture of 3-diacetamioindole (V) and 3-diacetamido-1-acetylindole (VI) is obtained when IV is heated with acetic anhydride, whereas heating for 40 min leads to V in 74% yield. An increase in the reaction time to 6 h leads to VI in 86% yield. Compound V is readily hydrolyzed in alkaline media to IV.

The acylation of amine I with p-toluene- and p-carbomethoxyaminobenzenesulfonyl chlorides leads to the corresponding monoacylation products VII and VIII. The alkaline hydrolysis of VIII leads to N-3-indolylsulfonamide IX. 3-Diacetylaminoindole V was also obtained by heating isocyanate III in acetic anhydride.



VII R=CH_3; VIII R=$NHCOCH_3$

The PMR spectrum of diacetyl derivative V in $(CD_3)_2CO$ contains a multiplet of aromatic protons at 6.82-7.38 ppm, a doublet of the proton attached to the C_2 atom of the indole ring at 7.18 ppm, and a singlet of the protons of the $COCH_3$ group at 2.25 ppm. The presence of coupling between the NH and C_2H protons of the indole ring was proved by the double resonance method: when a field is superimposed on the NH signal at 10.25 ppm, the C_2H doublet at 7.18 ppm is converted to a singlet. The PMR spectrum of triacetyl derivative VI in $(CD_3)_2CO$ contains a multiplet of aromatic protons at 7.12-7.36 ppm, a C_2H singlet at 7.76 ppm, and $(COCH_3)_2$ and $COCH_3$ singlets at 2.28 ppm.

The maximum of the short-wave absorption band in the UV spectrum of monoacetyl derivative IV is shifted hypsochromically relative to the absorption maximum of 3-aminoindole; this is probably associated with a

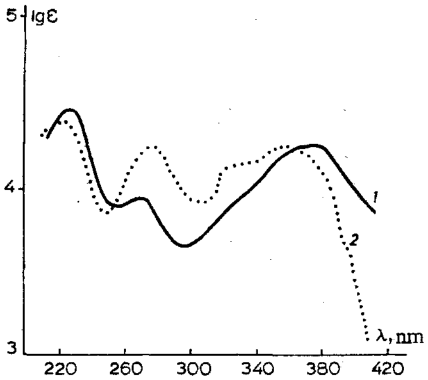
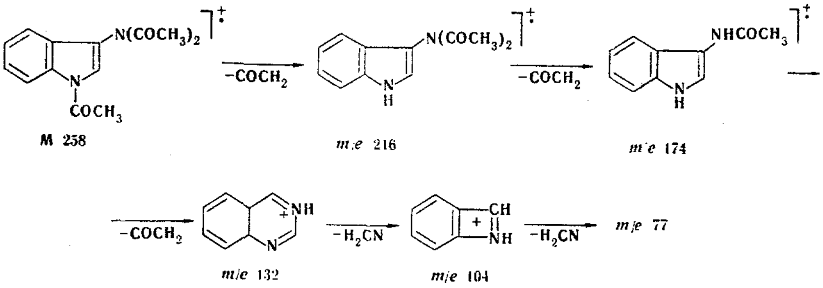


Fig. 3. UV spectra of alcohol solutions of: 1) 3-salicylideneaminoindole; 2) 3-(o-methoxybenzylidene)aminoindole.

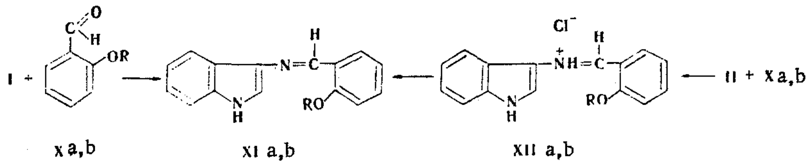
decrease in the p, π conjugation of the amide group with the ring. Replacement of the acetyl group by the more electron-accepting carbethoxy group [5] gives rise to an even greater hypsochromic shift of the short-wave absorption band (Fig. 1). The presence of two acetyl or sulfonyl groups evidently completely excludes p, π conjugation of the amide group with the ring, and in this case the UV spectra of V and IX are similar to the spectrum of indole (Fig. 2).

The maximum peaks in the mass spectra of IV–VI are the molecular ion peaks with m/e 174, 216, and 258, respectively. The molecular ions of the acetyl derivatives undergo fragmentation with the splitting out of one, two, or three $COCH_2$ particles to give a fragment ion with m/e 132, the subsequent fragmentation of which is identical for IV–VI.



The proposed mechanism of the fragmentation is confirmed by the presence of peaks of metastable ions in the spectrum.

Schiff bases XIa,b, are formed in 72 and 38% yields in the reaction of 3-aminoindole with aromatic aldehydes Xa,b. Compounds XIa,b were also obtained in better yields (84 and 52%) from their hydrochlorides (XIIa,b), which are formed by reaction of hydrochloride II with aldehydes Xa,b.



X–XII a R = H; b R = CH_3

The UV spectra of XIa,b (Fig. 3) contain three absorption bands that are characteristic for the UV spectra of Schiff bases. Salicylidene-3-aminoindole (XIa) and o-methoxybenzylidene-3-aminoindole (XIb) have similar UV spectra. On the basis of this, the possible quinoneamine structure possible for XIa and characteristic for salicylideneanilines [9] is excluded. The stretching vibrations of a C=N group appear at 1610–1620 cm^{-1} in the IR spectra (KBr pellets), the indole NH vibrations show up at 3400 cm^{-1}, and the vibrations of an associated OH group of XIb appear at 3200 cm^{-1}.

The PMR spectrum of XIa in $(CD_3)_2CO$ has a multiplet of aromatic protons at 6.60-7.72 ppm, an N=CH singlet at 8.84 ppm, and a broad singlet of an indole NH bond at 11.6 ppm. The character of the spectrum does not change when CD_3OD is added.

According to the data of E. N. Padeiska (chemotherapy department of the S. Ordzhonikidze All-Union Scientific-Research Pharamaceutical-Chemistry Institute, directed by G. N. Pershin), the minimum bacteriostatic concentration of IX in experiments with tuberculosis bacilli in vitro is 30-60 mg/m. In experiments with mice involving oral administration of 500 μg/kg doses of IX, it did not have activity vis-a-vis experimental infections caused by *Salmonella typhosa* and staphylococci.

EXPERIMENTAL

The course of the reactions and the purity of the products were monitored by thin-layer chromatography (TLC). The IR spectra were recorded with a UR-10 spectrometer. The UV spectra were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were obtained with a JNM MH-100 spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded with an MKh-1303 mass spectrometer. The pH values were determined in DMSO–water (1:20) with a pH-262 pH meter with a glass electrode at 20-21°.

3-Aminoindole (I). A solution of 0.35 g of $Na_2S_2O_4$ and 0.15 g of NaOH in 2 ml of water was added to a solution of 0.17 g (1.0 mmole) of hydrochloride II in 1 ml of water, and the resulting precipitate was removed by filtration, vacuum dried over P_2O_5, and purified by sublimation at 3-5 mm and 110° to give 0.09 g (68%) of a product with mp 117° (mp 117° [2]). UV spectrum (in alcohol), λ_{max}: 230, 284, and 291 nm (log ε 4.30, 3.59, and 3.58). IR spectrum (oil), cm^{-1}: 3080 w, 3120 w, 3170 w, 3310 w (NH), and 3380 s (indole NH). Found: C 72.6; H 6.4; N 21.4%. $C_8H_8N_2$. Calculated: C 72.7; H 6.1; N 21.2%.

3-Acetamidoindole (IV). A solution of 0.13 g (1.0 mmole) of I in 0.2 ml (2.5 mmole) of acetic anhydride was allowed to stand at room temperature for 1 h, after which water was added, and the precipitate was removed by filtration and washed with water to give 0.16 g (94%) of a product with mp 162-163° (water). No melting-point depression was observed for a mixture of this product with a sample of the compound obtained by the method in [2]; they also had identical IR spectra.

Acetylation of 3-Acetamidoindole (IV). A) A solution of 0.52 g (3.0 mmole) of IV in 2 ml of acetic anhydride was heated for 40 min, after which the acetic anhydride was vacuum evaporated, and the residual oil was crystallized by trituration with petroleum ether to give 0.48 g (74%) of 3-diacetamidoindole V with mp 156-157° (from isopropyl alcohol). IR spectrum (oil), cm^{-1}: 1750 s, 1790 w (C = O), 3140 w (NH), and 3280 s (indole NH). Found: C 66.6; H 5.6; N 12.9%; M 216 (mass spectrometrically). $C_{12}H_{12}N_2O_2$. Calculated: C 66.6; H 5.6; N 13.0%; M 216.

B) A solution of 0.52 g (3.0 mmole) of IV in 3 ml of acetic anhydride was heated for 1 h, after which it was worked up by method A. The product was crystallized from isopropyl alcohol to give 0.29 g (45%) of V. The mother liquor was evaporated to give 0.18 g (23%) of 3-diacetamido-1-acetylindole (VI) with mp 134-135° (benzene–petroleum ether). IR spectrum (oil), cm^{-1}: 1720 s (C = O). Found: C 64.8; H 5.5; N 10.7%; M 258 (mass spectrometrically). $C_{14}H_{14}N_2O_3$. Calculated: C 65.2; H 5.5; N 10.8%; M 258.

C) A solution of 0.52 g (3.0 mmole) of IV in 3 ml of acetic anhydride was heated for 6 h, after which it was worked up by method A to give 0.66 g (85%) of VI.

3-Diacetamidoindole (V). A solution of 0.32 g (3.0 mmole) of isocyanate III in 2 ml of acetic anhydride was heated for 4 h, after which the acetic anhydride was evaporated, and the residual oil was crystallized by trituration with petroleum ether to give 0.6 g (97%) of a product with mp 156-157°. The IR spectra of the product and the substance synthesized by the method presented above were identical.

3-(p-Toluenesulfamido)indole (VII). A 0.38-g (2.0 mmole) sample of p-toluenesulfonyl chloride and 0.16 g (2.0 mmole) of sodium acetate were added to a solution of 0.26 g (2 mmole) of amine I in 20 ml of alcohol, and the mixture was heated and stirred for 30 min. The alcohol solution was treated with activated charcoal and filtered, and the filtrate was evaporated to give 0.4 g (74%) of a product with mp 188-189°. IR spectrum (Oil), cm^{-1}: 1160 s (sym, SO_2), 1320 s (asym, SO_2), 3230 s (NH), and 3400 s (indole NH). UV spectrum (in alcohol), λ_{max}: 220, 279, and 289 nm (log ε 4.55, 3.83, and 3.75). Found: C 63.4; H 4.4; N 10.3; S 11.6%. $C_{15}H_{14}N_2O_2S$. Calculated: C 63.0; H 4.9; N 9.8; S 11.2%.

3-(p-Carbomethoxyaminobenzenesulfamido)indole (VIII). This compound, with mp 215-216°, was obtained in 83% yield by the method presented above. IR spectrum (oil), cm^{-1}: 1160 s (sym, SO_2), 1320 s (asym, SO_2), 3250 s, 3340 (NH), 3430 s (indole NH), and 1720 (C = O). Found: C 55.0; H 4.1; N 12.6; S 8.9%. $C_{16}H_{15}N_3O_4S$. Calculated: C 55.6; H 4.4; N 12.2; S 9.3%.

3-(p-Aminobenzenesulfamido)indole (IX). A solution of 0.6 g (1.0 mmole) of VIII in 20 ml of 5% NaOH solution was heated for 2 h, after which it was treated with activated charcoal and filtered. The filtrate was acidified to pH 6-7 with hydrochloric acid, and the resulting precipitate was removed by filtration and washed with water to give 0.28 g (93%) of a product with mp 229-230°. IR spectrum (oil), cm^{-1}: 1155 s (sym, SO_2), 1320 s (asym, SO_2), 1300 s, 1380 s (indole NH). UV spectrum (in alcohol), λ_{max}: 212, 269 nm (log ε 4.56 and 4.34). Found: C 58.47; H 4,72; N 14.75; S 11.2%. $C_{14}H_{13}N_3O_2S$. Calculated: C 58.52; H 4.56; N 14.62; S 11.16%.

3-(Salicylideneamino)indole (XIa). A) A 0.49-g (4 mmole) sample of salicylaldehyde was added with ice cooling to a solution of 0.52 g (4.0 mmole) of amine I in 40 ml of $CHCl_3$. After 30 min, the mixture was extracted with 20 ml of K_2CO_3 solution (pH 10-11), and the chloroform solution was washed with water, dried with $MgSO_4$, and filtered. The filtrate was evaporated to one fifth of its original volume, and petroleum ether was added to precipitate 0.68 g (72%) of XIa with mp 129-130°. IR spectrum (KBr pellet), cm^{-1}: 1620 s (C = N), 3200 s (associated OH), and 3400 (indole NH). Found: C 76.6; H 4.9; N 11.3%. $C_{15}H_{12}N_2O$. Calculated: C 76.3; H 5.1; N 11.8%.

3-(o-Methoxybenzylideneamino)indole (XIb). This compound, with mp 102-103°, was similarly obtained in 38% yield. IR spectrum (KBr pellet), cm^{-1}: 1610 s (C = N), 3400 s (indole NH). Found: C 76.7; H 5.8; N 10.9%. $C_{16}H_{14}N_2O$. Calculated: C 76.8; H 5.7; N 11.2%.

B) A 0.57-g (5.5 mmole) sample of salicylaldehyde was added to a solution of 0.84 g (5.0 mmole) of hydrochloride II in 10 ml of alcohol. After 2 h, the precipitated XIIa was removed by filtration, washed with absolute alcohol, and stirred with 30 ml of chloroform and 30 ml of K_2CO_3 solution (pH 10-11) until it dissolved. The chloroform solution was worked up by method A to give 1.05 g (84%) of a product with mp 129-130°. The IR spectra of this product and the substance synthesized by method A were identical.

Compound XIb, with mp 102-103°, was similarly obtained. The IR spectra of XIb and the substance obtained by method A were identical.

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