INDOLE DERIVATIVES

CXVI.* PREPARATION AND SOME PROPERTIES OF 3-AMINOINDOLES

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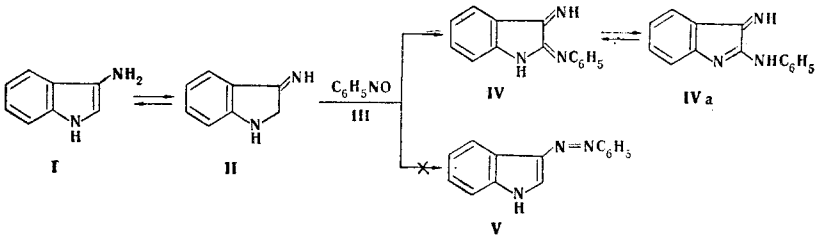
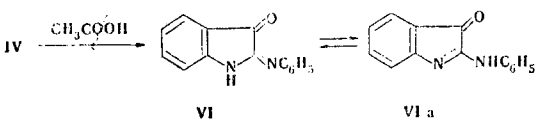
Reactions in which 3-aminoindole displays the properties of 3-imino-2H-indole were carried out. Condensation of aromatic amines (in the case of 3-aminoindole, p-toluidine, and p-nitrophenylamine) and of pyridoxamine with 1-acetylindoxyl is proposed as a convenient method for the preparation of secondary amines of the indole series.

We have established that 3-aminoindole (I) displays the properties not only of an amine (it forms Schiff bases with aldehydes and amides under the influence of acylating agents [2]) but also of an iminoindolenine (II) in a number of cases.



Thus amine I, like indoxyl derivatives [3], acts as a methylene component in the condensation with nitrosobenzene (III), and unstable imine IV is formed. Phenylazoindole (V) is not formed via the reaction characteristic for 2-substituted 3-aminoindoles [4] under these condition. Imine IV is obtained after brief heating of I and III in dioxane; the imine is stable only in the crystalline state and is rapidly converted to the previously described [3, 5] isatin anil (VI) in acetic acid.



The UV spectrum of IV is similar to the spectrum of anil VI; as in the case of anil VI [5], we observed a change in the form and color of the crystals after recrystallization of IV from alcohol, chloroform, and petroleum ether. This makes it possible to assume the existence in the case of IV of the VI ⇌ VIa tautomerism characteristic for isatin anil VI; this is confirmed by the presence in the PMR spectrum of the compound in $(CD_3)_2SO$ of two sets of signals of aromatic protons and NH groups corresponding to the two tautomeric forms.

The oxidation of amine I with iodosobenzene diacetate also proceeds via the pathway usual for indoxyls rather than via that usually observed for amines [6], as a result of which diiminoindigo VII [7] rather than phenylazoindole V is formed.

We were unable to use the condensation of imino form II with ketones for the preparation of 2-substituted 3-aminoindoles. The reaction of amine I with 1-acetylindoxyl (VIII) led to secondary amine X rather than primary amine IX.

* See [1] for communication CXV.

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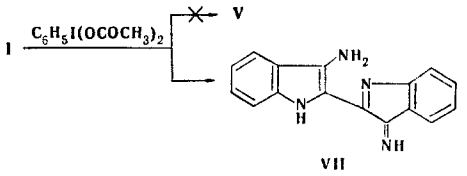
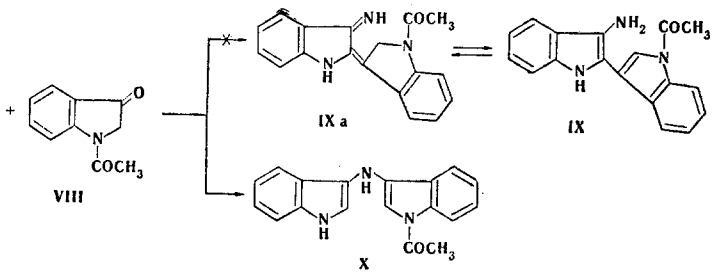
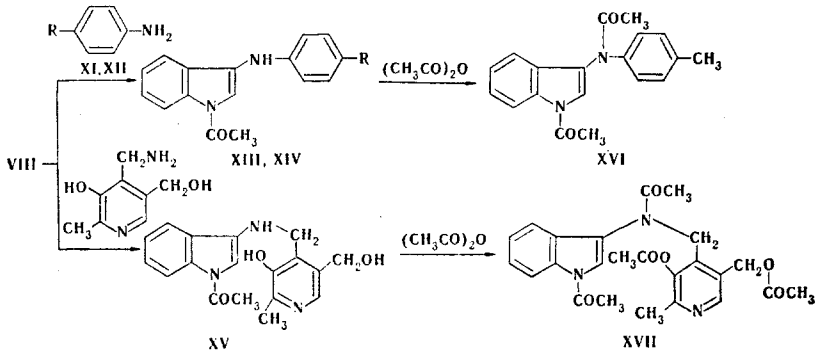


VII

Thus, as in the case of the condensation with aldehydes, I acts as an amine in the condensation with ketone VIII.



The condensation of indoxyl VIII with aromatic amines seems of interest for the preparation of aryl-(1-acetyl-3-indolyl)amines. p-Tolyl- and p-nitrophenylamines XIII and XIV were obtained by this method from indoxyl VIII and amines XI and XII.



XI, XIII R = CH_3; XII, XIV R = NO_2

Acetic acid is a better solvent for the preparation of aryl(1-acetyl-3-indolyl)amines; X, XIII, and XIV were obtained in high yields after brief heating in this solvent. The formation of amines X, XIII, and XIV can be judged only from the results of thin-layer chromatography (TLC) when the reaction is carried out in refluxing toluene in the presence of catalytic amounts of acetic acid, i.e., under the Nenitsecu conditions [8] for the preparation of 1-acetyl-3-piperidinoindole. In this case, in addition to the formation of side products, a considerable amount of the starting compounds remain even after prolonged heating.

Pyridoxamine was used as a possible subject for condensation with indoxyl VIII. The reaction proceeds by heating in alcohol in the presence of triethylamine or sodium acetate, and amine XV is obtained in high yield.

Amines X, XIII, and XV are stable only in the crystalline state; they undergo rapid decomposition in solution, frequently with the formation of blue substances. Amine XIII is especially unstable and turns yellow after isolation from the reaction mixture in the form of a white crystalline compound; however, it can be stored in the yellow state for a long time without appreciable signs of decomposition (in view of this, attempts to prepare amine XIII for analysis were unsuccessful). Amines XIII and XV undergo acylation with acetic anhydride to give stable acetyl derivatives XVI and XVII.

On the other hand, amine X gradually undergoes decomposition without forming individual substances under the influence of acetic anhydride at room temperature and when it is heated.

However, amine XIV is distinguished by its stability in the crystalline state and in solution, and it does not react with acetic anhydride on heating, even in the presence of potassium acetate and p-toluenesulfonic acid as catalysts.

The IR spectra of amines X and XIII-XV (Table 2) contain absorption bands of NH groups at 3330-3450 cm^{-1} and of acetyl group at 1680-1700 cm^{-1}. The PMR spectra of amines X, XIII, and XIV (Table 2) contain

TABLE 1. 1-Acetyl-3-indolylamines X and XIII-XV

Compound	mp, °C	Found, %			M (by mass spectrometry)	Empirical formula	Calculated, %			M	Yield, %
		C	H	N			C	H	N		
X[a]	208—210[b]	74,4	4,9	14,0	289	$C_{18}H_{15}N_3O$	74,9	5,2	14,5	289	93
XIII[a]	Above 65[b]	—	—	—	264	$C_{17}H_{16}N_2O$	—	—	—	264	94,5
XIV	204—205[c]	64,5	4,7	14,4	295	$C_{16}H_{13}N_3O$	65,0	4,4	14,5	295	95
XV	230—232[b]	66,9	6,1	12,9	325	$C_{18}H_9N_3O_3$	66,4	5,9	12,9	325	92,5

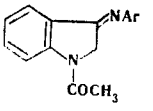
[a]Without recrystallization. [b]With decomposition. [c]From alcohol.

TABLE 2. IR, UV, and PMR Spectra of X and XIII-XV

Compound	IR spectra (in mineral oil), cm^{-1}		UV spectra in alcohol, λ_{max}, nm (log ε)	PMR spectra in $(CD_3)_2CO$—$(CD_3)_2SO$ (3:1), δ, ppm; multiplicity
	$COCH_3$	NH		
X	1700	3400, 3420	205, 241, 263 sh, 312 (4,47, 4,41, 4,43, 4,22)	2,41 (s, $COCH_3$), 7,36—9,14 (m, aromatic protons 11,3 (s, NH)
XIII[a]	1680	3370	208, 233, 260, 339 (4,45, 4,37, 4,25, 3,9)	2,22 (s, $COCH_3$), 2,59 (s, CH_3), 7,00—8,45 (m), aromatic protons
	1700[b]	3450		
XIV[a]	1680	3360	206, 229, 293, 308, 390 (4,41, 4,37, 3,79, 3,85, 4,27)	2,67 (s, $COCH_3$), 6,63—7,87 (m, aromatic protons 8,89 (s, NH)
XV	1685	3120, 3200 br., 3330[c]	208, 246, 290, 312 (4,58, 4,09, 3,97, 3,89)	

[a]The C=C bands of a p-substituted benzene ring are found at 1610 cm^{-1}. [b]In chloroform. [c]For NH and OH.

signals of protons of acetyl groups and aromatic protons; the signals of the protons of a methylene group that should have been observed in the spectra of the isomeric Schiff bases (Xa, XIIIa, and XIVa) are absent. We were unable to record the PMR spectrum of amine XV because of its rapid decomposition in alcohol, acetone, and DMSO.



Xa Ar=3-indolyl; XIIIa Ar= p-tolyl XIVa Ar=p-nitrophenyl

The assignment of the signals of the 2-H protons in the spectra of amines X, XIII, and XIV is difficult; however, these signals appear at 8.00 and 7.68 ppm in the spectra of acetyl derivatives XVI and XVII, i.e., at values close to the chemical shift of the 2-H proton (7.76 ppm) [2] in the spectrum of 1,3,3-triacetaminoindole.

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-20 spectrometer. The UV spectra were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were obtained with a Varian CFT-20 spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded with an MKh-1303 mass spectrometer with direct introduction of the samples into the ion source at an ionizing-electron energy of 50 eV and a cathode emission current of 1.25 mA. Silufol UV-254 and an acetone—chloroform system (1:20) were used for TLC.

2-Anilino-3H-indole-3-imine (IV). A solution of 0.13 g (1 mmole of 3-aminoindole in 5 ml of dioxane was added to a hot solution of 0.11 g (1 mmole) of nitrosobenzene in 5 ml of dioxane, and the mixture was heated for 3-5 min. It was then allowed to stand at room temperature for 30 min, after which it was diluted with water and worked up to give 0.15 g (72%) of imine IV with mp 167-168°C (from petroleum ether). UV spectrum (in alcohol): λ_{max} 204, 225, 259, 303, 435 nm (log ε 4.30, 4.05, 4.44, 3.52, 3.52). IR spectrum (oil): 1590 s, 1620 s, 1650 sh, and 1690 m (C=C, C=N); 3250 cm^{-1} (NH); (chloroform): 1590 s, 1620 s, 1610 s, 1630 s, and

1690 m (C=C, C=N); 3380 m and 3460 m cm^{-1} (NH). PMR spectrum in $(CD_3)_2SO$: 6.84-8.22 (m, aromatic protons); 9.62, 9.88, 14.50, and 17.80 (s, NH). Found: N 18.8%; M 221 (by mass spectrometry). $C_{14}H_{11}N_3$. Calculated: N 19.0%; M 221.

2-Anilino-3H-indol-3-one (VI). A solution of 0.22 g (1 mmole) of imine IV in 1 ml of acetic acid was allowed to stand at room temperature for 1 h, after which it was diluted with water, and the resulting precipitate was removed by filtration to give 0.2 g (90%) of a product with mp 123-124°C (from petroleum ether) (mp 123-124°C [5]). UV spectrum (in alcohol): λ_{max} 203, 225, 258, 303, 470 nm (log ε 4.21, 4.12, 4.39, 3.60, 3.60).

3-Amino-2-(3-imino-3H-indol-2-yl)indole (indigo imine) (VII). A solution of 0.65 g (5 mmole) of 3-aminoindole and 1.6 g (5 mmole) of iodosobenzene diacetate in 40 ml of acetic acid was allowed to stand at room temperature for 10-12 h, after which the precipitate was removed by filtration and washed with acetic acid, alcohol, and ether to give 0.8 g (62%) of VII with mp 215°C (mp 215°C [9]). Found: M 260 (by mass spectrometry). Calculated: M 260.

General Method for the Preparation of X, XIII, and XIV. A solution of 2 mmole of 1-acetylindoxyl VIII and 2 mmole of I, XI, or XII in 1 ml of acetic acid was heated for 10 min (for 1 h in the case of XII), after which it was cooled rapidly, and the precipitate was removed by filtration and washed with acetic acid, alcohol, and ether. Data on the compounds are presented in Tables 1 and 2.

N-(1-Acetyl-3-indolyl)pyridoxamine (XV). A mixture of 0.24 g (1 mmole) of pyridoxamine dihydrochloride, 0.18 g (1 mmole) of indoxyl VIII, 1 ml of triethylamine, and 3 ml of alcohol was heated for 1 h, after which the precipitate was removed rapidly by filtration and washed with water, alcohol, and ether. Data on the product are presented in Tables 1 and 2.

N-Acetyl-4-tolyl(1-acetyl-3-indolyl)amine (XVI). A solution of 0.1 g (0.38 mmole) of amine XIII in 1 ml of acetic anhydride was refluxed for 1 h, after which it was diluted with water and extracted with ether. The ether extracts were washed with 10% NaOH and water and dried with $MgSO_4$. The ether was removed by evaporation, and the resulting oil was crystallized by the addition of alcohol to give a product with mp 124-125°C (from alcohol). The yield was 0.07 g (60%). UV spectrum (in alcohol): λ_{max} 205, 232, 274, 293, 300 (log ε 4.49, 4.32, 3.92, 3.84, 3.89). IR spectra (oil): 1680 s ($COCH_3$) and 1610 s cm^{-1} (C=C band of a p-substituted benzene ring). PMR spectrum in $(CD_3)_2CO$; 2.03 and 2.27 (s, $COCH_3$); 2.64 (s, CH_3); 7.04-8.42 ppm (m, aromatic protons). Found: C 74.3; H 6.1; N 8.9; M 306 (by mass spectrometry). $C_{19}H_{18}N_2O_2$. Calculated: C 74.5; H 5.9; N 9.1%; M 3.06.

N-Acetyl(1-acetyl-3-indolyl)pyridoxamine Diacetate (XVII). A mixture of 0.1 g (0.34 mmole) of amine XV, 0.1 g of sodium acetate, and 1.5 ml of acetic anhydride was heated for 3 h, after which it was treated with water, and the resulting precipitate was removed by filtration and washed with water and alcohol to give 0.15 g (98%) of XVII with mp 149-150°C. UV spectrum (in alcohol): λ_{max} 204, 238, 267, 290, 301 (log ε 4.46; 4.21, 4.11, 3.81, 3.83). IR spectrum (oil): 1650 s, 1660 s ($COCH_3$); 1730, 1740, and 1770 s cm^{-1} (ester CO). PMR spectrum in $(CD_3)_2CO$–$(CD_3)_2SO$ (3:1): 1.84, 1.92, 2.09, 2.21, and 2.51 (s, $COCH_3$); 4.83 and 5.00 (s, CH_2); 7.1-8.2 ppm (m, aromatic protons). Found: C 63.5; H 5.7; N 9.3%; M 451 (by mass spectrometry). $C_{24}H_{25}N_3O_6$. Calculated: C 63.9; H 5.5; N 9.3%; M 451.

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