INDOLE DERIVATIVES

XXXVII.* STUDY OF THE FISCHER CYCLIZATION OF 2,2,6-TRIMETHYL-4-PIPERIDONE ARYLHYDRAZONES

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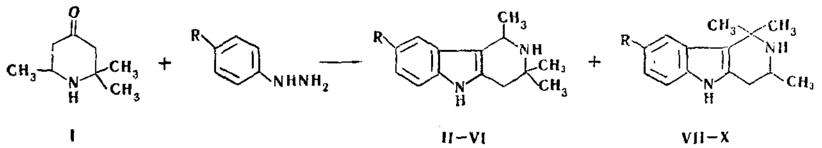
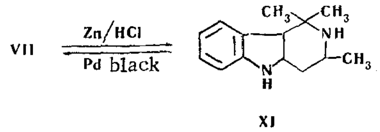
UDC 547.759.3

A mixture of isomeric 2,2,4-trimethyl- and 2,4,4-trimethyl-1,2,3,4-tetrahydro-γ-carbolines is formed as a result of the Fischer cyclization of 2,2,6-trimethyl-4-piperidone arylhydrazones.

In connection with a study of the direction of the Fischer cyclization of the arylhydrazones of unsymmetrical ketones [2-4], it seemed of interest to us to accomplish the cyclization of 2,2,6-trimethyl-4-piperidone arylhydrazones (I), since one might expect the formation of two series of isomeric tetrahydro-γ-carbolines.



II, VII R=H; III, VIII R=CH$_3$; IV, IX R=Cl; V, X R=Br; VI R=OCH$_3$



The reaction was carried out with phenylhydrazine, 4-methyl-, 4-methoxy-, 4-chloro-, and 4-bromophenylhydrazines without isolation of the corresponding hydrazones. In selecting the conditions for the cyclization, it was established that the most favorable cyclizing agent is a 7-14% solution of hydrogen chloride in alcohol. The cyclization products are mixtures of compounds without sharp melting points. Repeated fractional crystallization of these mixtures in the form of the hydrochlorides made it possible to isolate two individual isomeric compounds in all cases except for the product of the condensation with 4-methoxyphenylhydrazine. The structures of the compounds were proved by means of the PMR spectra.† For comparison, we used the previously [5] synthesized 2,2,4-trimethyl-1,2,3,4-tetrahydro-γ-carboline, which proved to be identical to carboline II obtained by the cyclization of phenylhydrazine with I. The singlet signals of the protons of the two CH$_3$ groups in the 2-position of the γ-carboline ring, whose nonequivalence is explained by

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[*] See [1] for communication XXXVI.

[†] The PMR spectra were obtained with an RS-60 spectrometer (also with a DA60-JZ spectrometer in the case of II) with an operating frequency of 60 MHz with hexamethyldisiloxane as the internal standard. The chemical shifts are given on the δ scale, and the relative intensities of the signals were determined by integration.

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1070-1073, August, 1971. Original article submitted July 7, 1970.

the different shielding of them on the part of the grouping in the 4-position, are situated at 0.95 and 1.1 ppm in the PMR spectrum of II (in $CHCl_3$). The chemical shift of the doublet signal (J 6.5 Hz) of the protons of the 4-CH_3 group is 1.44 ppm. At 1.7-2.7 ppm there are four lines of signals of the 1-H_2 protons of the AB system with J 16 Hz; the components of these signals are split (J 2 Hz) due to the long-range spin–spin interaction with the 4-H proton; the signal of the latter (4.2 ppm) appears as a quartet (J 6 Hz) in which the components have a fine structure. A broad signal from the $N_{(3)}H$ proton is found at 9.0 ppm. The $N_{(3)}H$ signal appears at 1.2 ppm and is partially overlapped by the 4-CH_3 and 2-CH_3 signals. Deuteration (the addition of CD_3OD followed by storage for several days) results in almost total disappearance of the $N_{(3)}H$ and $N_{(9)}H$ signals and to the more distinct appearance of the signals of the three CH_3 groups; in addition, the signal from 1-H_2 acquires the shape of a broad symmetrical peak at 2.5 ppm. We note that in pyridine solution the 1-H_2 signal (2.8 ppm) has a similar shape. An examination of the PMR spectrum of the other isomer indicates that it has the VII structure. The broad quartet characteristic for II is absent at ~4 ppm, since the 4-position in VII has been substituted by two CH_3 groups, the singlet signals of which are situated at weaker field (1.44 and 1.54 ppm) than the doublet signal (J 6.2 Hz) from 2-CH_3 (1.13 ppm). The chemical shifts of $N_{(3)}H$ and $N_{(9)}H$ are, respectively, 1.23 and 8.55 ppm. The complex 1-H_2 signal appears at 2.0-2.4 ppm, while an unresolved multiplet from 2-H appears at 2.78-3.57 ppm. The assignment of the other carbolines to the III-VI or VIII-X series does not yet present difficulties, since the first series of compounds was characterized by the presence of a quartet at ~4 ppm and by the situation of the signals of gem-dimethyl groups at higher field than the doublet from $C-CH_3$, while, for the second series of compounds, the signals of the gem-dimethyl groups were located at lower field than the $C-CH_3$ signal. (The most characteristic signals of the remaining compounds are presented in the experimental section.) The yields of the tetrahydro-α-carbolines that we obtained are low, chiefly because of the considerable losses in the isolation of the individual isomers.

The ability of the arylhydrazones of ketone I to cyclize to form two series of isomers is attractive, particularly because, according to the literature data, different arylhydrazones of 3-methyl- and 3-carboxycyclohexanones [6] give only one tetrahydrocarbazole isomer with a substituent in the 2-position under the conditions of the Fischer reaction.

We studied the reduction of VII by zinc dust in hydrochloric acid. In contrast to II, the reduction of which proceeds to form a mixture of approximately equal amounts of the normal reaction product – 2,2,4-trimethyl-1,2,3,4,4a,9a-hexahydro-α-carboline – and the decomposition product – 2-(2-amino-2-methylpropyl) indoline [7], under these conditions VII is unambiguously converted to 2,4,4-trimethyl-1,2,3,4,4a, 9a-hexahydro-α-carboline (XI). The structure of XI was proved by its dehydrogenation to the starting VII over Pd black.

EXPERIMENTAL

2,2,4-Trimethyl-1,2,3,4-tetrahydro-α-carboline (II) and 2,4,4-Trimethyl-tetrahydro-α-carboline (VII). A mixture of 20 g (0.14 mole) of I [8] and 20 g (0.138 mole) of phenylhydrazine hydrochloride in 280 ml of 7% HCl in alcohol was refluxed for 2 h. The alcohol was vacuum evaporated, and the residue was dissolved in 120 ml of hot water. The hydrochloride that precipitated on cooling was removed by filtration, crystallized three times from water, and converted to the base. Four crystallizations from benzene–petroleum ether gave 2.2 g (7.5%) of VII with mp 159.5-161 deg. Found: C 78.3; H 8.6; N 13.3%. $C_{14}H_{18}N_2$. Calculated: C 78.5; H 8.5; N 13.1%. UV spectrum (in alcohol, c 10^{-5}–10^{-2} M), λ_{max}, nm (log ε): 277 (3.85), 286 (3.78). In addition to γ_{NH} at 2500-3350 cm^{-1}, the IR spectrum of the product in mineral oil contains a series of weak bands at 1564-1623 cm^{-1} as well as an intense band at 1063 cm^{-1}, which is absent in the spectrum of II.

The combined aqueous mother liquors were evaporated in vacuo, and the residual hydrochloride was crystallized from benzene–petroleum ether to give 6 g (20%) of II* with mp 159-160 deg [5]. The mixture of isomers II and VII was not separated satisfactorily by thin-layer chromatography on Al203. The purities of II and VII were monitored by gas-liquid chromatography. Found: C 78.7; H 8.6; N 13.0%. $C_{14}H_{18}N_2$. Calculated: C 78.5; H 8.5; N 13.1%. UV spectrum (in alcohol), λ_{max}, nm (long ε): 277 (3.85), 286 (3.79). The IR spectrum (mineral oil) contains a series of weak bands at 1565-1624 cm^{-1}, and an intense band, which is absent in the spectrum of VII, is observed at 1240 cm^{-1}; γ_{NH} appears at 2500-3350 cm^{-1}.

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* The product yields in all cases were determined for analytically pure samples.

2,4,4-Trimethyl-1,2,3,4,4a,9a-hexahydro-α-carboline (XI). A 2.4 g (0.011 mole) sample of VII was reduced in the presence of 0.01 g of mercuric chloride in 10 ml of alcohol by means of 18 g (0.27 g-atom) of zinc dust and 57 ml of concentrated hydrochloric acid by refluxing for 14 h. (The zinc dust was added in 3 g portions, and the acid was added gradually.) The reaction mixture was made strongly alkaline with 40% KOH, and the oil that was liberated was extracted by ether and dried with magnesium sulfate. Removal of the ether by distillation gave 1.45 g (60%) of XI with mp 116-117 deg (from heptane). Found: C 77.4; H 9.6; N 13.2%. $C_{14}H_{20}N_2$. Calculated: C 77.7; H 9.3; N 13.0%. UV spectrum (in alcohol), λ_{max}, nm (log ε): 245 (3.87), 296 (3.50). The dihydrochloride of XI melted at 267-268 deg (from alcohol). Found: N 9.6; Cl 24.3%. $C_{14}H_{20}N_2 \cdot 2HCl$. Calculated: N 9.7; Cl 24.5%.

Compound VII with mp 159-160 deg (mixed melting point) was obtained in 66% yield by refluxing a solution of XI in xylene over Pd black for 1.5 h.

2,2,4,6-Tetramethyl-1,2,3,4-tetrahydro-γ-carboline (III) and 2,4,4,6-Tetramethyl-1,2,3,4-tetrahydro-γ-carboline (VIII). A mixture of 20 g (0.14 mole) of I and 18 g (0.113 mole) of p-tolylhydrazine hydrochloride in 160 ml of 7% alcoholic HCl was refluxed for 1.5 h. The alcohol was evaporated in vacuo, and the residue was dissolved in water. The solution was made alkaline with saturated aqueous potassium carbonate, and the precipitate (14.5 g) was crystallized repeatedly from ether and then from benzene–petroleum ether to give 7.3 g (28%) of III with mp 159-160 deg. Found: C 79.0; H 8.9; N 12.3%. $C_{15}H_{20}N_2$. Calculated: C 78.9; H 8.8; N 12.3%. PMR spectrum (in $CHCl_3$), ppm: 0.82-1.34 [7H, two singlets from 2-$(CH_3)_2$ and a signal from 3-NH], 1.49 (3H, doublet, J 6.5 Hz, 4-CH_3), 1.9-2.7 (5H, singlet from 6-CH_3 overlapped by the signal from 1-H_2), 4.22 (1H, insufficiently resolved quartet from 4-H). The combined ethereal mother liquors were evaporated to give 1.4 g (5.4%) of VIII with mp 131-132.5 deg (from benzene–petroleum ether). Found: C 79.0; H 9.1; N 12.5%. $C_{15}H_{20}N_2$. Calculated: C 78.9; H 8.8; N 12.3%.

2,2,4-Trimethyl-6-chloro-1,2,3,4-tetrahydro-γ-carboline (IV) and 2,4,4-Trimethyl-6-chloro-1,2,3,4-tetrahydro-γ-carboline (IX). The same sort of reaction was run with 15 g (0.106 mole) of I and 12 g (9.084 mole) of 4-chlorophenylhydrazine in 105 ml of 14% alcoholic HCl. (The mixture was refluxed for 2.5 h.) The reaction product (9.6 g) was crystallized from benzene to give 0.9 g (4.4%) of IV with mp 172.5-174 deg. Found: C 67.7; H 7.0; Cl 14.3; N 11.2%. $C_{14}H_{17}ClN_2$. Calculated: C 67.6; H 6.9; Cl 14.3; N 11.3%. PMR spectrum (in pyridine), ppm: 1.03 and 1.14 [6H, two singlets, 2-$(CH_3)_2$], 1.4 (3H, doublet, J 6.5 Hz. 4-CH_3), 2.5 (broad, unresolved signal, 1-H_2), 3.8-4.3 (1H, insufficiently resolved quartet, 4-H). The mother liquors yielded (after repeated crystallization from benzene) 0.85 g (4.2%) of IX with mp 194-195.5 deg. Found: C 67.6; H 7.1; Cl 14.4; N 11.2%. $C_{14}H_{17}ClN_2$. Calculated: C 67.6; H 6.9; Cl 14.3; N 11.3%. PMR spectrum (in pyridine), ppm: 1.03 (3H, doublet, J 6.5 Hz, 2-CH_3), 1.44 and 1.54 [6H, two singlets, 4-$(CH_3)_2$], 2.4-2.6 (unresolved signal, 1-H_2), 2.9-3.4 (unresolved multiplet, 2-H).

2,2,4-Trimethyl-6-bromo-1,2,3,4-tetrahydro-γ-carboline (V) and 2,4,4-Trimethyl-6-bromo-1,2,3,4-tetrahydro-γ-carboline (X). A solution of 15.2 g (0.107 mole) of I and 16 g (0.085 mole) of 4-bromophenylhydrazine was refluxed for 2 h in 120 ml of 14% alcoholic HCl. The alcohol was evaporated in vacuo, and the residue was crystallized from water. The mixture of hydrochlorides (4.5 g) thus obtained was dissolved in water, and the solution was made alkaline with aqueous potassium carbonate. The precipitate was filtered and recrystallized three times from benzene to give 2.3 g (9.2%) of V with mp 183-184.5 deg. Found: C 57.6; H 5.8; Br 27.5; N 9.6%. $C_{14}H_{17}BrN_2$. Calculated: C 57.3; H 5.8; Br 27.3; N 9.6%. PMR spectrum (in pyridine), ppm: 1.03 and 1.13 [two singlets, 2-$(CH_3)_2$], 1.43 (doublet, J 6 Hz, 4-CH_3), 2.5 (broad signal, 1-H_2), 4.1 (unresolved quartet, 4-H). The hydrochloride melted at 244-245 deg (from alcohol). Found: N 8.6; Cl 10.5%. $C_{14}H_{17}BrN_2 \cdot HCl$. Calculated: N 8.5; Cl 10.7%. The combined mother liquors obtained after the crystallization of V from benzene were evaporated in vacuo, and the residue was recrystallized twice from benzene to give 0.25 g (1%) of X with mp 189-190 deg. Found: C 57.3; H 5.7; Br 27.5; N 9.4%. $C_{14}H_{17}BrN_2$. Calculated: C 57.3; H 5.8; Br 27.3; N 9.6%. PMR spectrum (in pyridine), ppm: 1.13 (doublet, 2-CH_3); 1.44 and 1.51 [two singlets, 4-$(CH_3)_2$], 2.4-2.6 (unresolved signal, 1-H_2), 2.9-3.4 (unresolved broad signal, 2-H).

2,2,4-Trimethyl-6-methoxy-1,2,3,4-tetrahydro-γ-carboline (VI). A solution of 5 g (0.035 mole) of I and 5 g (0.028 mole) of 4-methoxyphenylhydrazine hydrochloride in 35 ml of absolute alcohol was refluxed for 1 h. The precipitated ammonium chloride was removed by filtration, and the alcohol solution was evaporated in vacuo. After cooling, the precipitated hydrochloride (2.9 g) was dissolved in water, and the solution was made alkaline with aqueous potassium carbonate. The liberated reaction product was crystallized three times from benzene to give VI with mp 169-170 deg. Found: C 74.0; H 8.3; N 11.6%. $C_{15}H_{20}N_2O$.

Calculated: C 73.8; H 8.3; N 11.5%. PMR spectrum (in $CHCl_3$), ppm: 0.9-1.3 [two singlets from 2-$(CH_3)_2$, $N_{(3)}H$], 1.54 (doublet, J 6.5 Hz, 4-CH_3), 1.9-2.8 (complex signal, 1-H_2), 3.81 (singlet, OCH_3), 4.0-4.4 (4-H). The hydrochloride of VI melted at 204-205 deg (from alcohol). Found: Cl 11.8%. $C_{15}H_{20}N_2O \cdot HCl$. Calculated: 12.0%.

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