RESEARCH ON LACTAMS.

XXIX.* SYNTHESIS AND SOME REACTIONS OF 2-OXO-3,3-DIHYDROXY-4-BROMOHEXAHYDROAZEPINE

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2-Oxo-3,3-dihydroxy-4-bromohexahydroazepine was obtained by bromination of an enamine of α-oxocaprolactam and subsequent hydrolysis of the resulting bromoimmonium salt and by direct bromination of α-oxocaprolactam. The reaction of the product with thiourea, N-substituted o-aminothiophenols, aminouracils, and acetoacetic ester gave derivatives of thiazolo[4,5-c]azepine, azepino[4,3-b][1,4]benzothiazine, azepino[3,4-b]pyrrolo[2,3-d]pyrimidine, and furo[2,3-c]azepine.

In developing our research on the synthesis of condensed heterocyclic compounds from lactams we studied methods for the preparation of 2-oxo-3,3-dihydroxy-4-bromohexahydroazepine (I) from enamine II [2] or oxocaprolactam III [3] and also worked out methods for the synthesis of new condensed azepines from bromolactam I.

The primary product in the bromination of enamine II with bromine in methylene chloride is imminium salt IV, which on treatment with aqueous $NaHCO_3$ solution is converted to bromoenamine V and under the influence of aqueous solutions of acids is hydrolyzed to dihydroxy compound I. This compound was also obtained by hydrolysis of bromoenamine V with aqueous acetic acid or by bromination of oxolactam III. We were unable to obtain the bromo compound in the keto form, and a product of covalent hydration of the C=O group was obtained in all cases; this constitutes evidence for high electrophilicity of the $C_{(4)}$ atom in the corresponding bromo ketone.

It should be noted that crystallization of dihydroxy compound I from methanol is accompanied by the formation of hemiketal VI.

Two absorption bands at 1685 and 1655 cm^{-1} (C=N and lactam C=O) are observed in the IR spectrum of imminium salt IV. The absorption band at 1655 cm^{-1} (C=N and lactam C=O) is retained in the spectrum of bromoenamine V, and a band of a C=C bond appears at 1620 cm^{-1}. The absorption band at 1715 cm^{-1} (ketone C=O) is absent in the spectrum of I, and only absorption at 1655 cm^{-1} (lactam C=O) is observed.

Reaction of I with o-aminothiophenol and its N-ethyl and benzyl analogs in alcoholic KOH gave azepinobenzothiazines VII-IX, treatment of which with excess triethyloxonium tetrafluoroborate gave ethylation products XII and XIII. Monoethylation of VII with an equimolar amount of triethyloxonium tetrafluoroborate gave VIII, which was identical to the compound synthesized by condensation of I with o-ethylaminothiophenol.

The method for the preparation of VII-IX was used to obtain X and XI from bromodihydroxy compound I and N-substituted o-aminothiophenols.

Thiazoloazepine XIV and furoazepine XV, respectively, were obtained by reaction of I with thiourea in water and by condensation of I with acetoacetic ester in alcohol in the presence of sodium ethoxide.

*See [1] for communication XXVIII.

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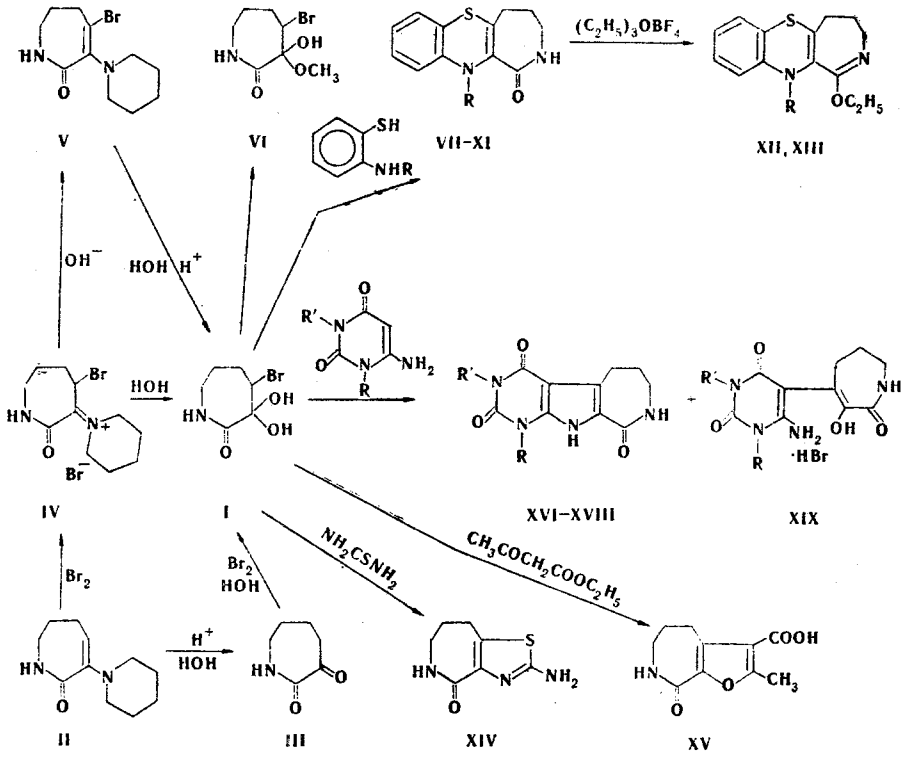
The structure of furoazepine XV was confirmed by its PMR spectrum, which contains multiplet signals of methylene protons in the 5, 4, and 6 positions of the azepine ring at 2.05, 2.84, and 3.30 ppm, respectively, a singlet of protons of a CH_3 group at 2.43 ppm, and a markedly broadened signal of protons of NH and OH groups at 7.5 ppm. The formation of furoazepine acid XV rather than the corresponding ester is explained by alkaline hydrolysis of the ester due to the water liberated during the condensation.

The reaction of I with 1-methyl- and 3-methyl-4-aminouracils in acetic acid proceeds with the formation of azepinopyrrolopyrimidines XVII and XVIII, respectively. The structure of XVII is confirmed by its PMR spectrum, which contains multiplets of protons of CH_2 groups of the azepine ring in the 6, 5, and 7 positions (2.30, 3.30, and 3.65 ppm) and of the azepine and pyrrole NH groups at 8.26 ppm (2H), the signal of an NH group of a uracil fragment at 8.29 ppm, and an NCH_3 singlet at 3.78 ppm. The PMR spectrum of XVIII is similar to the spectrum of azepinopyrrolopyrimidine XVII, but the signals of the protons of the NH groups are found at 8.26, 8.28, and 10.53 ppm; the weak-field signal is evidently related to the proton of the NH imide group in the 3 position of the uracil fragment.



VII R=H; VIII R=C_2H_5; IX R=$CH_2C_6H_5$; X R=$CH_2CH_2N(CH_3)_2$; XI R=$CH_2CH_2N(C_2H_5)_2$; XII R=C_2H_5; XIII R=$CH_2C_6H_5$; XVI R=R′=CH_3; XVII R=H, R′=CH_3; XVIII R=CH_3, R′=H; XIX R=R′=CH_3

Two substances, one of which, according to the UV and IR spectral data, is identical to 1,3-dimethyl-2,4,9-trioxo-9H,1,2,3,4,5,6,7,8-**octahydroazepino[3,4-b]pyrrolo[2,3-d]pyrimidine** XVI obtained previously by indolization of α-oxocaprolactam 1,3-dimethyl-4-hydrazone [1], were isolated in the case of the reaction of I with 1,3-dimethyl-4-aminouracil in acetic acid. The 4-(1,3-dimethyl-4-amino-5-uracilyl)-2-oxo-3-hydroxy-1H-2,5,6,7-tetrahydroazepine hydrobromide structure (XIX) was proposed for the second compound on the basis of its PMR spectrum. Attempts to cyclize XIX to three-ring compound XVI were unsuccessful.

EXPERIMENTAL

The UV spectra of alcohol solutions of the compounds were recorded with an EPS-3 spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin–Elmer 457 spectrometer. The PMR spectra of the compounds in the following solvents were recorded with a JMN-4H-100 spectrometer with tetramethylsilane as the internal standard: $(CD_3)_2SO$–CCl_4 for XV and trifluoroacetic acid for XVI-XIX. The melting points of the compounds were determined with an MP-1 apparatus manufactured by the Uamoto Scientific Co., Ltd. The purity of the compounds was monitored by chromatography on Silufol plates.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	bp, °C	Crystallization solvent	Found, %					Empirical formula	Calculated, %					IR spectrum, cm⁻¹		UV spectrum λ_{max}, nm (log ε)	Yield, %
			C	H	Br	N	S		C	H	Br	N	S	OH, NH	amide C=O, C=C, C=N		
I	120—121	Ethyl acetate	32,0	4,6	35,7	6,3	—	$C_6H_{10}BrNO_3$	32,2	4,5	35,7	6,3	—	3320, 3270, 3100	1655	—	61
V	120—121	Hexane	48,4	6,2	29,5	10,3	—	$C_{11}H_{17}BrN_2O$	48,4	6,2	29,3	10,3	—	3300, 3200, 3070	1655	308 (3,43)	57
VI	124—126	Methanol	34,9	5,1	33,3	6,1	—	$C_7H_{12}BrNO_3$	35,2	5,0	33,6	5,9	—	3400, 3300, 3260	1660	—	
VII	182—184	Ethyl acetate	61,9	5,0	—	11,9	13,6	$C_{12}H_{12}N_2OS$	62,1	5,2	—	12,1	13,8	3360, 3280, 3220	1645	Shoulder 235 (4,14), 315 (3,30)	77
VIII	214—215	Alcohol	64,4	6,2	—	10,6	12,2	$C_{14}H_{16}N_2OS$	64,6	6,2	—	10,8	12,3	3300, 3200, 3080	1660 1660	254 (4,24), 285 (3,84)	53
IX	201—202		70,8	5,7	—	8,9	9,8	$C_{19}H_{18}N_2OS$	70,8	5,6	—	8,7	9,9	3300, 3230, 3070	1610 1580	252 (4,14), 286 (3,73)	23
X	182—183	Benzene	64,3	7,2	—	13,1	10,2	$C_{17}H_{23}N_3OS$	64,3	7,3	—	13,2	10,1	3300, 3200, 3060	1660 1610 1650	253 (4,10), 286 (3,71)	30
XI	143—144	Hexane	64,6	7,6	—	—	9,5	$C_{18}H_{25}N_3OS$	65,2	7,6	—	—	9,7	3300, 3200, 3050	1605 1570 1630	220 (4,13), 254 (4,10) 286 (3,73)	60
XII	81—82	Hexane	66,4	6,7	—	9,6	11,0	$C_{16}H_{20}N_2OS$	66,7	6,9	—	9,7	11,1	— — —	1605 1575 1630	253 (4,10), 288 (3,66)	37
XIII	124—125	Hexane	72,1	6,4	—	8,2	9,1	$C_{21}H_{22}N_2OS$	72,0	6,3	—	8,0	9,1	— — —	1610 1585	252 (4,20), 283 (3,76)	49
XIV	268 (dec.)	Isopropyl aclohol	45,7	4,9	—	23,1	17,2	$C_7H_9N_3OS$	45,9	4,9	—	23,0	17,5	3420, 3270, 3140	1640 1605	284 (3,61)	75
XV	223—224		56,9	5,3	—	6,7		$C_{10}H_{11}NO_4$	57,4	5,3	—	6,7	—	3360, 3280 —	1740 1630	—	40
XVI	>300		54,5	5,4	—	21,5		$C_{12}H_{11}N_4O_3$	54,9	5,3	—	21,4	—	3185, 3140 —	1700 1640	—	4
XVII	>300 (dec.)	Aqueous dimethylformamide	52,7	4,9	—	22,9		$C_{11}H_{12}N_4O_3$	53,2	4,8	—	22,6	—	— — —	—	222 (4,88), 286 (3,26)	50
XVIII	>300		53,0	4,8	—	22,7		$C_{11}H_{12}N_4O_3$	53,2	4,8	—	22,6	—	— — —	—	241 (4,18), 305 (4,03)	50
XIX	303—305 (dec.)		39,8	4,7	22,3	15,5		$C_{12}H_{16}N_4O_4 \cdot HBr$	39,9	4,7	22,2	15,5	—	— — —	—	272 (3,13)	55

2-Oxo-3-(N-piperidyl)-4-bromo-2H-1,5,6,7-tetrahydroazepine (V). A solution of 9 g of bromine in 30 ml of methylene chloride was added dropwise at 10°C to a solution of 10 g (0.05 mole) of II in 70 ml of methylene chloride, and the mixture was heated at 30°C for 2 h, during which the immonium salt precipitated: The salt is extremely hydroscopic, as evidenced by the decrease in bromine content with time and the appearance in the IR spectrum of bands at 3450 and 3505 cm^{-1} (OH). The precipitated salt was suspended in 100 ml of methylene chloride, and the suspension was cooled to 0°C. A solution of triethylamine in methylene chloride was added dropwise to the cooled suspension until the solid dissolved, and the solution was stirred for 30 min. Water (50 ml) was added, and the organic layer was separated, washed with water, and vacuum evaporated. The residue was triturated with water, and the solid was removed by filtration and dried.

α,α-Dihydroxy-β-bromocaprolactam (I). A) From Oxolactam III. A solution of 22.5 g of bromine in 50 ml of methylene chloride was added dropwise at 5-7°C to a solution of 13.2 g (0.1 mole) of lactam III in 200 ml of methylene chloride. At the end of the addition, the mixture was at room temperature, for 2 h, after which it was evaporated, and the residue was triturated with cold water. The solid material was removed by filtration, washed successively with cold water and acetone, and dried.

B) From Salt IV. A suspension of 2.2 g (0.06 mole) of salt IV in 30 ml of water and 7 ml of acetic acid was heated at 40-45°C for 2 h, after which it was cooled to 0°C, and the precipitate was removed by filtration, washed with water, and dried.

2-Oxo-3-hydroxy-3-methoxy-4-bromohexahydroazepine (VI). This compound was obtained by heating (or crystallization) of I in methanol.

1-Oxo-1H,2,3,4,5-tetrahydroazepino[4,3-b][1,4]benzothiazines (VII-XI). A solution of 0.01 mole of I in 40 ml of absolute alcohol was added at 7-10°C to a solution of 0.01 mole of KOH and 0.01 mole of the corresponding aminothiophenol in 20 ml of absolute alcohol, and the mixture was stirred at 10°C for 1 h and at 20°C for 2 h. The precipitated KBr was removed by filtration and washed with absolute alcohol. The alcohol solution was evaporated to dryness, and 15 ml of water and 2 ml of 2 M HCl solution were added to the residue. Compounds VII-IX were removed by filtration and crystallized. For the isolation of X-XI the reaction mixture was made alkaline and extracted with benzene.

N-Ethyl-1-oxo-1H-2,3,4,5-tetrahydroazepino[4,3-b][1,4]benzothiazine (VIII) by Ethylation of VII with Triethyloxonium Tetrafluoroborate. A solution of 1.15 g (0.005 mole) of VII in 30 ml of chloroform was added at 6°C to a solution of 1.4 g (0.006) mole of triethyloxonium tetrafluoroborate in 10 ml of chloroform, and the mixture was stirred at 10°C for 4 h. It was then cooled to −3°C and made alkaline to pH 8 with aqueous potassium carbonate solution. It was then filtered, and the chloroform solution was separated, dried, and evaporated to dryness. The residue was triturated with ether, and the solid material was removed by filtration and dried.

1-Ethoxy-3H-4,5-dihydroazepino[4,3-b][1,4]benzothiazines (XII-XIII). A suspension of 0.011 mole of VII in 30 ml of methylene chloride was added at 5°C to a solution of 0.034 mole of triethyloxonium tetrafluoroborate in 30 ml of dry methylene chloride, and the mixture was maintained at 5°C for 2 h, after which it was allowed to stand overnight. It was then cooled to −3°C and made alkaline to pH 8 with a 20% aqueous solution of potassium carbonate. The mixture was filtered, and the organic layer was separated, dried, and evaporated to dryness. The residue was triturated with hexane, and the solid material was removed by filtration and dried.

2-Amino-4-oxo-4H-5,6,7,8-tetrahydrothiazolo[4,5-c]azepine (XIV). A mixture of 10.7 g (0.0475 mole) of I, 3.75 g (0.05 mole) of thiourea, and 200 ml of water was refluxed for 2 h, during which the solid material dissolved (the pH of the solution was ∿ 3). The mixture was then cooled to 20°C and neutralized to pH ∿ 7.5 with 2 M NaOH. The resulting precipitate was removed by filtration, washed with water, and dried.

2-Methyl-8-oxo-8H-4,5,6,7-tetrahydrofuro[2,3-c]azepine-3-carboxylic Acid. A 5.7-g (0.04 mole) sample of acetoacetic ester and (in portions) 8.25 g (0.04 mole) of I were added dropwise successively to a solution of sodium ethoxide (obtained from 1 g of Na and 80 ml of absolute alcohol) at 0°C, and the mixture was stirred at 0°C for 8 h and allowed to stand overnight at 20°C. It was then acidified to pH 7 with 2 M HCl and filtered, and the mother

liquor was evaporated to dryness. The residue was triturated with water and the solid material was removed by filtration and dried.

4-(1,3-Dimethyl-4-amino-5-uracilyl)-2-oxo-3-hydroxy-1H-2,5,6,7-tetrahydroazepine Hydrobromide (XIX) and 1,3-Dimethyl-2,4,9-trioxo-9H-1,2,3,4,5,6,7,8-octahydroazepino[3,4-b]pyrrolo-[2,3-d]pyrimidine (XVI). A 4.8-g (0.02 mole) sample of I was added at 20°C to a suspension of 3.1 g (0.02 mole) of 1,3-dimethyl-4-aminouracil in 30 ml of glacial AcOH, and the mixture was heated at 60°C for 1 h. It was then cooled to 20°C, and the precipitate was removed by filtration, washed with alcohol, and dried to give XIX.

Compound XIV was isolated from the acetic acid mother liquor when it was cooled to 5°C.

N-Methyl-2,4,9-trioxo-9H-1,2,3,4,5,6,7,8-octahydroazepino[3,4-b]pyrrolo[2,3-d]pyrimidines (XVII, XVIII). A suspension of 0.01 mole of 3-methyl- or 1-methyl-4-aminouracil and 0.01 mole of I in 15 ml of glacial AcOH was heated at 100°C for 8.5 h, after which it was cooled, and the precipitate was removed by filtration and suspended in 30 ml of water. The suspension was made alkaline to pH 8 with 1 N NaOH, and the precipitate was removed by filtration, washed with water, and dried to give XVII and XVIII.

LITERATURE CITED

1. R. G. Glushkov, I. M. Zasosova, and I. M. Ovcharova, Khim. Geterotsikl. Soedin., No. 10, 1398 (1977).
2. R. G. Glushkov, V. A. Volskova, V. G. Smirnova, and O. Yu. Magidson, Dokl. Akad. Nauk SSSR, 187, 327 (1969).
3. R. G. Glushkov, V. G. Smirnova, and N. A. Novitskaya, Khim.-Farm. Zh., No. 6, 14 (1972).
4. V. G. Smirnova and R. G. Glushkov, USSR Inventor's Certificate No. 458552; Byul. Izobr., No. 4, 51 (1975).
5. R. G. Glushkov and V. G. Granik, Usp. Khim., 38, 1989 (1969).

SYNTHESIS AND IONIZATION CONSTANTS OF N-(4-CARBETHOXY-5-PYRAZOLYL)AMIDINES*

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A number of N-(4-carbethoxy-5-pyrazolyl)amidines were synthesized by the reaction of acetals of amides and lactams with 4-carbethoxy-5-aminopyrazole, and their ionization constants in 50% alcohol were measured. It is shown that the increased basicities of the amidines obtained from the lactam acetals and dimethylacetamide acetal as compared with the basicity of N-(4-carbethoxy-5-pyrazolyl)-N',N'-dimethylformamidine are due to the smaller degree of steric hindrance to conjugation in the latter.

Acetals of amides and lactams readily react with aromatic and heteroaromatic amines (for example, see [2]) to give the corresponding amidines.

Amidines II-VI were synthesized in the present research by reaction of 4-carbethoxy-5-aminopyrazole (I) with the diethylacetals of dimethylformamide (DMF), dimethylacetamide, N-methylbutyrolactam, N-methylvalerolactam, and N-methylcaprolactam:

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