INDOLE DERIVATIVES

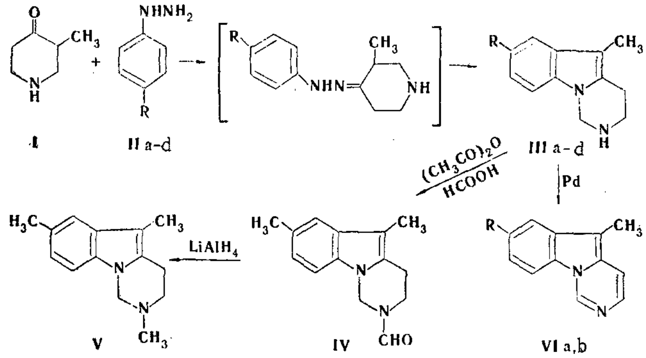
XXXIX.* FISCHER CYCLIZATION OF 3-METHYL-4-PIPERIDONE ARYLHYDRAZONES

L. N. Borisova, N. F. Kucherova,
T. A. Kartashova, and V. A. Zagorevskii

UDC 547.759.3'853.5

The Fischer cyclization of 3-methyl-4-piperidone arylhydrazones gives 1,2,3,4-tetrahydropyrimido[3,4-*a*]indoles, which are dehydrogenated to the corresponding pyrimido[3,4-*a*]-indoles.

In a previous study [2, 3] of the Fischer cyclization of 3-substituted N-methyl-4-piperidone arylhydrazones, we detected an unusual reaction leading to 1,2,3,4-tetrahydropyrimido[3,4-*a*]indoles. Under the conditions of the Fischer condensation, related ketones – 3-substituted tetrahydro-4-thiopyrones and their S,S-dioxides – form normal reaction products, i.e., the corresponding indoles and indolenines [4]. During this same period, Ebnöther and co-workers [5] established that 1-carbethoxy-3-methyl-4-piperidone phenylhydrazone is converted only to the corresponding indolenine derivative, while 1-carbethoxy-3-phenyl-4-piperidone also gives a substituted 1,2,3,4-tetrahydropyrimido[3,4-*a*]indole along with an indole compound (12%). We studied the condensation of 3-methyl-4-piperidone (I) with arylhydrazines (IIa-d) under the influence of alcoholic hydrogen chloride solution.



a R=H; b R=CH_3; c R=OCH_3; d R=$COOC_2H_5$

In all cases, we isolated one substance, to which, on the basis of the UV, IR, and PMR spectra, we assigned the 1,2,3,4-tetrahydropyrimido[3,4-*a*]indole structure (IIIa-d). The UV spectrum of IIIb has the absorption maxima characteristic for indoles at 233 and 284 nm. The NH absorption band at 3300-3500 cm^{-1} is absent in the IR spectrum of IIIb (in CCl_4); the usually weak ν_{NH} band of saturated amines cannot be detected reliably (it is possibly at 3340 cm^{-1}). The PMR spectrum of IIIb (in $CHCl_3$, δ scale) contains peaks at 1.1 (broad, NH), 2.1 and 2.4 ppm (singlets, two CH_3 groups), 1.8-3.0 (unresolved signals overlapped by the CH_3 signals, CH_2CH_2 fragment), and 4.4 ppm (singlet, $N-CH_2-N$).

---

* See [1] for communication XXXVIII.

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 645-647, May, 1972. Original article submitted March 16, 1971.

The structure of IIIb was proved by converting it through the N-formyl derivative (IV) to the previously described [2] 2,5,7-trimethyltetrahydropyrimido[3,4-*a*]indole (V). Compounds of the III type can be dehydrogenated over Pd black to give low-melting, bright-yellow substances (VIa, b), which are representatives of a new heterocyclic system – pyrimido[3,4-*a*]indole.

Except for the signals of two CH_3 groups (at 2.1 and 2.4 ppm), the signals of protons attached to saturated carbon atoms are absent in the PMR spectrum of VIb (in CD_3OD). The signal of the $C_{(1)}H$ proton appears as a doublet ($J \approx 1.5$ Hz, meta constant) at weakest field at 8.9 ppm. The signals of the remaining aromatic protons are concentrated at 6.5-7.5 ppm. An intense band, which is apparently caused by the stretching vibrations of the system of conjugated double bonds, appears in the IR spectrum of VIb (in mineral oil) at 1614 cm^{-1}; the bands at 1562 and 1515 cm^{-1} are of weak intensity. The UV spectrum of VIb is characterized by long-wave absorption at 390-395 nm (log ε 3.19).

EXPERIMENTAL

The UV spectra (in alcohol, c 10^{-5}-10^{-3} M) were recorded with an SF-4 spectrophotometer. The IR spectra were recorded with a UR-10 spectrometer. The PMR spectra were obtained with an RS-60 spectrometer with an operating frequency of 60 MHz.

5-Methyl-1,2,3,4-tetrahydropyrimido[3,4-*a*]indole (IIIa). A mixture of 1.6 g (0.011 mole) of the hydrochloride of I [6] and 1.45 g (0.01 mole) of the hydrochloride of IIa in 15 ml of ~7% alcoholic hydrogen chloride was refluxed for 5 min. The mixture was cooled, and the precipitate was removed by filtration and dissolved in water. The solution was made alkaline with ~5% ammonium hydroxide, and the resulting precipitate was removed by filtration and washed with water to give 1.2 g (63%) of IIIa with mp 76-77° (from heptane–benzene). Found: C 77.2; H 7.6; N 14.0%. $C_{12}H_{14}N_2$. Calculated: C 77.4; H 7.6; N 15.0%. The hydrochloride of IIIa had mp 179-181° (from absolute alcohol). Found: Cl 16.0; N 13.0%. $C_{12}H_{14}N_2 \cdot HCl$. Calculated: Cl 16.0; N 12.6%.

5,7-Dimethyl-1,2,3,4-tetrahydropyrimido[3,4-*a*]indole (IIIb). A mixture of 4.8 g (0.03 mole) of the hydrochloride of I and 4.8 g (0.03 mole) of the hydrochloride of IIb was refluxed for 30 min in 30 ml of ~7% alcoholic hydrogen chloride. The mixture was cooled, and the precipitate was removed by filtration and dissolved in water. The solution was made alkaline with 5% ammonium hydroxide and extracted with ether. The ether solution was dried with magnesium sulfate and evaporated to give 3.9 g (60%) of IIIb with mp 104-105° (from heptane). Found: C 78.0; H 8.0; N 14.0%. $C_{13}H_{16}N_2$. Calculated: C 78.0; H 8.0; N 14.0%. UV spectrum, λ_{max}, nm (log ε): 233 (4.40), 284 (3.90). The hydrochloride of IIIb had mp 184-186° (from absolute alcohol). Found: Cl 15.0; N 11.5%. $C_{13}H_{16}N_2 \cdot HCl$. Calculated: Cl 15.0; N 11.9%.

5-Methyl-7-methoxy-1,2,3,4-tetrahydropyrimido[3,4-*a*]indole (IIIc). This compound [0.8 g (32%)] was obtained in the same way as IIIa from 1.65 g (0.011 mole) of the hydrochloride of I and 1.75 g (0.01 mole) of the hydrochloride of IIc and had mp 110-112° (from heptane). Found: C 72.5; H 7.5; N 13.1%. $C_{13}H_{16}N_2O$. Calculated: C 72.2; H 7.5; N 13.0%. The hydrochloride of IIIc had mp 190-192° (from alcohol). Found: Cl 14.2; N 11.5%. $C_{13}H_{16}N_2O \cdot HCl$. Calculated: Cl 14.0; N 11.1%.

5-Methyl-7-carbethoxy-1,2,3,4-tetrahydropyrimido[3,4-*a*]indole (IIId). This compound [1.6 g (62%)] was obtained in the same way as IIIb from 1.65 g (0.011 mole) of the hydrochloride of I and 1.8 g (0.01 mole) of IIc in 20% alcoholic hydrogen chloride and had mp 140-141° (from benzene–petroleum ether). Found: C 69.6; H 7.0; N 11.2%. $C_{15}H_{18}N_2O_2$. Calculated: C 69.7; H 7.0; N 10.9%. The hydrochloride of IIId had mp 190-192° (from absolute alcohol). Found: Cl 12.0; N 9.5%. $C_{15}H_{18}N_2O_2 \cdot HCl$. Calculated Cl 12.0; N 9.5%.

2-Formyl-5,7-dimethyl-1,2,3,4-tetrahydropyrimido[3,4-*a*]indole (IV). A mixture of 4.8 ml of acetic anhydride and 1.95 ml of 100% formic acid was held at 20° for 1 h. It was then cooled with an ice bath, 3 g of IIIc was added, and the mixture was stirred for 30 min. Absolute ether (30 ml) was added, and the mixture was allowed to stand for 18 h and then poured into water. The precipitate was removed by filtration, washed thoroughly with water, and dried to give 3.1 g (91%) of IV with mp 149-150° (from alcohol). Found: C 73.2; H 7.0; N 12.3%. $C_{14}H_{16}N_2O$. Calculated: C 73.6; H 7.0; N 12.3%.

2,5,7-Trimethyl-1,2,3,4-tetrahydropyrimido[3,4-*a*]indole (V). A 1.9 g (0.008 mole) sample of IV was added to a stirred suspension of 2 g (0.05 mole of $LiAlH_4$ in 200 ml of cold tetrahydrofuran (THF), and the mixture was refluxed for 18 h. It was then cooled with ice, and 2 ml of water, 2 ml of 15% NaOH, and 6 ml of water were carefully added in succession. The mixture was stirred for 1 h, and the organic layer was separated, dried with magnesium sulfate, and evaporated to give 1.2 g (69%) of V with mp 59-60° [2] (from alcohol).

2-Acetyl-5,7-dimethyl-1,2,3,4-tetrahydropyrimido[3,4-*a*]indole (VII). A solution of 1.5 g of IIIb in 15 ml of acetic anhydride was refluxed for 2 h, the excess acetic anhydride was removed by vacuum distillation and the residue was triturated with ether. The resulting crystals were removed by filtration to give 1.35 g (73%) of VII with mp 106-108° (from absolute alcohol). Found: C 74.6; H 7.5; N 12.0%. $C_{15}H_{18}N_2O$. Calculated: C 74.3; H 7.5; N 11.6%.

2-Ethyl-5,7-dimethyl-1,2,3,4-tetrahydropyrimido[3,4-*a*]indole Hydrochloride (VIII). A solution of 1.3 g (0.006 mole) of VII in 200 ml of absolute ether was added dropwise to a suspension of 1.5 g (0.035 mole) of $LiAlH_4$ in 200 ml of cooled absolute ether at such a rate that the ether boiled uniformly. The reaction mixture was refluxed for another 3 h and cooled. Water (40 ml) was added gradually, and the ether layer was separated, dried with magnesium sulfate, and evaporated to a small volume. An ether solution of hydrogen chloride was added to the residue, and the resulting VIII was removed by filtration to give 1 g (70%) of a product with mp 180-182° (from absolute alcohol). Found: C 67.7; H 8.0; N 10.7; Cl 13.4%. $C_{15}H_{20}N_2 \cdot HCl$. Calculated: C 68.0; H 8.0; N 10.6; Cl 13.4%.

β-Dimethylaminoethyl-5-methyl-1,2,3,4-tetrahydropyrimido[3,4-*a*]indole-7-carboxylate Dihydrochloride (IX). Sodium (3-5 mg) was added to 1.5 g of IIId and 5 ml of β-dimethylaminoethanol in 60 ml of anhydrous toluene, and the mixture was refluxed for 1 h with distillation of two thirds of the toluene. The amino alcohol and toluene were added again, two thirds of the solution was again removed by slow distillation, and the residue was then vacuum evaporated. The residual oil was dissolved in ether, and the ether solution was washed with water, dried with magnesium sulfate, and filtered. An ether solution of hydrogen chloride was added to give 1.2 g (57%) of IX with mp 204-206° (from absolute alcohol). Found: Cl 18.8; N 10.8%. $C_{17}H_{23}N_3O_2 \cdot 2HCl$. Calculated: Cl 18.9; N 11.2%.

β-Dimethylaminopropyl-5-methyl-1,2,3,4-tetrahydropyrimido[3,4-*a*]indole-7-carboxylate Dihydrochloride (X). Similarly, 1.4 g (56%) of X with mp 150-152° (from absolute alcohol) was obtained from 1.5 g of ester IIId and 4.5 ml of β-dimethylaminopropanol. Found: Cl 16.2; N 9.7%. $C_{18}H_{25}N_3O_2 \cdot 2HCl \cdot C_2H_5OH$. Calculated: Cl 16.4; N 9.7%.

5-Methylpyrimido[3,4-*a*]indole (VIa). A 1 g sample of IIIa was refluxed in xylene over Pd black for ~3 h. The catalyst was removed by filtration, and the xylene was evaporated. The residue contained an oil, which was converted to the hydrochloride of VIa [0.5 g (46%)] with mp 280-284° (with decomposition, from absolute alcohol). Found: Cl 16.4; N 12.5%. $C_{12}H_{10}N_2HCl$. Calculated: Cl 16.2; N 12.8%. Base VIa was obtained by treatment of an aqueous solution of the hydrochloride with ammonia and subsequent extraction with ether to give a product with mp 103-104° (from petroleum ether). Found: C 79.2; H 5.5; N 15.4%. $C_{12}H_{10}N_2$. Calculated: C 79.1; H 5.5; N 15.4%.

5,7-Dimethylpyrimido[3,4-*a*]indole (VIb). Similarly, 0.8 g (66%) of the hydrochloride of VIb with mp 294-296° (with decomposition, from absolute alcohol) was obtained from 1 g of IIIb. Found: C 67.1; H 5.8; Cl 14.9; N 12.1%. $C_{13}H_{12}N_2 \cdot HCl$. Calculated: C 67.1; H 5.6; Cl 15.2; N 12.0%. Base VIb was obtained in the same way as VIa and had mp 92-93° (from petroleum ether). Found: C 79.4; H 6.2; N 14.2%. $C_{13}H_{12}N_2$. Calculated: C 79.6; H 6.2; N 14.3%. UV spectrum: λ_{max} (log ε), nm: 234 (4.23), 258 (4.70), 265 (4.76), 306 (3.76), 316 (3.78), 328 (3.62), 390-395 (3.19).

LITERATURE CITED

1. N. M. Sharkova, N. F. Kucherova, and V. A. Zagorevskii, Khim. Geterotsikl. Soedin., 81 (1972).
2. N. F. Kucherova, L. N. Borisova, N. M. Sharkova, and V. A. Zagorevskii, Khim. Geterotsikl. Soedin., 1219 (1970).
3. L. N. Borisova, N. F. Kucherova, and V. A. Zagorevskii, Khim. Geterotsikl. Soedin., 927 (1970).
4. L. N. Borisova, N. F. Kucherova, and V. A. Zagorevskii, Khim. Geterotsikl. Soedin., 935 (1970).
5. A. Ebnöther, P. Niklaus, and R. Süess, Helv. Chim. Acta, 52, 629 (1969).
6. É. A. Mistryukov and N. I. Aronova, Izv. Akad. Nauk SSSR, 877 (1962).