acid chloride IIb was added dropwise with stirring for 30 min. The reaction mixture was stirred for 5 h more at 20°C. Pyridine hydrochloride was filtered off, and the filtrate was evaporated in the vacuum of an aspirator. The residue was boiled with 150 ml of petroleum ether. After cooling of the extract, the precipitate was filtered off and crystallized from the appropriate solvent. Proton NMR spectrum of compound IVb: 3.87 (3H, singlet, OCH_3); 6.57 (1H, quadruplet, 4-H of furan); 6.75 (1H, singlet, =CH); 6.86 (1H, singlet, 5-H); 7.29...7.65 (7H, multiplet C_6H_5, 3-, 5-H of furan); 8.55 ppm (1H, singlet, 2-H).

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REACTIONS OF ARYLHYDRAZINES WITH α-FORMYL DERIVATIVES OF SIX- AND SEVEN-MEMBERED RING LACTAMS

G. P. Tokmakov and I. I. Grandberg

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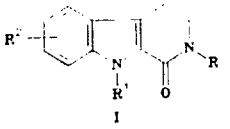
Reactions of α-formyl derivatives of N-methyl-δ-valerolactam and N-methyl-ε-caprolactam with arylhydrazines lead to the formation of 3,4,5,10-tetrahydroazepino[3,4-b]indole-1(2H)-one and 2,3,4,5,6,11-hexahydro-1H-azocino[3,4-b]indol-1-one derivatives. As the size of the lactam ring is increased the role of competing reactions, such as dealkylation at the indole nitrogen atom and the formation of 5-pyrazolone via reaction with α-unsubstituted phenylhydrazine, also increases.

In previous papers [1, 2] we have investigated the reactions of α-formyl-γ-lactam enamines with arylhydrazines, which lead to a series of 1-oxo-1,2,3,4-tetrahydro-β-carbolines I in high yields.



I

It was of interest to us to expand the scope of these reactions to include formyllactam derivatives of greater ring size. Success in this area would provide an approach to the preparation of azepino[3,4-b]indole derivatives, which are interesting from the point of view of their biological activity, as well as to derivatives of a previously unknown heterocyle, namely, azocino[3,4-b]-indole.

In the present paper we have examined the reactions of arylhydrazines with α-hydroxymethylene-N-methyl-δ-valerolactam (II), α,α'-hydroxybis(1-methyl-3-methylene-2-piperidone) (III), and an enamine of α-formyl-N-methyl-ε-caprolactam (IV), prepared via Villsmaier formylation of the corresponding N-methyllactams [3].

K. A. Timiryazev Moscow Agricultural Academy, Moscow.

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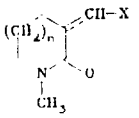
TABLE 1. Effect of α-Formyllactam Ring Size on the Ratio of Normal and Dealkylated Reaction Products I, V, and VI

Starting lactam	n	Reaction products		Yield, %		R^1=Alk / R^1=H
		R^1=Alk	R^1=H	R^1=Alk	R^1=H	
 X = OH, $N(CH_3)_2$	0*	I ($R^1=CH_2C_6H_5$)	I	80	7	11
	1	Vb ($R^1=CH_2C_6H_5$)	Va	57	8	7
	2	VIb ($R^1=CH_2C_6H_5$)	VIa	45	17	3
	2	VIc ($R^1=CH_3$)	VIa	40	19	2

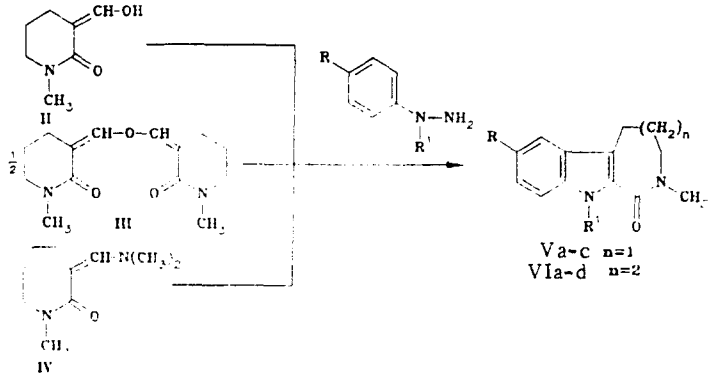
*Data taken from [1].

TABLE 2. Physical Characteristics of 3,4,5,10-Tetrahydroazepino[3,4-b]Indol-1(2H)-ones (V) and 2,3,4,5,6,11-Hexahydro-1H-azocino[3,4-b]indol-1-ones (VI)

Compound	R_f	mp, °C	Found, %		Molecular formula	Calculated, %		Yield, % (method)
			C	H		C	H	
Va	0,25	238*1, *2	73,0	6,7	$C_{13}H_{14}N_2O$	72,9	6,6	55 (A)
Vb	0,54	139*1	78,7	6,7	$C_{20}H_{20}N_2O$	78,9	6,6	57 (A) 70 (B)
Vc	0,25	232*1	73,1	7,0	$C_{14}H_{16}N_2O$	73,7	7,1	76 (A)
VIa	0,22	210*3	74,1	7,2	$C_{14}H_{16}N_2O$	73,7	7,1	10
VIb	0,50	78*4	79,4	6,9	$C_{21}H_{22}N_2O$	79,2	7,0	45
VIc	0,28	68	74,4	7,5	$C_{15}H_{18}N_2O$	74,3	7,5	40
VId	0,35	123*5	78,9	7,7	$C_{20}H_{20}N_2O$	78,9	6,6	45

*1From isopropyl alcohol.
*2According to [4], mp 237-238°C.
*3From benzene.
*4From a mixture of petroleum ether–cyclohexane.
*5From hexane.

Reactions of lactams II-IV with arylhydrazines gave the expected results. Heating the reaction components in an aqueous alcohol solution in the presence of sulfuric acid led to the formation of derivatives of 3,4,5,10-tetrahydroazepino[3,4-b]indol-1(2H)-one (V) in the case of the six-membered ring lactams II and III, and to derivatives of 2,3,4,5,6,11-hexahydro-1H-azocino[3,4-b]indole-1-one (VI) in the case of the α-formylcaprolactam enamine IV.



V a R=R¹=H; b R=H, R¹=$CH_2C_6H_5$; c R=CH_3, R¹=H; VI R=H, a R¹=H; b R¹=$CH_2C_6H_5$; c R¹=CH_3; d R¹=C_6H_5

The mechanism of formation of azepino- and azocinoindoles V and VI is apparently completely analogous to the mechanism of formation of their homologs, β-carboline derivatives I; the scheme proposed for the synthesis of these derivatives [1] involves two sequential rearrangements: Fisher reaction and lactam ring expansion. In the synthesis of azepino- and azocinoindoles Vb and VIb which are benzyl-substituted at the indole nitrogen atoms, as in the synthesis of the analogous β-carbolines, the corresponding unsubstituted compounds Va and VIa are also formed as by-products. In this regard, the amount of the debenzylated

TABLE 3. UV, IR, and PMR Spectra of Compounds V and VI

Compound	UV spectrum		IR spectrum,* ν, cm⁻¹		PMR spectrum,** δ, ppm (J, Hz)					
	λ_{max}, nm	lg ε	NH	C=O	2-CH_3 (s, 3H)	3-H (m)	4-H (m, 2H)	5-H (2H)	R¹	other protons
Va	228, 300	1,33; 4,20	3460 free 3300 assoc.	1613	3,24	3,58 (2H)	2,21	3,08 t (J=7,0)	9,47 br s (1H, H)	7,58 d, 1H, 6-H ($J_{6,7}$=8,1); 7,11 t, 1H, 7- or 8-H (J=8,1); 7,29 t, 1H, 8- or 7-H (J=8,1); 7,41 d, 1H, 9-H ($J_{8,9}$=8,1)
Vb	225, 297	4,37; 4,18	—	1642	3,07	3,28 (2H)	1,90 ... 2,24	2,98 t (J=7,5)	5,68 s (2H, CH_2)	7,56 m, 1H, 6-H; 6,90 ... 7,30 m, 8H, 7-, 8-, 9-H, and benzene ring protons
Vc	230, 301	4,31; 4,18	3470 free 3310 assoc.	1615	3,23	3,55 (2H)	2,18	3,03 t (J=6,5)	9,52 br s (1H, H)	7,33 br s, 6-H; 2,14 s, 3H, 7-CH_3; 7,11 br d, 1H, 8-H ($J_{8,9}$=8,3); 7,31 d, 1H, 9-H
VIa	225, 240 sh., 297	1,50; 4,32; 4,21	3160 free 3290 assoc.	1622	3,14	3,58 ... 3,76 (2H)	1,65 ... 2,20 m		9,58 br s (1H, H)	2,90 ... 3,08 m, 2H, 6-H; 6,95 ... 7,60 m, aromatic protons
VIb	222, 294	4,46; 4,09	—	1626	2,91	3,68 (1H)	1,10 ... 2,00 m		5,30 d (1H) and 5,54 d (1H) (CH_2, J=15,0)	2,75 ... 3,05 m, 3H, 3'-H and 6-H; 7,40 d, 1H, 7-H ($J_{7,8}$=7,7); 6,95 ... 7,30 m, 8H, 8-, 9- 10-H, and benzene ring protons
VIc	226, 295	4,51; 4,16		1650	3,03	3,97 (1H)	1,55 ... 2,00 m		3,74 s (CH_3)	2,70 ... 3,30 m, 3H, 3'-H and 6-H; 7,37 br d, 1H, 7-H ($J_{7,8}$ =7,8); 6,96 ddd 1H, 8- or 9-H (J_1 7,8; J_2 6,3; J_3 1,6); 7,13 t. d, 9- or 8-H (J_1=8,4; J_2= 1,0); 7,18 br d, 10-H
VId	212, 256, 291, 312 sh	1,47; 4,10; 4,10; 3,91	—	1650	2,93	4,13 (1H)	1,45 ... 2,10 m		(C_6H_5)	2,80 ... 3,40 m, 3H, 3'-H and 6-H; 6,65 ... 7,50 m, 9H, aromatic protons

*IR spectra of compounds Vb, VIc, d were taken in CCl_4.

**The PMR spectrum of compound VIb was recorded in CCl_4. For compounds Vb and VIa PMR spectra were recorded at 100 MHz; all other spectra were recorded at 250 MHz.

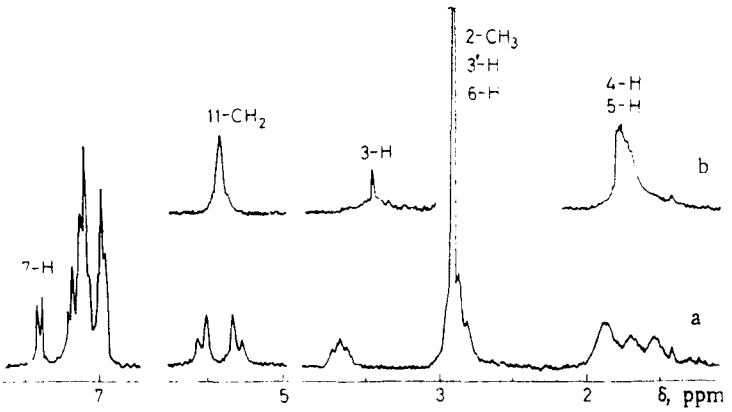
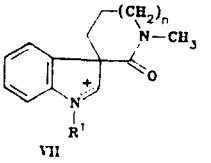


Fig. 1. PMR spectrum of 2-methyl-11-benzyl-2,3,4,5,6,11-hexahydro-1H-azocino-[3,4-b]indol-1-one (VIb) in CCl_4 (250 MHz): a) at room temperature; b) at 70°C.

compound increases as the size of the lactam ring is increased. In addition, in the synthesis of 11-methylazocinoindole VIc, demethylation at the phenylhydrazine α-nitrogen atom is also observed, which was not detected in the reaction of the analogs containing smaller lactam rings (Table 1).

Compounds Vb and VIb, which are alkylated at the indole nitrogen atom, do not undergo dealkylation under the reaction conditions; this was confirmed in an independent set of experiments. The dealkylation process apparently takes place in the intermediate spirocation VII, in which the amide functional group exerts an anchimeric effect assisting dealkylation. As the size of the lactam ring is increased its conformational freedom (flexibility) increases as well and the most favorable conformation for this type of anchimeric assistance becomes more probable.



VII

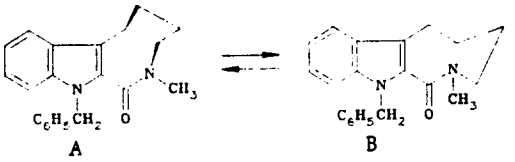
Of the two possible modes for rearrangement of cation VII, namely, migration of the amide or alkyl portion of the spirolactam ring, only the first pathway, leading to the formation of 1-oxo-derivatives of azepino- and azocinoindoles V and VI, is realized; the same observation was made in the case of the synthesis of β-carbolines I as well [1, 2]. Evidence for this conclusion is provided by the synthesis along the proposed reaction pathway of compound Va, which is a known compound that has been prepared by a different method [4]. In no cases were isomeric substances, arising via migration of the alkyl portion of the lactam ring, observed in the reaction products. These types of regioselective rearrangements, in which an electron withdrawing group migrates preferentially (or even exclusively) to an electron deficient center, are known, although not widespread. For example, in the rearrangement of α,β-epoxyketones only the acyl group is observed to migrate as long as certain geometric structural requirements are met [5]. It has also been shown that in classical rearrangement processes, such as the pinacol—pinacoline [6] and Wagner—Meerwein rearrangements, preferential or predominant migration of an ethoxycarbonyl [7] or carboxyl group [8] is possible. One factor which has been proposed to account for the preferential migration of electron withdrawing groups in cationic rearrangements is the formation of a more stable rearranged cation, in which the positive charge is far removed from the site of positive charge. An alternative explanation has also been proposed, based on the assumption that π-electrons in multiple bonds (among them C=O bonds) in these types of migrating (electron withdrawing) groups are capable of participation in a stabilization of the transition state [5]. The rearrangement elucidated herein represents another example of the migration of an (electron) withdrawing group to a site of positive charge, and the observed regioselectivity may be rationalized in terms of these hypotheses.

The physical characteristics of the newly prepared azepino- and azocinoindoles V and VI, and the spectral data confirming the assigned structures, are summarized in Tables 2 and 3.

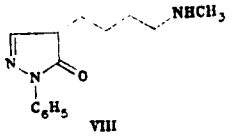
The PMR spectral patterns of the 11-substituted azocinoindoles and especially the spectrum of the 11-benzyl derivative VIb were somewhat unexpected (Fig. 1). The benzyl protons in compound VIb appear as two doublets with geminal SSCC of 15 Hz; this was not observed in the spectra of their homologs I and V containing smaller lactam rings. The protons in the 3-position also have different chemical shift values, and in the 3.69 ppm region, which is characteristic of these protons, only one proton is observed; the signal of the second (3-) proton coincides with the 6-position and methyl group protons. All of the lactam proton signals appear as broad unresolved bands. The form of the nonaromatic portion of the spectrum changes significantly as the spectral recording temperature is raised to 70°C. The lactam ring proton signals become narrower and the doublets due to the benzyl protons coalesce into a singlet.

These temperature-dependent PMR spectral changes can be interpreted in terms of hindered rotation of the benzyl group. However, comparison of the IR and UV spectral data for β-carbolines I, and the azepino- and azocinoindoles V and VI, reveals that as the size of the lactam ring is increased the three-dimensional structure of the two conjugated fragments, namely the indole ring and amide functional group, is practically invariant. In fact, the absorption frequency corresponding to the amide carbonyl stretching vibration (Table 3) decreases normally with increasing ring size ($\nu_{C=O}$ for compound I with $R^1 = CH_2C_6H_5$ is equal to 1644 cm^{-1} [1]). In contrast, the positions of the absorption maxima and intensities of the long-wavelength bands in the UV spectra of β-carboline (I) ($R^1 = CH_2C_3H_5$; λ_{max} 302 nm, log ε 4.11 [1]) and of azepino- and azocinoindoles are quite similar, which suggests that conjugation is retained in these compounds. Based on these results, we would not expect (conformational) hindrance to free rotation of the benzyl group to increase as the size of the lactam ring is increased.

A second, more probable explanation for the observation that the benzylic protons appear in the form of doublets in the PMR spectrum (of VIb) is that these protons are diastereotopic. Molecular chirality of the azocinoindole, which is necessary for the appearance of diastereotopicity, apparently arises due to slow (within the NMR time scale) conversion of the lactam ring (A ⇄ B) at room temperature; this is indicated as well by the very broad line widths observed for the lactam ring protons.



The drastically reduced yield of the 11-substituted azocinoindole VIa (10%) in the reaction of enamine IV with α-unsubstituted phenylhydrazine is also worthy of note. It was found that in this case two competing reactions occurred paralled with one another, namely, Fisher rearrangement to give the azocinoindole, and a reaction leading to the formation of pyrazolone VIII.



VIII

Unfortunately, other N-alkyllactams with smaller ring sizes did not react in this manner, although butyrolactams with other substituents attached to the nitrogen atom did give pyrazolones [2]; the amount of pyrazolone formed in the reaction products was found to depend very strongly on the nature of the substituent present (at the nitrogen atom). It is clear from these results that both the substituent attached to the lactam nitrogen atom as well as the size of the lactam ring affect the reaction pathway and hence the product ratio (indole versus pyrazolone). An increase in the size of the lactam ring facilitates pyrazolone formation.

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer using chloroform solutions; UV spectra were measured on a Hitachi EPS-3T spectrophotometer using isopropyl alcohol solutions,

PMR spectra were obtained on a Varian XL-100 or Bruker WM-250 spectrometer using deuterochloroform solutions and TMS as internal standard. Mass spectra were recorded on a Varian MAT-311A spectrometer; only peaks with intensities greater than 10% are reported. Melting points were measured on a Mettler FP-5 melting point apparatus. Chromatography was performed on Silufol UV-254 plates using benzene—ether, 1:1, as eluent; the chromatograms were visualized either with UV light or iodine vapor.

Compound II-IV were prepared according to [3].

General Method for the Synthesis of 3,4,5,10-Tetrahydroazepino[3,4-b]-indol-1(2H)-ones (Va-c) and 2,3,4,5,6,11-Hexahydro-1H-azocino[3,4-b]indol-1-ones (VIa-d). To a solution of 2.1 mmoles of arylhydrazine hydrochloride or sulfate in a mixture of 8 ml ethyl alcohol, 2 ml water, and 0.2 ml conc. H_2SO_4 was added a solution of 2 mmoles lactam II (method A), IV, or 1 mmole of ether III (method B) in 4 ml of 50% ethanol. The mixture was refluxed for 4 h and then cooled. The resulting crystals of compounds Va-c and VIa which precipitated out of solution were filtered and recrystallized from the appropriate solvent (see Table 2). In the case of compound VIb the crystalline precipitate of the side product VIa was removed by filtration first, and the filtrate was evaporated to dryness under vacuum; the residue was treated with equal volumes of ether (to 20 ml) and water, shaken, and the ether layer separated, filtered through a layer of Al_2O_3, and evaporated. The residue was crystallized from a mixture of petroleum ether—cyclohexane. Compounds VIc, d were purified by chromatography on a 27 × 1.5 cm column filled with 40/100 μm silica gel with benzene—ether, 3:1, as eluent. The physical constants and spectral characteristics of these compounds are summarized in Tables 2 and 3. Mass spectrum of azocinoindole VIa, m/e (I, %): 228 (32), 213 (13), 271 (13), 169 (17), 168 (10), 156 (13), 143 (44), 130 (19), 129 (27), 128 (18), 125 (13), 115 (14), 102 (13), 81 (17), 79 (16), 78 (100), 77 (46).

2-Methyl-2,3,4,5,6,11-hexahydro-1H-azocino[3,4-b]indol-1-one (VIa) and 4-(4-Methylaminobutyl)-1-phenylpyrazol-5-one (VIII). A solution of 3.6 g (20 mmole) enamine IV and 2.9 g (20 mmole) phenylhydrazine hydrochloride in a mixture of 55 ml alcohol, 20 ml water, and 0.7 ml conc. H_2SO_4 was refluxed for 6 h, cooled, and evaporated to dryness under vacuum. The residue was dissolved in 30 ml chloroform and dilute HCl (1:1), shaken, and the organic layer was separated. The organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was recrystallized from benzene. Yield 0.46 g (10%) of azocinoindole VIa; the sample of VIa prepared in this way did not give a melting point depression with a sample of VIa obtained as a side product in the synthesis of 11-alkyl-substituted azocinoindoles VIb and c. The acidic aqueous layer was basified with 30% KOH solution until the initially formed precipitate had dissolved completely (pH 11). The alkaline solution was then washed with chloroform to remove neutral impurities and neutralized with HCl to pH 7 and evaporated under vacuum. The residue was extracted with chloroform and the extract dried over $MgSO_4$ and evaporated; the remaining viscous oil was triturated with absolute ether and filtered. Yield 2.1 g (43%) of pyrazolone VIII in the form of an amorphous powder, R_f 0.22 (conc. NH_3—2—propanol, 2:7). UV spectrum, λ_{max} (log ε): 250 (4.09), 282 nm (3.70) sh. Mass spectrum, m/e (I, %): 246 (11), 245 (67), 244 (11), 202 (21), 187 (12), 174 (19), 173 (27), 160 (10), 145 (11), 95 (11), 93 (26), 92 (11), 91 (13), 87 (15), 85 (34), 84 (22), 83 (35), 82 (13), 77 (67). Found: M^+ 245. $C_{14}H_{19}N_3O$. Calculated: M^+ 245.

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