INDOLE DERIVATIVES

XXVII. 1,2,3,4-Tetrahydropyrrolo[3,4-b]indoles

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

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 1, pp. 81–87, 1969

UDC 547.751'743.1:543.422.6:541.67

The Fischer cyclization of arylhydrazones of 1-butyl-, 1-benzyl-, and 1-cyclohexyl-3-pyrrolidinones has been studied, as a result of which a synthesis of 1,2,3,4-tetrahydropyrrolo[3,4-b]indoles has been developed. The structure of the compounds obtained has been confirmed by their UV and NMR spectra and by a number of chemical properties.

We have previously [1] shown that in all cases the Fischer reaction of arylhydrazones of the unsymmetrical ketone 1-methyl-1-aza-4-cyclopentanone forms 1, 2, 3, 4, 5, 6-hexahydroazepino[4, 5-b]indoles, from which it followed that the position closest to the nitrogen atom of the azacyclopentanone, i.e., position 3, is less preferable in the closure of the indole ring than position 5, two carbon atoms distant from the amino group.

In order to study further the question of the influence of the structure of unsymmetrical ketones on orientation in the closure of the indole ring by Fischer's method, we turned to the 3-pyrrolidinone system. We took in account the fact that the development of a synthesis of the pyrroloindoles would open up additional possibilities for the search for new pharmacologically active compounds containing condensed indole systems. Only three representatives of the class of 1, 2, 3, 4-tetrahydropyrrolo[3, 4-b]indole have been described in the literature, and these were obtained by the condensation of arylhydrazones of 2, 3-pyrrolidinediones, with subsequent lithium aluminum hydride reduction of the lactams formed [2].

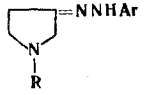
As the initial ketones we took 1-benzyl- [3], 1-n-butyl- [3], and 1-cyclohexyl-3-pyrrolidinones (**Ia, b, c**). With various arylhydrazines all these ketones give good yields of the corresponding hydrazones, which were isolated in the form of the hydrochlorides (Table 1). In some cases, the unpurified hydrazones were used for cyclization. In the cyclization of the hydrazones, we encountered a number of difficulties. Thus, boiling the hydrazones with 5–20% alcoholic solutions of hydrogen chloride, i.e., the use of conditions ensuring the successful cyclization of the hydrazones of 1-methyl-1-aza-4-cyclopentanone [4], led to a pronounced darkening of the reaction mixture and the reaction was not accompanied by the separation of ammonium chloride and, consequently, did not go in the direction of the formation of indoles. By a chromatographic check in a thin layer of alumina, it was found that even after heating for 3 min the initial hydrazone had disappeared and two other substances had appeared. The R_f value of one of them was always the same as that of the authentic arylamine formed by the decomposition of the hydrazone. In the case of the p-tolylhydrazone of ketone **Ic** and the phenylhydrazone, p-tolylhydrazone, and p-ethoxycarbonylphenylhydrazone of the ketone **Ib**, aniline, p-toluidine, and p-ethoxycarbonylaniline were isolated from the reaction mixtures with yields of 50–75% and identified by their R_f values and the melting points of the hydrochlorides and the free bases (for the two latter amines). The second substance always had the same R_f value (differing from the R_f value of the corresponding pyrrolidinone) in spite of the fact that different hydrazones of any given ketone were used. This substance, possessing basic characteristics and forming a hydrochloride, could not be identified because of its low stability; it can only be stated that the IR spectrum of the hydrochloride did not exhibit frequencies of the stretching vibrations of a carbonyl group. A similar decomposition of arylhydrazones has been observed in a 50% alcoholic solution of hydrogen chloride at room temperature.

It was possible to effect the closure of the indole ring of the arylhydrazones of the ketones I only in 30–35% ethanolic solutions of hydrogen chloride or ethanolic solutions of sulfuric acid (3 ml of concentrated H_2SO_4 to 7 ml of ethanol). The yields of the indole derivatives II–XII were variable, amounting to 11–60%. Under the given conditions the side reaction of the decomposition of the hydrazones was suppressed to some extent, but aromatic amines were always present in the reaction mixture.

As a consequence of the unsymmetrical structure of the pyrrolidones **I**, the formation of two series of isomers, for example **II** and **IIa**, is theoretically possible. In all cases we isolated only one series of isomers. We were unable to establish the presence of the second isomer in any of the experiments. The symmetrical structure of the hydropyrroloindoles was confirmed by the UV and NMR spectra of substances **III** and **IV**. The UV spectrum of compound **IV** had absorption maxima at 225 nm (log ε 4.49) and 275 nm (log ε 3.85). The UV spectra of compounds II–VII were similar. The spectra of 1, 2, 3, 4-tetrahydrocarbazole and of 1, 2, 3, 4-tetrahydrocyclopenta[b]indole [4] have approximately the same value, while the unsymmetrical 4H-2, 3-dihydrothieno[3, 2-b]indole, in the molecule of which sulfur is directly connected to the C_3 atom of the indole system has the second form of UV spectrum with a bathochromic shift of the long-wave maximum [4].

The NMR spectrum was taken on a JNM 44-100 instrument at a working frequency of 100 MHz in

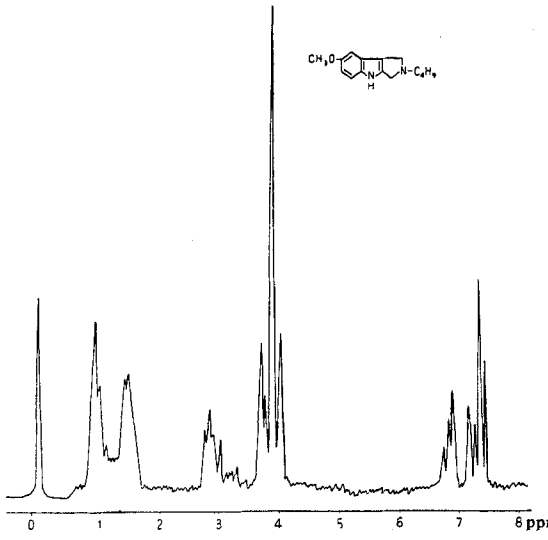
Table 1

Hydrochlorides of the Hydrazones 

Method of preparation	Ar	R	Empirical formula	Mp, °C	Found, %		Calculated, %		Yield, %
					N	Cl	N	Cl	
A	*p*-$CH_3C_6H_4$	*n*-C_4H_9	$C_{15}H_{23}N_3 \cdot HCl$	134—135	14.89 14.78	12.52* 12.46	14.91	12.57	53
A	*p*-$CH_3OC_6H_4$	*n*-C_4H_9	$C_{15}H_{23}N_3O \cdot HCl$	122—122.5	14.03 14.02	11.79 11.92	14.11	11.90	85
A	*p*-$CH_3C_6H_4$	cyclo-C_6H_{11}	$C_{17}H_{25}N_3 \cdot HCl$	170—171 (decomp.)	13.67 13.54	** —	13.65	—	87
A	C_6H_5	cyclo-C_6H_{11}	$C_{16}H_{23}N_3 \cdot HCl$	166—168 (decomp.)	14.51 14.40	12.27 12.34	14.31	12.06	100
B	*p*-$CH_3OC_6H_4$	$CH_2C_6H_5$	$C_{18}H_{21}N_3O \cdot HCl$	144—145	12.60 12.69	10.93 10.82	12.67	10.69	55.6
B	*p*-$COOC_2H_5C_6H_4$	$CH_2C_6H_5$	$C_{20}H_{23}N_3O_2 \cdot HCl$	153—154	11.68 11.51	9.20 9.13	11.24	9.48	83
B	*p*-$CH_3C_6H_4$	$CH_2C_6H_5$	$C_{18}H_{21}N_3 \cdot HCl \cdot C_2H_5OH$	136—137	11.94 11.87	9.54 9.49	11.61	9.77	89
B	β-Naphthyl	$CH_2C_6H_5$	$C_{21}H_{21}N_3 \cdot HCl$	153—153.5	11.63 11.72	9.64 9.44	11.94	10.08	98

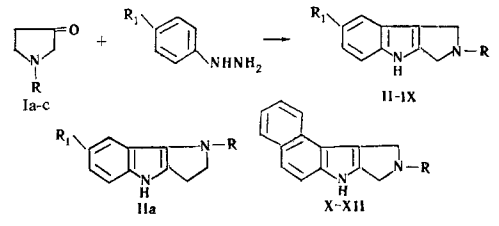
*Found, %: C 63.74; 63.97; H 8.46; 8.61. Calculated, %: C 63.95; H 8.58.
**Found, %: C 66.00; H 8.57. Calculated, %: C 66.31; H 8.51.

deuteriochloroform, with tetramethylsilane the internal standard. In the NMR spectrum of compound **III**, the signals with $\delta = 4.00$ and 3.70 ppm are due to the two CH_2 groups of the pyrrolidine ring in positions 1 and 3. The signal at 3.85 ppm is caused by the protons of the CH_3O group. The broad poorly-resolved signal in the 2.7–2.9 ppm region with an area of two proton units is due to the N—CH_2 group of the butyl radical.



NMR spectrum of 2-n-butyl-7-methoxy-1, 2, 3, 4-tetrahydropyrrolo[3, 4-b]indole (III) (δ scale).

The broad 4-proton signals of the C—CH_2—CH_2—C fragment and the three protons of the CH_3 group of the butyl radical are found at 1.55 and 0.95 ppm, respectively. The multiplet signal at 6.5–7.5 ppm is due to the protons of the benzene ring and the proton on the indole nitrogen atom.



Ia R = $CH_2C_6H_5$; **Ib** R = *n*-C_4H_9; **Ic** R = cyclo-C_6H_{11};
II R = *n*-C_4H_9, $R_1 = CH_3$; **III** R = *n*-C_4H_9, $R_1 = OCH_3$;
IV R = *n*-C_4H_9, $R_1 = H$; **V** R = cyclo-C_6H_{11}, $R_1 = CH_3$;
VI R = cyclo-C_6H_{11}, $R_1 = H$; **VII** R = cyclo-C_6H_{11}, $R_1 = OCH_3$; **VIII** R = $CH_2C_6H_5$, $R_1 = CH_3$;
IX R = $CH_2C_6H_5$, $R_1 = OCH_3$; **X** R = cyclo-C_6H_{11};
XI R = $CH_2C_6H_5$, **XII** R = *n*-C_4H_9,

An additional proof of the structure of the compounds synthesized as 1, 2, 3, 4-tetrahydropyrrolo[3, 4-b]indoles is formed by the identical values of the melting points of the hydrochloride and picrate of substance **VI** and the corresponding derivatives of the compound with the authentic structure obtained previously by the cyclization of 1-cyclohexyl-2, 3-pyrrolidinedione [2].

We may mention that we were unable to perform the cyclization of the *p*-ethoxycarbonylphenylhydrazone of the ketone **Ib** and of the N-methyl- and N-benzylphenylhydrazones of the ketone **Ic**. With N-methylphenylhydrazinehydrochloride in ethanol, Ic gives an unstable hydrazone readily decomposing in 5% ethanolic hydrochloric acid solution into N-methylaniline, which was identified by thin-layer chromatography, and a substance of unknown structure formed from the ketonic component. Under more severe conditions, pronounced resinification of the reaction mixture took place.

Compounds having substituents on the indole nitrogen atom, however, can easily be obtained by the alkylation of the sodium derivatives of the tetrahydropyrroloindoles in dimethylformamide. For example, in this way from substances V and II we synthesized in good yield 2-cyclohexyl-7-methyl-4-[γ-(4'-methyl-1-piperazinyl)propyl]-1, 2, 3, 4-tetrahydropyrrolo[3, 4-b]indole (**XIII**), 2-cyclohexyl-4-(β-dimethylaminoethyl)-7-methyl-1, 2, 3, 4-tetrahydropyrrolo[3, 4-b]indole (**XIV**), and 2-n-butyl-4-(β-dimethylaminoethyl)-1, 2, 3, 4-tetrahydropyrrolo[3, 4-b]indole (XV). The cyanoethylation of IV in the presence of Rodionov's catalyst led to the corresponding cyanoethyl derivative (XVI).

EXPERIMENTAL

N-(β-Methoxycarbonylethyl)cyclohexylamine (XVII). To a solution of 228 g (1.23 mole) of cyclohexylamine in 285 ml of methanol was added dropwise 200 g (2.3 mole) of methyl acrylate at such a rate that the temperature did not rise above 20–25° C. The reaction mixture was heated at 60° C for 1 hr 30 min, and the methanol was distilled off in vacuum. The yield was 380 g (89.5%), bp 126–128° C (9 mm), n_D^{20} 1.4623. Found, %: C 64.67, 64.46; H 10.28, 10.45; N 7.87; 7.70. Calculated for $C_{10}H_{19}NO_2$, %: C 64.82; H 10.33; N 7.56.

N-Ethoxycarbonylmethyl-N-(β-methoxycarbonylethyl)cyclohexylamine (XVIII). A mixture of 250 g (1.35 mole) of XVII, 165 g (1.35 mole) of ethyl chloroacetate, and 463 g (3.35 mole) of anhydrous potassium carbonate was heated in an autoclave at 100° C for 18 hr, cooled, and dissolved in water. The aqueous solution was extracted with ether to give 261 g (71.5%) of XVIII with bp 155–157° C (3 mm), n_D^{20} 1.4655. Found, %: C 62.03, 62.36; H 9.35, 9.12. Calculated for $C_{14}H_{25}NO_4$, %: C 61.95; H 9.28.

1-Cyclohexyl-3-pyrrolidinone (Ic). Over 30 min at 150° C, 170 g (0.63 mole) of XVIII in 250 ml of absolute xylene was added to the sodium ethoxide prepared from 15.2 g of sodium and dried in vacuum, and the mixture was heated at 120° C for 1 hr with simultaneous distillation of the ethanol; it was then cooled, and decomposed with 1300 ml of 18% hydrochloric acid. The aqueous layer was separated off, boiled for 6 hr, and evaporated in vacuum to about one third of its initial volume. With efficient cooling, the residue was made strongly alkaline with 50% caustic potash solution and was extracted with ether three times. Yield 55.4 g (52%), bp 96–97° C (2.5 mm), n_D^{20} 1.4910. Found, %: C 72.14; H 10.32; N 8.49. Calculated for $C_{10}H_{17}NO$, %: C 71.81; H 10.24; N 8.37.

Hydrochlorides of the arylhydrazones of the 1-R-3-pyrrolidinones (Table 1). A. A mixture of 0.01 mole of the ketone I and 0.01 mole of the hydrochloride of the corresponding arylhydrazine in 10 ml of ethanol was heated until solution was achieved. The reaction mixture was cooled, dry ether was added, and the hydrazone hydrochloride that separated out was filtered off.

B. A mixture of 0.018 mole of the ketone Ia and 0.01 mole of the hydrochloride of the appropriate arylhydrazine in 8 ml of ethanol was boiled for 30 min. After cooling with ice, the precipitate was filtered off and was washed with a mixture of alcohol and ether (1:10). For purification it was crystallized from absolute ethanol.

2-R-7-R_1-1, 2, 3, 4-Tetrahydropyrrolo[3, 4-b]indoles (II–IX). The appropriate hydrazone hydrochloride was boiled with a solution chloride in ethanol, cooled, and poured into cold water, and the resulting tetrahydropyrrolo[3, 4-b]-indole (Table 2) was isolated by the addition of saturated potassium carbonate solution.

2-Cyclohexyl-7-methyl-1, 2, 3, 4-tetrahydropyrrolo[3, 4-b]indole (V). Hot ethylsulfuric acid (a mixture of 21 ml of absolute ethanol

Table 2

2-R-7-R_1-1, 2, 3, 4-Tetrahydropyrrolo[3, 4-b]indoles

Compound	Amount of hydrazone hydrochloride, g	Ethanolic solution of hydrogen chloride		Time of heating, min	Empirical formula	Mp, °C	Found, %			Calculated, %			Yield, %	Derivatives	
		amount, ml	concentration, %				C	H	N	C	H	N		compound	mp, °C
II	15.3	35	34	2	$C_{15}H_{20}N_2$	168—169	79.09	8.91	12.47 12.46	78.94	8.83	12.27	54	Hydrochloride[a]	173—174
III	3	17.5	2.5	20	$C_{15}H_{20}N_2O$	146—148	73.73 73.73	8.29 8.11	11.85 11.78	73.73	8.25	11.46	11,5	Methiodide[b]	149—150
IV	8	24	32	2	$C_{14}H_{18}N_2$	150	78.46 78.29	8.51 8.62	13.31 13.30	78.46	8.46	13.07	11	—	
V	10.8	32	30	3	$C_{17}H_{22}N_2$	215—216	—	—	10.86 10.87	—	—	11.01	50	Hydrochloride[c]	206—208 (decomp.)
VI	5.2	25	30	3	$C_{16}H_{20}N_2$	200—210 (decomp.)	80.21 80.48	8.47 8.33	12.05	79.95	8.38	11.65	13	Picrate[d]	175—176 (decomp.)
VII	9	40	30	—	$C_{17}H_{22}N_2O$[e]	218—220 (decomp.)	75.27 75.48	8.35 8.27	10.46 10.53	75.51	8.20	10.36	62	Hydrochloride[f]	216—218 (decomp.)
VIII	4	12	35	5	$C_{18}H_{18}N_2$	141—142	81.64 81.86	6.80 6.70	10.53 10.34	82.39	6.92	10.67	61	Hydrochloride[g]	181—183 (decomp.)
IX	1	10	22	30	$C_{18}H_{18}N_2O$	143—143.5	78.02 78.01	6.48 6.65	—	77.67	6.52	—	25	—	

[a]Found, %: Cl 13.20, 13.00. Calculated, %: Cl 13.38. [b]Found, %: I 32.94; Calculated, %: I 32.85. [c]Found, %: Cl 9.50, 9.59. Calculated, %: Cl 9.63. [d]Found, %: N 14.88, 15.08; Calculated, %: N 14.79. [e]The reaction took place spontaneously; yield given on the hydrochloride. [f]Found, %: Cl 11.24; 11.39%; N 9.16; 9.21. Calculated, %: Cl 11.55; N 9.13. [g]Found, %: Cl 11.76; 11.61; N 9.48; 9.55. Calculated, %: Cl 11.86; N 9.38.

and 4 ml of concentrated sulfuric acid) was added to 7 g (0.0172 mole) of the hydrochloride of 1-cyclohexyl-3-pyrrolidinone p-tolylhydrazone, and the mixture was boiled for 5 min. Then it was poured into cold water and made alkaline with a saturated potassium carbonate solution to give 4.7 g (57.5%) of the indole V.

2-Cyclohexyl-1,2,3,4-tetrahydropyrrolo[3,4-b]benzo[e]indole (X). (X). This was obtained in a similar manner to compounds II–IX from 3.2 g (0.009 mole) of the hydrochloride of the β-naphthylhydrazone of ketone Ic with a yield of 2.2 g (82%), mp 200–210° C (decomp., from tetrahydrofuran). Found, %: C 82.88, 82.84; H 7.59, 7.60; N 9.67, 9.74. Calculated for $C_{20}H_{22}N_2$, %: C 82.73; H 7.60; N 9.64.

Hydrochloride of 2-benzyl-1,2,3,4-tetrahydropyrrolo[3,4-b]benz[e]indole (XI). This was obtained similarly. Yield 48%, mp 208–209° C. Found, %: Cl 10.09, 10.11; N 7.93, 7.99. Calculated for $C_{21}H_{18}N_2 \cdot HCl$, %: Cl 10.59; N 8.37. Base, mp 160–161° C. Found, %: N 9.22, 9.05. Calculated for $C_{21}H_{18}N_2$, %: N 9.39.

2-n-Butyl-1,2,3,4-tetrahydropyrrolo[3,4-b]benz[e]indole (XII). A mixture of 1.4 g (0.0072 mole) of β-naphthylhydrazine hydrochloride and 1.25 g (0.0088 mole) of the ketone Ib in 5 ml of a 17% solution of hydrogen chloride in absolute ethanol was boiled for 30 min, poured into water, and made alkaline with saturated potassium carbonate solution, and the liberated oil was extracted with ether. The ethereal extract was dried with anhydrous magnesium sulfate and evaporated to give 0.4 g (21%) of XII with mp 163–164° C. Found, %: C 81.63, 81.41; H 7.59, 7.71; N 10.64, 10.48. Calculated for $C_{18}H_{20}N_2$, %: C 81.76; H 7.55; N 10.59.

2-Cyclohexyl-7-methyl-4-[γ-(4-methyl-1-piperazinyl)propyl]-1,2,3,4-tetrahydropyrrolo[3,4-b]indole (XIII). In drops, a solution of 1.5 g (0.006 mole) of the indole V in 20 ml of anhydrous dimethylformamide was added to a suspension of 0.2 g (0.006 mole) of sodium hydride in 30 ml of anhydrous dimethylformamide, and the mixture was stirred for 1 hr at room temperature, heated to 60° C, treated in drops with 1.1 g (0.006 mole) of N-(γ-chloropropyl)-N-methylpiperazine, stirred at 60° C for 2 hr, cooled, and poured into water. Yield 1.7 g (71%), mp 64.5–65.5° C (from aqueous ethanol). Found, %: C 75.65; H 9.72; N 14.54. Calculated for $C_{25}H_{38}N_4$, %: C 76.09; H 9.73; N 14.20.

2-Cyclohexyl-4-(β-dimethylaminoethyl)-7-methyl-1,2,3,4-tetrahydropyrrolo[3,4-b]indole (XIV). This was obtained in a similar manner to compound XIII. Yield 79%, mp 85–87° C. Found, %: C 77.57, 77.71; H 9.37, 9.68; N 12.92, 13.04. Calculated for $C_{21}H_{31}N_3$, %: C 77.49; H 9.57; N 12.91.

Dimaleate of 2-n-butyl-4-(β-dimethylaminoethyl)-7-methyl-1,2,3,4-tetrahydropyrrolo[3,4-b]indole (XV). This was obtained in a similar manner to XIII. Yield 35%, mp 155–156° C. Found, %: C 61.10, 61.32; H 6.98, 7.10. Calculated for $C_{27}H_{37}N_3O_8$, %: C 61.00; H 7.01.

2-n-Butyl-4-(β-cyanoethyl)-1,2,3,4-tetrahydropyrrolo[3,4-b]indole (XVI). A mixture of 0.9 g (0.0039 mole) of the indole IV and 10 ml of acrylonitrile was carefully treated with 0.2 ml of a solution of Rodionov's catalyst, the reaction mixture boiling vigorously. Then it was evaporated and the residue was recrystallized from n-heptane. Yield 0.68 g (61.5%), mp 90–91° C. Found, %: C 76.18, 76.17; H 8.15, 8.10; N 15.62, 15.77. Calculated for $C_{17}H_{21}N_3$, %: C 76.36; H 7.91; N 15.77.

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27 September 1966

Institute of Pharmacology and Chemotherapy AMS USSR, Moscow