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SYNTHESIS OF NEW MACROCYCLIC LACTAMS, LACTONES, AND THIOLACTONES

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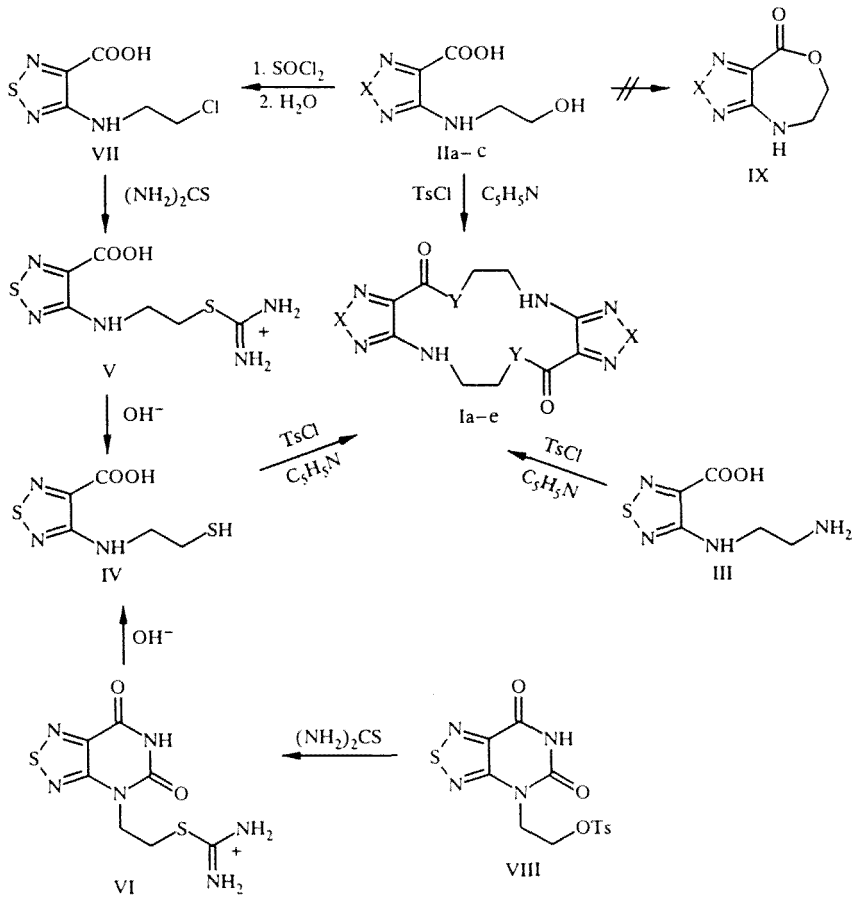
A general method has been developed for the preparation of 14-membered cyclic lactams, lactones, and thiolactones from heteroaromatic amino acids.

Polyfunctional macroheterocycles, including oxygen and sulfur containing azoles, are basic structural units of a number of biologically active compounds extracted from natural sources and their synthetic analogs [1-6].

In a continuation of our studies of the synthesis and properties of heteroaromatic amino acids of the 1,2,5-chalcodiazole series [7-10], we have developed a general method for the synthesis of 14-membered cyclic lactams, lactones, and thiolactones (I) from 3-amino-1,2,5-chalcodiazole-4-carboxylic acids substituted at position 3 (II-IV):



I a X = S, Y = NH; b X = O, Y = O; c X = S, Y = O; d X = Se, Y = O; e X = S, Y = S;
II a X = O; b X = S; c X = Se

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TABLE 1. Characteristics of Macrocyclic Lactams, Lactones and Thiolactones Ia-e

Compound	Molecular formula	mp °C	M+	^{1}H NMR Spectrum (DMSO-D_6), δ, ppm (J, Hz)	IR Spectrum, cm^{-1}	Yield, %
Ia	$C_{10}H_{12}N_8O_2S_2$	275...290	340	3,74 (8H, m, $2C_2H_4$), 7,23 (2H, t, J = 6, 2NH), 7,60 (2H, t, J = 6, 2NH)	3350, 3325, 1650, 1530	27
Ib	$C_{10}H_{10}N_6O_6$	270...280	310	3,57 (4H, q, J = 5, $2CH_2$), 4,53 (4H, t, J = 5, $2CH_2$), 6,44 (2H, t, J = 6, 2NH)	3390, 1700, 1580, 1540	32
Ic	$C_{10}H_{10}N_6O_4S_2$	>300	342	3,73 (4H, q, J = 5, $2CH_2$), 4,55 (4H, t, J = 5, $2CH_2$), 7,25 (2H, t, J = 6, 2NH)	3380, 1690, 1540	30
Id	$C_{10}H_{10}N_6O_4Se_2$	280...290	438	3,72 (4H, q, J = 5, $2CH_2$), 4,57 (4H, t, J = 5, $2CH_2$), 7,21 (2H, t, J = 6, 2NH)	3380, 1690, 1540	28
Ie	$C_{10}H_{10}N_6O_2S_4$	>300	374	3,79 (8H, t, $2C_2H_4$), 7,20 (2H, t, J = 6, 2NH)	3340, 1630, 1600	34

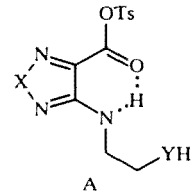
We have described the 3-(β-hydroxyethylamino)-1,2,5-oxa(thia, selena)diazole-4-carboxylic acids (IIa-c) and 3-(β-aminoethylamino)-1,2,5-thiadiazole-4-carboxylic acid (III) starting materials previously [7, 8, 10].

3-(β-Mercaptoethylamino)-1,2,5-thiadiazole-4-carboxylic acid (IV) was obtained by alkaline hydrolysis of the isothiouronium salts (V, VI) which were synthesized, in their turn, by the reaction of thiourea with 3-(β-chloroethylamino)-1,2,5-thiadiazole-4-carboxylic acid (VII) [10] and 4-(β-toluenesulfonylethyl)-1,2,5-thiadiazolo[3,4-*d*]pyrimidin-5,7-(4H,6H)-dione (VIII) [7] respectively.

Different products were obtained from the cyclization of amino acids II and III depending on the reagents used. Thus treatment of the hydroxy acids IIa-c with thionyl chloride did not give either of the possible cyclic products (I, IX), but instead gave the 3-(β-chloroethylamino)-1,2,5-chalcodiazole-4-carbonyl chlorides in quantitative yield and these were converted to I by treatment with water.

When the amino acids (III) were boiled with acetic anhydride in pyridine the main product was 5,8-diacetyl-1,2,5-thiadiazolo[4,3-*e*]-5,6,7,8-tetrahydro-4H-1,4-diazepin-4-one [10].

The method of mixed anhydrides with *p*-toluenesulfonic acid was used successfully to make compounds Ia-e. This method has been used successfully before to prepare linear and cyclic peptolides [11] and tosyllactams [12, 13]. The absence of products from intramolecular cyclization is probably explained by the presence in the intermediate (A) of a hydrogen bond between the carbonyl oxygen and the proton of the heteroaromatic amino group.



A

Y = O, S, N

With this geometry for the intermediate, stabilized by a hydrogen bond, the reaction centers are separated as far as possible from one another which determines the interemolecular nature of further reactions. The structures of the macroheterocycles were established by mass spectrometry, IR and ^{1}H NMR spectroscopy (Table 1). The mass spectra of the lactones Ib-d contain intense molecular ion peaks (relative intensity 50-70%). The principal direction of decomposition under electrton impact is β-scission of the ethyl fragment with hydrogen transfer. The molecular ions of the lactam Ia and the thiolactone Id are an order of magnitude less intense and their decomposition is more complex. Signals of the ethyl and NH groups are present in the ^{1}H NMR spectra of lactones Ib-d. Interestingly the signals of lactone Ib (especially the NH

TABLE 2. Elemental Analysis Data

Compound	Found, %			Molecular formula	Calculated, %		
	C	H	N		C	H	N
Ia	35,10	3,56	33,00	$C_{10}H_{12}N_8O_2S_2$	35,29	3,53	32,94
Ib	38,50	3,20	27,12	$C_{10}H_{10}N_6O_6$	38,71	3,23	27,10
Ic	35,20	2,95	24,55	$C_{10}H_{10}N_6O_4S_2$	35,09	2,92	24,56
Id	27,45	2,30	19,20	$C_{10}H_{10}N_6O_4Se_2$	27,40	2,28	19,18
Ie	32,18	2,66	22,40	$C_{10}H_{10}N_6O_2S_4$	32,09	2,67	22,46
IV	29,32	3,40	20,51	$C_5H_7N_3O_2S_2$	29,27	3,41	20,49
V	18,28	2,60	17,80	$C_6H_{10}N_5O_2S_2$	18,23	2,53	17,72
VI	37,92	3,85	18,96	$C_{14}H_{17}N_6O_5S_3$	37,84	3,83	18,92

groups), which has the most electronegative heterocycle, appear at the strongest field (Table 1). The ^{1}H NMR Spectra of lactam Ia and thiolactone Ie differ in the multiplicity of the signals of the ethylene fragment.

EXPERIMENTAL

Purity of products was monitored by TLC on Silufol UV-254-vis strips. Mass spectra were recorded with a Varian MAT-112 machine. IR spectra of Nujol mulls were recorded with a Specord-80 spectrometer. ^{1}H NMR Spectra of DMSO-D_6 solutions were obtained with a Bruker WM-250 instrument.

β-(4-Carboxy-1,2,5-thiadiazolo-3-amino)ethylisothiouronium Iodide (V, $C_6H_9N_5O_2S_2 \cdot HI$). A mixture of compound VII (2 g, 0.01 mol) and thiourea (0.8 g, 0.01 mol) in isopropanol (80 cm^3) was boiled until precipitation ceased. The reaction time could be shortened by addition of an equimolar amount of NaI. The precipitate was filtered off and washed with small amounts of cold water and ethanol to give compound V (2.3 g, 60%), mp 230°C (dec.). M^+ 247 (free base). IR Spectrum: 3300-3100, 1660, 1630, 1550, 1540 cm^{-1}.

β-(4-Isothiouronioethyl)-1,2,5-thiadiazolo[3,4-*d*]pyrimidin-5,7-(4H,6H)-dione Tosylate (VI, $C_7H_8N_4SO_2 \cdot C_7H_8SO_3$). A mixture of compound VIII (3.7 g, 0.01 mole) and thiourea (0.8 g, 0.01 mole) in dioxane (100 cm^3) was boiled until precipitation ceased. The precipitate was filtered off and washed with small amounts of cold water and ethanol to give compound VI (3.7 g, 83%), mp 280-282°C. M^+ 272 (free base). IR Spectrum: 3360, 3300, 3220-3040, 1720, 1690, 1650, 1540 cm^{-1}.

3-(β-Mercaptoethylamino)-1,2,5-thiadiazolo-4-carboxylic Acid (IV, $C_5H_7N_3S_2O_2$). A solution of compound V (3.8 g, 0.01 mole) and NaOH (6 g) in water (80 cm^3)was boiled for 1 h. The hot solution was filtered and HCl added to pH 3-2. After cooling, the precipitate was filtered off and recrystallized from ethanol to give thiol IV (1.9 g, 92%), mp 162-164°C. M^+ 205. IR Spectrum: 3320, 1680, 1670, 1555, 1540 cm^{-1}. Compound Iv was made analogously from salt VI.

General Method for the Preparation of di-1,2,5-thiadiazolo[3,4-*b,i*]-1,4,8,11-tetraazacyclotetradeca-4,13-dione (Ia, $C_{10}H_{12}N_8O_2S_2$), Di-1,2,5-oxa(thia, selena)diazolo[3,4-*c,j*]-1,8-dioxa-5,12-diazacyclotetradeca-4,13-dione (Ib, $C_{10}H_{10}N_6O_6$; Ic, $C_{10}H_{10}N_6O_4S_2$; Id, $C_{10}H_{10}N_6O_4Se_2$) and Di-1,2,5-thiadiazolo[3,4-*c,j*]-1,8-dithio-5,12-diazatetradeca-4,13-dione (Ie, $C_{10}H_{10}N_6O_4S_4$). A solution of TsCl (0.012 mole) in dry tetrahydrofuran (10 cm^3) was slowly added with intense stirring to a solution of compound II-IV (0.01 mole) in dry pyridine (20 cm^3). The mixture was then brought to the boil and most of the solvents were removed in vacuum. The residue was diluted with water (70 cm^3) and filtered, The products Ib-Id were recrystallized from dioxane or DMSO; Ia and Ie were precipitated from DMSO with water.

REFERENCES

1. B. M. Degnan, C. J. Hawkins, M. S. Levin, E. J. McCaffrey, D. L. Parry, and D. J.Watters, J. Med. Chem., **32**, 1354 (1989).
2. T. W. Hamblay, C. J. Hawkins, M. F. Lavin, A. Van den Brenk, and D. J. Watters, Tetrahedron, **48**, 341 (1992).
3. M. R. Prinsep, R. E. Moore, J. A. Levin, and G. M. L. Patterson, J. Nat. Prod., **56**, 140 (1992)
4. C. Clark, B. M. Olivera, and L. J. Cruz, Toxicon, **19**, 691 (1981).

5. D. Chatterjee, N. V. Harris, T. Parker, C. Smith, and P. J. Warren, UK Pat 2,206,577; Ref. Zhur. Khim., 8O150P (1991).
6. M. P. Foster, G. P. Concepcion, and Ch. B. Caraan, J. Org. Chem., **57**, 6671 (1992).
7. É. I. Ivanov, A. A. Yavolovskii, E. A. Kuklenko, and O. S. Timofeev, Khim. Geterotsikl. Soedin., No. 2, 272 (1991).
8. É. I. Ivanov, A. A. Yavolovskii, E. A. Kuklenko, and P. Yu. Ivanova, Zh. Org. Khim., **28**, 422 (1992).
9. Yu. A. Simonov, A. A. Dvorkin, É. I. Ivanov, A. A. Yavolovskii, and E. A. Kuklenko, Zh. Strukt. Khim., No. 4, 169 (1993).
10. É. I. Ivanov, A. A. Yavolovskii, E. A. Kuklenko, O. S. Timofeev, R. Yu. Ivanova, and L. V. Grishchuk, Zh. Org. Khim., **29**, 400 (1993).
11. A. Schroeder and K. Lyubke. Peptides [Russian translation], Mir, Moscow, 1967, Vol. 1, p.368.
12. V. Cut and J. Rudinger, Coll. Czech. Chem. Comm., **28**, 2953 (1963).
13. J. Rudinger, K. Poduska, M. Zaoral, and K. Jost, Coll. Czech. Chem. Comm., **21**, 770 (1956).