CHEMISTRY OF INDOLE

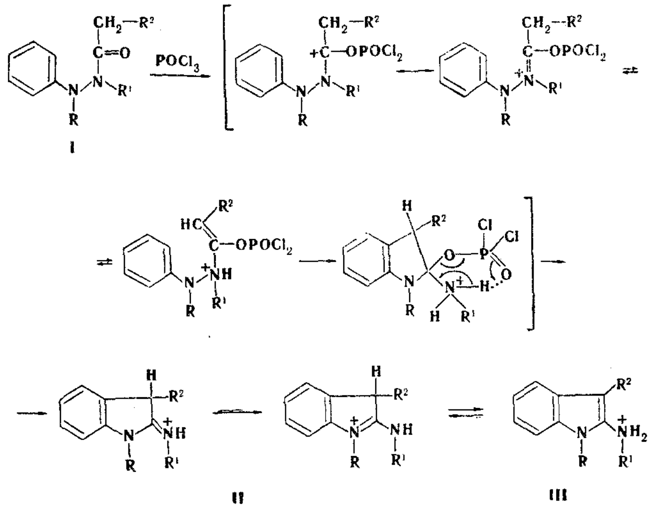
XXXV.* SYNTHESIS OF 2-AMINO-3-ALKYLINDOLES

G. A. Golubeva, Yu. N. Portnov,
and A. N. Kost

UDC 547.754.07:543.422.25.4.6

Under the influence of phosphorus oxychloride in an inert solvent, 1-aryl-2-acylhydrazines undergo intramolecular rearrangement to give 2-amino-3-alkylindoles. The latter are autooxidized in alkaline media to give 3-hydroxy-2-aminoindolenines or 3-hydroxy-2-iminoindolines. The structures of all of the compounds were proved by UV, IR, and PMR spectroscopy and also by mass-spectrometric data.

We have previously shown [2] that 1-aryl-2-acylpyrazolidines rearrange intramolecularly under the influence of phosphorus halides to give tetrahydropyrimido[1,2-a]indoles. In the present study we have shown that various 1-aryl-2-acylhydrazines (I) that have an α-methylene group in the acyl residue are converted to indole derivatives (II, III) under the influence of phosphorus oxychloride. The course of the reaction can be represented by the following scheme (Cl^- is the gegenion in all cases):



The reaction is a general one and makes it possible to obtain in good yields the previously very difficult-to-obtain 2-aminoindoles with substituents both in the amino group and in various positions of the indole ring (see Table 1). For example, when 1-methyl-1-phenyl-2-propionylhydrazine (Ia, $R^1 = H$, $R = R^2 = CH_3$) was refluxed with excess $POCl_3$ in absolute ether, a colorless salt (IIa) was isolated; the IR spectrum of this salt contains a broad absorption band at 2750-3100 cm^{-1} (ammonium group) and an intense absorption at 1690 cm^{-1}, which corresponds to the stretching vibrations of a $C=N$ group. The UV spectrum in methanol (λ_{max} 210, 260 nm; log ε 4.31, 3.90) is similar to the spectrum of 1-methyl-2-aminoindole hydriodide [3]. The PMR spectrum of IIa in CF_3COOH has a singlet of three protons of an $N-CH_3$ group (3.5 ppm), the doublet (3H) and quartet (1H) of a CH_3CH- grouping (1.53, 4.08 ppm), the multiplet of

---

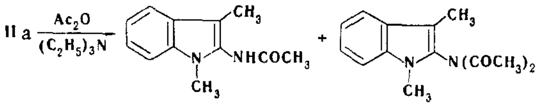
*See [1] for communication XXXIV.

M. V. Lomonosov Moscow State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 511-515, April, 1973. Original article submitted March 9, 1972.

four aromatic protons at 7.04-7.24 ppm, and two signals of protons attached to the nitrogen atom (7.64 and 7.90 ppm). The character of the spectrum of this substance in water does not change (singlet at 3.68, doublet at 1.78, quartet at 4.30 ppm, and broadened signals of NH_2 protons at 9.25 and 9.65 ppm); this is in conformity with the existence of 2-aminoindole salts in the imine form (with charge delocalization in the amidine system of bonds). The presence in the PMR spectrum of individual signals of the protons of the amino group attests to considerable double-bond character of the bond exocyclic nitrogen atom with the α-carbon atom, as a consequence of which these protons become nonequivalent (as observed also for protonated amides [4]).

The quartet of the proton in the 3 position and the splitting of the $3\text{-}CH_3$ signal vanish in the PMR spectrum of IIa in D_2O because of rapid deuterium exchange. This sort of deuterium exchange is associated with the existence of a rapid but markedly shifted equilibrium (II $\rightleftharpoons$ III). Thus the data from the PMR spectrum are evidence in favor of structure IIa. A preliminary communication in this regard has been published [5].

Compound IIa is smoothly acetylated by acetic anhydride in triethylamine to give a mixture of mono- (IV) and diacyl (V) derivatives, which are readily separated by crystallization:

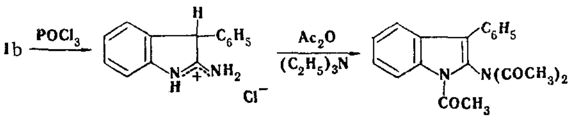


IV V

The PMR spectrum of IV in tetrachloroethylene has a singlet of three methyl groups (1.90, 2.1, and 3.35 ppm); this corresponds to structure IV. In CF_3COOH, the $\beta\text{-}CH_3$ signal is split into a doublet (1.53 ppm) and the quartet of a β-proton (4.88 ppm) appears. Consequently, the β position of the indole ring rather than the amide group or indole nitrogen atom proves to be the primary site of protonation; i.e., the maximum electron density in compounds of the IV type is concentrated, as in alkylindoles [6], in the 3 position. The singlet of a $\beta\text{-}CH_3$ group (3H, 2.03 ppm), the singlet of two CH_3CO groups (6H, 2.11 ppm), the singlet of an $N\text{-}CH_3$ group (3H, 3.27 ppm), and a multiplet from four aromatic protons at 6.9-7.3 ppm are observed in the PMR spectrum of V in tetrachloroethylene. In CF_3COOH the character of the PMR spectrum of V becomes quite complex, but thorough analysis of this spectrum makes it possible to conclude that V is protonated in the β position to the extent of 70%. It must be noted that the equilibrium state is reached after 1.5-2 h, and the character of the spectrum and the ratio of the integral intensities of the signals do not undergo any further changes (after 2-10 days). The fact that no disruption of the molecule or deacetylation occur during the action of trifluoroacetic acid was proved by re-isolation of V.

The ease of cyclization of acylhydrazines depends substantially on the presence of substituents attached to the nitrogen atoms. If both nitrogen atoms are unsubstituted, the rearrangement proceeds with resinification, and this complicates the isolation of the final products and leads to a decrease in the yield. We were able to isolate the aminoindole in the salt form in only one case for this sort of model, and the rest were identified in the form of their acetyl derivatives.

Thus the reaction of Ib ($R = R^1 = H$, $R^2 = C_6H_5$) with phosphorus oxychloride leads to IIb in good yield:



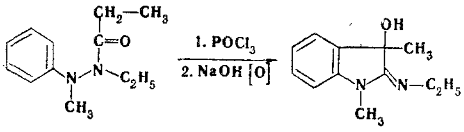
IIb VI

A singlet of the 3-H proton (5.11 ppm), a multiplet of the aromatic protons (9H, 6.9-7.5 ppm), and broadened signals of two protons attached to the exocyclic nitrogen atom (8.2 ppm) and a proton attached to N_1 (10.2 ppm) are observed in the PMR spectrum of IIb in CF_3COOH; this is in agreement with the IIb structure. Acetylation of IIb in triethylamine with excess acetic anhydride leads to triacetyl derivative VI. Its mass spectrum contains an intense molecular-ion peak with m/e 338 and intense peaks with m/e 296, 254, and 212, which correspond to successive splitting out of ketene from the molecular ion.

The PMR spectrum of VI in CF_3COOH contains a singlet of $(CH_3CO)_2N$ groups (6H, 2.22 ppm), a singlet of a CH_3CO group attached to N_1 (3H, 2.73 ppm), and a multiplet of nine aromatic protons (7.15-

7.52 ppm). The character of the spectrum of a solution of VI in $CHCl_3$ does not change; i.e., in this case the presence of three acetyl groups markedly lowers the electron density in the pyrrole ring and protonation at the β position in trifluoroacetic acid does not occur (in contrast to the mono- and diacetyl derivatives).

The 2-aminoindole bases are very sensitive to air oxygen and are rapidly autooxidized to give 3-hydroxy derivatives of 2-aminoindole, as was noted in [7]. Thus, for example, the product of the rearrangement of 1-phenyl-1-methyl-2-ethyl-2-propionylhydrazine (Ic, $R = R^2 = CH_3$, $R^1 = C_2H_5$) undergoes autooxidation, after isolation as the free base, in ether solution to give hydroxy compound VII:



Ic VII

The mass spectrum of VII contains an intense molecular-ion peak with m/e 204; this is in agreement with the value calculated for $C_{12}H_{26}N_2O$. An absorption band at 1660 cm^{-1}, which corresponds to the C = N stretching vibrations, is observed in its IR spectrum (in mineral oil), while the vibrations of the OH group do not appear because of intermolecular hydrogen bonding. However, absorption at 3600 cm^{-1} due to a free hydroxyl group is observed in the spectrum of a solution of VII in CCl_4.

A triplet (3H, 1.37 ppm) and quartet (2H, 4.11 ppm) of a C_2H_5 group, a singlet of a β-CH_3 group (3H, 1.88 ppm), a singlet of an $N-CH_3$ group (3H, 3.21 ppm), a singlet of an OH group (1H, 4.51 ppm), and a multiplet of four aromatic protons (6.60-7.80 ppm) are observed in the PMR spectrum in CCl_4.

EXPERIMENTAL

The UV spectra of methanol solutions of the compounds were recorded with a Cary-15 spectrometer, while the PMR spectra were recorded with a Varian T-60 spectrometer with an operating frequency of 60 MHz with hexamethyldisiloxane as the external standard.

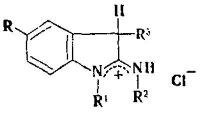
3-Alkyl-2-aminoindole Hydrochlorides (II). A mixture of 0.02 mole of the appropriate 1-acyl-2-arylhydrazine and 0.06 mole of phosphorus oxychloride or phosphorus trichloride in 150 ml of absolute ether was refluxed for 60-80 h. The precipitate was removed by filtration, washed with absolute ether, dried in a vacuum desiccator, and recrystallized from absolute alcohol. The physical constants and yields of the compounds obtained are presented in Table 1.

Acetylation of 1,3-Dimethyl-2-aminoindole. A mixture of 5 g (0.05 mole) of triethylamine and 2 g (0.02 mole) of acetic anhydride was added to 1 g (0.005 mole) of 1,3-dimethyl-2-aminoindole hydrochloride, and the mixture was allowed to stand at room temperature for 6 h with periodic shaking. The excess triethylamine and acetic anhydride were removed by distillation, and the residue was poured into water. The aqueous mixture was extracted with ether, and the extract was washed successively with water, sodium bicarbonate solution, and water and dried with potassium carbonate. The ether was removed by distillation, and the precipitate was treated with boiling heptane. The residue from treatment with heptane was recrystallized from aqueous alcohol to give 0.55 g (53%) of 1,3-dimethyl-2-acetamidoindole (IV) with mp 212-214°. UV spectrum: λ_{max} 225, 286 nm (log ε 4.49, 3.98). Found: C 71.3; H 7.0%. $C_{12}H_{14}N_2O$. Calculated: C 71.3; H 6.9%.

The heptane solution yielded 0.15 g (12.5%) of 1,3-dimethyl-2-diacetamidoindole (V) with mp 70-72°. UV spectrum: λ_{max} 226, 275, 285 nm (log ε 4.29, 3.96, 3.95). Found: C 69.2; H 6.8%. $C_{14}H_{16}N_2O_2$. Calculated: C 68.8; H 6.5%.

5-Bromo-3-methyl-1-acetyl-2-diacetamidoindole. A 4.6-g (0.03 mole) sample of phosphorus oxychloride was added to 2.5 g (0.01 mole) of 1-(p-bromophenyl)-2-propionylhydrazine in 50 ml of absolute ether, and the mixture was refluxed for 72 h. The ether was removed by distillation, and the excess phosphorus oxychloride was removed by vacuum distillation. A mixture of excess acetic anhydride and triethylamine was added to the residue, and the mixture was allowed to stand at room temperature for 24 h with periodic shaking. The excess triethylamine and acetic anhydride were removed by distillation, and the residue was dissolved in water. The solution was made alkaline to pH ~ 7 and extracted with ether. The extract was dried with potassium carbonate, and the ether was removed by distillation. The residue was recrystallized from benzene–heptane to give a product with mp 125-127° in 61% yield. UV spectrum:

TABLE 1. 2-Aminoindole Hydrochlorides



R	R^1	R^2	R^3	mp, °C	Empirical formula	Found, %		Calc., %		UV spectrum (in methanol)		Yield, %
						C	H	C	H	λ_{max}, nm	lg ε	
H	CH_3	H	CH_3	264—266	$C_{10}H_{12}N_2 \cdot HCl$	60,9	6,4	61,1	6,6	210 260	4,31 3,99	86
Br	CH_3	H	CH_3	285—287	$C_{10}H_{11}BrN_2 \times$ $\times HCl$	43,7	4,2	43,6	4,4	214 270	4,57 4,32	65
H	CH_3	CH_3	H	278—280	$C_{10}H_{12}N_2 \cdot HCl$	61,4	6,8	61,1	6,6	214 264	4,29 3,87	59
H	CH_3	H	C_2H_5	263—266	$C_{11}H_{14}N_2 \cdot HCl$	62,5	7,0	62,6	7,1	212 261	4,26 3,89	78
H	CH_3	H	C_6H_5	278—280	$C_{15}H_{14}N_2 \cdot HCl$	69,4	5,8	69,6	5,8	212 265	4,25 4,06	77
H	C_6H_5	H	CH_3	256—258	$C_{15}H_{14}N_2 \cdot HCl$	69,4	6,1	69,6	5,8	217 263	4,34 3,81	67
H	$C_6H_5CH_2$	H	CH_3	225—227	$C_{16}H_{16}N_2 \cdot HCl$	70,2	6,2	70,5	6,2	262	3,95	85
H	$C_6H_5CH_2$	H	C_2H_5	264—266	$C_{17}H_{18}N_2 \cdot HCl$	71,4	6,7	71,2	6,6	209 262	4,34 3,88	80
H	H	CH_3	C_6H_5	280—282	$C_{15}H_{14}N_2 \cdot HCl$	69,7	5,6	69,6	5,8	210 262	4,49 3,94	66
H	H	H	C_6H_5	220—223	$C_{14}H_{12}N_2 \cdot HCl$	68,6	6,1	68,6	5,3	210 261	4,39 3,94	48

λ_{max} 246, 297, 306 nm (log ε 4.41, 3.79, 3.77). PMR spectrum in CF_3COOH: singlet β-CH_3 (3H; 2.47 ppm), singlet of two CH_3CO groups attached to an exocyclic nitrogen atom (6H; 2.72 ppm), singlet of a CH_3CO group attached to N_1 (3H; 2.96 ppm). Aromatic region (in CH_3CN): meta-split doublet of the 6-H proton (1 H; 7.45 ppm), meta-split singlet of the 4-H proton (1 H; 7.78 ppm), doublet of the 7-H proton (1 H; 7.90 ppm). Found: C 51.3; H 4.3; N 8.0%. $C_{15}H_{15}BrN_2O_3$. Calculated: C 51.2; H 4.3; N 7.9%.

3-Phenyl-1-acetyl-2-diacetamidoindole (VI). A mixture of excess acetic anhydride and triethylamine was added to 1.2 g (0.005 mole) of 3-phenyl-2-aminoindole hydrochloride, and the mixture was refluxed for 4 h. The excess acetic anhydride and triethylamine were removed by vacuum distillation, and the residue was treated with water and made alkaline to pH ~ 7.5. The alkaline mixture was extracted with ether, and the ether extract was washed successively with water, sodium bicarbonate solution, and water and dried with sodium sulfate. The ether was removed by distillation, and the residue was recrystallized from benzene–heptane to give 0.68 g (44%) of 3-phenyl-1-acetyl-2-diacetamidoindole with mp 134-135°. UV spectrum: λ_{max} 231, 243, 296 nm (log ε 4.49, 4.47, 4.03). Found: C 72.1; H 5.2%. $C_{20}H_{18}N_2O_3$. Calculated: C 71.9; H 5.4%.

3-Hydroxy-3-methyl-2-aminoindolenine. A 4.6-g (0.03 mole) sample of phosphorus oxychloride and 20 ml of methylene chloride were added to 1.64 g (0.01 mole) of 1-phenyl-2-propionylhydrazine, and the mixture was heated in a sealed ampule at 75°. The excess oxychloride was removed by distillation, and the residue was treated with water and made alkaline to pH ~ 9. The alkaline mixture was extracted with ether, the ether was removed by distillation, and the residue was removed by filtration and recrystallized from aqueous methanol to give 0.61 g (37%) of a product with mp 198-200°. UV spectrum: λ_{max} 215, 270, 306 nm (log ε 4.49, 4.02, 3.49). Found: C 66.9; H 6.3%. $C_9H_{10}N_2O$. Calculated: C 66.7; H 6.2%.

3-Hydroxy-1,3-dimethyl-2-(ethylimino)indoline (VII). A 4.6-g (0.03 mole) sample of phosphorus oxychloride was added to 2.1 g (0.01 mole) of 1-methyl-2-ethyl-1-phenyl-2-propionylhydrazine in 50 ml of absolute ether, and the mixture was refluxed for 48 h. The ether was removed, and the excess phosphorus oxychloride was removed by vacuum distillation. The residue was dissolved in water, and the aqueous solution was extracted with ether to remove impurities. The solution was then acidified to pH ~ 9 and extracted with ether. The ether solution was dried with potassium carbonate and evaporated, and the residue was recrystallized from benzene–heptane to give 1.1 g (54%) of a product with mp 116-117°. UV spectrum: λ_{max} 273, 298 nm (log ε 4.12, 3.21). Found: C 70.3; H 7.8; N 13.7; active H 0.48; OH 8.4%. $C_{12}H_{16}N_2O$. Calculated: C 70.6; H 7.8; N 13.7; active H 0.49; OH 8.3%.

LITERATURE CITED

1. L. G. Yudin, A. N. Kost, and E. Ya. Zinchenko, Khim. Geterotsikl. Soedin., 332 (1973).
2. Yu. N. Portnov, G. A. Golubeva, and A. N. Kost, Khim. Geterotsikl. Soedin., 61 (1972).
3. R. S. Sagitullin, V. I. Gorbunov, A. N. Kost, N.B. Kuplet-skaya, and V. V. Chistyakov, Khim. Geterotsikl. Soedin., 364 (1970).
4. W. E. Stewart and T. H. Siddall, Chem. Rev., 70, 517 (1970).
5. A. N. Kost, G. A. Golubeva, and Yu. N. Portnov, Dokl. Akad. Nauk SSSR, 200, 342 (1970).
6. L. G. Yudin, V. A. Budylin, A. N. Kost, and V. I. Minkin, Dokl. Akad. Nauk SSSR, 176, 1096 (1967).
7. M. Nakagawa, H. Tamaguchi, and T. Hino, Tetrahedron Lett., 4035 (1970).