INDOLE DERIVATIVES

XXIV. Synthesis of Some 1, 2, 3, 4, 5, 6-Hexahydroazepino[4, 5-b]indoles

N. M. Sharkova, N. F. Kucherova, S. L. Portnova, and V. A. Zagorevskii

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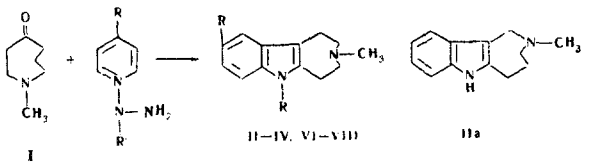
By expanding the ring of 1-methyl-4-piperidone with diazomethane we have obtained 1-methyl-1-azacyclopentan-4-one. The Fischer cyclization of arylhydrazones of 1-methyl-1-azacyclopentan-4-one has given 3-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole and a number of its derivatives for the first time. The structure of the compounds obtained was shown by a study of their PMR spectra and also by a number of chemical reactions.

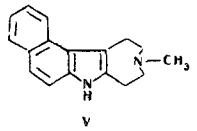
In the plan of our study of the Fischer condensation using various heterocyclic ketones, it was of interest to investigate the behavior in the Fischer reaction of ketones of the type of azacyclopentan-4-one, which would make it possible to answer a number of questions of the influence of the structure of an unsymmetrical ketone on the direction of the closure of the indole ring. Japanese authors [1] have reported that 1-benzyl-1-azacyclopentan-4-one does not take part in the Fischer condensation.

We have made renewed attempts to use azacyclopentan-4-ones for Fischer cyclization using 1-methyl-1-azacyclopentan-4-piperidone by means of diazomethane in a similar manner to the synthesis of 1-benzyl- and 1-phenethyl-1-azacyclopentan-4-ones [2]. Attempts to cyclize I with phenyl-, p-ethoxycarbonylphenyl-, p-tolyl-, p-methoxyphenyl-, β-naphthyl-, and N-methylphenyl-N-benzyl-p-ethoxycarbonylphenylhydrazines showed that the ketone readily takes part in the Fischer condensation with both primary and secondary hydrazines. For this purpose it is sufficient merely to boil the hydrochlorides of both reactants in ethanol or to boil the reactants with a 3–10% solution of hydrogen chloride in ethanol. In all cases, we performed the cyclization without isolating the intermediate arylhydrazones.

Since the ketone I has an unsymmetrical structure, the reaction was expected to form the two possible isomers of types II and IIa.



I II–IV, VI–VIII IIa



V

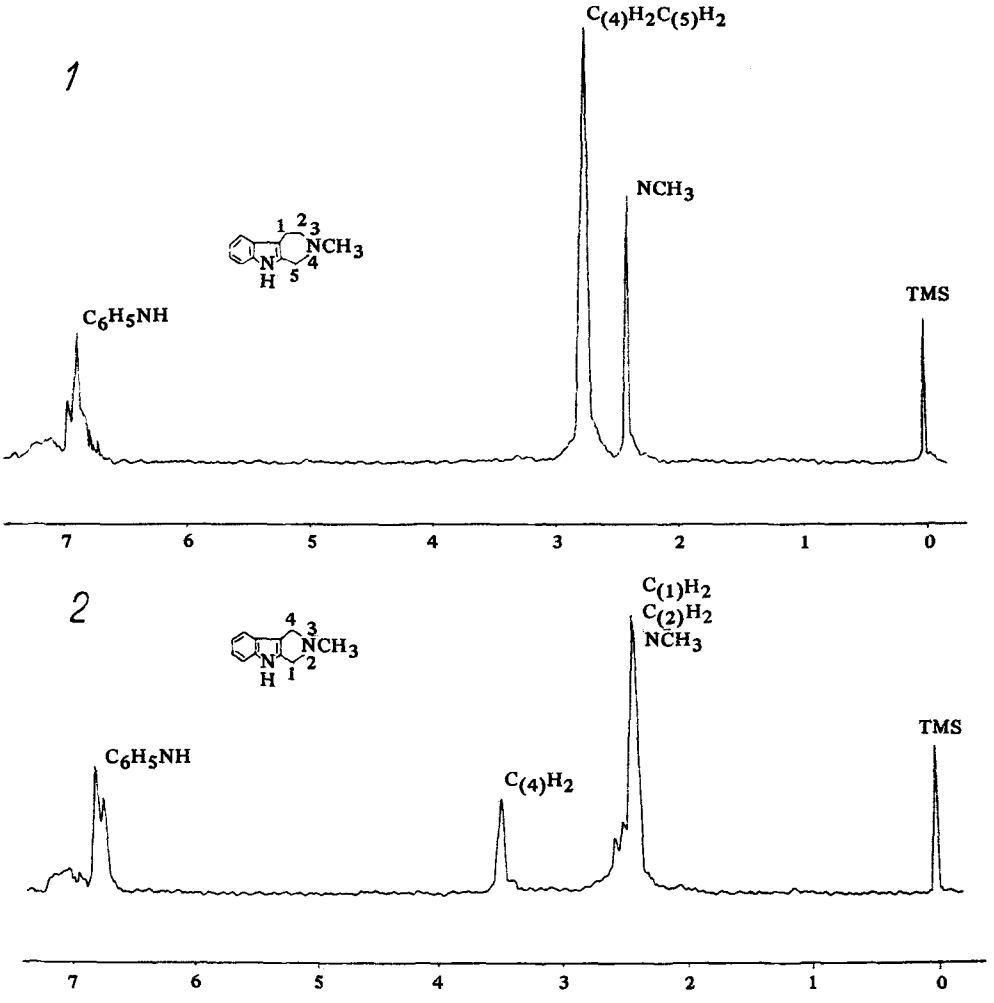
II R=R′=H;
III R=CH$_3$, R=H;
IV R=OCH$_3$, R=H;
VI R=H, R=CH$_3$;
VII R=COOC$_2$H$_5$, R=CH$_2$C$_6$H$_5$;
VIII R=COOH, R=H.

However, in all cases cyclization with both primary and secondary hydrazines gave us only one isomer, frequently with high yields (70–90%). Chromatography of the reaction products in a thin layer of alumina did not show the presence of a second isomer, either. The fact that our compounds were of type II was shown on the basis of a study of the PMR spectra of 3-methyl-1,2,3,4,5,6-hexahydroazepino[4,5–b]indole (figure, spectrum 1). For comparison, the PMR spectrum of the known 1,2,3,4-tetrahydro-γ-carboline (figure, spectrum 2) was also recorded; in this spectrum there there is a signal at 3.6 ppm of the two protons of the CH_2 group in position 4 between the nitrogen atom and the 3-indolyl radical. Such a value of the chemical shift might be expected if one bears in mind that the nitrogen atom of the amino group exerts approximately the same descreening influence on the neighboring methylene group as the 3-indolyl radical (for comparison we may give the value of the chemical shift of the protons of the CH_3 groups in trimethylamine, which is 2.12 ppm, and in 3-methylindole, which is 2.28 ppm [3].

This fact also leads to the situation that the signals of the two methylene groups in positions 1 and 2 and of the N—CH_3 group are located close to one another in the 2.5 ppm region (it must be borne in mind that the influence of the 2-indolyl radical is the same as that of the 3-indolyl radical, since the value of the chemical shift of the protons of the CH_3 group in 2-methylindole is also 2.28 ppm. The signals of the protons of the benzene ring and the NH group of the indole are located in the 6.7–7.3 ppm region.

The spectrum of compound II lacks signals in the 3–4 ppm region. The protons of the four methylene groups, which have similar chemical shifts, gave a single peak at 2.3 ppm. Consequently, in compound II there is no methylene group attached directly to the nitrogen of the amino group and to the indole ring, which shows the symmetrical arrangement of the amino group with respect to the indole system. The chemical shift of the N—CH_3 group in compound II is 2.4 ppm.

We adopted the structures of compounds III–VIII by analogy with the indole II. With compound III as an example, it was shown that in the Fischer reaction secondary hydrazines form the same series of isomers with the ketone I as primary hydrazines. This follows from the fact that the alkylation with methyl iodide of the sodium derivative of the indole II in diethylformamide gave the indole III. In view of the fact that the 3-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole system, which is a homotetrahydro-γ-carboline system, is of interest and difficultly accessible, we have studied some of its chemical reactions. Of the greatest interest was the question of the direction of Emde



PMR spectra:
1) 3-Methyl-1, 2, 3, 4, 5, 6-hexahydroazepino[4, 5-b]indole; 2) 1, 2, 3, 4-Tetrahydro-γ-carboline.

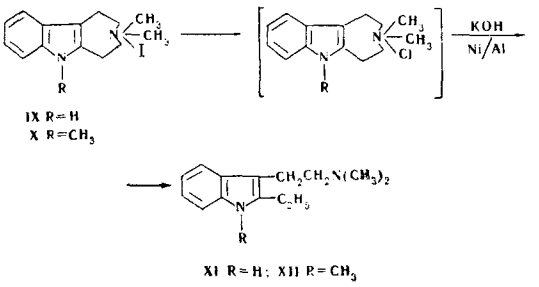
Characteristics of the Substances Obtained

Compound	Reaction conditions			Mp, °C	Empirical formula	Found				Calculated, %				Yield, %
	Concentration of the ethanolic hydrogen chloride solution, %	Amount of ethanolic solution, mg per g of substance I	Time of heating, min			C	H	Cl	N	C	H	Cl	N	
II	3	22	180	162 —162.5	$C_{13}H_{16}N_2$*	78.08, 78.29	8.11, 8.32		14.16, 14.21	77.95	8.05		13.98	58
III	5	33	60	150.5—152	$C_{14}H_{18}N_2$	78.42, 78.17	8.65, 8.46		12.99, 12.96	78.46	8.47		13.07	54
IV	7	8	15	231 —231.5	$C_{14}H_{18}N_2O \cdot HCl$			13.22, 13.03	10.45, 10.35			13.29	10.50	52
V	10	20	60	199 —200.5	$C_{17}H_{18}N_2$	81.43, 81.72	7.20, 7.27		11.22, 11.06	81.58	7.24		11.15	71
VI	6.8	16	30	231 —233	$C_{14}H_{18}N_2 \cdot HCl$**	66.87, 66.78	7.80, 7.82	14.17, 14.07	10.80, 10.73	67.01	7.59	14.13	11.17	94.5
VII	6	22	45	240 —242	$C_{23}H_{26}N_2O_2 \cdot HCl$			9.02, 9.04	7.12, 7.22			8.88	7.02	21

*Methiodide IX (obtained by boiling II with an excess of CH_3I in anhydrous acetone, mp 200°–201°C (from water). Found, %: I 36.77, 36.82. Calculated for $C_{13}H_{16}N_2 \cdot CH_3I$, %: I 37.08.

**The methiodide X (obtained similarly to IX, mp 237°–238° C (from anhydrous ethanol). Found, %: I 35.46, 35.63. Calculated for $C_{14}H_{18}N_2 \cdot CH_3I$, %: I 35.62.

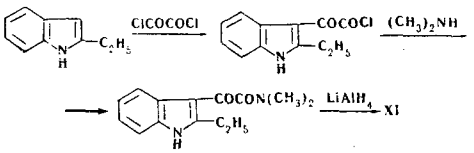
cleavage of the quaternary salts of this system, since the formation of derivatives of α- or β-tryptamine could have been expected. With methyl iodide in acetone, compounds II and III were converted into the methiodides IX and X, and then into the methochlorides, the Emde decomposition of which gave, respectively, 3-(β-dimethylaminoethyl)-2-ethylindole (XI) and 3-(β-dimethylaminoethyl)-2-ethyl-1-methylindole (XII).



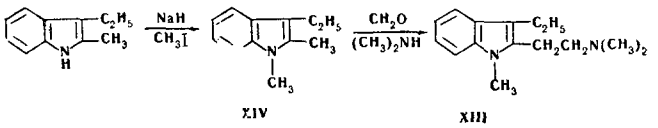
IX R=H
X R=CH$_3$

XI R=H; XII R=CH$_3$

The structure of the indole XI was shown by its identity with a sample obtained by independent synthesis by the following route.



The structure of compound XII was confirmed by its nonidentity in respect of R_f and melting point with 2-(β-dimethylaminoethyl)-3-ethyl-1-methylindole (XIII), which was obtained from 3-ethyl-1,2-dimethylindole (XIV) by dimethylaminoalkylation [4].



XIV XIII

Consequently, the Emde cleavage of compounds II and III takes place in such a way as to form β-tryptamine derivatives. The results of the cleavage simultaneously serve as confirmation of the assigned structure of compounds II and III.

The successful methylation of the sodium derivative of indole II to indole III in dimethylformamide mentioned above led to the use in this reaction of benzyl chloride and N-γ-chloropropyl-N-methylpiperazine, as well, which gave 6-benzyl-3-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (XV) and 3-methyl-6-[γ-(4-methyl-1-piperazinyl)propyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (XVI).

The occurrence of the alkylation reactions at the indole nitrogen atom shows that dimethylformamide, as a bipolar aprotic solvent weakly solvating the anion, ensures the successful competition of alkylation at the indole nitrogen atom (in the form of an anion) with the formation of an indolenine and a quaternary salt at the nitrogen atom of the amino group of the azepine ring, which possesses considerable basicity.

EXPERIMENTAL

1-Methyl-1-azacyclopentan-4-one (I). Over 4 hr with stirring at −5 to −10° C, 16 g (0.4 mole) of diazomethane in 800 ml of ether was added to 29 g (0.26 mole) of 1-methyl-4-piperidone in 100 ml of methanol. The mixture was kept at room temperature for 16 hr, and then the solvent was distilled off to 2/3 volume, another 400 ml of ether was added, and the solution was evaporated. The residue was distilled, giving 8.2 g (25%) of substance I with bp 67–71° C (7 mm), n_D^{20} 1.4710, which was characterized in the form of the hydrochloride, mp 166.5–167° C (from ethanol). Found, %: C 51.47; 51.23; H 8.55; 8.61; Cl 21.63; 21.66; N 8.67; 8.72%. Calculated for $C_7H_{13}NO \cdot HCl$, %: C 51.35; H 8.61; Cl 21.65; N 8.55%.

3-Methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (II). 6.8 g (0.047 mole) of phenylhydrazine hydrochloride and a solution of hydrogen chloride in anyhydrous ethanol were added to 6 g (0.047 mole) of the base I. The reaction mixture was boiled (whereupon the hydrazone that had separated out dissolved, and ammonium chloride gradually precipitated), cooled, poured into water, and made alkaline with a solution of potassium carbonate, and the precipitate that had deposited was filtered off and carefully washed with water. This gave 5.5 g of the indole II.

Substances III–VII were obtained similarly. Data on substances II–VII and the conditions for their preparation are given in the table.

Hydrochloride of 3-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b indole-9-carboxylic acid (VIII). A mixture of 1 g (0.0079 mole) of I and 1.45 g (0.0079 mole) of p-ethoxycarbonylphenylhydrazine in 12 ml of concentrated HCl was boiled for 10 min. It became very dark and foamed, and the hydrazone that first separated out gradually redissolved, after which a new precipitate was deposited; this was separated off, washed with a small amount of ethanol, and recrystallized from water. This yielded 1.6 g (72%) of substance VIII, mp 273–274° C (decomp.). Found, %: Cl 12.69; 12.57; N 9.78; 9.74%. Calculated for $C_{14}H_{16}N_2O_2 \cdot HCl$, %: Cl 12.62; N 10.01%.

3-(β-Dimethylaminoethyl)-2-ethylindole (XI). a) By treatment with AgCl, 7 g (0.02 mole) of the methiodide IX in 30 ml of water was converted into the corresponding chloride, and the resulting solution was slowly added in drops with stirring to a suspension of 0.5 g of finely pulverized Raney alloy in 100 ml of 20% sodium hydroxide. The reaction mixture was heated to 60–70° C, and at this temperature 6 g of Raney alloy was added in portions over 8 hr, with periodic cooling of the mixture and extraction with ether of the white crystalline substance. The ethereal solutions were combined, dried with anhydrous $MgSO_4$, and evaporated. The residue was recrystallized from petroleum ether to give 3.4 g (74%) of substance XI, mp 100–101° C. Found, %: C 77.58; 77.68; H 9.29; 9.28; N 12.84; 13.08%. Calculated for $C_{14}H_{20}N_2$, %: C 77.72; H 9.31; N 12.95%.

b) With stirring at 4–5° C, 6 g (0.047 mole) of oxalyl chloride was slowly added in drops to a solution of 5 g (0.0345 mole) of 2-ethylindole in 300 ml of absolute ether. The reaction mixture was stirred at 4–5° C for 30 min, and then a solution of 11 g (0.245 mole) of diethylamine in 100 ml of absolute ether was added. The mixture was stirred for 1 hr and decomposed with a saturated solution of sodium bicarbonate. The ethereal solution was separated off, washed with water, dried with anhydrous $MgSO_4$, and evaporated. The residual viscous oil was carefully dried in a vacuum desiccator over phosphorus pentoxide, dissolved in 60 ml of absolute dioxane, and, with stirring, at a temperature of 22° C, added dropwise to a suspension of 4.5 g (0.117 mole) of lithium aluminum hydride in 60 ml of absolute dioxane. The reaction mixture was boiled for 10 hr with stirring, cooled, decomposed with ice-water and with 50% potassium hydroxide solution, and the dioxane solution was separated off; the aqueous solution was extracted twice with ether. The combined solvents were washed with water, dried with anhydrous $MgSO_4$, and evaporated. The residue was recrystallized from petroleum ether to give 3.2 g (45%) of substance XI, mp 99.5–100.5° C.

Hydrochloride of 3-(β-dimethylaminoethyl)-2-ethyl-1-methylindole (XII). As for the preparation of substance IX (a), 8 g (0.0225 mole) of the methiodide X yielded 4 g (67%) of the hydrochloride of XII, mp 168–170° C (from acetone): R_f 0.63 in a thick layer of Al_2O_3 (basic, activity grade ~ IV, solvent $CHCl_3$). Found, %: C 83.37; H 6.66; N 7.99; 8.27%. Calculated for $C_{12}H_{15}N$, %: C 83.18; H 8.72; N 8.08%.

Hydrochloride of 2-(β-dimethylamino)-3-ethyl-1-methylindole (XIII). To 6 g (0.035 mole) of substance XIV were added 6.3 ml (0.05 mole) of 36% dimethylamine solution, 4.4 ml (0.04 mole) of 32% formaldehyde solution, and 35.5 ml of acetic acid. The reaction mixture was heated in the water bath for 2 hr, cooled, treated with 50 ml of ice-water, and extracted with ether. The ethereal solution was dried with anhydrous $MgSO_4$ and evaporated. The oily residue was dissolved in anhydrous ethanol, and a solution of hydrogen chloride in anhydrous ethanol was added to this solution. The precipitate that deposited was filtered off and recrystallized from anhydrous ethanol. This gave 2.5 g (27%) of substance XIII, mp 211-212° C. R_f 0.67 in a thin layer of Al_2O_3 (basic, activity grade ~IV, solvent $CHCl_3$). It gave a depression of the melting point in admixture with substance, XII, 155-160° C. Found, %: C 67.28; 67.14- H 8.83; 8.73; Cl 13.24; 13.12; N 10.47; 10.60%. Calculated for $C_{15}H_{22}N_2 \cdot HCl$, %: C 67.52; H 8.68; Cl 13.28; N 10.52%.

Hydrochloride of 3,6-dimethyl-1,2,3,4,5,6-hexahydroazepino [4,5-b]indole (VI). In a similar manner to the preparation of substance XIV, 1.3 g (0.0065 mole) of the indole II, 1.3 g (0.0065 mole) of methyl iodide, and sodium hydride in anhydrous dimethylformamide gave the hydrochloride of substance VI, mp 231-232° C.

Maleate of 6-benzyl-3-methyl-1,2,3,4,5,6-hexahydroazepino [4,5-b]indole (XV). The alkylation of 2 g (0.01 mole) of compound II with 1.27 g (0.01 mole) of benzyl chloride took place similarly, giving the maleate of substance XV. Yield 1.4 g (20%), mp 175-176°C C (from ethanol). Found, %: C 70.76; 70.62; H 6.44; 6.43; N 6.96; 6.98%. Calculated for $C_{20}H_{22}N_2 \cdot C_4H_4O_4$, %: C 70.91; H 6.44; N 6.89%.

Maleate of 3-methyl-6-[γ-(4-methyl-1-piperazinyl)propyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (XVI). This was obtained similarly from 2 g (0.01 mole) of the indole II and 1.76 g (0.01 mole) of N-γ-chloropropyl-N'-methylpiperazine. Yield 4 g (87%), mp 154-156° C (from ethanol). Found, %: N 8.46, 8.28. Calculated for $C_{21}H_{32}N_4 \cdot C_4H_4O_4$, %: N 8.13.

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Institute of Pharmacology and Chemotherapy, Academy of Medical Sciences, USSR, Moscow