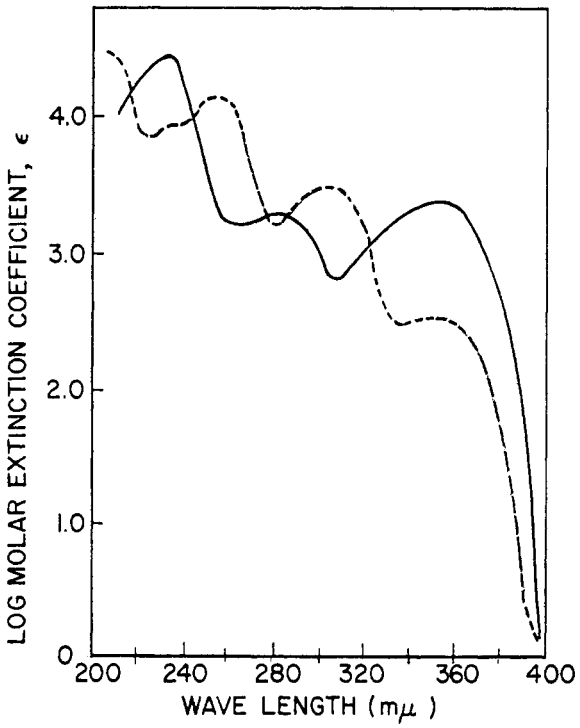


Fig. 1. Ultraviolet absorption spectra: ——— 1,2-dimethyl-1,2-dihydroquinoline. - - - - - - - - 1,2-dimethyl-1,2,3,4-tetrahydroquinoline. In 95% ethanol.

The ultraviolet absorption spectra of carefully weighed amounts of pure 1,2-dimethyl-1,2-dihydroquinoline and 1,2-dimethyl-1,2,3,4-tetrahydroquinoline in 95% ethanol were taken at several different concentrations (Fig. 1). A plot of optical density versus concentration at several different wave lengths gave straight lines showing that these solutions obeyed Beer's law.

The ultraviolet spectrum of the product of the reduction of 1,2-dimethylquinolinium bromide by lithium aluminum hydride in refluxing ether was determined and gave the following data.

	λ(Å)	D	E	E′	l(cm.)
λ_1	2555	0.20	2.45×10^3	1.17×10^4	1.003
λ_2	2315	0.94	3.74×10^4	6.96×10^3	1.003

where D is the optical density in 95% ethanol, E, and E′ are the molar extinction coefficients of similar solutions of pure 1,2-dimethyl-1,2-dihydroquinoline and pure 1,2-dimethyl-1,2,3,4-tetrahydroquinoline respectively and l is the thickness in cm. of the absorbing solution.

The concentration of the dihydroquinoline, C, was then calculated by substitution in the equation

$$C = \frac{D_{\lambda_2}E'_{\lambda_1} - D_{\lambda_1}E'_{\lambda_2}}{l(E_{\lambda_2}E'_{\lambda_1} - E'_{\lambda_2}E_{\lambda_1})} = 2.28 \times 10^{-5} \text{ moles/l.}$$

and the concentration of the tetrahydroquinoline by substitution in the equation

$$C' = \frac{D_{\lambda_2}E_{\lambda_1} - D_{\lambda_1}E_{\lambda_2}}{l(E_{\lambda_1}E'_{\lambda_2} - E_{\lambda_2}E'_{\lambda_1})} = 1.26 \times 10^{-5} \text{ moles/l.}$$

The mole per cent of dihydroquinoline in the mixture is then 64.4 and that of the tetrahydroquinoline is 35.6.

As a check on the accuracy of the method a synthetic mixture containing 75.5 mole per cent of the pure dihydroquinoline was examined. Using values of λ_1 = 2555 Å and λ_2 = 2315 Å the mole per cent of the two found in the mixture was 71.6 and 28.4 respectively. With λ_1 = 3505 Å and λ_2 = 3060 Å the values found were 71.8 and 28.2. The per cent error in this method based on Beer's law is thus 15.5 for the tetrahydro compound and 5.0 for the dihydro compound. Despite these relatively large errors, the data given in Table I are well within these limits and are therefore considered significant.

ANN ARBOR, MICH.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DEPARTMENT, CENTRAL RESEARCH DIVISION, AMERICAN CYANAMID CO.]

Pyrimidine Syntheses. I. Reaction of *s*-Triazine with Imidates and Amidines Containing an Acidic α-Methylene Group

FRED C. SCHAEFER, K. ROBERT HUFFMAN, AND GRACE A. PETERS

Received August 15, 1961

Reactions of *s*-triazine with amidines, amidine salts, and imidates having acidic α-methylene groups produce 5-substituted 4-aminopyrimidines in good yield. The corresponding imidate hydrochlorides and thioimidate hydrochlorides give 4-alkoxy- and 4-alkylthiopyrimidines, respectively.

Study of the reactions of *s*-triazine (1) with nucleophilic reagents has been a profitable approach to new synthetic uses for this versatile substance. Grundmann and his associates, for example, have reported several examples of reactions of I with amino compounds leading to substituted formamidines and heterocyclic compounds.[1] From our own work, reactions of I with amidines[2] and imidates[3] which produce substituted *s*-triazines have been reported. This and the following paper[4] deal with

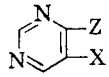
(1) (a) Ch. Grundmann and A. Kreutzberger, *J. Am. Chem. Soc.*, **77**, 6559 (1955). (b) Ch. Grundmann and R. Rätz, *Chem. Ber.*, **91**, 1766 (1958). (c) Ch. Grundmann and R. Rätz, *J. Org. Chem.*, **21**, 1037 (1956).

(2) F. C. Schaefer and G. A. Peters, *J. Am. Chem. Soc.*, **81**, 1470 (1959).

(3) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 2784 (1961).

(4) K. R. Huffman, F. C. Schaefer, and G. A. Peters, *J. Org. Chem.*, **27**, 551 (1962).

TABLE I

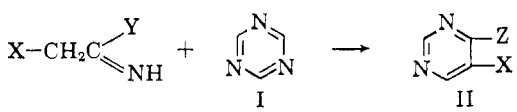
PREPARATION OF PYRIMIDINES,  , FROM *s*-TRIAZINE

Reagent		Reaction Conditions		Product			
Structure	Moles/ mole I	Time, hr.	Temp.	X	Z	Yield, %[a]	M.P.
$NH_2COCH_2C(NH)NH_2 \cdot HCl$[b]	1.0	1.0[c]	75	$CONH_2$	NH_2	72	257–258[d]
$NH_2COCH_2C(NH)NH_2$[e]	1.5	14	25–65	$CONH_2$	NH_2	53	257–258
$C_6H_5CH_2C(NH)NH_2$[e]	1.0	3[f]	25	C_6H_5	NH_2	75	152–154[g,h]
$C_2H_5OCOCH_2C(NH)NH_2 \cdot HCl$[b]	1.0	1.5[i]	80	$COOC_2H_5$	NH_2	85	102–104
$C_2H_5OCOCH_2C(NH)OC_2H_5$[j]	1.0[k]	24[l]	48–52	$COOC_2H_5$	NH_2	56	102–104
$NCCH_2C(NH)OC_2H_5$[m]	1.5[k]	0.5	60–80	CN	NH_2	67	250 dec.[n]
$NH_2COCH_2C(NH)OC_2H_5 \cdot HCl$[o]	0.86	2.0[l]	45–50	$CONH_2$	OC_2H_5	51	138–140[p]
$C_2H_5OCOCH_2C(NH)OC_2H_5 \cdot HCl$[q]	1.0	1.5[l]	20–50[r]	$COOC_2H_5$	OC_2H_5	51	25[s]
$C_6H_5COCH_2C(NH)OC_2H_5 \cdot HCl$[t]	1.0	1.5[l]	25–50[r]	COC_6H_5	OC_2H_5	100	67–69
$NCCH_2C(NH)SCH_3 \cdot HCl$	1.0	3.0[l]	20–25[r]	CN	SCH_3	64[u]	94.5–96[v]

[a] Yields are based on the imidate or amidine reagent. [b] Ref. 20. [c] In 1:1 ethanol-acetonitrile. [d] Ref. 10a gives m.p. 254–256°. [e] Prepared from the hydrochloride by reaction with sodium methoxide in methanol. [f] In methanol. [g] Lit.[7] m.p. 153°. [h] No 2-benzyl-*s*-triazine was found. [i] In acetonitrile. [j] A. Weissberger, H. D. Porter, and W. A. Gregory, *J. Am. Chem. Soc.*, 66, 1852 (1944). [k] Ten mole % of acetic acid based on I was used as catalyst. [l] In ethanol. [m] Ref. 12. [n] Recrystallized from ethanol. Lit.[9] m.p. 250°C. [o] Prepared by the Pinner synthesis as illustrated for malononitrile in ref. 12. [p] Recrystallized from ethanol. *Anal.* Calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.32; H, 5.52; N, 24.62. Hydrolysis in 6*N* hydrochloric acid gave 4-hydroxypyrimidine-5-carboxylic acid, m.p. 226–227° dec.[4] [q] Ref. 21. [r] Reaction was initially exothermic. [s] B.p. 82–85° at 0.1 mm. [t] Ref. 22. [u] Crude yield, satisfactory by infrared comparison with pure material but contaminated by a difficultly removable by-product. [v] Recrystallized several times from ethanol. *Anal.* Calcd. for $C_6H_5N_3S$: C, 47.66; H, 3.33; N, 27.79; S, 21.21. Found: C, 47.77; H, 2.97; N, 27.79; S, 21.18.

closely related reactions of acidic α-methylene compounds with I which give pyrimidine derivatives.[4a] In general, our intention in this and earlier work has been to open the *s*-triazine ring by attack of a nucleophilic reagent to give a transient linear adduct. This might then be able to recyclize to a new heterocyclic product or be further degraded to fragments which might lead to interesting compounds. In particular, we hoped to obtain derivatives containing at least two of the original three hydrogen cyanide residues from I or to obtain products not easily prepared from formamidine or formamide.

Reactions of I with amidines or imidates related to malonic acid have in nearly all cases led to the formation of pyrimidine derivatives (II) as indicated by the general equation,



I II

X = COOR, $CONH_2$, CN, COC_6H_5 Z = Y or NH_2
Y = NH_2, OR, SR

The amidine bases or salts and the free imidates give 4-aminopyrimidines (II. Z = NH_2). Usually the imidate hydrochlorides give 4-alkoxypyrimidines (II. Z = OR),[5] and thioimidate hydrochlorides react analogously. Yields are generally good, and the reactions, which proceed under mild conditions, provide an excellent route to the relatively difficulty accessible 2,6-unsubstituted pyrimidines.[6] The reactions investigated are summarized in Table I.

These reactions were carried out under essentially the conditions previously used for the preparation of substituted *s*-triazines. The absence of detectable amounts of triazines in the present work testifies to the very high tendency for α-methylene involvement in the malonic acid derivatives. It has been suggested that ethyl 2-carbethoxyacetimi-

(4) (a) Subsequent to the preparation of this paper A. Kreutzberger and Ch. Grundmann have reported work on reactions of I with certain acidic methylene compounds [*J. Org. Chem.*, 26, 1121 (1961)]. The relation of their work to our own is indicated in ref. 4.

(5) Reaction of I with ethyl 2-cyanoacetimidate hydrochloride to give a pyridine derivative is reported in the following paper.[4]

(6) The convenient synthesis of 4-amino-5-arylpyrimidines from arylacetonitriles and formamide by Davies and Piggott[7] is sharply limited by the strenuous reaction conditions as pointed out by these authors. It was shown to fail with malononitrile and ethyl cyanoacetate. Recent work by Bredereck and his co-workers[8] with formamides has been very fruitful in pyrimidine synthesis, but may be similarly limited. The reaction reported by Baddiley, Lythgoe, and Todd of formamidine with malonitrile to give 4-amino-5-cyanopyrimidine (45%) cannot be used with other active methylene compounds[9] although some modification of the cyano group in this product has been accomplished.[10] Illustrations of the use of the tedious conventional methods for elaboration of 2- or 6-unsubstituted pyrimidine derivatives are given by Kenner and Todd.[11]

(7) W. H. Davies and H. A. Piggott, *J. Chem. Soc.*, 347, 352 (1945).

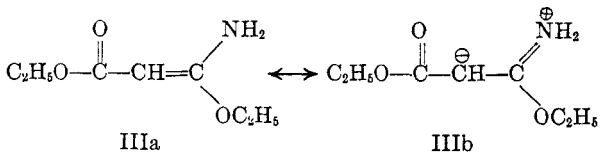
(8) H. Bredereck *et al.*, *Chem. Ber.*, 91, 2830, 2832 (1958); 93, 230 (1960); *Angew. Chem.*, 71, 753 (1959).

(9) J. Baddiley, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 386 (1943).

(10) (a) D. J. Brown and L. N. Short, *J. Chem. Soc.*, 331 (1953). (b) H. G. Mautner, *J. Org. Chem.*, 23, 1450 (1958).

(11) G. W. Kenner and A. R. Todd, in *Heterocyclic Compounds*, Vol. 6, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York (1957).

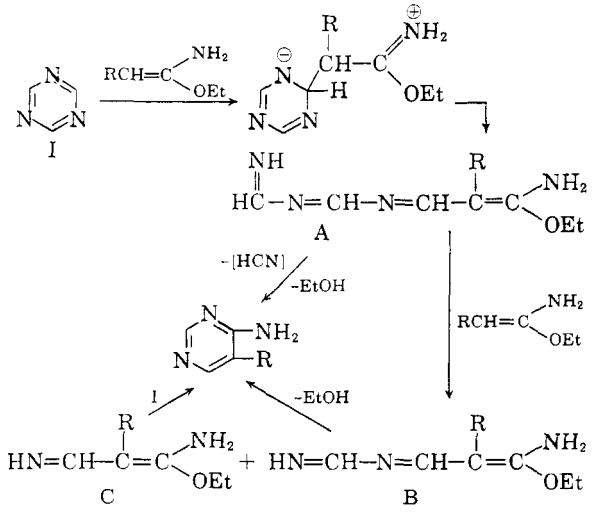
date[11a] and ethyl 2-cyanoacetimidate[12] are best represented by enamine structures such as III.[13]



IIIa IIIb

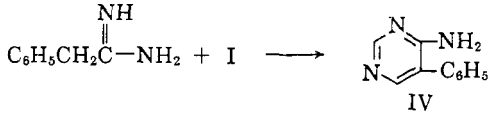
The dipolar canonical form IIIb best expresses the nucleophilic character of the α-carbon atom in these reagents. Analogous structures for the related amidines are equally acceptable. It is thus not unexpected that α-methylene involvement and pyrimidine formation compete with *s*-triazine formation.

Nucleophilic displacement reactions are involved in both the initial ring-opening attack of the reagent on I and the recyclization step. The reactions observed with amidines and their salts and with the imidate hydrochlorides can be formulated showing α-methylene involvement in either step. However, the formation of 4-aminopyrimidines when the imidate bases are used requires that the initial reaction take place at the α-carbon in these cases.[14] It is reasonable to conclude that this is true in all cases. This belief is supported by the reactivity of I toward additional acidic methylene reagents as reported in the following paper.[4] Possible reaction sequences are indicated below for the case of an imidate base; closely related processes can be visualized for the other reactions reported:



The cyclization of the intermediate A to give the aminopyrimidine would be analogous to the formation of a substituted *s*-triazine in a reaction of I with an imidate.[3,15] However, the possibility that A may be degraded by further reaction with the acidic methylene reagent to give B and C has been emphasized by related work.[4] The compound B and probably C would be converted easily to the aminopyrimidine under the reaction conditions.[17] The stoichiometry of the process is thus uncertain, but we have chosen to base our yield calculations (Table I) on the assumption that complete utilization of the *s*-triazine molecule is possible. In those reactions where a hydrochloride was used, essentially quantitative formation of by-product formamidine hydrochloride took place.

The methylene group in 2-phenylacetamidine is less acidic than that in the malonic acid derivatives. With this reagent, we have been able to direct the reaction to give either the pyrimidine or *s*-triazine derivative by controlling the acidity of the system and thus, presumably, the ionization of the methylene group. 2-Phenylacetamidine hydrochloride reacted with I in boiling acetonitrile to give a mixture of mono- and dibenzyl-*s*-triazine.[2] In boiling methanol approximately equal amounts of 2-benzyl-*s*-triazine and 4-amino-5-phenylpyrimidine (IV) were produced. However, free 2-phenylacetamidine reacted with I in methanol to give IV in 75% yield, and none of the isomeric *s*-triazine was found,[18]



IV

In a further effort to obtain an *s*-triazine derivative by suppressing α-methylene involvent, the reaction of 2-carbamylacetamidine hydrochloride

(11a) S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945).

(12) S. M. McElvain and J. P. Schroeder, *J. Am. Chem. Soc.*, **71**, 40 (1949).

(13) We find that the infrared spectrum of ethyl 2-carbethoxyacetimidate has a doublet at 3420 and 3300 cm.$^{-1}$ which may be attributed to the primary amino group in the structure, EtOCOCH=C(NH_2)OEt. Absorption bands at 1663 cm.$^{-1}$ (NH_2) and 1550 cm.$^{-1}$ (C=C) are consistent with this structure. W. J. Middleton and V. A. Engelhardt, *J. Am. Chem. Soc.*, **80**, 2788 (1958), have similarly interpreted the spectrum of $(CN)_2C{=}C(NH_2)OEt$.

(14) The amino group in the product must include the nitrogen atom of the original imidate group, thus excluding initial nucleophilic attack of the imidate structure on the *s*-triazine ring.

(15) It is possible that the hydrogen cyanide is eliminated as *s*-triazine. Easy formation of the latter from various *iminoformyl compounds* has been amply demonstrated.[16]

(16) (a) F. C. Schaefer, I. Hechenbleikner, G. A. Peters, and V. P. Wystrach, *J. Am. Chem. Soc.*, **81**, 1466 (1959). (b) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 2778 (1961).

(17) Although certain 3-aminoacrylonitrile derivatives, $NH_2{-}CH{=}C(R){-}CN$, related to C do not react with I to give aminopyrimidines,[4] the cyclization reaction is probably easier with the imidate or amidine. Compare the work of Z. Földi, *et al.*, *Ber.*, **74**, 1126 (1941); **75**, 755 (1942).

(18) The lower carbanionoid reactivity in the phenylacetonitrile derivatives is also illustrated by the reaction of ethyl 2-phenylacetimidate with I which gave only benzyl-*s*-triazine.[3] This imidate has the "normal" R—C(=NH)OEt structure characterized by a single infrared absorption band at 3320 cm.$^{-1}$ due to the N—H group and a strong band at 1650 cm.$^{-1}$ due to the C=N structure.

with I was carried out in glacial acetic acid. However, only the pyrimidine was obtained.

EXPERIMENTAL[19]

General. The essential features of several examples of the pyrimidine-forming reaction are summarized in Table I. The products often crystallized directly from the reaction mixture in good purity but could be recrystallized readily from water or alcohol. Detailed illustrations are given below.

4-Amino-5-carbethoxypyrimidine. A mixture of 12.2 g. (0.15 mole) of I and 25.1 g. (0.15 mole) of 2-carbethoxyacetamidine hydrochloride[20] in 45 cc. of acetonitrile reacted moderately exothermically when heated to about 75°. It was subsequently heated at reflux for 1.5 hr. The superior solution was then decanted hot from the partly crystallized insoluble formamidine hydrochloride and the residue was re-extracted with fresh boiling acetonitrile. The combined solutions gave on cooling 21.7 g. of the pyrimidine, m.p. 101–102°. (Yield, 85%.) After recrystallization from acetonitrile or benzene the product melted at 102–104°.

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43. Found: C, 50.11; H, 5.53.

Hydrolysis in hot 2*N* sodium hydroxide gave 4-amino-5-carboxypyrimidine, m.p. 274–275°; lit.[10a] m.p. 278–281°.

5-Carbethoxy-4-ethoxypyrimidine. Ethyl 2-carbethoxyacetimidate hydrochloride[21] (7.8 g., 0.040 mole) was shaken with 3.25 g. (0.040 mole) of I in 10 cc. of ethanol until the mildly exothermic reaction subsided. After an additional hour at room temperature, the mixture was filtered to remove 0.75 g. of ammonium chloride. Evaporation of the ethanol and crystallization of the residue from acetonitrile gave 2.5 g. of formamidine hydrochloride, m.p. *ca.* 80°. (75%.) The mother liquor was then distilled yielding 4.0 g. (51%) of the pyrimidine, b.p. 87–92° at 0.2 mm. The product was redistilled for analysis (b.p. 82–85° at 0.1 mm.).

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.18; H, 6.34; N, 14.39.

Hydrolysis of a small sample with 6*N* hydrochloric acid gave *4-hydroxypyrimidine-5-carboxylic acid,* m.p. 228.5–230.5° dec., identical with material previously[4] obtained by hydrolysis of 5-carbethoxy-4-hydroxypyrimidine.

5-Benzoyl-4-ethoxypyrimidine. A mixture of 8.1 g. (0.10 mole) of I and 22.8 g. (0.10 mole) of ethyl benzoylacetimidate hydrochloride[22] was shaken in 20 cc. of ethanol. As the mildly exothermic reaction proceeded a clear solution was obtained which solidified to a yellow cake when cooled. This was broken up and filtered, yielding 22.8 g., m.p. *ca.* 46°; crude yield, 100%. Recrystallization of the crude product from ethanol gave colorless needles, m.p. 67–69°.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 67.96; H, 5.42; N, 12.56.

The identity of this product was further established by hydrolytic degradation. Hydrolysis of 2.5 g. in boiling 10% hydrochloric acid followed by neutralization with sodium carbonate gave 1.3 g. of *5-benzoyl-4-hydroxypyrimidine.* After recrystallization from water this melted at 185–187°.

Anal. Calcd. for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 66.15; H, 4.27; N, 14.10.

Methyl 2-cyanothioacetimidate hydrochloride was prepared by passing methyl mercaptan into a cold solution of equimolar amounts of malononitrile and hydrogen chloride in ether. The product crystallized during the addition and during the following 24-hour storage under refrigeration. The yield was 65%, m.p. 134–137° dec. This compound appeared to be unstable in storage and was used shortly after preparation. Volhard analysis for chloride gave somewhat high results.

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(19) Melting points were determined by the capillary method and are uncorrected. Microanalyses were carried out in these laboratories under the direction of Dr. J. A. Kuck or by the Galbraith Microanalytical Laboratories. Infrared spectra were interpreted by Mr. N. B. Colthup and Dr. J. E. Lancaster.

(20) S. M. McElvain and B. E. Tate, *J. Am. Chem. Soc.*, **73**, 2760 (1951).

(21) A. Pinner, *Ber.*, **28**, 473 (1895).

(22) A. Haller, *Bull. soc. chim.*, [2] **48**, 24 (1887).

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DEPARTMENT, CENTRAL RESEARCH DIVISION, AMERICAN CYANAMID COMPANY]

Reaction of s-Triazine with Acidic α-Methylene Compounds[1]

K. ROBERT HUFFMAN, FRED C. SCHAEFER, AND GRACE A. PETERS

Received August 15, 1961

The condensation of *s*-triazine with a variety of active methylene compounds has been studied. In addition to 4,5-disubstituted pyrimidines, the products of these reactions include pyridines, aminomethylene derivatives, glutaconitrile derivatives, and substituted formamidines, depending upon the nature of the starting material and the experimental conditions. The mechanism of formation of the various products is discussed.

The reaction of *s*-triazine (I) with imidates, amidines, and amidine salts has been shown to be a synthetically useful method for the preparation of monosubstituted *s*-triazines in general[2,3] and also of 4,5-disubstituted pyrimidines in the particular case in which the imidate or amidine contains an acidic α-methylene group.[1] Consideration of the probable mechanism of pyrimidine formation, in which the initial step was assumed to be attack of the methylene group upon an electron deficient carbon atom in the triazine ring,[1] suggested that the amidine or imidate moiety was perhaps not a necessary feature and that other active methylene compounds might react similarly with I.

(1) Pyrimidine Synthesis, Part II. For Paper I, see F. C. Schaefer, K. R. Huffman, and G. A. Peters, *J. Org. Chem.*, **27**, 548 (1962).

(2) F. C. Schaefer and G. A. Peters, *J. Am. Chem. Soc.*, **81**, 1470 (1959).

(3) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 2784 (1961).