give 148 mg (0.43 mmol) of 1,3,3-triphenylisoindole, mp 145° (lit.[15] mp 145.5°), identified by comparison with a known sample.[15]

Pyrex-Filtered Irradiation of Benzophenone Azine (1) in Methanol.—The reaction procedure was the same as that described for the Vycor-filtered irradiation of 1 except that a Pyrex filter was used and the reaction time was extended to 72 hr. At the end of this time no reaction had taken place.

Vycor-Filtered Irradiation of Benzophenone Azine (1) in Benzene.—The procedure was again the same as the irradiation procedure for 1 in methanol except that the solvent was changed to benzene. The irradiation time was 72 hr. No reaction was observed.

Vycor-Filtered Irradiation of 1,1,1′,1′,-Tetraphenylazomethane (7) in Methanol.—The irradiation and isolation procedures were the same as those used in the Vycor-filtered irradiation of 1 except that 1.09 g (3.00 mmol) of 1,1,1′,1′-tetraphenylazomethane was irradiated and the irradiation time was 45 min.

Fractions 7 and 8 afforded 61 mg of a mixture of biphenyl and diphenylmethane. Rechromatography separated this pair into 9 mg (0.06 mmol) of biphenyl and 51 mg (0.30 mmol) of diphenylmethane, both identified by ir and nmr spectroscopy. Fraction 9 yielded 27 mg (0.15 mmol) of *cis*-stilbene, also identified by ir and nmr spectroscopy. Fractions 14–19 gave 180 mg of 1-(2-biphenylyl)-1,2-diphenylethane, mp 75–78°. Fractions 20–25 produced 511 mg (0.54 mmol) of 1,1,2,2-tetraphenylethane, mp 206°. Fractions 27–31 gave 22 mg of unreacted 1,1,1′,1′-tetraphenylazomethane.

(15) W. Theilacker, H.-J. Bluhm, W. Heitmann, H. Kalenda, and H. J. Meyer, *Justus Liebigs Ann. Chem.*, **673**, 96 (1964).

Vycor-Filtered Irradiation of Benzophenone Benzhydrylhydrazone (9) in Methanol.—The isolation and irradiation procedures were the same as those used in the Vycor-filtered irradiation of 1 except that the material irradiated was benzophenone benzhydrylhydrazone (9) and the irradiation time was 4.5 hr.

Fractions 7 and 8 gave 33 mg (0.20 mmol) of diphenylmethane, identified by ir spectroscopy. Fractions 14–19 gave 24 mg (0.07 mmol) of 1-(2-biphenylyl)-1,2-diphenylethane, mp 65–69°. Fractions 20–24 afforded 66 mg of 1,1,2,2-tetraphenylethane, mp 205–207°. Fractions 25–27 yielded 53 mg of a white solid, recrystallized from ethanol to give 38 mg (0.13 mmol) of benzhydrylidenebenzhydrylamine, mp 150° (lit.[10] mp 152°), identified by comparison with an authentic sample. Fractions 34–39 produced 189 mg (1.04 mmol) of benzophenone, identified by ir spectroscopy. Fractions 50–55 afforded 448 mg (1.21 mmol) of unreacted starting material.

Vycor-Filtered Photolysis of Benzhydrylidene Benzylidene Azine (12) in Methanol.—The photolysis and isolation procedures were the same as those described for the Vycor-filtered irradiation of 1 except that 3.00 mmol of benzhydrylidene benzylidene azine[16] (**14**) were irradiated. No single product could be isolated in sufficient quantity for identification; in particular, no benzonitrile, benzophenone, or benzaldehyde were isolated.

Registry No.—**1**, 983-79-9.

Acknowledgment.—The authors gratefully acknowledge the support of the National Science Foundation (GP 16664) for this research.

(16) S. S. Hirsch, *J. Org. Chem.*, **32**, 2433 (1967).

Studies on the Acylation of Some 6-Aminouracil Derivatives

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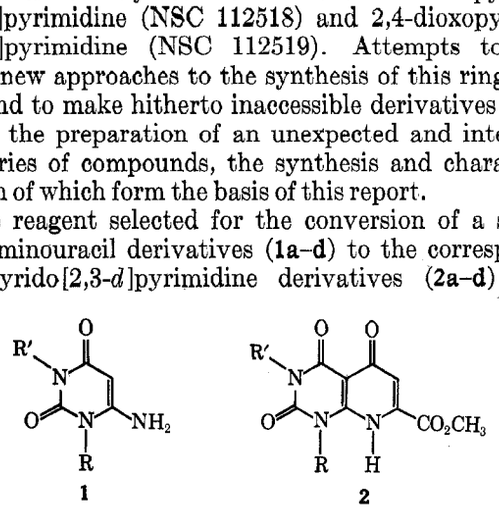
Received July 26, 1971

Attempts to prepare pyrido[2,3-*d*]pyrimidine derivatives by the reaction of various alkyl 6-aminouracils with dimethyl acetylenedicarboxylate have led instead to the synthesis of 6-amino-5-(3-carbomethoxy-2-propynoyl)-uracils (**3**). It was found, using acetylation as a model reaction, that acylation occurs at C-5 if an alkyl group is present on N-1 of 6-aminouracil; in the absence of such a substituent the 6-acetamido derivative is formed. Reduction of **3** leads to cis olefin formation. The pmr spectra and some mechanistic considerations are discussed.

Antitumor activity against Walker muscular tumor in rats has recently been demonstrated for 4-oxopyrido-[2,3-*d*]pyrimidine (NSC 112518) and 2,4-dioxopyrido-[2,3-*d*]pyrimidine (NSC 112519). Attempts to develop new approaches to the synthesis of this ring system and to make hitherto inaccessible derivatives have led to the preparation of an unexpected and interesting series of compounds, the synthesis and characterization of which form the basis of this report.

The reagent selected for the conversion of a series of 6-aminouracil derivatives (**1a–d**) to the corresponding pyrido[2,3-*d*]pyrimidine derivatives (**2a–d**) was dimethyl acetylenedicarboxylate. This compound has been widely used in the synthesis of a variety of heterocyclic compounds.[2] Attack usually occurs at the triple bond in a Michael-type reaction followed by cyclization either through the other carbon of the acetylene or through the β-carbomethoxy group, depending on whether nucleophilic or electrophilic attack is appropriate. The only reported use of an acetylenic compound in the synthesis of pyrido[2,3-*d*]pyrimidines appeared in a 1958 German patent[3] and involved the use of 3-phenylprop-1-yn-3-one with 6-aminouracil to give 2,4-dioxo-7-phenylpyrido[2,3-*d*]-pyrimidine. This product would require attack upon the triple bond by carbon 5 of the pyrimidine. Such attack is reasonable based upon the elegant studies of Taylor and coworkers on the total synthesis of the antibiotic fervenulin and its derivatives,[4] in which a 6-aminouracil reacted with diethyl azodicarboxylate yielding the product of attack by the pyrimidine carbon 5 on the nitrogen of the reagent.



1 **2**

a, R = R′ = CH_3
b, R = CH_3; R′ = H
c, R = R′ = $CH_2C_6H_5$
d, R = R′ = H

(1) (a) This research was supported by Research Grant T491 from the American Cancer Society; (b) to whom correspondence should be addressed.

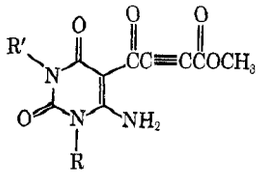
(2) J. B. Hendrickson, R. Rees, and J. F. Templeton, *J. Amer. Chem. Soc.*, **86**, 107 (1964).

(3) H. Pasedach and M. Seefelder, German Patent 1,040,040 (1958); *Chem. Abstr.*, **55**, 6507e (1961).

(4) E. C. Taylor and F. Sowinski, *J. Amer. Chem. Soc.*, **90**, 1374 (1968); **91**, 2143 (1969).

Results and Discussion

Treatment of 1,3-dimethyl-6-aminouracil with dimethyl acetylenedicarboxylate in DMF led, however, not to **2a**, but to a compound having nearly the correct elemental analysis for **2a** but spectral properties incompatible with it. The observed pmr spectrum for new compound **3a** had, as expected, one *O*-methyl and two *N*-methyl groups, but there was no peak corresponding to the expected "aromatic" proton and there were two downfield peaks (δ 9.97 and 9.37) corresponding to two protons and readily exchangeable upon addition of D_2O to DMSO-d_6 solution. These data strongly suggest the structure designated as **3a**. The downfield position of the amino group relative to that in the starting 1,3-dimethyl-6-aminouracil is readily accounted for on the basis of the deshielding effect of the anisotropy of the carbonyl and the acetylene moiety, which are coplanar with the amino group and in close proximity to it.

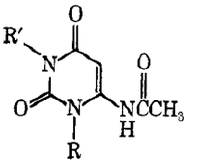


3a, R = R′ = CH_3
b, R = CH_3; R′ = H
c, R = R′ = $CH_2C_6H_5$
d, R = R′ = H

The same reaction was carried out with compounds **1b–d**. Treatment of **1b** and **1c** with dimethyl acetylenedicarboxylate in DMF gave good yields of the corresponding 5-acyl derivatives **3b** and **3c**. 6-Aminouracil itself (**1d**), however, gave only a complex mixture of products from which none of the 5-acyl derivative could be isolated. It thus appeared that substitution at position 1 might be essential for the success of this reaction. In an attempt to resolve this apparent anomaly, the reaction of 6-aminouracil derivatives with acetic anhydride was evaluated.

Examination of the literature revealed a study by Pfleiderer[5] in which treatment of 1,3-dimethyl-6-aminouracil (**1a**) with acetic anhydride at reflux gave as the only isolated product the 5-acetyl derivative **4a**. Repetition of this experiment did indeed give **4a**. The specific reaction conditions of Pfleiderer were not applicable to the other compounds in this series, however, because of solubility difficulties. It was found that solubility problems could be overcome by the use of acetic anhydride–acetic acid mixtures, however, and the reaction was run on 6-aminouracil[6] (**1d**) and its 1-methyl[7] (**1b**), 3-methyl[8] (**5**), and 1,3-dimethyl[9] (**1a**) derivatives. In the two cases in which the **1** position was substituted by methyl, only the 5-acetyl product was obtained; identical treatment of compounds **1d** and **5**, each of which has a proton at N-1, gave as the only compound isolated the *N*-6-acetyl derivative (**6a,b**).

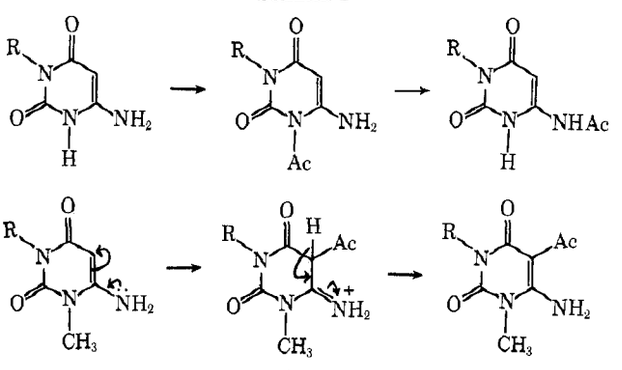
4a, R = R′ = CH_3
b, R = CH_3; R′ = H



6a, R = R′ = H
b, R = H; R′ = CH_3

It is felt that the reason for this difference in position of acylation may lie in the finding that uracil and thymine may be acylated at position 1, and that these 1-acyl derivatives are very unstable and are powerful acylating agents.[10] It is suggested that the initial attack in the N-1 unsubstituted derivatives occurs at N-1, and that this is followed by intramolecular rearrangement to the exocyclic acetamido derivatives. This mechanism is precluded in those compounds which are substituted at N-1; in these cases, acylation at C-5 is preferred over the unassisted acylation of the exocyclic amino group (Scheme I). This argument, then, supports the finding that only in the case of 1-substituted compounds can acylation at position 5 of the pyrimidines studied occur with dimethyl acetylenedicarboxylate.

Scheme I



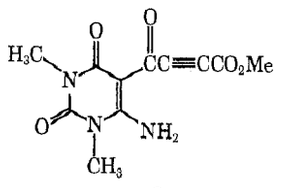
7
R = CH_3, H

Examination of the pmr data on these compounds strongly supports the structure assignments. Comparison of the C-5 protons of the two 6-acetamidouracils (**6a,b**) with those of the corresponding starting materials (**1d, 5**) shows a downfield shift in the former of δ 0.87 in each case as a result of acylation. This shift is expected based both on the electron-withdrawing effect and the anisotropic effect of the acetyl group. Acylation at the 5 position causes even larger shifts

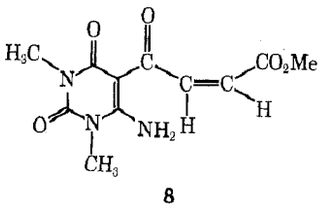
(5) W. Pfleiderer and G. Strauss, *Justus Liebigs Ann. Chem.*, **612**, 173 (1958).
(6) Commercially available from Aldrich Chemical Co.
(7) (a) T. Takeda, Japanese Patent 7026 (1954); *Chem. Abstr.*, **50**, 4240*d* (1956). (b) T. Ukai, Y. Yamamoto, and S. Kanetomo *J. Pharm. Soc. Jap.*, **74**, 674 (1954); *Chem. Abstr.*, **48**, 10743*f* (1954).
(8) W. Pfleiderer, *Chem. Ber.*, **90**, 2272 (1957).
(9) Commercially available from Heterocyclic Chemical Corp.
(10) (a) D. J. Brown, "The Pyrimidines," 1st ed, Wiley, New York, N. Y., 1962, pp 25, 252; (b) L. B. Spector and E. B. Keller, *J. Biol. Chem.*, **232**, 185 (1958).

in the resonance of the amino protons. This is readily accounted for on the basis of the anisotropic and electron-withdrawing effects cited above. In addition to these effects, however, in this series of compounds, which may be regarded as vinylogous amides, restricted rotation around the N–C bond would be expected.[11] This accounts for the high degree of nonequivalence of the amino protons, since such restricted rotation would result in continuous exposure of one amino proton to the anisotropic deshielding field of the carbonyl.

Catalytic hydrogenation of 1,3-dimethyl-6-amino-5-(3-carbomethoxy-2-propynoyl)uracil (**3a**) gave the cis olefin **8**. It is interesting to note that olefin **8** is extremely resistant to further reduction. Numerous attempts to reduce **8** to the succinoyl derivative using a variety of catalysts gave no reaction.

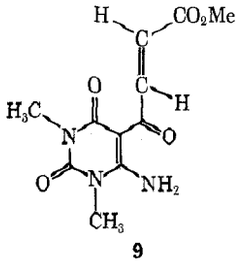


3a



8

The trans isomer **9** was synthesized by an alternate route. Treatment of 1,3-dimethyl-6-aminouracil (**1a**) with methyl 3-chloroformyl-*trans*-acrylate[12] gave, as expected, the product of acylation at C-5 (**9**). Com-



9

pounds **8** and **9** were readily characterized by pmr spectroscopy. Each had the expected peaks corresponding to two *N*-methyl groups, one *O*-methyl, two low-field nonequivalent protons of the amino group, and two doublets corresponding to olefinic protons. For the cis isomer the coupling constant J was found to be 9 Hz, while for the trans compound J was 16 Hz. The chemical shifts of the olefinic protons of **9** (δ 8, 37, 6.47) were downfield from the corresponding protons of **8** (δ 6.77, 5.80) as would be predicted from the anisotropic deshielding effect of a carbonyl group on an adjacent cis proton.[13]

Alternative procedures have led to the formation of the initially sought pyrido[2,3-*d*]pyrimidines. A report of this work will be forthcoming shortly.

(11) H. E. A. Kramer and R. Gompper, *Z. Phys. Chem.*, **43**, 292 (1964).

(12) R. M. Acheson, R. S. Feinberg, and A. R. Hands, *J. Chem. Soc.*, 526 (1963).

(13) L. M. Jackman and S. Sternhell, "Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1969, p 185.

Experimental Section

Materials and Methods.—Pmr spectra were run on a Jeolco C60H spectrometer using DMSO-d_6 as solvent and TMS or DSS as an internal reference. Uv spectra were run on a Cary 15 spectrophotometer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected.

Acetylation of 6-Aminouracil Derivatives. General Procedure.—Compounds **1a**, **1b**, **1d**, and **5** (100 mg each) were refluxed (unless otherwise specified) in a solution of acetic acid (15 ml) and acetic anhydride (5 ml). Each of the reaction mixtures formed a clear solution. Reflux times, yields, and melting points of the products are shown in the following table.

Starting material	Reflux time, min	Yield, %	Mp, °C
1,3-Dimethyl-6-aminouracil	120 (80°)	83	202–205
1-Methyl-6-aminouracil	50	99	308–310
3-Methyl-6-aminouracil	50	50	280–281
6-Aminouracil	70	76	>350

1,3-Dimethyl-5-acetyl-6-aminouracil (**4a**).—After reflux (by the above general procedure), the reaction mixture was evaporated to dryness and the residue was recrystallized from ethyl acetate yielding 107 mg (83%) of product: uv (pH 1) 276 nm (ϵ 15,600), 247.5 (10, 240), (pH 7) 276 (15,450), 247.5 (10,190), (pH 11) 276 (15,600), 247.5 (10, 310); nmr (DMSO-d_6) δ 11.1, 8.13 (2 s, 2, NH_2), 3.25, 3.08 (2 s, 6, NCH_3), 2.42 (s, 3, CH_3CO).

Anal. Calcd for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.58; N, 21.32. Found: C, 48.69; H, 5.50; N, 21.41.

1-Methyl-5-acetyl-6-aminouracil (**4b**).—After reflux (general procedure) the reaction mixture was cooled and filtered, the filtrate was evaporated to dryness, and the residue was recrystallized from a MeOH–H_2O (1:1) mixture yielding 129 mg of pure product (99%): uv (pH 1) 275 nm (ϵ 13,800), 244 (10,630), (pH 7) 275 (13,200), 244 (10,250), (pH 11) 279 (13,200), 245 (8700), 229 (9040); nmr (DMSO-d_6) δ 11.20, 8.20 (2 s, 2, NH_2), 10.77 (s, 1, CONHCO), 3.18 (s, 3, NCH_3), 2.40 (s, 3, CH_3CO).

Anal. Calcd for $C_7H_9N_3O_3$: C, 45.90; H, 4.92; N, 22.95. Found: C, 45.67; H, 5.01; N, 22.62.

3-Methyl-6-acetamidouracil (**6b**).—Reaction conditions were identical with those for the preparation of **4b**, yielding 62 mg (50%): uv (pH 1) 278 nm (ϵ 11,200), (pH 7) 280 (8970), (pH 11) 288 (6430); nmr (DMSO-d_6) δ 10.52 (broad s, 2, 2 NH), 5.35 (s, 1, CH), 3.03 (s, 3, NCH_3), 2.07 (s, 3, CH_3CO).

Anal. Calcd for $C_7H_9N_3O_3 \cdot {}^1/_2H_2O$: C, 43.75; H, 5.21; N, 21.88. Found: C, 43.89; H, 5.14; N, 22.73.

6-Acetamidouracil (**6a**).—After reflux, the reaction mixture was cooled to room temperature, and a white solid precipitated. Filtration gave 101 mg of pure product (76%): uv (pH 1) 278 nm (ϵ 17,600), (pH 7) 280 (14,400), (pH 11) 288 (10,300); nmr (DMSO-d_6) δ 10.90 (s, 1, OCHNCO), 10.48 (s, 2, 2 NH), 5.22 (s, 1, CH), 2.07 (s, 3, CH_3CO).

Anal. Calcd for $C_6H_7N_3O_3$: C, 42.60; H, 4.14; N, 24.85. Found: C, 42.58; H, 4.24; N, 24.57.

1,3-Dimethyl-6-amino-5-(3-carbomethoxy-2-propynoyl)uracil (**3a**).—To the suspension of 1,3-dimethyl-6-aminouracil (1.55 g, 10 mmol) in 20 ml of DMF, the dimethyl acetylenedicarboxylate (1.56 g, 11 mmol) was added, and the mixture was heated at 110° for 2 hr. A clear, red solution resulted. After cooling to room temperature, 25 ml of ether was added to give an orange precipitate which was filtered and washed with 10 ml of ether, yielding 1.6 g (60%). To a filtered solution of 1.0 g of the product in warm DMF was added H_2O (10 ml). The solution was cooled and the product was filtered, yielding 0.7 g of pure product: mp 300–301° dec (285° getting dark); uv (pH 1) 436 nm (ϵ 4370), 338 (6900), 268 (16,700), (pH 7) 327 (19,900), 273 (7420), (pH 11) 327 (19,900), 273 (7420); nmr (DMSO-d_6) δ 9.97, 9.37 (2 s, 2, NH_2), 3.77 (s, 3, OCH_3), 3.17, 3.13 (2 s, 6, NCH_3).

Anal. Calcd for $C_{11}H_{11}N_3O_5$: C, 49.81; H, 4.18; N, 15.84. Found: C, 49.73; H, 4.23; N, 15.78.

1-Methyl-6-amino-5-(3-carbomethoxy-2-propynoyl)uracil (**3b**).—1-Methyl-6-aminouracil (1.41 g, 10 mmol) was suspended in 20 ml of DMF, and dimethyl acetylenedicarboxylate (1.56 g, 11 mmol) was added to it. This mixture was heated at 110° for 5 hr and cooled to 5° and the product was filtered to yield 0.7 g of a yellow-orange compound (28%), mp 326–329°.

Recrystallization of a 0.5-g sample from DMF–H_2O gave 0.35 g: mp 332° dec; uv (pH 1) 437 nm (ε 5780), 336 (7300), 268 (15,600), (pH 7) 328 (22,800), 268 (8900), (pH 11) 328 (22,900), 268 (9670); nmr (DMSO-d_6) δ 10.80 (s, 1, OCHNCO), 9.64, 9.37 (2 s, 2, NH_2), 3.70 (s, 3, OCH_3), 3.07 (s, 3, NCH_3).

Anal. Calcd for $C_{10}H_9N_3O_5 \cdot {}^1/_2H_2O$: C, 46.15; H, 3.85; N, 16.15. Found: C, 46.21; H, 3.64; N, 16.23.

1,3-Dibenzyl-6-amino-5-(3-carbomethoxy-2-propynoyl)uracil (3c).—To a suspension of 1,3-dibenzyl-6-aminouracil (3.07 g, 10 mmol) in 20 ml of DMF was added dimethyl acetylenedicarboxylate (1.56 g, 11 mmol) and the mixture was heated at 110° for 2 hr. To the dark red solution was added 150 ml of ether. The resulting precipitate was filtered and washed with 40 ml of ether to yield 1.62 g (39%), mp 235°. Recrystallization of a 1.1-g sample from DMF–H_2O gave 0.9 g: mp 239–240° uv (pH 1) 438 nm (ε 5500), 336 (6850), 270 (15,830), (pH 7) 330 (22,400), 273 (7930), (pH 11) 330 (22,100), 273 (7930); nmr (DMSO-d_6) δ 9.93, 9.63 (2 s, 2, NH_2), 7.20 (s, 10, 2 C_6H_5), 4.97 (s, 2, CH_2), 4.87 (s, 2, CH_2), 3.68 (s, 3, OCH_3).

Anal. Calcd for $C_{23}H_{19}N_3O_5$: C, 66.18; H, 4.59; N, 10.07. Found: C, 66.32; H, 4.55; N, 10.12.

1,3-Dimethyl-6-amino-5-(*cis*-3-carbomethoxypropenoyl)uracil (8).—1,3-Dimethyl-6-amino-5-(3-carbomethoxy-2-propynoyl)-uracil (**3a**) (500 mg, 1.9 mmol) was dissolved in a dimethoxyethane–water (1:1) mixture with warming and hydrogenated at 46 psi using PtO_2 (200 mg) as catalyst overnight.

The reaction mixture was filtered through Celite and washed thoroughly with hot dimethoxyethane. The filtrate was evaporated to dryness, and the residue was triturated with MeOH and filtered to give 340 mg (68%): mp 310° dec; uv (pH 1) 346 nm (ε 18,400), 276 (18,330), 230 (9950), (pH 7) 347 (18,850), 277 (18, 450), 230 (9950), (pH 11) 345 (18,700), 277 (18,800), 231 (9350); nmr (DMSO-d_6) δ 8,48, 7.87 (2 s, 2, NH_2), 6.77, 5.80 (2 d, 2, CH, J = 9 Hz), 3.58 (s, 3, OCH_3), 3.05, 2.97 (2 s, 6, NCH_3).

Anal. Calcd for $C_{11}H_{13}N_3O_5$: C, 49.44; H, 4.87; N, 15.73. Found: C, 49.63; H, 4.88; N, 15.61.

1,3-Dimethyl-6-amino-5-(*trans*-3-carbomethoxypropenoyl)-uracil (9).—1,3-Dimethyl-6-aminouracil (0.8 g, 5 mmol) and methyl 3-chloroformyl-*trans*-acrylate (1 g) were stirred in 30 ml of DMF at room temperature overnight. The reaction mixture was filtered, the filtrate was evaporated, and the oily residue was allowed to stand overnight at room temperature. The product was filtered and recrystallized from methanol, giving 300 mg of pure product (22%): mp 220–223°; uv (pH 1) 314 nm (ε 9100), 223 (20,800), (pH 7) 314 (8280), 223 (21,600), (pH 11) 307 (6360), 245 (sh), 229 (25,600); nmr (DMSO-d_6) δ 11.07 (s, 1, NH), 8.60 (s, 1, NH overlaps with CH), 8.37, 6.47 (2 d, 2, CH, J = 16 Hz), 3.77 (s, 3, OCH_3), 3.35, 3.17 (2 s, 6, NCH_3).

Anal. Calcd for $C_{11}H_{13}N_3O_5$: C, 49.44; H, 4.87; N, 15.73. Found: C, 49.59; H, 5.10; N, 15.79.

Registry No.—**3a**, 32970-29-9; **3b**, 32970-30-2; **3c**, 32970-31-3; **4a**, 32970-32-4; **4b**, 32970-33-5; **6a**, 32970-34-6; **6b**, 32970-35-7; **8**, 33016-10-3; **9**, 33016-11-4.

The Synthesis of 2-Methyl-7-ketoundecanolide, 8-Ketoundecanolide, and 2,4,6-Trimethyl-7-ketodecanolide[1]

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Received June 24, 1971

The Michael addition of acrylate esters to cyclic enamines has been extended to synthesize 2,4,6-trimethyl-7-ketodecanolide and 2-(3′-hydroxypropyl)cyclooctanone. The latter is converted to 8-ketoundecanolide by previously described procedures. The pyrrolidine enamines of 2-methylcycloheptanone (**3**) or *cis,trans*-2,*cis*-4,6-trimethylcycloheptanone (**4**) failed to give C-alkylation with 4-bromobutyl acetate (**12**). Attempted alkylation of the anions of the corresponding cyclohexylamine or aniline imines gave complex product mixtures. The 7-carbethoxy derivatives of **3** or **4** were alkylated with either **12** or 4-bromobut-1-ene to give intermediates which were converted to the desired 7-(4′-hydroxybutyl)cycloheptanones. These hydroxy ketones were cyclized, with difficulty, to give isomeric mixtures of the corresponding "7-7" enol ethers which could be oxidized with *m*-chloroperbenzoic acid (MCPBA) to 2-methyl-7-ketoundecanolide but not to 2,4,6-trimethyl-7-ketoundecanolide. A new synthesis of 7-carbethoxy-*cis,cis*-2,4,6-trimethylcycloheptanone from *cis,cis*-2,4,6-trimethylcyclohexanone is described. Extensions of aromatic solvent-induced nmr shifts to some of the intermediates are discussed.

We have previously reported the synthesis of bicyclic enol ethers *via* (a) the lithium–amine reduction of chromans[3] and (b) the acid-catalyzed closure of 2-(ω-hydroxyalkyl)cycloalkanones derived from enamine alkylations.[4] The enol ethers have been oxidized by a variety of reagents[3-6] to 10–12-membered ring ketolactones, including 7-ketoundecanolide, which represents the structural system of the methymycin group of macrolide antibiotics.

We now report extensions of these synthetic methods as well as new approaches involving β-keto esters which lead to 2,4,6-trimethyl-7-ketodecanolide and undecanolides. The substituents are located at some of the positions where methyl groups are found in methymycin.

We had originally planned on extending the synthesis of 2-(ω-hydroxyalkyl)cycloalkanones to methyl-substituted 7-ketoundecanolides *via* the alkylation of the pyrrolidine enamines **1** and **2** of 2-methylcycloheptanone (**3**) and 2,4,6-trimethylcycloheptanone (**4**) with 4-bromobutyl acetate (**12**). The cycloheptanones **3** and **4** were prepared by the diazoethane ring expansion of cyclohexanone (**5**) and 3,5-dimethylcyclohexanone (**6**) in 46 and 52% yields, respectively.[7] Commercial

(1) This investigation was supported by Public Health Service Research Grants AI 06303 and 07455 from the National Institute of Allergy and Infectious Diseases and by the Eli Lilly Co. This is part VII of the series, Medium Ring Compounds.

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(3) (a) I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp, and G. J. Williams, *J. Org. Chem.*, **31**, 3032 (1966); (b) I. J. Borowitz and G. Gonis, *Tetrahedron Lett.*, 1151 (1964).

(4) I. J. Borowitz, G. J. Williams, L. Gross, and R. Rapp, *J. Org. Chem.*, **33**, 2013 (1968).

(5) I. J. Borowitz and R. Rapp, *ibid.*, **34**, 1370 (1969).

(6) I. J. Borowitz and R. Rapp, *Chem. Commun.*, 1202 (1969).

(7) (a) By a modification of the procedure of D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 181 (1939), suggested by Dr. Adnan Sayigh. (b) For related cycloheptanone syntheses *via* a higher yield procedure and for stereochemical relationships see J. Marshall and J. J. Partridge, *J. Org. Chem.*, **33**, 4090 (1968).