On the Synthesis of 3,4-Dihydro-2(1*H*)-pyrimidinones and the Mechanism of the Biginelli Reaction[1]

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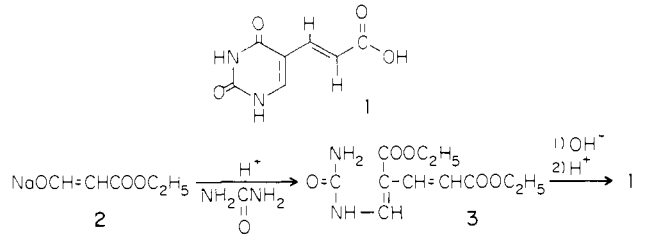
Abstract: The acid-catalyzed synthesis of substituted 3,4-dihydro-2(1*H*)-pyrimidinones from a variety of precursors was studied. The major products of the condensation of 3-methoxyacrylate with urea and monomethylurea are 5-carbomethoxy-4-carboxymethyl-3,4-dihydro-2(1*H*)-pyrimidinone and its N-1 methyl derivative. The decarboxylated derivatives, 5-carbomethoxy-4-methyl-3,4-dihydro-2(1*H*)-pyrimidinone and 5-carbomethoxy-1,4-dimethyl-3,4-dihydro-2(1*H*)-pyrimidinone, are minor products of the same reaction. *sym*-Dimethylurea produces 5-carbomethoxy-3,4-dihydro-1,3,4-trimethyl-2(1*H*)-pyrimidinone and 1,3-dimethyluracil, both in small yield. An integrated mechanism for these reactions is proposed involving a preliminary acid-catalyzed aldol condensation and subsequent reactions of a carbonium ion formed from the aldol intermediate. An interaction, probably through hydrogen bonding, is shown to occur between the carboxylic group on the substituent at C-4 and the N-3 group in 5-carbomethoxy-4-carboxymethyl-3,4-dihydro-2(1*H*)-pyrimidinone. Its effect upon the hydrolysis of an ester of the same carboxylic group has been demonstrated. The reaction of methyl 2-dimethoxymethyl-3-methoxypropionate with ureas also produces 5-carbomethoxy-3,4-dihydro-2(1*H*)-pyrimidinones. Factors influencing the orientation of these condensations are considered. It is concluded that the more nucleophilic of the two nitrogens in a substituted urea reacts first by displacing the protonated alkoxy group, which is activated through an enol–allyl system derived from the aldehyde function. Cyclization to the 3,4-dihydro-2(1*H*)-pyrimidinone is completed by reaction of the free ureide nitrogen with the aldehyde group. The results of the condensations of 2-dimethoxymethyl-3-methoxy-1-propanol and 2-hydroxymethyl-1,1,3,3-tetramethoxypropane with ureas are consistent with the proposed enhanced reactivity of an allylic center as compared to an aldehyde function and with the corollary carbonium ion mechanism. This mechanism also applies to the Biginelli pyrimidine synthesis in which the limiting step is now considered to be an *in situ* aldol condensation required to produce the reactive unit which condenses with a urea to give the corresponding 3,4-dihydro-2(1*H*)-pyrimidinone. The mechanism proposed here for the Biginelli synthesis explains the course of reactions which had previously been considered "anomalous."

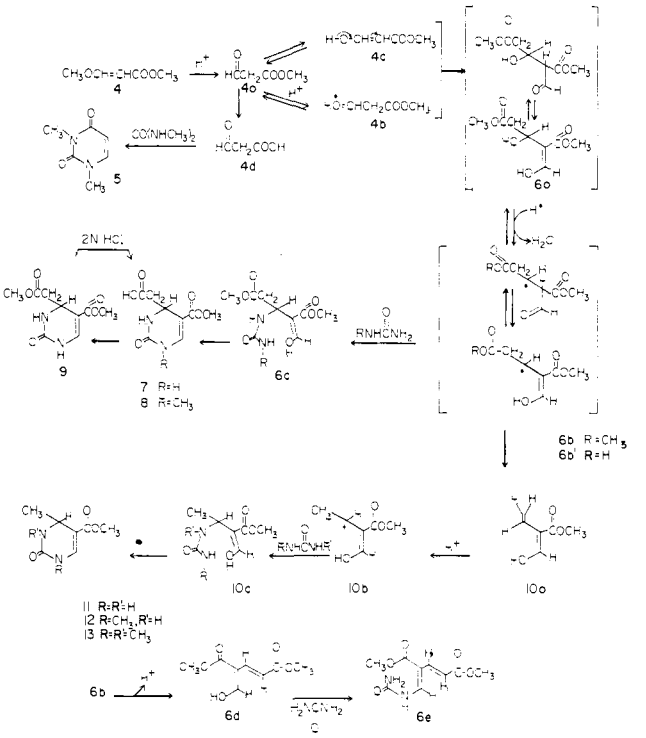
In our studies of the synthesis of 5-vinyluracil, 3-(5-uracilyl)propenoic acid (**1**) (Scheme I) was required as an intermediate. It was prepared by a condensation of 5-formyluracil with malonic acid.[2] An alternate synthesis of **1** from the ureide **3** has been reported[3] (Scheme I). The ureide **3** was obtained in crystalline form when urea and sodium formylacetic ester were treated with concentrated HCl.[3] When we attempted to condense methyl 3-methoxyacrylate (**4**) (Scheme II)[4] with ureas in the comparable stoichiometric ratio of 2:1, the only products isolated under a variety of conditions were 3,4-dihydro-2(1*H*)-pyrimidinones.[2]

Scheme I



The acid-catalyzed consensation of a urea with a 2-formyl ester, or a 2-formyl lactone, gives a ureide that can readily cyclize to a uracil in the presence of base.[5]

Scheme II



However, similar condensations with a 3-alkoxy-2-formyl ester lead directly to 3,4-dihydro-2(1*H*)-pyrimidinones.[6,7] Similar compounds are also produced

(1) This investigation was supported in part by funds from the National Cancer Institute (Grant No. CA 08748) and the American Cancer Society (Grant No. P 295).

(2) J. D. Fissekis and F. Sweet, *J. Org. Chem.*, **38**, 264 (1973).

(3) D. Davidson and O. Baudisch, *J. Amer. Chem. Soc.*, **48**, 2379 (1926).

(4) The use of this ester was considered preferable to that of **2**, since the purity of preparations of the latter was highly questionable.

(5) J. D. Fissekis and B. Markert Creegan, *J. Org. Chem.*, **32**, 3595 (1967), and references therein.

(6) A. Takamizawa, K. Hirai, Y. Sato, and K. Tori, *ibid.*, **29**, 1740 (1964).

(7) (a) A. Takamizawa and K. Hirai, *Chem. Pharm. Bull.*, **12**, 804 (1964); (b) *ibid.*, **12**, 1418 (1964).

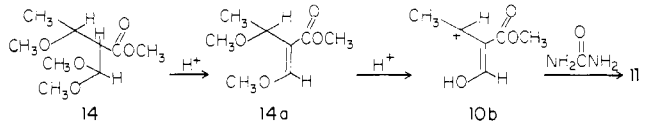
in the Biginelli reaction[8] which involves an acid-catalyzed condensation of an aldehyde, a keto ester, and urea.

Despite the apparently dissimilar precursors employed, these syntheses of 3,4-dihydro-2(1*H*)-pyrimidinones appeared to have some common features. This paper explores the mechanistic aspects of the various syntheses and proposes a unifying mechanism that readily accommodates all of the available results.

The 3,4-dihydro-2(1*H*)-pyrimidinones **7** and **8** (Scheme II) as well as the related decarboxylated products **11** and **12** were isolated from the condensation of 3-methoxyacrylate ester (**4**)[9] and urea or *N*-methylurea. Dimethylurea led to the formation of a small amount of 1,3-dimethyluracil (**5**) and, unexpectedly, to the decarboxylated derivative **13**.

An integrated mechanism for these reactions is proposed in Scheme II. The acid-catalyzed aldol condensation[10,11a] of the formylacetate **4a** yields the ketol **6a**. From this, the dihydro-2(1*H*)-pyrimidinones **7**, **8**, **11**, **12**, and **13** as well as the ureide **6e** are formed through a common transitional intermediate **6b** (or **6b'**) that possesses carbonium ion character.[12a] The derivatives **7** and **8** proved to be stable under the experimental conditions used, and **11** or **12** could not be derived from these compounds.[12b] The decarboxylated derivative **11** was previously obtained from the acid-catalyzed condensation of methyl 2-dimethoxymethyl-3-methoxybutyrate (**14**) and urea (Scheme III),[15] which can now be interpreted as proceeding *via*

Scheme III

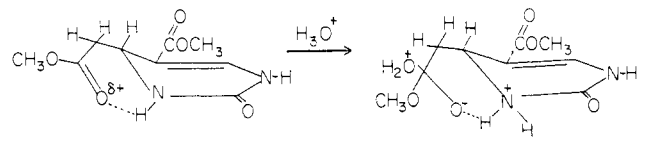


10b. This and the formal similarity between the proposed intermediates **6a** and **14** support the proposals in Scheme II.

Formation of a free carboxylic group on the substituent at C-4 in **7** and **8** is of interest. It is not established whether the hydrolysis of the related ester group is completed before or after the cyclization to the dihydropyrimidinones. The diester derivative **9**, prepared from **7**, is stable in neutral aqueous solutions even after boiling for 1 hr or upon standing at room temperature in buffer solution at pH 4 and 3. Hydrolysis also proceeds extremely slowly at pH 2; however, in 2 *N* HCl[16] (conditions used in the condensation that yield **7** or **8**) the selective hydrolysis at the C-4 side chain proceeds rapidly. These results suggest a participation by the N-3 group of the heterocyclic ring.[17]

An interaction between the side chain at C-4 and the pyrimidinone can be demonstrated spectrophotometrically in **7** and **8**. Each compound produces a hypochromic shift of the uv absorption curve (Table I) associated with the ionization of the free carboxylic group between pH 3 and 7. Since conjugation between the pyrimidinone ring and the side chain carboxylic group at C-4 is not possible, the interaction may occur through space, probably as represented for the ester **9** in Scheme IV. Within the same range of pH no uv absorption

Scheme IV



shifts are observed in compounds **11** and **12** which differ from compounds **7** and **8** only by the absence of the side chain carboxylic group.

Syntheses of 1- and 3-substituted 3,4-dihydro-2(1*H*)-pyrimidinones *via* acid-catalyzed condensations of 3-alkoxy-2-alkoxymethylenepropionates or propionitriles

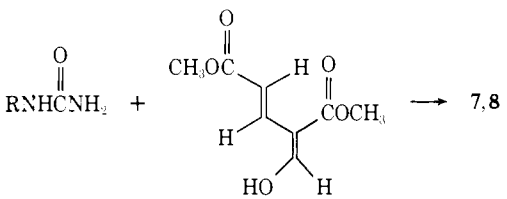
(8) (a) D. J. Brown, "The Pyrimidines," Wiley, New York, N. Y., 1962, p 440; (b) *ibid.*, Supplement I, 1970, p 326.

(9) E. Winterfeldt and H. Preuss, *Chem. Ber.*, **99**, 450 (1966).

(10) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 695.

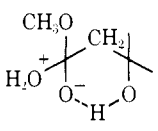
(11) (a) C. K. Ingold, "Structure and Mechanisms in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, p 1003; (b) *ibid.*, p 1005.

(12) (a) The selective formation of the N^1-methyl derivatives **8** and **12** with monomethylurea supports the proposed mechanism (Scheme II) in which the initial reaction occurs at an electrophilic center (*i.e.*, at the carbonium ion of **6b** or **10b**) rather than at the formyl group. It also suggests that an alternative mechanism involving acid-catalyzed Michael-type additions of ureas to a stereoisomer of **6d** as illustrated below is not likely since a primary reaction at the hydroxymethylene



end should be at least competitive and should yield in the case of monomethylurea mixtures of both the N^1- and N^3-methyldihydro-2(1*H*)-pyrimidinones. (b) The proposed path **6a** through **10a** involves an initial anchimerically assisted hydrolysis[13] of one of the ester groups, followed by the decarboxylation of the resulting acid. Several examples of carbonium ion intermediates in decarboxylations of acids, as the proposed (**6b**[1] to **10a**) have been suggested.[14]

(13) The specific hydrolysis of only one of the ester groups may reasonably be explained by participation of the tertiary hydroxyl group of **6a** in the stabilization of the transition state, *viz.*



This proposal is analogous to that suggested for the hydrolysis of acetoacetate esters (B. Capon, *Quart. Rev., Chem. Soc.*, **18**, 85 (1964)). As discussed later, the specific reactivity of only one of the ester groups of **9** is also explained in terms of a stabilized transition state which involves the N-3 center.

(14) (a) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, p 309; (b) ref 10, p 879.

(15) J. D. Fissekis and F. Sweet, *J. Org. Chem.*, **38**, 1963 (1973).

(16) $H_0 = -0.69$: M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).

(17) Anchimeric catalysis of the imidazole type [T. C. Bruice and T. H. Fife, *J. Amer. Chem. Soc.*, **83**, 1124 (1961)] would involve the formation of a four-membered ring. However, an intramolecular association through a hydrogen bond (Scheme IV) could explain the facilitation of the specific hydrolysis of **9**. Labilization of ester bonds has frequently been observed when an intramolecular hydrogen bond between a neighboring hydroxyl or ammonium group is possible. Enhanced reactivity has been attributed to stabilization of the hydrolysis transitional state in a manner similar to that shown in **9a** (Scheme IV).[13,18] Protonation of the heterocyclic ring appears to be obligatory since the hydrolysis proceeds at a perceptible rate only when H_0 of the medium is less than zero.[19]

(18) M. L. Bender, *Chem. Rev.*, **60**, 70 (1960).

(19) It is presumed that the basic pK_a of the pyrimidinone **9** is about 0, close to those of urea (0.1,[20a] 0.4–0.5[20b]) or *N*-methylurea (0.9[20a]). The reported basic pK_a of 3,4-dihydro-2(1*H*)-pyrimidinone is 2.73.[21]

(20) (a) N. F. Hall, *J. Amer. Chem. Soc.*, **52**, 5115 (1930); (b) H. Lemaire and H. J. Lucas, *ibid.*, **73**, 5198 (1951).

(21) V. Škarić, B. Gašpert, and D. Škarić, *Croat. Chem. Acta*, **36**, 87 (1964).

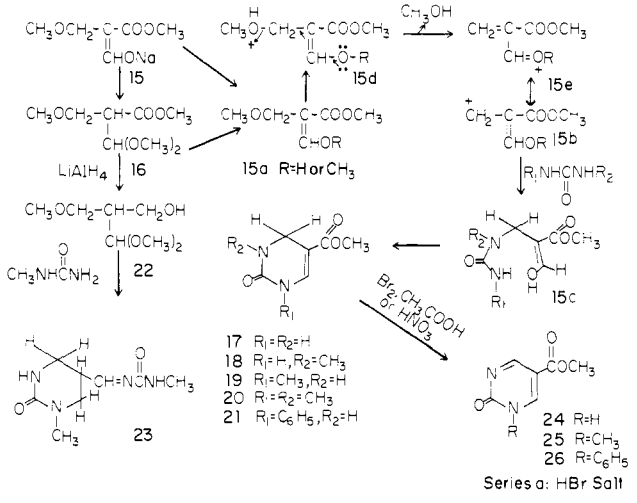
Table I. Uv Spectral Properties of 3,4-Dihydro-2(1*H*)-pyrimidinones

Compd	Charge	λ, nm (ε × 10^{-3}) Max	λ, nm (ε × 10^{-3}) Min	Apparent pK_a's Acidic	Apparent pK_a's Basic
7	0	281.5 (9.65) 209 (7.90)	241 (1.45)		
	−1	282 (9.05) 209 (7.75)	241 (1.45)	4.30 ± 0.03 (side chain)	
8	0	294 (10.4) 212 (7.75)	247 (0.90)		
	−1	295 (9.80) 209 (8.00)	249 (0.95)	4.40 ± 0.03 (side chain)	
9	0	282 (9.35)	241 (1.20)		
12	0	293 (9.60)	250 (9.70)		
13	0	299 (10.00)	254 (1.05)		
17	0	289 (8.80)	242 (0.80)		
18	0	294 (8.35)	249 (0.70)		
19	0	302 (9.95)	250 (0.45)		
20	0	307 (9.15)	255 (0.50)		
21	0	298 (12.30)	256 (2.40)		
24	+1	311 (4.95) 229 (20.70)	266 (0.65)		0.53 ± 0.04
	0	298 (3.80) 242 (22.05)	268 (3.05)		
	−1	257 (21.90)		7.29 ± 0.03	
25	+1	314 (6.10) 231 (17.05)	~265 broad		0.65 ± 0.06
	0	302 (4.35) 246 (18.85)	268 (0.75)		
26	0	308 (4.20) 275 sh 246 (17.60)	298 (3.85)		
31	0	319 (11.40) 233 (8.35)	265 (1.35)		
32	0	300 (12.70)	253 (1.05)		

with ureas[6,7] have been reported. Since these condensations are related to the ones we are studying, we reinvestigated and extended them.

The sodium enolate of methyl 2-formyl-3-methoxypropionate (**15**) (Scheme V) was prepared in one step

Scheme V



from methyl acrylate.[22] Reaction of either **15** or **16** with urea in aqueous HCl gave a crystalline solid that, by elemental analysis and pmr, was 5-carbomethoxy-3,4-dihydro-2(1*H*)-pyrimidinone (**17**) homologous with the ethoxy derivative reported earlier.[6] Condensation of *N*-methylurea with **15** gave a 1:1 mixture of the isomers **18** and **19**. These were readily separated by chromatography on alumina and structural assignments were made on the basis of their pmr and uv absorption spectra. *sym*-Dimethylurea was condensed with **16** to form **20** in 45% yield. As before,[6] *N*-phenylurea and **16** gave a 50% yield of a single pure isomer. Compounds **17** and **21** as well as the mixture of **18** and **19** were easily dehydrogenated to the corresponding 5-carbomethoxy-2(1*H*)-pyrimidinone (**24–26**) either by treatment with bromine in boiling acetic acid or with hot 50% nitric acid.

The reaction of ureas with compounds such as **16** or **15** can follow either of two pathways to give 3,4-dihydro-2(1*H*)-pyrimidinones. One possible route is represented in Scheme V. The other involves the formation of a ureide intermediate, by the reaction of urea with the aldehyde function of **15a**, followed by rapid cyclization.[23] The results obtained with *N*-methylurea and *sym*-dimethylurea indicate that either of the active sites on **15a** can react with the methylated amino group.

In contrast, the reaction of *N*-phenylurea with **16** gives only one of the two possible isomers. The *N*-methyl- and *N*-phenylureas differ in that the phenyl substituent is expected to decrease the nucleophilicity of the substituted nitrogen and the methyl group to enhance it. Therefore the first step in the condensation of **15a** with *N*-phenylurea involves the attack by the un-

(22) Compound **15** had been previously prepared by treating methyl 3-methoxypropionate in benzene with 1 equiv each of sodium and methyl formate: M. Tomita, S. U. Yeo, A. Takamizawa, and R. Maeda, *J. Pharm. Soc. Jap.*, 74, 752 (1954).

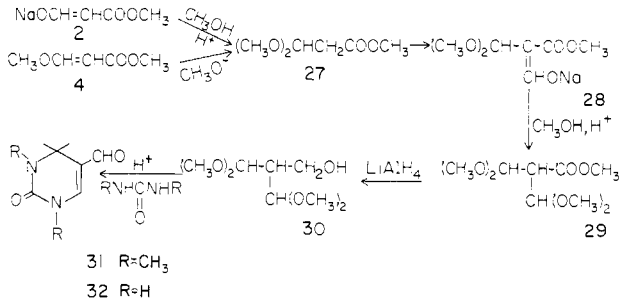
(23) Under similar conditions *N*-methylurea reacted with a 2-formyl butyrolactone to give exclusively the ureide derivative in which the unsubstituted end of the urea molecule had reacted with the aldehyde function.[6]

substituted nitrogen at one of the two reactive centers of **15a** (Scheme V). Since only **21** is obtained, it is the 3-methoxy group that is first displaced by the unsubstituted nitrogen, as in Scheme V.

Because aliphatic ethers do not ordinarily react with urea, the aldehyde and possibly the ester function must activate the 3-methoxy group. This activation involves the enolic form of the molecule (**15a**), since in that tautomer the hydroxymethylene oxygen can assist the breaking of the C–O bond of the protonated 3-methoxy group (species **15d**) by electron-pair donation through the conjugated system to yield the oxo carbenium ion **15e** and its mesomeric carbonium ion **15b**. The resonance-stabilized carbonium ion species **15b** reacts initially with urea to give a substituted ureide intermediate (**15c**), which then cyclizes to the 3,4-dihydro-2(1*H*)-pyrimidinone.[24]

Additional evidence supporting this mechanism was obtained. Reduction of methyl 2-dimethoxymethyl-3-methoxypropionate (**16**) with $LiAlH_4$ gave 2-dimethoxymethyl-3-methoxy-1-propanol (**22**) which was condensed with methylurea to yield, mainly, the ureide of 5-formyl-1-methyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (**23**). In a related experiment (Scheme VI) the

Scheme VI

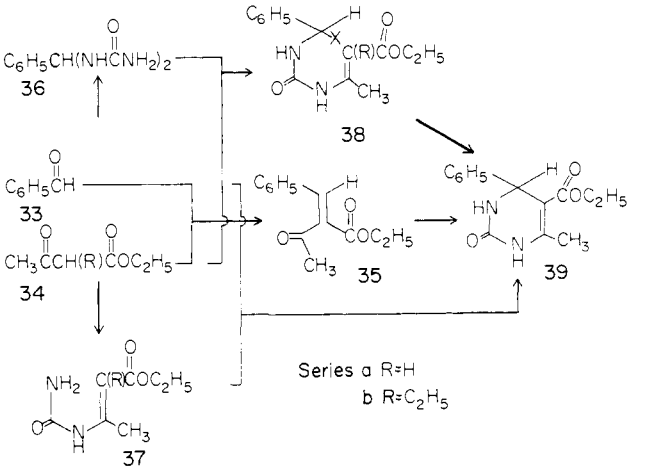


sodium enolate of methyl 2-formyl-3-dimethoxypropionate (**28**) was converted to the corresponding dimethyl acetal **29**[25] which was then reduced with $LiAlH_4$ to 2-hydroxymethyl-1,1,3,3-tetramethoxypropane (**30**). The latter compound was condensed with dimethylurea or urea to give 3,4-dihydro-1,3-dimethyl-5-formyl-2-(1*H*)-pyrimidinone (**31**) or 3,4-dihydro-5-formyl-2(1*H*)-pyrimidinone (**32**).

These results are all consistent with a greater reactivity of the allylic centers by comparison to the aldehyde function, and with the corollary carbonium ion mechanism in the cyclization reactions.

Closely related to the reactions discussed in Schemes II, V, and VI are the condensations with urea of (a) an aldehyde, (b) an aldehyde and a ketone, (c) a ketone, or (d) an aldehyde and a 3-keto ester, all of which produce 3,4-dihydro-2(1*H*)-pyrimidinones. In the former three instances, the early formation of aldol condensation products followed by reaction with urea has been suggested.[26,27] In the fourth case, the Biginelli reaction[8] involves the condensation of an aldehyde, acetoacetate ester, and urea, and has been studied more thoroughly. Its dependence upon acid catalysis has been experimentally established[28,29] and a mechanism proposed (Scheme VII) has been accepted.[8] The disubstituted

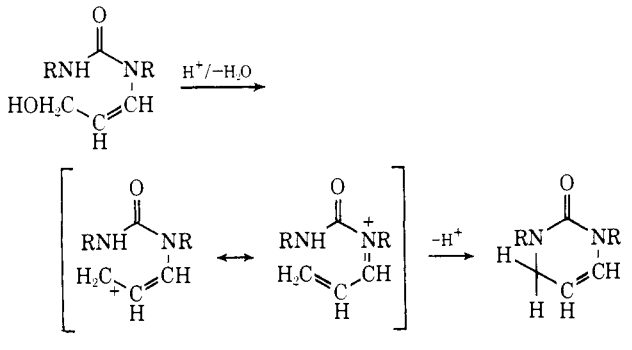
Scheme VII



urea **38** derived from the benzalbisureide **36** was proposed as the key intermediate.[30] That conclusion was based upon the behavior of the derivatives **35**, **36**, and **37** which were then considered to be the products of the three possible primary bimolecular reactions from **33**, **34**, and urea. Of these only preformed **36** gave a significant yield of the 3,4-dihydro-2(1*H*)-pyrimidinone **39**.[31]

We repeated several of these earlier reported experiments to obtain a better understanding of the mechanism of the Biginelli reaction. In 2 *N* HCl solution (50% MeOH) ethyl acetoacetate alone and urea failed to give a pyrimidine derivative. The ester underwent rapid decarboxylation[32] and only enolic products, as judged from their uv absorption, were formed.[33] In contrast, under the same conditions benzaldehyde (**33**), ethyl acetoacetate (**34a**) and urea, or *N*-methylurea gave the 3,4-dihydro-2(1*H*)-pyrimidinones **39** and **40** (Scheme

(24) A similar type of activation was recently discussed in relation with the following cyclization: H. Peterson, *Justus Liebigs Ann. Chem.*,



726, 89 (1969).

(25) The corresponding ethyl ester was previously prepared by condensing ethyl chloroformate and 1,1,3,3-tetramethoxypropane in a solution of potassium in liquid ammonia: H. Bredereck, F. Effenberger, and E. H. Schweizer, *Chem. Ber.*, **95**, 803 (1962).

(26) K. Folkers and T. B. Johnson, *J. Amer. Chem. Soc.*, **55**, 3361 (1933).

(27) V. P. Mamaev, *Aktiv. Soedin., Akad. Nauk SSSR*, 38 (1965); *Chem. Abstr.*, **63**, 18081 (1965).

(28) K. Folkers, H. J. Harwood, and T. B. Johnson, *J. Amer. Chem. Soc.*, **54**, 3751 (1932).

(29) K. Folkers and T. B. Johnson, *ibid.*, **55**, 3784 (1933).

(30) In this connection it was also considered significant[8] that ethyl 2-ethylacetoacetate (**34b**) failed to produce a pyrimidine in the preceding reaction,[29] presumably because it lacks one of the α-hydrogen atoms.

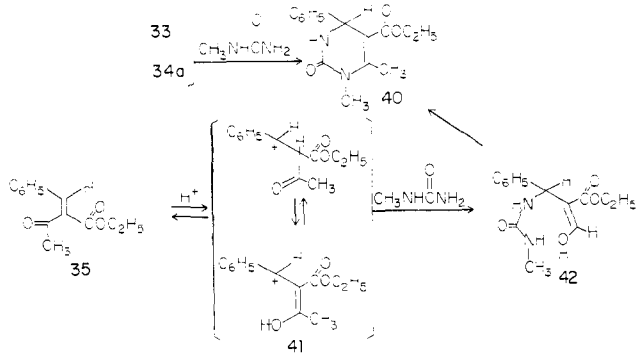
(31) The yield of **39** from the ethyl benzalacetoacetate (**35**) was only 1.5–3.8%. The ethyl carbamidocrotonate (**37**) was found to be hydrolyzed with ease into urea and ethyl acetoacetate under the experimental conditions used so that the production of **39** from **37** was considered to proceed essentially *via* the intermediate **38**.[29]

(32) A tightly stoppered reaction flask burst.

(33) The reaction mixture was chromatographed on a column of Dowex-50 (200–400 mesh, H^+, water).

VIII), respectively, in 77 and 85% yields. The formation of only one isomer (**40**) with *N*-methylurea parallels the formation of **8** (Scheme II) which strongly indicates that an aldol condensation precedes the reactions with urea. Benzaldehyde and ethyl acetoacetate were condensed in the presence of a catalytic amount of piperidine to produce a cis–trans mixture of ethyl benzalacetoacetate (**35**). This material was reacted with *N*-methylurea in a methanolic solution containing a catalytic amount of HCl under reflux for 2 weeks to give only **40** in a 36% yield. The difference between this utilization of preformed **35** and the results previously obtained[29] can be rationalized. Contrary to a previous statement,[29] **35** is not the primary but a secondary product of the aldol condensation between **33** and **34a** formed by dehydration of the corresponding ketol. Regardless of the precise mechanism involved [E2(C$^+$) or E1)[11b] in that fully reversible process, the transitional state possesses a carbonium ion character. Thus the first step of the reaction of **35** with urea is the protonation of **35** to produce the resonance stabilized carbonium ion **41** (Scheme VIII). This protonation would be expected to proceed particularly slowly if the E2(C$^+$) mechanism were operative. The reaction of **41** with the unsubstituted nitrogen of urea in a manner analogous to that of **6b** (Scheme II) yields the ureide **42**, which cyclizes to **40**.

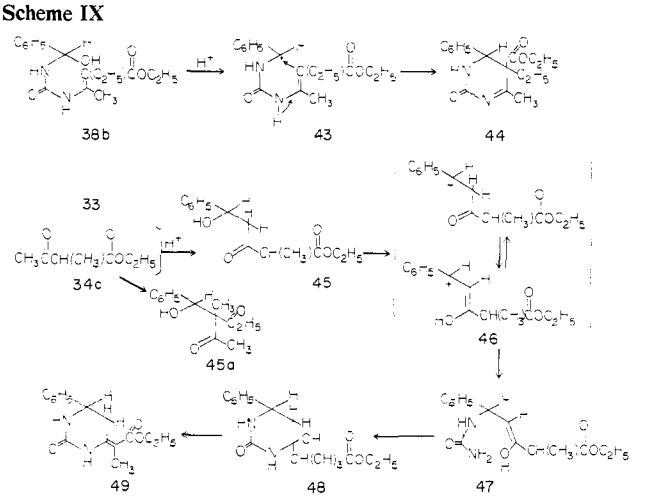
Scheme VIII



The reported failure[29] to obtain a pyrimidine derivative from the reaction of benzaldehyde (**33**), ethyl 2-ethylacetoacetate (**34b**), and urea (Scheme VII) was perplexing because the production of the pyrimidine derivative **44** (Scheme IX) from the postulated key intermediate **38b** appeared to be feasible. This was reinvestigated and from a reaction mixture of benzaldehyde (**33**), ethyl 2-methylacetoacetate (**34c**), and urea in ethanol containing a catalytic amount of HCl, and after heating under reflux for ~76 hr, a pyrimidine derivative was isolated in a small (9%) yield. Both analytical and pmr data were consistent with structure **49** in Scheme IX. No derivative analogous to **44** was found. The formation of **49** albeit in low yield clearly indicates that an acid-catalyzed aldol condensation between benzaldehyde and 2-alkyl-substituted acetoacetate takes place with the unsubstituted terminal methyl group of the ester, yielding **45**.[34] The favored homologous ketol **45a** is presumably cleaved rapidly, thus failing to give a pyrimidine analogous to **44**, while **45** is being continuously diverted from the reaction mixture by dehydration or reaction with urea to form **49** (Scheme IX). The postulated hydroxytetrahydro-2(1*H*)-pyrimidinone **48** is similar to the 3,4,5,6-tetrahydro-5,6-dicarbethoxy-6-hydroxy-4-phenyl-2(1*H*)-pyrimidinone reported to have been isolated[29] by Biginelli from the reaction of ethyl oxalacetate, benzaldehyde, and urea. The formation of this pyrimidine derivative can be accounted for by mechanisms similar to those proposed in Schemes VIII and IX, although not if an intermediate analogous to **38** (Scheme VII) is postulated. The accepted mechanism for the Biginelli reaction, shown in Scheme VII,[8] is inadequate. An alternate pathway that accommodates all of the present and previous results is proposed in Schemes VIII and IX. It is emphasized that the initial formation of a primary aldol condensation product that leads to an activated carbonium ion which in turn determines the ultimate course of the condensation reaction with urea is a feature common to each of the proposed mechanisms in Schemes II, III, V, VIII, and IX. The evidence that we have presented consistently indicates that this type of carbonium ion is the key intermediate in the formation of substituted 3,4-dihydro-2(1*H*)-pyrimidinones from a variety of precursors.

Such 2(1*H*)-pyrimidinones and 3,4-dihydro-2(1*H*)-pyrimidinones lacking a 4-carbonyl group are significant to our studies of H-bonding interactions between the 5-hydroxyalkyl substituents and the carbonyls or the π-electron system of the pyrimidine.

Scheme IX

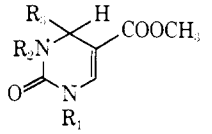


Experimental Section

Melting points were determined with a Mel-Temp apparatus and are uncorrected. The pmr spectra were obtained using a Varian A-60 spectrometer with tetramethylsilane as an internal reference. Uv (H_2O) and infrared spectra were determined with a Unicam SP800 and an Infracord spectrophotometer, respectively. All solvents were removed in a Büchler flash evaporator under reduced pressure, unless otherwise indicated. All solids were dried under reduced pressure over P_2O_5 at suitable temperatures An Eastman chromagram silica gel sheet was used for tlc and developed as indicated. Composition and homogeneity of liquid samples were monitored by an Aerograph gas chromatograph using a column (i.d. = 1/8 in., *l* = 100 in.) packed with 20% silicon SP-30 on 30/70 Aeropack 30. Satisfactory elemental analyses for all new compounds were obtained.

(34) Studies on catalyst selectivity in the reactions of benzaldehyde with unsymmetrical ketones have shown that acidic reagents favor attack of the more substituted and basic reagents favor the less substituted of two α carbons of the ketone. However, it has also been established that of the hydroxy ketones produced, the branched ones undergo rapid cleavage as well as dehydration in acid and that the homolog which lacks branching next to the carbonyl is dehydrated much faster than the branched compound: M. Stiles, D. Wolf, and G. V. Hudson, *J. Amer. Chem. Soc.*, **81**, 628 (1959).

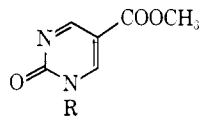
Table II. Pmr Properties of Some 3,4-Dihydro-2(1*H*)-pyrimidinones



Pyrimidinones	Chemical shifts τ[a] (no. of protons, coupling constants)					
	R_1[b]	R_2[b]	R_3[c]	C_4–H	C_6–H	$COOCH_3$
7	0.99 d (1, 6 Hz)	2.9 (1)	7.56 d (2, 5.5 Hz)	5.53 pair t (5.5 Hz, 3.5 Hz)	2.82 d (1, 6 Hz)	6.28 s (3)
8	6.98 s (3)	2.83 d (1, 3 Hz)	7.57 d (2, 5.5 Hz)	5.56 pair t (1, 5.5 Hz, 3 Hz)	2.63 s (1)	6.37 s (3)
9[d]	0.99 d (1, 6 Hz)	2.75 (1)	7.50 d (2, 5.5 Hz)	5.52 pair t (1, 5.5 Hz, 3 Hz)	2.82 d (1, 6 Hz)	
11	1.15 d (1, 6 Hz)	2.85 (1)	8.83 d (3, 6.5 Hz)	5.83 pair t (2, 6.5 Hz, τ_{gem} 3 Hz)	2.90 d (1, 6 Hz)	6.38 s (3)
12	6.98 s (3)	2.68 (1)	8.85 d (3, 6.5 Hz)	5.82 pair t (1, 6.5 Hz, 3 Hz)	2.62 s (1)	6.37 s (3)
13	6.92 s (3)	7.12 s (3)	8.83 d (3, 6.5 Hz)	5.78 g (1, 6.5 Hz)	2.63 s (1)	6.33 s (3)
17	1.25 (1)	3.09 (1)		6.20 s (2)	2.94 d (1, 5.5 Hz)	6.38 s (3)
18	1.00 (1)	7.17 s (3)		5.97 s (2)	2.88 d (1, 5.5 Hz)	6.35 s (3)
19	6.97 s (3)	2.88 (1)		6.02 s (2)	2.64 s (1)	6.33 s (3)
20	6.95 s (3)	7.17 s (3)		5.95 s (2)	2.62 (1)	6.35 s (3)
21	2.62 s (5)	~2.60 (1)		5.90 s (2)	2.54 s (1)	6.33 s (3)

[a] In $(CD_3)_2SO$. [b] R_1 and/or R_2 = H, CH_3, or C_6H_5. [c] R_3 = H, CH_3, or CH_2COOH. [d] Two singlets at τ 6.38 and 6.41 for the two OCH_3.

Table III. Pmr Properties of Some 2(1*H*)-Pyrimidinones



Pyrimidinones	Chemical shifts τ[a] (no. of protons, coupling constants)			
	R[b]	C_4–H	C_6–H	$COOCH_3$
24	4.15 (1)	1.35 s (2)		6.21 s (3)
24a		1.00 s (2)		6.13 s (3)
25	6.48 s (3)	1.10 s (2)		6.18 s (3)
25a	6.34 s (3)	0.65 d (1, 3 Hz)	0.90 d (1, 3 Hz)	6.13 s (3)
26a	2.42 s (5)	0.94 d (1, 3 Hz)	1.27 d (1, 3 Hz)	6.18 s (3)

[a] In $(CD_3)_2SO$. [b] R = H, CH_3, or C_6H_5.

Methyl 3-Methoxyacrylate (4). It was obtained as described[9] in an average 77% yield that remained unchanged when an equimolar amount of triethylamine instead of *N*-methylmorpholine was used as the catalyst.

Reactions of Methyl 3-Methoxyacrylate (4) with Urea or *N*-Methylurea. A mixture of 4.64 g (0.04 mol) of **4** and 2.4 g (0.04 mol) of urea or 2.94 g (0.04 mol) of *N*-methylurea dissolved in 40 ml of 2 *N* HCl was stirred in a sealed flask for 72 hr at room temperature and then refrigerated for 2–3 hr. The precipitated solid (consisting of **7** or **8**) was collected, washed three times each with a small volume of cold water, and dried. The filtrate was diluted with water and neutralized (pH ~4) with Dowex-1 (20 ml, 20–50 mesh, HCO_3^-). The mixture was then transferred in a column and the resin was washed with water until the uv absorption of the eluate was negligible. The combined washings were concentrated and the residue was chromatographed on a silica gel G column (80 g, 4 cm × 14 cm) that was developed with 2 l. of C_6H_6–EtOAc (8:2) followed by an equal volume of C_6H_6–EtOAc–MeOH (8:1:1). Homogeneous fractions, as indicated by tlc using the same solvent systems, were pooled and the solvents were removed *in vacuo* to yield the crude decarboxylated product **11** or **12**.

5-Carbomethoxy-4-carboxymethyl-3,4-dihydro-2(1*H*)-pyrimidinone (7). The obtained solid (2.0 g, 46.5%) was recrystallized from methanol to give small white rosettes, mp 203–204°.

5-Carbomethoxy-4-carboxymethyl-3,4-dihydro-1-methyl-2(1*H*)-pyrimidinone (8). The crude product (3.10 g, 68%) was recrystallized from methanol to give small white prisms, mp 198–200°.

5-Carbomethoxy-4-methyl-3,4-dihydro-2(1*H*)-pyrimidinone (11). The material obtained from the silica gel G column was recrystallized from petroleum ether (40–60°)–ethyl acetate in small white rosettes. The pure product was identical (melting point and mixture melting point, pmr, ir, uv) with that reported and obtained from the condensation of methyl 2-dimethoxymethyl-3-methoxybutyrate and urea.[15]

5-Carbomethoxy-3,4-dihydro-1,4-dimethyl-2(1*H*)-pyrimidinone (12). The crude product was purified by vacuum sublimation at 70°. The yield of the pure material was 300 mg, mp 112–113°.

Reaction of Methyl 3-Methoxyacrylate with Dimethylurea. A mixture of 2.32 g (0.02 mol) of methyl 3-methoxyacrylate, 1.76 g (0.002 mol) of *sym*-*N*,*N*′-dimethylurea, and 20 ml of 2 *N* HCl was stirred at room temperature in a sealed flask for 4 days. The mixture was lyophilized and the residue was dissolved in water; the resulting solution was passed through a column of Dowex-1 (20 ml, 20–50 mesh, $HCOO^-$) followed by a washing with water until the uv absorption of the eluate was negligible. The combined washings were concentrated, the residue was dissolved in methanol, and the resulting solution was again concentrated. The residue was chromatographed on a silica gel G column (60 g, 4 cm × 13 cm) and eluted with the system C_6H_6–EtOAc (8:2). Two compounds were isolated. The first one to emerge was purified by vacuum sublimation at 50–55°, and proved to be 5-carbomethoxy-3,4-dihydro-1,3,4-trimethyl-2(1*H*)-pyrimidinone (**13**), 730 mg (36.8%), mp 61–63°. The second isolated compound (100 mg, 14%) was identified by melting point, uv, pmr, and ir as 1,3-dimethyluracil.

5-Carbomethoxy-4-carboxymethyl-3,4-dihydro-2(1*H*)-pyrimidinone (9). A solution of 430 mg (0.002 mol) of **7** in 50 ml of dry methanol containing 2–3 ml of Dowex-50 (20–50 mesh, H^+) was heated at reflux for 72 hr and cooled, and the resin was removed by filtration and washed thoroughly with methanol. The combined filtrates were concentrated and the residue was recrystal-

lized from EtOAc. The pure product was collected and washed with a small volume of ether. An additional crop was recovered from the mother liquors, raising the total yield to 810 mg (90%), mp 140–141°.

Hydrolysis Experiments. (a) A solution of 75 mg of **9** in 10 ml of 2 *N* HCl was stirred at room temperature for 24 hr, then the mixture was lyophilized, and the residue dried *in vacuo* and checked by pmr and tlc (C_6H_6–EtOAc–MeOH, 8:1:1). Both these tests confirmed that the hydrolysis to **7** was complete. (b) When water instead of 2 *N* HCl was used in the previous experiment, no hydrolysis occurred, even when the solution was kept at 40° overnight. (c) Similar experiments at room temperature in buffers at pH 3.89, 3.0, and 2.0 were also run, and the progress of the hydrolysis was checked chromatographically with a Dowex-50 (200–400 mesh, H^+, 1 cm × 14 cm) column and an ISCO UA-4 absorbance monitor. Only at pH 2.0 and after ~72 hr did some hydrolysis occur. On longer Dowex columns (1 > 17 cm) hydrolysis of **9** occurs *in situ* to a small degree.

Methyl 2-Formyl-3-methoxypropionate Sodium (15).[22] Methyl formate (225 ml), freshly distilled from anhydrous sodium carbonate, was slowly added to a stirred suspension of sodium methoxide (70 g, 1.35 mol) in 1 l. of dry ether. During the addition of methyl formate (~25 min), the temperature of the mixture, which began to thicken, was maintained near 30°. After all of the methyl formate had been added, stirring was continued for ~15 min. Methyl acrylate (103.2 g, 1.19 mol) was added dropwise so that gentle reflux of the solvent occurred. The white paste thickened and an additional 300 ml of dry ether was added and stirring was continued overnight at room temperature. The reaction mixture was filtered and the white residue efficiently washed with several portions of dry ether. The product was dried overnight at room temperature over P_2O_5, giving 153.2 g of a white powdery salt. An aqueous solution of the salt had a uv absorption at 275 nm and upon acidification was suppressed.

Methyl 2-Dimethoxymethyl-3-methoxypropionate (16). To a solution of 17 g of HCl in 200 ml of anhydrous methanol was added 22.3 g of methyl 2-formyl-3-methoxypropionate sodium (**15**). After stirring for 0.5 hr at room temperature the mixture was heated under reflux for 4 hr. To the cooled mixture was added sufficient solid sodium carbonate to neutralize the acid, and then it was filtered. The salt was washed with ether. The methanolic filtrate was concentrated to ~35 ml, and the oily residue was diluted with 250 ml of ether and added to the ethereal filtrate, and the combined solutions were successively washed with dilute aqueous Na_2CO_3 and water, and finally dried (Na_2SO_4). After filtering and concentrating the crude oily material was distilled to give 9.5 g of the pure product: bp 92° (4.5 mm) (lit. bp 62° (2 mm),[35] 93–95° (5 mm)[36]); pmr ($CDCl_3$) τ 5.43 (d, 1, J = 8 Hz, $-CH(O)_2$), 6.3 (s, 3, $-COOCH_3$), 6.42 (d, 2, J = 4.5 Hz, OCH_2-), 7.0 (pair of t, 1, J = 8 Hz, J = 4.5 Hz, $-CHC{=}O$). The signals of the three OCH_3 groups appear at τ 6.65–6.75; ir (film) cm^{-1}, 1740 ($COOCH_3$), 1010, 1070 ($-OCH_3$, $-(OCH_3)_2$). These values are in agreement with the reported ones.[36]

5-Carbomethoxy-3,4-dihydro-2(1*H*)-pyrimidinone (17). Method A. To a solution of urea (12.01 g, 0.2 mol) in 175 ml of 3 *N* HCl was added 16.9 g of **15**. After 24 hr of refrigeration, the solution was concentrated to ~50 ml. The addition of methanol to the syrup resulted in precipitation of a solid (NaCl and product) which was extracted with several portions of boiling methanol. The combined methanolic extracts were evaporated to dryness and the solid residue was recrystallized twice with H_2O to give, after drying overnight (P_2O_5), 2.5 g of **17**, mp 249–250° (sharply with dec).

Method B. To a solution of 1.2 g (0.02 mol) of urea in 25 ml of 1 *N* HCl was added 1.92 g (0.01 mol) of **16**. The mixture was heated to boiling with occasional agitation and after ~5 min all of the acetal **16** had dissolved. After boiling for 25 min the solution was diluted with 150 ml of water and passed through a column of ion exchange resin (IR-45, OH^-). The column was washed with an additional 200 ml of water and the combined eluates were concentrated to ~25 ml. Cooling the concentrate overnight provided a crystalline solid that was recrystallized from water to give 780 mg (50%) of pure **17**.

5-Carbomethoxy-3,4-dihydro-1(3)-methyl-2(1*H*)-pyrimidinone (18,19). Employing the preceding method B, 1.4 g (0.02 mol) of urea and 1.92 g (0.01 mol) of **16** in 25 mol of 1 *N* HCl were heated to boiling for 25 min. After neutralization and concentration the solid obtained was recrystallized from water to give 860 mg (56%) of a 50:50 mixture (determined by the integrated peak area of the 1-methyl and 3-methyl signals in the nmr spectrum) of **18** and **19**.

Separation of 18 and 19. The 50:50 mixture of **18** and **19** was separated on a column of neutral alumina (Bio-Rad, AG-7, 100–200 mesh) using chloroform as eluent. The isomer **19** was first to emerge from the column.

Recrystallization of **19** from methanol or water gave needles, mp 177–179°.

For isomer **18** (recryst. from methanol) the mp was 165–167°.

5-Carbomethoxy-3,4-dihydro-1,3-dimethyl-2(1*H*)-pyrimidinone (20). Following the preceding method B, 1.76 g (0.02 mol) of *sym*-dimethylurea, 1.92 g (0.01 mol) of **16**, and 25 mol of 1 *N* HCl were heated to boiling for 30 min. After work-up and recrystallization from a small amount of water, 860 mg (46%) of pure **8** was obtained, mp 104–106°.

5-Carbomethoxy-3,4-dihydro-1-phenyl-2(1*H*)-pyrimidinone (21). Following the preceding method B, 2.78 g (0.02 mol) of *N*-phenylurea, 1.92 g (0.01 mol) of **16**, and 60 ml of 1 *N* HCl were heated to boiling for 30 min. After dilution of the reaction mixture with 300 ml of water, the work-up procedure was the same as in the above cases. Recrystallization from water gave fine white needles of pure **21**, mp 167–168°.

Dehydrogenation of 3,4-Dihydro-2(1*H*)-pyrimidinones. Method A. Dehydrogenation with Br_2 in Glacial HOAc. A solution of 1.6 g (0.1 mol) of bromine in 10 ml of acetic acid was added dropwise to a gently boiling solution of the 3,4-dihydro-2(1*H*)-pyrimidinone (0.1 mol) in glacial HOAc (25 ml). A crystalline precipitate accumulated during the addition of the bromine solution. Heating was continued for 20 min during which time the volume of the solution was allowed to be concentrated to ~1/2. After standing overnight at room temperature the separated yellow crystals were collected and dried.

5-Carbomethoxy-2(1*H*)-pyrimidinone Hydrobromide (24a). The crude product was recrystallized from ethanol in tan plates, mp 177–178° dec.

5-Carbomethoxy-1-methyl-2(1*H*)-pyrimidinone Hydrobromide (25a). The product was obtained in 75% yield from a mixture of 5-carbomethoxy-3,4-dihydro-1(3)-methyl-2(1*H*)-pyrimidinones. It was recrystallized from ethanol in small pale yellow prismatic needles, mp 186° dec.

5-Carbomethoxy-1-phenyl-2(1*H*)-pyrimidinone Hydrobromide (26a). The product was precipitated from the reaction mixture by cooling and the addition of an equal volume of ethyl acetate. After recrystallization from ethanol it melted at 176–177°.

Method B. Dehydrogenation with HNO_3. 5-Carbomethoxy-2(1*H*)-pyrimidinone (24). The 3,4-dihydro-2(1*H*)-pyrimidinone **17** (1 g, 6.4 mmol) was added at room temperature to 10 ml of 50% HNO_3 in an evaporating dish. Upon this addition brown fumes were observed. The solution was then heated on a steam bath and during the first 3 min dense brown fumes evolved and subsided after 4 min. Heating was continued for an additional 2 min. After cooling the mixture was concentrated to ~1 ml. Two 25-ml portions of ethanol were added and evaporated under reduced pressure to remove residual HNO_3. The solid residue was recrystallized three times from methanol–water, mp 192°.

5-Carbomethoxy-1-methyl-2(1*H*)-pyrimidinone (25). An aqueous solution of the hydrobromide **25a** was treated first with Amberlite IR-45 (OH^-) and then concentrated. The residue was recrystallized from methanol, mp 204°.

2-Dimethoxymethyl-3-methoxy-1-propanol (22). To a solution of 2.8 g (0.05 mol) of $LiAlH_4$ in 100 ml of anhydrous ether was added dropwise with stirring a solution of 8.1 g (0.05 mol) of **16** in 10 ml of ether. The rate of addition was adjusted so that the ether refluxed. After the addition was completed the mixture was stirred overnight at room temperature and heated for 2 hr under reflux. To the cooled (0°) mixture was carefully added dropwise in succession 2 ml of H_2O, 2 ml of 5% aqueous KOH, and 2 ml of H_2O. Stirring of the resultant mixture was continued at room temperature for 30 min and it was then filtered. The ethereal filtrate was dried (Na_2SO_4) and the aluminum hydroxide residue was continuously extracted for 24 hr with ether and the extract dried (Na_2SO_4). The combined ethereal solutions were concentrated to an oily residue which was distilled under reduced pressure to give 5.77 g (78%) of a colorless oil boiling at 73–74° (0.35 mm).

Reaction of 2-Dimethoxy-3-methoxy-1-propanol (22) with *N*-Methylurea. A solution of 3.28 g (0.02 mol) of **22** and 2.96 g (0.04 mol) of *N*-methylurea in 25 ml of ethanol containing 0.5 ml of

(35) T. Nishino, Y. Miichi, and K. Tokuyama, *Tetrahedron Lett.*, 4335 (1970).

(36) E. Takamizawa, Japanese Patent 10,776 (1956); *Chem. Abstr.*, **52**, 15585a (1958).

concentrated HCl was heated to reflux for 3 days. After removing the solvents the residue was triturated with ether, then dissolved in methanol (~25 ml). Sufficient ether was added to induce turbidity and the resultant solution was chilled for several days. The separated solid was (collected and) recrystallized once from methanol and then from ethanol to give **23** in small white crystals (200 mg): mp 260–261°; pmr (CD_3COOD) τ 7.4 (m, 1, C*H*CH=N), 7.03, 7.06 (two s, 3 H each, NCH_3, $NHCH_3$), 6.6 [m, 4, $(CH_2N)_2$], 5.1 (d, 1, J = 4 Hz, CH=N).

Methyl 3-Dimethoxypropionate (27). (A) To 11.6 g (0.1 mol) of methyl 3-methoxyacrylate (**4**) containing 500 mg of *N*-phenyl-2-naphthylamine was added dropwise and with stirring a solution of 100 mg (4.3 mmol) of Na in 3.2 g (4 ml, 0.1 mol) of MeOH. The addition was followed by a brief exothermic reaction and occasional cooling was needed to maintain the temperature at <50°. Upon completion of the addition the reaction mixture was a jell. Addition of dry ether resulted in the separation of salts that were removed by filtration and washed well with dry ether. The combined ethereal filtrates were dried with Na_2SO_4 and concentrated and the residue was distilled. Material boiling at 72–74° (18 mm) was collected (12.8 g, 86%) and then redistilled in a spinning band column (Nester-Faust). The product (gc) boiled at 82–83° at 24–25 mm (lit. bp 77° (20 mm),[37] 91–92° (30 mm)[38]); pmr data were in accord with the reported ones.[38]

(B) Alternatively, 21.0 g (0.25 mol) of methyl propiolate was dissolved in 400 ml of dry ether and to that solution was added dropwise and with stirring 22.4 ml (0.552 mol) of dry methanol containing 400 mg (17.4 mmol) of Na. After stirring overnight at room temperature the mixture was worked up as in method A, and the product **27** was obtained in 85% yield.

Methyl 3-Dimethoxy-2-formylpropionate Sodium (28). To a suspension of 4.08 g of NaH (7.3 g of a 56% oil suspension, equiv to 0.17 mol of pure NaH) in 200 ml of anhydrous ether was added with stirring 22.23 g (0.15 mol) of methyl 3-dimethoxypropionate, then 18.02 g (0.30 mol) of methyl formate freshly distilled from Na_2CO_3. After stirring at room temperature for 48 hr, the thick mixture was filtered and the salt rapidly washed with anhydrous ether and dried *in vacuo*. This gave 25.5 g of a white powdery sodium enolate (86% yield on the basis of ester starting material and assuming 100% purity of the salt). The uv spectrum of the salt in water had an absorption max at 275 nm followed by suppression that shifted to lower wavelengths on acidification, a characteristic of an enolate conjugated with an ester function.

Methyl 3-Dimethoxy-2-dimethoxymethylpropionate (29). To an ice-cold solution of 15 g of anhydrous HCl in 250 ml of dry methanol was added with stirring 23 g of methyl 3-dimethoxy-2-formylpropionate sodium (**28**). The mixture was stirred at room temperature for 20 hr and then heated under reflux for 1 hr. After the mixture was cooled, sufficient solid $NaHCO_3$ was added to neutralize the acid, and the mixture was filtered. The salt residue was washed with ether and the combined filtrates were concentrated to an oily residue. The addition of ether to the residue resulted in precipitation of salt which was removed by filtration. After three repeated concentrations, additions of ether, and filtration, no further precipitate formed. The final oily residue was distilled to give 18.5 g (71%) of product: bp 82° (0.9 mm); pmr ($CDCl_3$) τ 5.39 [d, 2, J = 6.5 Hz, $(RO)_2CH$], 6.3 (s, 3, $COOCH_3$), 6.6 [s, 12, $(OCH_3)_2$], 6.91 (t, 1, J = 6.5 Hz, CHCOOR).

3-Dimethoxy-2-dimethoxymethyl-1-propanol (30). To a stirred and chilled solution of $LiAlH_4$ (1.89 g, 0.05 mol) in 100 ml of anhydrous ether was added dropwise a solution of methyl 3-dimethoxy-2-dimethoxymethylpropionate (11.1 g, 0.05 mol) in 25 ml of ether. After stirring at room temperature overnight (~18 hr) the now thickened mixture was diluted with 100 ml of ether, cooled to 0°, and to it was added dropwise with care 5 ml of ethyl acetate, 2 ml of H_2O, 2 ml of 5% aqueous NaOH, and 2 ml of H_2O, in succession. The mixture was stirred for 0.5 hr at room temperature and filtered, and the residue washed with two 25-ml portions of ether. The combined ethereal filtrates were dried (Na_2SO_4), filtered, and concentrated to 8 g of a clear oil, and shown by gc to contain ~95% of one component. The aluminum salt residue was continuously extracted with ether (soxlet) for 24 hr and the dried and filtered extract was concentrated to 1.8 g of oil identical (gc) with that obtained previously. Distillation of the combined oils gave 9.04 g (91%) of product: bp 61° (0.4 mm); pmr ($CDCl_3$) τ 5.52 [d, 2, J = 5.5 Hz, $(RO)_2CH$], 6.2 (broad s, 2, CH_2O). The signals of the methoxy groups appear as two singlets at τ 6.58 and 6.60, and that of the center methine proton as a multiplet centered at τ 8.0.

Reaction of 3-Dimethoxy-2-dimethoxymethyl-1-propanol (30) with Ureas. 3,4-Dihydro-1,3-dimethyl-5-formyl-2(1*H*)-pyrimidinone (31). A mixture of 1.94 g (0. 01 mol) of **29**, 0.97 g (0.011 mol) of *sym*-dimethylurea, and 2 ml of concentrated HCl in 120 ml of ethanol was heated to reflux for 1 hr and then cooled in an ice bath. To the cooled mixture was added 2.0 g (0.024 mol) of sodium acetate and the solvent removed under reduced pressure. The solidified residue was extracted with 200 ml of chloroform and the extract dried (Na_2SO_4) and concentrated to a pinkish solid. Dissolving the solid in 100 ml of ethyl acetate and treating with Norit gave a nearly colorless solution after filtration. Upon removal of the solvent an off-white solid appeared that was recrystallized from heptane–ethyl acetate (~3:1) to give 820 mg of white crystals, mp 85–93°. Alternatively, the crude material could be purified by sublimation *in vacuo* at 50–55°.

3,4-Dihydro-5-formyl-2(1*H*)-pyrimidinone (32). It was prepared in an analogous manner. The crude product was recrystallized from methanol, mp 238–239°.

Ethyl 2-Benzalacetoacetate (35). A modification of the method of Knoevenagel[39] was used. A mixture of 10.4 g (0.08 mol) of ethyl acetoacetate, 8.5 g (0.08 mol) of benzaldehyde, and 0.1 g of piperidine was stirred at room temperature for 5 days. The viscous residue was distilled and a fraction was collected at 112° (0.4 mm). This material was a mixture of a waxy solid and a viscous oil, although chromatographically (gc) it appeared to be homogeneous. It was dissolved in ether and the solution chilled for several days. The separated solid was collected, washed once with a small volume of ethanol and then with ether, and air dried (6.71 g): mp 55–59°; pmr ($CDCl_3$) τ 8.71 (t, 3, J = 7 Hz, CH_2CH_3), 7.58 (s, 3, $COCH_3$), 5.67 (q, 2, J = 7 Hz, $-CH_2-$), 2.59 (s, 5, ArH), 2.31 (s, 1, ArCH). The mother liquors were concentrated and the residue was crystallized from ethanol giving an additional 4.3 g of a solid, mp 30–31°; the pmr ($CDCl_3$) spectrum of that material showed two duplicate sets of signals, as expected from a cis–trans mixture. One set was identical with that of the pure isomer (presumably the trans) isolated first. For the second the corresponding values are: (τ) 8.67 (t, 3, J = 7 Hz, CH_2CH_3), 7.64 (s, 3, $COCH_3$), 5.69 (q, 2, J = 7 Hz, –CH–), 2.61 (s, 5, ArH), 2.25 (s, 1, ArCH).

3,4-Dihydro-5-carbethoxy-6-methyl-4-phenyl-2(1*H*)-pyrimidinone (39) and 3,4-Dihydro-1,6-dimethyl-5-carbethoxyphenyl-2(1*H*)-pyrimidinone (40). A solution of 3.18 g (0.03 mol) of benzaldehyde, 3.9 g (0.03 mol) of ethyl acetoacetate, and 3.6 g (0.06 mol) of urea, or 4.4 g (0.06 mol) of *N*-methylurea in 15 ml of 2 *N* HCl solution (1:1 methanol–water) was stirred for 3 days at room temperature. The precipitated solid was collected, washed several times with water, and dried. The yield averaged 80%.

39 was recrystallized from methanol in white needles, mp 207–208° (lit.[28] mp 202.4°).

40 was recrystallized from methanol in small plates, mp 176–178°.

Preparation of 40 from Ethyl 2-Benzalacetoacetate. A solution of **33** (1.09 g, 5 mmol) and *N*-methylurea (740 mg, 10 mmol) in 25 ml of methanol containing 0.5 ml of concentrated HCl was heated to reflux for 2 weeks, then was concentrated. The residue was dissolved in methanol and the solvent was again removed. Finally the residue was chromatographed on a silica gel G column (80 g, 4 cm × 14 cm) and eluted with 1.5 l. of a mixture of C_6H_6–EtOAc (9:1), and fractions of 10 ml each were collected and checked by tlc with the system C_6H_6–EtOAc (8:2). Those containing the product **40** were pooled and concentrated to dryness, and the obtained solid was washed with ether and dried (500 mg, 36.5%). It was recrystallized from methanol. The pure product had identical R_f (tlc), ir and uv spectra, melting point, and mixture melting point with that obtained as described from benzaldehyde, ethyl acetoacetate, and *N*-methylurea.

Reaction of Benzaldehyde with Ethyl 2-Methylacetoacetate and Urea. Benzaldehyde (1.06 g, 10 mmol), ethyl 2-methylacetoacetate (1.44 g, 10 mmol), and urea (1.2 g, 20 mmol) were dissolved in 25 ml of ethanol containing 0.5 ml of concentrated HCl and the solution was heated to reflux for 72 hr. The solid that separated was removed by filtration (300 mg). It showed no specific uv absorption.

(37) Prepared by the addition of dimethyl carbonate to acetylene in the presence of basic catalysts: W. J. Croxall and H. J. Schneider, *J. Amer. Chem. Soc.*, **71**, 1257 (1949).

(38) Prepared by the reaction of potassium methoxide and methyl 3-chloroacrylate: H. O. House, W. L. Roelofs, and B. M. Trost, *J. Org. Chem.*, **31**, 646 (1966).

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The filtrate was concentrated, the residue dissolved in methanol, and the solvent again removed. The residue was chromatographed on a silica gel G column (80 g, 4 cm × 14 cm) and eluted with the system C_6H_6–EtOAc (8:2). Fractions (20 ml each) containing a uv absorbing component with R_f's 0.7 (C_6H_6–EtOAc–MeOH, 8:1:1) or 2.5 (C_6H_6–EtOAc, 8:2) were pooled and concentrated, and the crystalline residue was washed with ether and dried (250 mg). It was recrystallized from methanol, and the obtained pure **49** was washed with ether and dried *in vacuo:* mp 191–192°; pmr (DMSO-d_6) τ 8.8 (t, 3, J = 7 Hz, OCH_2CH_3), 8.3 (s, 3, CH_3C), 7.1 (d, sharpens upon addition of D_2O, 2, J = 6 Hz, CH_2C), 5.86 (q, 2, J = 7 Hz, OCH_2CH_3), 5.35 (m, sharpens upon addition of D_2O to a triplet, J = 6 Hz, ArCH), 2.65 (s, 5, ArH). A signal of an exchangeable proton appears at τ 2.25 and that of a second is masked by that of the protons of the phenyl group: uv (H_2O), for the neutral species, λ_{max} 277 nm (ϵ 15.9 × 10^3); λ_{min} 230 nm (ϵ 2.17 × 10^3).

Uv Absorption Properties. The uv spectrum (neutral species) of the various 5-carbalkoxy-3,4-dihydro-2(1*H*)-pyrimidinones showed a major symmetrical absorption peak at 280–310 nm (Table I) with no shift in weak acid except for **7** and **8**. For those unsubstituted at N-1, only a slight shift was observed in weak base. However, with the latter 3,4-dihydro-2(1*H*)-pyrimidinones in stronger basic solutions (~0.5 *N* NaOH), a second peak appeared and rapidly decayed (half-life ~10 min) while the principal absorption underwent ultimately a small hypsochromic and hypochromic (loss of ~15% of o.d.) shift. The fleeting band observed is most likely due to extension of the conjugated system resulting from ionization at N-1 position. Its disappearance is the result of the concomitant hydrolysis of the ester function at C-5. Since the resulting carboxylic acid function is expected to be more acidic than the pyrimidinone, the original conjugated system is reestablished. In strongly alkaline solutions in which both the pyrimidinone ring and the C-5 carboxylic group are ionized, the absorption at 330–345 nm is stable.

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Structure and Synthesis of Dihydroxypentyluracil from Bacteriophage SP-15 Deoxyribonucleic Acid

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Abstract: The structural elucidation and synthesis of (*S*)-(+)-5-(4′,5′-dihydroxypentyl)uracil, a base which replaces thymine in bacteriophage SP-15 DNA, is described. The synthesis starting from (*S*)-(−)-malic acid establishes the 4′ configuration as being *S*, which is opposite to that at C-4′ in D-ribose. The optical purity (100%) of a synthetic intermediate has been checked from the nmr of a di-MTPA ester. The synthesis involves a C_1-homologation which can be carried out under the presence of acid-sensitive groups, and which also allows further modifications of functionalities during the course of homologation.

In 1948, 5-methylcytosine was detected in DNA;[2] since then a large number of modified bases have been isolated and identified.[3] About 40 modified bases from tRNA have been identified; structural modifications range from simple methylated bases to the highly modified Y series[4–6] in which there is a third ring fused to a guanine moiety. In contrast, only seven modified bases have been identified in DNA including (*S*)-(+)-5-(4′,5′-dihydroxypentyl)uracil (DHPU).[7–9]

The structural variety of modified bases in DNA decreases as one proceeds up the evolutionary scale from bacteriophage to mammalian tissue. The only modified base detected in the DNA of animals and plants is 5-methylcytosine, while in bacteria 5-methylcytosine and N^6-methyladenine have been identified. Bacteriophages can be divided into two classes depending on the modified base content of their DNA. In one class the DNA contains only trace amounts of modified bases, most commonly 5-methylcytosine and N^6-methyladenine, while in the other class the modified base completely replaces one of the major bases.[3] The bacteriophages SP-15 from which DHPU was recently isolated and ϕW-14 from which *N*-thyminylputrescine[10] was isolated appear to form a third class on the basis of DNA base composition in that the relatively highly modified bases replace almost half of the thymine.[11]

Bacteriophage SP-15 is a large, generalized transducing phage of *Bacillus subtilis* and *Bacillus licheniformis*. Its DNA was first isolated in 1963[12] and has unusual

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