INDOLES

XXX.* α-ACYLPHENYLHYDRAZINES IN THE SYNTHESIS OF TRYPTAMINES

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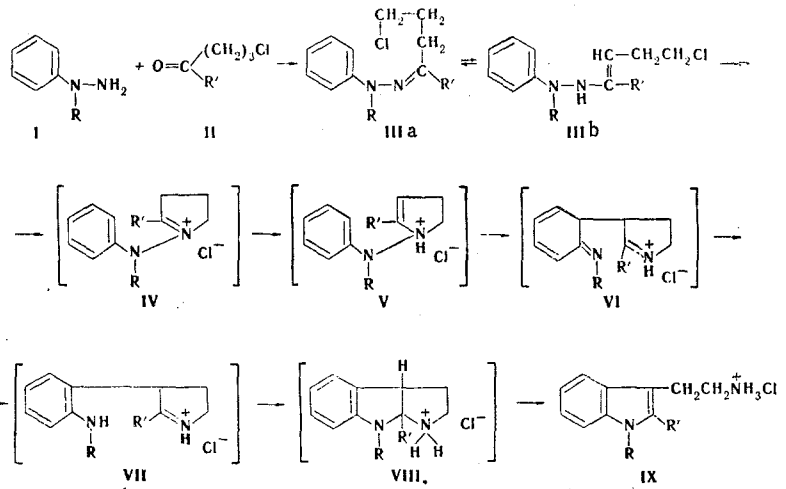
The unexpected 1-acetyl-2-methyltryptamine was isolated in an attempt to use α-acetylphenylhydrazine in the synthesis of tryptamines (reaction with γ-chloropropyl methyl ketone), and one of the intermediates was N-acetylanilino-Δ^2-2-methylpyrroline, which underwent hydrolytic opening of the pyrroline ring. Subsequent heat treatment of it made it possible to obtain 3-(2-acetamidophenyl)-2-methyl-Δ^2-pyrroline, which is also one of the intermediates in the synthesis of tryptamines. On treatment with acetic anhydride, the latter was converted to 1-acetyl-2-methyl-3-(2-acetamidoethyl)indole. Thus the isolation of a number of intermediates in various stages of the investigated reaction was one of the most important proofs of the correspondence of the previously proposed scheme to the real mechanism of the process.

A scheme for the synthesis of tryptamines from arylhydrazines and γ-halo carbonyl compounds was previously proposed in [2]. A confirmation of it was the isolation of several intermediates [3,4].



When 1-acetylphenylhydrazines are used in this reaction, one should have expected the production of 1-acyltryptamines, which are hard to obtain by direct acylation because of the presence of the more basic side-chain NH_2 group in the tryptamines.

However, we observed that the reaction of α-acetylphenylhydrazine with γ-chloropropyl methyl ketone does not result in the formation of the expected 1-acetyl-2-methyltryptamine. When equimolar amounts of the starting compounds were refluxed, we were able to isolate a substance that proved to be an alkylation product – α-acetyl-β-acetopropylphenylhydrazine (X).

*See [1] for communication XXIX.

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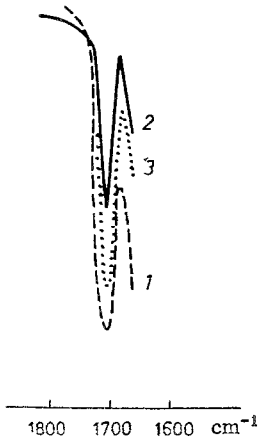
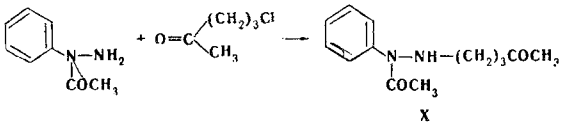


Fig. 1. Change in the intensity of the carbonyl band in the IR spectrum during the reaction of α-acetylphenylhydrazine with γ-chloropropyl methyl ketone: 1) starting ketone; 2) after 15 min; 3) after 120 min.



X

The PMR spectrum of this compound in CCl_4 is in complete agreement with the structure. The spectrum contains two triplets at 1.57 and 2.67 ppm (J = 7 Hz), which are affiliated with the γ- and α-methylene groups, respectively. The diffuse quintet at 2.32 ppm (J = 7 Hz) is related to the protons of the β-methylene group. The two singlets at 1.87 and 1.95 ppm are affiliated with the protons of the C- and N-acetyl groups, respectively, while the multiplet centered at 7.48 ppm is affiliated with the aromatic protons. The signal of the proton of the NH group appears at 5.42 ppm as a broad singlet.

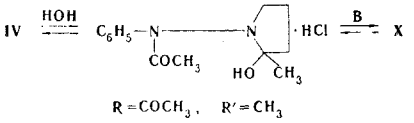
The UV spectrum of a freshly prepared sample has an absorption maximum at 2.38 nm (log ε 3.82), which is characteristic for substituted phenylhydrazines [5].

The IR spectrum of a KBr pellet of X contained an absorption band at 3264 cm^{-1}, which is related to the stretching vibrations of the NH group, and absorption bands at 1710 and 1630 cm^{-1}, which were assigned to the vibrations of the C=O groups of the ketone and amide fragments, respectively.

Intense peaks of ions with masses 135 and 93, which are formed as a result of cleavage of the N–N bond and correspond to the fragments of the N-acetylaniline and aniline fragments, are observed in the mass spectrum of X. The absence of a molecular peak in the mass spectrum is associated with dehydration in the mass-spectrometer system, which leads to cyclization and formation of N-acetylanilino-Δ^2-2-methylpyrroline (XI). The characteristic direction of fragmentation of the molecular ion of the latter is elimination of a hydrogen molecule.

The reaction between α-benzoylphenylhydrazine and γ-chloropropyl methyl ketone proceeded similarly.

It seemed unlikely that the formation of X proceeds due to the usual alkylation of the NH_2 group of the acylhydrazine. To prove the more probable scheme presented below, we investigated the change in the intensity of the absorption band of the carbonyl group in the IR spectra during the interaction of deuterated α-acetylphenylhydrazine and γ-chloropropyl methyl ketone in CH_3OD* (Fig. 1).



Fifteen minutes after the reaction of the starting substances, the intensity of the carbonyl band (1710 cm^{-1}) was halved, then began to increase, and reached the value corresponding to the intensity of the carbonyl band of the final compound (X).

α-Acetylphenylhydrazine (I, R = $COCH_3$) apparently reacts with the carbonyl group of the chloro ketone to form phenylhydrazone III (R = $COCH_3$, R' = CH_3). This is followed by the cyclization of the hydrazone to the hydrochloride of N-anilinopyrroline IV (R = $COCH_3$, R' = CH_3), which undergoes hydrolytic opening of the ring to form X.

Hydrazine X loses a water molecule very readily. Thus, even on treatment with picric acid, it undergoes cyclization with splitting out of water and the formation of the picrate of N-acetylanilino-Δ^2-2-methylpyrroline (XI) – an intermediate of the V type, from which base XII was isolated as dimer XIII after treatment with liquid ammonia and simultaneous removal of the acetyl group. The formation of a stable dimer

*Deuterated preparations were used so that the 1700 cm^{-1} region would be free of extraneous absorption (CH_3OH, H_2O).

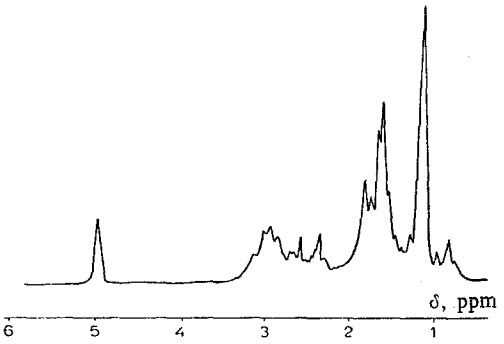
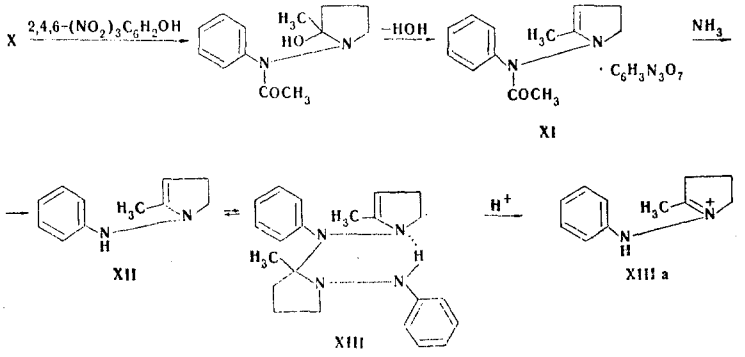


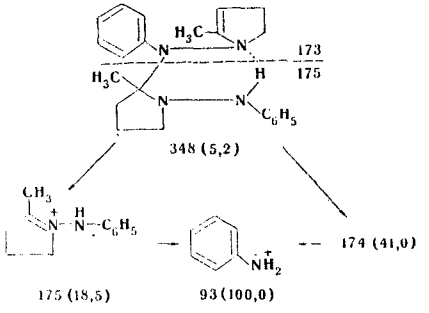
Fig. 2. PMR spectrum of dimer XIII.

of this type was previously observed by one of us in the reaction of α-hydrazinopyridine with γ-chloropropyl methyl ketone [1]. An absorption band at 244 nm (log ε 3.82) and inflections at 261 nm (log ε 3.75) and 297 nm (log ε 3.40) are present in the UV spectrum of dimer XIII. The IR spectrum of a liquid film of the dimer contains an absorption band of the stretching vibrations of an associated NH group at 3280 cm^{-1}, the usual absorption bands for an aromatic system, and an absorption band of a C=C bond at 1640 cm^{-1}.

The PMR spectrum of the compound in CCl_4 has a rather complex form (Fig. 2). The proton signals were assigned by comparison of the PMR spectrum of dimer XIII with the spectrum of the analogous dimer of N-(α-methylpyrrolino)-2-aminopyridine [1]. The PMR spectrum of dimer XIII contains a broad signal at 5.05 ppm, which is related to the proton attached to the double bond of the pyrroline ring. The protons of the methyl group of the pyrroline ring appear as a singlet at 1.15 ppm. When the UV spectrum of this compound was recorded in aqueous alcohol at various pH values,* it was observed that a maximum at 273 nm, which becomes sharply expressed at pH 1.6, appears in acid media (pH 2.7). Moreover, the absorption maximum at 244 nm vanishes. All of this clearly indicates the conversion of dimer XIII to a monomer with the formation of a protonated structure (XIIIa) [1].

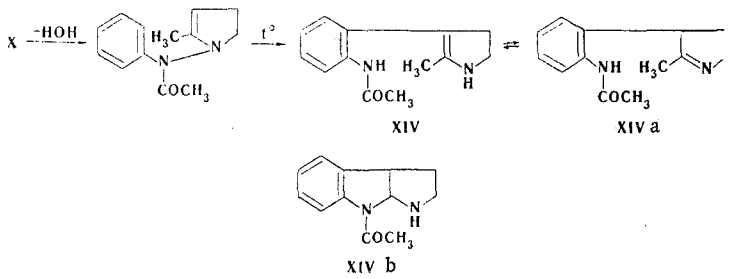


The mass spectrum of XIII also confirms the structure of this dimer. The mass spectrum contains a peak of an ion with mass 348, which corresponds to the molecular weight of the dimer. The mass spectrum corresponds qualitatively to the previously investigated mass spectrum of the dimer of N-(α-methylpyrrolino)-2-aminopyridine [1]. The first step in the fragmentation of XIII is associated with cleavage of the C–N bond and migration of the hydrogen atom to form an ion with mass 174. Simple cleavage of the C–N bond, which leads to an ion with mass 175, is expressed considerably more weakly as compared with the aza analog. The maximum peak in the mass spectrum corresponds to an ion with mass 93, which correlates with the aniline structure. The formation of this ion (or a homologous ion) is particularly characteristic for the N-anilinopyrroline structure. The pyrroline fragment is represented in the mass spectrum by fragment ions with masses 83 and 82.



Refluxing of X in xylene with removal of an equimolar amount of water by distillation and subsequent fractionation of the reaction mixture gave a crystalline substance (XIV), which, according to analysis and the PMR, IR, and UV spectra, proved to be an intermediate of the VII type (R = $COCH_3$, R' = CH_3).

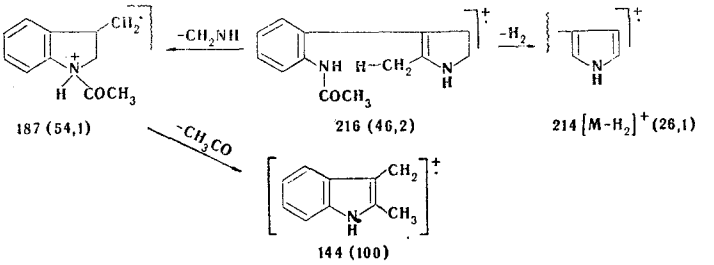
*See [6] for the method for recording the UV spectra at various pH values.



XIV XIVa XIVb

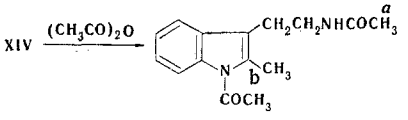
Analysis of the PMR spectrum in $CDCl_3$ at 20° demonstrates the presence of two forms (XIV and XIVa) in a ratio of about 3:1. When the temperature is raised to 75°, the amount of the XIVa form increases by approximately 50%. When the spectrum is recorded in CD_3OD at both 20 and 70°, the signals of the protons of the CH_3 group attached to the double bond vanish as a consequence of tautomerism [6], and only the signals of the CH_3CO group (2.15 ppm) and the diffuse triplets of the α- and β-methylene groups of the pyrroline ring (3.92 and 1.85 ppm, respectively) remain. Both the band of the vibrations of an associated NH group (3180 cm^{-1}) and the bands of the amide C=O (1690 cm^{-1}) and C=C (1640 cm^{-1}) groups appear in the IR spectrum of a KBr pellet. The pK_a value (4.9) indicates predominance of structure XIV over XIVa, since a considerably higher pK_a value should have been expected for XIVa. Alternative cyclic structure XIVb is unacceptable because of a different direction of fragmentation during electron impact.

The principal directions of dissociative ionization of XIV are associated with the elimination of H_2, CH_2NH, and CH_3CONH_2 particles. The presence of intense $(M-H_2)^+$ ion peaks in the mass spectrum indicates a structure that contains a pyrroline ring. It should be noted that the formation of $(M-2H)^+$ ions is a process that is considerably more characteristic for Δ^2-pyrrolines than for Δ^1-pyrrolines [7]. The maximum peak in the mass spectrum of XIV corresponds to an ion with mass 144, which is typical for the mass spectra of 2-methyl-3-alkylindoles, 2-methyltryptamines, and dinordeoxy-9-methyleseroline [8, 9]. The formation of this ion is possible as a result of cyclization of the molecular ion and subsequent elimination of CH_2NH and CH_3CO particles.



187 (54,1) 216 (46,2) 214 $[M-H_2]^+$ (26,1) 144 (100)

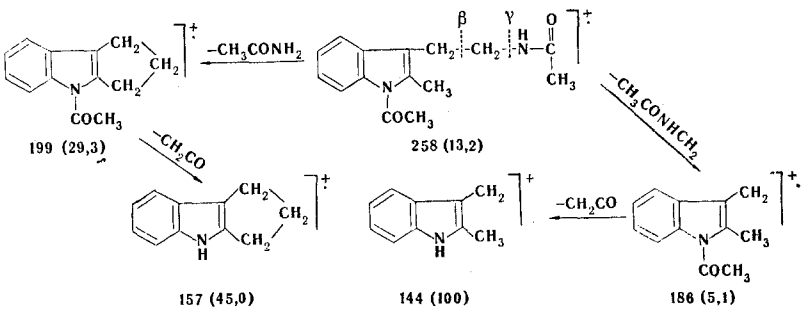
Treatment of XIV with boiling acetic anhydride gave an acetyl derivative, the analysis and PMR and mass spectra of which speak in favor of a diacylated 2-methyltryptamine structure (XV).



XV

The mass spectrum of XV corresponds to the 1-acetyl-2-methyl-3-(2-acetamidoethyl)indole structure. A comparison of the mass spectra of diacetyl derivative XV and 2-methyl-3-(2-acetamidoethyl)indole [10] demonstrates that the primary directions of fragmentation of these compounds are equivalent. In both cases, the most important directions for disintegration of the molecular ion are cleavage of the β bond with subsequent elimination of a ketene molecule (for the diacetyl derivative), which leads to a maximum of the peak of an ion with mass 144, and cleavage at the γ bond with migration of a hydrogen atom and splitting out of an acetanilide particle. Removal of the acetyl group bonded to the nitrogen atom of the indole system always occurs in the second step of the fragmentation.

An analysis of the PMR spectrum in pyridine also demonstrates that XV has the tryptamine structure [11]. The signals of the protons of the methylene groups in the α and β positions appear as triplets at 2.82 and 3.40 ppm (J = 7 Hz), respectively. The singlet at 2.37 ppm is related to the protons of the methyl group



in the 2 position of the indole ring. The two singlets at 1.90 and 2.32 ppm are affiliated with the protons of the *a* and b methyl groups, respectively. A comparison of the PMR spectrum of XV with the spectrum of model compound 2-methyl-3-(2-acetamidoethyl)indole made it possible to draw a definite conclusion regarding the structure of acyl derivative XV.

The latter was smoothly converted to 2-methyltryptamine on heating with HCl in methanol. It should be noted that all of the intermediates indicated above were also converted to 2-methyltryptamine on heating in the presence of HCl.

EXPERIMENTAL

The pK_a values were determined by means of 0.1 N HCl with an RT-3 titrator (Japanese) in 80% Methyl Cellosolve. The UV spectra of ethanol solutions were recorded with an EPS-3T spectrophotometer (Hitachi). The IR spectra were recorded with a JASCO-IR-S spectrophotometer with a NaCl prism or with a UR-20 spectrophotometer with a LiF prism. The PMR spectra were recorded with a JNM-4H-60 spectrophotometer with tetramethylsilane as the internal standard. The chemical shifts are given on the δ scale. The mass spectra were obtained with an SN-6 spectrometer with a system for direct introduction of the sample into the ion source at an ionizing voltage of 70 eV and an ionization-chamber temperature of 180°. The numbers before the parentheses denote the mass number, while the numbers in parentheses are the relative intensities of the ion peaks with respect to the maximum peak.

α-Acetylphenylhydrazine. This compound was obtained in 69% yield from β-formyl-α-acetylphenylhydrazine [12] and had mp 124° (from benzene), R_f 0.50 [activity II Al_2O_3, benzene–ethanol (9:1), development with iodine], 0.84 [fast paper from the Volodarsk factory, butanol–pyridine–water (1:1:1)], and pK_a 2.09. UV spectrum: λ_{max} 238 nm, log ε 3.76. IR spectrum (KBr), cm^{-1}: 1710 (C=O). PMR spectrum (in dimethyl sulfoxide), ppm: singlet 2.15 ($COCH_3$), singlet 5.41 (NH_2), multiplet centered at 7.48 (aromatic ring protons).

α-Acetyl-β-acetopropylphenylhydrazine (X). A solution of 6 g (0.05 mole) of γ-chloropropyl methyl ketone in 20 ml of methanol was added to a refluxing solution of 7.6 g (0.05 mole) of α-acetylphenylhydrazine in 50 ml of methanol, and the reaction mixture was refluxed for 2 h. The solvent was removed in vacuo (with a water aspirator), and the residue was dissolved in 100 ml of hot water. The aqueous solution was extracted with ether to remove impurities and was then made carefully alkaline to pH 8-9 with sodium hydroxide solution and salted out with potassium carbonate. The liberated oil was extracted with ether, and the extracts were dried with Na_2SO_4 and filtered. The ether was removed by distillation, and the residual oil began to crystallize on trituration with a small amount of absolute ether to give 7.5 g (64%) of X with mp 37-39° (from benzene–hexane), R_f 0.42 [activity II Al_2O_3, benzene–isopropyl alcohol (47:3), development with iodine], 0.65 (activity II Al_2O_3, ethyl acetate, development with iodine), and pK_a 2.82. Found: C 66.8; 66.5; H 7.7, 7.7%. $C_{13}H_{18}N_2O_2$. Calculated: C 66.6; H 7.7%.

α-Benzoyl-β-acetopropylphenylhydrazine. This compound was prepared in the same way as hydrazine X from 10.6 g (0.05 mole) of α-benzoylphenylhydrazine [12]. Purification with a column filled with activity II Al_2O_3 yielded 9.4 g (64%) of α-benzoyl-β-acetopropylphenylhydrazine with R_f 0.76 [benzene–methanol (9:1)]. UV spectrum: λ_{max} 263 nm, log ε 3.84. IR spectrum (in CCl_4), cm^{-1}: 3240 (NH), 1715 (C=O), 1634 (amide C=O). PMR spectrum (in CCl_4), ppm: singlet 1.92 (CH_3), triplet 2.75 (J = 7 Hz, α-CH_2), multiplet 2.27 (β-CH_2), triplet 1.60 (J = 7 Hz, γ-CH_2), multiplet 6.60-7.30 (aromatic ring protons). Found: C 72.9, 72.8; H 6.8, 6.7%. $C_{18}H_{20}N_2O_2$. Calculated: C 72.9; H 6.8%.

Action of Picric Acid on α-Acetyl-β-acetopropylphenylhydrazine. Picrate XI with mp 112-113° (from a small amount of methanol) was obtained in absolute ether from a molar quantity of picric acid. Found: C 51.1, 51.2; H 4.3, 4.4%. $C_{13}H_{16}N_2O \cdot C_6H_3N_3O_7$. Calculated: C 51.2; H 4.31.

Isolation of Base XIII from the Picrate. A 2.2-g (0.005 mole) sample of picrate XI was treated with excess liquid ammonia until the salt dissolved completely. The reaction mass was allowed to stand until half of the ammonia had evaporated, and the residue was extracted with hexane in a Soxhlet apparatus. The extract was filtered, and the hexane was removed on a rotary evaporator to give dark crystals with mp 29-30°, R_f 0.90 (activity II Al_2O_3, ethyl acetate, development with iodine), and pK_a 5.82. Mass spectrum: 39 (27.4), 43 (43.6), 55 (24.4), 57 (27.5), 59 (12.4), 64 (7.2), 65 (35.8), 66 (45.1), 67 (10.9), 69 (11.9), 77 (71.5), 78 (9.3), 80 (7.7), 81 (9.8), 82 (10.9), 83 (16.6), 87 (7.7), 85 (14.0), 91 (14.5), 92 (31.1), 93 (100.0), 94 (13.7), 97 (9.3), 105 (16.6), 106 (7.5), 108 (5.2), 109 (7.7), 111 (7.7), 118 (17.7), 119 (8.8), 132 (11.9), 134 (6.7), 135 (10.4), 144 (13.5), 173 (13.0), 174 (43.5), 175 (18.3), 217 (5.2), 348 (5.2). Found: C 75.5, 75.6; H 8.3, 8.2%. $C_{22}H_{28}N_4$. Calculated: C 75.8; H 8.1%. The picrate of base XII [6] had mp 132° (from methanol). Found: C 50.5, 50.4; H 4.5, 4.5%. $C_{11}H_{14}N_2 \cdot C_6H_3N_3O_7$. Calculated: C 50.6; H 4.3%.

3-(2-Acetamidophenyl)-2-methyl-Δ^2-pyrroline (XIV). A solution of 23.4 g (0.1 mole) of hydrazine X in 200 ml of absolute xylene was refluxed for 5 h in an apparatus fitted with a Dean–Stark adapter. After an equimolar amount of water had separated, the xylene was removed to dryness in vacuo (with a water aspirator). The residue was vacuum-distilled in a stream of nitrogen to give 13.8 g (64%) of pyrroline XIV with bp 179-186° (2 mm), mp 88-90° (from ether), R_f 0.42 (activity II Al_2O_3, ethyl acetate), 0.39 [activity II Al_2O_3, benzene–isopropyl alcohol (47:3)], and pK_a 4.97. UV spectrum, λ_{max}, nm (log ε): 229 (3.79), 289 (2.36). The compound had a retention time of 9.9 min during gas-liquid chromatography (GLC).* Mass spectrum: 43 (51.2), 54 (8.1), 55 (30.1), 63 (8.1), 65 (8.5), 77 (30.5), 82 (7.1), 89 (12.6), 90 (8.1), 91 (15.0), 101 (10.0), 102 (12.0), 103 (14.3), 104 (13.9), 115 (35.0), 117 (36.0), 118 (35.1), 119 (20.0), 127 (10.0), 128 (18.1), 129 (15.1), 130 (58.1), 131 (15.0), 132 (70.1), 133 (40.0), 143 (16.1), 144 (100.0), 145 (40.1), 147 (35.0), 155 (8.3), 156 (37.0), 157 (73.3), 158 (20.1), 171 (23.6), 172 (25.4), 173 (21.0), 187 (54.1), 198 (7.0), 214 (26.1), 216 (46.2). PMR spectrum in $CDCl_3$ at 20° of a mixture of the two forms: singlet of the protons of the $COCH_3$ groups (2.15 ppm), triplet of α-CH_2 (3.90 ppm), triplet of β-CH_2 (1.86 ppm), singlets of the CH_3 groups attached to double bonds (Δ^1 and Δ^2) (2.42 and 1.72 ppm), aromatic ring protons (6.75-7.2 ppm); in CD_3OD at 20°: the signals of the protons of the $COCH_3$, α-CH_2 and β-CH_2 groups and the aromatic ring do not change, and signals of protons of CH_3 groups attached to double bonds are absent. Found: C 72.0, 71.8; H 7.3, 7.2%. $C_{13}H_{16}N_2O$. Calculated: C 72.2; H 7.5%. The picrate had mp 126-127° (from methanol). Found: C 51.1, 51.0; H 4.4, 4.4%. $C_{13}H_{16}N_2O \cdot C_6H_3N_3O_7$. Calculated: C 51.2; H 4.3%.

1-Acetyl-2-methyl-3-(2-acetamidoethyl)indole (XV). A solution of 2.1 g (0.01 mole) of pyrroline XIV in excess acetic anhydride was heated on a boiling-water bath for 2 h. The reaction mass was decomposed with ice water, and the excess acetic anhydride was neutralized with potassium carbonate. The resulting crystals were washed with water and recrystallized from benzene to give 1.8 g (68%) of indole XV with mp 175-176°, R_f 0.64 (activity II Al_2O_3, ethyl acetate) and 0.46 [activity II Al_2O_3, benzene–methanol (9:1)]. UV spectrum, λ_{max}, nm (log ε): 227 (4.30), 245 (4.29), 264 (4.10), 292 (3.88), 298 (inflection) (3.85). Mass spectrum: 30 (12.3), 43 (24.2), 77 (5.8), 115 (6.2), 143 (11.4), 144 (100.0), 145 (12.4), 156 (5.1), 157 (45.0), 158 (6.9), 186 (5.1), 199 (29.3), 200 (5.8), 258 (13.2). Found: C 70.1, 70.2; H 7.2, 7.1%. $C_{15}H_{18}N_2O_2$. Calculated: C 69.7; H 7.0%.

2-Methyl-3-(2-acetamidoethyl)indole. This compound [1.7 g (79%)] was obtained via the method used to prepare indole XV from 1.7 g (0.01 mole) of 2-methyltryptamine [13]. The product had bp 250-253° (2 mm), mp 95-96° (from ether), and R_f 0.57 [activity II Al_2O_3, benzene–isopropyl alcohol (9:1)]. UV spectrum, λ_{max}, nm (log ε): 225 (4.63), 275 (inflection) (3.96), 282 (3.97), 289 (3.89). PMR spectrum (in $CDCl_3$), ppm: singlet at 2.35 (2-CH_3), singlet at 1.85 ($COCH_3$), triplet at 2.93 (J = 7.5 Hz, α-CH_2), triplet at 3.47 (J = 7.5 Hz, β-CH_2), singlet at 8.78 (ring NH), broad singlet at 5.95 (amide NH), and multiplet at 7.05-7.79 (aromatic ring protons). Found: C 72.2, 72.0; H 7.3, 7.3%. $C_{13}H_{16}N_2O$. Calculated: C 72.2; H 7.5%.

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*With a G-800 chromatograph (Vanaco); stationary phase: the solid support was porolit + 10% stationary phase of polyethylene glycol 15,000 + 1% KOH. The column was 2 m long and 4 mm in diameter, the column temperature was 220°, and the hydrogen flow rate was 20 ml/min. The chromatograph had a thermal conductivity detector.

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