INDOLE DERIVATIVES. XXXI†. THE FISCHER CYCLIZATION OF ARYLHYDRAZONES OF α-SUBSTITUTED-4-PIPERIDONES

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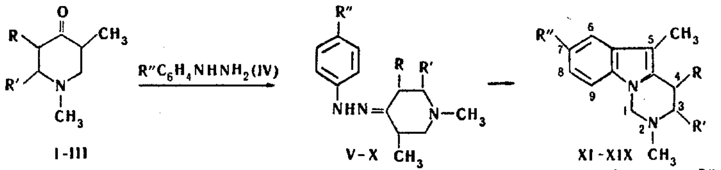
The Fischer cyclization of arylhydrazones of 1,3-dimethyl-, 1,3,5-trimethyl-, and 1,3,6-trimethyl-4-piperidones is examined. An unusual duration of the reaction is found, resulting in rearrangement products (1,2,3,4-tetrahydropyrimido[3,4-a]indoles). It is shown that hydrogenation of the latter gives 2-(β-dimethylaminoalkyl)-3-methylindoles.

We have previously examined the effects of various factors on the course of the Fischer reaction with hydrazones of some cyclic α-substituted ketones. In the present paper, we have examined in detail the condensation of 1,3-dimethyl-, 1,3,5-trimethyl-, and 1,3,6-trimethyl-4-piperidones (I-III) with various arylhydrazines (IV).



V-IX R = R' = H; V R″ = H; VI R″ = CH_3; VII R″ = OCH_3; VIII R″ = $COOC_2H_5$; IX R″ = Cl; X R = R″ = H, R' = CH_3. XI-XVI R = R' = H; XI R″ = H; XII R″ = CH_3; XIII R″ = OCH_3; XIV R″ = $COOC_2H_5$; XV R″ = Cl; XVI R″ = COOH; XVII R = R″ = H, R' = CH_3; XVIII R = CH_3, R' = R″ = H; XIX R = R″ = CH_3, R' = H

The condensation was carried out in 5-10% alcoholic hydrogen chloride, either with or without isolation of the hydrazones. It was shown by chemical and spectral methods that the products obtained were not the normal condensation products, i.e., the corresponding indolinines or 1,2,3,4-tetrahydro-γ-carbolines, but compounds with the new ring structure 1,2,3,4-tetrahydropyrimido[3,4-a]indole (XI-XIX). The properties of the pyrimidoindoles were examined in the greatest detail for the examples XI, XII, XVII, and XVIII. These compounds did not exhibit a labile hydrogen atom on the indole imino-group (with the Chugaev reagent, lithium aluminohydride in ether, or sodium hydride in dimethylformamide), and formed monohydrochlorides in anhydrous media. In contrast to 1,2,3,4-tetrahydro-γ-carbolines unsubstituted on the indole nitrogen [3], no N-alkylated indoles could be obtained from the compounds synthesized. The UV spectra of the hydrochlorides of XI, XII, XVII, and XVII exhibited absorption maxima at 232 and 285 nm, which is characteristic of indoles. The IR spectra of these compounds did not show absorptions in the 3400-3500 cm^{-1} region due to indole NH group stretching. The NMR spectra of XI and XII agreed well with the suggested structures, and excluded the indolinine and 1,2,3,4-tetrahydro-γ-carboline structures. The NMR spectrum of XI (Fig. 1) showed two singlets at δ1.90 and 2.00 ppm due to the protons of the C–CH_3 and N–CH_3 groups. An unresolved signal of area 4 proton units at 2.2-2.5 ppm corresponded to the protons of the CH_2CH_2 fragment, and the signal of 2 proton units with δ3.93 ppm was due to the protons of the isolated methylene group N–CH_2–N. The NMR spectrum of XI hydrochloride (in D_2O + CD_3OD), showed a shift of

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† For Part XXX, see [1].

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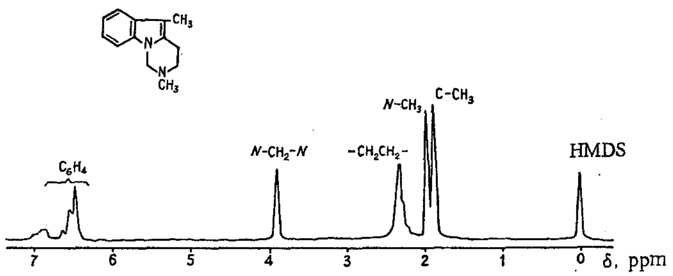
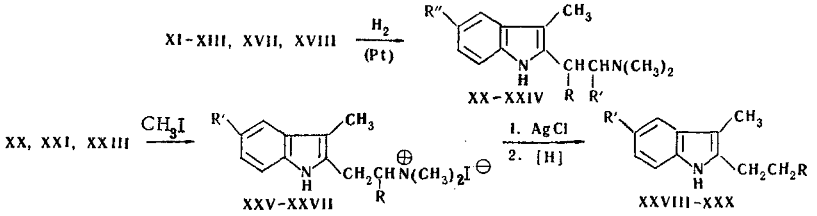


Fig. 1. NMR spectrum of 2, 5, -dimethyl-1, 2, 3,4-tetrahydropyrimido[3, 4-*a*]-indole (XI) in $CDCl_3$.

the $N-CH_3$ and $N-CH_2-N$ signals to lower field (by ~30 Hz), and also of $N-CH_2-C$, in consequence of which the signals of the $N-CH_2CH_2$ group were much broadened, to occupy a region of about 40 Hz. The NMR spectrum of XII (in $CDCl_3$, Fig. 2) showed signals, ppm: 2.13; 2.28; 2.33 (three CH_3 groups); 2.65 (CH_2CH_2); 4.28 ($N-CH_2-N$); 6.5-7.0 (2H, protons of the benzene ring in the 8- and 9-positions); 7.20 (1H, benzene proton at C_6).

Hydrogenation of XI, XII, XIII, XVII, and XVIII over Pt results in hydrogenolysis of the bond between the indole nitrogen atom and the $C_{(1)}$ atom to give isotryptamines (XX-XXIV).



XX-XXII R = R′ = H; XX R″ = H; XXI R″ = CH_3; XXII R″ = OCH_3; XXIII R = R″ = H, R′ = CH_3;
XXIV R = CH_3, R′ = R″ = H; XXV, XXVIII R = R′ = H; XXVI, XXIX R = H, R′ = CH_3; XXVII, XXX R = CH_3, R′ = H

Compounds XX-XXIV contain one labile hydrogen atom, and their UV and IR spectra correspond to the indole structure. The structure of XX is also confirmed by its NMR spectrum (in $CDCl_3$), ppm: 2.04 (3H, singlet, $C=C-CH_3$); 2.10[6H, singlet, $N(CH_3)_2$]; 2.2-2.7 (4H, group of signals from CH_2CH_2); 6.7-7.5 (4H, C_6H_4, in addition the multiplet from $C_{(4)}H$ is located at 7.2-7.5); 9.4 (1H, broad NH signal).

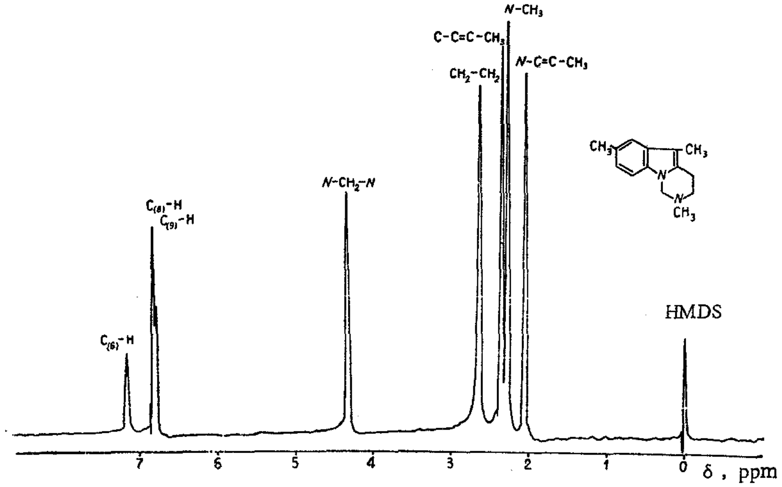
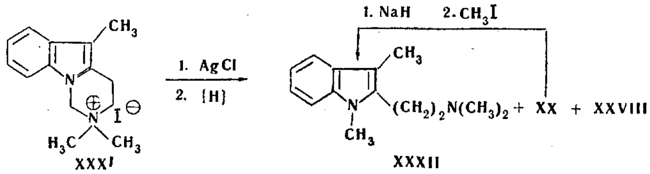


Fig. 2. NMR spectrum of 2, 5, 7-trimethyl-1, 2, 3, 4-tetrahydropyrimido[3, 4-*a*]-indole (XII) in $CDCl_3$.

Reaction of CH_3I with XX, XXI, and XXIII gave the quaternary salts XXV-XXVII. After conversion of these methiodides to the chlorides by treatment with silver chloride, they were subjected to the Emde degradation to give the indoles XXVIII-XXX, which were identical with samples prepared by known methods [4, 5]. Reductive degradation by the Emde reaction of the chloride obtained from the iodide XXXI did not proceed cleanly, giving a mixture of indolic compounds (XX, XXVIII, and XXXII).



The structure of XXXII was proved by its preparation from XX by methylation of the indole nitrogen by the method described previously [3].

It is important to note that the ketone III, by virtue of its structure, is not in general capable of forming the normal indole-type Fischer reaction product. In the light of our results, the structure of the compounds synthesized previously [6, 7] by condensation of arylhydrazones with the ketone II should be further investigated. The formation of XI-XIX under the Fischer reaction conditions probably involves opening of the piperidine ring, followed by cationoid rearrangement of the intermediate indolenines.

EXPERIMENTAL

The NMR spectra were taken on an RS-60 instrument with a working frequency of 60 MHz, using the δ-scale, relative to HMDS. The UV spectra were taken in alcoholic solution on an SF-4 instrument.

1, 3-Dimethyl-4-piperidione Hydrazone, Hydrochloride (V). To a solution of 3.4 g (0.023 mole) of phenylhydrazine hydrochloride in 10 ml of water was added 3 g (0.023 mole) of the ketone I. The mixture was kept for 1 h at room temperature, then the water was removed by distillation in vacuo, and the residue was recrystallized from absolute alcohol to give 4.15 g (70.4%) of V, mp 180-181.5°. Found: Cl 14.1; N 16.7%. $C_{13}H_{19}N_3$. HCl. Calculated: Cl 14.03; N 16.57%.

Hydrochlorides VI-X (Table 1) were obtained similarly.

2, 5-Dimethyl-1, 2, 3, 4-tetrahydropyrimido[3, 4-*a*]indole (XI). A. Two grams (0.008 mole) of V in 20 ml of 10% alcoholic hydrogen chloride was boiled for 30 min. The precipitate which separated on cooling was filtered off to give 1.5 g (83%) of XI hydrochloride, mp 189-190° (from absolute alcohol). Found: C 66.2; H 7.1; Cl 14.8; N 11.6%. $C_{13}H_{16}N_2 \cdot HCl$. Calculated: C 65.97; H 7.24; Cl 14.98; N 11.84%. The free base had bp 137-138° (1 mm). Found: C 77.6; H 8.5; N 13.8%. $C_{13}H_{16}N_2$. Calculated: C 77.96; H 8.05; N 13.99%. UV spectrum, λ_{max}, nm, (log ε): 234 (4.39), 284 (3.82).

B. To a solution of 1 mole of the appropriate arylhydrazine hydrochloride in alcoholic hydrogen chloride was added 1 mole of the ketone, and the mixture was boiled for 30 min. The product separated as the free base or the hydrochloride.

Compounds XII-XIX were obtained by these methods (Table 2). XII was crystallized from heptane, XIV from light petroleum, and XIII and XV from alcohol.

TABLE 1. Piperidone Arylhydrazone Hydrochlorides (VI-X)

Compound	Mp, °C (from alcohol	Molecular formula	Found, %		Calculated, %		Yield, %
			Cl	N	Cl	N	
VI	186,5—188	$C_{14}H_{21}N_3 \cdot HCl$	13,1	15,0	13,24	15,69	84
VII	159—160	$C_{14}H_{21}N_3O \cdot HCl$	12,2	14,6	12,49	14,81	100
VIII	217—218,5	$C_{16}H_{23}N_3O_2 . HCl$	10,8	13,1	10,88	12,89	100
IX	198—200	$C_{13}H_{18}ClN_3 \cdot HCl$	—	14,6	—	14,59	60
X	207—209	$C_{14}H_{21}N_3 \cdot HCl$	13,1	15,8	13,24	15,69	90

TABLE 2. 1, 2, 3, 4-Tetrahydropyrimido[3, 4-*a*]indoles (XII-XIX)

Compound	Method of prep.	Mp, °C	Molecular formula	Found, %				Calculated, %				Yield, %
				C	H	Cl	N	C	H	Cl	N	
XII · HCl[a]	A	183—185	$C_{14}H_{18}N_2 \cdot HCl$	—	—	13,6	11,0	—	—	14,14	11,17	76
XII	—	63—64	$C_{14}H_{18}N_2$	78,6	8,5	—	13,3	78,45	8,46	—	13,08	—
XIII · HCl	A	171,5—173	$C_{14}H_{18}N_2O \cdot HCl$	—	—	—	10,3	—	—	—	10,51	60
XIII	—	78—78,5	$C_{14}H_{18}N_2O$	73,0	8,0	—	12,2	73,00	7,87	—	12,17	—
XIV · HCl	A[b]	214—216	$C_{16}H_{20}N_2O_2 \cdot HCl$	—	—	11,4	9,0	—	—	11,48	9,07	85,7
XIV	—	68,5—70	$C_{16}H_{20}N_2O_2$	—	—	—	10,4	—	—	—	10,29	—
XV · HCl	Ab	204—206	$C_{13}H_{15}ClN_2 \cdot HCl$	—	—	25,7	10,2	—	—	26,18	10,33	87
XV	—	103—104	$C_{13}H_{15}ClN_2$	—	—	15,0	12,2	—	—	15,10	11,92	—
XVI · HCl	A[c]	220—222	$C_{14}H_{16}N_2O_2 \cdot HCl$	59,8	6,2	12,3	10,0	59,89	6,10	12,62	9,97	36
XVII · HCl	A[d]	181—183	$C_{14}H_{18}N_2 \cdot HCl$	—	—	14,0	11,1	—	—	14,14	11,17	86
XVII	—	167—168 (2)[e]	$C_{14}H_{18}N_2$	78,1	8,6	—	13,2	78,45	8,46	—	13,06	—
XVIII · HCl[f]	B	137—138	$C_{14}H_{18}N_2 \cdot HCl$	66,9	8,0	13,7	11,0	67,50	7,64	14,14	11,17	36
XIX · HCl	B	157—159	$C_{15}H_{20}N_2 \cdot HCl$	68,0	8,2	13,5	10,3	68,05	7,99	13,39	10,58	56,4

Note: [a] λ_{max}, nm (log ε): 228 (4.49), 279 (3.84). [b] The cyclization was carried out in a 35% solution of hydrogen chloride in alcohol. [c] The cyclization was carried out in conc. HCl. [d] λ_{max}, nm (log ε): 246 (4.66), 283 (3.78). [e] Bp. [f] λ_{max}, nm (log ε): 232 (4.53), 286 (3.88).

2-(1-R-2-R'-2-Dimethylaminoethyl)-3-methyl-5-R"-indoles (XX-XXIV, Table 3). 0.1 mole of the hydrochloride (XI-XIII, XVI, and XVII) in 300 ml of methanol was hydrogenated over 0.2 g of Pt-black until 0.1 mole of hydrogen had been taken up. The methanol was distilled off in vacuo, and the residue was dissolved in water, basified with ammonia, and extracted with ether. The ether was removed and the residue was recrystallized to give XX-XXIV.

2-(2-R-2-Dimethylaminoethyl)-3-methyl-5-R'-indole methiodides (XXV-XXVII, Table 4). 0.1 mole of XX, XXI, or XXII and 0.2 moles of methyl iodide in 75 ml of acetone were boiled for 30 min. The precipitate was filtered off and recrystallized from absolute alcohol. Yields were quantitative.

2-Ethyl-3-methylindole (XXVIII). A portion of XXV [6.3 g (0.018 mole)] in 30 ml of water was converted into the corresponding chloride by treatment with AgCl, and the resulting solution was added dropwise, slowly with stirring, to a suspension of 0.5 g of finely ground Raney alloy in 100 ml of 20% NaOH. The mixture was heated to 60-70°, and 6 g of Raney nickel was added in portions at this temperature during 5 h. The mixture was extracted with ether, and the ether was removed. The residue was recrystallized from light petroleum to give 2 g (70%) of XXVIII, mp 65-65.5°. Found: C 82.7; H 8.4; N 9.2%. $C_{11}H_{13}N$. Calculated: C 83.00; H 8.17; N 8.80%. The compound was identical (mixed mp and R_f on thin layer chromatography on alumina) with a sample obtained by the literature method [5].

2-Ethyl-3, 5-Dimethylindole (XXIX). Similarly, from 2.5 g (0.007 mole) of XXVI was obtained 0.4 g (35%) of XXIX, mp 67-68°. (from light petroleum). Found: C 83.2; H 8.9; N 8.1%. $C_{12}H_{15}N$. Calculated: C 83.19; H 8.72; N 8.08%.

2-Propyl-3-methylindole (XXX). Similarly, from 4.5 g (0.014 mole) of XXVII was obtained 0.9 g (45%) of XXX, bp 146-147° (6 mm), n_D^{20} 1.5800. Found: C 83.8; H 9.1; N 7.8%. $C_{12}H_{15}N$. Calculated: C 83.16; H 8.90; N 7.81%. Identical by R_f (thin layer chromatography) and n_D with a sample obtained by reduction of 2-propyl-3-formylindole with lithium aluminohydride [4].

2, 5-Dimethyl-1, 2, 3, 4-tetrahydropyrimido[3, 4-*a*]indole methiodide (XXXI). Similarly to XXV, there was obtained from 8.5 g (0.04 mole) of XI 14 g (97%) of XXXI, mp 218.5-220° (from alcohol). Found: I 36.6; N 8.3%. $C_{14}H_{19}IN_2$. Calculated: I 37.08; N 8.19%.

Emde Degradation of XXXI. A portion of XXXI [13 g (0.04 mole)] was subjected to the Emde degradation as for XXV. Gas-liquid chromatography of the ether extract revealed the presence of three components. Addition of an alcoholic solution of hydrogen chloride to the extract precipitated a basic compound. The ether extract was washed with water and dried to give 1.2 g (20%) of XXVIII, mp 64.5-65.5°, identical by thin layer and gas-liquid chromatography, and by mixed mp, with an authentic sample of 2-ethyl-3-methylindole [4]. The mixture of hydrochlorides was crystallized from absolute alcohol to give 4 g (42%) of XXXII hydrochloride, mp 220-221°. Found: 66.7; H 8.5; Cl 14.1; N 11.1%. $C_{14}H_{20}N_2 \cdot HCl$. Calculated: C 66.51; H 8.37; Cl 14.03; N 11.09%.

TABLE 3. 2-(1-R-2-R'-2-Dimethylaminoethyl)-3-methyl-5-R indoles (XX-XXIV)

Compound	Mp, °C	Molecular formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
XX	97—98,5	$C_{13}H_{18}N_2$	76,9	9,1	14,1	77,18	8,96	13,86	93
XXI	120—121	$C_{14}H_{20}N_2$	77,9	9,4	13,0	77,73	9,32	12,95	80
XXII	181—182	$C_{14}H_{20}N_2O \cdot HCl$**	62,6	7,9	10,6	62,56	7,87	10,42	80
XXIII	72,5—73,5	$C_{14}H_{20}N_2$	77,6	9,5	13,2	77,73	9,32	12,95	65,6
XXIV	215,5—217	$C_{13}H_{20}N_2 \cdot HCl$	Cl 13,8		11,2	Cl 14,03		11,09	66

*XXII and XXIV recrystallized from alcohol, the rest from heptane.

** Found: Cl 13.1%. Calculated: Cl 13.19%.

TABLE 4. 2-(2-R-2-Dimethylaminoethyl)-3-methyl-5-R'-indole Methiodides (XXV-XXVII)

Compound	Mp, °C	Molecular formula	Found, %		Calculated, %	
			I	N	I	N
XXV	226—228	$C_{14}H_{21}IN_2$	36,7	8,0	36,85	8,14
XXVI	225—227	$C_{15}H_{23}IN_2$	35,0	7,6	35,41	7,82
XXVII	219—220	$C_{15}H_{23}IN_2$	35,3	7,7	35,41	7,82

The alcoholic mother liquors were poured into water, basified with ammonia, and extracted with ether. The ether layer was found by gas liquid chromatography to contain XX.

2-(β-Dimethylaminoethyl)-1,3-dimethylindole (XXXII). To a suspension of 0.24 g (0.01 mole) of NaH in 20 ml of anhydrous dimethylformamide was added dropwise a solution of 2 g (0.01 mole) of XX in 15 ml of dimethylformamide. The mixture was stirred for 1 h at ~20°, heated to 35°, and 1.4 g (0.01 mole) of methyl iodide was added dropwise. The mixture was stirred at 35° for 1 h, cooled, poured into water, and extracted with ether. The ether solution was dried, and alcoholic hydrogen chloride was added. The precipitate which separated was filtered off to give 1.7 g (80%) of XXXII hydrochloride, mp 220-221°, identical with a sample obtained as above by mp and R_f on thin layer chromatography.

LITERATURE CITED

1. L. A. Aksanova, N. F. Kucherova, and L. M. Sharkova, KhGS, 995 (1969).
2. L. N. Kakurina, N. F. Kucherova, and V. A. Zagorevskii, ZhOrKh, 1, 1108 (1965).
3. N. M. Sharkova, N. F. Kucherova, S. L. Portnova, and V. A. Zagorevskii, KhGS, 131 (1968).
4. L. A. Aksanova, N. F. Kucherova, S. L. Portnova, and V. A. Zagorevskii, KhGS, 1058 (1967).
5. G. Plancher, Gazz. Chim. Ital., 28, 338 (1898).
6. N. F. Kucherova and N. K. Kochetkov, ZhOKh, 26, 3149 (1956).
7. N. K. Kochetkov, N. F. Kucherova, and I. G. Zhukova, ZhOKh, 36, 924 (1961).