INDOLE DERIVATIVES

XXXII.* THE FISCHER CYCLIZATION OF ARYLHYDRAZONES OF SOME β-ALKOXYCARBONYLETHYL KETONES

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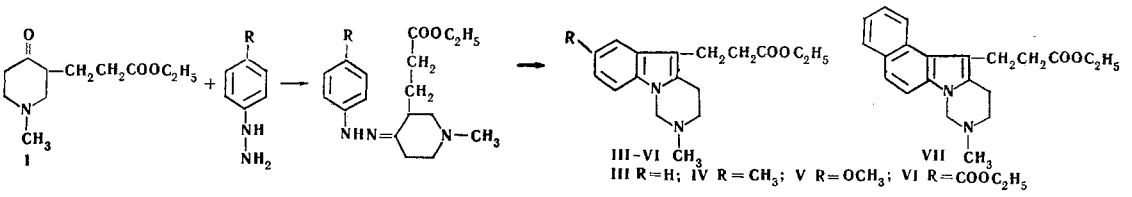
It has been established that the cyclization of arylhydrazones of 3-(β-ethoxycarbonylethyl)-1-methylpiperidin-4-one is accompanied by a rearrangement and leads to a 1,2,3,4-tetrahydropyrimido[3,4-a]indole derivative [1]. The cyclization of arylhydrazones of 2-(β-methoxycarbonylethyl)cyclohexanone under the same conditions forms indole and 3H-indole derivatives.

In a study of the Fischer cyclization of arylhydrazones of 3-(β-methoxycarbonylethyl)tetrahydro-4-thiopyrone we previously [2] detected the influence of substituents in the benzene ring of the hydrazine component on the direction of cyclization in favor of the formation of an indole or a 3H-indole system. In addition, an unusual course of the reaction of arylhydrazines with α-methylpiperidin-4-ones was found, leading to rearrangement products – 1,2,3,4-tetrahydropyrimido[3,4-a]indoles [1]. In view of this, it appeared desirable to continue the investigation of the Fischer cyclization of arylhydrazones of α-substituted ketones.

In the present work condensation was carried out with 3-(β-ethoxycarbonylethyl)-1-methylpiperidin-4-one (I) [3] and with 2-(β-methoxycarbonylethyl)cyclohexanone (II). In agreement with their structure, the arylhydrazones of these ketones can form two types of compounds, belonging to the indole and to the 3H-indole series. In the majority of cases we did not isolate the arylhydrazones. The hydrazine components used were phenyl-, p-tolyl-, p-methoxyphenyl-, p-ethoxycarbonylphenyl-, and β-naphthylhydrazines. The cyclization of the arylhydrazones of 3-(β-ethoxycarbonylethyl)-1-methylpiperidin-4-one was carried out with a 20% solution of hydrogen chloride in ethanol, with the exception of the p-ethoxycarbonylphenylhydrazone, the cyclization of which was carried out in concentrated hydrochloric acid or in a 35% solution of hydrogen chloride in ethanol. In each case mentioned, we isolated only one substance. The chromatography of the reaction products on alumina in a thin layer did not show the presence of a second isomer.



The UV spectra of the compounds obtained have the absorption maxima at approximately 228 and 285 nm that are characteristic for indoles. These compounds form monohydrochlorides. At the same time, they do not contain mobile hydrogen while according to elementary analysis and IR spectra (for example, in the IR spectra of compound III in CCl_4, the NH vibrations of indole are lacking and there is a strong band of the C=O of an ester at 1733 cm^{-1}), the compounds obtained are not the corresponding lactams, the formation of which took place in the case of the cyclization of 3-(β-methoxycarbonylethyl)tetrahydro-4-thiopyrone

*For Communication XXXI, see [1].

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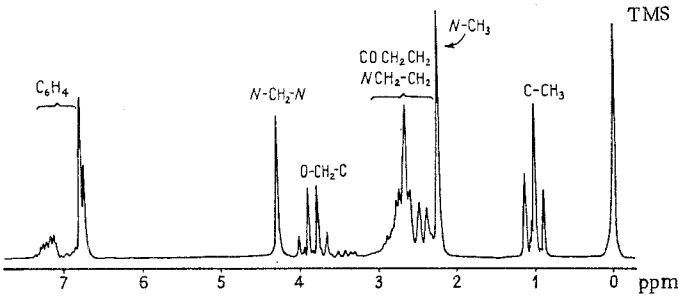

Fig. 1. PMR spectrum of 5-(β-ethoxycarbonylethyl)-2-methyl-1,2,3,4-tetrahydropyrimido[3,4-a]-indole (III) in CCl_4.

[2]. The lactamization of the esters obtained could not be effected under various conditions (heating to 200-250°C; boiling in xylene with polyphosphoric acid, or heating in xylene with the addition of sodium hydride).

In view of the results that we obtained in the cyclization of the α-methylpiperidin-3-ones [1] and also of the NMR spectrum of III (Fig. 1), these compounds must be ascribed the structure of 7-R-5-(β-ethoxycarbonylethyl)-1,2,3,4-tetrahydropyrimido[3,4-a]indoles (III-VII).

In the PMR spectrum of III (RS-60 instrument with a working frequency of 60 MHz in CCl_4 solution on the δ scale relative to HMDS) there are the following characteristic signals (ppm): 220 (3H, singlet, $N-CH_3$), 2.27-3.0 (8H, multiplet, two CH_2-CH_2 fragments), 4.30 (2H, singlet, $N-CH_2-N$), and 6.6-7.3 (4H, four protons of a benzene ring).

The formation of this type of compound apparently takes place through the rearrangement of the 3H-indoles formed initially.

In order to determine the influence of the nature of the ketone and hydrazine components on the type of substances formed on cyclization, we have made a fairly detailed study of the cyclization of 2-(β-methoxycarbonylethyl)cyclohexanone (II) with the same hydrazines under analogous conditions.

The cyclization of the arylhydrazones of ketone II took place differently from that of the arylhydrazones of ketone I. In the reaction of II with phenyl-, p-tolyl-, and β-naphthylhydrazines cyclization took place with the formation both of 1-methoxycarbonylethyl-1,2,3,4-tetrahydrocarbazoles, spontaneously rearranging into the lactams VIII-X, and of esters of β-(1,2,3,4-tetrahydro-4aH-carbazol-4a-yl)propionic acid (XI-XIII). The cyclization of the p-methoxyphenylhydrazone of the ketone II gave only the lactam XIV. The cyclization of the p-ethoxycarbonylphenylhydrazone of the ketone II took place with the formation of the corresponding 4aH-carbazole XV. The structure of the last-mentioned products was confirmed by analysis and their capacity for forming hydrochlorides. Thus, the results of the cyclization of arylhydrazones of 3-(β-ethoxycarbonylethyl)-1-methylpiperidin-4-one under the conditions of the Fischer reaction, together with the examples of the cyclization of the arylhydrazones of α-methylpiperidin-4-ones that we described previously [1], show the fairly general tendency of arylhydrazones of such ketones to form rearrangement products belonging to the 1,2,3,4-tetrahydropyrimido[3,4-a]indole system. Analogous ketones belonging to the cyclohexanone or the tetrahydro-4-thiopyrone series undergo Fischer cyclization normally, giving compounds of the indole or 3H-indole type.

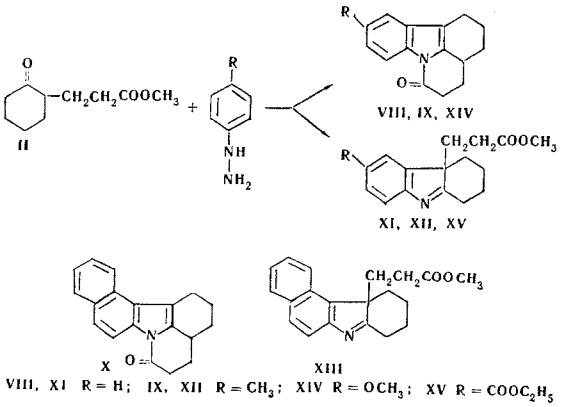

TABLE 1. 5-Ethoxycarbonylethyl-2-methyl-1,2,3,4-tetrahydropyrimido[3,4-a]indoles (III-V, VII)

Compd.	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
			C	H	Cl	N	C	H	Cl	N	
III	169—170,5	$C_{17}H_{22}N_2O_2 \cdot HCl$	63,09 63,06	7,25 7,32	10,45 10,46	9,24 9,15	63,24	7,18	10,98	8,68	59
III*	bp 159—160° (0,08 mm)	$C_{17}H_{22}N_2O_2$	71,30 71,19	7,91 7,91	—	9,94 10,05	71,29	7,74	—	9,78	
IV	163—164,5	$C_{18}H_{24}N_2O_2 \cdot HCl$	64,33 64,38	7,59 7,48	10,45 10,45	8,38 8,46	64,19	7,48	10,53	8,32	56
V	163—164	$C_{18}H_{24}N_2O_3 \cdot HCl$	61,27 61,46	7,14 7,10	9,46 9,29	8,40 8,47	61,30	7,14	10,05	7,94	38
VII	173—175	$C_{21}H_{24}N_2O_2 \cdot HCl$	67,60 67,66	6,68 6,73	9,34 9,29	7,44 7,48	67,63	6,76	7,51	9,51	65

*Base III. UV spectrum, λ_{max}, nm (log ε): 228 (4.46) and 285 (3.83).

EXPERIMENTAL

7-R-5-(β-Ethoxycarbonylethyl)-2-methyl-1,2,3,4-tetrahydropyrimido[3,4-a]indoles (III-V, VII). A mixture of 0.01 mole of I and 0.01 mole of the appropriate arylhydrazine was boiled in 20 ml of 20% ethanolic hydrogen chloride for 30 min. The ammonium chloride that had deposited was filtered off, and the reaction mixture was poured into dry ether. The precipitate was filtered off and recrystallized from absolute ethanol. This gave the hydrochlorides of III-V and VII. The base III was isolated in the usual way and distilled in vacuum. Information on compounds III-V and VII is given in Table 1.

7-Ethoxycarbonyl-5-(β-ethoxycarbonylethyl)-2-methyl-1,2,3,4-tetrahydropyrimido[3,4-a]indole (VI). A mixture of 2 g (0.009 mole) of the ketone I and 2 g (0.009 mole) of p-ethoxycarbonylphenylhydrazine hydrochloride in 10 ml of absolute ethanol was boiled for 10 min. The ethanol was distilled off, giving 3.2 g (84.2%) of the hydrochloride of the hydrazone, mp 171-173°C (from absolute ethanol). Found %: N 10.20, 10.06. $C_{20}H_{29}N_3O_4 \cdot HCl$. Calculated %: N 10.21. 3.2 g of the hydrochloride of the hydrazone was boiled in 20 ml of 35% ethanolic hydrogen chloride for 1 h 30 min, the reaction mixture was poured into water, and the mixture was made alkaline with potassium carbonate and extracted with ether. The ethereal solution was dried with $MgSO_4$, and then ethereal hydrogen chloride precipitated 1.6 g (51.6%) of the hydrochloride of VI, mp 171-173°C (from absolute ethanol). Found %: C 60.67, 60.59; H 6.89, 6.95; Cl 8.89, 8.64; N 7.05, 6.82. $C_{20}H_{26}N_2O_4 \cdot HCl$. Calculated %: C 60.82; H 6.89; Cl 8.98; N 7.09.

2-(β-Methoxycarbonylethyl)cyclohexanone (II). A mixture of 20.5 g (0.126 mole) of 1-piperidinocyclohex-1-ene [4] and 22.2 g (0.258 mole) of methyl acrylate in 120 ml of dimethylformamide was boiled for 37 h, treated with 20 ml of water, and boiled for another 1 h, after which the mixture was poured into 500 ml of water and extracted with ether. The ethereal extract was washed with 5% hydrochloric acid, with 5% potassium carbonate solution, and with water, and was dried with $MgSO_4$. Distillation yielded 10.4 g (45%) of II, bp 113-115°C (5 mm) [bp 140-142°C (15 mm) [5]). Found %: C 65.25, 65.57; H 8.70, 8.77. $C_{10}H_{16}O_3$. Calculated %: C 65.29; H 8.69.

2,3,3a,4,5,6-Hexahydro-1H-pyrido[1,2-b]carbazol-1-one (VIII) and Methyl γ-(1,2,3,4-tetrahydro-4aH-carbazol-4a-yl)propionate (XI). A mixture of 5.7 g (0.03 mole) of II and 4.2 g (0.03 mole) of phenylhydrazine hydrochloride in 40 ml of 20% ethanolic hydrogen chloride was boiled for 1 h and poured into 200 ml of water, and the mixture was left for 2 h. The precipitate that had deposited was filtered off, giving 2 g (29%) of VIII, mp 125-126°C (from ethanol) [6]. The aqueous solution was neutralized with ammonia and extracted with ether. The ether was distilled off, giving 2.6 g (33%) of XI, mp 87-88.5°C (from petroleum ether). Found %: C 74.16, 74.13; H 7.86, 7.84; N 5.09, 5.12. $C_{16}H_{19}NO_2$. Calculated %: C 74.67; H 7.44; N 5.44.

8-Methyl-2,3,3a,4,5,6-hexahydro-1H-pyrido[1,2-b]carbazol-1-one (IX) and Methyl γ-(6-Methyl-1,2,3,4-tetrahydro-4aH-carbazol-4a-yl)propionate (XII). As in the preceding case, 4.7 g (0.025 mole) of II and 3 g (0.02 mole) of p-tolylhydrazine hydrochloride yielded 2.2 g (86%) of IX, mp 107-108°C (from ethanol). Found %: C 80.39, 80.37; H 7.06, 7.25; N 5.80, 6.02. $C_{16}H_{17}NO$. Calculated %: C 80.34; H 7.11; N 5.85.

Also obtained was 1.2 g (17%) of XII, mp 88.5-89°C (from heptane). Found %: C 75.46, 75.28; H 7.95, 8.13. $C_{17}H_{21}NO_2$. Calculated %: C 75.24; H 7.80.

2,3,3a,4,5,6-Hexahydro-1H-7,8-benzopyrido[1,2-b]carbazol-1-one (X) and Methyl γ-(1,2,3,4-Tetrahydro-4aH-5,6-benzocarbazol-4a-yl)propionate (XIII). Similarly, 3.8 g (0.02 mole) of II and 3.9 g (0.02 mole) of β-naphthylhydrazine hydrochloride yielded 1.7 g (31%) of X, mp 182-183°C (from ethanol). Found %: C 82.65, 82.40; H 6.18, 6.29; N 5.19, 5.12. $C_9H_{17}NO$. Calculated %: C 82.87; H 6.22; N 5.08. In addition to this, 2 g (32%) of XIII, with mp 93-94°C (from heptane) was obtained. Found %: C 78.20, 78.22; H 7.14, 7.19; N 4.78, 4.79. $C_{20}H_{21}NO_2$. Calculated %: C 78.11; H 6.88; N 4.55. Hydrochloride of XIII, mp 157-159°C (from ethanol). Found %: C 70.38, 70.15; H 6.83, 6.82; Cl 9.80, 9.76; N 3.85, 3.86. $C_{20}H_{21}NO_2 \cdot HCl$. Calculated %: C 69.87; H 6.45; Cl 10.32; N 4.07.

8-Methoxy-2,3,3a,4,5,6-hexahydro-H-pyrido[1,2-b]carbazol-1-one (XIV). A mixture of 5.3 g (0.03 mole) of p-methoxyphenylhydrazine hydrochloride and 5.7 g (0.03 mole) of II was boiled with 40 ml of 20% of ethanolic hydrogen chloride for 40 min and poured into water. This gave 4 g (50.6%) of XIV, mp 96-97°C (from heptane). Found %: C 75.34, 75.41; H 6.79, 6.88. $C_{16}H_{17}NO_2$. Calculated %: C 75.27; H 6.71.

Methyl γ-(6-Ethoxycarbonyl-1,2,3,4-tetrahydro-4aH-carbazol-4a-yl)propionate (XV). A mixture of 3.8 g (0.02 mole) of II and 3.6 g (0.02 mole) of p-ethoxycarbonylphenylhydrazine in 25 ml of 25% ethanolic hydrogen chloride was boiled for 1 h, poured into water, neutralized with ammonia, and extracted with ether. The residue after the ether had been driven off was chromatographed on Al_2O_3 (grade II), benzene elution giving 2.5 g (34%) of XV, mp 63-64°C (from heptane). Found %: C 69.47, 69.42; H 7.34, 7.36; N 4.10, 4.32. $C_{19}H_{23}NO_4$. Calculated %: C 69.27; H 7.04; N 4.25. Hydrochloride of XV, mp 151-153°C (from absolute ethanol). Found %: Cl 9.36, 9.32; N 3.80, 3.82. $C_{19}H_{23}NO_4 \cdot HCl$. Calculated %: Cl 9.69; N 3.83.

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