precipitate recrystallized from dilute ethanol. This yielded 5.5 g. (49%) of XI, obtained as white crystals.

2,4-Diaminopyrimidine (XLVIII).[21] To a solution of sodium ethylate prepared from 12.7 g. (0.55 mole) sodium in 400 ml. absolute ethanol was added 47.7 g. (0.5 mole) guanidine hydrochloride. After stirring for 10 min., 48.6 g. (0.5 mole) of β-ethoxyacrylonitrile was added. The mixture was heated under reflux for 7 hr., allowed to stand overnight, and filtered from salt. Most of the ethanol was distilled, and the residue was refrigerated overnight. A yellow solid was then filtered off; weight, 31.3 g. (57% crude). This crude 2,4-diaminopyrimidine contained a yellow impurity which was removed by recrystallization from absolute ethanol-ether or -ethyl acetate mixtures. The recrystallized product (XLVIII) was white and melted at 145–146.5°. Ultraviolet absorption maxima ($E \times 10^{-3}$) were as follows: (a) $0.1N$ hydrochloric acid, λ max. = 267 mμ (5.6); λ min. = 253 mμ (4.8). (b) pH 11.0 buffer, λ max. = 282 mμ (7.1); λ min. = 253 mμ (1.7).

Ultraviolet absorption spectra. The ultraviolet absorption spectra of the compounds listed in Tables I–III are shown in Tables IV–VI. Measurements were made on the Beckman model DU spectrophotometer at a concentration of 10 mg. per liter, in $0.1N$ hydrochloric acid and in Sørensen glycine–sodium hydroxide buffer at pH 11.0, except where otherwise stated.

Acknowledgment. The authors are indebted to Eva Hart Gold for technical assistance in the preparation of many of the compounds reported here, and to Samuel W. Blackman, Charles Marr, and Veronica Purdey for the microanalyses.

TUCKAHOE, N.Y.

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(21) E. Büttner, *Ber.*, **36**, 2233 (1903).

[CONTRIBUTION FROM THE STAMFORD LABORATORIES, CENTRAL RESEARCH DIVISION, AMERICAN CYANAMID CO.]

Synthesis of the s-Triazine System. III.[1] Trimerization of Imidates

FRED C. SCHAEFER AND GRACE A. PETERS

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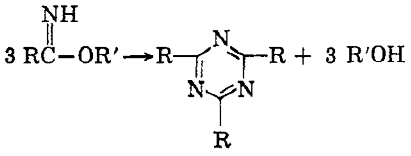
Alkyl imidates, RC(=NH)OR′, derived from a wide variety of nitriles are converted to symmetrically trisubstituted s-triazines by acid catalysts. The reaction provides a useful route to many rare or previously unknown members of this class.

In this paper we report the results of an investigation of the trimerization of imidates to form 2,4,6-trisubstituted s-triazines and the development of this reaction into a useful synthetic method of broad scope.



R
I. C_6H_5
II. CH_3
III. CH_2Cl

The formation of 2,4,6-triphenyl-s-triazine (I) by spontaneous decomposition of alkyl benzimidates has been reported by several authors.[2] In most cases the yields obtained were acknowledged to be negligible or the reaction was exceedingly slow.[3] Wheeler and Johnson[4] became interested in this spontaneous trimerization reaction, and in 1900 they carefully purified and stored samples of methyl p-toluimidate and of methyl, ethyl, and isobutyl benzimidates. These were examined in 1922 by Johnson and Bass[5] who found that in the interim the methyl benzimidate and p-toluimidate had been completely converted to 2,4,6-triaryl-s-triazines and methanol. The other imidates were also partly converted to 2,4,6-triphenyl-s-triazine but both starting material and benzonitrile were present. Our own observation is that the spontaneous formation of 2,4,6-triphenyl-s-triazine from either crude or purified alkyl benzimidates is less than 1% complete in the first year of storage.

The original preparation of s-triazine itself by Nef involved trimerization of ethyl formimidate although this was not appreciated,[6] but until the present work was undertaken no case had been

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

(2)(a) A. Pinner, *Die Imidoäther und ihre Derivate*, Robert Oppenheim, (Gustav Schmidt), Berlin, Germany, 1892, p. 58; (b) G. Glock, *Ber.*, **21**, 2650 (1888); (c) W. Wislicenus and M. Goldschmidt, *Ber.*, **33**, 1467 (1900); (d) H. L. Wheeler, P. T. Walden, and H. F. Metcalf, *Am. Chem. J.*, **20**, 68 (1898).

(3) A. Pinner, *Ber.*, **22**, 1610 (1889), recommended the gradual spontaneous decomposition of crude ethyl benzimidate as the best available method for the preparation of 2,4,6-triphenyl-s-triazine, but he did not indicate the yield to be expected or the time required. A. H. Cook and D. G. Jones, *J. Chem. Soc.*, 278 (1941), were subsequently unable to obtain any s-triazine compound by decomposition of ethyl m- and p-nitrobenzimidates in the manner suggested by Pinner.

(4) H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, **23**, 135 (1900).

(5) T. B. Johnson and L. W. Bass, *J. Am. Chem. Soc.*, **44**, 1341 (1922).

(6) J. U. Nef, *Ann.*, **287**, 337 (1895). The product was erroneously believed to be a dimer of hydrogen cyanide until 1954 when its true nature was discovered by Ch. Grundmann and A. Kreutzberger, *J. Am. Chem. Soc.*, **76**, 632, 5646 (1954).

reported of the analogous trimerization of an aliphatic imidate to gave a 2,4,6-trialkyl-*s*-triazine.[7]

We have now established that a very broad group of 2,4,6-trisubstituted-*s*-triazines can be prepared simply and in good yield by acid catalyzed trimerization of alkyl imidates derived from a wide variety of nitriles. The 2,4,6-trialkyl-*s*-triazines have hitherto been a very difficultly accessible class except for a few special cases. With their new availability many are attractive for exploitation. This process also makes available a number of 2,4,6-triaryl-*s*-triazines which cannot be prepared by earlier methods and offers considerable improvement in yield over known acid or base catalyzed aromatic nitrile trimerizations in general.[8]

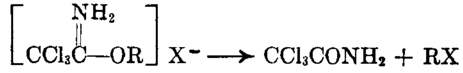
In the course of our work, we have repeatedly observed the gradual formation of 2,4,6-trimethyl-*s*-triazine (II) in various samples of ethyl acetimidate. At room temperature this compound decomposes essentially completely in three to six months depending upon its original purity. Although the principal products are acetonitrile and ethanol,[9] 20 to 30% of the imidate is converted to II. Ethyl propionimidate has appreciably greater stability, but on very long standing it decomposes analogously. The present work was begun as an attempt to develop the minor *s*-triazine-forming reaction into a useful process.

A search for possible catalysts for the conversion of imidates to *s*-triazines was almost immediately successful when it was discovered that ethyl or isopropyl acetimidate reacted exothermically when approximately 10 mole per cent of glacial acetic acid was added, and that in the course of one or two hours an approximately 80% yield of II, was produced. It was easily demonstrated that considerably lower catalyst ratios were also operable, although the reaction was then quite slow, and that 100 mole per cent or more of acetic acid also could be used. The latter was a remarkable result in view of the known behavior of the imidate hydrochlorides which easily produce alkyl chloride and acetamide under very similar conditions. Subsequently, we investigated other possible catalysts for the trimerization of ethyl acetimidate and found that a very large group of acids were satisfactory.

Extension of the trimerization reaction to alkyl benzimidates was not immediately successful. It was apparent that the reaction is much slower than with ethyl acetimidate and that reversion of the imidate to benzonitrile and the alcohol is a serious competing reaction. Methyl benzimidate was considerably more reactive than the ethyl ester, however, and in the presence of 50 mole per cent of acetic acid gave a 67% yield in twenty-four hours and a 79% yield in seventy-two hours. Other experiments demonstrated that the reaction is impeded by diluents. It was also shown that in refluxing methanol the reaction was faster than at room temperature, but the higher temperature promoted decomposition to benzonitrile and benzamide was formed in appreciable quantity.

Methyl and ethyl imidates derived from a wide variety of nitriles have been subjected to the conditions found appropriate for the acetimidates and benzimidates. In many cases good results were obtained; in others higher catalyst concentrations or higher reaction temperatures were more effective. The results are summarized in Table I.

The trimerization of methyl trichloroacetimidate is noteworthy in view of recent work by Cramer, Pawelzik, and Lichtenhaler,[11] who studied the "Pinner cleavage" of trichloroacetimidates with various acids,



$$\left[CCl_3\overset{\overset{+}{NH_2}}{\overset{\|}{C}}{-}OR\right]X^- \longrightarrow CCl_3CONH_2 + RX$$

A remarkable feature of our work has been the absence of significant competiton by this process, although trichloroacetimidates are exceptionally easily decomposed in this way. Cramer *et al.* considered acetic acid to be a rather sluggish reactant but at about 115° obtained an 80% yield of methyl acetate. They apparently did not observe the trimerization which takes place fairly readily at lower temperatures and with much smaller quantities of acetic acid.

The observation that trimerization of ethyl acetimidate proceeded even in the presence of 100 mole per cent of acetic acid suggested that mixing the imidate hydrochloride with an equivalent amount of sodium acetate should bring

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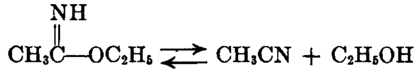
(7) K. Gundermann and H. Rose, *Chem. Ber.*, **92**, 1081 (1959), mention the formation of a small amount of 2,4,6-tris(1-chloro-2-methoxyethyl)-*s*-triazine during distillation of methyl 2-chloro-3-methoxypropionimidate. This can be interpreted as trimerization of the imidate catalyzed by hydrogen chloride which the authors mention as being present during the distillation.

(8) Methods for the preparation of 2,4,6-trisubstituted-*s*-triazines have been reviewed recently by E. M. Smolin and L. Rapoport in *s-Triazines and Derivatives*, Interscience Publishers, Inc., New York 1959, Chapter II. Notable further work which is pertinent has been reported by T. K. Brotherton and J. F. Bunnett, *Chem. & Ind.* (*London*), **1957**, 80; J. J. Ritter and R. D. Anderson, *J. Org. Chem.*, **24**, 208 (1959); and I. S. Bengelsdorf, *J. Am. Chem. Soc.*, **80**, 1442 (1958).

(9) This well known mode of degradation of imidates is probably the result of autocatalysis of the base-catalyzed dissociation:



$$CH_3\overset{\overset{NH}{\|}}{C}{-}OC_2H_5 \rightleftarrows CH_3CN + C_2H_5OH$$

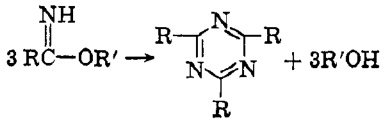
See F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 412 (1961). The equilibrium for this reaction lies far to the right.

(10) R. Wache, *J. prakt. Chem.* [2], **39**, 256 (1889), incorrectly suggested that A. Pinner had obtained 2,4,6-tribenzyl-*s*-triazine by polymerization of benzyl cyanide in the presence of potassium cyanide, *Ber.*, **17**, 2010 (1889). The compound in question, m.p. 221°, remains unidentified.

(11) F. Cramer, K. Pawelzik, and F. W. Lichtenhaler, *Chem. Ber.*, **91**, 1955 (1958).

TABLE I

PREPARATION OF 2,4,6-TRISUBSTITUTED s-TRIAZINES



	Imidate Used				Reaction Conditions			s-Triazine
R	R′	Moles	Catalyst[a] Mole %	Temp.	Time, hours	Yield, %	M.p. or b.p.
C_6H_5[b]	CH_3	0.07	46	25	72	79	M.p. 235–237°[c]
p-$CH_3OC_6H_4$[d]	CH_3	0.04	50	70–90	2	68[e]	M.p. 214–216°[f]
p-$NO_2C_6H_4$[g]	CH_3	0.04	100	70–80	4	54[h]	M.p. >360°[i]
m-$NO_2C_6H_4$[j]	CH_3	0.09[k]	150	70–90	2.5	79	M.p. 348–350°
			(Methanol present)				
m-$NO_2C_6H_4$[l]	C_2H_5	0.05	125	70–80	4	68	
CH_3[k]	C_2H_5	4.0	8	25	16	85–90	B.p. 155°
C_2H_5[m]	C_2H_5	0.075[n]	9	25	24	74[o]	B.p. 128–130°/90 mm.; f.p. 25°[p]
$(CH_3)_2CH$	C_2H_5	0.20[q]	6	25	24[r]	75[o]	B.p. 98°/15 mm.[s]
CH_3CHCl	C_2H_5	0.30[t]	12	50	20[u]	86[o]	B.p. 125°/3 mm.[v]; f.p. 27°
$C_6H_5CH_2$[w]	C_2H_5	0.07	12	25	16[x]	50	B.p. 238–239°/2 mm.[y]
$C_3H_7OCH_2OCH(CH_3)$[j]	CH_3	0.90	30	25	72	59[o]	
				Plus 70	2		B.p. 192–194°/3 mm.[z]
$(CH_3)_2CHOCH_2$[j]	CH_3	0.03	10	25	72	57[o]	B.p. 153–156°/1.5 mm.[aa]
			(90% formic acid)				
CCl_3[bb]	CH_3	0.017	100	25	n	40–60	

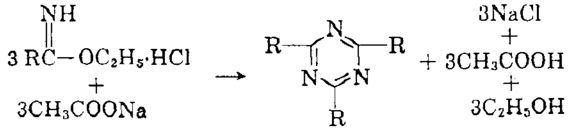
[a] Catalyst is acetic acid except as noted; concentration is in mole per cent, based on imidate used. [b] H. L. Wheeler, *Am. Chem. J.*, **17**, 398 (1895). [c] The product was filtered, washed with ether and water, and air-dried. Reference 2a, p. 58, gives m.p. 231°. [d] Prepared by Pinner's method, reference 2a, m.p. 36°. [e] The product was filtered, washed with methanol and air-dried. [f] F. E. Francis and O. C. M. Davis, *J. Chem. Soc.*, **85**, 259 (1904), give m.p. 217°. [g] Prepared by the method of reference 9 at 25°. Yield, 72%; purity, 87.5%; m.p. 75–80°. [h] The crude yield was 83%. The very difficultly soluble product was washed exhaustively with boiling ethanol, acetone and water to give the analytical sample in 54% yield. No satisfactory solvent was found for recrystallization. [i] *Anal.* Calcd. for $C_{21}H_{12}N_6O_6$: N, 18.92; found: N, 18.90. [j] Prepared by the general method of reference 9. [k] See Experimental Section. [l] W. Lossen and M. Neubert, *Ann.*, **265**, 144 (1891). [m] Reference 2a, p. 28. [n] Purity 72%. [o] The product was recovered by fractional distillation of the reaction mixture. [p] Reference 24 gives b.p. 193–195°, m.p. 29–30°. [q] Prepared as described for ethyl acetimidate. B.p. 116°, purity 93.5%. [r] Infrared comparison indicated that the reaction was less than 25% complete in two hours. [s] *Anal.* Calcd. for $C_{12}H_{21}N_3$: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.51; H, 10.05; N, 20.42; n_D^{25} 1.4563. [t] Prepared as described for ethyl acetimidate. B.p. 72° at 60 mm., purity 92%. [u] Titration indicated 25% reaction in two hours, 45% in five hours, and 75% in twenty hours. [v] *Anal.* Calcd. for $C_9H_{12}N_3Cl_3$: C, 40.24; H, 4.54; N, 15.64. Found: C, 40.05; H, 4.77; N, 15.63. [w] Reference 2a, p. 66. [x] Infrared indicated that the reaction was over in about 1.5 hours. The reaction mixture was diluted with water and the product was extracted with ether and distilled. Some by-product ethyl phenylacetate was obtained. [y] *Anal.* Calcd. for $C_{24}H_{21}N_3$: C, 82.01; H, 6.02; N, 11.96. Found: C, 81.64; H, 6.01; N, 11.69. See Footnote 10. [z] *Anal.* Calcd. for $C_{21}H_{39}N_3O_6$: C, 58.72; H, 9.15; N, 9.78. Found: C, 59.84; H, 9.24; N, 10.04. [aa] *Anal.* Calcd. for $C_{15}H_{27}N_3O_3$: C, 60.58; H, 9.15; N, 14.12. Found: C, 60.55; H, 9.31; N, 14.41; n_D^{26} 1.4609. [bb] F. Cramer, K. Pawelzik, and H. Baldauf, *Chem. Ber.*, **91**, 1049 (1958).

about the reaction. This has been shown to be true; mixing of the two dry solids leads very quickly to an exothermic reaction in which a 50–60% yield of II is formed. This technique is attractive for use with those imidates which are unstable or inconvenient to prepare as the free base. The results obtained with several imidate hydrochlorides are summarized in Table II.

We were particularly interested in applying the imidate trimerization process to the preparation of s-triazine itself. Nef originally obtained this compound by reaction of sodium hydroxide with ethyl formimidate hydrochloride suspended in ether.[6] The yield of s-triazine was only about 10%, however, undoubtedly because of hydrolysis by the water formed in the primary reaction. We have found no way to improve upon Nef's results by using other inorganic bases such as calcium oxide, potassium carbonate or ammonia with various procedures intended to remove the reaction water. However, several tertiary amines have been used with good results. Tri-n-butylamine appears to be most useful for this purpose because it forms a low melting hydrochloride from which s-triazine and by-product ethanol can be distilled easily. s-Triazine can then be crystallized from the alcoholic distillate in 75–80% yield. When triethylamine was used, it was impossible to distill the product efficiently from the bulky residue of solid triethylamine hydrochloride, and various process modifications failed to make the use of this reagent attractive. Sodium ethoxide or sodium acetate gave substantial amounts of s-triazine in the initial reactions with ethyl formimidate hydrochloride, but the product could not be recovered efficiently when these reagents were used.

TABLE II

PREPARATION OF 2,4,6-TRISUBSTITUTED *s*-TRIAZINES

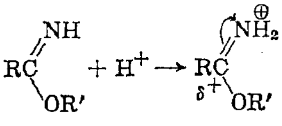


Imidate Hydrochloride		Reaction Conditions[a]		
R	Moles	Solvent	Time, days	Yield, %
CH_3[b]	0.53	None	4[c]	60
C_2H_5[d]	0.21	None	6[c]	47
n-$C_{11}H_{23}$[e]	0.04	5 cc. ethanol	1[c]	30
CH_2Cl[g]	0.50	50 cc. ethanol	1[h]	69[i]
CH_3CH_2Cl[j]	0.50	50 cc. ethanol	1[c]	59
C_2H_5OCO[k]	0.02	1 cc. ethanol	1[h]	67[l]

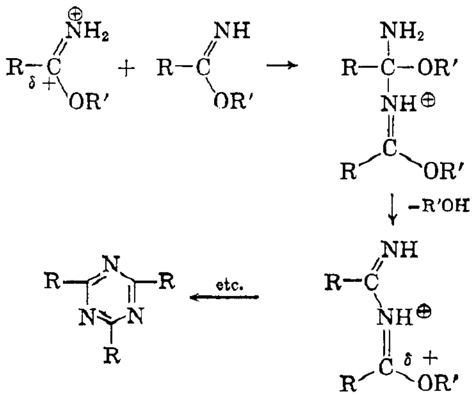
[a] Reaction temperature 25°. [b] Reference 2a, p. 27. [c] The work-up procedure was that described in the Experimental Section for the preparation of II. [d] Reference 2a, p. 28. [e] Prepared as described by A. Pinner for ethyl stearimidate hydrochloride, reference 2a, p. 31. The crude product, m.p. 69–73° was used. [f] Identification was established by infrared comparison with related compounds. The product, b.p. 260°/3 mm., contained a slight amount of ethyl laurate. [g] E. Schmidt, *Ber.*, **47**, 2547 (1914). [h] Diluted reaction mixture with water; filtered and washed product with methanol and ether. [i] See Experimental Section. [j] Prepared as described for ethyl acetimidate hydrochloride; yield 99%. *Anal.* Calcd. for $C_5H_{10}ClNO \cdot HCl$; Cl (Volhard), 20.7. Found: Cl, 20.2. [k] J. U. Nef, *Ann.*, **287**, 337 (1895). See Footnote 12. [l] M.p. 168–169°; A. Weddige, *J. prakt. Chem.* [2], **10**, 208 (1814) gives m.p. 165°.

Recently, Cramer, Pawelzik, and Kupper[13] reported the conversion of benzyl formimidate hydrochloride and benzyl acetamidate hydrochloride to *s*-triazine and 2,4,6-trimethyl-*s*-triazine in 50% and 63% yields, respectively, by heating the hydrochlorides with *N*,*N*-diethylaniline at reduced pressure. Since this publication appeared, we have tried diethylaniline in our procedure with ethyl formimidate hydrochloride with fair success, obtaining a 63% yield of *s*-triazine. The reaction is much slower than with tri-*n*-butylamine, however, presumably because of the lower basicity of the aromatic amine.[14] In further comparison of Cramer's procedure with our earlier work, reaction of ethyl acetimidate hydrochloride with diethylaniline was tried. This produced only ethyl chloride and acetamide, the usual thermal decomposition products of the imidate salt.[15]

Much of the work in which we are currently involved stems from the possibility that through the use of the imidates, amidines and related nitrile derivatives and their conjugate acids reactions can be accomplished which are impossible with the nitriles themselves. The trimerization reaction which is the subject of this paper is a good example in support of this thesis. We presume that the acidic catalysts promote the trimerization reaction by increasing the polarization of the C=N bond in the imidate and thus making the carbon atom of the functional group more electrophilic,



Such activated molecules are then attacked by the imidate base to produce a dimeric intermediate which loses alcohol and continues the process, leading eventually to the resonance-stabilized *s*-triazine system,[16]



The trimerization process as represented here is evidently quite similar to the reaction of an ester with an amine to produce an amide. Variations in the group R would be expected to influence the electrophilic character of the carbon atom of the functional group and, in an inverse fashion, the basicity of the imidate group. It is to be expected, therefore, that different strength acids may be required for optimum catalysis of different imidates. It is apparent too that with larger R and R′

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(12) The mention of spontaneous trimerization of ethyl 1-carbethoxyformimidate base by G. D. Lander, *J. Chem. Soc.*, 406 (1903) is misleading. We have observed that about 15% 2,4,6-triscarbethoxy-*s*-triazine is formed in three months at room temperature.

(13) F. Cramer, K. Pawelzik, and J. Kupper, *Angew. Chem.*, **68**, 649 (1956).

(14) Cramer, German patent **1,053,513** (1959), has since disclosed the use of triethylamine in ether–methylene dichloride at room temperature for conversion of benzyl acetimidate and propionimidate hydrochlorides to II and 2,4,6-triethyl-*s*-triazine in 50% and 60% yields, respectively. This technique is one of those we have evaluated for the preparation of *s*-triazine.

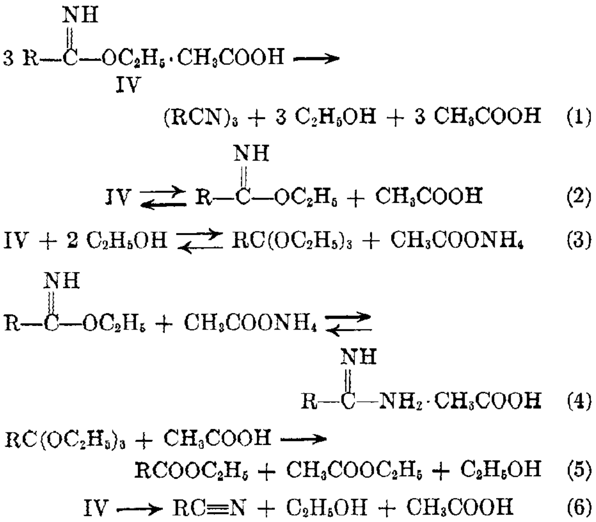
(15) The acetimidate hydrochloride was insoluble in the amine which acted as an inert suspending medium. Cramer's use of benzyl imidates appears to be fortuitous, providing compatability of the reactants.

(16) This conception of the trimerization process ignores the earlier opinion[2] that the formation of *s*-triazines from imidates proceeds by degradation to the nitrile which then trimerizes. It is evident that the acid-catalyzed imidate trimerization reported here gives a great many *s*-triazines which cannot be obtained from the nitriles themselves. We may also discard the concept advanced by Johnson and Bass[5] that dissociation of the imidate gives an active diradical form of the nitrile which either trimerizes or degenerates to the normal nitrile. This view is incompatable with acid catalysis and with modern theory.

groups steric interference may be important. The greater ease of trimerization of methyl *vs.* ethyl benzimidate and the sluggish reaction of ethyl isobutyrimidate compared to ethyl propionimidate probably are reflections of steric effects. On the other hand no impedance to reaction has been observed in isopropyl formimidate or acetimidate compared with the ethyl imidates. In the present work acetic acid has been used most frequently as the catalyst and the effect of imidate basicity is only discernible in the response of different imidates to differing catalyst concentrations.[17]

Influences which impede the trimerization process will favor acid-catalyzed side reactions. The trimerization of ethyl acetimidate by an equivalent amount of acetic acid is a convenient example to consider in discussing the nature of these competing reactions.

CHART I



$$3\ \underset{\mathrm{IV}}{\mathrm{R{-}\overset{NH}{\overset{\|}{C}}{-}OC_2H_5\cdot CH_3COOH}} \longrightarrow \mathrm{(RCN)_3 + 3\ C_2H_5OH + 3\ CH_3COOH} \quad (1)$$

$$\mathrm{IV} \rightleftarrows \mathrm{R{-}\overset{NH}{\overset{\|}{C}}{-}OC_2H_5 + CH_3COOH} \quad (2)$$

$$\mathrm{IV + 2\ C_2H_5OH} \rightleftarrows \mathrm{RC(OC_2H_5)_3 + CH_3COONH_4} \quad (3)$$

$$\mathrm{R{-}\overset{NH}{\overset{\|}{C}}{-}OC_2H_5 + CH_3COONH_4} \rightleftarrows \mathrm{R{-}\overset{NH}{\overset{\|}{C}}{-}NH_2\cdot CH_3COOH} \quad (4)$$

$$\mathrm{RC(OC_2H_5)_3 + CH_3COOH} \longrightarrow \mathrm{RCOOC_2H_5 + CH_3COOC_2H_5 + C_2H_5OH} \quad (5)$$

$$\mathrm{IV} \longrightarrow \mathrm{RC{\equiv}N + C_2H_5OH + CH_3COOH} \quad (6)$$

As the trimerization proceeds (reaction 1, Chart I), liberated ethanol and acetic acid become impeding diluents. The increasing acetic acid concentration also tends to suppress the dissociation of the imidate acetate (2) which is needed to provide the nucleophilic imidate reactant. However, the principal side reaction, alcoholysis of the imidate salt to give ortho ester and ammonium acetate (3), is promoted by these factors. Further degradation of these initial by-products leads to the amidine acetate and the normal ester (4 and 5). For these reasons the yield of II which is about 50% in a few hours is only 60% after four days and all imidate is consumed. Nitrile regeneration (6) also occurs but may not be an important side reaction except with aromatic imidates.

Production of the respective amidine salts has been observed to a greater or lesser degree in all of the acid catalyzed trimerization reactions. The ease of ortho ester formation which is responsible for this certainly varies with both the acyl and alkyl groups in the imidate used. It is apparently not serious with ethyl acetimidate which trimerizes very rapidly with low catalyst requirement, but with the aromatic imidates and such others as ethyl 2-phenylacetimidate large amounts of amidine were sometimes obtained.

The mechanism indicated above is analogous to that which we have advocated for the trimerization of amidines.[19] The latter reaction was only effective in a small number of cases, however, because of a less advantageous balance of the nucleophilic and electrophilic centers in amidines compared to imidates. The comparison provides a good illustration of the shadings in reactivity which can be exploited when using nitriles in the form of these close derivatives.

EXPERIMENTAL[20]

Ethyl acetimidate.[21] Ethyl acetimidate hydrochloride was prepared by the following modification of Pinner's method which has proved satisfactory for large scale work.

A mixture of 492 g. (12.0 moles) of acetonitrile, 552 g. (12.0 moles) of absolute ethanol, and 1000 cc. of benzene was treated at 20–25° with hydrogen chloride until 12.0–13.0 moles had been absorbed (2 hr.). Stirring was continued for 16–20 hr. thereafter until the crystallization of the product, which began at about the end of the hydrogen chloride addition, was completed. The process was strongly exothermic for several hours, and the temperature was held below 40–50° to avoid decomposition of the product into acetamide and ethyl chloride. The apparatus outlet was equipped with a drying tube to prevent access of moisture which would cause hydrolysis of the product to ethyl acetate and ammonium chloride. The crystallized product was filtered and pumped as dry as possible under a rubber dam. It was finally dried under water pump vacuum at room temperature. The yield was 90–100%. The compound has no characteristic melting point; values in the range of 110–115° usually are obtained.

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(17) It is significant that the reaction of ethyl 2-chloropropionimidate hydrochloride and ethyl chloroacetimidate hydrochloride with sodium acetate gave 2,4,6-tris(1-chloroethyl)-*s*-triazine and 2,4,6-tris(chloromethyl)-*s*-triazine (III) in 59% and 69% yields, respectively, these being at least 10% higher than the yields of the respective unsubstituted compounds under the same conditions. This difference may be attributed partly to the lower basicity of the chloro imidates[18] and partly to the increased electrophilic character of the carbon atom of the functional group in these compounds.

(18) The chloro imidates have pK_a approximately 4.9 *vs.* 7.6 for ethyl acetimidate and propionimidate. These values were determined by potentiometric titration in anhydrous nitromethane, C. A. Streuli, *Anal. Chem.*, **31**, 1652 (1959).

(19) F. C. Schaefer, I. Hechenbleikner, G. A. Peters, and V. P. Wystrach, *J. Am. Chem. Soc.*, **81**, 1466 (1959).

(20) Melting points are uncorrected. Microanalyses were carried out in these laboratories under the direction of Dr. J. A. Kuck and by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Infrared spectra were interpreted by Mr. N. B. Colthup and Dr. J. E. Lancaster. Mass spectroscopic analyses were carried out under the supervision of Mr. A. H. Struck.

(21) Reference 2a, p. 27.

To prepare the free base, 432 g. (5.0 moles) of ethyl acetimidate hydrochloride was added quickly at 20–25° to a vigorously stirred mixture of 875 cc. of methylene dichloride and 5.2 moles of potassium carbonate dissolved in 2500 cc. of water (slightly endothermic). The organic phase was separated after mixing for 7–10 min., and the aqueous phase was reextracted by mixing with 500 cc. of fresh methylene dichloride for another 20–30 min. The extracts were combined and dried over anhydrous potassium carbonate overnight in a refrigerator. The dry solution was then concentrated by rapid distillation of the solvent through an efficient column. When the boiling point could no longer be held below 60° at a useful distillation rate, the distillation was stopped. The residue then contained 85–90% ethyl acetimidate, as shown by titration of an aliquot to the methyl orange end point with standard acid. Yield, 80–85%. This material was suitable for conversion to II.

To recover pure ethyl acetimidate the concentrated residue was distilled further at atmospheric pressure. Small quantities of ethyl acetate, ethanol, and acetonitrile were obtained in the forerun. Ethyl acetimidate has b.p. 91°; n_D^{25} 1.4052; *d.* 0.88. Usually a small amount of 2,4,6-trimethyl-*s*-triazine was obtained as a still residue. The product was stored at low temperature in glass bottles which had been rinsed with acetic acid and then with acetone and dried.

It has been observed that at room temperature ethyl acetimidate samples of 80–100% original purity slowly decompose but at an increasing rate as the imidate content decreases. It is not known how the sample composition changes with time but about 20–30% of the starting imidate has been converted to 2,4,6-trimethyl-*s*-triazine when the imidate has disappeared (2–3 months). The remainder has dissociated into the nitrile and alcohol. This decomposition proceeds at essentially the same rate in polyethylene, in ordinary glass bottles, or in acid-washed glass bottles. Refrigerated samples have been quite stable however.

Ethyl propionimidate.[22] Because of its high solubility, ethyl propionimidate hydrochloride cannot be isolated in good yield when prepared by the common techniques of the Pinner synthesis. In this work the hydrochloride was prepared in methylene dichloride, and after 48 hr. the product solution was run into aqueous potassium carbonate to liberate the imidate base. The product was worked up as described for ethyl acetimidate. A concentrate containing 65–75% ethyl propionimidate was normally obtained (unconverted propionitrile and ethanol remain); yield, 70–75%. The solution was used as such for conversion to 2,4,6-triethyl-*s*-triazine or was distilled further to recovery the imidate in moderately pure form. Ethyl propionimidate boils at 110–111°. After this boiling point is reached, further distillation should be carried out at reduced pressure to avoid decomposition which is appreciable at atmospheric pressure. Distilled propionimidate may be expected to be ~93% pure, containing minor amounts of propionitrile and ethyl propionate.

Ethyl formimidate hydrochloride. The following procedure avoids the hazard of violent reactions such as reported by Pinner[23] and has been used successfully on a thirty-six mole scale.

A solution of 150 g. (4.1 moles) of anhydrous hydrogen chloride in a mixture of 184 g. (4.0 moles) of absolute ethanol and 285 g. of ether was prepared. To this 108 g. (4.0 moles) of hydrogen cyanide, previously dried over calcium chloride, was added over a period of 1 hr. at 10–20°. Crystallization of the product began during this period accompanied by considerable heat evolution. The mixture was stirred for 3 hr. longer at 15° and then was allowed to stand overnight. The crystals were collected, washed with ether, and dried at reduced pressure; yield 379 g. (89%). Volhard analysis gave theoretical values for chlorine. The product is extremely susceptible to hydrolysis by atmospheric moisture.

Preparation of 2,4,6-trisubstituted s-triazines. Trimerization of a variety of imidates is summarized in Table I.

2,4,6-Trimethyl-s-triazine (II).[24] To an 80–85% ethyl acetimidate concentrate prepared as described above eight mole per cent of glacial acetic acid based on the imidate content was added gradually (20–30 min.). During this addition and for an hour longer, the reaction mixture was held at 25–30°. The mixture was then allowed to stand for 16 hr. During this time, the imidate content decreased to 4–7% of the original value. The reaction mixture was then stripped of most of the ethanol formed, and the residue was diluted with 2–3 volumes of methylene dichloride. The solution was filtered from acetamidine acetate which had crystallized, and residual acetic acid was neutralized by mixing with solid potassium carbonate and a minimum volume of water. The methylene dichloride solution of II was separated from the aqueous phase and dried with calcium chloride. The solution was then stripped of solvent, and the product was distilled. The yield of material boiling at 150–155° was 85–90%, based on the crude imidate used.

2,4,6-Tris(m-nitrophenyl)-s-triazine. A solution of methyl *m*-nitrobenzimidate was prepared by reaction of 0.15 mole of *m*-nitrobenzonitrile with 50 cc. of methanol in the presence of 0.01 mole of sodium methoxide for 2.5 hr. at 25°. On the basis of other work,[8] this was expected to give a 70–75% yield of the imidate. The solution obtained was treated with 0.17 mole of glacial acetic acid. The solvent methanol was then evaporated, and the residue was heated at 70–90° for 2.5 hr. The cake obtained was extracted with hot water and with methanol. The undissolved material was 2,4,6-tris(*m*-nitrophenyl)-*s*-triazine, m.p. 348–350.[25] *m*-Nitrobenzonitrile was recovered from the washings and amounted to 40% of the starting material. The yield of *s*-triazine was 79%, based on the unrecovered nitrile.

Trimerization of methyl trichloroacetimidate. A mixture of 3.0 g. (0.017 mole) of methyl trichloroacetimidate and 1.0 cc. (0.017 mole) of glacial acetic acid was stored at room temperature. Infrared examination[26] at intervals showed that slow formation of *2,4,6-tris(trichloromethyl)-s-triazine* took place over a period of 45 days, but that some imidate still remained after this time. Crystals of *trichloroacetamidine acetate* separated gradually, m.p. 160–162°. The yield of *s*-triazine was 40–60%.

When a mixture of 0.012 mole of methyl trichloroacetimidate and 0.003 mole of acetic acid was heated at 80° for 6.5 hr., infrared examination showed that the imidate was largely converted to 2,4,6-tris(trichloromethyl)-*s*-triazine and little or no trichloroacetamide was produced.

Preparation of 2,4,6-trisubstituted s-triazines by the imidate hydrochloride-sodium acetate procedure; 2,4,6-tris(chloromethyl)-s-triazine (III). A mixture of 78.5 g. (0.50 mole) of ethyl 2-chloroacetimidate hydrochloride, 41.0 g. (0.50 mole) of anhydrous sodium acetate and 50 cc. of ethanol was allowed to stand at room temperature for 20 hr. Water was then added, and after 2 hr. the crystalline product was filtered; yield, 26.0 g. (69%); m.p. 73–74°. Recrystallization from ethanol raised the m.p. to 78–79°.

Anal. Calcd. for $C_6H_6N_3Cl_3$: C, 31.81; H, 2.67; N, 18.55. Found: C, 31.60; H, 2.95; N, 18.41.

Preparation of s-triazine.[6,19] Ethyl formimidate hydrochloride (40.0 g., 0.366 mole) was added at 10° to 68 g. (0.37 mole) of tri-*n*-butylamine. The mixture was stirred for 1.5 hr. at about room temperature and was then distilled at

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[22] Reference 2a, page 28.

[23] Reference 2a, p. 14.

[24] T. L. Cairns, A. W. Larcher, and B. C. McKusick, *J. Am. Chem. Soc.*, **74**, 5633 (1952).

[25] O. C. M. Davis, *J. Chem. Soc.*, **87**, 1834 (1905) gives m.p. 342°.

[26] The imidate content was estimated from its absorption band at 1670 cm.$^{-1}$ 2,4,6-Tris(trichloromethyl)-*s*-triazine[19] has characteristic absorption bands at 690 and 760 cm.$^{-1}$

25–50 mm. pressure as the residue temperature was slowly raised to 110°. The distillate was collected in a receiver cooled with solid carbon dioxide. A total of 7.8 g. of s-triazine was crystallized from the distillate by chilling after dilution with petroleum ether; yield 79%. The presence of an additional 7% yield was demonstrated by recovery of an equivalent amount of 2-phenyl-s-triazine after addition of benzamidine hydrochloride to the mother liquor.[27]

STAMFORD, CONN.

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

[CONTRIBUTION FROM THE STAMFORD LABORATORIES, CHEMICAL RESEARCH DEPARTMENT, AMERICAN CYANAMID CO.]

Synthesis of the *s*-Triazine System. IV.[1] Preparation of Monosubstituted *s*-Triazines by Reaction of *s*-Triazine with Imidates

FRED C. SCHAEFER AND GRACE A. PETERS

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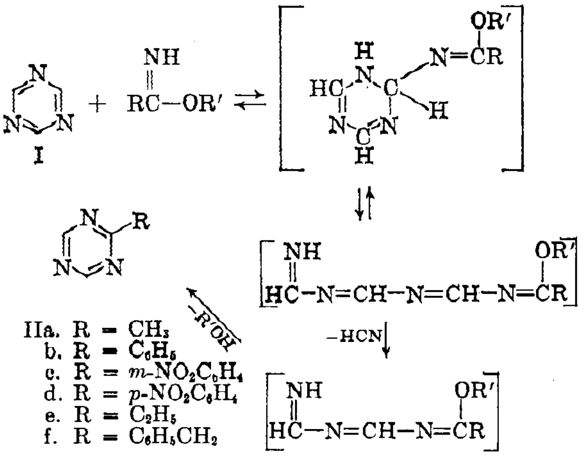
The reaction of imidates with s-triazine is shown to be a useful method for the preparation of monosubstituted s-triazines.

In an earlier paper[2] the preparation of monosubstituted s-triazines by the reaction of s-triazine (I) with amidines was reported. A reaction path closely related to that proposed for this process could also be envisioned for the reaction of I with imidates. It would similarly involve opening of the triazine ring and recyclization with inclusion of the reagent residue as outlined below. The cyclization step for the present case corresponds with that postulated for the trimerization of imidates to s-triazines.[1]



IIa. R = CH_3
b. R = C_6H_5
c. R = m-$NO_2C_6H_4$
d. R = p-$NO_2C_6H_4$
e. R = C_2H_5
f. R = $C_6H_5CH_2$

Our present results show that reaction of I with imidates can indeed give useful yields of monosubstituted s-triazines (II) despite several well known competing side reactions.[3] However, the relative ease of these side reactions is markedly dependent on the nature of the nitrile residue in the imidate. We therefore feel that to a considerable degree each imidate presents a separate problem and in this work have not gone beyond successful demonstration of a few examples of the reaction. The present work should encourage evaluation of this method for the preparation of specific monosubstituted s-triazines as interest may arise.

Reaction of s-triazine with ethyl acetimidate to form 2-methyl-s-triazine (IIa) has been studied in greatest detail. It was readily demonstrated that IIa is obtained under a variety of conditions. Process variables were evaluated roughly by semiquantitative analysis of the reaction mixtures by infrared spectroscopy. A limited number of the reaction mixtures which appeared to have been prepared under efficient conditions were worked up by distillation. The mixture of triazines recovered was finally analyzed by mass spectroscopy to obtain yield data. Instructive experiments from this work are summarized in Table I.

At 80° I and ethyl acetimidate reacted slowly in the absence of catalysts, but although all imidate was destroyed in twenty-two hours only a 20% yield of IIa was obtained. Both acetonitrile and 2,4,6-trimethyl-s-triazine were by-products. Although reaction at 25° was much slower, the yield of IIa was about 75%. Ethanol which is produced in the reaction must act as a catalyst for the formation of IIa. When a small amount was present at the start an induction period was avoided. A further benefit obtains in such case because the diluent alcohol inhibits trimerization of the imidate to 2,4,6-trimethyl-s-triazine.[1] Water also showed a slight catalytic influence and substantially aided reaction in added ethanol at 25°.

Water and alcohol may act as acids in catalyzing the desired reaction, probably participating in the ring-opening step. Therefore, the use of stronger acids was considered. Used alone, acetic acid accelerated the trimerization of ethyl acetimidate at the expense of the desired reaction, but in the presence of diluent ethanol use of acetic acid led to a

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[1] Paper III, F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 2778 (1961).

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

[3] We have discussed in reference 1 the conditions favoring the principal side reactions: (a) trimerization of the imidate, (b) dissociation of the imidate to nitrile and alcohol, (c) acid-catalyzed alcoholysis of the imidate to orthoester and concurrent formation of amidine salt, and (d) decomposition of the imidate salt to amide.