point, and comparison of the infrared spectrum with that of an authentic sample prepared by electrolytic reduction[4] of *o*-(nitrophenyl)-1-nitronaphthalene. The residue from the extraction was identical with the main product obtained under A.

1-Phenyl-2-naphthoylhydrazide.—Methyl 1-phenyl-2-naphthoate (24.64 g.)[24] was refluxed with hydrazine hydrate (36 ml.) for 24 hr. with stirring. The resulting **hydrazide** crystallized from ethanol as a white powder (19.4 g., 79%) which after recrystallization had m.p. 189–190.5°.

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.69. Found: C, 77.99; H, 5.50; N, 10.90.

Ethyl 2-(1-Phenylnaphthyl)carbamate.—1-Phenyl-2-naphthoylhydrazide (19.6 g.) was added portionwise over 2 hr. at 5° to a stirred solution of nitrosyl chloride (4.9 g.) in dry ethanol (330 ml.). The solution was stirred at 5° for another hour, then refluxed overnight. Water (35 ml.) was added and the hot solution was left to cool in a freezer (−15°) when crystals of the **carbamate** (17.8 g., 81%) separated. After two recrystallizations from 90% ethanol it had m.p. 112–6–112.8°.

(24) R. Huisgen and H. Rist, *Ann.*, **594**, 151 (1955).

Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88. Found: C, 78.20; H, 6.05.

1-Phenyl-2-naphthylamine.—Ethyl 2-(1-phenylnaphthyl)-carbamate (17.8 g.) was refluxed for 10 hr. with alcoholic potassium hydroxide (260 ml. of ethanol, 8.4 g. of potassium hydroxide). The amine was precipitated by addition to water (1 l.) affording 13.4 g. (100%) of a product with m.p. 94–102°. Recrystallization (charcoal) from petroleum ether (b.p. 60–68°) gave the pure amine, m.p. 95–96°, lit.[10-12] m.p. 94 and 96°.

Attempted Preparation of 5-Chloro-5,6-borazarobenzo[*c*]-phenanthrene.—The cyclization of 1-phenyl-2-aminonaphthalene was attempted in the same way and with the same lack of success as that of 1-naphthylamine.

Attempted Preparation of 6-Chloro-6,5-borazarobenzo[*c*]phenanthrene.—1-(*o*-Nitrophenyl)naphthalene was prepared from 1-iodonaphthalene and *o*-bromonitrobenzene,[22] m.p. 94–96°, lit.[21] m.p. 90–92° and 93–94°. 1-(*o*-Aminophenyl)naphthalene was obtained from the nitro compound (21.5 g.) by catalytic (palladium-charcoal 10%) reduction in absolute ethanol (475 ml.) under 50 lb./sq. in. initial pressure, m.p. *ca.* 62°, lit.[21] m.p. 65°. The cyclization of 1-(*o*-aminophenyl)naphthalene was attempted in the same way, and with the same lack of success, as that of 1-naphthylamine.

Pyrimidines. III. A Novel Rearrangement in the Syntheses of Imidazo- or Pyrimido[1,2-*c*]pyrimidines[1]

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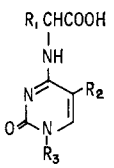
Pyrimidinylamino acids [*e.g.*, N-(1H-2-oxo-4-pyrimidinyl)-β-alanine (**1**)], when treated with acetic anhydride, cyclize with rearrangement to 2-oxopyrimido- or 2-oxoimidazo[1,2-*c*]pyrimidines (*e.g.*, **2**, **15**, **23**, and **30**). This novel rearrangement occurs with pyrimidinyl-α or -β simple amino acid derivatives. A mechanism is given which involves the cleavage of the C^2–N^3 linkage of the pyrimidine ring of **1** with the formation of an amide linkage between the carboxyl group of the amino acid moiety and N^3 to form B. Recyclization occurs between C^2 and N^4 of intermediate B to furnish **2**. The presence of a hydrogen on N^1 of the pyrimidinyl amino acids is essential for the rearrangement. N^1-Alkylated pyrimidinyl amino acids do not undergo the rearrangement; instead other reactions predominate. γ-Amino acid derivatives yield N-4-pyrimidinylbutyrolactams (**35**).

In a previous paper in another series,[2] the preparation of a number of pyrimidinylamino acids and their nucleosides of the general structure shown in Chart I

CHART I



was reported as part of our program in the synthesis of compounds of potential biochemical interest. During this investigation, the reactions of the β-alanyl derivative **1** with several reagents, particularly with acetic anhydride, were studied. The present paper deals with an interesting rearrangement which led to a general investigation into the reactions of pyrimidinylamino acids with acetic anhydride.

Treatment of N-(1H-2-oxo-4-pyrimidinyl)-β-alanine (**1**) with acetic anhydride could yield several possible products, among them the N^4-acetyl derivative of the mixed anhydride of **1** (Chart II). Such a compound would be expected to cyclize with the loss of acetic acid to form **3**, 1H-1,2,3,4-tetrahydro-4,6-dioxopyrimido[1,2-*c*]pyrimidine or its N^1-acetyl derivative. When **1** was refluxed with acetic anhydride, a 70% yield was obtained of a product with an elemental analysis in accord with **3**. The ultraviolet spectrum of this product differed from **1**, as expected. If this product is **3**, hydrolysis with acid or alkali should regenerate **1**, since it has been reported that ring acylated purines[3] or pyrimidines[4,5] (*e.g.*, 1,3,4-tribenzoylcytosine)[4] regenerate to their parent compounds under hydrolytic conditions.

Mild acid or alkaline hydrolysis of the product obtained from the reaction of **1** with acetic anhydride did not regenerate **1**. Instead, a new product was obtained which was proved to be 3-(2-carboxyethyl)cytosine (**4**) by ultraviolet absorption studies[6,7] (similarity to 3-methylcytosines) and by further alkaline hydrolysis of **4**

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 03190-07). A preliminary report of this work has appeared in the Abstracts of the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 39L. For part II of this series, see I. Wempen and J. J. Fox, *J. Med. Chem.*, **7**, 207 (1964).

(2) T. Ueda and J. J. Fox, *ibid.*, **6**, 697 (1963).

(3) L. Birkofer, *Chem. Ber.*, **76**, 769 (1943); J. A. Montgomery, *J. Am. Chem. Soc.*, **78**, 1928 (1956); B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957); A. H. Schein, *J. Med. Pharm. Chem.*, **5**, 302 (1962).

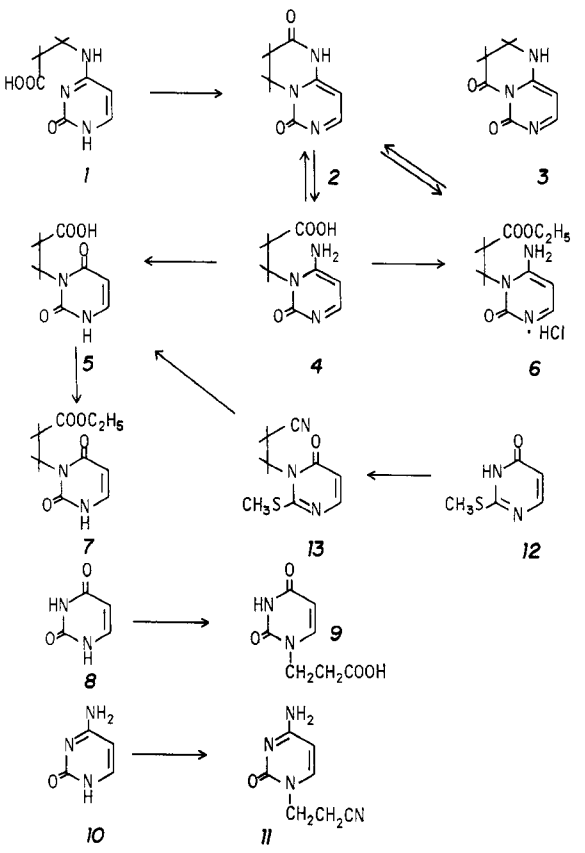
(4) D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2384 (1956).

(5) M. Fytelson and T. B. Johnson, *J. Am. Chem. Soc.*, **64**, 306 (1942); L. B. Spencer and E. B. Keller, *J. Biol. Chem.*, **232**, 185 (1958).

(6) P. Brookes and P. D. Lawley, *J. Chem. Soc.*, 1348 (1962).

(7) T. Ueda and J. J. Fox, *J. Am. Chem. Soc.*, **85**, 4024 (1963).

CHART II



to 3-(2-carboxyethyl)uracil (**5**). The structure of **5** was confirmed by an alternate synthesis which will be described later.

The conversion of **1** → **4** *via* a dehydrated product requires a rearrangement. Structures **2** and **3** are possibilities for the structure of the dehydrated product. If this product is **3**, which could form *via* the expected cyclization of **1** with acetic anhydride, it is necessary to postulate a rearrangement in the conversion of **3** to **4**. If the dehydrated product is **2**, a rearrangement obviously must have occurred during its formation from **1**, and the formation of **4** from **2** would find ready explanation by simple cleavage of the lactam. The following reactions support the conclusion that the dehydrated product is **2** (1H-1,2,3,4-tetrahydro-2,6-dioxopyrimido[1,2-*c*]pyrimidine).

Treatment of **4** with acetic anhydride regenerated **2**. The ethyl ester **6** is formed by treatment of **4** with ethanolic hydrogen chloride. When **6** was dissolved in sodium bicarbonate solution, **2** was obtained. Treatment of **2** with ethanolic hydrogen chloride yielded **6**. These interconversion (pairs **2** ⇌ **4** and **2** ⇌ **6**) establish **2** as the product of the reaction of **1** with acetic anhydride. The ethyl ester of **1** did not cyclize when treated with bicarbonate; instead **1** was regenerated. It is noted that 3-methylcytosine[6] does not undergo rearrangement under these reaction conditions.

The ready cleavage and re-formation of lactams has been observed previously with certain pyrimidines such as with 6-amino-5-carboxymethylthiouracils[8] and with the more closely related 1-(2-carboxyethyl)isocytosine.[9]

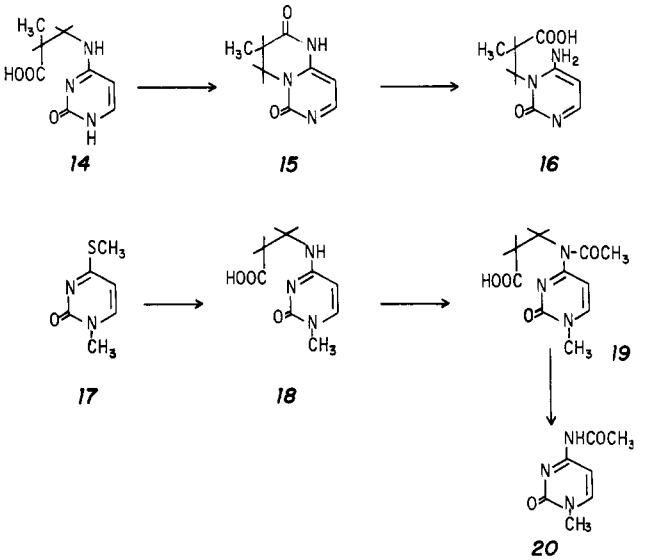
(8) E. F. Schroeder and R. M. Dodson, *J. Am. Chem. Soc.*, **84**, 1904 (1962).
(9) R. B. Angier and W. V. Curran, *J. Org. Chem.*, **26**, 1891 (1961).

The assignment of structure **2** rests in the final analysis on the proof of structure **4** and **5**. The ultraviolet absorption spectrum of **5** is very similar to that for 3-alkyluracils,[10] again indicating that **5** is 3-alkylated. Esterification of **5** with alcoholic hydrogen chloride afforded **7**, which also exhibited spectral properties akin to 3-alkyluracils.

The structures of **5** and **7** were confirmed by synthesis. Angier and Curran[9,11] demonstrated that acrylonitrile is a useful reagent for the introduction of a 2-carboxyethyl group on the ring nitrogen of certain pyrimidines and pteridines. This method was adapted to the synthesis of **7**. Treatment of uracil (**8**) with acrylonitrile in alkali afforded 1-(2-carboxyethyl)uracil (**9**) in high yield. The spectrum of **9** resembled that for 1-substituted uracils,[10] and no evidence for any 3-isomer was observed. Reaction of cytosine (**10**) with acrylonitrile in 50% aqueous pyridine gave only 1-(2-cyanoethyl)cytosine (**11**). Treatment of 2-methylthiouracil (**12**) with acrylonitrile in aqueous pyridine gave 3-cyanoethyl-2-methylthiouracil (**13**) in good yield. The position of alkylation in **13** is established by the close similarity of its ultraviolet spectrum to that of 2-methylthio-3,6-dimethyl-4-pyrimidinone and the dissimilarity to 2-ethylthio-1-methyl-4-pyrimidinone.[12] Hydrolysis of **13** in 5 *N* hydrochloric acid yielded **5**, which was identical by ultraviolet and infrared spectral comparison and migration in paper electrophoresis with **5** obtained from **4**. The ethyl ester **7** was also synthesized from **5** derived from acid hydrolysis of **13**. These syntheses prove structures **5** and **4** and thereby establish structure **2** as the product of the reaction of **1** with acetic anhydride.

A study of the generality of this rearrangement with pyrimidinyl amino acids was undertaken next. Treatment of 4-methylthio-2-pyrimidinone with β-aminoisobutyric acid yielded **14** (Chart III). When refluxed with acetic anhydride, **14** was converted to the dehydrated product **15**, which exhibited ultraviolet spectral properties similar to **2**. The hydrolytic behavior of **15**

CHART III



(10) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952).
(11) R. B. Angier and W. V. Curran, *J. Am. Chem. Soc.*, **81**, 5650 (1959); W. V. Curran and R. B. Angier, *J. Org. Chem.*, **26**, 2364 (1961); **27**, 1366 (1962).
(12) D. Shugar and J. J. Fox, *Bull. soc. chim. Belges*, **61**, 293 (1952).

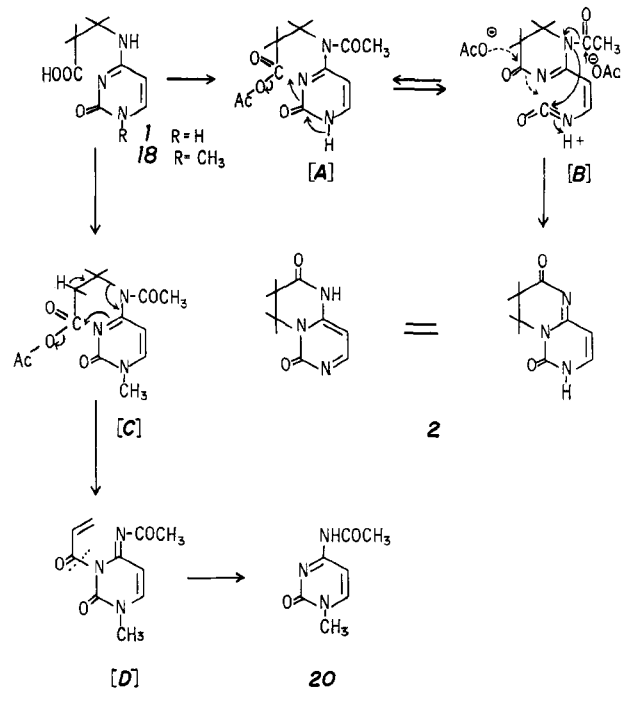
was also similar to **2** since **15** was easily converted to **16**. The spectrum of **16** was akin to **4** and also to other 3-alkylcytosines. It appears that alkyl substituents vicinal to the carboxyl function in **1** do not prevent the transformation to type **2** compounds.

The importance of a proton on N^1 of **1** in this reaction was examined. For the appropriate model compound, 1-methyl-4-methylthio-2-pyrimidinone (**17**) was treated with β-alanine to yield **18**, the 1-methyl analog of **1**. Reaction of **18** with acetic anhydride at reflux temperature for 15 min. gave the N-acetyl derivative **19** as the major product. The absorption spectrum of **19** was fairly similar to that for **20** (see below); however, the elemental analyses and electrophoretic behavior are consistent with **19**. Alkaline hydrolysis of **19** yielded starting material, **18**. With longer reflux of **18** in acetic anhydride, the reaction solution darkened considerably, and a low yield of **20** was obtained and was identified by comparison with authentic material prepared by an alternate route.[13] No other product (not even **19**) could be isolated from the reaction mixture. However, paper electrophoretic examination of the mother liquor showed the presence of three other minor components in addition to **19** and **20**. One of these components showed an ultraviolet absorption maximum at ~312 mμ. The conversion of **19** to **20** was most unexpected. A possible reaction pathway to explain this conversion is discussed below. In general, substitution at N^1 of **1** by alkyl, as in **18**, prevented the type of transformation illustrated by the conversion of **1** to **2**.

The formation of **19** as a major product in the short-term treatment of **18** with acetic anhydride suggested that an N^4-acylated intermediate also formed in the transformation of **1** to **2**. It is to be noted that treatment of cytosine, 1-methylcytosine, or 1,N^4-dimethylcytosine with acetic anhydride gives N^4-acetyl derivatives.[13] Attempts to isolate a crystalline intermediate in the reaction of **1** → **2** were unsuccessful. However, after mild treatment of **1** with acetic anhydride and examination of the reaction solution, spectra were obtained supporting an N^4-acylated intermediate (see Experimental section).

A plausible mechanism for the conversion of **1** to **2** is given in Chart IV. The first intermediate in the reaction of **1** with acetic anhydride is A, in which the carboxyl group is activated as a mixed anhydride. Intermediate B would form from A by cyclization at N^3 accompanied by cleavage of the 2,3 bond. Ring closure on C^2 of the isocyanate would be competitive between N^3 and N^4.[14] If the N^3 attack is on C^2, intermediate A would be re-formed. However, if N^4 is involved in this attack (as depicted in Chart IV), compound **2** is formed with the elimination of acetic anhydride as a result of attack by acetate ion on the acetyl

CHART IV



of N^4. The stability of **2** under these reaction conditions (attempts to acetylate **2** have been unsuccessful and **2** was recovered unchanged) accounts for its formation as the sole reaction product.

This mechanism helps to explain the failure of **18** to form the 1-methyl analog of **2**. Here it is reasonable to postulate the formation of the mixed anhydride C (see Chart IV) as the first intermediate, and the isolation of **19** in Chart III is readily explained by the hydrolysis of anhydride C. The presence of a methyl group on N^1 prevents the electron migration to the 1,2-position necessary for the formation of B from A. Therefore, cleavage of the 2,3 bond did not occur. Under prolonged reflux of **18** with acetic anhydride, attack at N^3 was accompanied by cleavage of the N^4–C bond in C resulting in the acryloyl derivative D. Under the reaction conditions employed, D would be expected to undergo acetolysis to **20**. It is known that N^3-acyl derivatives of 1-methyl-N^4-benzoylcytosine hydrolyze easily to 1-methyl-N^4-benzoylcytosine.[4] The intense darkening of the reaction mixture **18** → **20** may be explained by the polymerization of acrylic acid or its derivatives.

It is interesting to compare the rearrangement of **1** → **2** with the Dimroth rearrangement which has recently been reviewed and elaborated by Brown[15a] and others.[15b] The course of the reaction of **1** → **4** is just the reverse of that which occurs in the Dimroth rearrangement. In the latter rearrangement, the ring alkylated amino- or iminopyrimidine rearranges to an exocyclic alkyl aminopyrimidine. In the conversion of **1** → **4**, however, the exocyclic alkyl aminopyrimidine (**1**) rearranged to a ring alkylated isomer **4**. In both rearrangements, an exchange of ring nitrogen by exocyclic nitrogen occurs.

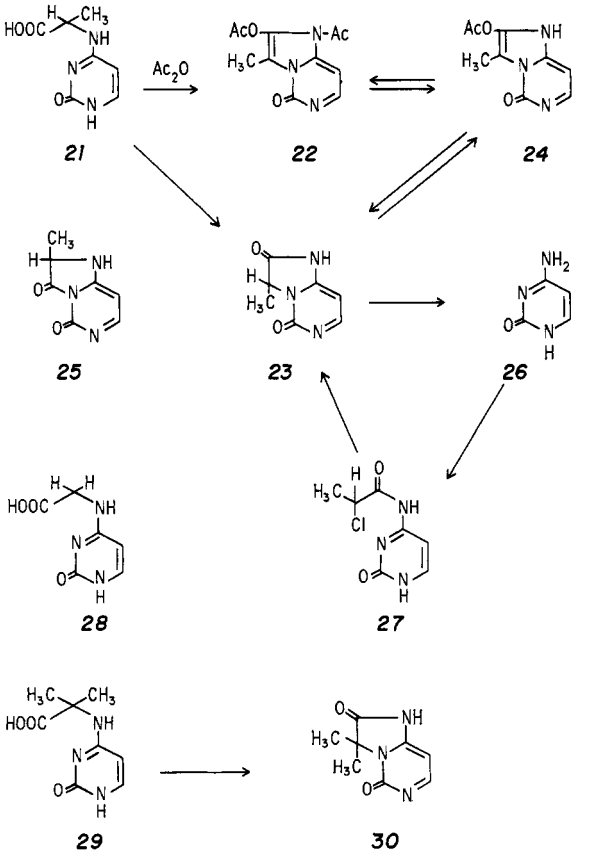
The reaction of pyrimidinyl-α-amino acids with acetic anhydride was also investigated (see Chart V).

(13) G. W. Kenner, C. B. Reese, and A. R. Todd, *J. Chem. Soc.*, 855 (1955).

(14) N^4 in A, B, and **2** refers to the exocyclic nitrogen atom linked to C^4 as in the original pyrimidine, **1**. In the condensed ring compounds (*e.g.*, **2** of Chart IV or **30** of Chart V) this corresponding nitrogen atom should be referred to as N^1. The carbonyl derived from the amino acid should be designated as "2-oxo" and the carbonyl derived from the original pyrimidine as "6-oxo" (in the case of **2**) and "5-oxo" (in **23** or **30**). To facilitate the discussion, we call the exocyclic nitrogen atom of **1**, **18**, **21**, and **29**, as well as the corresponding nitrogen atom in the condensed ring compounds, as N^4. Similarly, C^2 in B refers to the position corresponding to C^2 of **1**. The *Chemical Abstracts* nomenclature of the condensed ring compounds is given in the Experimental section.

(15) (a) D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1276 (1963), and references therein; (b) J. Goerdeler and W. Roth, *Chem. Ber.*, **96**, 534 (1963).

CHART V



N-(1H-2-Oxo-4-pyrimidinyl)-L-alanine (**21**)[2] was refluxed with acetic anhydride to yield **22**, a compound with analysis of a dehydrated **21** with two acetyl groups. The O-acetyl group was indicated by infrared spectra (see Experimental). On hydrolysis in acid or alkali under mild conditions, **22** was converted to **23**. The structure of **23** was confirmed by an alternate synthesis (*vide infra*). Compound **22** was regenerated from **23** by refluxing the latter with acetic anhydride. **22** was a rather unstable compound. In boiling water, **22** was converted to **24**, the structure of which was confirmed on the basis of elemental analyses and the presence of an O-acetyl band (1780 and 1205 cm.$^{-1}$) in the infrared spectrum. Mild alkaline hydrolysis of **24** afforded **23**.

Direct cyclization (with rearrangement) of **21** to **23** was carried out in high yield in refluxing acetic acid–acetic anhydride (10:1) solution for a relatively short time. The ultraviolet absorption spectrum of **23** was similar to that for **2**. A comparison of the pK_a values of **2** (4.00 and ~8) to **23** (2.11 and 7.80) also showed similarity. It is to be noted that **22**, **23**, and **24** were optically inactive.

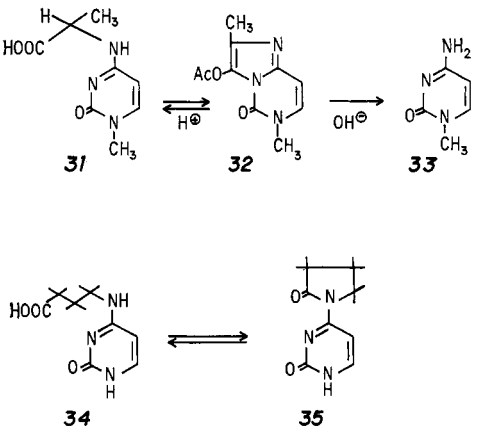
Hydrolysis experiments with **23** failed to establish the structure of **23** as *vs.* **25**. Unlike **2** and **15** (Charts II and III), **23** was rather stable to hydrolysis. After prolonged treatment of **23** with boiling 1 *N* hydrochloric acid or with warm alkali only cytosine (**26**) was found in the hydrolyzate.

Firm proof of structure **23** was established by an alternate synthesis. Prokofév, *et al.*,[16] have synthesized certain imidazo[1,2-*a*]pyrimidines by reaction of 6-methylisocytosine with α-bromopropionic anhydride followed by cyclization in base. During the course of our investigation, Noell and Robins[17] reported the synthesis of imidazo[1,2-*c*]pyrimidines by the use of similar procedures on 4-aminopyrimidines. We used similar procedures for the synthesis of **23**. Treatment of cytosine (**26**) with 2-chloropropionyl chloride yielded crude **27**. The structure of **27** was confirmed by the similarity of its absorption spectrum to N^4-acetylcytosines.[4,13] Cyclization of **27** in methanolic sodium methoxide yielded **23**, identical with that obtained by acetic anhydride treatment of **21**. It is, therefore, concluded that pyrimidinyl-α-amino acids, like the pyrimidinyl-β-amino acids, cyclize *with rearrangement* when treated with acetic anhydride.

Attempts to cyclize the glycine derivative **28** with acetic anhydride resulted in the formation of intractable colored products which were not investigated further. A similar phenomenon has been noted by McKay and Kreling[18] on 3H-3-oxo-1,2,5,6-tetrahydroimidazo-[1,2-*a*]imidazole, and its pyrimidine analog, in which ready oxidation of the active methylene group in the imidazolone ring to indigo-like products was observed. It is highly likely that a similar type of oxidation occurring on the methylene group of the imidazolone moiety when **28** is ring closed with acetic anhydride accounts for intense coloration of the reaction mixture.

When both hydrogen atoms of the 2-methylene group of α-amino acids are substituted by methyl functions, the cyclization–rearrangement reaction occurs. N-(1H-2-Oxo-4-pyrimidinyl)-α-isobutyric acid (**29**) prepared by reaction of 4-methylthio-2-pyrimidinone with α-aminoisobutyric acid was refluxed with acetic acid–acetic anhydride to yield **30**. Intense coloration of the reaction mixture did not occur. The spectrum and the pK_a of **30** were very similar to **23**. When **29** was refluxed in acetic anhydride for 1 hr. (without acetic acid added) the cyclization and rearrangement did not occur. Compounds **1** and **21** rearrange to **2** and **22** within 30 min. under these conditions. Spectral examination of the reaction solution from **29** indicated that only N^4-acetylation of **29** occurred. Upon addition of acetic acid to this reaction solution, **30** was obtained. These experiments also support the view expressed above that the first step in the rearrangement of **1** to **2** (Chart IV) is the formation of A. The requirement of additional

CHART VI



(16) M. A. Prokofév, E. G. Antonovich, and Yu. P. Shvachkin, *Dokl. Akad. Nauk SSSR*, **87**, 783 (1952).

(17) C. W. Noell and R. K. Robins, Abstracts, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 28L.

(18) A. F. McKay and M. E. Kreling, *Can. J. Chem.*, **40**, 205 (1962).

acetic acid may be a reflection of steric effects of the two α-methyl groups which inhibit acetate attack on the carbonyl of the N^4-acetyl in the intermediate corresponding to B (as in Chart IV). Compound **30**, unlike **23**, **15**, or **2**, was resistant to hydrolysis, and no decomposition was observed when **30** was refluxed for prolonged periods in 1 *N* hydrochloric acid or 1 *N* alkali. Like **2**, but unlike **23**, **30** was resistant to acetylation. This aspect will be discussed later.

The effect of N^1-alkylation on the susceptibility of pyrimidinyl-α-amino acids to rearrangement with acetic anhydride was also investigated (see Chart VI). Compound **31**, prepared by reaction of α-DL-alanine with **17** (Chart III) was refluxed with acetic anhydride. A product, **32**, was obtained which showed the presence of an O-acetyl by infrared spectra and the presence of three methyl functions by n.m.r. spectral examination.[19] Compound **32** is strongly basic and forms an acetate salt. Proof that **32** is the cyclized *but not rearranged* product was shown by the fact that acid hydrolysis of **32** regenerated starting material, **31**. Hydrolysis of **32** with alkali gave varying results. With a 10^{-4} *M* concentration of **32** in 1 *N* sodium hydroxide, complete conversion to 1-methylcytosine (**33**) occurred. A higher concentration (~0.03 *M*) of **32** in 1 *N* alkali yielded a mixture of starting material **31**, as well as **33**. These data suggest that the cleavage between N^4 and the amino acid carbon is pH dependent. This matter was not investigated further.

As a final aspect of this study of the generality of the cyclization–rearrangement type reaction of pyrimidinyl amino acids, we examined the behavior of a γ-amino acid homolog of **1** in refluxing acetic anhydride (Chart VI). N-(1H-2-Oxo-4-pyrimidinyl)-γ-aminobutyric acid (**34**) was prepared by reaction of 4-methylthio-2-pyrimidinone with γ-aminobutyric acid and then was refluxed with acetic anhydride with or without acetic acid. A single product was obtained in both cases in high yield, and exhibited ultraviolet spectral properties similar to those for N^4-acetylcytosine[13] and unlike those for **2** (Chart I) or **23** (Chart V). Compound **35** on treatment with alkali regenerated **34**. These data warrant the assignment of the butyrolactam structure to **35** as shown in Chart VI rather than a seven-membered cyclized or rearranged structure.

It is concluded that both α and β simple amino acid derivatives of N-1H-2-oxo-4-pyrimidine in refluxing acetic anhydride will undergo cyclization at N^3 with rearrangement to give 2-oxoimidazo- or -pyrimido-[1,2-*c*]pyrimidines (*Chemical Abstracts* nomenclature) of type **2** or **23**. When the N^1-position of these pyrimidinylamino acids is substituted, this rearrangement does not occur. With γ-amino acid derivatives, butyrolactam formation predominates.

An interesting difference between the pyrimidinyl-α- and -β-amino acid derivatives is to be found in the reactivity of the hydrogen α to the carboxyl group especially after the cyclization–rearrangement reaction occurred. As mentioned previously (Chart V), **23** is easily acetylated to **22**, whereas **30**, **15**, or **2** are resistant to acetylation. This phenomenon may be explained by the presence of an active hydrogen in **23** which is absent in **30**. Since N^4 (ref. 14) of **30** is unacetylatable, it is reasonable to expect that N^4 of **23** is equally resistant. The conversion of **23** to **22** proceeds most likely by O-acetylation to **24**. In this latter compound, N^4 has lost its amide character so that it now undergoes acetylation to **22**. This mechanism (**23** → **24** → **22**) requires tautomerism of **23** to the enolized form. Such tautomerism is not possible with **30**; therefore, the latter fails to acetylate. The failure of **2** and **15** to acetylate (Chart II) under conditions which acetylate **23** is explained by the less active nature of the methylene group alpha to the carbonyl in the former compounds. It is noted that in **23**, the active hydrogen is located on carbon which is adjacent to both a carbonyl and nitrogen.

The mobility of the α-hydrogen in **23** is evidenced by n.m.r. spectroscopy.[19] When the spectrum of **23** was taken in deuterated dimethyl sulfoxide, coupling of the methyl group and hydrogen was observed as a doublet and quartet, respectively (CH_3, τ 8.53; H, τ 5.66; J_{H-CH_3} = 7 c.p.s.). When the spectrum of **23** was taken in D_2O, the methyl group gave a singlet (CH_3, τ 8.77) and no hydrogen peak was observed, indicating that the α-hydrogen was being exchanged.

The lack of optical activity in **22**, **23**, and **24** is consistent with the enolization of the keto group by the α-hydrogen during the cyclization reaction from **21**. It is known[20] that L-amino acids give optically inactive N-acetyl derivatives when treated with acetic anhydride.

Experimental[21]

1H-1,2,3,4-Tetrahydro-2,6-dioxopyrimido[1,2-*c*]pyrimidine (2).—A suspension of N-(1H-2-oxo-4-pyrimidinyl)-β-alanine[2] (**1**, 10 g.) in acetic anhydride (100 ml.) was refluxed for 30 min. and allowed to stand overnight. The precipitate was collected by filtration and washed with ethanol and ether, and recrystallized from 50% ethanol–water, giving 6.0 g. (67%), m.p. >280°; ultraviolet absorption properties: at pH 1, maxima at 304 and 240 mμ (ϵ_{max} 15,000 and 6550), minima at 263 and 227 mμ (ϵ_{min} 2500 and 5050); at pH 6.17, maxima at 312 mμ (ϵ_{max} 17,000), minimum at 253–260 mμ (ϵ_{min} 1800); at pH 9.17, maxima at 325 and 227 mμ (ϵ_{max} 23,600 and 9700), minimum at 273 mμ (ϵ_{min} 1100). In 1 *N* sodium hydroxide, **2** was hydrolyzed quickly and gave a spectrum identical with that for 3-(2-carboxyethyl)cytosine (**4**); pK_{a_1} 4.00, pK_{a_2} ~8; infrared spectrum (potassium bromide): ν_{max} at 1740 (doublet), 1690, 1650, and 1580 cm.$^{-1}$. The same product was obtained when acetic acid–acetic anhydride were used as reagents in the reaction of **1**.

Anal. Calcd. for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.44. Found: C, 50.78; H, 4.21; N, 25.33.

3-(2-Carboxyethyl)cytosine (4).—Compound **2** (2.5 g.) was dissolved in boiling water and, after cooling, the separated crystals (starting material) were collected by filtration (0.7 g.). The mother liquor was concentrated to dryness and the residue was recrystallized from a small amount of water, 0.97 g., m.p. 277° dec.; ultraviolet absorption properties: at pH 4.72, maximum at 276 mμ (ϵ_{max} 8700), minimum at 242 mμ (ϵ_{min} 2100); at pH 10.58, maximum at 297 mμ (ϵ_{max} 10,700), minimum at 249 mμ (ϵ_{min} 570); in 3 *N* sodium hydroxide, maxima at 294 and 233 mμ (ϵ_{max} 8600 and 7000), minimum at 258 mμ (ϵ_{min} 1700); pK_{a_2} 7.53, pK_{a_3} ~13.5; infrared spectrum (potassium bromide): ν_{max} 1730, 1650, 1615, 1570, 1950, and 2420 (weak and broad) cm.$^{-1}$. The same product was also obtained by treating **2** with 0.1 *N* sodium hydroxide at room temperature for 18 hr. or with concentrated ammonium hydroxide for 3 days at room temperature.

(19) The authors are indebted to Dr. E. Billeter of Hoffmann-LaRoche, Inc., Nutley, N. J., for the determination and interpretation of the n.m.r. spectra.

(20) D. M. Greenberg in "Amino Acids and Proteins," Charles C. Thomas Publishers, Springfield, Ill., 1951, p. 33.

(21) All melting points were taken on a Thomas–Hoover capillary melting point apparatus and are corrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Anal. Calcd. for $C_7H_9N_3O_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 45.84; H, 4.83; N, 22.89.

3-(2-Carbethoxyethyl)cytosine Hydrochloride (6).—Compound **2**, (0.7 g.) was suspended in 20 ml. of ethanol containing dry hydrogen chloride and refluxed for 30 min. After concentration to a small volume, the residue was taken up in ethanol and evaporated to dryness. The residual solid was recrystallized from hot ethanol (0.7 g., m.p. 173–174° dec.); ultraviolet absorption properties showed a maximum in water at 275 mμ. On addition of a few drops of 10% sodium bicarbonate solution the spectrum changed rapidly and gave a new maximum at 325 mμ which is identical with that for **2**. Upon acidification the maximum shifted to 304 mμ.

Anal. Calcd. for $C_9H_{13}N_3O_3 \cdot HCl$: C, 43.64; H, 5.70; Cl, 14.32; N, 16.96. Found: C, 43.58; H, 5.66; Cl, 14.26; N, 16.84.

The same compound was obtained by similar treatment of **4**.

Reaction of 4 with Acetic Anhydride.—Compound **4** was refluxed in acetic anhydride for 15 min. After cooling, the separated crystals were filtered, washed with ethanol, and dried. The ultraviolet and infrared spectra of this compound were identical with those for **2**.

3-(2-Carboxyethyl)uracil (5). **Method A from 2.**—A solution of **2** (6.0 g.) in 100 ml. of 1 *N* sodium hydroxide was refluxed for 3 hr. Hydrolysis of **2** to **4** was complete within 15 min. The solution was applied to a column (Dowex 50 × 8, H^+ form, 50–100 mesh) and washed with water. The washings containing the product were combined and concentrated to dryness; the residue was taken up in ethanol and precipitated with ethyl acetate. The precipitate (1.0 g., plus 1.7 g. from the mother liquor) gave an absorption maximum at 259 mμ in acid or water and at 285 mμ in alkaline solution, A_{max} in water/A_{max} in OH^- = 0.68, m.p. 169–174°.

Method B from 13.—A solution of 1.08 g. of **13** in 20 ml. of 5 *N* hydrochloric acid was refluxed for 18 hr., and concentrated to dryness; the residue was treated with 30 ml. of acetone. The acetone-insoluble products were separated by filtration and discarded. The filtrate was concentrated to dryness and gave 1.1 g. of crude solid. This solid was recrystallized from acetone, m.p. 168–170°. The infrared absorption spectra of this product and the compound obtained from method A above are almost identical [potassium bromide; ν_{max} 1750, 1670 (sh), 1645, and 1625 cm.$^{-1}$].

Anal. Calcd. for $C_7H_8N_2O_4$: C, 45.40; H, 4.29; N, 15.21. Found: C, 45.65; H, 4.38; N, 15.22.

The product from method A and B showed similar paper electrophoretic properties: at pH 9.3 (borate buffer, 800 v., 1 hr.), +5.8 cm. Ultraviolet absorption properties follow: at pH 4–7, maximum 259 mμ (ε 7160), minimum 229 mμ (ε 2580); at pH 14, maximum 284 mμ (ε 10,520), minimum 244 mμ (ε 600); maximum at pH 7/maximum at pH 14 = 0.68; pK_{a_2}, 10.47.

3-(2-Cyanoethyl)-2-methylthiouracil (13).—A solution of 6 g. of 2-methylthiouracil[22] and 30 ml. of acrylonitrile in 180 ml. of 50% pyridine was refluxed for 8 hr. After concentration of the solution, the residue was treated with a small amount of water and the solid (7.4 g.) was collected by filtration. One recrystallization from ethanol gave a pure compound **13**. Ultraviolet absorption properties showed maxima in water at 295 and 225 mμ, and minima at 255 and 215 mμ; maximum in 1 *N* hydrochloric acid at 280 mμ, a minimum at 252 mμ; infrared spectra (potassium bromide): ν_{max} 1710, 1505, and 2280 (weak) cm.$^{-1}$.

Anal. Calcd. for $C_8H_9N_3OS$: C, 49.21; H, 4.65; N, 21.52; S, 16.42. Found: C, 49.22; H, 4.22; N, 21.49; S, 16.72.

Ethyl Ester of 3-(2-carboxyethyl)uracil (7). **Method A.**—Crude **5** (30 mg.) obtained from the hydrolysis of **4**, was dissolved in ethanolic hydrogen chloride and heated at 50° for 1 hr. After evaporation of the solvent, the residue was dissolved in ethanol and concentrated to a small volume from which white crystals separated. Recrystallization from ethanol–hexane gave needles, 20 mg., m.p. 101–103°; ultraviolet absorption in ethanol: maximum at 259 mμ, minimum at 230 mμ; infrared spectra (potassium bromide): ν_{max} 1760, 1730, 1650, 1620, and 1215 cm.$^{-1}$.

Method B.—Compound **5** (0.5 g.) obtained from **13** was dissolved in 30% saturated ethanolic hydrogen chloride (15 ml.) and refluxed for 30 min. After removal of solvent, the solid residue was recrystallized from ethanol–hexane, yielding 450 mg., m.p. 101–102°. Mixture melting point with **7** gave 102–103°; ultraviolet and infrared spectra were identical.

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found (A and B): C, 50.83, 50.76; H, 5.67, 5.56; N, 13.03, 13.03.

1-(2-Carboxyethyl)uracil (9).—A solution of uracil (**8**, 2 g.) and acrylonitrile (3.8 g.) in 100 ml. of 1 *N* sodium hydroxide was refluxed for 2 hr. The solution was treated with excess Dowex 50 (H^+) resin. The filtered solution was concentrated to dryness and the residue recrystallized from water–acetone, yielding 2.5 g., m.p. 183–185°; ultraviolet absorption properties: maximum in water at 266 mμ, in 0.01 *N* sodium hydroxide at 265 mμ.

Anal. Calcd. for $C_7H_8N_2O_4$: C, 45.65; H, 4.38; N, 15.22. Found: C, 44.83; H, 4.26; N, 15.76.

1-(2-Cyanoethyl)cytosine (11).—A solution of 2 g. of cytosine (**10**) and 10 ml. of acrylonitrile in 80 ml. of 50% pyridine was refluxed for 7 hr. After removal of solvent by evaporation, the residue was crystallized from a large amount of ethanol–water, yielding 1.6 g., m.p. 249–250° dec.; ultraviolet absorption properties: maximum in water or 1 *N* sodium hydroxide at 272 mμ, minimum at 250 mμ; maximum at pH 1, 280 mμ, minimum at 240 mμ; $A_{272}(H_2O)/A_{280}(H^+)$ = 0.675. Infrared spectrum shows the presence of a nitrile group at 2280 cm.$^{-1}$.

Anal. Calcd. for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.10; H, 5.58; N, 33.72.

N-(1H-2-Oxo-4-pyrimidinyl)-DL-β-aminoisobutyric Acid (14).—This compound was synthesized by the general method[2] from 4-methylthio-2-pyrimidinone (4.25 g.) and DL-β-aminoisobutyric acid (3.4 g.). Crude material (5 g.) was recrystallized from water, m.p. 177–178° dec.

Anal. Calcd. for $C_8H_{11}N_3O_3 \cdot 0.5H_2O$: C, 46.59; H, 5.87; N, 20.38. Found: C, 46.62; H, 5.84; N, 20.75.

1,2,3,4-Tetrahydro-3-methyl-2,6-dioxopyrimido[1,2-*c*]pyrimidine (15).—Compound **14** (2.0 g.) in acetic acid (10 ml.) and acetic anhydride (5 ml.) was refluxed for 15 min. After concentrating the solution to dryness, the residue was taken up in ethanol, filtered, and dried to yield 1.65 g. of yellow crystals. One recrystallization from ethanol containing a small amount of water gave pure material, m.p. >290°; ultraviolet properties are almost identical with those for **2**.

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.62; H, 5.06; N, 23.45. Found: C, 53.38; H, 4.84; N, 23.72.

3-(2-Carboxypropyl)cytosine (16).—Compound **15** (0.5 g.) was treated with 10 ml. of 0.5 *N* sodium hydroxide solution under reflux for 20 min. The solution was acidified with acetic acid and concentrated to a small volume. The precipitate was collected by filtration and recrystallized from water, yielding 0.2 g., m.p. >290°; ultraviolet properties were very similar to those for compound **4**.

Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 49.05; H, 5.91; N, 20.97.

N-(1-Methyl-2-oxo-4-pyrimidinyl)-β-alanine (18).—A solution of 1-methyl-4-methylthio-2-pyrimidinone[23] (**17**, 7 g.), β-alanine (4.8 g.), and sodium carbonate (2.4 g.) in water (40 ml.) was refluxed for 12 hr. and worked up in the usual manner,[2] yielding 5.1 g. of pure **18**, m.p. 231–233°; ultraviolet absorption properties: maximum in water or 1 *N* sodium hydroxide at 276 mμ, minimum at 252 mμ; at pH 1, maximum at 288 mμ, minimum at 245 mμ.

Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48.63; H, 5.45; N, 21.29.

Reaction of 18 with Acetic Anhydride. Method A. Synthesis of 19.—Compound **18** (0.35 g.) in acetic anhydride (5 ml.) was refluxed for 15 min. After concentration of the solution to a small volume, ethanol was added and evaporated again. The residue was recrystallized twice from a small amount of ethanol to give **19** (0.15 g.); ultraviolet properties: in water, maxima at 304 and 252 mμ, minima at 277 and 232 mμ; in 0.1 *N* hydrochloric acid, maxima at 306 and 251 mμ, minima at 275 and 230 mμ. In 0.1 *N* sodium hydroxide, the compound reacted rapidly to give a spectrum identical with that for **18**. Paper electrophoretic mobility at pH 5.16 (0.1 *M* acetate buffer, 800 v., 1 hr.) was +3.8 cm. (due to presence of a carboxyl group). The same compound was obtained as a main product when acetic acid and acetic anhydride (2:1) were used as a reagent for a short time reaction (15 min. refluxing).

Anal. Calcd. for $C_{10}H_{13}N_3O_4$: C, 50.21; H, 5.48; N, 17.56. Found: C, 50.26; H, 5.26; N, 17.68.

(22) H. L. Wheeler and H. F. Merrian, *Am. Chem. J.*, **29**, 478 (1903).

(23) H. L. Wheeler and T. B. Johnson, *ibid.*, **42**, 30 (1909).

Method B. Synthesis of 20.—Compound **18** (1.0 g.) in acetic anhydride (15 ml.) and acetic acid (2 ml.) was refluxed for several hours. After several minutes, the ultraviolet absorption spectra showed the formation of **19** as a main product but, after 30 min., the spectrum changed. After 4 hr., the solvent was removed under reduced pressure and the residue was dissolved in ethanol and left overnight in the refrigerator. The precipitated material was separated and recrystallized from ethanol as needles of **20**, 0.1 g., m.p. 271–272°; ultraviolet absorption properties: in water, maxima at 298 and 244 mμ, minima at 267 and 226 mμ; in strong acid, maximum at 310 mμ, minimum at 261 mμ (almost identical with reported values)[13]; mixture melting point with an authentic sample 273–274°, lit.[13] m.p. 268°. The infrared spectrum was identical with an authentic sample.

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.10; H, 5.42; N, 24.97.

The mother liquor was subjected to paper electrophoresis (pH 5.36, acetate buffer, 800 v., 3 hr.). Five spots were obtained (+4.5, −0.5, −2.5, −6.4, −8.0 cm.), two of which (+4.5- and −0.5-cm. spots) were identified as **19** and **20**, respectively. The other spots were minor and not identified, but the −2.5-cm. spot, after excision and elution with water, showed an ultraviolet absorption spectrum with a maximum at 312 mμ and two inflections at 290 and 325 mμ.

1-Acetyl-2-acetoxy-3-methyl-5-oxoimidazo[1,2-*c*]pyrimidine (22).—A suspension of compound **21**[2] (L or DL form, 2.0 g.) in 25 ml. of acetic anhydride was refluxed for 1 hr. After removal of the solvent *in vacuo*, the residual solid was treated with ethanol, filtered (2.1 g.), and recrystallized from boiling ethanol to yield white needles, 1.2 g., m.p. 130–132°. The mother liquor was used for the next experiment (see below). The ultraviolet absorption spectrum in ethanol showed a broad maximum at 300–305 and 222 mμ (ϵ_{max} 8600 and 17,000), minimum at 245 mμ (ϵ_{min} 1300); infrared spectrum (potassium bromide): ν_{max} 1785 (sh), 1765, 1670, 1660, 1625, 1230 (sh), and 1210 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 52.95; H, 4.34; N, 17.02.

The same compound was obtained by treating **23** (0.4 g.) with acetic anhydride (5 ml.) in the same manner. The product (0.3 g.), m.p. 127–128.5°, had the same ultraviolet absorption spectrum as **22**.

1H-2-Acetoxy-3-methyl-5-oxoimidazo[1,2-*c*]pyrimidine (24).—The mother liquor from the above experiment was concentrated to dryness and the residue was heated with dilute acetic acid solution at 80° for 1 hr. The solution was concentrated and the separated crystals were recrystallized from dilute ethanol, yielding 0.4 g., m.p. 204–206°, sintered at 195°; ultraviolet absorption spectrum: maxima at 290 and 282 mμ (ϵ_{max} 9740 and 9800), shoulder at 304 mμ (ϵ_{max} 5500), minimum at 231 mμ (ϵ_{min} 1100); infrared spectra: ν_{max} 1780, 1755, 1650, 1615 and 1205 cm.$^{-1}$.

Anal. Calcd. for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.81; H, 4.16; N, 20.51.

When this compound was treated with dilute alkali, the ultraviolet spectrum changed rapidly to that of **23**.

1H-3-Methyl-2,3-dihydro-2,5-dioxoimidazo[1,2-*c*]pyrimidine (23) from 21. Method A.—Compound **21** (L-form,[2] 2.0 g.) was suspended in 2 ml. of acetic anhydride and 20 ml. of acetic acid and refluxed for 30 min. The solution was concentrated to dryness, the residue was treated with water and filtered, and the solid was recrystallized from dilute ethanol. Pure crystals (1.5 g. in two crops) were obtained, m.p. 280° dec. Ultraviolet absorption properties follow: in 1 *N* hydrochloric acid, maxima at 299 and 237 mμ (ϵ_{max} 14,500 and 4700), minima at 262 and 224 mμ (ϵ_{min} 1900 and 3700); at pH 4.20, maximum at 303 mμ (ϵ_{max} 18,600), minimum at 238–242 mμ (ϵ_{min} 1800); at pH 9.73, maximum at 318 mμ (ϵ_{max} 19,800), minimum at 266–270 mμ (ϵ_{min} 300); pK_{a_1} 2.11, pK_{a_2} 7.12; infrared spectrum: ν_{max} 1740, 1630, 1565, and 1450 cm.$^{-1}$; n.m.r. spectra in d_6-dimethyl sulfoxide: τ 8.53 (3-CH_3), 5.66 (3-H) ($J_{H^3-CH_3^3}$ = 7 c.p.s.), 3.79 (8-H), and 2.74 (7-H) ($J_{H^7-H^8}$ = 7 c.p.s.), in D_2O and a drop of trifluoroacetic acid, τ 8.77 (3-CH_3) and 3.85 (8-H), 2.30 (7-H) ($J_{H^7-H^8}$ = 7 c.p.s.).

Method B. Synthesis of 23 from 22.—A solution of **22** (0.1 g.) in water (10 ml.) was refluxed for 20 hr. After removal of solvent *in vacuo*, the residue was recrystallized from methanol, 0.05 g., m.p. 278° dec.; ultraviolet spectra are identical with those for the compound prepared by method A. When compound **22** was dissolved in 1 *N* sodium hydroxide, the hydrolysis was very rapid (within 1 hr.) and the solution gave a spectrum identical with that for **23**.

Method C. Synthesis of 23 from Cytosine.—To a suspension of cytosine (**26**, 3 g.) in 30 ml. of dimethylformamide, α-chloropropionyl chloride (5 g.) was added dropwise and the reaction mixture was stirred for 2 hr. at 40–50°. Excess ethyl acetate then was added to the solution, from which the precipitate **27** formed gradually. The solid was collected by filtration, washed with ethyl acetate, and dried (3.6 g.); ultraviolet spectra in water showed maxima at 299 and 244 mμ, minima at 269 and 227 mμ; A_{244}/A_{299} = 2.0.

Crude **27** (1.5 g.) was dissolved in sodium ethoxide in ethanol (1 g. of sodium dissolved in 100 ml. of ethanol), and kept at 40–50° for 30 min. The solution was neutralized to pH 7 with acetic acid, the precipitate was removed by filtration, and the filtrate was concentrated to dryness. The residue was triturated with ethanol to remove colored material, and the insoluble residue then was dissolved in hot ethanol. Upon cooling, crystals separated and were filtered (0.4 g.). One recrystallization from ethanol gave pure material, m.p. 282° dec.; ultraviolet and infrared spectra were identical with those for the product obtained by method A.

Anal. Calcd. for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.44. Found (by methods A, B, and C, respectively): C, 50.80, 50.91, 50.93; H, 4.40, 4.28, 4.31; N, 25.35, 25.38, 25.09.

Alkaline Hydrolysis of 23 to Cytosine.—A solution of **23** (0.25 g.) in 50 ml. of 1 *N* sodium hydroxide was allowed to stand at 30–40°. After 4 days, about 60% of the starting material was converted to cytosine (as measured spectrally). After 6 days, the solution was neutralized to pH 5 with acetic acid. Paper electrophoresis of an aliquot of this solution at pH 5.16 (0.1 *M* ammonium acetate), 700 v., and 90 min., gave two spots migrating −2.8 and −0.5 cm. (weak spot). Starting material migrates at −0.5 cm. and cytosine migrates at −2.8 cm. The spot migrating at −2.8 cm. was excised and eluted with water; its spectrum[10] was determined: in water, maximum at 267 mμ; at pH 1, maximum at 276 mμ; at pH 14, maximum at 283 mμ; R_f 0.47 [ethanol–concentrated ammonium hydroxide–water (85:5:15); cytosine also gives R_f 0.47]. Picric acid in ethanol was added to the solution and the precipitated yellow needles were filtered, washed with water, then with ethanol, and dried (0.25 g.). One hundred milligrams recrystallized from ethanol gave 60 mg., m.p. 268° dec.; cytosine picrate, prepared from commercially available cytosine, had m.p. 270° dec.

Anal. Calcd. for $C_{10}H_8N_6O_8$: C, 35.39; H, 2.73; N, 25.81. Found: C, 35.31; H, 2.37; N, 24.70.

Acid Hydrolysis of 23 to Cytosine.—A small sample of **23** in 1 *N* hydrochloric acid was refluxed. After 4 hr. very little change in absorption spectra was observed. The solution was kept at room temperature for 2 weeks and subjected to paper electrophoresis (pH 9.4, borate buffer, 700 v., 60 min.). Two spots were obtained, one of which migrated at −1.8 cm. and was identical with that of cytosine under the same conditions. The −1.8-cm. spot was excised and eluted with water. The ultraviolet spectrum was like that for cytosine.[10] The second electrophoretic spot (spread over +0.7 → +5.0 cm.) was shown to be starting material **23** by spectral examination. Measurement of the ultraviolet extinctions of the two spots showed that 70% of **23** had been converted to cytosine.

N-(1H-2-Oxo-4-pyrimidinyl)-α-aminoisobutyric Acid (29).—A mixture of 4-methylthio-2-pyrimidinone[22] (4.26 g.), α-aminoisobutyric acid (3.4 g., 1.1 equiv.), and sodium carbonate (1.75 g., 0.55 equiv.) in 40 ml. of water was refluxed for 60 hr. The solution was acidified to pH 3 by the addition of formic acid and concentrated to half of its volume. The precipitated material (1.7 g.) was filtered and the filtrate was discarded (this filtrate contains 1.4 g. of uracil). The precipitate was dissolved in hot dilute ammonium hydroxide solution and decolorized with charcoal, filtered, and the filtrate was acidified by the addition of formic acid. Crystallization was slow. After filtration, the precipitate was washed with water, with alcohol, and dried, yielding 0.73 g., m.p. 288–289°; ultraviolet spectra: in water, maxima at 266 and 235 mμ; in 1 *N* hydrochloric acid, maximum at 282 mμ; and in 0.1 *N* sodium hydroxide, maximum at 283 mμ.

Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48 99; H, 5.68; N, 21.49.

1H-2,3-Dihydro-3,3-dimethyl-2,5-dioxoimidazo[1,2-*c*]pyrimidine (30).—A solution of **29** (0.1 g.) in 1 ml. of acetic anhydride and 2 ml. of acetic acid was refluxed for 15 min. After removal of the solvent the residue was taken up in ethanol and concentrated to dryness. This procedure was repeated three times, and the final residue was taken up in ethanol and treated dropwise

with ether. The precipitate of white crystals was collected and dried, yielding 0.08 g., m.p. 292.5–293.5°; ultraviolet absorption properties: in 1 *N* hydrochloric acid, maxima at 300 and 236 mμ (ϵ_{max} 15,000 and 5200), minima at 262 and 223 mμ (ϵ_{min} 1700 and 3900); at pH 4.27, maxima at 303 and 212.5 mμ (ϵ_{max} 19,200 and 8600), minimum at 235–245 mμ (ϵ_{min} 2300); in 0.1 *N* sodium hydroxide, maximum at 318 mμ (ϵ_{max} 20,200), minimum at 265–270 mμ (ϵ_{min} 230); pK_{a_1} 2.47, pK_{a_2} 7.28; n.m.r. spectrum in d_6-dimethyl sulfoxide: τ, 8.54 (3-CH_3), 3.80 (8-H), and 2.30 (7-H) ($J_{H^7-H^8}$ = 7.0 c.p.s.).

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.54; H, 5.18; N, 23.64.

When the reaction was carried out in acetic anhydride only, the reaction seemed to stop after acetylation of N^4. On addition of acetic acid to the reaction, rapid cyclization (rearrangement) occurred which could be followed by the change in the ultraviolet spectrum of the reaction solution.

The Reaction of N-(1H-2-Oxo-4-pyrimidinyl)glycine (28) with Acetic Anhydride.—Compound **28**[2] (1 g.) was suspended in 10 ml. of acetic anhydride and refluxed for 1 hr. With heat, an orange color formed that turned to dark red within 20 min. Aside from some starting material, no other product was characterizable. Similar results were obtained when acetic anhydride–acetic acid was used as the reagent.

N-(1-Methyl-2-oxo-4-pyrimidinyl)-DL-alanine (31).—A mixture of 1-methyl-4-methylthio-2-pyrimidinone[23] (3.1 g.), DL-alanine (2.14 g.), and sodium carbonate (1.27 g.) in 50 ml. of water was refluxed for 20 hr. The solution was acidified with formic acid to pH 3, an equal volume of ethanol was added, and the solution was chilled overnight. The separated crystals were collected by filtration, washed with ethanol, and dried (3.0 g., m.p. 248–249° dec.). One recrystallization from ethanol–water gave a pure material, m.p. 250–251° dec.; ultraviolet absorption properties: at pH 9.72, maxima at 275 and 233 mμ (ϵ_{max} 9900 and 7000), minima at 250 and 228 mμ (ϵ_{min} 5300 and 6800); in 0.1 *N* hydrochloric acid, maxima at 288 and 217 mμ (ϵ_{max} 13,500 and 8500), minimum at 246 mμ (ϵ_{min} 1400); pK_{a_2} 4.25.

Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48.35; H, 5.47; N, 21.74.

3-Acetoxy-2,6-dimethyl-5-oxoimidazo[1,2-*c*]pyrimidine (32).—A solution of **31** (0.5 g.) in acetic acid (5 ml.) and acetic anhydride (2 ml.) was refluxed for 30 min. After removal of the solvent *in vacuo*, the residue was taken up in chloroform and the chloroform solution was washed with cold saturated sodium bicarbonate solution until the water layer became neutral. The chloroform layer was dried over sodium sulfate and filtered, and the filtrate was evaporated to a sirup which, on trituration with ether, crystallized as prisms, 0.4 g., m.p. 133–135° after recrystallization from chloroform–ether; ultraviolet absorption properties: in ethanol, broad maximum at 283–290 mμ, minimum at 236 mμ; on addition of 1 drop of 5 *N* hydrochloric acid to the 3-ml. cuvette, the maximum shifted to 305 mμ, with a second maximum at 255 mμ; in 1 *N* alkali the compound was converted rapidly to 1-methylcytosine[24] and gave the final curve (2 hr.) with a maximum at 273 mμ, which, when acidified, shifted to 283 mμ; infrared spectrum (potassium bromide): ν_{max} 1810, 1730, 1653, and 1195 cm.$^{-1}$; n.m.r. spectra in d_6-dimethyl sulfoxide τ 7.90, 7.65 (2-methyl and 3-acetyl), 6.56 (6-CH_3), 3.54 (8-H), 2.64 (7-H) ($J_{H^7-H^8}$ = 7.0 c.p.s.).

Anal. Calcd. for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 18.99. Found: C, 54.17; H, 5.01; N, 19.27.

The acetate salt of **32** was obtained when the reaction solution was concentrated to a sirup and ethyl acetate was added. The acetate crystallized from the solution, m.p. 88–92°; ultraviolet absorption properties were the same as those of **32**; infrared spectra showed additional weak broad peaks at 1920 and 2560 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{15}N_3O_5$: C, 51.24; H, 5.38; N, 14.94. Found: C, 51.42; H, 5.43; N, 15.23.

Hydrolysis of 32 in Water.—Crude **32** (0.4 g.) was dissolved in water and refluxed for 10 min. The spectrum of the solution changed completely and, after cooling, white crystals were collected, 0.15 g., m.p. 245–247°, which were identical with **31** (ultraviolet spectra and paper electrophoretic behavior). Acid hydrolysis or weak alkaline hydrolysis (1 *N* sodium carbonate) gave similar results.

Alkaline Hydrolysis of 32.—Crude **32** (0.4 g.) was dissolved in 60 ml. of 1 *N* sodium hydroxide and allowed to stand overnight. Spectral examination of the reaction solution indicated the formation of a large amount of **31**, along with **33**. The solution was acidified with acetic acid to pH 4, and picric acid in ethanol was added. The crude picrate precipitated and was collected by filtration and recrystallized from water, 250 mg., m.p. 294° dec. The melting point of 1-methylcytosine picrate prepared from authentic 1-methylcytosine (**33**) was 293–295° dec.

Anal. Calcd. for $C_5H_7N_3O \cdot C_6H_3N_3O_7$: C, 37.29; H, 2.84; N, 23.73. Found: C, 37.52; H, 3.00; N, 22.81.

N-(1H-2-Oxo-4-pyrimidinyl)-γ-aminobutric Acid (34).—This compound was synthesized by essentially the same method previously described.[2] Crude material was obtained in nearly quantitative yield; ultraviolet absorption properties: in water, maximum at 266 mμ; in acid, at 280 mμ; and in 1 *N* alkali, at 283 mμ.

Anal. Calcd. for $C_8H_{11}N_3O_3 \cdot H_2O$: C, 44.65; H, 6.09; N, 19.53. Found: C, 44.65; H, 5.97; N, 19.67.

N-(1H-2-Oxo-4-pyrimidinyl)butyrolactam (35).—A suspension of **34** (2 g. of hydrate) in acetic acid (5 ml.) and acetic anhydride (10 ml.) was refluxed for 30 min. and allowed to stand overnight. The precipitate was collected and, after washing with hot ethanol, gave 1.2 g. The mother liquor yielded an additional 0.3 g., m.p. >290°; ultraviolet absorption spectrum: in water, maxima at 294 and 251 mμ, minima at 275 and 228 mμ; on addition of 2 drops of concentrated hydrochloric acid to the 3-ml. cuvette, maxima at 310 and 245 mμ, minima at 270 and 227 mμ; in alkali, the compound reacted and gave a spectrum identical with that for **34**; infrared spectra: ν_{max} 1765 (γ-lactam), 1668, 1480, and 1450 cm.$^{-1}$.

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.62; H, 5.06; N, 23.45. Found: C, 53.36; H, 5.23; N, 23.09.

Spectral Measurements.—Ultraviolet absorption data were determined with a Cary recording spectrophotometer, Model 15, and apparent pK_a values were determined spectrophotometrically by methods previously employed,[10,12,25] and are accurate to ±0.05 pH units. Infrared spectra (potassium bromide disk) were measured with a Perkin-Elmer Infracord spectrophotometer, and only major and key bands were listed. N.m.r. spectra[19] were taken on a Varian Associates Model A-60 spectrometer. Tetramethylsilane was used as the internal standard.

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(24) J. J. Fox and D. Shugar, *Biochim. Biophys. Acta*, **9**, 369 (1952).

(25) J. J. Fox and D. Shugar, *Bull. soc. chim. Belges*, **61**, 44 (1952).