SYNTHESIS OF DERIVATIVES OF PYRIDO[3,4-b]- AND AZEPINO[3,4-b]PYRROLO[2,3-d]PYRIMIDINES FROM ENAMINES OF α-OXO LACTAMS*

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UDC 547.75'824.4'866'891

The reaction of enamines of some α-oxo lactams with 1,3-dimethyl- and 1,3-dibenzyl-4-hydrazinouracils gave the uracilyl-4-hydrazones of these lactams, the catalytic and thermal indolization of which yielded derivatives of pyrido[3,4-b]- and azepino[3,4-b]pyrrolo[2,3-d]pyrimidines. Some reactions of the latter were studied.

The recently developed synthesis of enamines of α-oxo lactams (Ia, b) [2] has opened up possibilities for the preparation of various condensed heterocyclic compounds, including potentially biologically active substances.

The present paper is devoted to a study of the synthesis of representatives of new heterocyclic systems – derivatives of pyrido[3,4-b]- (VIII, IX) and azepino[3,4-b]pyrrolo[2,3-d]pyrimidines (X, XI) – from enamines Ia, b and oxocaprolactam II [3]. On the basis of the ability of enamines Ia, b to undergo "transamination" with arylhydrazines and hydrazinopyrimidines [4], we studied the "transamination" of enamines Ia, b by 1,3-dimethyl- (IIIa) and 1,3-dibenzyl-4-hydrazinouracils (IIIb).

We found that the "transamination" of enamine Ia with hydrazinouracil IIIa proceeds smoothly when the reagents are heated in alcohol to give two geometrical isomers of α-oxovalerolactam 1,3-dimethyluracilyl-4-hydrazone in the form of monohydrates – the anti form (IVb), which is only slightly soluble in alcohol, and the more soluble syn isomer (IVa). The assignment of these isomers to the syn and anti forms was made in analogy with the data for α-oxocaprolactam arylhydrazones [4] and derivatives of α-oxovalerolactam [5, 6]. A bathochromic shift of the long-wave absorption maximum of 22 nm is observed in the UV spectrum of syn form IVa as compared with anti form IVb. The anti isomer (IVb) undergoes thermal indolization at ~ 190°C (rapid heating) to give VIII, whereas in the case of syn form IVa this process takes place under more severe conditions (> 200°C).

Compounds V-VII were synthesized in the same way as hydrazones IVa, b. It does not seem possible to draw conclusions regarding the stereoisomerism of these compounds because of the absence of the corresponding pairs of geometrical isomers and also because of their low solubilities in organic solvents, which hinders attempts to obtain their spectral characteristics. It may be assumed that hydrazone V is the syn isomer, since its UV spectrum is similar to the spectrum of syn isomer IVa.

During a study of the conversion of hydrazones IV-VII to three-ring compounds VIII-XI we established that their thermal indolization by heating at 215-220°C in diethylene glycol gives the products in higher yields than in the case of the catalytic process [in polyphosphoric acid (PPA)]. It is interesting to note that the indolization of anti isomer IVb (IVb → VIII) gives the product in higher yield than the indolization of syn isomer IVa. This is in agreement with data that indicate that the hydrogen bond in syn isomers may hinder the indolization of hydrazones [7].

Compounds VIII-XI and their derivatives may be of definite interest as potential biologically active substances, since they contain a pyrrolo[2,3-d]pyrimidine fragment, which constitutes the basis of the antitumorigenic antibiotics tubercidin, toikomycin, and sangivomycin [8]. In this connection we investigated the possibility

*Communication XXVIII from the series "Investigation of Lactams." See [1] for communication XXVII.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1398-1403, October, 1977. Original article submitted October 18, 1976.

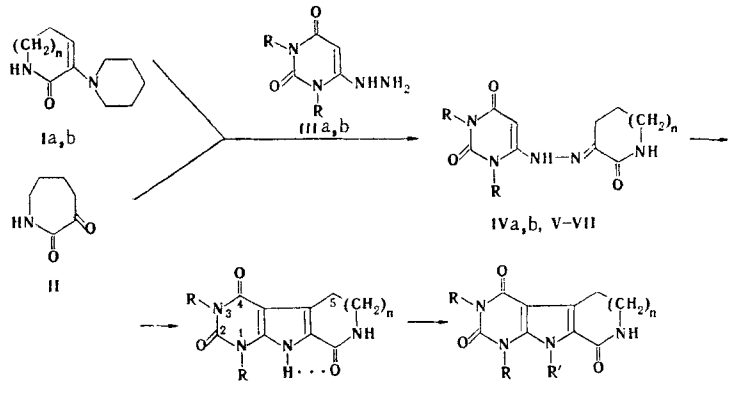
0009-3122/77/1310-1122$07.50

of the preparation of derivatives of three-ring compounds VIII-XI with respect to the pyrrole nitrogen atom and lactam ring carbon atom.

The alkylation of VIII-XI by alkyl halides at the pyrrole NH group (the acidity of which is reduced due to the electron-acceptor effect of the C = O groups in the 4 position of the uracil fragment) takes place under mild conditions in dimethylformamide (DMF) at 50-60°C to give the corresponding alkyl derivatives XII-XIX.

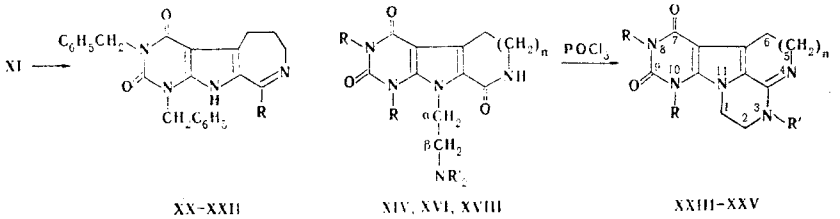
Reaction of XI with phosphorus oxychloride gave chloro derivative XX, from which 9-ethoxy- and 9-[β-(N,N-diethylamino)-1,3-dibenzyl]-2,4-dioxo-7H-1,2,3,4,5,6-hexahydroazepino[3,4-b]pyrrolo[2,3-d]pyrimidines (XXI, XXII) were obtained by treatment with sodium ethoxide in alcohol and β-(N,N-diethylamino)ethylamine.

On the basis of the ability of lactam XI to react with phosphorus oxychloride to give the highly reactive chloroimide XX, we accomplished the intramolecular cyclization of XIV, XVI, and XVIII with phosphorus oxychloride, as a result of which we obtained four-ring compounds XXIII-XXV.



Ia n=1, b n=2; IIIa R=CH$_3$, b R=CH$_2$C$_6$H$_5$; IVa, b n=1, R=CH$_3$; V n=1, R=CH$_2$C$_6$H$_5$; VI n=2, R=CH$_3$; VII n=2, R=CH$_2$C$_6$H$_5$; VIII n=1, R=CH$_3$; IX n=1, R=CH$_2$C$_6$H$_5$; X n=2, R=CH$_3$; XI n=2, R=CH$_2$C$_6$H$_5$; XII n=1, R=CH$_3$, R′=CH$_2$CH$_2$N(C$_2$H$_5$)$_2$; XIII n=1, R=CH$_2$C$_6$H$_5$, R′=CH$_2$CH$_2$N(C$_2$H$_5$)$_2$; XIV n=1, R=CH$_3$, R′=CH$_2$CH$_2$N(CH$_3$)$_2$; XV n=1, R=CH$_2$C$_6$H$_5$, R′=CH$_2$CH$_2$N(CH$_3$)$_2$; XVI n=2, R=CH$_3$, R′=CH$_2$CH$_2$N(C$_2$H$_5$)$_2$; XVII n=2, R=CH$_3$, R′=CH$_2$C$_6$H$_5$; XVIII n=2, R=CH$_2$C$_6$H$_5$, R′=CH$_2$CH$_2$N(C$_6$H$_5$)$_2$; XIX n=2, R=CH$_3$, R′=CH$_2$CH$_2$N(CH$_3$)$_2$

Two groups of absorption bands at 3360-3380 and 3180-3200 cm^{-1}, which correspond to the pyrrole and lactam NH groups, respectively, are observed in the IR spectra of solid samples of three-ring compounds VIII-XI. The presence in VIII-XI of an intramolecular hydrogen bond was proved in the case of XI. In the IR spectrum of this compound in CCl_4 the absorption band of the pyrrole NH groups is shifted to 3440 cm^{-1} and corresponds to the position of the absorption band of the pyrrole NH group in chloroimide XX. Absorption bands at 1700, 1670, 1640, and 1610 cm^{-1}, which correspond to two "uracil" and "lactam" carbonyl groups, and of a C = C bond are observed in the IR spectrum of XXI.



XX R=Cl; XXI R=OC$_2$H$_5$; XXII R=NHCH$_2$CH$_2$N(C$_2$H$_5$)$_2$; XXIII n=1, R=R′=CH$_3$; XXIV n=2, R=CH$_3$, R′=C$_2$H$_5$; XXV n=2, R=CH$_2$C$_6$H$_5$, R′=C$_2$H$_5$

The PMR spectrum of lactam XI contains multiplets at 1.87 (6-CH_2 protons of the azepine ring) and 3.04 (5-CH_2 and 7-CH_2 protons of the azepine ring), singlets at 5.04 and 5.34 (CH_2 of the benzyl fragments in the 1 and 3 positions), and multiplets at 7.75 (azepine ring NH), 11.77 (pyrrole ring NH), and 7.20 ppm (aromatic protons).

A doublet of protons of a dimethylamino group at 3.09 and 3.14 ppm, as well as multiplets at 2.28 (β-CH_2), 5.01 (α-CH_2), and 3.47 ppm (protons in the 3 and 4 positions of the carboline ring), are observed in the PMR spectrum of XIV, in addition to singlets of protons of CH_3 groups of a uracil fragment at 3.55 and 3.94 ppm.

TABLE 1. Physical Characteristics of the Synthesized IVa, b, V, VII, and VIII-XXV

Compound	mp, °C*	Found, %				Empirical formula	Calc., %				IR spectrum, ν, cm⁻¹			UV spectrum, λmax, nm (log ε)	Yield, %
		C	H	Cl	N		C	H	Cl	N	OH	NH	C=O, C=C, C=N		
IVa	290	46,5	5,9	—	24,6	$C_{11}H_{15}N_5O_3 \cdot H_2O$	46,6	6,0	—	24,7	3460	3420	1700, 1630—1660 (br.)	249 (4,31) 330 (4,20)	30
IVb	190	47,1	6,0	—	25,3	$C_{11}H_{15}N_5O_3 \cdot H_2O$	46,6	6,0	—	24,7	3450	3190	1680, 1635	244 (4,24) 308 (4,11)	14
V	207—209	66,3	5,6	—	17,1	$C_{23}H_{23}N_5O_3$	66,2	5,6	—	16,8	—	3230	1695, 1630	252 (4,36) 330 (4,23)	25
VII	180—182	66,9	6,1	—	15,9	$C_{24}H_{25}N_5O_3$	66,8	5,8	—	16,2	—	3250	1695, 1630	250 (4,25) 315 (4,11)	37
VIII	>300	53,0	5,0	—	22,7	$C_{11}H_{12}N_4O_3$	53,2	4,8	—	22,6	—	3130, 3380	1605, 1640, 1650, 1705	249 (4,36) 324 (4,13)	78
IX	282—284	69,1	4,8	—	13,8	$C_{23}H_{20}N_4O_3$	69,0	5,0	—	14,0	—	3200, 3380	1595, 1640, 1655, 1695	250 (4,30) 325 (4,06)	53
X	>300	54,9	5,8	—	21,1	$C_{12}H_{11}N_4O_3$	54,9	5,3	—	21,4	—	3185, 3140	1620, 1640, 1660, 1700	268 (4,04) 295 (4,21)	84
XI	283—285	69,8	5,3	—	13,5	$C_{24}H_{22}N_4O_3$	69,6	5,3	—	13,5	—	3180, 3360	1605, 1630, 1670, 1700	268 (4,16) 293 (4,23)	73
XII	214—216	58,8	7,2	—	20,1	$C_{17}H_{25}N_5O_3$	58,8	7,2	—	20,2	—	3210	1660, 1690	220 (4,30) 297 (4,06)	80
XII	275—277	—	—	9,4	18,0	$C_{17}H_{25}N_5O_3 \cdot HCl$	—	—	9,3	18,2	—	—	—	—	—
XIII	176—178	69,6	6,6	—	13,9	$C_{29}H_{33}N_5O_3$	69,7	6,6	—	14,0	—	3220	1670, 1700	280 (4,13) 295 (4,05)	72
XIII	240—241	—	—	6,8	12,9	$C_{29}H_{33}N_5O_3 \cdot HCl$	—	—	6,6	13,1	—	—	—	—	—
XIV	250—253	56,2	6,5	—	21,8	$C_{15}H_{21}N_5O_3$	56,4	6,6	—	21,9	—	3210	1670, 1700	280 (3,94) 296 (4,01)	64
XIV	282—285	—	—	9,8	19,7	$C_{15}H_{21}N_5O_3 \cdot HCl$	—	—	10,0	19,7	—	—	—	—	—
XV	163—166	69,1	6,5	—	14,8	$C_{27}H_{29}N_5O_3$	68,8	6,2	—	14,9	—	3200	1670, 1710	280 (4,18) 296 (4,01)	25
XVI	188—190	59,9	7,4		19,4	$C_{18}H_{27}N_5O_3$	59,8	7,5	—	19,4	—	3240	1650, 1690	280 (4,17) 292 (4,16)	70
XVI	265—267	—	—	8,6	17,4	$C_{18}H_{27}N_5O_3 \cdot HCl$	—	—	8,9	17,6	—	—	—	—	—
XVII	226—227	65,4	5,5	—	16,2	$C_{19}H_{29}N_5O_3$	64,8	5,6	—	15,9	—	3240	1660, 1750	280 (4,15) 292 (4,47)	25
XVIII	185—188	70,3	6,8	—	13,4	$C_{30}H_{35}N_5O_3$	70,2	6,8	—	13,6	—	3220	1660, 1696	280 (4,16) 290 (4,18)	63
XVIII	255—256	—	—	8,8	18,7	$C_{30}H_{35}N_5O_3 \cdot HCl$	—	—	8,9	18,9	—	—	—	—	—
XIX	210—213	58,0	7,0	—	21,4	$C_{16}H_{23}N_5O_3$	57,7	6,9	—	21,0	—	3240	1650, 1695	280 (4,15) 292 (4,45)	15
XX	178—180	66,5	4,9	8,3	12,6	$C_{24}H_{21}ClN_4O_2$	66,6	4,9	8,2	12,9	—	3400	1715, 1680 (br.)	313 (4,25)	33
XXI	111—112	67,5	6,1	—	12,1	$C_{26}H_{26}N_4O_3 \cdot H_2O$	67,8	6,1	—	12,2	3470	3150	1680, 1640	271 (4,20) 292 (4,19) 352 (4,19)	39
XXII	201—203	70,3	7,2	—	16,5	$C_{30}H_{36}N_6O_2$	70,3	7,0	—	16,4	—	3340	1690, 1645	256 (4,20) 340 (4,38)	61
XXIII	279—281	58,6	6,0	—	24,3	$C_{14}H_{17}N_5O_2$	58,5	5,9	—	24,4	—	—	1670, 1660, 1600	322 (4,16)	67
XXIII	301—303	—	—	11,0	21,7	$C_{14}H_{17}N_5O_2 \cdot HCl$	—	—	11,0	21,6	—	—	—	—	—
XXIV	216—220	61,0	6,7	—	22,2	$C_{16}H_{21}N_5O_2$	60,9	6,7	—	22,2	—	—	1695, 1660, 1600	320 (4,29)	65
XXIV	262 (dec.)	—	—	9,9	20,1	$C_{16}H_{21}N_5O_2 \cdot HCl$	—	—	10,1	19,9	—	—	—	—	—
XXV	222—223	71,9	6,3	—	14,9	$C_{28}H_{29}N_5O_2$	71,9	6,2	—	15,0		—	1690, 1650, 1600	320 (4,28)	71
XXV	242—243	—	—	7,1	13,7	$C_{28}H_{29}N_5O_2 \cdot HCl$	—	—	7,0	13,9			—	—	—

*The compounds were recrystallized: IVb, V, VII, XII-XIX, and XXII-XXV from alcohol, IVa from ethyl acetate, XX from alcohol—ethyl acetate (1 : 1), and VIII-XI from DMF. Compound XXI was precipitated from alcohol solution by the addition of water.

Singlets of protons of CH_3 groups of a uracil fragment at 3.57 and 3.92 ppm are retained in the spectrum of XXIII; the spectrum also contains a singlet of the CH_3 group of a piperazine fragment at 3.25 (protons in the 2 position), 3.92 (5-CH_2 and 6-CH_2), and 4.80 ppm (1-CH_2).

EXPERIMENTAL

The UV spectra of alcohol solutions of the compounds were recorded with an EPS-3 spectrophotometer. The IR spectra of mineral oil pastes or CCl_4 solutions of the compounds were recorded with a Perkin–Elmer 457 spectrometer. The PMR spectra of CF_3COOH (for XIV and XXIII) and $(CD_3)_2SO$ (XI) solutions of the compounds were recorded with a JNM-4H-100 spectrometer.

α-Oxocaprolactam 1,3-Dimethyluracilyl-4-hydrazone (VI). A) From enamine Ib. A 6.1-g (30 mmole) sample of 2-oxo-3-(1-piperidyl)-1H-2,5,6,7-tetrahydroazepine Ib was added to a suspension of 5 g (30 mmole) of hydrazinouracil IIIa in 80 ml of alcohol, and the mixture was refluxed for 4 h. It was then cooled, and the resulting precipitate was removed by filtration, washed with alcohol, and dried to give 6.1 g (73%) of hydrazone VI with mp 233°C (from DMF). IR spectrum: 3215 (NH); 1695, 1620-1650 br cm^{-1} (amide C = O, C = N). UV spectrum, λ_{max} (log ε): 246 (4.23) and 318 nm (4.09). Found: C 51.5; H 6.2; N 25.1%. $C_{12}H_{17}N_5O_3$. Calculated: C 51.6; H 6.1; N 25.1%.

B) From α-oxocaprolactam II. A 1.35-g (10 mmole) sample of oxocaprolactam II and a catalytic amount of p-toluenesulfonic acid were added to a suspension of 1 g (6 mmole) of hydrazinouracil IIIa in 12 ml of alcohol, and the mixture was heated at 50°C for 30 min. It was then cooled, and the resulting precipitate was removed by filtration, washed with alcohol, and dried to give 1.5 g (95%) of hydrazone VI with mp 233°C.

Compounds IVa, b, V, and VII were similarly obtained (see Table 1).

Derivatives of 2,4,9-Trioxoazepino- (X, XI) and 2,4,8-Trioxopyrido[3,4-b]pyrrolo[2,3-d]pyrimidines (VIII, IX). Thermal Indolization. A) From the hydrazones of oxolactams IV-VII. A suspension of 16.6 g (60 mmole) of oxocaprolactam hydrazone VI in 150 ml of diethylene glycol was heated at 215-220°C for 3 h, after which it was cooled to 20°C, and 100 ml of water was added. The resulting precipitate was removed by filtration, washed with water and alcohol, and dried to give X (Table 1).

Compound XI (Table 1) was similarly synthesized. Cyclization of syn isomer IVa under similar conditions gave VIII in 51% yield, while indolization of anti isomer IVb gave VIII in 81% yield.

B) From uracilyl-4-hydrazones and enamines Ia, b without isolation of the oxolactam hydrazones. A suspension of 1.2 g (6.7 mmole) of enamine Ia and 1 g (6 mmole) of uracilylhydrazine IIIa in 10 ml of diethylene glycol was heated in a stream of nitrogen at 80°C for 2 h, and the resulting solution was heated at 200-220°C for 30 min. A precipitate formed during the heating process. The reaction mixture was cooled and treated with 25 ml of water, and the resulting precipitate was removed by filtration, washed successively with water and alcohol, and dried to give VIII (Table 1).

Compound IX (Table 1) was similarly synthesized from enamine Ia and uracilylhydrazine IIIb.

Catalytic Indolization. A mixture of 1.4 g (5 mmole) of hydrazone VI and polyphosphoric acid (PPA) (obtained from 5 g of P_2O_5 and 3 g of H_3PO_4) was heated at 130°C for 10 min, after which it was cooled, and ice was added. The resulting precipitate was removed by filtration, washed with water, and dried to give X in 67% yield.

9-(N,N-Diethylaminoethyl)-1,3-dimethyl-2,4,8-trioxo-1,2,3,4,5,6,7,8-octahydropyrido[3,4-b]pyrrolo[2,3-d]pyrimidine (XII). A suspension of 1.25 g (5 mmole) of VIII and 0.7 g (5 mmole) of anhydrous potassium carbonate was heated at 80°C for 1 h, after which it was cooled to 50-60°C, and 0.9 g (6 mmole) of N,N-diethylaminoethyl chloride was added dropwise at this temperature. The mixture was then heated at 90°C for 2 h, after which the hot mixture was filtered, and the filtrate was cooled. The precipitate was removed by filtration, washed with water, and dried to give XII (Table 1). Compounds XIII-XIX (Table 1) were similarly synthesized.

1,3-Dibenzyl-2,4-dioxo-9-chloro-7H-1,2,3,4,5,6-hexahydroazepino[3,4-b]pyrrolo[2,3-d]pyrimidine (XX). A solution of 2 g (5 mmole) of lactam XI in 30 ml of phosphorus oxychloride was heated at 80°C for 1 h, after which it was evaporated to dryness, and the residue was washed with ether. Ice was added, and the mixture was extracted with chloroform. The extract was dried with calcined sodium sulfate, the solvent was removed by evaporation, and the residue was crystallized from ethyl acetate–alcohol (1 : 1) to give XX (Table 1).

1,3-Dibenzyl-2,4-dioxo-9-ethoxy-7H-1,2,3,4,5,6-hexahydroazepino[3,4-b]pyrrolo[2,3-d]pyrimidine (XXI). A solution of sodium ethoxide (from 50 mg of Na and 2 ml of alcohol) was added dropwise at 20°C to a solution of 1 g (2 mmole) of chloroimide XX in 10 ml of absolute alcohol, and the mixture was stirred at 20°C for 1.5 h. The mixture was evaporated to a small volume and filtered to give 0.5 g of product (mp 107-108°C), which was dissolved by heating in 5 ml of alcohol. Water was added dropwise to the hot solution until crystals began to precipitate. The mixture was cooled, and the precipitate was removed by filtration to give XXI (Table 1).

1,3-Dibenzyl-2,4-dioxo-9-(N,N-diethylaminoethyl)amino-7H-1,2,3,4,5,6-hexahydroazepino[3,4-b]pyrrolo-[2,3-d]pyrimidine (XXII). A 0.6-g (5 mmole) sample of N,N-diethylaminoethylamine was added to a suspension of 1.1 g (2.5 mmole) of chloroimide XX in 10 ml of chlorobenzene, and the mixture was heated at 100°C for 1.5 h until the precipitate dissolved. The mixture was vacuum evaporated, and the residue was dissolved in 20 ml of water. The aqeuous solution was extracted with chloroform, and the extract was evaporated. The residue was triturated with ethyl acetate, and XXII was separated (Table 1).

3-Ethyl-8,10-dioxo-9,11-dimethyl-5H-1,2,6,7,8,9,10,11-octahydropyrazino [3,2,1-*lm*]azepino[3,4-b]-pyrrolo[2,3-d]pyrimidine (XXIV). A suspension of 4.7 g (13 mmole) of XVI in 75 ml of phosphorus oxychloride was refluxed for 4 h until the solid dissolved, after which the mixture was evaporated to dryness, the residue was treated with 50 ml of alcohol, and the mixture was refluxed for 1 h. It was then evaporated, and the residue was dissolved in 80 ml of water. The solution was decolorized with charcoal and made alkaline with 1 M NaOH to pH ~ 10. The resulting precipitate was removed by filtration, washed with water, and crystallized to give XXIV (Table 1).

Compounds XXIII and XXV (Table 1) were similarly synthesized.

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