INVESTIGATION OF LACTAMS. XXVI.* "TRANSAMINATION" OF ENAMINES OF α-OXOLACTAMS AND NEW SYNTHESIS OF α-AMINO-CAPROLACTAM

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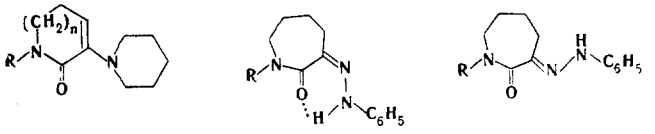
α-Substituted lactams, including the syn (IIa, b) and anti (IIIa, b) isomers of α-oxo- and N-methyl-α-oxocaprolactam phenylhydrazones, were synthesized by reaction of enamines of α-oxolactams (I) with hydrazine, phenyl- and 4-pyrimidylhydrazines, thiosemicarbazide, and hydroxylamine. A new synthesis of α-aminocaprolactam was accomplished by hydrogenation of enamine Ia over Raney nickel in an alcohol solution of ammonia.

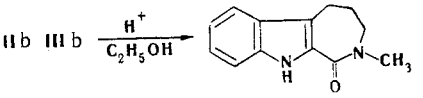
We have previously shown that enamines of α-oxocaprolactam (Ia) and α-oxovalerolactam (Ic) react relatively readily with arylhydrazines in the presence of acid catalyst to give derivatives of azepino[3,4-b]indole and β-carboline [2].

In an investigation of the reaction of enamines Ia, b with phenylhydrazine under conditions of their acid hydrolysis to the corresponding α-oxolactams [3] it was found that this reaction gives a mixture of syn (IIa, b) and anti (IIIa, b) isomers of phenylhydrazones with predominance of the syn isomer.

Isomers IIa and IIIa were obtained in approximately the same ratio under similar conditions by reaction of α-oxocaprolactam with phenylhydrazine.



I a-c II a,b III a,b



IIb IIIb → IV

I a $n=2$, R=H; b $n=2$, R=CH_3; c $n=1$, R=H; II, III a R=H; b R=CH_3

The assignment of these isomers to the syn and anti forms was made in analogy with the arylhydrazones of α-oxovalerolactam [4, 5], for the syn isomers of which a bathochromic shift of the absorption maxima in the UV spectra is characteristic. In our case the shift of the absorption maxima is 16-20 nm.†

It is known that the considerable stability of the intramolecular hydrogen bond in the syn isomer if ethyl pyruvate hexahydrobenzo[e]-7-indenylhydrazone [6] prevents cycliza-

*See [1] for communication XXV.

†Proof of the chelate structure of syn isomers IIa, b by means of the IR spectra was hindered by their limited solubilities in organic solvents.

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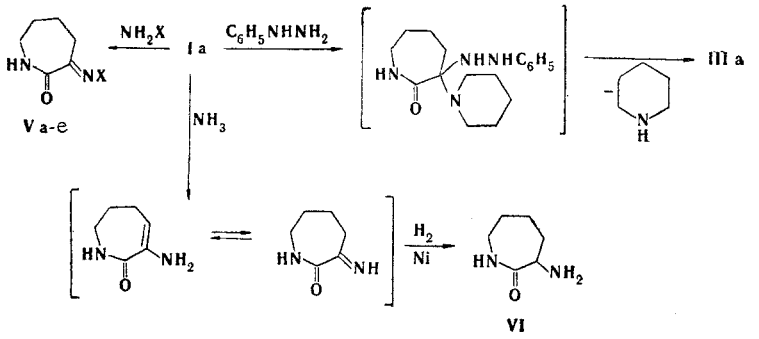
tion of this compound to an indeno[5, 4-e]indole derivative. On comparison of our isomers (II, III) we found that the chelate ring in the syn forms is unstable. Although the syn isomers are not isomerized to the anti forms in boiling alcohol, both the anti (IIIb) and syn (IIb) isomers are converted to 1-oxo-2-methyl-1H,2,3,4,5-tetrahydro[3,4-b]indole (IV) readily and approximately in equal yields when the isomers are heated in alcohol in the presence of sulfuric acid.

The presence in enamines I of an electron-acceptor carbonyl group conjugated with a C=C bond made it possible to assume that their conversion to the corresponding arylhydrazones should proceed quite readily even in the absence of an acid catalyst. In fact, we were able to isolate anti isomers IIIa in high yield when enamine Ia was heated with phenylhydrazine in alcohol in the absence of an acid. The reaction probably proceeds through the intermediate formation of a compound with a geminal orientation of the substituents in which the bulky piperidine ring hinders the formation of an intramolecular hydrogen bond.



Va X=NH2; b X=4-pyrimidinylamino c X=6-oxo-4-pyrimidylamine d X=NHCSNH2; e X=OH

It should be emphasized that the possibility of the intermediate formation of syn form IIa or a mixture of isomers (IIa and IIIa) in this reaction is excluded, inasmuch as syn isomer IIa, as noted above, does not undergo isomerization when it is heated in alcohol.

A further investigation of the "transamination" reaction showed that enamine Ia also readily reacts with hydrazine, 4-hydrazinopyrimidine, 4-hydrazino-6-hydroxyprimidine, thiosemicarbazide, and hydroxylamine to give the corresponding α-oxocaprolactam derivatives (V).

The development of the "transamination" of enamines of α-oxolactams enabled us to realize a new method for the synthesis of α-aminocaprolactam (VI), which consists in hydrogenation of a solution of enamine Ia in alcoholic alkali over Raney nickel.

EXPERIMENTAL METHOD

The UV spectra of alcohol solutions of the compounds were recorded with an EPS-3 spectrophotometer. The IR spectra of mineral oil suspensions were recorded with a Perkin–Elmer 457 spectrometer. The melting points were determined with an MP-1 apparatus from the Yamato Scientific Co., Ltd.

syn (IIa) and anti (IIIa) Isomers of α-Oxocaprolactam Phenylhydrazone. A 6-ml sample of 20% sulfuric acid was added dropwise at −3° to a solution of 4 g of enamine Ia in 30 ml of chloroform, after which the mixture was cooled to −7°, and a solution of 2.5 g of phenylhydrazine in 10 ml of chloroform was added dropwise. The mixture was then stirred at −3 to 0° for 1.5 h, after which it was made alkaline to pH 8 with 2 N NaOH and filtered to give 1.1 g of anti isomer IIIa with mp 213° (from alcohol). IR spectrum: ν_{NH} 3240, 3060 cm^{-1}; $\nu_{C=O}$ amide, C=N 1640 cm^{-1}. UV spectrum, λ_{max} (log ε): 282 (4.14) and 313 nm (4.24). Found: C 65.9; H 6.7; N 19.6. $C_{12}H_{15}N_3O$. Calculated: C 66.4; H 6.9; N 19.4%.

The chloroform solution obtained after isolation of anti isomer IIIa was separated from the aqueous layer, and the latter was extracted with chloroform. The combined chloroform solutions were dried with sodium sulfate and vacuum evaporated. The residue was triturated with ether, the mixture was filtered, and the solid was dried to give 2 g of a product with mp 130-206°. Crystallization of 0.5 g of the product from 20 ml of alcohol gave 0.1 g of syn form IIa with mp 137-138°. IR spectrum: ν_{NH} 3310, 3270, and 3230 cm^{-1}; $\nu_{C=O}$ amide, C=N 1640-1660 (broad), 1580-1600 cm^{-1}. UV spectrum, λ_{max} (log ε): 245 (3.95),

298 (3.72), and 340 nm (4.10). Found: C 66.7; H 7.2; N 19.5%. $C_{12}H_{15}N_3O$. Calculated: C 66.4; H 6.9; N 19.4.

syn (IIb) and anti (IIIb) Isomers of N-Methyl-α-oxocaprolactam Phenylhydrazone. These compounds were similarly synthesized from enamine Ib. The anti isomer (IIIb), with mp 214-214.5° (from alcohol), was obtained in 22.8% yield. IR spectrum: ν_{NH} 3260 cm^{-1}; $\nu_{C=O}$ amide, C=N 1620, 1605 cm^{-1}. UV spectrum, λ_{max} (log ε): 285 (4.17) and 310 nm (4.24). Found: C 67.2; H 7.3; N 18.2%. $C_{13}H_{17}N_3O$. Calculated: C 67.5; H 7.4; N 18.2%. The syn isomer (IIb), with mp 96-96.5° (from hexane), was obtained in 40.7% yield. IR spectrum: ν_{NH} 3280 cm^{-1}; $\nu_{C=O}$ amide, C=N 1620, 1605 cm^{-1}. UV spectrum, λ_{max} (log ε): 246 (4.05), 290 (3.14), and 330 nm (3.99). Found: C 67.6; H 7.4; N 18.1%. $C_{13}H_{17}N_3O$. Calculated: C 67.5; H 7.4; N 18.2%.

anti Isomer of α-Oxocaprolactam Phenylhydrazone (IIIa). A mixture of 5.9 g of enamine Ia, 3.5 g of phenylhydrazine, and 100 ml of alcohol was refluxed with stirring for 6 h. During the heating period the solid dissolved, and anti isomer IIIa precipitated from the solution. The mixture was cooled and filtered, and the solid was washed with alcohol and dried. The mother liquor was vacuum evaporated to dryness, the residue was triturated with a small amount of alcohol, and the mixture was filtered. The solid was washed with alcohol and dried. The overall yield of anti isomer IIIa, with mp 208-212°, was 5.4 g (84%).

α-Oxovalerolactam Phenylhydrazone. This compound, with mp 229-230° (from methanol) (mp 242-243° [9]), was synthesized in 50% yield under similar conditions from enamine IC. IR spectrum: ν_{NH} 3230, 3190 cm^{-1}; $\nu_{C=O}$ amide, C=N 1655, 1595 cm^{-1}. UV spectrum, λ_{max} (log ε): 232 (4.09), 294 (4.00), and 324 nm (4.34). Found: C 65.1; H 6.3; N 20.5%. $C_{11}H_{13}N_3O$. Calculated: C 65.0; H 6.4; N 20.7%.

α-Oxocaprolactam Hydrazone (Va). This compound, with mp 214° (from alcohol), was synthesized in 42.5% yield from enamine Ia and hydrazine hydrate by the method used to prepare IIIa. IR spectrum: ν_{NH,NH_2} 3380, 3170 cm^{-1}; $\nu_{C=O}$ amide, C=N 1660, 1620 cm^{-1}. Found: C 51.2; H 8.0; N 29.7%. $C_6H_{11}N_3O$. Calculated: C 51.1; H 7.8; N 29.8%.

α-Oxocaprolactam 4-Pyrimidylhydrazone (Vb). This compound, with mp 198-200° (from alcohol), was synthesized in 68.5% yield from enamine Ia and 4-hydrazinopyrimidine by the method used to prepare IIa. IR spectrum: ν_{NH} 3190, 3060 cm^{-1}; $\nu_{C=O}$ amide, C=N 1670, 1660 cm^{-1}. UV spectrum, λ_{max} (log ε): 235 (3.90) and 285 nm (4.31). Found: C 54.8; H 5.9; N 32.4%. $C_{10}H_{13}N_5O$. Calculated: C 54.8; H 5.9; N 32.0%.

α-Oxocaprolactam 6-Hydroxy-4-pyrimidylhydrazone (Vc). This compound, with mp 284-288° (from 50% alcohol), was synthesized in 46% yield from enamine Ia and 6-hydroxy-4-hydrazino pryimidine by the method used to prepare IIIa. IR spectrum: ν_{NH} 3220 cm^{-1}; $\nu_{C=O}$ amide, C=N 1630 cm^{-1}. UV spectrum, λ_{max} (log ε): 220 (4.30) and 295 nm (4.29). Found: C 50.7; H 5.6; N 29.5%. $C_{10}H_{13}N_5O_2$. Calculated: C 51.1; H 5.5; N 29.8%.

α-Oxocaprolactam Thiosemicarbazone (Vd). This compound, with mp 239-241° (from water), was synthesized in ~100% yield from enamine Ia and thiosemicarbazide by the method used to prepare IIIa. IR spectrum: $\nu_{NH_2, NH}$ 3300, 3170 cm^{-1}; $\nu_{C=O}$ amide, C=N 1640, 1620 cm^{-1}. UV spectrum, λ_{max} (log ε): in 1 N NaOH 258 (4.18) and 308 nm (3.66); in 1 N HCl 268 nm (4.26). Found: C 42.3; H 6.3; N 28.1; S 15.8%. $C_7H_{12}N_4OS$. Calculated: C 42.0; H 6.0; N 28.0; S 16.0%.

α-Oxocaprolactam Oxide (Ve). A mixture of 4 g enamine Ia, 1.7 g of hydroxylamine hydrochloride, and 1.8 g of sodium acetate was dissolved by heating in 50 ml of alcohol and 10 ml of water, after which the solution was refluxed for 5 h. It was then vacuum evaporated to dryness, and the residue was triturated with water. The mixture was filtered, and the solid was dried to give 1.4 g (50%) of oxime Ve with mp 201-202° (mp 205° [10]).

1-Oxo-2-methyl-1H,2,3,4,5-tetrahydroazepino[3,4-b]indole (IV). A 3-g sample of anti isomer IIIb was added to a solution of 2 ml of concentrated H_2SO_4 in 50 ml of absolute alcohol, after which the mixture was refluxed for 4 h. During the heating period, a precipitate formed from the solution. The mixture was cooled, and the precipitated crystals were removed by filtration, washed with alcohol and ether, and dried to give 2.65 g (95.5%) of azepinoindole IV with mp 237-238° (mp 240-242° [11]).

Azepinoindole IV, with mp 237-238°, was similarly obtained in 93.5% yield from syn isomer IIb.

α-Aminocaprolactam (VI). A 19.4-g sample of enamine Ia and 5 g of a Raney nickel paste were added to 550 ml of a 15% solution of ammonia in absolute alcohol, after which the mixture was hydrogenated at 80° and an initial hydrogen pressure of 80 atm for 3 h until the theoretical amount of hydrogen had been absorbed. The mixture was cooled and filtered, the catalyst was washed with alcohol, and the mother liquor was vacuum evaporated to dryness. The residue was triturated with ether, the mixture was filtered, and the solid was dried to give 11.5 g (90%) of α-aminocaprolactam with mp 68-70° (mp 68-71° [12]). Found: C 56.3; H 9.6; N 21.9%. $C_6H_{12}N_2O$. Calculated: C 56.2; H 9.4; N 21.9%. α-Aminocaprolactam hydrochloride had mp 291-295° (mp 294-296° [12]). Found: Cl 21.4; N 16.7%. $C_{16}H_{13}ClN_2O$. Calculated: Cl 21.6; N 17.0%.

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