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The Chemistry of the Base-Catalyzed Condensation of Some 3-Alkoxy- and 3-Alkoxy-2-dialkoxymethyl Esters with Ureas. Synthesis of 5-Substituted Uracils[1]

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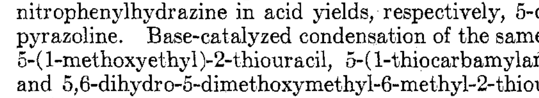
The formylation reaction of methyl 3-methoxybutyrate and the scope and limitations of the condensation of methyl 2-dimethoxymethyl-3-methoxybutyrate with ureas were studied. The former reaction is a complex one yielding numerous products, a number of which [*i.e.*, dimethyl (2-ethylidene-3-methyl)glutarate, methyl 2-dimethoxymethyl-3-methoxybutyrate, and dimethyl 4-methylisophthalate] were isolated. Under conditions favoring formation or accumulation of ionic intermediates, the yields of the glutarate and isophthalate derivatives increases while that of the 2-dimethoxymethyl-3-methoxybutyrate decreases. A mechanism is proposed explaining the formation of these products. The condensation of 2-dimethoxymethyl-3-methoxybutyrate with urea or dinitrophenylhydrazine in acid yields, respectively, 5-carbomethoxy-4-methyl-3,4-dihydropyrimidin-2-one and a pyrazoline. Base-catalyzed condensation of the same material with ureas produces 5-substituted uracils such as 5-(1-methoxyethyl)-2-thiouracil, 5-(1-thiocarbamylaminoethyl)-2-thiouracil, 5-vinyl-2-thiouracil, 5-vinyluracil, and 5,6-dihydro-5-dimethoxymethyl-6-methyl-2-thiouracil. Factors affecting the course of this reaction were explored and a comprehensive mechanism is proposed in which a series of interconvertible intermediates lead to the several pyrimidines obtained. The synthesis of 5,6-dihydro-6-methyl-2-thiouracil from methyl crotonate or methyl 3-methoxybutyrate and thiourea, and studies on the chemical reactivity of that reduced pyrimidine, are reported.

In a previous report we described the synthesis of 5-vinyluracil by the decarboxylation of 3-(5-uracilyl)-propenoic acid.[2] Because of the low yield obtained in that synthesis, and the need for larger quantities of the vinyl compound to study its chemical and biological activity, we explored alternative preparative routes. One procedure that appeared to be of greater synthetic value in the pyrimidine field was the base-catalyzed condensation of urea derivatives with esters of 3-alkoxycarboxylic acids such as $CH_3CH(OCH_3)C(H)(X)COOR$ where X represents a vinyl ether (=CHOR) or an acetal $[-CH(OR)_2]$ function. Appropriate derivatives of the resulting 5-(1-hydroxyethyl)uracil (I, Scheme I) should be more readily converted *via* an elimination reaction to the 5-vinyl compound, in contrast to those of the 2′ isomer which, through the furan derivative II, preferentially give substitution products (III).[2] However, I, being a vinylogous carbinolamine which also possesses a C-1′ allylic carbon atom, could, in addition, be reactive toward nucleophiles in the presence of either an acidic or a basic catalyst. Numerous examples of substitution reactions involving uracil derivatives structurally related to I have been reported[3-7] and mechanistically rationalized.[8-11] Those mechanistic interpretations have been considered in relation to the results reported here.

SCHEME I



I (X = O, S) II III

A. Formylation of Methyl 3-Methoxybutyrate.— Conversion of methyl crotonate (1) to methyl 3-methoxybutyrate (3) was accomplished by the general method of Rehberg and Fisher,[12] with the crude product usually obtained in over 70% yield. The subsequent formylation of 3 (Scheme II) proved to be complex, with numerous products resulting, and its mechanistic aspects deserve consideration. Several prod-

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[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] J. A. Carbon, *ibid.*, **25**, 1731 (1960).

[4] A. Giner-Sorolla and L. Medrek, *J. Med. Chem.*, **9**, 97 (1966).

[5] Z. A. Martiroyan, V. I. Gundar, and S. I. Zav'yalov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1841 (1970); *Chem. Abstr.*, **74**, 54134 (1971).

[6] H. Guglielmi and B. Athen, *Hoppe-Seyler's Z. Physiol. Chem.*, **350**, 809 (1969).

[7] R. Brossmer, *Angew. Chem., Int. Ed. Engl.*, 702 (1967).

[8] R. W. Chambers, *Progr. Nucl. Acid Res. Mol. Biol.*, **5**, 349 (1966).

[9] D. V. Santi, *J. Heterocycl. Chem.*, **4**, 475 (1967).

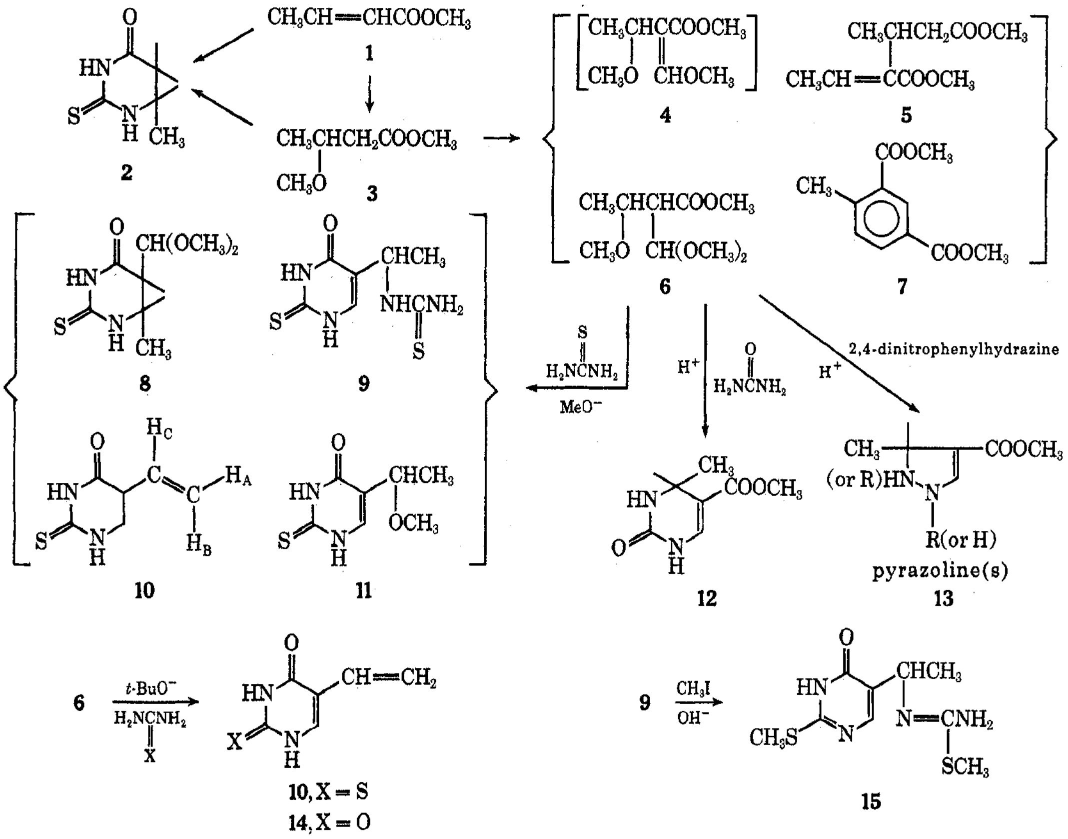
[10] D. V. Santi and A. L. Pogolotti, Jr., *ibid.*, **8**, 265 (1971).

[11] U. Lerch, M. G. Burdon, and J. G. Moffatt, *J. Org. Chem.*, **36**, 1507 (1971).

[12] C. E. Rehberg and C. H. Fisher, U. S. Patent 2,504,151 (April 18, 1950).

ucts of this reaction were isolated and characterized, *i.e.*, dimethyl (2-ethylidene-3-methyl)glutarate (**5**), methyl 2-dimethoxymethyl-3-methoxybutyrate (**6**), and dimethyl 4-methylisophthalate (**7**); some others, apparently polymeric, were not identified. A modification of the procedure used for the formylation of 3-alkoxypropionates[13–15] was applied to the reaction of methyl 3-methoxybutyrate (**3**) with methyl formate in the presence of CH_3ONa. The intermediate resonance-stabilized ambident anion $[CH_3CH(OCH_3)C(CHO)COOCH_3]^-$ was then alkylated with dimethyl sulfate. By analogy to the products obtained from the 3-alkoxypropionates,[13–15] the methyl 2-methoxymethylene-3-methoxybutyrate (**4**), which is the initial product expected, is then converted to the corresponding acetal, methyl 2-dimethoxymethyl-3-methoxybutyrate (**6**), which was isolated. Since the alkylation of the ambident anion is a highly heterogeneous reaction, no meaningful conclusions can be drawn regarding factors affecting the oxygen *vs.* carbon alkylation ratio.[16] The base-catalyzed addition of alcohols to enol ethers is well known[17–19] and formation of **6** undoubtedly occurs by addition of excess CH_3O^- to the vinyl ether **4**.

SCHEME II



The formation of the dimeric dimethyl (2-ethylidene-3-methyl)glutarate (**5**), which arose during the formylation of **3**, is reasonably interpreted by a Michael-type addition as shown in Scheme III. The species **3a**[20] can react competitively, either with the formate[21] leading eventually to **4** (Scheme II), or with **1** formed *in situ*,[22,23] to give **5** by either of two routes.

Dimethyl 4-methylisophthalate (**7**) was also isolated from the formylation mixture and identified by comparison (melting point, mixture melting point, ir, and pmr spectra) with an authentic sample prepared (Scheme IV) by the oxidation of 2,5-dimethylbenzoic acid with potassium permanganate,[24] followed by esterification of the resulting 4-methylisophthalic acid (**17**).

A mechanism (Scheme V) for the formation of **7** involves the reaction, *via* a Michael condensation, of two of the obligatory intermediates from the overall formylation reaction **3a** and **4**[26] to form **7a**, which then gives

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[13] A. Takamizawa, *Yakugaku Zasshi*, **74**, 752 (1954).

[14] A. Takamizawa, K. Tokuyama, and H. Satch, *ibid.*, **79**, 664 (1959).

[15] A. Takamizawa, K. Hirai, and S. Sumimoto, *Chem. Pharm. Bull.*, **14**, 238 (1966).

[16] W. J. LeNobel and H. F. Morris, *J. Org. Chem.*, **34**, 1969 (1969).

[17] E. Schmitz and I. Eichhorn, "The Chemistry of the Ether Linkage," S. Patai, Ed., Interscience, New York, N. Y., 1967, p 323.

[18] M. F. Shostakovskii, A. V. Bogdanova, and G. I. Plotnikova, *Russ. Chem. Rev.*, **33**, 66 (1964).

[19] E. Takamizawa, Japanese Patent 10,776 (1956); *Chem. Abstr.*, **52**, 15585 (1958).

[20] J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 568.

[21] H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 735.

[22] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, p 1019.

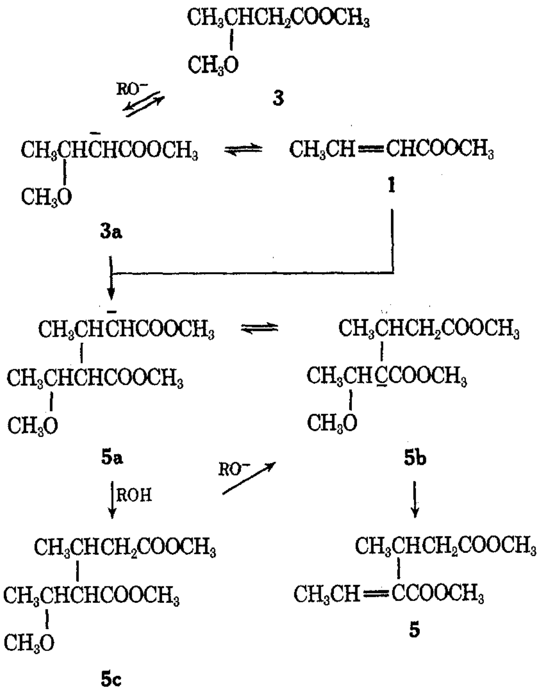
[23] The ElcB mechanism of the retrograde process has been confirmed: S. Patai, S. Weinstein, and Z. Rappoport, *J. Chem. Soc.*, 1741 (1962).

[24] W. H. Bentley and W. H. Perkin, Jr., *J. Chem. Soc.*, **71**, 157 (1897). The oxidation produced only **17** and none of the isomeric 4-methylphthalic acid. This was established by chromatography on a Sephadex G-10 column and comparison of its pmr spectrum to that of 4-methylphthalic acid.[25]

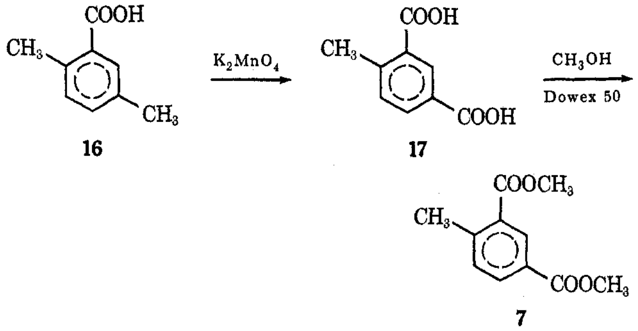
[25] Purchased from Eastman Kodak.

[26] The inclusion of species **3a** is supported by the fact that unreacted starting material, *i.e.*, **3**, has always been found in the final crude mixture containing **6**.

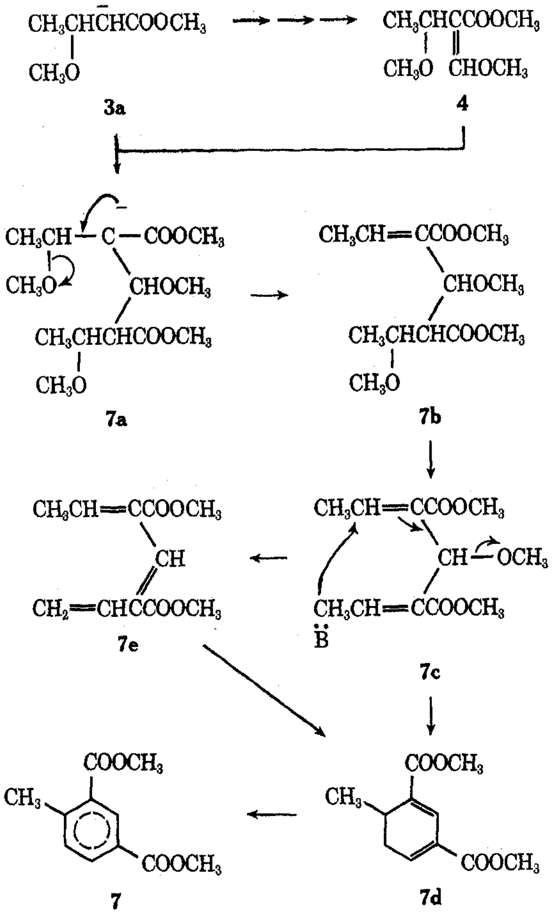
Scheme III



Scheme IV



Scheme V



7c. Cyclization[27] to the cyclohexadiene derivative 7d is presumed to be followed by air oxidation to dimethyl 4-methylisophthalate (7), an aromatization known to occur with atmospheric oxygen.[31]

With the intermediates **3a** and **4** common to the reactions in Schemes II, III, and V, and with similar addition–elimination steps involved, the mechanisms proposed in those schemes are consistent and mutually support each other. Under conditions which promote the formation or accumulation of the ionic species **3a**, the secondary products, **5** and **7**, predominate in the reaction mixture. With a small volume of benzene as solvent and slowly reacting slices of sodium, a satisfactory yield, up to 36%, of the acetal **6** was obtained. On the other hand, when the more polar solvent ethyl ether and/or the faster reacting sodium hydride were used, the yield of **6** was decreased, or became nil, while that of the products **5** and **7** increased. This control of the course of the reaction supports the ionic mechanisms proposed in Schemes III and V.

B. Cyclizations of Methyl 2-Dimethoxymethyl-3-methoxybutyrate to Pyrimidines.—The acid-catalyzed condensation of **6** with urea gives the 5-carbomethoxy-4-methyl-1,2,3,4-dihydropyrimidin-2-one (**12**).[32] Analytical and pmr data were consistent with structure **12** and it possessed the characteristic uv absorption properties of the 5-carbomethoxy-1,2,3,4-dihydropyrimidin-2-ones.[33] In an analogous manner the reaction of **6** with 2,4-dinitrophenylhydrazine in acid led to the pyrazoline derivative(s) **13**. Tlc data suggest the presence of only one isomer. However, because of poor solubility, pmr measurements were not conclusive as to the position of attachment (N^1 *vs.* N^2) of the dinitrophenyl group.

Base-catalyzed condensation of **6** with ureas yielded products of much greater interest. To our knowledge syntheses of pyrimidines by base-catalyzed condensation of such compounds with weak nucleophiles such as urea and thiourea were previously unknown. Although pyrimidines are commonly obtained by condensations of acetals of 1-aldehydo-2-alkoxy esters or nitriles with

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[27] The cyclization to **7d** could be a concerted reaction involving the abstraction of an allylic proton from one of the terminal methyl groups, followed by an intramolecular attack of the incipient carbanion to the opposite chain with displacement of methoxide ion. Alternatively, the abstraction of an allylic proton leads to a conjugated triene **7e**, which then cyclizes to **7d**. Thermally induced ring closure of conjugated trienes, having a central cis double bond to give cyclohexadienes, is a well-established reaction, but it requires, in general, rather vigorous conditions (*e.g.*, heating at 130–200°).[28,29] Mechanistically, taking into consideration the electronic structure of the open-chain triene **7e**, such an electrocyclic transformation to **7d**, seems feasible.[30]

[28] E. N. Marrell, G. Caple, and B. Schatz, *Tetrahedron Lett.*, 385 (1965).

[29] E. Havinga and J. L. M. A. Schlatmann, *Tetrahedron*, **16**, 146 (1961).

[30] R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 395 (1965).

[31] J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 861.

[32] The formation of **12** is in harmony with the results obtained from the acid-catalyzed condensation of 2-alkoxymethylene-3-alkoxypropionates with ureas: (a) A. Takamizawa and K. Hirai, *Chem. Pharm. Bull.*, **12**, 1418 (1964); (b) A. Takamizawa and K. Hirai, *ibid.*, **12**, 804 (1964).

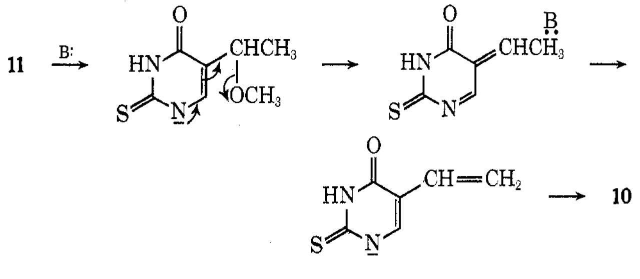
[33] F. Sweet, unpublished results.

amidines,[34–38] the only examples with a urea involve the more nucleophilic *N*-benzyloxyurea.[39]

From the reaction of the acetal **6** and thiourea in sodium methoxide–methanol, the following four products were isolated and characterized: 5-(1-methoxyethyl)-2-thiouracil (**11**), 5-(1-thiocarbamylaminoethyl)-2-thiouracil (**9**), 5-vinyl-2-thiouracil (**10**), and 5-dimethoxymethyl-5,6-dihydro-6-methyl-2-thiouracil (**8**). The substituted 5-alkyl-2-thiouracils **11** and **9** are the major ones. It is thus apparent that **6** in basic media reacts either as an aldehyde–ester giving **9**, **10**, and **11** or as an ether–ester leading to **8**. The synthesis of **11** by this reaction is of particular importance. 5-Hydroxymethyl-2-thiouracil, of which **11** is the next higher homolog, has been prepared by the condensation of formaldehyde with 2-thiouracil;[40,41] however, attempts to form higher homologs by condensation of pyrimidines with aldehydes have had but limited success.[42]

Mechanistic aspects of the complex reaction of **6** with thiourea were investigated. The possibility that **11** could react in a manner analogous to that described for the O-1′ *p*-nitrophenyl ethers or acetates of 5-hydroxymethyluracils[10] (Scheme VI) was considered.

SCHEME VI



However, it was established that the products **9**, **10**, and **11** are not interconvertible under the experimental conditions used. When **11** was refluxed in methanol–sodium methoxide in the presence or absence of thiourea, it was stable, as shown by chromatography over a Dowex-50 (H$^+$) column and by tlc. Similar negative results were obtained under more vigorous conditions with *tert*-butyl alcohol and sodium *tert*-butoxide at reflux or heated at 140°. The 5-vinyl compound **10** is less stable in the methanol–sodium methoxide solvent but still no **9** or **11** could be derived from it. The acetal **6** must therefore be undergoing specific changes, before the several final cyclizations. Despite considerable studies, the mechanism of condensation of 2-dialkoxymethyl-3-alkoxypropionitriles or esters to give pyrimidines remains controversial.[43] We now propose, and present support for, a more comprehensive mechanism (Scheme VII) in which a series of interconvertible intermediates lead to the several pyrimidines obtained.

From the carbanion **6a** (Scheme VII), elimination of a methoxide ion could proceed in either of two ways to give the vinyl ether **6c** or the crotonamide **6b**. Cyclization of **6c** will produce **11**. A similar intramolecular Michael addition will produce **8** from **6b**. Alternatively, **6b** leads to **9** and **10**.

Several additional experiments provide support for these mechanisms. Methyl crotonate (**1**) or methyl 3-methoxybutyrate (**3**) were treated with thiourea in methanol–sodium methoxide, and the product of these reactions proved to be 5,6-dihydro-6-methyl-2-thiouracil (**2**).[45] As the 5,6-dihydro-2-thiouracils can be readily oxidized to the corresponding 2-thiouracils[47] and thence to uracils, the present method provides a synthetic route for the preparation of 6-substituted uracil derivatives from 2,3-unsaturated or 3-alkoxy esters.

The 5,6-dihydro-6-methyl-2-thiouracil (**2**) is unstable in alkaline solution. This was evidenced by rapid loss of uv absorption at 272 nm which was accompanied by the appearance of a new band at 238 nm. Data suggesting that the new absorption band is due to the species $NH_2C(=S)NHCH(CH_3)CH_2COO^-$ are in the Experimental Section. These results are reminiscent of the reported reactivity of 5,6-dihydro-2-thiouracils toward nucleophiles.[48,49] By analogy it is proposed that in alkaline solutions **2** undergoes the addition of OH$^-$ to give first **2a**, which is then cleaved to **2b** (Scheme VIII). Upon neutralization of the latter **2d** results. This sequence is comparable to the $B_{Ac}2$ mechanism of amide hydrolysis.[50] The uv spectral properties and chemical reactivity of the product obtained are in harmony with those expected for **2d**. Although adducts of the **2a** type (neutral form) have been prepared,[49] that structure is excluded by pmr data, which do support structure **2d**.

The susceptibility of 5,6-dihydro-2-thiouracils to base-catalyzed nucleophilic addition both explains the low yield of **8** and provides further support for portions of the mechanism proposed in Scheme VII. The addition of CH_3O^- to the C-4 carbonyl group of **8** followed

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(34) A. Takamizawa, K. Hirai, and T. Ishiba, *Chem. Pharm. Bull.*, **14**, 1450 (1966).

(35) A. Takamizawa, K. Tokuyama, and K. Tori, *Bull. Chem. Soc. Jap.*, **32**, 188 (1959).

(36) A. Takamizawa and K. Hirai, *Chem. Pharm. Bull.*, **12**, 393 (1964).

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

(38) T. Nishino, M. Kiyokawa, Y. Miichi, and K. Tokuyama, *Bull. Chem. Soc. Jap.*, **45**, 1127 (1972).

(39) (a) W. Klötzer, *Monatsh. Chem.*, **95**, 1729 (1964); (b) *ibid.*, **96**, 169 (1965).

(40) M. Calligaris, S. Fabrissin, M. DeNardo, and C. Nisi, *J. Org. Chem.*, **36**, 602 (1971).

(41) L. Monti and C. Pacini, *Gazz. Chim. Ital.*, **78**, 638 (1948).

(42) T. L. V. Ulbricht, *Progr. Nucl. Acid Res. Mol. Biol.*, **4**, 199 (1965).

(43) For example, Takamizawa[44] favors the initial formation of $C_2H_5OCH_2C(CN){=}CHN{=}C(CH_3)NH_2$ from 1-methoxy-1-ethoxypropionitrile and acetamidine, which then undergoes cyclization to the 5-ethoxymethyl-4-amino-2-methylpyrimidine. On the other hand, Nishino and coworkers[34,35] have proposed different mechanisms, arguing against the involvement of the previously described intermediate because of the known inertness of acetals to solvolysis.

(44) A. Takamizawa, K. Tokuyama, and K. Tori, *Bull. Chem. Soc. Jap.*, **32**, 188 (1959).

(45) This represents a facile one-step method for the preparation of 5,6-dihydro-2-thiouracils previously prepared by cyclization of substituted thioureas: V. Skaric, B. Gaspert, I. Jerkunica, and D. Skaric, *Croat. Chem. Acta*, **37**, 199 (1965). In a similar reaction unsaturated ketones have been condensed directly with thiourea under alkaline conditions, but the products were 3,4,5,6-tetrahydropyrimidines.[46]

(46) (a) E. J. Nikawitz, U. S. Patent 3,152,122 (1964); *Chem. Abstr.*, **62**, 1670 (1965). (b) R. Zimmermann, B. Brähler, and H. Hotze, German Patent 1,065,849 (1959); *Chem. Abstr.*, **55**, 8439 (1961).

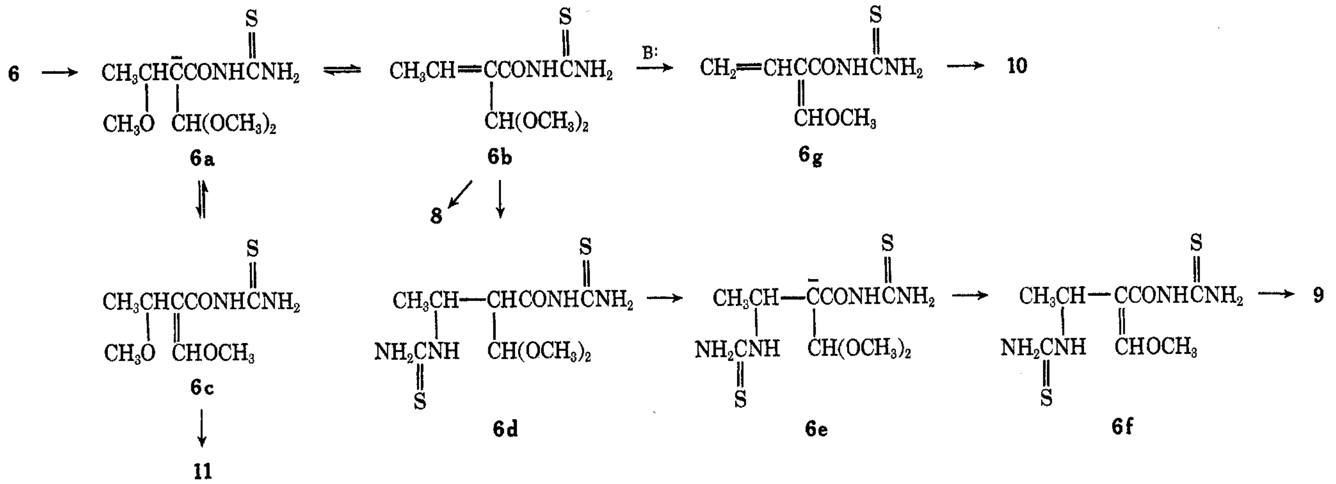
(47) B. R. Baker and J. L. Kelley, *J. Med. Chem.*, **11**, 682 (1968).

(48) V. Skaric and B. Gaspert, *Chem. Commun.*, 550 (1968).

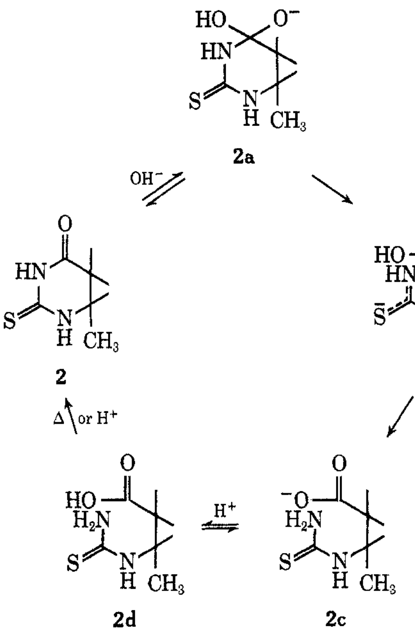
(49) V. Skaric and B. Gaspert, *J. Chem. Soc. C*, 2631 (1969).

(50) (a) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 314. (b) The work of Sander on the alkaline hydrolysis of the 5,6-dihydrouracils also supports our proposal: E. G. Sander, *J. Amer. Chem. Soc.*, **91**, 3629 (1969).

SCHEME VII



SCHEME VIII



by opening of the ring and reaction of the resulting ester with a second molecule of thiourea would give intermediate **6d**. Thus **8** could be a precursor of **9**, although we did not investigate this possibility because of the very small quantity of **8** available. An analogous overall conversion of 5,6-dihydro-2-methyl-5-dimethoxymethyl-4-pyrimidinone to 5-acetiminoaminomethyl-2-methyl-4-pyrimidinone has been reported.[37]

C. Factors Influencing the Condensation of 6 with Ureas.—Control of the course of this condensation reaction could be achieved by treating **6** with thiourea or with urea in *tert*-butyl alcohol–sodium *tert*-butoxide. Under these conditions the only major products were 5-vinyl-2-thiouracil (**10**) or 5-vinyluracil (**14**), in yields of ~30%. This is a much more practical yield for 5-vinyluracil than that obtained *via* 3-(5-uracilyl)-propenoic acid.[2] The thio analog **10** was accompanied by traces of **9** and **11**, and the 5-vinyluracil **14** by a very small amount of a material which appeared, from its uv and pmr porperties, to be 5-(1-hydroxyethyl)uracil. The alternative reaction pathways proposed in Scheme VII are strongly supported by the results with *tert*-butyl alcohol. The stronger basicity of the *tert*-butoxide anion *vs.* that of the methoxide[51,52] should promote the abstraction of the allylic proton from the terminal methyl group of **6b** (Scheme VII). Thus in *tert*-butyl alcohol–sodium *tert*-butoxide the formation of **10** (or **14**) (Scheme II) should be favored, as observed. In this system the concentration of species **6c**, which depends in part upon the reverse addition of CH_3O^- to **6b**, should be greatly lowered and the yield of **11** thus reduced, because the addition of the more bulky *tert*-butoxide anion to **6b** is sterically prevented. Further evidence that **11** arises *via* **6c** was obtained by performing the reaction in the system ethanol–sodium ethoxide, in which case a 1:2 mixture (as evidenced by pmr) of 5-(1-methoxyethyl)-2-thiouracil (**11**) and 5-(1-ethoxyethyl)-2-thiouracil was obtained. This demonstrates the reversibility of the alkoxide addition as described in Scheme VII and the influence of the basicity of the alkoxide on the course of the reaction. It should be emphasized that reversible addition ⇄ elimination of alkoxide anion is a feature common to each of the mechanisms in Schemes III, V, and VII. In two instances another common step is the abstraction of an allylic proton and ultimate cyclization (**7c** → **7d**, Scheme V; **6b** ⇄ **6g** ⇄ **10**, Scheme VII). In each of these cases, regardless of the immediate following step, *i.e.*, intramolecular Michael addition (Scheme V) or "rearrangement" of the incipient carbanion to a more stable resonance form (Scheme VII), the initial proton abstraction results in displacement of a methoxide group.

The condensation reactions of trifunctional molecules such as **6** with ureas are being further explored with respect to their general applicability to the synthesis of 5-substituted pyrimidines of biological importance.

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are uncorrected. Pmr spectra were obtained using a Varian A-60 spectrometer with tetramethylsilane as an internal reference. Uv (H_2O, Table I) and infrared spectra were determined with a Unicam SP800A recording spectrophotometer and a Perkin-Elmer Infracord spectrophotometer, respectively. All solvents were removed in a Buchler flash evaporator under reduced pressure, unless otherwise indicated. All solids were dried under

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(51) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 220.

(52) W. K. McEwen, *J. Amer. Chem. Soc.*, **58**, 1124 (1936).

TABLE I

ULTRAVIOLET ABSORPTION PROPERTIES

Compd	Charge	λ_{max}, nm ($\epsilon \times 10^{-3}$)	λ_{min}, nm ($\epsilon \times 10^{-3}$)
2	0	271 (13.8)	246 (3.5)
		228 (9.5)	
12	0	284 (9.3)	243 (1.4)
8	0	275 (14.7)	248 (4.2)
		234 (8.6)	
11		sh 285 (15.1)	240 (3.2)
		274 (15.4)	
		214 (13.9)	
	−1	315 (9.1)	289 (5.7)
		259.5 (11.9)	243.5 (9.0)
		234 (10.4)	219 (8.5)
		209 (11.2)	
	−2	292 (9.1)	279 (8.2)
		260 (12.2)	244 (9.7)
9	0	sh 294 (15.2)	254 (9.9)
		276 (16.8)	230 (13.1)
		238 (13.5)	

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 (0.125 in. i.d. × 100 in. l.) packed with 20% silicon SP-30 on 30/70 Aeropack 30.

Methyl 3-Methoxybutyrate (3).—A solution of 1 g of Na in 40 ml of CH_3OH was added dropwise and with stirring to 100 g (1 mol) of methyl crotonate containing 5 g of *N*-phenyl-2-naphthylamine. The addition was often followed by a brief exothermic reaction and occasional cooling was needed to maintain the temperature at <50°. After overnight stirring the mixture was acidified with 3 ml of glacial acetic acid and submitted to exhaustive distillation under vacuum. An optimum rate of distillation was obtained by slowly raising the temperature of the heating bath from 50 to 90° while gradually reducing the pressure to ~9 mm. The crude product, which contained ~20–25% of starting material, was fractionated in a stainless steel spinning-band column (Nester–Faust) to give 96.8 g (73.5%) of methyl 3-methoxybutyrate: bp 71–72° (41–42 × 10^{-3} mm); ir $\lambda_{max}^{film\ liq}$ 2820 cm^{-1} (symmetrical stretching of methoxyl CH_3[53]) pmr ($CDCl_3$) τ 8.82 (d, 3, J = 6 Hz, CH_3CH–), 6.7 (s, 3, $CHOCH_3$), 6.33 (s, 3, $COOCH_3$). The methylene and methine protons produced a typical ABX spectrum. The AB part (eight lines, 2, J_{AB} = 15 Hz, –CH_2–) centered at τ 7.55 and the X part (multiplet, 1, –CH–) centered at τ 6.22.

Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.36; H, 9.20.

Methyl 2-Dimethoxymethyl-3-methoxybutyrate (6).—To a mixture of benzene (25 ml) and sodium (4.6 g, 0.2 mol, cut in small cubes) cooled to 0° in an ice bath, 4.8 g (0.15 mol) of methanol was added dropwise. After stirring for 1 hr at 0°, a mixture of 13.3 g (0.1 mol) of methyl 3-methoxybutyrate and 12 g (0.2 mol) of methyl formate was also added dropwise over 30 min. The temperature of the cooling bath was slowly raised to 8°, where it was maintained for 5 hr and then allowed to reach ambient temperature. After stirring for 72 hr, the reaction mixture (a yellow-orange paste) was again cooled to 0°, 25.2 g (0.2 mol) of dimethyl sulfate was added dropwise over a 3-hr period, and the mixture was then heated at 50° for an additional 3 hr. After cooling the mixture was filtered and the salts were repeatedly washed with benzene (or ether). The combined filtrates (~250 ml) were extracted once with 5% $NaHCO_3$ solution, then with water, and dried over Na_2SO_4. After removal of the solvents below 30°, the residue was distilled in a short path apparatus under high vacuum at a bath temperature of 50–55°. The fraction boiling at 40–44° (5–10 × 10^{-3} mm)[54] was collected. The yield of the product varied between 6.8 and 8 g (~36%). A considerable amount of the polymerized residue remained in the boiling flask: ir $\lambda_{max}^{film\ liq}$ 2820 cm^{-1} (strong, –OCH_3[53]); pmr ($CDCl_3$) τ 8.72 (d, 3, J = 6 Hz, CH_3CH–), 6.23 (s, 3, –$COOCH_3$), 6.58 (s, 3, –$CHOCH_3$); signals due to the acetal methoxy groups appear at τ 6.59 and 6.63.

Anal. Calcd for $C_9H_{18}O_5$: C, 52.41; H, 8.80. Found: C, 52.06; H, 8.70.

Reaction of 6 with 2,4-Dinitrophenylhydrazine. Preparation of Pyrazoline Derivatives (13).—An ethanolic solution of **6** was slowly added to a cold solution of 2,4-dinitrophenylhydrazine in 3 *N* HCl. After the solution had stood at room temperature for 24 hr, the yellow precipitated product was collected, repeatedly washed on the filter with 3 *N* HCl (until the washings were colorless) and then water, and dried; it shrinks near 170° and melts to a deep red liquid at 187–188°.

Anal. Calcd for $C_{12}H_{12}N_4O_6$: C, 46.76; H, 3.92; N, 18.17. Found: C, 46.80; H, 3.86; N, 18.15.

The pmr spectrum of the material shows the absence of any ether OCH_3 and the presence of an ester OCH_3. Interestingly, a solution of the material in $CDCl_3$ produces one set of signals, while the spectrum of a solution in DMF-d_6 clearly shows the presence of two sets of similar signals. In the second set the signals of –$COOCH_3$ and –$NCHCH_3$ groups appear, respectively, 4 Hz downfield and 15 Hz upfield from the corresponding ones of the first set. When the solvent (DMF-d_6) was removed (lyophilization) and the pmr spectrum of the residue in CDCl was examined, the signals of the second set were shifted and tended to overlap with the corresponding ones of the first, while the ratio between similar signals of each set remained the same.

Dimethyl (2-Ethylidene-3-methyl)glutarate (5) and Dimethyl 4-Methylisophthalate (7).—The general procedure as described for **6** was used, with the following modifications. Ether (75 ml) and 9.6 g of a 56.5% suspension of NaH were used instead of benzene and sodium. Instead of distilling the crude residue, it was chromatographed on a silica gel G column (100 g) and eluted with 3 l. of petroleum ether (bp 30–60°). Fractions containing the products (as shown by vpc) were pooled, the solvent was removed, and the residue was rechromatographed in a similar manner. Homogeneous fractions were again combined and the solvent was removed, leaving a viscous residue. The residue was chilled for 24 hr, during which time crystals separated. The supernatant was removed with a capillary pipet and dissolved in a small amount of petroleum ether, and the solution was again chilled to yield a second crop of crystals. This procedure was repeated until no more crystalline product could be obtained. The combined crops of crystals and the final supernatant liquid were treated as follows.

Dimethyl 4-Methylisophthalate (7).—This was recrystallized from ether–petroleum ether to give white needles (200 mg): mp 76–77° (subsequent vacuum sublimation did not raise the melting point); pmr ($CDCl_3$) τ 7.35 (s, 3, –CH_3), 6.1 [s, 6, $(COOCH_3)_2$], 2.69 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 1.95 (pair of d, 1, $J_{6,5}$ = 8 Hz, $J_{6,2}$ = 2 Hz, C_6 H), 1.48 (d, 1, $J_{2,6}$ = 2 Hz, C_2 H).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.80. Found: C, 63.19; H, 5.74.

Dimethyl (2-Ethylidene-3-methyl)glutarate (5).—The supernatant liquid previously mentioned was distilled and a main fraction boiling at 48–49° (85 × 10^{-3} mm) was collected. Pmr ($CDCl_3$) indicated that two isomers were present in an approximate ratio 5 or 6:1. The major isomer produced absorptions at τ 8.81 (d, 3, J = 7 Hz, $CH_3CH<$), 8.16 (d, 3, J = 7 Hz, $CH_3CH=$), 3.2 (q, 1, J = 7 Hz, $CH_3CH=C$). The minor isomer displayed corresponding signals at approximately τ 8.9, 8.1, and 4.0.[55]

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.00; H, 8.10.

An authentic sample of dimethyl 4-methylphthalate was prepared by a modification of a procedure by Bentley and Perkin.[24] A solution of 632 mg (4 mmol) of $KMnO_4$ in 20 ml of H_2O was added to a solution containing 300 mg (2 mmol) of 2,5-dimethylbenzoic acid and 210 mg (2 mmol) of Na_2CO_3 in 5 ml of water, and the resulting mixture was stirred at 60° for 5 hr, then allowed to stand at room temperature overnight. After the mixture was briefly heated on a steam bath, the brown precipitate was removed by filtration and washed several times with hot water. The combined filtrates were acidified to pH <2 with concentrated HCl and chilled. The precipitated crude product, which was

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[53] K. Nakanishi, "Infrared Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 36.

[54] The boiling point varies slightly depending upon the rate of distillation.

[55] These values are in agreement with those reported for the cis and trans isomers of dimethyl 2-methylpent-3-ene-1,3-dicarboxylate (*i.e.*, **5**): T. Saegusa, Y. Ito, S. Kobayashi, and S. Tomita, *Chem. Commun.*, 273 (1968); M. Ikeda, T. Hirano, and T. Tsuruta, *Tetrahedron Lett.*, 4477 (1972).

contaminated with starting material, was collected and chromatographed on a Sephadex G-10 column (50 cm) eluted with 0.05 M NaH_2PO_4 buffer at pH 7. The product-containing fractions were pooled and evaporated to ~10 ml. The concentrate was acidified to pH <2 with concentrated HCl and extracted continuously with ether. The ether extract was evaporated to a few milliliters and filtered, an equal volume of benzene was added, and the solvents were boiled until the solid product started separating. After cooling, the precipitated product was collected, washed with a small volume of benzene, and dried. The yield of 4-methylisophthalic acid was 225 mg (62%): pmr ($CDCl_3$) τ 7.38 (s, 3, CH_3–), 2.56 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 1.97 (pair of d, 1, $J_{6,5}$ = 8, $J_{6,2}$ = 2 Hz, C_6 H), 1.54 (d, 1, $J_{2,6}$ = 2 Hz, C_2 H), −2.40 [broad s, 2, (–COOH)$_2$].

A solution of 180 mg (1 mmol) of the 4-methylisophthalic acid in ~40 ml of CH_3OH was heated under reflux in the presence of 1 ml of Dowex-50 (20–50 mesh, H^+) for 48 hr. The resin was removed by filtration and washed well with methanol, and the combined filtrates were concentrated to dryness. The residue was dissolved in 3 ml of ether, and the solution was filtered. An equal volume of petroleum ether was added to the filtrate. Then the total volume was reduced to ~3 ml on a steam bath and adjusted again to ~6 ml with petroleum ether. After cooling, the precipitated product was collected, washed with a small volume of petroleum ether, and dried. The yield of the dimethyl 4-isophthalate was 155 mg (74.5%) and it melted at 75.5–76.5°. The ir (KBr) and pmr spectra of this product were identical with those of the by-product obtained from the formylation reaction of methyl 3-methoxybutyrate previously described.

5,6-Dihydro-6-methyl-2-thiouracil (2).—To a solution of 920 mg (40 mmol) of Na in ~30 ml of methanol was added 1.67 g (22 mmol) of thiourea, and then 2.64 g (20 mmol) of methyl 3-methoxybutyrate or 2.00 g (20 mmol) of methyl crotonate. The mixture was heated under reflux for 72 hr, the solvent was removed under vacuum, and a solution of 3 ml of glacial acetic acid in 40 ml of cold water was added to the residue. After standing at 0–4° for a few hours the precipitated product was collected, washed with cold water, and dried. The methoxy butyrate gave a higher yield (1.04 g, 36%) than the crotonate (815 mg, 28%). The crude product was either recrystallized directly from methanol or extracted continuously for several days in a small Soxlet extractor with ether (in which it is sparingly soluble). The pure product melts at 220–222°: pmr (pyridine-d_5) τ 8.81 (d, 3, J = 6.5 Hz, $-CH_3$); the C_5 and C_6 proton signals comprise an ABX system; the signal of the AB part is centered at τ 7.49 (seven lines, J_{AB} = 16 Hz); a poorly resolved multiplet, the X part, is centered at approximately τ 6.25.

Anal. Calcd for $C_5H_8N_2OS$: N, 19.43; S, 22.23. Found: N, 19.47; S, 22.25.

The uv absorption properties of 2 are interesting. At pH 7, 5,6-dihydro-6-methyluracil shows only a shoulder at ~210 nm,[56] and thiourea alone exhibits an absorption maximum at 238 nm. However, 5,6-dihydro-6-methyl-2-thiouracil (2) at neutral pH shows two distinct maxima at 271 nm (ϵ 13.8 × 10^3) and 228 (9.5 × 10^3). The absorption at a higher wavelength of 2 is certainly not due to the presence of the monoanion, since its spectrum is essentially unchanged in 20% sulfuric acid.[57] When 2 is treated with aqueous alkali, it is rapidly converted to a material with the uv absorption spectrum of thiourea (*i.e.*, showing λ_{max} at 238 nm), and that transition can be followed spectrophotometrically. Reversal to the original uv absorption was not observed upon acidification of a dilute aqueous solution of the product even after prolonged standing. When this product was charged on a Dowex-50 (H^+) column that was washed with water after an incubation period of 24 hr, the only uv-absorbing fraction obtained exhibited the uv spectrum of the starting material 2.[58] The reverse reaction is extremely slow or inhibited in dilute aqueous solution but proceeds on the matrix of the Dowex-50 resin. Repeated attempts to crystallize the product from a variety of solvent systems failed, although, upon attempted sublimation under vacuum at 80°, the viscous material solidified to give 2, and sublimation proceeded very slowly.

5-Carbomethoxy-4-methyl-3,4-dihydropyrimidin-2-one (12).—A solution of the acetal 6 (1.03 g, 5 mmol) and urea (300 mg, 5 mmol) in 25 ml of methanol containing 0.5 ml of concentrated HCl was heated under reflux for 8 hr. The mixture was taken to dryness, the residue was dissolved in a fresh volume of methanol, and the solution was again taken to dryness. This treatment was repeated several times in order to remove most of the HCl. The final residue was charged on a silica gel G column (80 g, 4 × 14 cm) and 1.5 l. of a mixture of C_6H_6–CH_3OH (9:1) was passed through. The fractions obtained (20 ml each) were checked by tlc using the solvent system C_6H_6–CH_3OH (8:2) and those containing the product were pooled, and the mixture was evaporated to a few milliliters. The solution was filtered and the filtrate was taken to dryness. The residue was dissolved in a small volume of benzene containing a few drops of methanol and sufficient solvent was removed on a steam bath to induce separation of a solid. Crystallization was completed in the cold and the product was collected, washed with a small volume of ether, and dried (430 mg, 50.5%): mp 171–172°; pmr (DMSO-d_6) τ 8.8 (d, 3, J = 6 Hz, CH_3CHN–), 6.35 (s, 3, CH_3O–), 5.81 (eight lines, 1, J = 6, $J_{4,3}$ = 3 Hz, CH_3CHN–), 2.89 (d, 1, $J_{6,1}$ = 6 Hz, =CHN–), 1.10 (d, 1, $J_{3,4}$ = 6 Hz, $-NHCHCH_3$). The N^3 H signal is concealed by that of the C_6 proton.

Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.41; H, 5.92; N, 16.46. Found: C, 49.47; H, 5.99; N, 16.43.

Condensation of 6 with Thiourea in Methanol–Sodium Methoxide. Preparation of 5-(1-Methoxyethyl)-2-thiouracil (11), 5-(1-Thiocarbamylaminoethyl)-2-thiouracil (9), 5-Vinyl-2-thiouracil (10), and 5-Dimethoxymethyl-5,6-dihydro-6-methyl-2-thiouracil (8).—To a solution of 460 mg (20 mmol) of Na in ~15 ml of methanol was added 836 mg (11 mmol) of thiourea followed by 2.06 g (10 mmol) of the acetal 6. The mixture was heated under reflux for 72 hr, then was taken to dryness, and the residue was dissolved in a small volume of cold water. The resulting solution was passed through a column (i.d. 1 cm) of Amberlite IRC-50 (H^+), 20–50 mesh, 20 ml. The column was heated to 40–50° while the resin was washed with water (3 l.) until the eluate showed negligible uv absorption. The combined eluates were taken to dryness and the residue was washed once with a small volume of benzene, which was discarded. The crude product was applied on a silica gel G column (80 g, 4 × 15 cm), which was developed first with 2 l. of C_6H_6–EtOAc (8:2) and then with C_6H_6–EtOAc–CH_3OH (8:1.5:0.5), and finally with 1 l. of C_6H_6–CH_3OH (8:2). Each of the 20-ml fractions collected was analyzed by tlc (C_6H_6–CH_3OH, 8:2).[59] The products emerge in the order 10, 8, 11, and 9.

5-Vinyl-2-thiouracil (10).—Fractions 22–31 were pooled, the solvent was removed, and the residue was triturated with a small volume of benzene. The remaining solid was dissolved in methanol, and the solution was treated with Norit and then filtered through a pad of Celite. The volume of the filtrate was reduced by boiling on a steam bath and then a few milliliters of benzene was added. This was repeated several times until crystals began to form. The mixture was cooled and the product was collected, washed once with benzene, and dried (65 mg). It slowly decomposed above 170° without melting. The pmr (DMSO-d_6) spectrum of the side chain showed a pattern similar to that of 5-vinyluracil:[2] for H_A, τ 4.8 (pair of d, J_{AB} = 3.5, J_{AC} = 10 Hz); H_B, 3.98 (pair of d, J_{BC} = 17, J_{BA} = 3.5 Hz); H_C, 3.52 (pair of d, J_{CB} = 17, J_{CA} = 10 Hz).

Anal. Calcd for $C_6H_6N_2OS$: N, 18.17; S, 20.79. Found: N, 18.13; S, 20.78.

5,6-Dihydro-5-dimethoxymethyl-6-methyl-2-thiouracil (8).—Fractions 32–44 were combined, the solvent was removed under vacuum, and the solid residue was recrystallized from methanol (after treatment with Norit) to give 75 mg of a product with mp 208–210°: pmr (DMSO-d_6) τ 8.92 (d, 3, J = 6.5 Hz, CH_3CH–), 7.4 (multiplet, 1, C_5 H), 6.78 [s, 6, $(-OCH_3)_2$], 6.47 [multiplet, 1, $-CH(OCH_3)_2$], 5.5 (d, 1, J = 6.5 Hz, CH_3CHN–).

Anal. Calcd for $C_8H_{14}N_2O_3S$: N, 12.83; S, 14.69. Found: N, 12.83; S, 14.71.

5-(1-Methoxyethyl)-2-thiouracil (11).—Fractions 51–85 were combined and then taken to dryness. The residue was triturated with a small volume of benzene, and the supernatant was discarded. The remaining solid (440 mg) was dissolved in benzene containing sufficient methanol (several drops) to bring about

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(56) For comparison 6-methyluracil shows λ_{max} 260 nm (ϵ 9.5 × 10^3) and λ_{min} 230 (1.8 × 10^3).

(57) H_0 = −1.06. C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.*, **91**, 6654 (1969).

(58) The crude mixture can be resolved readily on a silica gel G column which is eluted with the system acetone–water (95:5), or on a Sephadex G-10 column with 0.025 M NaH_2PO_4 buffer at pH 7.

(59) If the solvents were allowed to evaporate slowly over several days until the volume of the fractions was reduced by one half, the products crystallized and the determination of the range for each component by tlc was facilitated.

solution. The solvent was evaporated on a steam bath until the solution was turbid. After chilling, the deposited crystals were collected and dried. The product melted at 168–169°: pmr (DMSO-d_6) τ 8.75 (d, 3, J = 6.5 Hz, -CHC**H**$_3$), 6.82 (s, 3, -OCH$_3$), 5.8 (pair of q, 1, $J_{1',2'}$ = 6.5 Hz, allylic coupling $J_{1',6}$ = 1 Hz), 2.85 (d, 1, $J_{6,1'}$ = 1 Hz); pK_a's 7.80 ± 0.04 and 13.0 ± 0.2.[60]

Anal. Calcd for $C_7H_{10}N_2O_2S$: N, 15.04; S, 17.22. Found: N, 14.96; S, 17.27.

5-(1-Thiocarbamylaminoethyl)-2-thiouracil (**9**).—Fractions 117–128 were allowed individually to evaporate slowly to about 5 ml (25% of the original volume), when rosettes of crystals deposited. In the last fractions the rosettes were mixed with some amorphous solid. Each of the latter fractions was briefly mixed with a Vortex Mixer, and the turbid solvent was removed with a pipet. The isolated rosettes were collected and then added to the combined total contents of the remaining fractions. The resulting mixture was dried, the residue was dissolved in hot methanol, and the solution was filtered through a thin pad of Norit deposited on Celite. The clear filtrate was evaporated under vacuum to a few milliliters and enough benzene was added to induce turbidity. The resulting mixture was allowed to stand at room temperature in an open flask which permitted slow evaporation of the solvent. After 3 days a crystalline material had deposited. A few drops of benzene were added, causing the supernatant to become turbid. After standing overnight the deposited crystals were collected, washed with benzene, and dried. The yield of the product was 400 mg, and it melted at 202–203°: pmr (DMSO-d_6) τ 8.7 (d, 3, J = 7 Hz, -CHCH$_3$), 5.05 (multiplet, 1, -NCHCH$_3$), 2.92 (s, 2, -NH$_2$), 2.85 [s, 1, -NHC(=S)-NH$_2$], 2.25 (d, 1, $J_{6,1}$ = 8 Hz).

Anal. Calcd for $C_7H_{10}N_4OS_2$: N, 24.33; S, 27.84. Found: N, 24.28; S, 27.82.

The combined yield for products **10**, **8**, **11**, and **9** was 54%.

5-[1-(Methylthio)carbamylimino)ethyl]-2-methylthiouracil (**15**).—The pyrimidine **9** (230 mg, 1 mmol) was dissolved in 4 ml of water containing 2.2 mmol of NaOH, 312.5 mg (2.2 mmol) of CH$_3$I was added, and the mixture was stirred at room temperature for several days. The white precipitate was collected, washed with cold water, and dried. It weighed 200 mg (77%) and after recrystallization from methanol it melted at 186–188°. Pmr (DMSO-d_6) indicates the presence of both cis and trans isomers. For the predominant one the nmr values (DMSO-d_6) are 8.57 (d, 3, J = 7 Hz, -CHCH$_3$), 7.66 and 7.52 (CH$_3$S- groups), 5.22 (q, 1, J = 7 Hz, -NCHCH$_3$), 2.3 (s, C$_6$ H).

Anal. Calcd for $C_9H_{14}N_4OS_2$: N, 21.68; S, 24.82. Found: N, 21.73; S, 24.79.

Condensation of 6 with Urea (or Thiourea) in *tert*-Butyl Alcohol–Sodium *tert*-Butoxide. 5-Vinyluracil (**14**).—To ~200 ml of *tert*-butyl alcohol containing 1.38 g (60 mmol) of Na was added 3.6 g (60 mmol) of urea, the mixture was heated to boiling, and 6.18 g (30 mmol) of the acetal **6** was added. Heating under reflux with stirring continued for 48 hr, the solvent was then removed, the residue was dissolved in cold water, and the solution was neutralized batchwise with 50 ml of Amberlite IRC-50 (H$^+$). The supernatant was decanted and saved and the exchange resin was washed in a column with warm (60°) water until the uv absorption of the washings was negligible (~3 l.). The combined washings were filtered and the filtrate was evaporated to ~100 ml and then chilled. The separated solid was collected, washed once with water, and dried (825 mg). An additional crop (380 mg) was obtained from the mother liquors. The total yield averaged ~29%. The crude product was purified on a silica gel G column (100 g, 4 × 18 cm) by elution first with 1.5 l. of C$_6$H$_6$–EtOAc (8:2), then with 2 l. of C$_6$H$_6$–CH$_3$OH (9:1), followed by 1 l. of C$_6$H$_6$–CH$_3$OH (8:2). The fractions containing the product were pooled, the solvent was removed, and the residue was recrystallized from methanol. The pure product was collected, washed once with ether, and then dried. Its melting point and uv absorption properties were identical with those reported.[2]

Alternatively, the crude product could be purified on a Dowex-50 (H$^+$) column which was washed with water. The elution had to be completed within the same day because 5-vinyluracil is unstable on the Dowex-50 resin. A small quantity of a second product was isolated from such a Dowex-50 column and the pmr and uv spectra suggested it to be 5-(1-hydroxyethyl)uracil.

5-Vinyl-2-thiouracil (**10**).—A mixture of 80 ml of *tert*-butyl alcohol containing 460 mg (20 mmol) of Na and 1.52 g (20 mmol) of thiourea was heated to boiling, then 2.06 g (10 mmol) of the acetal **6** was added, and boiling with stirring was continued for 72 hr. After the solvent had been removed, the residue was dissolved in water and the solution was passed through a column of Amberlite IRC-50 (H$^+$, 20 ml) which was exhaustively washed well with water (3 l.). The combined eluates were evaporated to dryness and the residue was dissolved in methanol. The solvent was again removed and the residue was applied to a silica gel G column (100 g, 4 × 14 cm) which was developed with 3 l. of C$_6$H$_6$–EtOAc (8:2). The fractions containing the product were pooled and the solvent was removed. The residue was first triturated with a small volume of benzene, and recrystallized as described previously for the same compound. The yield was 270 mg (17.5%).

Registry No.—**1**, 18707-60-3; **2**, 6300-93-2; **3**, 3136-17-2; (*E*)-**5**, 16657-04-8; (*Z*)-**5**, 16657-03-7; **6**, 39541-78-1; **7**, 23038-61-1; **7** free acid, 3347-99-7; **8**, 39550-26-0; **9**, 39550-27-1; **10**, 39550-28-2; **11**, 39550-29-3; **12**, 39541-81-6; **13**, 39526-93-7; **14**, 37107-81-6; (*E*)-**15**, 39541-83-8; (*Z*)-**15**, 39541-84-9; methanol, 67-56-1; methyl formate, 107-31-3; 2,4-dinitrophenylhydrazine, 119-26-6; thiourea, 62-56-6; urea, 57-13-6; 5-(1-hydroxyethyl)uracil, 39541-85-0.

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(60) The pK_a's were determined by methods described spectrophotometrically in 0.01 M buffers with a Beckman DU spectrophotometer.[61]

(61) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962, p 69.