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INVESTIGATION OF LACTAMS

33.* SYNTHESIS OF 2-OXO-1H,2,3,4,5-TETRAHYDROAZEPINO-[4,5-b]INDOLE DERIVATIVES

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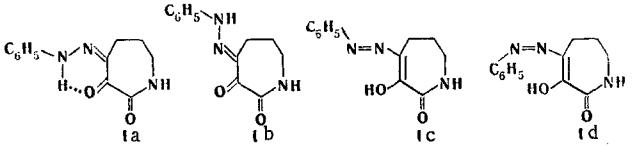
2,3,4-Trioxohexahydroazepine 4-phenylhydrazone with a ^{15}N-labeled atom bonded to the phenyl fragment was obtained in order to establish its structure. It was established by means of the PMR spectra that this substance is a mixture of syn and anti isomers of the hydrazone form. 2,3,4-Trioxohexahydroazepine 3-phenylhydrazone was isolated when an attempt was made to indolize the 4-phenylhydrazone. Both hydrazones react with phenylhydrazine to give the same 2,3,4-trioxohexahydroazepine 3,4-bis(phenylhydrazone). Derivatives involving the carbonyl group were obtained for both hydrazones, and the conditions for their indolization were studied, as a result of which a number of azepino[4,5-b]indole derivatives were synthesized.

Continuing our research on the synthesis of condensed heterocyclic compounds from enamines of α-oxolactams, in the present communication we report the development of a new synthesis of the azepino[4,5-b]indole system.

The starting compound in this synthesis was 2,3,4-trioxohexahydroazepine 4-phenylhydrazone (I), which was obtained by reaction of the enamine of α-oxocaprolactam with benzenediazonium chloride [2].

We have studied the structure of I with allowance for the fact that the arylhydrazones of 1,2-dicarbonyl compounds can exist in two tautomeric forms, viz., the azo and hydrazone forms [3], and that two geometrical isomers (Ia,b and Ic,d) are possible for each of these forms.

The limited solubility of I in organic solvents hindered the use of IR and UV spectroscopy for the solution of our problem. The IR spectrum of I in the solid state did not enable us to draw an unambiguous conclusion regarding its structure, since the absorption bands in the literature (3300, 3080, 1675, 1620, and 1600 cm^{-1}) could have been assigned equally satisfactorily to any of the forms.



The following signals are present in the PMR spectrum of I (in solution in d_6-DMSO + CCl_4): 1.85 (6-CH_2, q), 2.66 and 2.86 (5-CH_2, t), 3.18 (7-CH_2, m), 6.80-7.40 (aromatic protons, m), and 8.33 and 8.44 ppm (1-NH,t);

*See [1] for communication 32.

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TABLE 1. PMR Spectra of Azepino[4,5-b]indoles XII-XIV and XVI

Compound	Solvent	Chemical shift, δ, ppm							
		1-CH	3-NH	4-CH	5-CH_2	OH or NH	10-NH	aromatic protons	other signals
XII	d_7-DMF	—	8,17	3,54	2,86	11,12 (OH)	—[a]	6,87—7,75	—
XIII	d_7-DMF	—	8,42	3,59	2,99	12,42 (N—NH)	10,89	6,65—7,50	—
XIV	C_5D_5N	5,32[b]	8,72	3,54	2,79	—	—[c]	7,00—7,60	2,07 (CH_3COOH)
XVI	d_6-DMSO + CCl_4	6,07[d]	7,92	3,54	2,84	7,77 (1-C—NH)	10,27	6,82—7,41	2,00 ($COCH_3$)

a) The NH signal of the indole ring is overlapped by the signal of the protons of the crystallization water. b) $\Sigma^5J_{1\text{-}CH-5\text{-}CH_2} \approx 3$ Hz. c) The NH signal of the indole ring is overlapped by the COOH signal of acetic acid. d) $^3J_{1\text{-}CH-1\text{-}NH} = 7.9$ Hz; $\Sigma^5J_{1\text{-}CH,5\text{-}CH_2} = 3.75$ Hz.

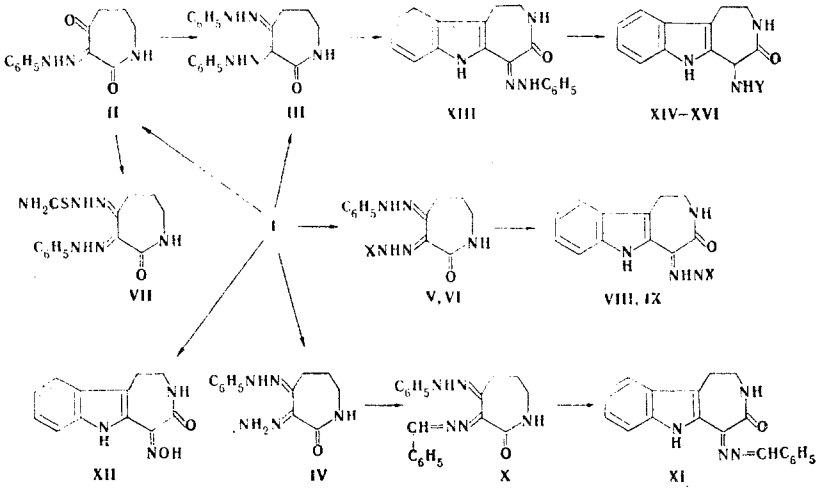
in addition, there are two singlets at 10.58 and 13.68 ppm with relative intensities of 55 and 45%, respectively. The fact of the doubling of the signals of the 5-CH_2 and 1-NH protons and the presence of two weak-field signals in the spectrum constitute evidence that I is a mixture of two forms.

We synthesized I with a ^{15}N atom bonded to the phenyl fragment from ^{15}N-aniline and α-oxocaprolactam enamine by the method in [2]. Splitting of both weak-field signals with spin–spin coupling constant (SSCC) $^1J_{^{15}NH} = 96$ Hz is observed in the PMR spectrum of this compound. This unambiguously confirms the hydrazone structure of I, while the observed doubling of the 5-CH_2 and 1-NH signals provides evidence that it is a mixture of geometrical isomers of the hydrazone (Ia + Ib).

The signal at 13.68 ppm corresponds to syn isomer Ia, in which the NH group of the hydrazone fragment participates in the formation of a hydrogen bond; the stronger-field signal at 10.58 ppm corresponds to the NH group of anti isomer Ib.

In addition to a molecular peak with m/e 231, the mass spectrum of I contains peaks of fragments with m/e 93, 92, and 65, which evidently correspond to the structures $PhNH_2^{+\cdot}$, $PhNH^+$, and $[PhNH-HCN]^+$. The presence of these ions also confirms hydrazone structure I. It should be noted that an ion with m/e 105, to which one should assign the PhN_2^+ structure, is also observed in the mass spectrum of phenylhydrazone I. It may be assumed that the formation of the PhN_2^+ structure is due to fragmentation of the azo form, which is evidently formed due to isomerization of the hydrazone form under the conditions used to record the spectrum.

In an attempt to indolize phenylhydrazone I by heating in a mixture of acetic and hydrochloric acids we isolated II, which, according to the results of elementary analysis and the mass-spectral data, is an isomer of I but differs from the latter with respect to its physicochemical characteristics, Signals at 6.9-7.5 (aromatic CH, m) and at 8.01 (55%) and 8.41 ppm (45%) (1-NH, t) are present in the PMR spectrum of II. There are also two weak-field singlets at 12.37 and 14.20 ppm. In the PMR spectrum of ^{15}N-labeled II (obtained from ^{15}N-labeled phenylhydrazone I) these two singlets are converted to doublets due to spin–spin coupling of the proton attached to ^{15}N with this atom ($^1J_{15} = 96$ Hz). The existence of this splitting confirms the 2,3,4-trioxohexahydroazepine 3-phenylhydrazone structure for II, and the doubling of the NH signal of the hydrazone



V, VIII X = $CSNH_2$; VI, IX X = 2,4-$(NO_2)C_6H_3$; XIV Y = H; XV Y = CHO; XVI Y = $COCH_3$

TABLE 2. Characteristics of the Synthesized Compounds

Compound	mp, °C	Crystallization solvent	Color	IR spectrum, cm^{-1}		UV spectrum λ_{max}, nm (log ε)	Found, %			Empirical formula	calc., %			Yield, %
				NH	C=O; C=N		C	H	N		C	H	N	
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
II	185—188	Ethyl acetate	Lemon-yellow	3200 3070	1670 1645 1600	242 (4,03) 370 (4,26)	62,2	5,9	18,3	$C_{12}H_{13}N_3O_2$	62,3	5,6	18,2	62
III	205—207	Aqueous DMF	Yellow	3370 3240 (br)	1640 1595	277 (4,30) 400 (4,20)	67,3	5,9	22,0	$C_{18}H_{19}N_5O$	67,3	5,9	21,8	97
IV	177—178	Aqueous DMF	Dark-yellow	3460 3340 3270	1640 1595	260 (4,21) 355 (4,04)	58,7	6,3	28,1	$C_{12}H_{15}N_5O$	58,8	6,2	28,5	49
V[a]	228 (dec.)	Alcohol	Yellow	3380, 3270 3180, 3060	1660 1615 1595	261 (4,36) 406 (4,07)	51,3	5,4	27,4	$C_{13}H_{16}N_6SO$	51,3	5,3	27,6	81
VI	250—252	DMF	Dark-red	3200, 3130 3060	1655 1605	—	52,1	4,1	23,7	$C_{18}H_{17}N_7O_5$	52,5	4,2	23,8	90
VII[b]	225—226	Alcohol	Yellow	3420, 3260 3230, 3160	1650 1595	246 (4,34) 406 (4,12)	51,0	5,4	27,5	$C_{13}H_{16}N_6SO$	51,3	5,3	27,6	71
VIII[c]	268 (dec.)	Aqueous DMF	Orange	3360, 3220 3160 (br)	1640 1590	220 (4,47) 390 (4,40)	54,3	4,5	24,2	$C_{13}H_{13}N_5SO$	54,3	4,6	24,4	70
IX	310	DMF	Dark-red	3460, 3280 3205	1645 1605	—	54,3	3,7	21,0	$C_{18}H_{14}N_6O_5$	54,8	3,6	21,3	94
X	189—191	Alcohol	Orange	3230 (br)	1680 1645 1600	244 (4,19) 292 (4,24) 435 (4,21)	68,8	5,8	21,2	$C_{19}H_{19}N_5O$	68,4	5,7	21,0	94
XI	247 (dec.)	Aqueous DMF	Light-yellow	3440 3210	1645 1610 1590	247 (4,50) 280 (3,93) 362 (4,05)	71,2	5,1	17,8	$C_{15}H_{16}N_4O$	71,2	5,1	17,7	97
XII[d]	226—228 (dec.)	Aqueous DMF	„	3460 3300 (br)	1640 1595	318 (4,21)	58,3	5,5	16,6	$C_{12}H_{11}N_3O_2 \cdot 0,5\ H_2O$	58,3	5,3	17,0	58
XIII[e]	227—230	AcOH	Yellow	3450, 3280 3160, 3060	1645 1595	236 (4,38) 295 (3,94) 384 (4,28)	69,4	5,4	17,7	$C_{18}H_{16}N_4O \cdot 0,5\ H_2O$	69,0	5,5	17,8	71
XIV	166—167 (dec.)	Aqueous alcohol	White	3485, 3245 3060 (br)	1670 1550	285 (3,68)	60,7	6,2	15,6	$C_{12}H_{13}N_5O \cdot CH_3COOH$	61,0	6,2	15,3	72
XV	256—258	Aqueous alcohol	„	3290, 3210 3160	1680 1645	222 (4,50) 283 (3,93)	64,0	5,3	17,5	$C_{13}H_{13}N_3O_2$	64,2	5,4	17,3	54
XVI	268—270 (dec.)	Aqueous alcohol	„	3370, 3240 3120	1670 1640	222 (4,50) 283 (3,93)	65,2	6,1	16,1	$C_{14}H_{15}N_3O_2$	65,3	5,9	16,3	71

a) Found: S 10.4%. Calculated: S 10.5%. b) Found 10.9%. Calculated: S 10.5%. c) Found: S 11.2%. Calculated: S 11.1%. d) Found: H_2O 7.5%. Calculated: H_2O 7.3%. e) Found: H_2O 3.0%. Calculated: H_2O 2.9%.

fragment and of the 1-NH signal makes it possible to conclude that this substance is present in solution in d_6-DMSO + CCl_4 in the form of two geometrical isomers (IIa, b).

The molecular-ion peak with m/e 231 has the maximum intensity in the mass spectrum of II. With respect to the principal fragmentation pathways and the intensity ratios of the peaks, the spectrum of II differs substantially from the spectrum of phenylhydrazone I, since a decrease in the relative intensities of the $PhNH_2^{+\cdot}$ $PhNH^+$, and $[PhNH-HCN]^+$ ions, and an increase in the intensity of the molecular ion are observed in it. Intense peaks of PhN_2^+ (m/e 105) and $[M-Ph]^+$ (m/e 154) ions, which, as in the case of phenylhydrazone I, can be assigned to fragmentation of the azo form (IIc) that evidently is produced under the conditions used to record the spectrum, are observed in the spectrum of II.

Compounds I and II react when they are heated with phenylhydrazine in alcohol to give the same bis(phenylhydrazone) (III). In the case of the reaction of I with hydrazine, 2,4-dinitrophenylhydrazine, and thiosemicarbazide the reaction also takes place at the carbonyl group in the 3 position of phenylhydrazone I to give IV-VI. Thiosemicarbazone VII was similarly obtained from phenylhydrazone II and thiosemicarbazide. A study of the indolization of V and VI showed that the most favorable conditions for the synthesis of azepin[4,5-b]indoles involve heating the phenylhydrazones in a mixture of acetic and hydrochloric acids.

Attempts to indolize phenylhydrazone IV thermally and by means of various catalysts were unsuccessful because of pronounced resinification. In this connection, we obtained a benzylidene derivative (X) from IV; when X was heated in a mixture of acetic and hydrochloric acids, it was converted to azepinoindole XI in almost quantitative yield. It is interesting to note that in the case of the reaction of phenylhydrazone I with hydroxylamine hydrochloride in acetic acid the process took place immediately to give an azepinoindole (XII). Azepinoindole XIII was synthesized from bis(phenylhydrazone) III; amino and formylamino derivatives (XIV, XV) were obtained by reduction of XIII with zinc in acetic and formic acids, respectively, while azepinoindole XVI was synthesized by reduction of XIII with zinc in acetic acid in the presence of acetic anhydride. The structures of azepinoindoles XII, XIII, and XVI were confirmed by data from the PMR spectra (Table 1).

EXPERIMENTAL

The UV spectra of solutions of the compounds in alcohol were recorded with an EPS-3 spectrophotometer. The IR spectra of mineral oil pastes were recorded with JNM-4H-100 and C-60HL spectrometers with tetramethylsilane as the internal standard. The purity of the substances was monitored by chromatography on Silufol UV-254 plates.

2,3,4-Trioxohexahydroazepine 3-Phenylhydrazone (II). A suspension of 2.3 g (10 mmole) of hydrazone I in 8 ml of acetic acid and 3 ml of concentrated hydrochloric acid was heated at 70°C for 1 h, after which the solution was poured into 60 ml of water, and the resulting precipitate was removed by filtration and dissolved by refluxing in 100 ml of methanol. The solution was decolorized with charcoal and evaporated in vacuo, and the precipitate was triturated with ether. The solid was removed by filtration and dried (Table 2).

2,3,4-Trioxohexahydroazepine 3,4-Bis(phenylhydrazone) (III). A) A 6.5-g (60 mmole) sample of phenylhydrazine and a catalytic amount of p-toluenesulfonic acid were added to a solution of 7 g (30 mmole) of I in 80 ml of alcohol, and the mixture was refluxed for 3 h. It was then cooled, and the resulting precipitate was washed with alcohol and dried.

B) This method was similar to method A. The product was obtained in 87% yield from 2,3,4-trioxohexahydroazepine phenylhydrazone.

3-Hydrazino-2,3,4-trioxohexahydroazepine 4-Phenylhydrazone (IV). A suspension of 11 g of I in 90 ml of alcohol was cooled to 0°C, 5 ml of hydrazine hydrate was added, and the temperature of the mixture was raised to 20°C. The mixture was heated at 50°C for 2.5 h, after which it was cooled, and the resulting precipitate was removed by filtration, washed with alcohol, and dried.

3-Thiosemicarbazono-2,3,4-trioxohexahydroazepine 4-Phenylhydrazone (V). A suspension of 5.8 g (25 mmole) of I, 2.3 g (25 mmole) of thiosemicarbazide, and a catalytic amount of p-toluenesulfonic acid in 120 ml of alcohol was refluxed for 1 h, after which it was cooled, and the resulting precipitate was removed by filtration, washed with alcohol, and dried.

3-(2,4-Dinitrophenylhydrazono)-2,3,4-trioxohexahydroazepine 4-Phenylhydrazone (VI). A suspension of 4.6 g (120 mmole) of hydrazone I, 4 g (20 mmole) of 2,4-dinitrophenylhydrazine, and a catalytic amount of p-toluenesulfonic acid in 100 ml of alcohol was refluxed for 4 h, after which it was cooled, and the resulting precipitate was removed by filtration, washed with alcohol, and dried.

3-Phenylhydrazono-2,3,4-trioxohexahydroazepine 4-Thiosemicarbazone (VII). A solution of 0.8 g (3.4 mmole) of hydrazone II, 0.31 g (3.4 mmole) of thiosemicarbazide, and a catalytic amount of p-toluenesulfonic acid in 20 ml of alcohol was refluxed for 45 min, after which it was cooled, and the precipitate was washed with water and dried.

1,2-Dioxo-1H-2,3,4,5-tetrahydroazepino[4,5-b]indole 1-Thiosemicarbazone (VIII). A suspension of 1.5 g (5 mmole) of V in 4 ml of acetic acid and 1 ml of concentrated hydrochloric acid was heated at 100°C for 1 h, after which it was cooled and poured into water. The resulting precipitate was removed by filtration, washed with water and alcohol, and dried.

1,2-Dioxo-1H-2,3,4,5-tetrahydroazepino[4,5-b]indole 1-(2,4-Dinitrophenylhydrazone) (IX). A suspension of 7.4 g (18 mmole) of VI in 63 ml of acetic acid and 7 ml of concentrated hydrochloric acid was refluxed for 3 h, after which it was cooled, and the precipitate was removed by filtration, washed with water and alcohol, and dried.

3-Benzalhydrazono-2,3,4-trioxohexahydroazepine 4-Phenylhydrazone (X). A suspension of 6.75 g (28 mmole) of IV and 3.5 g (33 mmole) of benzaldehyde in 40 ml of alcohol was refluxed for 1.5 h, after which the solution was cooled, and the precipitate was removed by filtration, washed with alcohol, and dried.

1,2-Dioxo-1H-2,3,4,5-tetrahydroazepino[4,5-b]indole 1-N-Benzalhydrazone (XI). A solution of 5.5 g (16.5 mmole) of X in 34 ml of acetic acid and 6 ml of concentrated hydrochloric acid was heated at 100°C for 30 min, after which it was cooled and poured into water. The resulting precipitate was removed by filtration, washed with water, and dried.

1,2-Dioxo-1H-2,3,4,5-tetrahydroazepino[4,5-b]indole 1-Oxime (XII). A suspension of 1.15 g (5 mmole) of hydrazone I and 0.5 g (5.2 mmole) of hydroxylamine hydrochloride in 20 ml of acetic acid was heated at 65°C for 2 h, after which it was cooled and poured into water. The precipitate was separated, washed with water, and dried.

1,2-Dioxo-1H-2,3,4,5-tetrahydroazepino[4,5-b]indole 1-Phenylhydrazone (XIII). A solution of 8.45 g (26 mmole) of III in 47 ml of acetic acid and 3 ml of concentrated sulfuric acid was heated at 60°C for 1 h, after which it was cooled, and the resulting precipitate was washed with water and alcohol and dried.

1-Amino-2-oxo-1H-2,3,4,5-tetrahydroazepino[4,5-b]indole (XIV). A suspension of 5.4 g (17.8 mmole) of XIII and 10 g of zinc dust in 80 ml of acetic acid was maintained at 20°C for 1 h, after which the precipitate was removed by filtration and washed with 10 ml of acetic acid. The filtrate was evaporated to dryness in vacuo, and the residue was triturated with ether. The solid material was removed by filtration, washed with ether, and dried.

1-Formamido-2-oxo-1H-2,3,4,5-tetrahydroazepino[4,5-b]indole (XV). A 3-g sample of zinc dust was added to a suspension of 1.5 g (5 mmole) of XIII in 15 ml of formic acid heated to 50°C, and the mixture was stirred at this temperature for 2 h. It was then cooled, and the precipitate was removed by filtration and washed with formic acid. The mother liquor was evaporated in vacuo, and the residue was triturated with ether, removed by filtration, and dried.

1-Acetamido-2-oxo-1H-2,3,4,5-tetrahydroazepino[4,5-b]indole (XVI). A 6-g sample of zinc dust in 15 ml of acetic acid and 8 ml of acetic anhydride was added to a suspension of 1.5 g (5 mmole) of XIII in 30 ml of acetic acid at 60°C, and the mixture was heated at 60°C for 3 h. The precipitate was removed by filtration and washed with 10 ml of acetic acid. The filtrate was evaporated to dryness in vacuo, and the residue was triturated with water, removed by filtration, and dried.

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