3-FORMYL-2-PYRROLIDONE DERIVATIVES IN THE FISCHER REACTION

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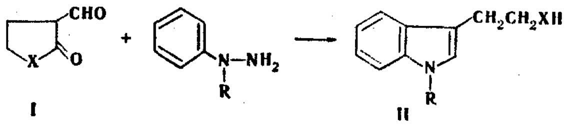
A method for the synthesis of 1-oxo-1,2,3,4-tetrahydro-β-carboline derivatives based on the Fischer reaction of 3-formyl-2-pyrrolidone derivatives with arylhydrazines is proposed.

We have previously shown [1] that α-formyl-γ-butyrolactone (I, X=O) reacts with N_1-substituted phenylhydrazines to give 1-substituted tryptophols II (X=O).



In the present research we have investigated the analogous reaction of 3-formyl-2-pyrrolidone derivatives I (X=N—R), as a result of which we hoped to arrive at tryptamines II (X=N—R). We used the dimer (III) of 1-methyl-3-formyl-2-pyrrolidone and enamines IVa,b as derivatives of this type, since it is known that enamines behave like carbonyl compounds in the Fischer reaction [2]. Enamines IV and dimer III were obtained by Vilsmeier formylation of 1-alkylpyrrolidones [3].

However, we obtained 1-oxo-1,2,3,4-tetrahydro-β-carboline derivatives VI (Tables 1 and 2) in good yields instead of the expected tryptamines when we carried out the reaction of enamines IV and dimer III with both N_1-substituted and N_1-unsubstituted arylhydrazines V. The previously known method for the synthesis of such compounds is a multistep process and is complicated. It is based on the Fischer cyclization of 2,3-dioxopiperidine arylhydrazones, which in turn are obtained via the Japp—Klingemann reaction [4]. In addition, this method does not make it possible to obtain tetrahydro-β-carbolines with substituents in the 2 and 9 positions. Additional steps are required for their synthesis [5].

TABLE 1. Characteristics of 1-Oxo-1,2,3,4-tetrahydro-β-carbolines (VIa-i)

Compound	R	R′	R″	mp, °C	R_f	Found, %		Empirical formula	Calc., %		Yield, % (method)
						C	H		C	H	
VIa	CH_3	H	H	$234^{a,b}$	0.14	72.0	6.2	$C_{12}H_{12}N_2O$	72.0	6.0	60 (A)
VIb	CH_3	H	CH_3	$74^{c,d}$	0.51	73.0	6.5	$C_{13}H_{14}N_2O$	72.9	6.6	68 (A)
VIc	CH_3	H	C_6H_5	160^e	0.47	78.2	5.8	$C_{18}H_{16}N_2O$	78.2	5.8	62 (A)
VId	CH_3	H	$CH_2C_6H_5$	149^f	0.65	78.8	6.2	$C_{19}H_{18}N_2O$	78.6	6.3	80 (A) 62 (B)
VIe	CH_3	6-CH_3	H	273^a	0.13	72.9	6.5	$C_{13}H_{14}N_2O$	72.9	6.6	58 (A)
VIf	CH_3	8-CH_3	H	253^a	0.23	72.8	6.8	$C_{13}H_{14}N_2O$	72.9	6.6	31 (A)
VIg	CH_3	6-OCH_3	H	260^a	0.09	67.7	6.2	$C_{13}H_{14}N_2O_2$ g	67.8	6.1	63 (A)
VIh	n-C_4H_9	H	H	213^a	0.33	73.9	7.6	$C_{15}H_{18}N_2O$	74.3	7.5	60 (A)
VIi	n-C_4H_9	H	$CH_2C_6H_5$	64^c	0.81	79.4	7.4	$C_{22}H_{24}N_2O$	79.5	7.3	60 (A)

[a] From isopropyl alcohol. [b] According to the data in [6], this compound has mp 237-238°C. [c] From hexane. [d] According to the data in [6], this compound has mp 69-71°C. [e] From methanol. [f] From benzene. [g] Found: N 12.1%. Calculated: N 12.2%.

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TABLE 2. UV, IR, PMR, and Mass Spectra of VIa-i

Compound	λ_{max}, nm (lg ε)	ν, cm^{-1}		Chemical shift, δ, ppm					m/e (relative intensity, %)[a]
		NH	C=O	3-H (t)	4-H (t)	R′ (s)	R″ (s)	R	
VIa	227 (4.17) 238 (4.04)[b] 302 (4.11)	3469 3240	1645	3.64	3.00	—	10.55 (H)	3.14 s (CH_3)	201 (9), 200 (64), 158 (6), 157 (43), 156 (5), 130 (15), 129 (100), 128 (15), 102 (12), 101 (7), 77 (7)
VIb	225 (4.28)[b] 230 (4.30) 240 (4.24)[b] 302 (4.19) 327 (3.77)[b]	—	1640	3.40	2.79	—	3.92 (CH_3)	2.91 s (CH_3)	215 (10), 214 (68), 213 (6), 171 (28), 144 (13), 143 (100), 142 (13), 128 (11), 116 (6), 115 (11), 107 (6), 102 (5), 101 (5)
VIc	224 (4.43) 236 (4.30)[b] 302 (4.20) 326 (3.85)[b]	—	1650	3.67	3.08	—		3.04 s (CH_3)	277 (15), 276 (79), 274 (7), 248 (6), 247 (29), 246 (10), 234 (8), 233 (39), 219 (20), 218 (25), 217 (7), 206 (8), 205 (50), 204 (100), 138 (15), 102 (7), 77 (10)
VId	227 (4.25)[b] 231 (4.25) 302 (4.11) 309 (4.07)[b] 327 (3.69)[b]	—	1644	3.56	2.98	—	5.87 (CH_2)	3.05 s (CH_3)	291 (22), 290 (100), 289 (6), 247 (28), 246 (8), 232 (6), 219 (13), 218 (70), 217 (11), 213 (25), 199 (6), 170 (5), 156 (6), 145 (9), 128 (13), 115 (5), 101 (7), 92 (5), 91 (61), 78 (6), 77 (11), 65 (12)
VIe	228 (4.41) 306 (4.28)	3470 3240	1644	3.65	2.98	2.39 (6-CH_3)	9.95 (H)	3.12 s (CH_3)	
VIf	231 (4.41) 239 (4.39)[b] 304 (4.25) 324 (3.87)[b]	3472 3280	1643	3.67	3.04	2.53 (8-CH_3)	10.20 (H)	3.12 s (CH_3)	
VIg	216 (4.53) 221 (4.52)[b] 300 (4.35)b 309 (4.39) 336 (3.83)[b]	3475 3260	1643	3.69	3.03	3.84 (6-OCH_3)	9.63 (H)	3.15 s (CH_3)	
VIh	224 (4.35)[b] 228 (4.36) 240 (4.24)[b] 304 (4.23) 324 (3.83)[b]	3475 3250	1640	3.67 or 3.62	3.02	—	10.96 (H)	1.00 t, 1.10—1.90 m; 3.62 t or 3.67 t (n-C_4H_9)	
VIi	226 (4.37)[b] 232 (4.37) 304 (4.22) 331 (3.78)[b]	—	1644	3.48 or 3.41	2.87	—	5.80 (CH_2)	0.94 t; 1.10—1.60 m; 3.41 t or 3.48 t (n-C_4H_9)	

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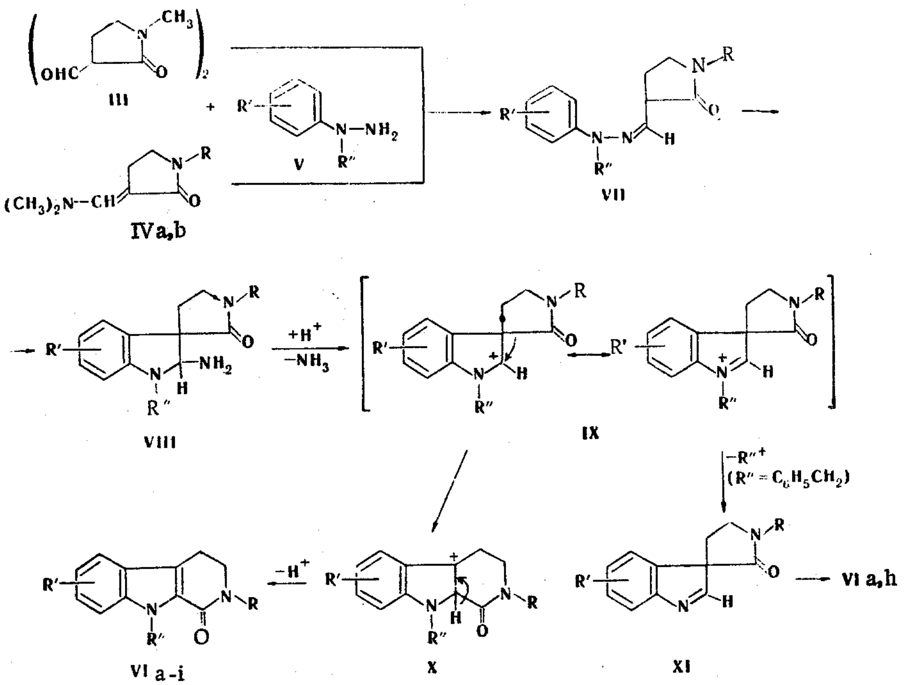
[a] Only the peaks with relative intensities no lower than 5% are indicated. [b] These values correspond to inflections.

The formation of the three-ring β-carboline system in the reaction that we investigated can be represented as follows:



IV a $R=CH_3$; b $R=n\text{-}C_4H_9$; VI a $R=CH_3$, $R'=R''=H$; b $R=R''=CH_3$, $R'=H$; c $R=CH_3$, $R'=H$, $R''=C_6H_5$; d $R=CH_3$, $R'=H$, $R''=C_6H_5CH_2$; e $R=CH_3$, $R'=6\text{-}CH_3$, $R''=H$; f $R=CH_3$, $R'=8\text{-}CH_3$, $R''=H$; g $R=CH_3$, $R'=6\text{-}CH_3O$, $R''=H$; h $R=n\text{-}C_4H_9$, $R'=R''=H$; i $R=n\text{-}C_4H_9$, $R'=H$, $R''=C_6H_5CH_2$

Hydrazone VII is formed in the first step in the reaction of enamines IV or dimer III with the arylhydrazine, after which it undergoes Fischer cyclization to spiroindoline VIII. After protonation of the amino group, spiroindoline VIII loses a molecule of ammonia to give cation IX, which undergoes rearrangement to cation X. The latter is stabilized by the ejection of a proton to give 1-oxo-1,2,3,4-tetrahydro-β-carboline (VI).

This difference in the behavior of formylbutyrolactone (I, X=O) and formylpyrrolidone derivatives III and IV in the Fischer reaction can be explained by the greater resistance of the pyrrolidone ring to acid hydrolysis.

The fact that the corresponding 9-unsubstituted VIa,h are also formed in 10-15% yields as side products in addition to 9-benzyl derivatives VId,i in the reaction of N_1-benzylphenylhydrazine with III and IV may serve as an indirect confirmation of our proposed scheme. In fact, cation IX in the case $R'' = C_6H_5CH_2$ is partially debenzylated to give indolenine XI, which is rearranged to 9-unsubstituted tetrahydro-β-carboline after protonation at the indolenine nitrogen atom. In principle, the rearrangement of cation IX may include migration of either the amide or alkyl part of the spirolactam ring to give, respectively, 1-oxo-β- or 4-oxo-γ-carboline systems. The synthesis by means of our method of the 1-oxo-β-carboline compounds VIa [6] and VIb [5, 6] was evidence that the amide part of the spirolactam ring migrates in this case.

Thus, we have observed a new experimentally simple reaction that makes it possible to obtain 1-oxo-1,2,3,4-tetrahydro-β-carboline derivatives.

EXPERIMENTAL

The IR spectra of solutions of the compounds in chloroform were recorded with a UR-20 spectrometer. The UV spectra of solutions in isopropyl alcohol were recorded with a Hitachi EPS-3T spectrophotometer. The PMR spectra of solutions of the compounds in deuterochloroform were recorded with a Varian XL-100 spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded with a Varian MAT-311 spectrometer. The melting points were measured with a Mettler FP-5 apparatus. Chromatography was carried out in a thin layer of activity II Al_2O_3 in an ether–benzene system (7:3); the chromatograms were developed with iodine vapors.

1-Oxo-1,2,3,4-tetrahydro-β-carbolines (VIa-i). A solution of 0.03 mole of enamine IV [3] (method A) or dimer III [3] (method B) in 10 ml of a 50% solution of isopropyl alcohol in water was added to a solution of 0.03 mole of the hydrochloride or sulfate of the arylhydrazine in a mixture of 35 ml of isopropyl alcohol, 15 ml of water, and 5 ml of concentrated hydrochloric acid, and the mixture was refluxed for 3 h. It was then cooled to room temperature, and the precipitated crystals of VIa,c-h were removed by filtration. In the case of VIb and VIi the reaction mixture was evaporated to dryness with a rotary evaporator, 100 ml of benzene and 100 ml of water were added to the residue, and the mixture was shaken. The benzene layer was separated and filtered through a layer of Al_2O_3, the benzene was removed by evaporation, and the residue was crystallized from hexane.

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RING—CHAIN ISOMERISM OF 3-HYDROXY-3-(2-IMIDAZOLYL)ISOINDOLINONES

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It was established by IR, UV, and PMR spectroscopy that N-unsubstituted and N-(n-alkyl, sec-alkyl, or aryl)-2-(2-imidazolylcarbonyl)benzamides obtained from imidazo[1,2-b]isoquinoline-5,10-dione and ammonia or amines have the 3-hydroxy-3-(2-imidazolyl)isoindolinone chain structure in the crystalline state and in solutions in dimethyl sulfoxide. The N-(tert-alkyl)amides exist in the open form under these conditions. Protonation of the imidazole nitrogen atom in the N-(tert-butyl)amide molecule leads to its cyclization to 3-hydroxyisoindolinone.

It is known [1] that N-unsubstituted and N-monosubstituted 2-acylbenzamides exist in the stable 3-hydroxyisoindolinone chain form. Those cases in which the formation of a hydroxyisoindolinone ring is impossible because of the large volume of the substituent attached to the nitrogen atom or the keto group, as well as because of the strong—I effect of the substituent attached to the nitrogen atom, constitute exceptions.

TABLE 1. 3-Hydroxy-3-(2-imidazolyl)isoindolinones (IIIa-f)

Compound	mp, °C	IR spectra, ν, cm⁻¹			Found, %			Empirical formula	Calc., %			Yield, %
		in Nujol		in DMSO								
		C=O	O—H	C=O	C	H	N		C	H	N	
IIIa	201—202*	1677	3290	1708	61.3	4.7	19.7	$C_{11}H_9N_3O_2$	61.4	4.2	19.5	93
IIIb	187—188	1678 1667	3255 3160	1700	62.9	4.7	18.5	$C_{12}H_{11}N_3O_2$	62.9	4.8	18.3	96
IIIc	186—187	1678	3160	1699	65.0	5.5	17.6	$C_{13}H_{13}N_3O_2$	64.2	5.4	17.3	91
IIId	199—200	1675	3187	1700	65.7	5.9	16.4	$C_{14}H_{15}N_3O_2$	65.4	5.9	16.3	92
IIIe	202—203*	1670	3147	1695	65.1	6.2	15.8	$C_{14}H_{15}N_3O_2$	65.4	5.9	16.3	96
IIIg	196—197	1676	3196	1699	71.2	4.9	13.5	$C_{18}H_{15}N_3O_2$	70.8	5.0	13.8	85
IIIh	190—191	1679	3193	1705	70.2	4.3	14.3	$C_{17}H_{13}N_3O_2$	70.1	4.5	14.4	93
IIIf	205—206*	1689	3183	1706	70.8	5.1	13.5	$C_{18}H_{15}N_3O_2$	70.8	5.0	13.8	95

*With decomposition.

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