DERIVATIVES OF OROTIC ACID AND ITS ANALOGS

VI. 2,4,6-Trisubstituted 7-Oxo-5,7-dihydropyrrolo[3,4-d]pyrimidines*

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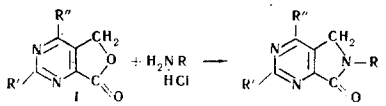
A number of 2,4,6-trisubstituted derivatives of 7-oxo-5,7-dihydropyrrolo[3,4-d]pyrimidine has been synthesized by the reaction of hydrochlorides of primary amines with 2,4-disubstituted derivatives of the lactone of 5-(hydroxymethyl)pyrimidine-6-carboxylic acid.

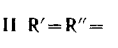
The present work is devoted to a further study of the properties of 2,4-diamino-substituted derivatives of the lactone of 5-(hydroxymethyl)pyrimidine-6-carboxylic acid (I) [1] and the synthesis from them of lactams which are derivatives of 2,4,6-trisubstituted 7-oxo-5,7-dihydropyrrolo[3,4-d]pyrimidines. In a preceding paper [2] we reported the synthesis of 2,4,7-trioxo derivatives of pyrrolo[3,4-d]pyrimidine obtained by the reaction of the lactone of 5-(hydroxymethyl)-orotic acid with ammonia and primary amines and their hydrochlorides. A study of the properties of the 2,4-diamino-substituted lactones I [1] showed that in contrast to the lactone of 5-(hydroxymethyl)orotic acid, it was possible to obtain from them derivatives of pyrrolo[3,4-d]pyrimidine only under the action of hydrochlorides of primary amines in ethylene glycol at a high temperature (140–180° C). Only in individual cases did the action of hydrochlorides of primary aromatic amines yield derivatives of pyrrolo[3,4-d]pyrimidine at a lower temperature (78–100° C).

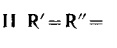
Under similar conditions, the action of amines in the form of bases on the 2,4-diamino-substituted lactones I containing a tertiary amino group (R") in position 4 did not lead to a reaction, and the initial lactones I were recovered quantitatively from the reaction mixture. A small amount of pyrrolo[3,4-d]-pyrimidine derivatives was obtained only when a secondary amino group was present in position 4 of the lactone I.

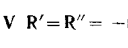
The absence of a reaction between primary amines and the lactones I and the comparatively ready formation of derivatives of pyrrolo[3,4-d]pyrimidine by the reaction of the lactones I with hydrochlorides of primary amines is connected with the necessity for the presence of a proton in the reaction medium. It is possible that the activation of the molecule of the lactone I then takes place through the addition of a proton to it, which facilitates the action of nucleophilic reagents on I.

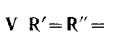


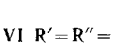
*For part V, see [1].

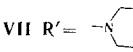
II R′=R″=  ; R=—C_6H_5

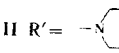
III R′=R″=  ; R=—$(CH_2)_2OH$

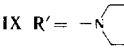
IV R′=R″=  ; R=—C_6H_5

V R′=R″=  ; R=—$CH_2—C_6H_5$

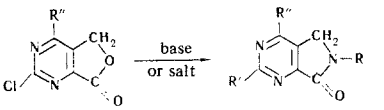
VI R′=R″=  ; R=—$CH_2—C(=O)OCH_2—CH_2OH$

VII R′=  ; R″=—NHC_6H_5; R=—$C_6H_4OCH_3$

VIII R′=  ; R″=—NHC_6H_5; R=—$C_6H_4OCH_3$

IX R′=  ; R″=—$NH(CH_2)_2Cl$; R=—C_6H_5

If there is not an amine group but a chlorine atom in position 2 of the pyrimidine ring in the lactone I, it is possible to obtain derivatives of pyrrolo[3,4-d]-pyrimidine from such a lactone both by the action of hydrochlorides of primary amines and by the action of ammonia or primary amines in the form of the bases. In this case possibly the aminolysis of the chlorine takes place, and the hydrochloric acid liberated is sufficient for the protonation of the lactone I.



X R′=R″=—NHC_6H_5; R=—C_6H_5

XI R′=—NH_2; R″=—NHC_6H_5; R=H

XII R′=—NHC_6H_5; R″=—NHC_6H_4OH; R=—C_6H_5

XIII R′=—$NHC_6H_4OCH_3$; R″=NHC_6H_5; R=$C_6H_4OCH_3$

XIV R′=—NHC_4H_9; R″=—NHC_6H_5; R=—C_4H_9

The fact that the presence of a proton is necessary for the formation of pyrrolo[3,4-d]pyrimidines in the case of the 2,4-diamino-substituted lactones I is confirmed by the fact that in such aprotic solvent as dimethylformamide this reaction does not take place at all. For lactones containing oxo groups in positions 2 and 4, the absence of protons from the medium does not have such a marked effect on the formation of pyrrolo[3,4-d]pyrimidine derivatives [1].

In a study of the reaction of the lactones I with hydrochlorides of primary amines, we were interested in the question of what compounds could be intermediates in the synthesis of the pyrrolo[3,4-d]pyrimidine derivatives. It was found that in the reaction with amine hydrochlorides, depending on the reaction conditions,

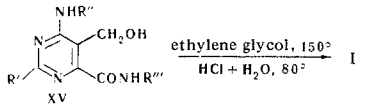
Characteristics of 2,4,6-Trisubstituted 7-Oxo-5,7-dihydropyrrolo[3,4-d]pyrimidines

Compound	Bases of their salts used in the synthesis	Mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
				C	H	Cl	N	C	H	Cl	N	
II	$C_6H_5NH_2 \cdot HCl$	247	$C_{22}H_{27}N_5O$	70.20	7.16		19.11	70.02	7.16		18.56	64
III	$H_2N(CH_2)_2OH \cdot HCl$	166	$C_{18}H_{27}N_5O_2$	62.35	7.85		20.03	62.60	7.82		20.28	52
IV	$C_6H_5NH_2 \cdot HCl$	273	$C_{20}H_{23}N_5O_3$	62.49	6.01		18.68	62.99	6.03		18.37	72
V	$C_6H_5CH_2NH_2 \cdot HCl$	242	$C_{21}H_{25}N_5O_3$	63.88	6.58		17.54	63.79	6.32		17.72	79
VI	$H_2NCH_2COOH + HCl$	208	$C_{19}H_{27}N_5O_6$	54.26	6.37		16.58	54.15	6.41		16.62	60
VII	$H_2NC_6H_4OCH_3 \cdot HCl$	284	$C_{24}H_{25}N_5O_2$	69.15	6.01		16.76	69.39	6.02		16.86	74
VIII	$H_2NC_6H_4OCH_3 \cdot HCl$	280	$C_{23}H_{24}N_5O_3$	66.01	5.82		16.71	66.02	5.74		16.74	82
IX	$C_6H_5NH_2 \cdot HCl$	259	$C_{19}H_{22}ClN_5O$*	61.20	5.77	9.56	18.73	61.37	5.92	9.55	18.84	48
X	$C_6H_5NH_2$ or $C_6H_5NH_2 \cdot HCl$	183	$C_{24}H_{19}N_5O \cdot CH_3OH$	70.97	5.10		16.55	70.58	5.41		16.45	71
XI	NH_3	250	$C_{12}H_{11}N_5O \cdot HCl \cdot 0.5H_2O$**	50.38	4.99	12.25	24.33	50.26	4.53	12.32	24.43	54
XII	$C_6H_5NH_2 \cdot HCl$	283	$C_{24}H_{19}N_5O_2$	70.50	4.64		17.08	70.41	4.91		17.11	36
XIII	$H_2NC_6H_4OCH_3 \cdot HCl$	169	$C_{26}H_{23}N_5O \cdot H_2O$	66.53	5.21		14.84	66.23	5.30		14.86	58
XIV	$C_4H_9NH_2$	186	$C_{20}H_{27}N_5O$	68.52	7.35		19.99	67.98	7.64		19.83	

*Found, %: Cl 9.56. Calculated, %: Cl 9.55.

**Found, %: Cl 12.25. Calculated, %: Cl 12.32.

either the initial lactone I or the final reaction products—the pyrrolo[3,4-d] derivatives—were isolated. It was impossible to isolate any intermediate substances whatever. The derivatives of 5-(hydroxymethyl)pyrimidine-6-carboxyamide (XV) that we obtained previously by the action of primary amines on a lactone I containing a secondary amino group in position 4 [2] likewise proved not to be intermediates in the synthesis of the pyrrolo[3,4-d]pyrimidine derivatives. Such amides are unstable compounds: on heating in ethylene glycol to 150° C they lose the amino group with simultaneous cyclization, i.e., with the formation of the lactone ring of I. We obtained the same lactones I previously by the hydrolysis of the amides XV in dilute hydrochloric acid [2].



All the 2,4,6-trisubstituted 7-oxo-5,7-dihydropyrrolo[3,4-d]pyrimidine derivatives synthesized are stable crystalline compounds which dissolve in dimethylformamide and are sparingly soluble in ethanol and insoluble in water. The IR absorption spectra show the characteristic bands in the region of the stretching vibrations of carbonyl groups. Pyrrolo[3,4-d]pyrimidine derivatives containing a tertiary amino group in position 4 show an absorption band at 1710–1700 cm^{-1} for the C=O group in position 7, and derivatives containing a secondary amino group in position 4 show this band in the 1690–1670 cm^{-1} region. Furthermore, the latter compounds show characteristic bands of the stretching vibrations of the secondary amino group in the high-frequency region in the range from 3400 to 3200 cm^{-1}. The IR spectra of all the compounds were recorded on a UR-10 spectrometer in the form of mulls in paraffin oil.

EXPERIMENTAL

7-Oxo-6-phenyl-2,4-dipiperidino-5,7-dihydropyrrolo[3,4-d]pyrimidine (II). A mixture of 30.2 g (0.1 mole) of the 2,4-dipiperidinolactone I (R′ = R″ = piperidino) and 32.4 g (0.25 mole) of aniline hydrochloride was heated in ethylene glycol (1:10) at 140° C for 1 hr 30 min. After cooling and dilution of the mixture with water, crystalline sodium bicarbonate was added to neutrality. The precipitate of II was filtered off, washed with water, and crystallized from ethanol.

6-(β-Hydroxyethyl)-7-oxo-2,4-dipiperidino-5,7-dihydropyrrolo-[3,4-d]pyrimidine (III). A mixture of 30.2 g (0.1 mole) of the 2,4-dipiperidinolactone I (R′ = R″ = piperidino) and 24.4 g (0.25 mole) of ethanolamine hydrochloride was heated in ethylene glycol (1:5) at 200° C for 3 hr. The ethylene glycol was distilled off in vacuum. The residue consisted of III, which was crystallized from aqueous ethanol.

7-Oxo-2,4-dimorpholino-6-phenyl-5,7-dihydropyrrolo[3,4-d]-pyrimidine (IV). A mixture of 30.6 g (0.1 mole) of the 2,4-dimorpholinolactone I (R′ = R″ = morpholino) with 32.4 g (0.25 mole) of aniline hydrochloride was heated in ethylene glycol (1:10) to 180° C for 1 hr 30 min. The precipitate was treated in a similar manner to II. This gave IV, which was crystallized from dimethylformamide.

6-Benzyl-2,4-dimorpholino-7-oxo-5,7-dihydropyrrolo[3,4-d]-pyrimidine (V) was obtained in the same way as IV by the reaction of the 2,4-dimorpholinolactone I (R′ = R″ = morpholino) with benzylamine hydrochloride. The V was crystallized from ethanol and dried in vacuum over P_2O_5.

Ethylene glycol monoester of 2,4-dimorpholino-7-oxo-5,7-dihydropyrrolo[3,4-d]pyrimidine-6-acetic acid (VI) [2]. A mixture of 3.06 g (0.01 mole) of the 2,4-dimorpholinolactone I (R′ = R″ = morpholino) and 1.5 g (0.02 mole) of glycine was heated in 8 ml of ethylene glycol in the presence of 1.5 ml of conc HCl as in the preparation of IV. The precipitate was treated in a similar manner to II. The VI was crystallized from ethanol.

6-p-Methoxyphenyl-7-oxo-4-phenylamino-2-piperidino-5,7-dihydropyrrolo[3,4-d]pyrimidine (VII) and 6-p-methoxyphenyl-2-morpholino-7-oxo-4-phenylamino-5,7-dihydropyrrolo[3,4-d]pyrimidine (VIII). Compounds VII and VIII were obtained from a mixture of 31.0 g (0.1 mole) of the 4-phenylamino-2-piperidinolactone I (R′ = piperidino; R″ = NHC_6H_5) or 31.2 g (0.1 mole) of the 2-morpholino-4-phenylaminolactone I (R′ = morpholino; R″ = NHC_6H_5) and 40 g (0.25 mole) of p-anisidine hydrochloride in a similar manner to IV, with the difference that to obtain VIII the reaction was carried out at 140–150° C. Compound VII was crystallized from acetone and VIII from ethanol.

4-(β-Chloroethylamino)-7-oxo-6-phenyl-2-piperidino-5,7-dihydropyrrolo[3,4-d]pyrimidine (IX). A mixture of 31.6 g (0.1 mole) of the 4-(β-chloroethylamino)-2-piperidinolactone I (R′ = piperidino; R″ = = $NHCH_2CH_2Cl$) and 25.9 g (0.2 mole) of aniline hydrochloride was heated in ethanol (1:25) at 78° C for 10 hr. The ethanol was distilled off in vacuum, the residue was treated with water, and the compound IX was filtered off. It was crystallized from ethanol.

Under the same conditions, X was obtained by the reaction of 26.2 g (0.1 mole) of the 2-chloro-4-phenylaminolactone I with 49.3 g (0.35 mole) of aniline hydrochloride. The X was crystallized from ethanol. In addition, X was obtained from the 2-chloro-4-phenylaminolactone I (R′ = Cl; R″ = NHC_6H_5) and aniline base or aniline hydrochloride in ethylene glycol by heating the mixture at 140° C under the conditions described for II.

2-Amino-7-oxo-4-phenylamino-5,7-dihydropyrrolo[3,4-d]pyrimidine hydrochloride (XI). A mixture of 1 g (~4 mM) of the 2-chloro-4-phenylaminolactone I (R′ = Cl; R″ = NHC_6H_5) and 20 ml of ethanolic ammonia (16%) was heated in a closed metal tube at 140° C for 5 hr. The solvent was distilled off in vacuum and the XI was crystallized from water acidified with hydrochloric acid.

7-Oxo-4-(p-hydroxyphenylamino)-6-phenyl-2-phenylamino-5,7-dihydropyrrolo[3,4-d]pyrimidine (XII). A mixture of 27.8 g (0.1 mole) of the 2-chloro-4-(p-hydroxyphenylamino)lactone I (R′ = Cl; R″ = = NHC_6H_4OH-p) and 45.3 g (0.35 mole) of aniline hydrochloride was heated in ethylene glycol at 120° C in a similar manner to the preparation of II. The XII was purified by reprecipitation with water from a solution in dimethylformamide.

6-(p-Methoxyphenyl)-2-(p-methoxyphenylamino)-7-oxo-4-phenylamino-5,7-dihydropyrrolo[3,4-d]pyrimidine (XIII) was obtained and purified in the same way as XII.

6-Butyl-2-butylamino-7-oxo-4-phenylamino-5,7-dihydropyrrolo-[3,4-d]pyrimidine (XIV) was obtained in a similar manner to III from a mixture of 26.2 g (0.1 mole) of the 2-chloro-4-phenylaminolactone I (R′ = Cl; R″ = NHC_6H_5) and 25.5 g (0.35 mole) of butylamine. The XIV was purified by crystallization from aqueous ethanol.

The characteristics of all the compounds synthesized are given in the table.

REFERENCES

1. N. E. Britikova, K. A. Chkhikvadze, and O. Yu. Magidson, KhGS [Chemistry of Heterocyclic Compounds], 2, 783, 1966.

2. N. E. Britikova, E. I. Metel'kov, K. A. Chkhikvadze, and O. Yu. Magidson, KhGS [Chemistry of Heterocyclic Compounds], 3, 1089, 1967.

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