# INDOLE DERIVATIVES

## XXXVIII.* FISCHER CONDENSATION OF 1-METHYL-3-PIPERIDONE WITH ARYLHYDRAZINES

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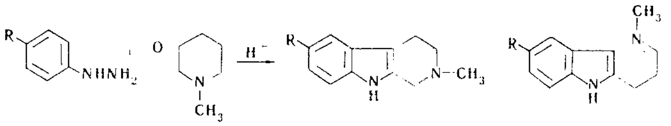
The Fischer condensation of 1-methyl-3-piperidone with arylhydrazines, which is accompanied by side processes, leads to the corresponding 1,2,3,4-tetrahydro-β-carbolines.

The cyclization of arylhydrazones of 4-piperidones is used extensively in the synthesis of 1,2,3,4-tetrahydro-γ-carbolines [2-6]. Other methods for the preparation of these compounds are used considerably less frequently. The Pictet–Spengler [7] and Bischeler–Napieralsky [8] reactions have recently been applied to 2-(β-aminoethyl)indoles (isotryptamines) for closure of the piperidine ring of the indicated heterocyclic systems. In contast to this, in the synthesis of 1,2,3,4-tetrahydro-β-carbolines, the latter two methods are the major ones, since they rely upon the comparatively readily accessible tryptamines. There is no information in the literature regarding the use of the Fischer reaction of 3-piperidone.

We attempted to introduce 1-methyl-3-piperidone (I) into the Fischer condensation with arylhydrazines. We were unable to accomplish the reaction of I with phenylhydrazine and 4-bromophenylhydrazine when the conditions were varied quite extensively, and we were also unable to cyclize the previously prepared 4-carbethoxyphenylhydrazone of I (II) because of pronounced resinification, although the precipitation of small amounts of ammonium chloride was observed in some experiments. Nevertheless, the fundamental possibility of closing the indole ring was demonstrated in the case of the reaction of I with 4-methyl- and 4-methoxyphenylhydrazines. However, the cyclizations in these cases were also accompanied by resinification to form mainly bright-yellow impurities. The structures of the thoroughly purified individual cyclization products – 1,2,3,4-tetrahydro-β-carbolines (III,IV) – were proved by means of UV, IR, and PMR spectroscopy, by the determination of the ionization constant of III, and by the alternative synthesis of IV. The possible isomeric compounds of the 1,2,3,4-tetrahydro-δ-carboline series (V) were not isolated.



I III, IV V

III R -$CH_3$; IV R $OCH_3$

The curves of the UV spectra of III and IV are characteristic for the simplest indole derivatives.

The PMR spectrum of the piperidine portion of molecule III (in $CHCl_3$) is similar to the spectrum of 3-methyl-1,2,3,4-tetrahydro-γ-carboline [9], since the unshielding effect on the alicyclic protons in this sort of system is approximately the same from the α and β positions of the indole ring [10]. The singlet signals of the two methyl groups have similar chemical shifts of 2.41 and 2.48 ppm; the $A_2B_2$ type spectrum of the $CH_2CH_2$ grouping is situated at 2.9 ppm as an unresolved, somewhat broadened peak; the signal

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*See [1] for communication XXXVII.

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of the protons of the isolated 1-$CH_2$ group (of similar form) is found at higher field at 3.6 ppm. Protonation of the nitrogen atom in the 2 position of III (solution in $CD_3OD-CF_3COOH$) has practically no effect on the chemical shift of the 6-$CH_3$ signal but appreciably affects the shifts and form of the other signals: 2.8 ppm (singlet, $N^+-CH_3$), 2.5-3.6 ppm (group of broad $CH_2CH_2$ signals), 3.6-4.5 ppm (four lines of the AB spectrum of the 1-$CH_2$ group; $\delta$ 3.8 and 4.3 ppm, $J \approx 16$ Hz). These PMR spectral values are not in agreement with structure V.

The basicity of III (see the Experimental section) is close to that of model compound VI and is apparently too high for possible isomer V. The $\nu_{NH}$ band appears distinctly in the IR spectrum of III (in mineral oil or in chloroform). This is evidence that III does not have the indolenine structure of V.

The low yields of carbolines are probably explained by the fact that in a mixture of two tautomeric forms of enehydrazines – intermediates of the Fischer reaction – the one with a $\Delta^{2,3}$-C = C bond is especially unstable in acid media, since it contains the enediamine grouping ($CH_3-N-C=C-N-$).

The results to a certain degree confirm the principle according to which the reaction during the Fischer cyclization of nitrogen heterocyclic ketones [9, 11] and keto sulfones [12, 13] proceeds, with the participation of the methylene group of the ring that is furthest removed from the electron-acceptor groups – the protonated heterocyclic nitrogen atom or the $SO_2$ group.

## EXPERIMENTAL

The UV spectra of alcohol solutions (c $10^{-3}$-$10^{-5}$ M) were recorded with an SF-4 spectrometer. The IR spectra were recorded with a UR-10 spectrometer. The PMR spectra were obtained with RS-60 (III) and Varian T-60 (IV) spectrometers with operating frequencies of 60 MHz.

2,6-Dimethyl-1,2,3,4-tetrahydro-β-carboline (III). A mixture of 0.5 g (3.1 mmole) of 4-tolylhydrazine hydrochloride and 0.5 g (3.3 mmole) of the hydrochloride of I [14] in 5 ml of absolute alcohol was refluxed for 5 min. The hot reaction mass was poured into 50 ml of cold water, and the mixture was made alkaline with saturated potassium carbonate solution. The precipitate was separated, washed thoroughly with water, and dried to give 0.31 g (49%) of III with mp 218-219° (from benzene). IR spectrum (in $CHCl_3$), $cm^{-1}$: 3480 (strong, $\nu_{NH}$), 1600 (weak, indole ring). UV spectrum, $\lambda_{max}$, nm (log ε): 228 (4.46), 278 (3.81). 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%.

The basicity of this compound was determined* in nitromethane as compared with a standard substance – diphenylguanidine (DPG):

$$\Delta pK_a = pK_a(\text{DPG}) - pK_a\ (\text{substance}).$$

Found: $\Delta pK_a = 0.97 \pm 0.05$ for III, and $\Delta pK_a = 1.27$ for VI.

2-Methyl-6-methoxy-1,2,3,4-tetrahydro-β-carboline (IV). A) A mixture of 2.2 g (12.5 mmole) of 4-methoxyphenylhydrazine hydrochloride and 2.2 g (13.4 mmole) of the hydrochloride of I in 20 ml of absolute alcohol was refluxed for 9 min. The mixture was poured into 50 ml of cold water and made alkaline with saturated potassium carbonate solution. The resulting precipitate (colored by bright-yellow impurities) was washed thoroughly with water and recrystallized from isopropyl alcohol to give 0.7 g (26%) of IV with mp 213-214°. IR spectrum (in $CHCl_3$), $cm^{-1}$: 3480 (strong, $\nu_{NH}$), 1632 and 1605 (weak). UV spectrum, $\lambda_{max}$, nm (log ε): 224 (4.46), 278 (3.86). PMR spectrum (in $CDCl_3$), ppm: 2.5 (singlet, $N-CH_3$), 2.8 (broad signal, $CH_2CH_2$), 3.5 (broad signal, 1-$CH_2$), 3.9 (singlet, $OCH_3$).

B) A mixture of 2.6 ml of 100% formic acid and 6.4 ml of acetic anhydride was held at 20° for 1 h, after which 3.6 g (0.02 mole) of 6-methoxy-1,2,3,4-tetrahydro-β-carboline [15] was added to it. The reaction mass was stirred for 20 min, 15 ml of absolute ether was added, and the mixture was allowed to stand overnight. The precipitate was removed by filtration, washed with water, and air dried to give 2.8 g (64%) of 2-formyl-6-methoxy-1,2,3,4-tetrahydro-β-carboline (VII) with mp 200-201° (from alcohol). Found: C 67.7; H 6.1; N 12.3%. $C_{13}H_{14}N_2O_2$. Calculated: C 67.8; H 6.1; N 12.2%.

A mixture of 1.9 g (8.3 mmole) of VII in 200 ml of absolute tetrahydrofuran and 2.2 g of $LiAlH_4$ was refluxed for 3 days, after which it was decomposed successively with 3 ml of water, 3 ml of 15% NaOH, and 9 ml of water. The combined filtrates were vacuum evaporated until crystallization started, and 200

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*We sincerely thank I. V. Persianova for determining the basicities.

ml of water was added. The precipitate was separated, washed with water, and dissolved in 10% hydrochloric acid. The solution was filtered, and the filtrate was made alkaline with 10% KOH. The precipitate was separated and washed with water to give 1.45 g (82%) of IV with mp 213-215° (from isopropyl alcohol).

1-Methyl-3-piperidone 4-Carbethoxyphenylhydrazone (II). A 0.8-g (4.3 mmole) sample of 4-carbethoxyphenylhydrazine was dissolved by heating in 5 ml of absolute benzene, and a solution of 0.5 g (4.5 mmole) of I in 2 ml of benzene was added. The mixture was refluxed for 2 min and cooled. Addition of petroleum ether precipitated 1.2 g (100%) of II with mp 126-127° (from dry benzene). Found: N 15.1%. $C_{15}H_{21}N_3O_2$. Calculated: N 15.3%.

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