DERIVATIVES OF OROTIC ACID AND ITS ANALOGS

V. Synthesis Of Oxo Derivatives Of Pyrrolo[3,4-d]Pyrimidine

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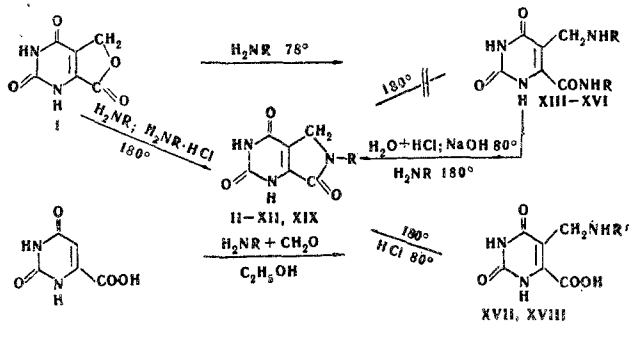
The synthesis of oxo derivatives of pyrrolo[3, 4-d]pyrimidine has been effected by the reaction of the lactone of 5-(hydroxymethyl)-orotic acid with ammonia or primary amines. In a number of cases, in place of the free organic bases their salts with mineral acids were used successfully. A number of 2, 4, 7-trioxo derivatives of pyrrolo[3, 4-d]pyrimidine and some new derivatives of orotic acid have been synthesized.

In previous papers we have reported the synthesis of the lactone of 5-(hydroxymethyl)orotic acid [1] and its chemical reactions [2]. The present work is a continuation of investigations of the chemical properties of the lactone of 5-(hydroxymethyl)orotic acid (I) with the object of obtaining from it lactones forming oxo derivatives of pyrrolo[3,4-d]pyrimidine.

In recent years syntheses of amino and oxo derivatives of pyrrolo[3,4-d]-pyrimidine have been published which were carried out by the condensation of guanidine or urea with derivations of oxopyrroline and dioxopyrroline [3,4], and of guanidine with derivatives of pyrroline [5]. Starting from the lactone of 5-(hydroxymethyl)orotic acid (I), we have carried out a new synthesis of oxo derivatives of pyrrolo[3,4-d]pyrimidine, i. e., in contrast to the syntheses mentioned above [3,5], not from pyrrole derivatives with the subsequent construction of the pyrimidine ring but from compounds already containing a pyrimidine ring with the subsequent building up of the oxopyrroline ring. When gaseous ammonia was passed into a solution of the lactone I in ethylene glycol at 130° C or when a mixture of I with a primary amine was heated, again in ethylene glycol, at a temperature of 150°–180° C, derivatives of 2,4,7-trioxypyrrolo[3,4-d]pyrimidine (II–VII) were obtained (Table 1).

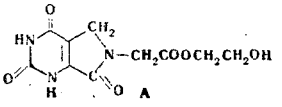


The use of salts of primary amines with mineral acids instead of the primary amines themselves enabled us to obtain derivatives of pyrrolone[3,4-d]-pyrimidine in high yield. By the reaction of I with the hydrochlorides of aniline, p-anisidine, and cyclohex-1-enylethylamine, compounds III, IV, and VII mentioned above were obtained, while the hydrochlorides of n-butylamine and of benzylamine gave compounds VIII and IX.

In addition to the mineral salts of the alkylamines and arylamines, we used the hydrochloride of a heterocyclic amine, 4-aminoantipyrine, and obtained compound XII.

In individual cases, in particular in the case of weak primary amines, for example α-aminoacids, their use in the presence of a mineral acid proved to be the only suitable method for the formation of pyrrolopyrimidine derivatives. Thus, for example, it was impossible to obtain a pyrrolopyrimidine derivative by the action of gylcine on I at 180° C in ethylene gylcol but the reaction with α-amino acids under the same conditions but in the presence of hydrochloric acid led to the formation of derivatives of pyrrolo[3,4-d]-pyrimidine containing in position 6 a carboxymethyl group (X) when glycine was used and a carboxyethyl group (XI) were also obtained by the reaction of I with the hydrochlorides of the ethyl ester of glycine and the methyl ester of β-alanine.

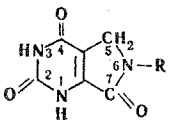
In the reaction of I with glycine in ethylene glycol in the presence of concentrated hydrochloric acid, the initial product was not X but its mono(ethylene glycol) ester (A), which was converted into X by brief boiling with dilute hydrochloric acid.



A

Compound A differs markedly from X in its melting point and IR spectra, particularly in the high-frequency region. It contains a well-defined narrow absorption band at 3530 cm^{-1} which is absent from the spectrum of X and which can be assigned to the OH stretching vibrations. The structure of compound A was confirmed by its synthesis from X by heating the latter in ethylene glycol in the presence of hydrochloric acid. The reaction of the lactone I with β-alanine took place similarly. In this case the intermediate ester was not isolated but after the excess of ethylene glycol had been distilled off in vacuum the residue was saponified directly by boiling with dilute hydrochloric acid, and XI was obtained in the crystalline state.

Table 1



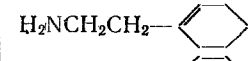
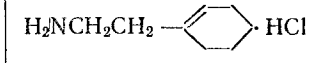
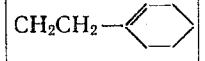
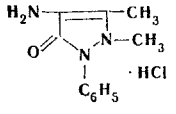
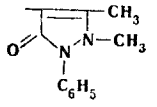
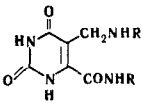
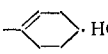
Compound	Amines or amine salts used	R	Mp, ° C	Empirical formula	Found, %				Calculated, %				Yield, %
					C	H	Cl	N	C	H	Cl	N	
II	NH_3 NH_4Cl	H	>340	$C_6H_5N_3O_3$	42.79	3.02	—	25.07	43.11	2.99	—	25.14	55.6 36.3
III	$C_6H_5NH_2$ $C_6H_5NH_2 \cdot HCl$	C_6H_5 "	>330	$C_{12}H_9N_3O_3$	59.32	3.96	—	16.89	59.25	3.70	—	17.28	76.2 86.5
IV	p-$CH_3OC_6H_4NH_2$ p-$CH_3OC_6H_4NH_2 \cdot HCl$	$C_6H_4OCH_3$ "	>330	$C_{13}H_{11}N_3O_4$	57.19	4.02	—	15.97	57.56	4.05	—	15.49	62.0 96.2
V	p-$ClC_6H_4NH_2$	C_6H_4Cl	~300	$C_{12}H_8ClN_3O_3$	51.91	2.96	12.74	15.38	51.89	2.88	12.79	15.13	81.7
VI	$H_2NCH_2CH_2OH$	CH_2CH_2OH	283	$C_8H_9N_3O_4$	45.50	4.30	—	19.98	45.49	4.26	—	19.90	37.3
VII	 	 "	266	$C_{14}H_{17}N_3O_3$	60.65	5.90	—	15.09	61.09	6.18	—	15.27	47.2 61.4
VIII	n-$C_4H_9NH_2 \cdot HCl$	C_4H_9	244	$C_{10}H_{13}N_3O_3$	53.58	6.07	—	18.82	53.81	5.82	—	18.83	50.0
IX	$C_6H_5CH_2NH_2 \cdot HCl$	$CH_2C_6H_5$	306	$C_{13}H_{11}N_3O_3$	61.00	4.70	—	16.56	60.70	4.28	—	16.34	69.5
X	$H_2NCH_2COOC_2H_5 \cdot HCl$ $H_2NCH_2COOH + HCl$	CH_2COOH "	316	$C_8H_7N_3O_5$	42.76	3.28	—	18.49	42.66	3.11	—	18.66	45.0 60.8
XI	$H_2NCH_2CH_2COOCH_3 \cdot HCl$ $H_2NCH_2CH_2COOH + HCl$	CH_2CH_2COOH "	253—255	$C_9H_9N_3O_5$	45.01	3.92	—	17.35	45.18	3.76	—	17.57	57,0
XII			323	$C_{17}H_{17}N_5O_4 \cdot H_2O$	55.19	4.69	—	18.97	54.98	4.58	—	18.86	54.0

Table 2



Compound	R	Mp of the base, °C	Mp of the hydrochloride, °C	Empirical formula	Found, %				Calculated, %				Yield, %
					C	H	Cl	N	C	H	Cl	N	
XIII	CH_2CH_2OH	191	—	$C_{10}H_{16}N_4O_5$	44.19	6.06	—	20.59	44.11	5.88	—	20.58	55.5
XIV	CH_2CH_2  · HCl	—	205—208	$C_{22}H_{32}N_4O_3 \cdot HCl$	60.31	7.35	8.27	12.71	60.48	7.33	8.36	12.82	83.8
XV	C_4H_9	167	—	$C_{14}H_{24}N_4O_3$	56.40	8.39	—	18.12	56.75	8.10	—	18.91	45.0
	$C_4H_9 \cdot HCl$	—	225	$C_{14}H_{24}N_4O_3 \cdot HCl$	50.52	7.38	10.57	17.20	50.52	7.51	10.67	16.84	—
XVI	$CH_2C_6H_5$	185	—	$C_{20}H_{20}N_4O_3$	65.15	5.70	—	15.49	65.93	5.49	—	15.38	77.0

In our study of the reaction of the lactone of 5-(hydroxymethyl)-orotic acid with primary amines we were interested in the question of what compounds could be the intermediates in the formation of the pyrrolopyrimidine derivatives. We had previously studied the action on I of such strong amines as piperidine and diethylaminoethylamine and as the main reaction products we had isolated, respectively, 5-piperidinomethylorotic and 5-(diethylaminoethylaminomethyl)orotic acid [1].

In the present work, in order to obtain possible intermediates in the synthesis of the pyrrolopyrimidine derivatives we studied the action on lactone I of a number of primary amines of different basicities. It was found that in the case of weak aromatic primary amines such as aniline, p-anisidine, and p-chloroaniline the reaction did not take place at all below 140° C, while in the range 140°–180° C the pyrrolopyrimidine was formed and it was impossible to isolate any intermediate compound. Similar results have recently been obtained in the action of primary aromatic amines on α-amino-γ-butyrolactone [6].

In the action on lactone I of stronger primary amines such as ethanolamine, cyclohex-1-enylethylamine, n-butylamine, and benzylamine (pK_a of these bases 9–10) it was found that in an alcoholic medium, even at 75°–78° C, opening of the lactone ring took place with the formation of the corresponding amides of 5-aminomethyl-substituted orotic acids XIII–XVI) (Table 2).

On being heated in ethylene glycol at 180° C, these amides resinified with the formation of a mixture difficult to separate, but under the same conditions in the presence of an additional amount of the corresponding primary amine they were smoothly converted into pyrrolopyrimidine derivatives. The reaction also took place smoothly if the amides were heated in water in the presence of an alkali or a mineral acid. For example, in aqueous alkali or aqueous hydrochloric acid amides XIII and XV were converted even at 80°–100° C into pyrrolopyrimidine derivatives which were absolutely identical with the above-mentioned compounds VI and VII.

Apparently in an alkaline or acid medium the amides of 5-aminomethyl-orotic acid that were obtained undergo hydrolysis or alcoholysis of the amide group and the 5-aminomethyl derivative of orotic acid so produced immediately cyclizes with the formation of the pyrrolinone ring. To confirm this hypothesis we synthesized the 5-β-hydroxyethylaminomethyl derivative of orotic acid (XVII) by the action of ethanolamine and formalin on orotic acid in a Mannich reaction. When XVII was heated with concentrated hydrochloric acid at 80–100° C or was heated in ethylene glycol at 140–180° C without hydrochloric acid the 6-β-hydroxyethyl derivative of pyrrolopyrimidine was obtained and this was identical with compound VI synthesized by heating I with ethanolamine in ethylene glycol. Similarly, when 5-γ-hydroxypropylaminomethylorotic acid (XVIII) [1] was heated in ethylene glycol at 140–180° C a pyrrolopyrimidine derivative (XIX) containing a γ-hydroxypropyl group in position 6 was obtained.

The results obtained in our study of the reactions of amides of 5-aminomethylorotic acid and of the 5-aminomethyl derivatives of orotic acid XVII and XVIII show that they can act as intermediates in the synthesis of the 2,4,7-trioxo derivatives of pyrrolo[3,4-d]pyrimidine from I.

All the 2,4,7-trioxo derivatives of 6-substituted pyrrolo[3,4,-d]pyrimidines are crystalline compounds having high melting points (with decomposition) and, as a rule, they are sparingly soluble in water and the usual organic solvents. Compounds containing an aliphatic residue in position 6 are slightly more soluble.

The IR spectra of the 2,4,7-trioxo derivatives of pyrrolo[3,4-d]pyrimidine show characteristic bands in the high frequency region 3330–3190 cm^{-1} (NH) and contain three bands in the region of the stretching vibrations of carbonyl groups in the ranges 1750–1730, 1715–1700, and 1690–1665 cm^{-1} depending on the

substituents in position 6. (The IR spectra of all the compounds were taken on a UR-10 spectrophotometer in the form of mulls in paraffin oil.)

EXPERIMENTAL

2, 4, 7-Trioxo-1, 2, 3, 4, 5, 6, 7-heptahydropyrrolo[3, 4-d]pyrimidine (II). a) Gaseous ammonia was passed into a mixture of 0.1 mole of I and 150 ml of ethylene glycol at 130° C for 6 hr. The dark brown solution was filtered and the filtrate was diluted with 75 ml of water and neutralized with concentrated hydrochloric acid, after which the precipitate was filtered off with suction. After recrystallization from water (1:160), II was obtained in the form of a yellowish microcrystalline powder [3].

b) Compound II was also obtained by heating a mixture of I with ammonium chloride in ethylene glycol (2 hr at 180° C).

2, 4, 7-Trioxo derivatives of pyrrolo[3, 4-d]pyrimidine substituted in position 6.

Compounds III-V, VIII, IX, and XII (Table 1). A mixture of 0.1 mole of I and 0.25 mole of the appropriate primary amine or its hydrochloride was heated in ethylene glycol (1:20) at 180° C for 2 hr. This gave compounds III, IV, V, VIII, IX, and XII, which precipitated when the reaction mixture was cooled and diluted with water. They were filtered off and washed with water. Compounds III, IV, V, and IX were crystallized from dimethylformamide and VIII from water or ethanol, and XII was purified by reprecipitation from a dilute aqueous alkaline solution with hydrochloric acid.

Compounds VI and VII. A mixture of 0.1 mole of I and 0.25 mole of ethanolamine or cyclohexenylethylamine was heated in ethylene glycol in a ratio of 1:10 (2 hr, 150° C). The ethylene glycol was distilled off in vacuum and the residual VI was crystallized from water and VII from alcohol. If the starting material was cyclohexenylethylamine hydrochloride, VII was obtained in ethylene glycol with heating (180° C) in the same way as described in method (a).

Compounds X and XI. a) A mixture of 0.1 mole of I and 0.02 mole of glycine was heated in 6 ml of ethylene glycol in the presence of 2 ml of concentrated hydrochloric acid at 180° C for 1.5 hr. The crystalline precipitate (compound A was filtered off with suction and heated with 18% hydrochloric acid for 20 min. Compound X was obtained in the form of colorless prismatic crystals from water).

b) Compound X was obtained by heating a mixture of 0.01 mole of the lactone I and 0.02 mole of the hydrochloride of the ester of glycine in ethylene glycol (8 ml) at 180° C. After the intermediate ester had been boiled with dilute hydrochloric acid, compound X was isolated in the same way as described in method (a).

c) Compound XI was obtained under the same conditions as those described in methods (a) and (b) by the reaction of the lactone I with β-aniline or with the hydrochloride of the methyl ester of β-aniline with the difference that after the reaction the ethylene glycol was distilled off in vacuum and the residue, without purification, was boiled with 18% hydrochloric acid and the XI obtained was crystallized from water.

Mono(ethylene glycol) ester of 2, 4, 7-trioxo-1, 2, 3, 4, 5, 6, 7-heptahydropyrrolo[3, 4-d]pyrimid-6-ylacetic acid (A). a) A mixture of 0.01 mole of I and 0.02 mole of glycine was heated in ethylene glycol (6 ml) in the presence of 2 ml of hydrochloric acid at 180° C for 1.5 hr. After cooling, the precipitate of A was filtered off with suction, washed with cold water, and crystallized from water, Yield 80%. Colorless prisms, mp 261° C. Found, %: C 44.33; H 4.20; N 15.53. Calculated for $C_{10}H_{11}N_3O_6$, %: C 44.60; H 4.08; N 15.61.

b) A mixture of 0.01 mole of X and 6 ml of ethylene glycol was heated in the presence of 2 ml of concentrated hydrochloric acid at 180° C for 1.5 hr and, after cooling, the precipitate was separated off. Mp 261° C (from water); a mixture with compound A obtained by method (a) gave no depression of the melting point; the ester obtained was identical with compound A in its elementary analysis and IR spectrum.

Amides of 5-aminomethyl derivatives of orotic acid (XIII-XVI). A mixture of 0.01 mole of I and 0.03 mole of a primary amine (ethanolamine, cyclohex-1-enylethylamine, butylamine, or benzylamine) was heated in ethanol (1:30) under reflux for 6-10 hr. Compounds XIII and XV were purified by crystallization from ethanol, and XVI was precipitated with water from its solution in dimethylformamide. The hydrochlorides of XIV and XV were obtained by crystallizing them from an ethanolic solution of hydrogen chloride (Table 2).

Conversion of the 5-aminomethylorotamides XIII and XV into derivatives of pyrrolo[3, 4-d]pyrimidine VI and VIII. a) A solution of 0.3 g of XIII in 15 ml of water containing 0.08 g of sodium hydroxide was heated at 80°-100° C for 6 hr, after which it was cooled, neutralized with hydrochloric acid, and evaporated in vacuum, and the residual VI was crystallized from water.

b) A mixture of 0.15 g of XIII and 0.1 g of ethanolamine was heated in 1 ml of ethylene glycol at 180° C for 1.5 hr. After the solvent had been distilled off in vacuum, the residue was neutralized with 5% hydrochloric acid, and crystallization from water yielded VI.

c) A mixture of 1 g of XV and 50 ml of concentrated hydrochloric acid was heated at 80°-100° C for 6 hr. After the solution had been evaporated in vacuum, the residue was crystallized from water, giving VIII.

5-(β-Hydroxyethylaminomethyl)orotic acid (XVII). To a mixture of 1.74 g of orotic acid and 1.83 g of ethanolamine in 80% aqueous ethanol was added 1.89 g of 39% aqueous formalin and the mixture was boiled for 8 hr, after which the precipitate was filtered off and crystallized from ethanol. Yield 0.7 g, mp 230-233° C. Found, %: N 18.43. Calculated for $C_8H_{11}N_3O_5$, %: N 18.34. Unchanged orotic acid was isolated from the mother liquor.

Conversion of the 5-aminomethyl derivatives of orotic acid XVII and XVII [1] into the pyrrolo[3, 4-d]pyrimidine derivatives VI and XIX. a) Compound XVII was heated with concentrated hydrochloric acid at 80°-100° C for 2 hr. After the solvent had been distilled off in vacuum, the residual VI was crystallized from water.

b) Compound XVII was heated in ethylene glycol at 180° C for 1.5 hr and, after the solvent had been distilled off in vacuum, crystallization of the residue from water yielded VI. Under the same conditions as for (a) and (b), 5-γ-hydroxypropylaminomethylorotic acid XVIII [1] gave XIX (R = $CH_2CH_2CH_2OH$) with mp 253° C. Found, %: C 48.00; H 4.90; N 18.54. Calculated for $C_9H_{11}N_3O_4$, %: C 48.00; H 4.88; N 18.66.

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