REACTION OF ARYLHYDRAZINES WITH α-FORMYLBUTYROLACTAM DERIVATIVES

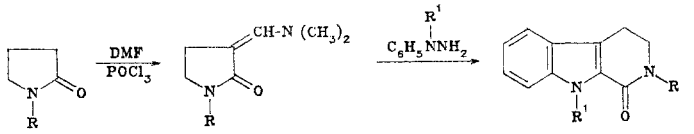
G. P. Tokmakov, T. G. Zemyanova, and I. I. Grandberg

UDC 547.556.8'745'836.3.07:543.422

The Vilsmeier formylation of butyrolactam and of N-phenylbutyrolactam has given their α-dimethylaminomethylene derivatives. The reaction of the latter with α-substituted arylhydrazines leads to the formation of 1-oxo-1,2,3,4-tetrahydro-β-carbolines. When unsubstituted phenylhydrazine is used, the occurrence of a competing reaction leading to β-aminoethyl derivatives of 5-pyrazolone is also possible. It has been established that the direction of the reaction and the ratio of the products are affected by the substituent at the lactam nitrogen atom.

In preceding papers [1, 2] we have reported on a new reaction that we have found for obtaining 1-oxo-1,2,3,4-tetrahydro-β-carbolines (I) which is based on the Fischer reaction of α-formylbutyrolactone derivatives with arylhydrazines. However, in these investigations the reaction was studied only with N-alkyl-substituted lactams, and the corresponding 2-substituted β-carbolines (I)(R = Alk) were obtained. In view of the interest in 1-oxo-1,2,3,4-tetrahydro-β-carboline derivatives connected with their biological activity and their possible further transformation into more complex heterocyclic systems [3-5], we have undertaken a more detailed study of this reaction with the aim of expanding the range of its application.

In the present investigation, we have studied the possibility of synthesizing 2-unsubstituted and 2-aryl-substituted oxocarbolines (I)(R = H, C_6H_5) from the corresponding α-dimethylaminomethylene derivatives of butryolactam (IIa) and of N-phenylbutyrolactam (IIb).



IIa-c Ia-i

I a R=H, $R^1=CH_3$; b R=H, $R^1=C_6H_5$; c R=H, $R^1=CH_2C_6H_5$; d $R=C_6H_5$, $R^1=CH_3$; e $R=R^1=C_6H_5$; f $R=C_6H_5$, $R^1=CH_2C_6H_5$; g R=CHO, $R^1=CH_2C_6H_5$; h $R=C_6H_5$, $R^1=H$; i $R=R^1=H$; II a R=H; b $R=C_6H_5$; c R=CHO

The synthesis of the initial enamines (II) was effected by the Vilsmeier formylation of the corresponding lactams under the action of DMFA and $POCl_3$ by a method analogous to that for the formylation of N-alkyl-substituted lactams [6]. However, the alkaline hydrolysis of the reaction mixture with a saturated solution of potassium carbonate usually used did not give the expected product in the case of the enamine (IIa). In this case, chlorine-containing products were formed which were not identified, together with a small amount (4%) of α-dimethylaminomethylene-N-formyl-γ-butyrolactam (IIc). The enamine (IIa) was obtained by the acid hydrolysis of the reaction mixture and, unlike the N-substituted enamines, proved to be an unstable compound apparently tending to undergo polymerization.

In the reaction of the enamines (IIa-c) with α-substituted phenylhydrazines in aqueous isopropanol, as we expected, the corresponding 9-substituted 1-oxo-1,2,3,4-tetrahydro-β-carbolines (Ia-f) were obtained in good yields. As we have already reported [2], when α-benzylphenylhydrazine is used in reactions of the Fischer type, partial debenzylation takes place and therefore together with the 9-benzyl derivatives (Ic, f) we also isolated the 9-unsubstituted oxocarbolines (Ih, i) with a yield of 3-5%. In the synthesis of the 2-formyl oxocarboline derivative (Ig) in order to prevent the hydrolytic elimination of the formyl group the

K. A. Timiryazev Moscow Agricultural Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 56-60, January 1984. Original article submitted July 11, 1983.

0009-3122/84/2001-0047$08.50

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

Compound	mp, °C	R_f[a]	Found, %		Empirical formula	Calculated, %		Yield, %
			C	H		C	H	
Ia	159—160[b,f]	0,14	71,8	6,1	$C_{12}H_{12}N_2O$	72,0	6,0	70
Ib	249—250[c]	0,12	77,7	5,3	$C_{17}H_{14}N_2O$	77,8	5,4	54
Ic	183—184[d]	0,24	78,6	6,0	$C_{18}H_{16}N_2O$	78,2	5,8	82
Id	133—134[c]	0,69	78,1	5,8	$C_{18}H_{16}N_2O$	78,2	5,8	68
Ie	172—172,5[b]	0,71	82,1	5,6	$C_{23}H_{18}N_2O$	81,6	5,4	76
If	174—174,5[d]	0,80	81,9	5,9	$C_{24}H_{20}N_2O$	81,8	5,7	86
Ig	136—139	0,75	—	—	$C_{19}H_{16}N_2O_2$[e]	—	—	16
Ih	222—223[b]	0,44	77,6	5,4	$C_{17}H_{14}N_2O$	77,8	5,4	64

[a] Benzene—ether (2:1). [b] From benzene. [c] From ethyl acetate. [d] From isopropanol. [e] Found: mol. wt. 304 (mass-spectrometrically). Calculated: mol. wt. 304. [f] According to the literature [9], mp 157-158°C.

TABLE 2. UV, IR, and PMR Spectra of Compounds (I)

Compound	UV spectrum		ν, cm⁻¹		Chemical shifts, ppm					J_{34}, Hz	J_{56}, Hz
	λ_{max}, nm	lg ε	NH	C=O	2-R	3-H (t)	4-H (t)	9-R	5-H (d)		
Ia[a]	230 302 328[b]	4,38 4,16 3,70	3430	1674	6,47 br.s H	3,63	3,02	4,10 s CH_3	7,59	6,5	8,5
Ib[a]	226 302 328[b]	4,46 4,22 3,87	3433	1682	6,08 br.s H	3,63	3,08	7,15—7,55 m C_6H_5	7,66	7,0	7,7
Ic[a]	230 302 328[b]	4,32 4,13 3,70	3482	1675	6,37 br.s H	3,60	3,03	5,89 s CH_2	7,60	6,5	8,0
Id[c,d]	228[b] 233 309	4,45 4,46 4,39		1675	7,38 s C_6H_5	4,08	3,15	4,10 s CH_3	7,60	6,9	8,3
Ie[c,d]	220 240 308	4,54 4,42 4,46		1660	7,10—7,50 m C_6H_5	4,18	3,23	7,10—7,50 m C_6H_5	7,66	6,7	8,4
If[c,d]	234 310	4,47 4,43		1660	7,10—7,45 m C_6H_5	4,12	3,21	5,93 s CH_2	7,64	6,9	8,0
Ig[c]	242 315 340[b]			1693 ум.	9,18 s CHO	3,81	2,80	5,50 s CH_2	7,33	6,5	8,4
Ih[a]	226 240[b] 310	4,43 4,30 4,44	3475 3270	1685	6,75—7,35 m C_6H_5	3,84	2,88	10,38 s H		6,5	

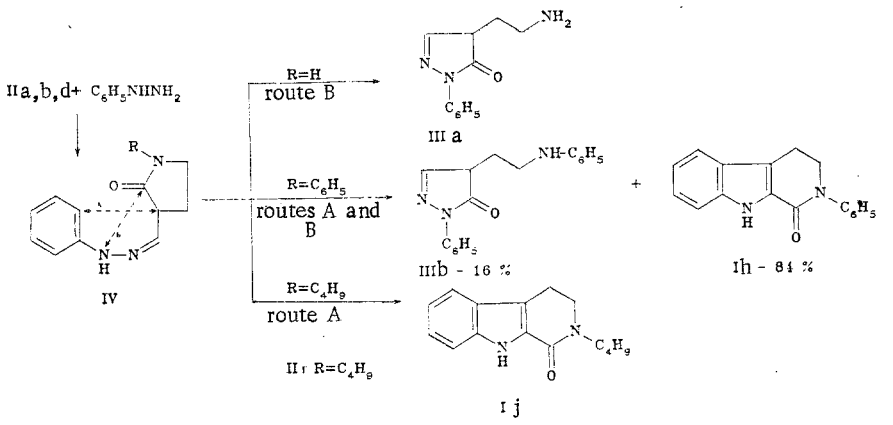
[a] IR spectrum taken in CH_2Cl_2. [b] Shoulder. [c] IR spectrum taken in a KBr tablet. [d] PMR — 250 MHz.

reaction was performed in anhydrous dioxane. In this case, because of the use of small amounts of the starting materials and of the low yield, it was impossible to isolate the debenzylated product. Suggested mechanisms of the formation of oxocarbolines and of the debenzylation process have been given previously [2]. The characteristics and spectral features of the oxocarbolines obtained in the present investigation are given in Tables 1 and 2.

In an attempt to synthesize the unsubstituted oxocarboline (Ii) by the reaction of the enamine (IIa) with unsubstituted phenylhydrazine, we obtained only 4-(2-aminoethyl)-1-phenyl-5-pyrazolone (IIIa), and it was impossible to detect the expected oxocarboline in the reaction mixture. Consequently, in this case the α-formylbutryolactam phenylhydrazone first formed (IV, R = H) then cyclizes not in the "Fischer" manner (route A) but by analogy with the cyclization of β-oxo ether hydrazones with the formation of pyrazolones (route B). A similar cyclization has also been observed for α-acetylbutyrolactone phenylhydrazone [7] but has not been reported for the phenylhydrazones of N-alkyl-substituted formyllactams. This induced us to

make a careful analysis, also, of the mixtures obtained on the reaction of phenylhydrazine with other amines — (IIb and d).

As a result, it was found that in this reaction the enamine (IIb, R = C_6H_5) gives both the oxocarboline (Ih) and the pyrazolone (IIIb) in a ratio of 84:16, while the enamine IId, (R = n-C_4H_9) gives only the oxocarbolines (Ij).



It can be seen from the results obtained that the substituent R has a very pronounced influence on the direction of the cyclization of the phenylhydrazones (IV). Although the set of substituents studied in the present work is not very large, nevertheless it is possible to conclude that in the interaction of enamines of α-formylbutyrolactam (II) with phenylhydrazine electron-donating and voluminous substituents at the lactam nitrogen atom will favor the Fischer reaction and the formation of 1-oxo-1,2,3,4-tetrahydro-β-carboline derivatives (I), and, conversely, electron-accepting substituents and those not causing steric hindrance will favor the formation of the pyrazolone derivative (III).

EXPERIMENTAL

IR spectra were taken on a UR-20 instrument in KBr tablets or in CH_2Cl_2 solution, UV spectra on a Hitachi EPS-3T instrument in isopropanol, and PMR spectra on a Bruker CXP (200 MHz) and Bruker WM (250 MHz) instruments in $CDCl_3$ with TMS as internal standard. Mass spectra were obtained on a Varian MAT-311A instrument, the peaks of ions with intensities greater than 10% being given. R_f values were determined on Silufol UV-254 plates, the spots being revealed in UV light or with iodine vapor.

Compound (IId) was obtained as described previously [6].

α-Dimethylaminomethylene-γ-butyrolactam (IIa). With vigorous stirring and cooling in an ice bath, 8.5 g (0.1 mole) of γ-butyrolactam and 17.6 g (0.24 mole) of DMFA in 50 ml of absolute benzene were added to a solution of 52.2 g (0.34 mole) of $POCl_3$ in 70 ml of absolute benzene. The reaction mixture was boiled with continuous stirring (two layers formed) for 6 h, the benzene was evaporated off, and the residue was heated at 80°C for 1 h and was cooled. The resulting mass was carefully treated with 30 ml of water, and the mixture was stirred and left at room temperature for 2 h. Then the solution was neutralized with an excess of anhydrous potassium carbonate until the water had been bound and a viscous mass had been formed, and this was extracted several times with chloroform with decantation, and the combined extracts were dried over $MgSO_4$ and evaporated. The residue was extracted with hot benzene and the benzene was evaporated off, and the resulting oil, on standing in the refrigerator, deposited crystals, which were filtered off and recrystallized from benzene, the residual oil being distilled in vacuum. This gave 4.5 g of the initial butyrolactam and 2.5 g of the enamine (IIa). Yield 38% (on the butyrolactam that reacted), mp 163°C. IR spectrum (KBr; cm^{-1}): 3200 (NH), 1690 (C=O), 1627 (C=C). UV spectrum, λ_{max} (nm; log ε); 212 (3.64); 290 (4.38). PMR spectrum (100 MHz; ppm): 2.97 [6H, s $(CH_3)_2N$]; 3.03 (2H, m, β-CH_2); 3.39 (2H, t, J = 7.5 Hz, γ-CH_2); 6.77 (1H, broad s, NH); 6.85 (1H, t, J = 1.8 Hz, C=CH-N). Mass spectrum, m/z (%): 140 (30), 125 (79), 123 (13), 111 (33), 110 (15), 98 (19), 97 (23), 96 (44), 94 (11), 84 (18), 83 (50), 82 (100), 81 (13), 80 (15), 70 (13), 69 (15), 68 (48), 67 (25). Found: C 60.0; H 8.6%; M^+ 140. $C_7H_{12}N_2O$. Calculated: C 59.9; H 8.6%; mol. wt. 140. It gave a blue-green coloration with $FeCl_3$.

α-Dimethylaminomethylene-N-formyl-γ-butyrolactam (IIc). This was obtained in a similar manner to (IIa) from the same amounts of starting materials, with the exception of the fact that the reaction mixture, after being kept at 80°C for 1 h and cooling, was hydrolyzed with 20 ml of saturated K_2CO_3 solution, and then powdered K_2CO_3 was added until the evolution of CO_2 had ceased and the water had been bound. The resulting mass was extracted with chloroform, the extract was dried over $MgSO_4$, the chloroform was evaporated off, and the residue was distilled in vacuum. Fractions containing chlorinated products and giving no color reaction with $FeCl_3$ were not identified. Fractions boiling at 150-160°C (3 hPa) crystallized, and consisted of the enamine (IIc). Yield 0.6 g (4%), mp 130°C (from methanol). R_f 0.75 (acetone). IR spectrum (KBr, cm^{-1}): 1707 (aldehyde C=O), 1680 (lactam C=O), 1630 (C=C). UV spectrum, λ_{max} (nm; log ε): 230 (3.95), 328 (4.54). PMR spectrum (100 MHz; ppm): 3.02 (2H, m, β-CH_2); 3.14 [6H, s, $(CH_3)_2N$]; 3.69 (2H, t, J = 7.5 Hz, γ-CH_2); 7.26 (1H), t, J = 1.5 Hz, C=CH-N); 9.09 (1H, s, CHO). Mass spectrum, m/z (%): 168 (59), 140 (39), 139 (13), 125 (12), 123 (14), 111 (20), 110 (58), 97 (15), 96 (16), 95 (13), 85 (12), 83 (47), 82 (100), 81 (15), 71 (17), 69 (21), 68 (21), 67 (20). Found: C 57.2; H 7.3%; M^+ 168. $C_8H_{12}N_2O_2$. Calculated: C 57.1; H 7.2%; mol. wt. 168. It gave a blue coloration with $FeCl_3$.

α-Dimethylaminomethylene-N-phenyl-γ-butyrolactam (IIb). This was obtained in a similar manner to (IIc) from 22.4 g (0.15 mole) of N-phenyl-γ-butyrolactam, 11 g (0.15 mole) of DMFA, and 46.1 g (0.3 mole) of $POCl_3$. After evaporation of the chloroform, the residue was crystallized from benzene, which yielded 11.3 g (35%) of the enamine (IIb), mp 173°C. IR spectrum (in CH_2Cl_2; cm^{-1}): 1730 (C=O), 1668 (C=C). UV spectrum, λ_{max} (nm; log ε): 236 (3.59 shoulder), 2.54 (3.53), 318 (4.52). PMR spectrum (200 MHz; ppm); 2.53 [6H, s, $(CH_3)_2N$]; 2.58 (2H t, J = 7.5 Hz, β-CH_2); 3.29 (2H, t, J = 7.5 Hz, γ-CH_2); 6.60 (2H, m, C=CH-N and the p-proton in C_6H_5); 6.89 (2H, t, J = 7.5 Hz, the m-protons in C_6H_5); 7.27 ppm (2H, d, J = 7.8 Hz, the o-protons in C_6H_5). Found: C 72.2; H 7.5%. $C_{13}H_{16}N_2O$. Calculated: C 72.2; H 7.5%.

General Procedure for Obtaining the 1-Oxo-1,2,3,4-tetrahydro-β-carbolines (Ia-f). A solution of 5 mmole of the hydrochloride or sulfate of an α-substituted phenylhydrazine and 5 mmole of the enamine (IIa) or (IIb) in a mixture of 35 ml of isopropanol, 5-10 ml of water, and 1 ml of concentrated HCl was boiled for 3 h, and cooled, and the crystals of the carbolines (Ie, f) that deposited were filtered off. In the other cases the reaction mixture was evaporated to dryness, the residue was dissolved in 30 ml of chloroform, the solution was washed with dilute HCl and then with water, and the organic layer was dried over $MgSO_4$ and the chloroform was evaporated. The residue was recrystallized from a suitable solvent (Table 1).

From the mother liquor after the isolation of the carboline (Ic) 50 mg (5%) of unsubstituted 1-oxo-1,2,3,4-tetrahydro-β-carboline (Ii) was isolated chromatographically (column 25 × 1 cm containing silica gel 40/100 μ, with ether as the eluent), mp 189°C; M^+ 186. According to the literature [8], mp 188-189°C.

The filtrate obtained after the separation of the carboline (If) was evaporated to dryness, the residue was dissolved in chloroform, and the solution was washed with dilute HCl and with water and was dried over $MgSO_4$. The chloroform was evaporated off and the residue was crystallized from benzene to give the carboline (Ih). Yield 3%, mp 218°C. A mixture with an authentic sample gave no depression of the melting point.

9-Benzyl-2-formyl-1-oxo-1,2,3,4-tetrahydro-β-carboline (Ig). A drop of concentrated H_2SO_4 was added to a solution of 0.17 g (1 mmole) of the enamine (IIc) and 0.24 g (1 mmole) of α-benzylphenylhydrazine hydrochloride in 50 ml of absolute dioxane, and the resulting solution was boiled for 6 h, the dioxane was evaporated off, the residue was dissolved in chloroform, the solution was washed with dilute HCl and with water and was dried over $MgSO_4$, and the chloroform was evaporated off. The residue was chromatographed on a column (23 × 2 cm) of silica gel 40/100 μ with chloroform as the eluent. This gave 50 mg of the carboline (Ig) (Tables 1 and 2).

4-(2-Aminoethyl)-1-phenyl-5-pyrazolone Hydrochloride (IIIa·HCl). A solution of 1.40 g (0.01 mole) of the enamine (IIa) and 1.45 g (0.01 mole) of phenylhydrazine hydrochloride in a mixture of 60 ml of isopropanol, 20 ml of water, and 3 ml of concentrated HCl was boiled for 3 h, the solvents were evaporated off, and the residue was dissolved in 30 ml of 10% HCl. The resulting acid solution was washed several times with chloroform to eliminate impurities, and then the medium was made strongly alkaline with a concentrated solution of NaOH, and the alkaline solution was likewise washed with chloroform, after which it was neutralized with

HCl to pH 7. The neutral solution was evaporated to dryness in vacuum, the residue was extracted with isopropanol, the alcohol was evaporated off, and the crude product was recrystallized from propanol. This gave 1.45 g (61%) of the hydrochloride of the pyrazolone (IIIa), mp 220°C. R_f 0.72 (methanol–25% ammonia (3:1)). IR spectrum (in CH_2Cl_2; cm^{-1}): 3450, 3390 (NH_2, NH_3^+), 1720 (C=O). UV spectrum, λ_{max} (nm; log ε): 248 (3.94), 296 (3.20) shoulder. PMR spectrum (200 MHz, DMSO-d_6; ppm): 2.74 (2H, t, J = 7.2 Hz, 4-CH_2–); 3.02 (2H, t, J = 7.2 Hz, –CH_2–N); 3.80 (1H, br.s, OH); 7.26 (1H, t, J = 7.0 Hz, p-proton in C_6H_5); 7.48 (2H, t, J = 7.0 Hz, m-protons in C_6H_5); 7.60 (1H, s, 3-H); 7.77 (2H, d, J = 7.0 Hz, o-protons in C_6H_5); 8.25 (3 H, br.s, NH_3^+). Found: C 55.2; H 5.9%. $C_{11}H_{13}N_3O \cdot HCl$. Calculated: C 55.1; H 5.9%.

1-Oxo-2-phenyl-1,2,3,4-tetrahydro-β-carboline (Ih) and 1-Phenyl-4-(2-phenylaminoethyl)-5-pyrazolone (IIIb). These were obtained under the same conditions as (IIIa·HCl) from 3.06 g (0.015 mole) of the enamine (IIb) and 2.25 g (0.015 mole) of phenylhydrazine. After the reaction mixture had cooled, it deposited crystals of the carboline (Ih), which were filtered off and recrystallized from benzene, giving a yield of 1.8 g. The filtrate from the reaction mixture and the mother solution were combined, the solvents were evaporated off, and the residue was dissolved in 30 ml of 10% HCl. The acid solution was extracted with chloroform, the chloroform was evaporated, and the residue was crystallized from benzene, which gave another 0.7 g of the carboline (Ih) (total yield and characteristics are given in Tables 1 and 2). Then the acid solution was made strongly alkaline with NaOH, washed free from impurities with chloroform, and neutralized with dilute HCl. The precipitate that deposits was extracted with chloroform, and the extract was dried over $MgSO_4$ and evaporated to give 0.5 g (12%) of the pyrazolone (IIIb), mp 154°C (from methanol). R_f 0.57 (ether). IR spectrum (in KBr; cm^{-1}): 3430, 3360 (NH). UV spectrum, λ_{max} (nm; log ε); 247 (4.48), 284 (3.00) shoulder. PMR spectrum (200 MHz, ppm): 2.41 (2H, t, J = 5.6 Hz, 4-CH_2); 3.03 (2H, t, J = 5.6 Hz, –CH_2–N); 5.25 (2H, br.s, NH and OH); 6.50-7.40 (11H, m, arom. protons and 4-H). Mass spectrum, m/z (%): 279 (5), 174 (13), 167 (14), 151 (10), 145 (14), 137 (11), 133 (15), 127 (12), 125 (21), 123 (24), 120 (11), 119 (32), 113 (17), 112 (10), 111 (40), 110 (15), 109 (30), 107 (14), 106 (43), 105 (28). Found: C 73.1; H 6.1; N 15.2%; M^+ 279. $C_{17}H_{17}N_3O$. Calculated: C 73.1; H 6.1; N 15.0%; mol. wt. 279.

2-n-Butyl-1-oxo-1,2,3,4-tetrahydro-β-carboline (Ij). This was obtained under the same conditions as the carbonyl (Ih) from 3 g (0.015 mole) of the enamine (IId) [6] and 2.25 g (0.015 mole) of phenylhydrazine. Yield 60%, mp 212°C (from isopropanol). According to the literature [2], mp 213°C.

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