CONDENSED PYRIMIDINE, PYRAZINE, AND PYRIDINE SYSTEMS.

XXXVIII.* SYNTHESIS OF 2,4,5-TRIOXOPYRROLO[2,3-d]PYRIMIDINES FROM 5-CHLOROACETYL-6-AMINOURACILS

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A simple method was develeped for the synthesis of N_1- and N_3-alkyl- and N_1,N_3-dialkyl(aryl, alkyl)-5-chloroacetyl-6-aminouracil by reaction of 6-aminouracils with chloroacetyl chloride in monochloroacetic acid. 2,4,5-Trioxopyrrole[2,3-d]-pyrimidines were obtained by the action of aqueous alkali on N_1-alkyl-5-chloro-acetyl-6-aminouracils and by the action of sodium ethoxide on N_3-alkyl- and N_1,N_3-dialkyl(aryl, alkyl)-5-chloroacetyl-6-aminouracils. When there is an alkyl substituent attached to the 3-N atom in 2,4,5-trioxopyrrolo[2,3-d]pyrimidines, the pyrrole ring readily opens up under the influence of alkali to give 5-hydroxy-acetyl-6-amino uracils.

It has been reported [2] that the synthesis of 5-acyl-6-aminouracils from 6-aminouracil and its N_1- and N_3-alkyl(aryl) derivatives and acid chlorides is accompanied by the formation of a number of side products, the removal of which by purification leads to significant losses of the required compounds. In the present research in order to work out a convenient method for the preparation of 5-chloroacetyl-6-aminouracils — key compounds in the synthesis of two-ring systems based on pyrimidine — we made a detailed study of the conditions for the reaction of 1-alkyl(aryl)-, 3-alkyl-, and 1,3-dialkyl(aryl, alkyl)-6-aminouracils (I-VI) with chloroacetyl chloride. 5-Chloroacetyl-6-aminouracils A (VII-XII) are formed in 70-90% yields in the reaction of these compounds in monochloroacetic acid in the presence of pyridine or sodium monochloroacetate. Proceeding from the data in [3-5], the alternative structure (B) of 6-chloroacetylamino derivatives might have been assigned to VII-XII, whereas for N_1- and N_3-monosubstituted derivatives, structure C or D of N_1- and N_3-chloroacetyl derivatives might have been assigned. The choice in favor of structure A was made on the basis of the spectral data. The PMR spectra of VII-XII do not contain the signal of a proton attached to 5-C that is present in the spectrum of the model compound 3-methyl-6-acetamidouracil [4] (5.35 ppm). The UV spectra of these substances are characterized by two absorption maxima at 240-246 and 275-281 nm, while the spectra of compounds of the B type contain only one absorption maximum at 278-288 nm [4]. The presence in the IR spectra of the absorption bands of a ketone CO group at 1725 cm^{-1} and of stretching and deformation vibrations of an NH_2 group (3200, 3335, and 1650 cm^{-1}; the intensity of the latter decreases when the compound is deuterated) also provides evidence in favor of structure A.

We synthesized pyrrolo[2,3-d]pyrimidines from the 5-chloroacetyl-6-aminouracils VII-XII. Thus, 2,4,5-trioxopyrrolo[2,3-d]pyrimidines (XIII-XV) are formed in quantitative yield in the reaction of VII, X, and XI with aqueous alkali; XIV was initially isolated in the monohydrate form and was dehydrated *in vacuo* at 130°C.

Compounds corresponding to monohydrates of pyrrolopyrimidines or to 5-hydroxyacetyl-6-aminouracils (XIX-XXI) were obtained under similar conditions from VII, IX, and XII. The choice between these structures was made on the basis of the mass spectra. Elimination of neutral C_2HOH, CH_2O, and $COCH_2OH$ particles, which confirms the presence of a hydroxyacetyl group, is observed in the mass spectra of XIX and XX. The intensity of the molecular ion

*See [1] for our preceding communication.

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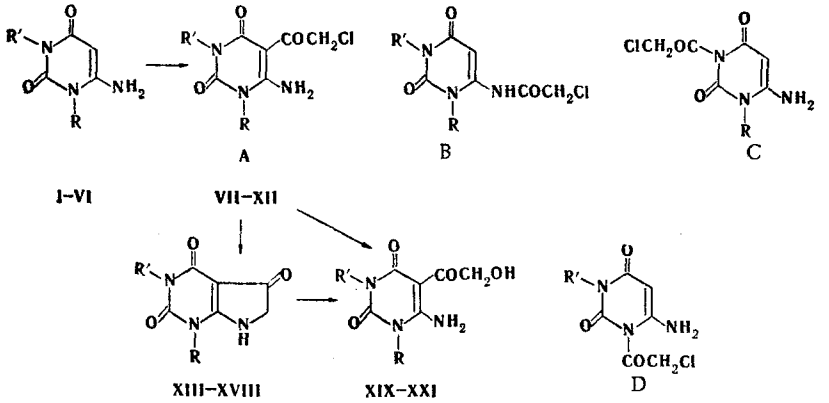
TABLE 1. Mass Spectra of XIII, XVI, XVII, and XIX

Compound	m/e (relative intensity, %)
XIII	181 (100) $M^{+\cdot}$, 164 (29), 153 (86), 152 (14), 151 (13), 138 (17), 137 (7), 125 (8), 124 (6), 108 (14), 96 (6), 93 (7), 83 (18), 81 (6), 80 (19), 69 (23), 68 (18), 67 (10), 66 (13), 56 (24), 55 (29), 54 (14), 43 (14)
XVI	181 (100) $M^{+\cdot}$, 152 (3), 139 (43), 123 (28), 81 (95), 80 (9), 69 (7), 68 (6), 53 (6), 52 (5), 43 (7), 42 (9), 41 (6)
XVII	195 (89) $M^{+\cdot}$, 167 (6), 166 (13), 138 (36), 137 (11), 112 (7), 111 (7), 110 (18), 109 (11), 98 (9), 97 (7), 83 (17), 82 (64), 81 (100), 80 (18), 71 (12), 70 (9), 69 (24), 57 (53), 56 (11), 55 (25)
XIX	198 (8) $M^{+\cdot}$, 169 (93), 168 (75), 141 (21), 111 (9), 68 (19), 45 (32), 44 (19), 43 (100)

peak for these compounds amounts to only 7-9% of the maximum, and this also constitutes evidence in favor of a one-ring structure with a side chain.



I, VII, XIII R=CH_3, R′=H; II, VIII, XIV, XIX R=H, R′=CH_3; III, IX, XVII, XX R=R′=CH_3; IV, X, XIV R=C_2H_5, R′=H; V, XI, XV R=C_6H_5, R′=H; VI, XII, XVIII, XXI R=C_6H_5, R′=CH_3

However, we actually obtained pyrrolopyrimidines XVI-XVII when we treated VII-IX and XII with sodium ethoxide in anhydrous alcohol. Their structures and the XIII-XV structures were confirmed by PMR and mass spectrometric data. The molecular ion peak in the spectra of XIII and XIV is the maximum peak, whereas in the spectrum of XVII it constitutes 89% of the maximum peak (m/e 81); this confirms the presence in these substances of a stable two-ring structure. The first steps in the fragmentation of XVI and XVIII are determined by cleavage of the uracil ring with the elimination of $\dot{H}CO$, $\dot{N}{=}C{=}C$, and $CH_3{-}N{=}C{=}O$ particles. The compositions of the detached fragments were confirmed by analysis of the spectrum of the deutero analog of XVI, obtained by exchange of the labile protons attached to 1-N, 6-C, and 7-N by deuterium by recrystallization of XVI from CD_3OD.

Unexpectedly, the mass spectrum of XIII differs greatly from the spectrum of its structural isomer XVI. This can be explained by the fact that in the ionized state XIII exists in the hydroxy form because of the high lability of the hydrogen located between two carbonyl groups. The elimination of $\dot{O}H$ and HOCN particles from the molecular ion of XIII and the presence of an intense $M - CO^{+\cdot}$ ion (86%), which is in good agreement with the mass spectra of 6-aminouracils [6], serve as a confirmation for this.

The possibility of the existence of excited 6-aminouracil molecules in the hydroxy form is discussed in [6]. In particular, an M − 17 ion (10.2 and 15.6% of the molecular ion, respectively) is observed in the mass spectra of 5,6-diamino- and 1-methyl-5,6-diaminouracils, whereas this ion peak is absent in the spectrum of 1,3-dimethyl-5,6-diaminouracil. This also confirms our interpretation of the mass spectrum of XIII.

The PMR spectra of XIII-XVIII contain the signal of protons of a CH_2 group (3.6 ppm), which is in agreement with the 5-oxo structure assigned to them rather than with a hydroxy structure.

N_1-Alkyl(aryl)pyrrolo[2,3-d]pyrimidinetriones XIII-XV are stable with respect to aqueous alkalis, but the presence of a methyl substituent attached to 3-N weakens the stability of the pyrrole ring. The corresponding 5-hydroxyacetyl derivatives XIX-XXI are formed when XVI-

TABLE 2. 5-Acyl-6-aminouracils VII-XII and XIX-XXI and 2,4,5-Trioxopyrrolo[2,3-d]pyrimidines XIII-XVIII

Compound	mp, °C	Found, %				Empirical formula	Calculated, %				IR spectrum, cm^{-1}	UV spectrum, λ_{max} (log ε), nm	Yield, % (synthetic method)
		C	H	Cl	N		C	H	Cl	N			
VII	>300[a] (dec.)	39,1	3,8	16,5	18,3	$C_7H_8ClN_3O_3$	38,7	3,6	16,3	19,3	1720	243 (3,96), 278 (4,10)	95 (B)
VIII	235[b]	38,7	3,5	16,2	19,7	$C_7H_8ClN_3O_3$	38,7	3,6	16,3	19,3	1720	243 (3,93), 275 (4,10)	89,5 (B)
IX	182—184	41,8	4,0	15,4	18,1	$C_8H_{10}ClN_3O_3$	41,5	4,3	15,3	18,2	1720	244 (3,56), 281 (4,02)	72 (B)
X	312	41,3	4,5	15,7	18,4	$C_8H_{10}ClN_3O_3$	41,5	4,3	15,3	18,2	1720	243 (3,90), 276 (4,12)	54 (A)
XI	277—278	51,7	3,6	12,6	14,8	$C_{12}H_{10}ClN_3O_3$	51,9	3,6	12,2	15,1	1710	243 (4,02), 278 (4,18)	76 (C)
XII	221—222	53,6	4,4	11,9	14,0	$C_{13}H_{12}ClN_3O_3$	53,4	4,0	11,7	14,0	1720	244 (3,60), 277 (3,82)	77 (B)
XIII	>350	46,5	4,0	—	23,1	$C_7H_7N_3O_3$	46,4	3,9	—	23,1	1710	275 (4,34),	94
XIV[c]	256—257	49,5	5,0	—	21,2	$C_8H_9N_3O_3$	49,2	4,6	—	21,5	1700	275 (4,35)	70
XV	298	58,8	3,0	—	16,9	$C_{12}H_9N_3O_3$	59,2	3,7	—	17,2	1720	244 (3,80), 278 (4,09)	87
XVI	318	46,6	4,1	—	23,4	$C_7H_7N_3O_3$	46,4	3,9	—	23,1	1720	268 (4,23)	94
XVII	292—294	48,8	4,8	—	21,3	$C_8H_9N_3O_3$	49,2	4,6	—	21,5	1700	250 (3,82), 278 (4,11)	67
XVIII	296—297	60,7	4,10	—	16,1	$C_{13}H_{11}N_3O_3$	60,7	4,3	—	16,3	1690	250 (4,01), 278 (4,09)	60
XIX	271	41,9	4,6	—	21,2	$C_7H_9N_3O_4$	42,2	4,5	—	21,1	1720	244 (3,95), 277 (4,19)	89
XX	227	45,4	5,2	—	19,6	$C_8H_{11}N_3O_4$	45,0	5,2	—	19,7	1720	247 (3,91), 276 (4,15)	58
XXI	251—252	56,6	4,6	—	15,6	$C_{13}H_{13}N_3O_4$	56,7	4,7	—	15,3	1710	248 (4,03), 276 (4,11)	70

a) According to [2], this compound has mp 290°C. b) According to [2], this compound has mp 225°C. c) Initially isolated in the form of the monohydrate. Found: C 45.0; H 5.3; N 19.6%. $C_8H_9N_3O_3 \cdot H_2O$. Calculated: C 45.1; H 5.2; N 19.7%.

XVIII are treated with aqueous alkali. This also explains the difference in the conditions for the cyclization of uracils VII, X, and XI and VIII, X, and XII.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The UV spectra of ethanol (VII-XII and XIX-XXI) and water (XIII-XVIII) solutions of the compounds were recorded with an SF-16 spectrophotometer. The mass spectra were obtained with an MKh-1303 mass spectrometer, equipped with a system for direct introduction into the ion source at an ionizing-electron energy of 30 eV. The PMR spectra of d_6-DMSO solutions of the compounds were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard.

5-Chloroacetyl-6-aminouracils (VII-XII). A) A 0.1-mole sample of chloroacetyl chloride was added with stirring and cooling to a mixture of 0.1 mole of I-VI and 0.1 mole of dry pyridine, and the mixture was stirred at 85-95°C for 1 h. It was then mixed with 50 ml of water, and the precipitate was removed by filtration, washed with water, and dried. A sample for analysis was recrystallized from acetic acid.

B) A 0.1-mole sample of chloroacetyl chloride was added to a mixture of 0.1 mole of I-VI, 0.1 mole of dry pyridine, and monochloroacetic acid in an amount equal to the weight of the starting 6-aminouracil, and the mixture was heated at 90-95°C for 1 h. It was then mixed at 50°C with 250 ml of water, and the resulting precipitate was removed by filtration.

C) A 0.11-mole sample of chloroacetyl chloride was added at 50°C to a mixture of 25 g of monochloroacetic acid and 0.11 mole of sodium monochloroacetate, and the mixture was heated at 70°C for 15 min. A 0.1-mole sample of I-VI was added, and the mixture was stirred at 115-120°C for 1 h. It was then cooled and treated with 250 ml of water, and the mixture was worked up to give the corresponding VII-XII.

1-Methyl-2,4,5-trioxopyrrolo[2,3-d]pyrimidine (XIII). A 10.9-g (0.05 mole) sample of VII was added to 20 ml of 10% NaOH solution, and the mixture was refluxed for 2-3 min. It was then acidified to pH 5 with acetic acid, and the precipitated XIII was removed by filtration. Compounds XIV and XV were similarly obtained.

3-Methyl-2,4,5-trioxopyrrolo[2,3-d]pyridimine (XVI). A 10.85-g (50 mmole) sample of VIII was added to a solution of 1.2 g (50.2 mmole) of sodium in 50 ml of ethanol, and the mixture was refluxed for 3 h. It was then acidified with 1.2 ml of acetic acid, and the precipitated XVI was removed by filtration. Compounds XVII and XVIII were similarly obtained.

3-Methyl-5-hydroxyacetyl-6-aminouracils (XIX-XXI). A) A solution of 2.17 g (10 mmole) of VIII in 10 ml of 10% NaOH was refluxed, after which it was diluted with 30 ml of water, and the aqueous mixture was acidified with acetic acid. The precipitate was removed by filtration to give 1.8 g (83%) of XIX. Compounds XX and XXI were similarly obtained.

B) A mixture of 0.72 g (4 mmole) of XVI and 6 ml of 10% NaOH was heated at 100°C for 5 min, after which it was diluted with water, acidified, and worked up to give 0.7 g (88%) of XIX. No melting-point depression was observed for a mixture of this product with a sample obtained by method A. The product was the monohydrate (the amount of H_2O determined by the Fischer method was 8.2%). The spectrum of the product was identical to the spectrum of XIX obtained by method A. Found: C 39.0; H 4.8; N 19.4%. $C_7H_9N_3O_4 \cdot H_2O$. Calculated: C 38.7; H 5.0; N 19.3%.

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