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XXXVI.* REARRANGEMENT OF 1-PHENYL-2-ACETYLHYDRAZINES AND 1-PHENYL-2-ACETYLPYRAZOLIDINES

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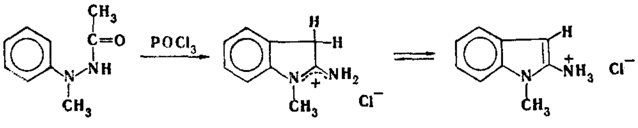
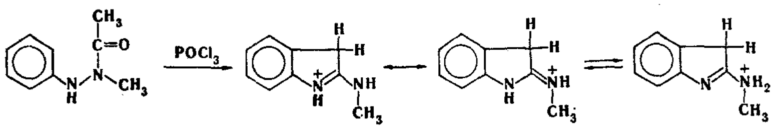
Under the influence of halide compounds of phosphorus, acetic acid β-phenylhydrazides that have an alkyl group attached to at least one of the nitrogen atoms form 2-aminoindoles that do not have substituents in the 3 position. Similarly, 1-phenyl-2-acetylpyrazolidines are converted to 1,2,3,4-tetrahydropyrimido[1,2-a] indoles.

As we have previously shown [1,2], 1-aryl-2-acylhydrazines with various acyl groups smoothly undergo conversion to 2-aminoindole derivatives under the influence of phosphorus oxychloride or phosphorus trichloride. However, the rearrangement of the analogous arylhydrazides of acetic acid proceeds with complications. When the compounds are refluxed in ether with $POCl_3$, the reaction is accompanied by considerable resinification, and the individual products cannot be isolated. However, if the process is carried out in an argon atmosphere in a sealed ampul with methylene chloride as the solvent, the yields of the 2-aminoindoles reach 41-63%. Raising the temperature to 70-90° C sharply decreases the reaction time. Thus 1-methyl-2-aminoindole hydrochloride (I) was obtained in 45% yield from 1-methyl-1-phenyl-2-acetylhydrazine under the conditions described above. The IR spectrum of I contains a broad absorption band at 2700-3100 cm^{-1}, which corresponds to the vibrations of an ammonium group, and an intense absorption at 1700 cm^{-1}, which is characteristic for the $C = \overset{+}{N}$ vibrations in such systems [3].



I II

An N-CH_3 singlet (3.28 ppm), a 3-CH_2 singlet (4.07 ppm), a multiplet of four aromatic protons (6.8-7.3 ppm), and two broadened signals of protons attached to the nitrogen atom (7.63 and 8.00 ppm) are observed in the PMR spectrum of I in CF_3COOH; this is in agreement with the proposed structure. In H_2O, the character of the spectrum does not change, while in D_2O the signals of the protons attached to the nitrogen atom and the signals of the 3-CH_2 protons vanish because of rapid deuterium exchange, which is due to the I ⇄ II equilibrium.



III A IV B C

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* See [1] for communication XXXV.

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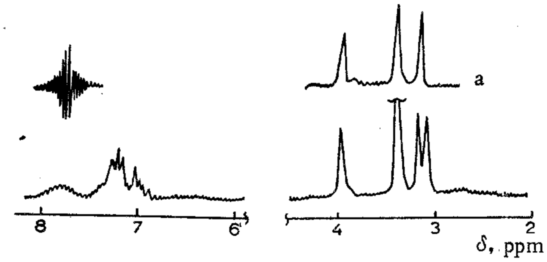
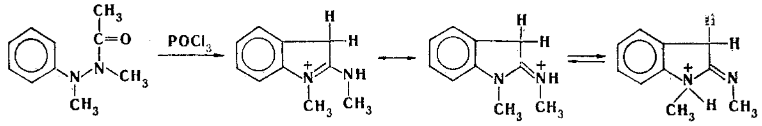


Fig. 1. PMR spectrum of VI in CH_3COOH: a) after saturation of the NH signal.

The rearrangement of 1-phenyl-2-methyl-2-acetylhydrazine (III) to give IV proceeds similarly. The IR and PMR spectra of IV are almost identical to the spectra of I. The UV spectrum of IV (λ_{max} 244, 256 nm) differs somewhat from the UV spectra of 1-substituted 2-aminoindoles (λ_{max} 257-260 nm). The appearance of additional maxima and inflections is apparently associated with the high percentage of tautomeric indolenine form IVC, which cannot exist in the case of substitution of the heterocyclic nitrogen atom.

Rearrangement is facilitated when there are substituents attached to both nitrogen atoms in the starting acetylhydrazine. It can be carried out under the same conditions as those used for other acylhydrazines. Thus, for example, V is converted to the corresponding 2-aminoindole (VI) on prolonged refluxing in ether with $POCl_3$ (or PCl_3).

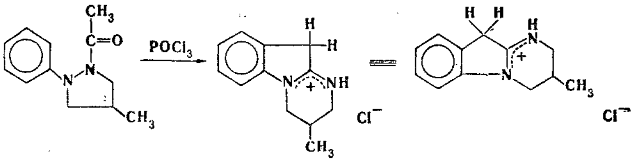


V A VI B C

As seen from the PMR spectrum (see Fig. 1), here one observes splitting of the signals of one of the methyl groups into a doublet due to interaction with the N–H proton. When double resonance is superimposed on the signal of the N–H proton, this splitting vanishes, just as in the recording of the spectrum of a solution in D_2O, in which the signals of the β protons also vanish. From the available data, it is difficult to draw a conclusion as to which nitrogen atom bears the proton and which of the methyl groups is split. On the basis of the fact that the doublet is found at strongest field as compared with the remaining signals, one can yield preference to structure A. Thus it proved possible to synthesize hard-to-obtain but most interesting 2-aminoindoles with no substituents in the 3 position.

An attempt to introduce β-acetylphenylhydrazine itself (which does not have substituents attached to either N_1 or N_2) into the reaction under the conditions described above proved unsuccessful. Despite variation of the reaction conditions, we were unable to isolate identifiable compounds. Thus, in this case a certain analogy to acetyldehyde phenylhydrazone, which does not form indole under the usual conditions of the Fischer reaction, is observed.

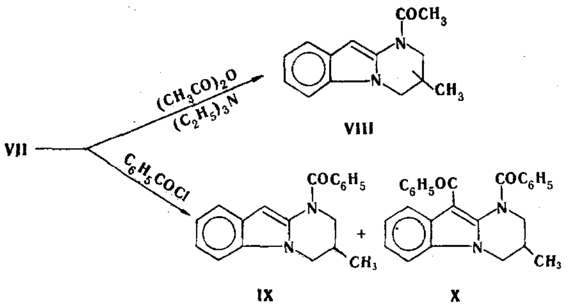
The rearrangement of acetylpyrazolidines proceeds with better yields. Thus 1-phenyl-4-methyl-2-acetylpyrazolidine is converted in 55% yield to the corresponding tetrahydropyrimido[1,2-a]indole (VII) on prolonged (up to 100 h) refluxing with $POCl_3$ in ether.



VII

The structure of VII was confirmed by the UV, IR, and PMR spectra. Compound VII is acetylated with acetic anhydride under mild conditions to give monoacyl derivative VIII, while Schotten–Baumann benzoylation gives a mixture of mono- (IX) and dibenzoyl derivatives (X), in which the second benzoyl group appears due to acylation of the pyrrole ring in the 3 position.

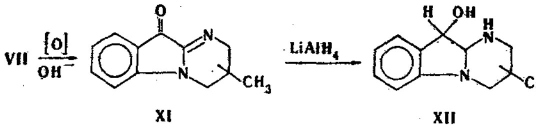
The position of this group is confirmed by the fact that, as has been previously demonstrated [4], 2-aminoindoles with a free β position (and with no substituents attached to the nitrogen atoms) are benzoylated



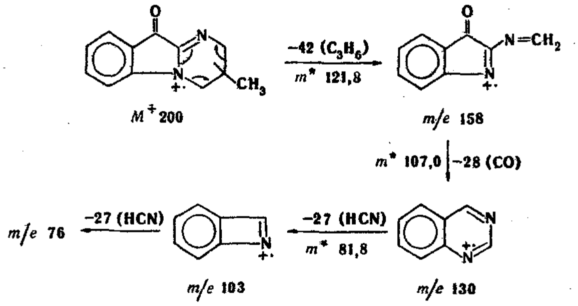
under similar conditions in the 3 position. In addition, benzoylation of IX leads to X. However, if the 3 position is occupied, only monobenzoyl derivatives are formed. The set of UV, PMR, and mass spectral data also constituted evidence in favor of structure X.

As previously noted, free aminoindole bases are unstable and are rapidly oxidized in air to give 3-hydroxy compounds [2, 5].

The autooxidation of 2-aminoindoles that do not have substituents in the 3 position gives uncrystallizable oils that are difficult to purify. In the case of tetrahydropyrimido[1,2-a]indoles, colored 10-oxo derivatives (XI), i.e., cyclic analogs of α-aminoisatin, were isolated in low yields. The mass spectrum of XI contains an intense peak of a molecular ion with M^+ 200, which coincides with the value calculated for $C_{12}H_{12}N_2O$, and the primary path of disintegration, confirmed by the metastable transitions, does not contradict the proposed structure.



Other 10-oxo-2,3,4,10-tetrahydropyrimidoindoles also undergo similar disintegration. Absorption bands at 1720 cm^{-1} (conjugated C = O) and at 1660 cm^{-1} (C = N) are observed in the IR spectrum of XI. Simultaneous reduction of the C = O and C = N groups to give the corresponding tetrahydropyrimido[1,2-a]-indoline (XII) occurs in the reduction of XI with lithium aluminum hydride. In this case, the absorption at 1720 and 1660 cm^{-1} vanishes in the IR spectrum, and the absorption of an NH group at 3300 cm^{-1} appears on the background of a broad band of a chelated OH group at 2500-3400 cm^{-1}. Its mass spectrum contains an intense molecular-ion peak with M^+ 204, which coincides with the value calculated for $C_{16}H_{12}N_2O$. Splitting out of water with simultaneous acetylation of the nitrogen atom and the formation of VIII occurs under the influence of acetic anhydride on XII. The IR spectra of the derivatives obtained by acetylation of XII and VII are identical.



EXPERIMENTAL

The UV spectra of methanol solutions were recorded with a Cary-15 spectrophotometer. The PMR spectra of trifluoroacetic acid solutions were recorded with a T-60 Varian spectrometer with an operating frequency of 60 MHz with hexamethyldisiloxane as the external standard. The mass spectra were recorded by A. B. Belikov with an MKh-1303 mass spectrometer.

1-Methyl-2-aminoindole Hydrochloride (I). A mixture of 4 g (0.025 mole) of 1-methyl-2-acetylphenylhydrazine and 7.7 g (0.05 mole) of phosphorus oxychloride in 20 ml of absolute methylene chloride was heated at 90° in a sealed ampul under argon for 40 h. The precipitate was removed by filtration, washed with ether, dried in a vacuum desiccator, and recrystallized from absolute alcohol to give 1.9 g (42%) of a product that decomposed above 230°. UV spectrum: λmax 209, 258 nm (log ε 4.30, 4.03). Found: C 59.0; H 6.1%. $C_9H_{10}N_2 \cdot HCl$. Calculated: C 59.2; H 6.0%.

Under the same conditions, heating a mixture of 5 g (0.031 mole) of 1-methyl-2-acetylphenylhydrazine and 8.3 g (0.06 mole) of phosphorus trichloride for 20 h gave 2.5 g (47%) of 1-methyl-2-aminoindole hydrochloride. The IR spectra of the compounds obtained in both experiments were completely identical.

2-(Methylamino)indole Hydrochloride (IV). This compound was obtained as in the preceding case from 2 g (0.012 mole) of 1-methyl-2-phenyl-1-acetylhydrazine and 3.6 g (0.024 mole) of phosphorus oxychloride. The product [0.9 g (41%)] decomposed above 230°. UV spectrum: λ_{max} 244, 250 nm (log ε 4.02, 4.02). PMR spectrum: N-CH_3 singlet (3.41 ppm), 3-CH_2 singlet (4.01 ppm), multiplet of four aromatic protons (6.8-7.42 ppm), broad N–H signals (7.6-8.26 ppm). Found: C 58.9; H 5.9; N 15.3%. $C_9H_{10}N_2 \cdot HCl$. Calculated: C 59.2; H 6.0; N 15.4%.

1-Methyl-2-methylaminoindole Hydrochloride (VI). A mixture of 2.4 g (0.013 mole) of 1,2-dimethyl-1-phenyl-2-acetylhydrazine and 4.6 g (0.03 mole) of phosphorus oxychloride in absolute ether was refluxed for 100 h. The resulting precipitate was removed by filtration, washed with ether, dried in a vacuum desiccator, and recrystallized from absolute propanol to give 1.65 g (63%) of a product that decomposed above 240°. UV spectrum: λ_{max} 262 nm (log ε 4.11). Found: C 60.2; H 6.8; N 14.3%. $C_{10}H_{12}N_2 \cdot HCl$. Calculated: C 60.1; H 6.6; N 14.2%.

3-Methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole Hydrochloride (VII). This compound [6.7 g (55%)] was similarly obtained from 11 g (0.054 mole) of 4-methyl-1-phenyl-2-acetylpyrazolidine and 16.5 g (0.108 mole) of phosphorus oxychloride. It decomposed above 200°. UV spectrum: λ_{max} 212, 262 nm (log ε 4.41, 4.16). PMR spectrum: 3-CH_3 doublet (1.11 ppm), 3-CH_3 multiplet (2.62 ppm), multiplet of four protons attached to $C_{(2)}$ and $C_{(4)}$ (2.96-3.90 ppm), 10-CH_2 singlet (4.04 ppm), multiplet of four aromatic protons (6.88-7.40 ppm), and broad N–H signal (8.44 ppm). Found: C 64.4; H 6.8%. $C_{12}H_{14}N_2 \cdot HCl$. Calculated: C 64.7; H 6.7%.

1,2,3,4-Tetrahydropyrimido[1,2-a]indole Hydrochloride. Similarly, 3.35 g (0.015 mole) of 1-phenyl-2-acetylpyrazolidine and 4.65 g (0.03 mole) of phosphorus oxychloride gave 1.6 g (52%) of a substance that decomposed above 220°. UV spectrum: λ_{max} 213, 262 nm (log ε 4.31, 4.12). Found: C 63.5; H 5.9%. $C_{11}H_{12}N_2 \cdot HCl$. Calculated: C 63.4; H 6.2%.

8-Bromo-3-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole Hydrochloride. A mixture of 3.3 g (0.012 mole) of 4-methyl-1-(p-bromophenyl)-2-acetylpyrazolidine and 3.7 g (0.024 mole) of phosphorus oxychloride in 20 ml of absolute methylene chloride was heated in a sealed ampul under argon at 90° for 25 h. The methylene chloride and excess phosphorus oxychloride were removed by vacuum distillation, the unchanged acetylpyrazolidine was washed away with benzene, and the residue was recrystallized from absolute propanol to give 2 g (55%) of a product that decomposed above 220°. UV spectrum: λ_{max} 212, 267 nm (log ε 4.52, 4.20). Found: N 9.2%. $C_{12}H_{13}BrN_2 \cdot HCl$. Calculated: N 9.3%.

3-Methyl-1-acetyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole (VIII). A mixture of 10 g (0.1 mole) of triethylamine and 2 g (0.02 mole) of acetic anhydride was added to 2.2 g (0.01 mole) of 3-methyl-1,2,3,4-tetrahydropyrimido [1,2-a]indole hydrochloride, 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, water was added to the residue, and the resulting precipitate was removed by filtration and recrystallized from benzene–heptane to give 1.6 g (70%) of a product with mp 147.5-148.5°. UV spectrum: λ_{max} 212, 297 nm (log ε 4.42, 4.35). Found: C 73.7; H 7.2; N 12.4%. $C_{14}H_{16}N_2O$. Calculated: C 73.7; H 7.0; N 12.3%.

A similar method was used to obtain 1-acetyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole, with mp 126-127° (benzene–heptane), in 57% yield. UV spectrum: λ_{max} 222, 297 nm (log ε 4.46, 4.23). Found: C 73.2; H 6.9%. $C_{13}H_{14}N_2O$. Calculated: C 72.9; H 6.5%. The method was also used to obtain 8-bromo-3-methyl-1-acetyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole, with mp 173-174° (benzene–methanol), in 67% yield. UV spectrum: λ_{max} 226, 307 nm (log ε 4.54, 4.25). Found: C 55.2; H 4.8%. $C_{14}H_{15}BrN_2O$. Calculated: C 54.7; H 4.9%.

Benzoylation of 3-Methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole. Schotten–Baumann benzoylation of 2.7 g of 3-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole hydrochloride (VII) gave 1.2 g of a mixture of two substances, which was separated preparatively in a thick layer of aluminum oxide [benzene—methanol (12:1)]. The substance with R_f 0.76 was identified as 3-methyl-1-benzoyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole (IX) with mp 175.5-176.5° (from benzene). UV spectrum in $CHCl_3$: λ_{max} 303 (log ε 4.07). Found: C 78.6; H 6.2%; Mol.wt.(mass-spectrally) 290. $C_{19}H_{18}N_2O$. Calculated: C 78.6; H6.2%; Mol.wt. 290.

The substance with R_f 0.40 was identified as 3-methyl-1,10-dibenzoyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole (X) with mp 222-223° (from butanol). UV spectrum in chloroform: λ_{max} 298 nm (log ε 4.11). Found: C 79.2; H 5.6; N 7.0%; Mol.wt. (mass-spectrally) 394. $C_{26}H_{22}N_2O$. Calculated: C 79.2; H 5.6; N 7.1%; Mol. wt. 394.

3,10-Dimethyl-1-benzoyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole. A 2.36-g sample of 3,10-dimethyl-1,2,3,4-tetrahydropyrimidoindole hydrochloride was benzoylated under conditions similar to the preceding conditions. The product was recrystallized from benzene—heptane to give 2.35 g (77.5%) of a benzoyl derivative with mp 80-82°. Found: C 78.9; H 7.6%; Mol.wt.(mass-spectrally) 304. $C_{20}H_{20}N_2O$. Calculated: C 78.9; H 7.9%; Mol. wt. 304.

3-Methyl-10-oxo-2,3,4,10-tetrahydropyrimido[1,2-a]indole (XI). A 2.2-g (0.01 mole) sample of 3-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole hydrochloride was dissolved in water, and the solution was made alkaline to pH 9. The precipitate was then 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 0.5 g (25%) of a product with mp 132-133°. Found: C 71.8; H 6.1; N 14.0%. $C_{12}H_{12}N_2O$. Calculated: C 72.0; H 6.0; N 14.0%.

A similar procedure was used to obtain 10-oxo-2,3,4-10-tetrahydropyrimido[1,2-a]indole, with mp 114-115° (benzene—heptane), in 33% yield. Found: C 70.9; H 5.4%. $C_{11}H_{10}N_2O$. Calculated: C 71.0; H 5.4%; This procedure was also used to obtain 8-bromo-3-methyl-10-oxo-2,3,4,10-tetrahydropyrimido[1,2-a]indole, with mp 162-163° (benzene—heptane). Found: C 51.5; H 3.7%. $C_{12}H_{11}BrN_2O$. Calculated: C 51.6; H 3.9%.

10-Hydroxy-3-methyl-1,2,3,4,5,10-hexahydropyrimido[1,2-a]indole (XII). A suspension of 1 g of lithium aluminum hydride in 25 ml of absolute tetrahydrofuran (THF) was added to 2.0 g (0.01 mole) of 10-oxo-3-methyl-2,3,4,10-tetrahydropyrimido[1,2-a]indole in 50 ml of absolute THF, and the mixture was refluxed for 8 h and then decomposed successively with moist ether and water. The precipitate was removed by filtration and washed thoroughly with ether. The ether solutions were dried with sodium sulfate, the solvent was removed by distillation, and the residue was recrystallized from benzene—heptane to give 1.55 g (76%) of a product with mp 206-208°. Found: C 70.9; H 8.1%. $C_{12}H_{16}N_2O$. Calculated: C 70.6; H 7.8%.

Heating of the indoline with acetic anhydride gave 3-methyl-1-acetyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole, which was identical to a sample of VIII obtained by acetylation of 3-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole hydrochloride.

LITERATURE CITED

1. G. A. Golubeva, Yu. N. Portnov, and A. N. Kost, Khim. Geterotsikl. Soedin., 511 (1973).
2. A. N. Kost, G. A. Golubeva, and Yu. N. Portnov, Dokl. Akad. Nauk SSSR, 200, 342 (1971).
3. R. S. Sagitullin, V. I. Gorbunov, A. N. Kost, N. B. Kuplet-skaya, and V. V. Chistyakov, Khim. Geterotsikl. Soedin., 364 (1970).
4. A. Deberly and I. Bourolais, Tetrahedron Lett., 3049 (1971).
5. T. Hino, M. Nakagawa, T. Hashizumo, and Y. Miwa, Tetrahedron Lett., 2205 (1970).