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DERIVATIVES OF OROTIC ACID AND ITS ANALOGS

IV. Synthesis and Properties of Amino Derivatives of the Lactone of 5-(Hydroxymethyl) pyrimidine-4-Carboxylic Acid*

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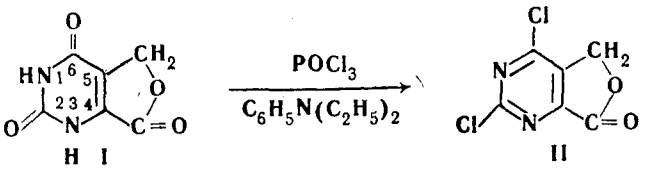
The lactone of 2, 6-dichloro-5-(hydroxymethyl)pyrimidine-4-carboxylic acid is synthesized, and various 2-chloro-6-amino and 2, 6-diamino derivatives are prepared from it by ammonolysis. It is shown that treatment of these compounds with alkaline reagents leads to lactone ring opening when there is a primary or secondary amino group at position 6, while the lactone ring is unaffected if there is a tertiary amino group at that position.

A study is made of the action of dilute solutions of hydrochloric acid on the amino derivatives obtained by opening the lactone ring, and their reverse conversion to the corresponding 2, 6-substituted lactones of 5-(hydroxymethyl)pyrimidine-4-carboxylic acid is demonstrated.

A previous communication [1] described a method of preparing the lactone (I) of 5-(hydroxymethyl)orotic acid.

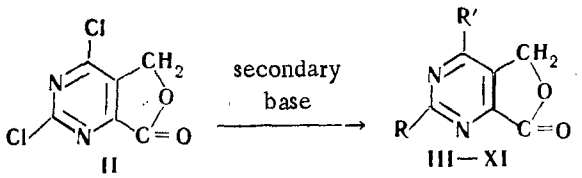
The present work aimed to study the chemical reactions of this lactone, to prepare the 2, 6-dichlorolactone and to synthesize from it mono and di-amino substituted derivatives of the lactone of 5-(hydroxymethyl)pyrimidine-4-carboxylic acid.

Boiling the lactone I with phosphorus oxychloride in the presence of diethylaniline gave the lactone of 2, 6-dichloro-5-(hydroxymethyl)pyrimidine-4-carboxylic acid (II). The IR spectrum of this dichlorolactone had an absorption band at 1780 cm^{-1}, characteristic of the previously prepared lactone of 5-(hydroxymethyl)orotic acid [1], as well as of all the lactones of 5-(hydroxymethyl)pyrimidine-4-carboxylic acid, investigated in the course of the present work.

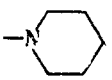


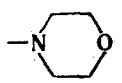
H I II

In the course of the ammonolysis it was found that the chlorine at position 6 is much more active than that at position 2, and this is in complete accord with what has been stated in the literature of recent years [2]. Treatment of 2, 6-dichlorolactone II with 2 moles of secondary amine in alcohol solution at room temperature gave 2-chloro-6-amino derivatives of the lactone of 5-(hydroxymethyl)pyrimidine-4-carboxylic acid. Because of the lower activity of the chlorine at position 2, a strong base had to be used (when reaction proceeded at room temperature), or, if ammonolysis was carried out using weaker bases, prolonged heating.



II III—XI

III R=Cl R′= 

IV R=Cl R′= 

V R=Cl R′=—$N(CH_2CH_2OH)_2$

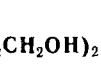
VI R=Cl R′=—$N(CH_3)_2$

VII R=R′= 

VIII R=R′= 

IX R=R′=—$N(CH_3)_2$

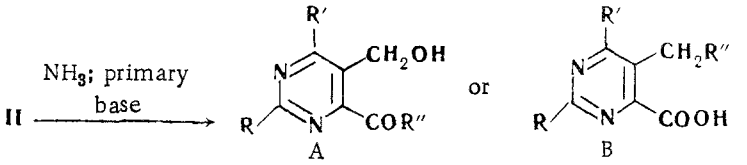
X R=R′=—$N(CH_2CH_2OH)_2$

XI R=—$N(CH_2CH_2OH)_2$ R′= 

* For Part III see [1].

IR spectra confirmed the presence of a lactone ring in all the compounds prepared.

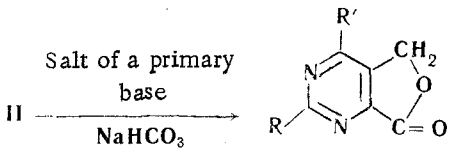
Reaction of 2, 6-dichlorolactone II with ammonia or strong primary amines gave compounds with two or three amino groups (depending on the quantity of amine taken, and on its basicity), but no longer containing a lactone ring. Hence these reactions involved not only substitution of one of the two chlorine atoms, but also opening of the lactone ring to give either amides of 5-(hydroxymethyl)pyrimidine-4-carboxylic acid (type A compounds), or the corresponding 5-aminomethyl derivatives (type B compounds).



XII R=Cl R′=R″=—$NHCH_2CH_2OH$
XIII R=Cl R′=R″=—NHC_4H_9-*n*
XIV R=R′=R″=—$NHCH_3$
XV R=Cl R′=R″=—NH_2

The action of weak primary bases or their salts on 2, 6-dichlorolactone II at room temperature led in both cases to replacement of the chlorine at position 6, without lactone ring opening. When salts of weak primary bases with mineral acids were used, the reaction was carried out in chloroform solution in the presence of aqueous sodium bicarbonate solution [3, 4].

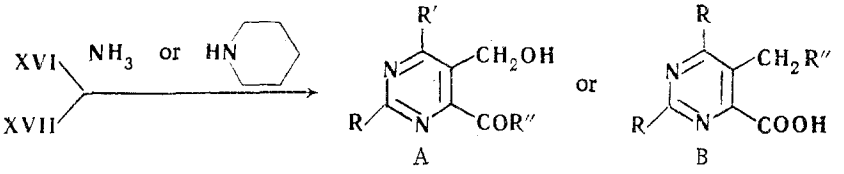
When the resultant lactones, with a secondary amino group at position 6, were further treated with ammonia or with any strong base, compounds without a lactone ring (of type A or type B) were obtained. In this connection a special study was made of the stability of the lactone ring as a function of the nature of the substituents at positons 2 and 6. It was found that the nature of the substituent at position 2 does not affect opening of the lactone ring by amines, and that lactone ring opening is directly dependent on the nature of the substituent at position 6. If there were a primary or secondary amino group at position 6, the action of ammonia or organic bases gave derivatives not containing a lactone ring.



XVI R′=—NHC_6H_5
XVII R′=—$NHCH_2CH_2Cl$
XVIII R′=—NHC_6H_4OH-*p*
XIX R′=—$NHCH_2COOC_2H_5$

With a tertiary amino group at position 6, attempts to open the lactones with bases in boiling ethanol were unsuccessful, even with prolonged heating. Thus when III was treated with ammonia, it was recovered unchanged. Treatment of III with n-butylamine gave the lactone of 2-n-butylamino-6-piperidino-5-(hydroxymethyl)pyrimidine-4-carboxylic acid (XXIV).

Compounds XII–XV and XX–XXIII crystallized well. The IR spectra of these compounds already did not evidence a lactone ring, but there were intense absorption bands, characteristic of amides of acids, in the 1690–1630 cm^{-1} region.



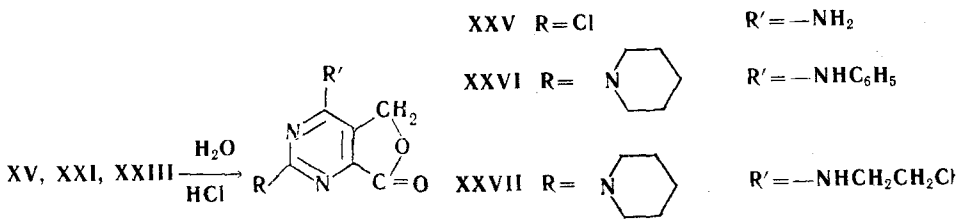
XX R=Cl R′=—NHC_6H_5 R″=—NH_2

XXI R= R′=—NHC_6H_5 R″=

XXII R=Cl R′=—$NHCH_2CH_2Cl$ R″=—NH_2

XXIII R= R′=—$NHCH_2CH_2Cl$ R″=

When compounds such as XV, XXI, and XXIII were hydrolyzed with dilute hydrochloric acid, they readily lost an amino group, and were converted into lactones of 2-chloro-6-amino- (XXV) or of 2, 6-diamino derivatives of 5-(hydroxymethyl)pyrimidine-4-carboxylic acid (XXVI and XXVII).

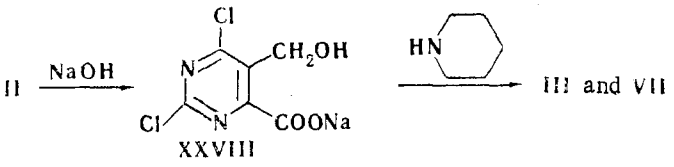


Apart from elementary analyses, the presence of a lactone ring in these compounds was confirmed by the IR spectra showing an absorption band at 1780 cm^{-1}.

Compounds XII–XV and XX–XXIII differed markedly in respect of ease of hydrolysis from 5-aminomethyl derivatives of orotic acid unsubstituted at positions 1 and 3. 5-Aminomethyl derivatives of orotic acid were resistant to hydrolysis, and were recovered unchanged after heating with hydrochloric acid [1].

The stability of the lactone ring in the 2, 6-dichlorolactone II was also investigated. When dissolved in the calculated amount of dilute aqueous sodium hydroxide, it gave the monosodium salt of 2, 6-dichloro-5-(hydroxymethyl)pyrimidine-4-carboxylic acid (XXVIII), whose IR spectrum did not show the lactone absorption band. So with chlorine at position 6, the action of alkali led to lactone ring opening.

Treatment of XXVIII with 2 or 4 moles of piperidine gave compounds which were respectively identical with the lactones III and VII, which, as stated above, are obtained by the action of piperidine on II.



This reaction of piperidine with XXVIII showed that with 2 molecules of piperidine, the chlorine at position 6 is replaced, while with excess pyridine, the chlorines at position 2 and 6 are replaced. There the sodium salt is not unchanged. On the contrary, as soon as a tertiary amino group appears at position 6, a compound with a lactone ring is precipitated even in alkali.

Thus it was shown that when the compounds studied had chlorine, a primary or a secondary amino group at position 6, treatment of them with alkali, ammonia, or organic bases opened the lactone ring to give the corresponding type A or type B amino derivatives. With a tertiary amino group at position 6, bases did not open the lactone ring. It is possible that substituents such as chlorine, which are electron acceptors, at position 6, facilitate ring opening by nucleophilic reagents. So it can be postulated that primary and secondary amines, present under the reaction conditions in the imino form, and behaving as electron acceptors, facilitate ring opening.

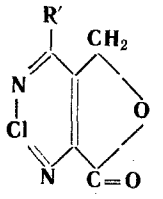
The structures of type A and B compounds were not conclusively demonstrated, but their having absorption bands characteristic of amides of acids, the facile hydrolysis of one amino group in compounds XV, XXI, and XXIII, to give lactones XXV, XXVI, and XXVII, leads to the view that when lactones with a primary or secondary amino group at position 6 are treated with ammonia or organic bases, lactone ring opening apparently involves type A compounds, i.e., amides, and not type B 5-aminomethyl derivatives.

Experimental

Lactone of 2, 6-dichloro-5-(hydroxymethyl)pyrimidine-4-carboxylic acid (II). A suspension of 6.7 g (0.04 mole) lactone of 5-(hydroxymethyl)orotic acid (I) in 100 ml $POCl_3$ and 9.6 ml $PhNEt_2$ were heated together for 3 hr at 104°–106°. After solution of lactone I, the $POCl_3$ was vacuum-distilled off, the residue treated with ice, crystals of II filtered off, and washed with cold water. Insoluble in cold water, soluble in EtOH and $CHCl_3$, yield 6.2 g (76%), mp 132°–134°C (ex $CHCl_3$). Found: C 35.31; H 1.04; Cl 33.84; N 13.88%. Calculated for $C_6H_2Cl_2N_2O_2$: C 35.12; H 0.97; Cl 34.63; N 13.65%.

Lactones of 2-chloro-6-amino-5-(hydroxymethyl)pyrimidine-4-carboxylic acid. a) Compounds III, IV, V, and VI were obtained by reacting the 2, 6-dichloro lactone II with the calculated quantity of secondary amine in EtOH at room temperature for 10–12 hr. They were insoluble in water. They were recrystallized from EtOH or EtOH-acetone. Their

Table 1



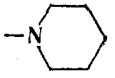
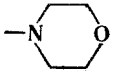
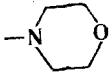
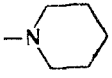
Compound number	R	R′	Mp, °C	Formula	Found, %				Calculated, %				Yield, %
					C	H	Cl	N	C	H	Cl	N	
III	Cl		221	$C_{11}H_{12}ClN_3O_2$	52.05	4.65	14.80	16.55	52.07	4.73	14.00	16.56	59.5
IV	Cl		248	$C_{10}H_{10}ClN_3O_3$	46.76	4.05	13.92	16.37	46.96	3.91	13.81	16.43	47.2
V	Cl	$N(CH_2CH_2OH)_2$	191—194	$C_{10}H_{12}ClN_3O_2$	43.52	4.73	13.08	15.24	43.87	4.38	12.98	15.35	68.0
VI	Cl	$N(CH_3)_2$	192	$C_8H_8ClN_3O_2$	45.05	3.84	16.78	19.45	44.96	3.74	16.62	19.67	58.0
VII			217	$C_{16}H_{22}N_4O_2$	63.30	7.45	—	18.50	63.57	7.28	—	18.54	53.0
VIII			240	$C_{14}H_{18}N_4O_4$	54.58	6.06	—	18.57	54.90	5.88	—	18.30	
IX	$N(CH_3)_2$	$N(CH_3)_2$	208—209	$C_{10}H_{14}N_4O_2$	54.27	6.20	—	25.46	54.05	6.30	—	25.22	76.5
X	$N(CH_2CH_2OH)_2$	$N(CH_2CH_2OH)_2$	153	$C_{14}H_{22}N_4O_6$	49.49	6.56	—	16.47	49.15	6.43	—	16.37	
XI	$N(CH_2CH_2OH)_2$		123—124	$C_{15}H_{22}N_4O_4$	55.90	6.88	—	17.35	55.90	6.83	—	17.39	69.6
XVI	Cl	NHC_6H_5	235	$C_{12}H_8ClN_3O_2$	54.95	3.00	13.67	16.26	55.06	3.05	13.57	16.06	70.8
XVII	Cl	$NHCH_2CH_2Cl$	138	$C_8H_7Cl_2N_3O_2$	38.30	2.88	29.24	16.48	38.70	2.82	28.62	16.93	62.4
XVIII	Cl	NHC_6H_4OH-*p*	251	$C_{12}H_8ClN_3O_3 \cdot 0{,}5H_2O$	50.11	3.40	12.45	14.74	50.26	3.14	12.32	14.65	58.0
XIX	Cl	$NHCH_2COOC_2H_5$	168	$C_{10}H_{10}ClN_3O_4 \cdot H_2O$	41.48	4.00	12.31	14.23	41.45	4.14	12.26	14.50	69.4

Table 2

Compound number	R	R'	R''	Mp, °C	Formula	Found, %				Calculated, %				Yield, %
						C	H	Cl	N	C	H	Cl	N	
XII	Cl	$NHCH_2CH_2OH$	$NHCH_2CH_2OH$	186—188	$C_{10}H_{15}ClN_4O_4$	41.30	4.53	12.30	19.21	41.30	5.16	12.22	19.27	63.6
XIII	Cl	NHC_4H_9-*n*	NHC_4H_9-*n*	99	$C_{14}H_{23}ClN_4O_2$	53.61	7.22	11.59	17.90	53.41	7.31	11.28	17.80	63.8
XIV	$NHCH_3$	$NHCH_3$	$NHCH_3$	163	$C_9H_{15}N_5O_2$	48.30	7.00	—	30.52	48.00	6.66	—	31.11	88.8
XV	Cl	NH_2	NH_2	237	$C_6H_7ClN_4O_2$	35.04	3.35	17.79	27.55	35.55	3.45	17.53	27.30	
XX	Cl	NHC_6H_5	NH_2	160	$C_{12}H_{11}ClN_4O_2$	51.56	4.09	12.84	19.98	51.70	3.94	12.74	20.07	
XXI	—N⟨ ⟩	NHC_6H_5	—N⟨ ⟩	169	$C_{22}H_{29}N_5O_2$	66.50	7.13	—	17.88	66.83	7.34	—	17.72	62.5
XXII	Cl	$NHCH_2CH_2Cl$	NH_2	140	$C_8H_{10}Cl_2N_4O_2$	35.96	3.93	27.16	20.91	36.22	3.77	26.79	21.13	58.0
XXIII	—N⟨ ⟩	$NHCH_2CH_2Cl$	—N⟨ ⟩	115	$C_{18}H_{28}ClN_5O_2$	56.53	7.04	9.63	18.19	56.60	7.33	9.30	18.34	69.6

IR spectra all had the 1780 cm^{-1} absorption band, c. istic of the lactone.* Table 1 gives yield of purified ucts, mps, and analytical data.

b) Compounds XVI, XVII, XVIII, and XIX were obtained by the action of primary amine hydrochlorides on II in $CHCl_3$ solution, at room temperature. They were insoluble in water, and were recrystallized from EtOH. All the IR spectra had the characteristic lactone absorption band at 1780 cm^{-1}. Table 1 gives yields of purified products, mps, and analytical data.

Lactones of 2, 6-diamino-5-(hydroxymethyl)pyrimidine-4-carboxylic acid (VII–XI). 2, 6-Diamino substituted lactones were prepared by reaction of II with excess secondary amines in EtOH, by heating for 6–12 hr or in the case of strong bases (piperidine, dimethylamine) at room temperature for 24–36 hr. In all cases the IR spectra contained the lactone absorption bonds at 1780 cm^{-1}. They crystallized from EtOH. Yield of purified product, mp and analytical data are shown in Table 1.

Action of ammonia or strong primary amines on the 2, 6-dichlorolactone (II). a) Compounds XII, XIII, XIV, and XV were prepared by heating together for a short time ammonia or the strong primary amine and II in EtOH solution. They did not contain a lactone ring, and their IR spectra had an intense band in the 1685–1630 cm^{-1} region, characteristic of amides of acids. They were somewhat soluble in water, and were recrystallized from EtOH. Table 2 gives yields, mps, and analytical data.

b) Compounds XX and XXII were prepared by the action of ammonia on XVI and XVII, and compounds XXI and XXIII by the action of piperidine on XVI and XVII. Reaction was effected by allowing the mixed reactants to stand for a long time at room temperature. The compounds were recrystallized from EtOH. They did not contain the lactone ring, and the IR absorption spectra showed absorption bands at 1685–1630 cm^{-1}, characteristic of amides of acids. Table 2 gives the yields of purified products, mps, and analytical data.

Lactone of 2-piperidino-6-anilino-5-(hydroxymethyl)-pyrimidine-4-carboxylic acid (XXVI). A suspension of XXI was boiled in water, brought to pH 1 with HCl, for 30 min. XXVI was recrystallized from EtOH. Unlike the starting compound XXI, its IR spectrum had the characteristic lactone absorption band at 1780 cm^{-1}. Yield quantitative, mp 256° (ex EtOH). Found: C 66.00; H 5.97; N 17.93%. Calculated for $C_{17}H_{18}N_4O_2$: C 65.80; H 5.80; N 18.06%.

Lactone of 2-piperidino-6-(β-chloroethylamino)-5-(hydroxymethyl) pyrimidine-4-carboxylic acid (XXVII). Prepared similarly to XXVI and XXIII. Unlike XXIII, XXVII gives an IR spectrum with the lactone absorption band at 1780 cm^{-1}. Yield quantitative, mp 196° (ex EtOH). Found: C 52.97; H 5.56; Cl 12.03; N 19.22%. Calculated for $C_{13}H_{17}ClN_4O_2$: C 52.97; H 5.09; Cl 12.05; N 19.01%.

* The IR spectra of all the compounds were determined with a UR-10 spectrophotometer, using a paste in vaseline.

Lactone of 2-n-butylamino-6-piperidino-5-(hydroxymethyl)pyrimidine-4-carboxylic acid (XXIV). 1.6 g (22 mM) n-butylamine was added to a suspension of 1.27 g (5 mM) III in 30 ml EtOH, and the mixture refluxed for 11 hr. After vacuum-distilling off the solvent, the residue was recrystallized from aqueous EtOH. XXIV has an IR spectrum with the lactone absorption band at 1780 cm^{-1}. Yield of XXIV 55%, mp 154° (ex EtOH). Found: C 62.16; H 7.59%. Calculated for $C_{15}H_{22}N_4O_2$: C 62.06; H 7.58%.

Sodium salt of 2, 6-dichloro-5-(hydroxymethyl)pyrimidine-4-carboxylic acid (XXVIII). 2.05 g (0.01 mole) II was dissolved in 100 ml water, containing the calculated amount of NaOH. The solution was evaporated at low temperature under vacuum, and the dry residue washed with absolute EtOH. The sodium salt XXVIII does not show the characteristic lactone absorption band in its IR spectrum, showing that sodium salt formation in alkaline solution is accompanied by opening of the lactone ring.

Action of piperidine on the sodium salt of 2, 6-dichloro-5-(hydroxymethyl)pyrimidine-4-carboxylic acid. a) 2 moles piperidine was added to an aqueous solution of XXVIII, and the mixture left at room temperature for a day. A crystalline compound completely identical with lactone III (Table 1), was isolated.

b) Excess piperidine (over 4 moles) was added to an aqueous solution of XXVIII, and the solution left at room temperature for a day. The precipitate was filtered off, and recrystallized from EtOH. The compound obtained was completely identical with lactone VII (Table 1).

Lactone of 2-chloro-6-amino-5-(hydroxymethyl)pyrimidine-4-carboxylic acid (XXV). NH_3 gas was passed for 6 hr into a suspension of 3 g (15 mM) II in 90 ml absolute EtOH at 80°. After vacuum-distilling off the solvent, a crystalline compound completely identical with compound XV (Table 2) was obtained. It was boiled in water which had been brought to pH 1 with HCl. Recrystallization from water gave XXV, mp 270° (decomp). The IR spectrum had an absorption band at 1780 cm^{-1}. Found: C 38.97; H 2.00; Cl 19.47; N 22.79%. Calculated for $C_6H_4ClN_3O_2$: C 38.81; H 2.15; Cl 19.13; N 22.64%.

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