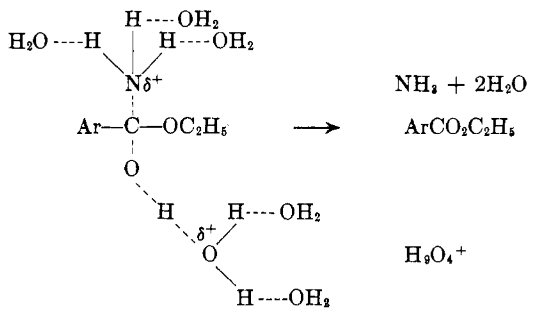
It is also possible to rationalize substituent effects on reactivity and activation parameters in terms of this mechanism. Since the equilibrium of eq. 1 is far to the right for all of the esters in dilute acid solutions, reactivity is determined by the effects of substituents on equilibrium 2 and rate-determining step 3. The tetrahedral product of equilibrium 2 forms one more strong hydrogen bond to water than does the ester conjugate acid. ΔS should therefore be negative, and should be more negative the greater the electron-attracting power of the aryl substituent. Electron-attracting substituents should also make ΔH more negative. Substituent effects on ΔH and ΔS of 2 should be compensatory, and the value of the equilibrium constant may be relatively insensitive to substituent effects.

Reaction 3, however, should be facilitated by electron-attracting substituents. In the transition state for this reaction the entropy decrease associated with solvation of the developing hydronium ion should be relatively insensitive to structural changes in the aryl group. On the other hand, the entropy increase accompanying C–N bond cleavage should be greater when the aryl group has an electron-attracting substituent than when it has an electron-repelling substituent, since the hydrogen bonds being broken are stronger in the former case than in the latter. Therefore ΔS^* for reaction 3 should be less negative for aryl groups with electron-attracting substituents. ΔH^* for reaction 3 should be relatively insensitive to substituent effects. If a concerted mechanism is involved, the electronic effects of substituents on O–H bond breaking and C–N bond breaking should be in opposite directions and might nearly cancel. In summary, equilibrium 2 should be relatively insensitive to the nature of the aryl group, and substituents should have a much greater effect on ΔS^* than on ΔH^* for rate-determining reaction 3. The proposed mechanism correctly predicts that ΔS^* should be less negative for esters having electron-attracting substituents than for those having electron-releasing substituents.



This mechanism fulfills the minimum requirement of rationalizing all of the available data. It accounts for the reaction products, the observed general acid catalysis, the solvent isotope effect, the large dependency of reaction rate on water activity, the positive ρ-value, and the fact that ΔS^* and not ΔH^* determines reactivity.

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s-Triazines. II.[1a] Syntheses of Dialkyl-s-triazines by Grignard Reaction

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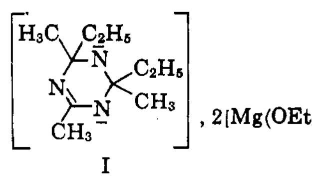
2,4-Dialkyl-6-halo- and 6-alkoxy-1,3,5-triazines were obtained from reactions of alkyl cyanurates, cyanuric chloride, or mixed alkoxyhalo-*s*-triazines with alkylmagnesium halides. Limitations of the individual reactions are discussed in terms of relative reactivities of groups displaced and of competing reactions, such as quaternization and additions leading to *gem*-dialkyldihydrotriazines.

Reactions of alkylmagnesium halides with cyanuric chloride have been reported as giving 2-monoalkyl or 2-monoaralkyl-4,6-dichloro-*s*-triazines.[2] A generalization was made to the effect that "one of the chlorine atoms of cyanuric acid reacts with alkyl Grignard reagents; in the case of some aryl Grignard reagents, two chlorine atoms undergo replacement."[3] No work has been reported in the literature on reactions of other organometallic reagents with cyanuric chloride, or on displacements with Grignard reagents on triazines other than cyanuric chloride.

Recently, however, Ostrogovich and Simonescu[4] studied the behavior of trimethyl-*s*-triazine with ethylmagnesium bromide. They showed that the solid products formed resulted from single or double additions of the Grignard reagent to the double bonds of the triazine. They postulated structures such as I.



I

We have found that, under milder, more controlled conditions than those used in earlier[2,3] work, halo- and alkoxy-*s*-triazines can be converted with alkyl Grignard reagent to the dialkylhalo- or dialkylalkoxy-*s*-triazines. Our results are summarized in Table I.

It seems clear that at low temperature (about −15°) smaller amounts of solid complexes and higher yields of

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(1) (a) Part I: H. Bader and N. M. Smyth, *J. Org. Chem.*, **29**, 952 (1964). (b) To whom correspondence should be addressed at Aldrich Chemical Co., Milwaukee, Wis.

(2) W. Hentrich, F. Wieners, and R. Stroebel, U. S. Patent 1,897,428 (Feb. 14, 1933); W. Hentrich and M. Hardtmann, U. S. Patent 1,911,689 (May 30, 1933); R. Hirt, H. Nidecker, and R. Berchtold, *Helv. Chim. Acta*, **33**, 1364 (1950); G. Ostrogovich, *Chem. Ztg.*, **36**, 738 (1912).

(3) E. M. Smolin and L. Rapoport, "*s*-Triazines and Derivatives," Interscience Publishers, Inc., New York, N. Y., 1959, p. 58.

(4) G. Ostrogovich and T. Simonescu, *Studii Cercetari Sti., Chim.* (Baza Cercetari Sti., Timosoara), **7**, 69 (1960).

TABLE I

EFFECT OF EXPERIMENTAL CONDITIONS ON THE DISTRIBUTION OF ALKYL-s-TRIAZINES

Run[a]	Starting triazine[b]	Ratio of EtMgCl/ triazine	Solvent for EtMgCl	Co-solvent[c]	Reactn. time, hr.[d]	Products,[b] % yield			
1	$(OMe)_3$ II	2.0	Et_2O	CH_2Cl_2	5	1.2 Et_3 V	18.5 $Et_2(OMe)$ VI	47.2 $Et(OMe)_2$ VII	33.1 $(OMe)_3$ II
2	$(OMe)_3$ II	4.0	Et_2O	CH_2Cl_2	6	1.0	27.8	42.0	0
3	$(OMe)_3$ II	4.0	Et_2O	CH_2Cl_2	24	3.4	20.7	37.8	2.8
4	$(OMe)_3$ II	4.0	Et_2O	PhMe	24	3.2	25.4	27.9	0
5	$(OMe)_3$ II	4.0	Et_2O	THF	24	0	0	1.0	99.0
6	Cl_3 III	3.5	Et_2O	CH_2Cl_2	3	1.2 Et_3 V	48.3 $Et_2(OM)$[e] VI	4.4 $Et(OMe)_2$[e] VII	
7	Cl_3 III	3.5[f]	THF	CH_2Cl_2	0.5	1.0	30.4	0	
8	Cl_2 III	3.5	Bu_2O	CH_2Cl_2	2	0	31.6	14.5	
9	Cl_2(O-*i*-Pr) IV	2.5	THF	CH_2Cl_2	10		34.1 Et_2(O-*i*-Pr) VIII	33.5 EtCl(O-*i*-Pr) IX	
10	Cl_2(O-*i*-Pr) IV	3.5	THF	CH_2Cl_2	10		42.5	6.9	
11	Cl_2(O-*i*-Pr) IV	3.0	Et_2O	CH_2Cl_2	4		15.6	33.4	
12	Cl_2(O-*i*-Pr) IV	3.0	Bu_2O	CH_2Cl_2	6		14.1	23.1	
13	Cl_2(O-*i*-Pr) IV	3.0	THF	PhMe	4		27.1	44.5	
14	Cl_2(O-*i*-Pr) IV	3.0	THF	THF	6		19.2	20.9	

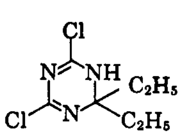
[a] All the reactions were performed at −15°. The distribution of the products was obtained by analysis of the distilled triazines by g.l.c.[12] For details, see the Experimental section. [b] The 2,4,6-substituents of *s*-triazine are denoted in abbreviated form; *viz.*, Cl_3 means cyanuric chloride, EtCl(O-*i*-Pr) means 2-chloro-4-ethyl-6-isopropoxy-*s*-triazine, etc. [c] Ratio of cosolvent to solvent for EtMgCl was 2:1. [d] Reaction time usually corresponds to the one giving maximum yield of diethyltriazine under given conditions. Only in the runs 3, 4, and 5, the reaction time was fixed arbitrarily. [e] The products were analyzed after conversion of chloro- to methoxytriazines. [f] Reverse addition was used. This allowed faster addition of reagents in cases where direct addition resulted in excessive exothermic effect.

alkyl-*s*-triazines are produced. The ratio of Grignard reagent (ethylmagnesium chloride was used as Grignard reagent throughout this work) to halo- or alkoxy-*s*-triazine affects significantly the proportion of mono-, di-, and trialkyl-*s*-triazines. For example, optimum yields of dialkyl-*s*-triazines are attained when this ratio is between 3:1 and 3.5:1.

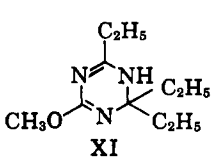
In all cases the best yields of dialkyl-*s*-triazines were obtained when methylene chloride was used in conjunction with an ether as a solvent.

The over-all effect of temperature, ratio of Grignard reagent to triazine, and solvent can be observed from the data in Table I. For instance, under the conditions of run 2, 2,4-diethyl-6-methoxy-*s*-triazine (VI) was obtained in 28% yield from a reaction of trimethoxy-*s*-triazine (trimethyl cyanurate) (II) with ethylmagnesium chloride; in addition, 42% of 2-ethyl-4,6-dimethoxy-*s*-triazine (VII) and 1% of triethyl-*s*-triazine (V) were isolated.

The effect of tetrahydrofuran as the solvent is of particular interest. The rate of displacement of chlorine on cyanuric chloride or mixed haloalkoxytriazines is greatly enhanced in solvent mixtures containing tetrahydrofuran (runs 7 and 13), but the formation of byproducts of the types X and XI is also favored with resulting lowering of the yields of dialkyl-*s*-triazines (run 14). Consequently tetrahydrofuran diluted with other solvents (runs 9, 10, and 13) was the solvent of choice with the less reactive haloalkoxy-*s*-triazines, such as 2,4-dichloro-6-isopropoxy-*s*-triazine (IV). In sharp contrast, trimethoxy-*s*-triazine was recovered unchanged from an ether–tetrahydrofuran solution of ethylmagnesium chloride (run 5).



X



XI

Reaction of trimethoxy-*s*-triazine with the Grignard reagent was observed in a mixed toluene–diethyl ether solvent (run 4). However, in this solvent mixture, 2,4-dichloro-6-isopropoxy-*s*-triazine (IV) gave a lower yield of dialkyl-*s*-triazine. We had no success in effecting a reaction even of trichloro-*s*-triazine with ethylmagnesium chloride prepared in toluene alone,[5] or in toluene containing 1 equiv. of dimethylaniline.[6] In both cases, starting material was recovered.

Runs 6 and 2 show that trichloro-*s*-triazine reacted much faster than trimethoxy-*s*-triazine. The former gave a relatively high yield of 2-chloro-4,6-diethyl-*s*-triazine (45%).

The results of the reactions of ethylmagnesium chloride with a series of substituted *s*-triazines are summarized in Table II.

The order of reactivity in trialkoxy-*s*-triazines was OMe > OEt ≫ O-*i*-Pr (*cf.* runs 15 and 16, Table II, and run 2, Table I). The starting material was recovered to the extent of 92% in the case of triisopropoxy-*s*-triazine (XIII).

Runs 18, 19, and 20 give the results of reactions of ethylmagnesium chloride with dichloromethoxy- (XV) and dichloroethoxy-*s*-triazine (XVI). Note that the ratio of chlorodiethyltriazine (XX) to diethylalkoxytriazine (VI or XVII, respectively) is much greater in the case of the ethoxy compound (6.5) than it is in the case of the methoxy compound (1.3–1.8). The reaction of chlorodimethoxy-*s*-triazine (XIV) with Grignard reagent (run 17) gives a ratio of alkyldimethoxy VII to alkylchloromethoxytriazine XXI of 3.9; that of dialkylmethoxy-*s*-triazine VI to dialkylchloro-*s*-triazine XX is, however, 11.5. This point will be discussed further.

From the lack of reactivity of the triisopropoxy-*s*-triazine and from the ratios of the various substituted alkylhalo- and alkylalkoxy-*s*-triazines mentioned above, it seemed desirable to employ 2,4-dichloro-6-isopropoxy-*s*-triazine (IV) to develop a simple preparation of the desired dialkylalkoxy-*s*-triazines. Run 21 was in agreement with this expectation. *From this starting*

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(5) E. T. Blues and D. Bryce-Smith, *Chem. Ind.* (London), 1535 (1960).

(6) R. Barré and J. de Repentigny, *Can. J. Research*, **27B**, 716 (1949).

TABLE II

REACTIONS OF VARIOUS 2,4,6-TRISUBSTITUTED TRIAZINES WITH ETHYLMAGNESIUM CHLORIDE

			Products,[a] % yield			
Run	Starting triazine[a]	Procedure[b]	Et_3 (V)	Et_2X	EtXY	Recovered starting triazine
15	$(OEt)_3$ XII	A	0	1.5 $Et_2(OEt)$ XVII	12.1 $Et(OEt)_2$ XVIII	57.4
16	$(O\text{-}i\text{-}Pr)_3$ XIII	A	0	0	2.3 $Et(O\text{-}i\text{-}Pr)$ XIX	92.2
17	$Cl(OMe)_2$ XIV	B	1.8	16.2 $Et_2(OMe)$ VI	31.0 $Et(OMe)_2$ VII	0
				1.4 Et_2Cl XX	7.9 $EtCl(OMe)$ XXI	0
18	$Cl_2(OMe)$ XV	B	1.8	26.0 $Et_2(OMe)$ VI	14.7 $EtCl(OMe)$ XXI	0
				19.2 Et_2Cl XX		
19	$Cl_2(OMe)$ XV	C	3.4	16.5 $Et_2(OMe)$ VI	31.4 $EtCl(OMe)$ XXI	0
				8.9 Et_2Cl XX		
20	$Cl_2(OEt)$ XVI	C	2.2	28.9 $Et_2(OEt)$ XVII	14.9 $EtCl(OEt)$ XXII	0
				4.3 Et_2Cl XX		
21	$Cl_2(O\text{-}i\text{-}Pr)$ IV	C	0	44.0 $Et_2(O\text{-}i\text{-}Pr)$ VIII	15.5 $EtCl(O\text{-}i\text{-}Pr)$ IX	0
22	$Et(OMe)_2$ VII	B	0.5	10.4 $Et_2(OMe)$ VI	13.0 $Et(OMe)_2$ VII	13.0
23	$Et_2(OMe)$ VI	B	1.0	56.4 $Et_2(OMe)$ VI		56.4
24	$EtCl(O\text{-}i\text{-}Pr)$ IX	C	0	33.9 $Et_2(O\text{-}i\text{-}Pr)$ VIII	17.8 $EtCl(O\text{-}i\text{-}Pr)$ IX	17.8

[a] The nomenclature is abbreviated, as in Table I. [b] All the reactions were performed at −15° using CH_2Cl_2 as solvent. Variations in reagent–triazine ratio and reaction time are given: (A) 4.0 moles of EtMgCl–triazine, ether as solvent for EtMgCl, 6-hr. reaction time; (B) same as A but 18-hr. reaction time; (C) 3.0 moles of EtMgCl–triazine, tetrahydrofuran as solvent for EtMgCl, 10-hr. reaction time. All the reaction mixtures were distilled and analyzed by g.l.c. (see ref. 12).

material only chloride atoms and not alkoxy groups were displaced and the yield of 2,4-diethyl-6-isopropoxy-*s*-triazine VIII was 44%. Furthermore, for practical convenience, the only by-product from this reaction, 2-chloro-4-ethyl-6-isopropoxy-*s*-triazine (IX) was converted *in situ* to high boiling derivatives, such as 2-dialkylamino-, 2-phenoxy-, or 2-hydroxyethoxy-4-ethyl-6-isopropoxy-*s*-triazine, thus permitting easy separation of the desired 2,4-diethyl-6-isopropoxy-*s*-triazine.

One of the difficulties encountered during the isolation and storage of dialkylhalo-*s*-triazines is their conversion into solid products. This tendency is not shared by either alkyldichloro-*s*-triazines or dialkylalkoxy-*s*-triazines. Their formation from pure materials, their hydrocarbon insolubility, and data from their infrared spectra suggest a quaternary ammonium salt structure caused by self-condensation. To obviate this complication we treated the original reaction mixtures before hydrolysis with sodium methoxide in methanol or with a suspension of anhydrous potassium carbonate in methanol to convert all of the halo-*s*-triazines to the more easily handled alkoxy-*s*-triazines.[7]

It was mentioned earlier that *gem*-dialkyldihydro-*s*-triazines X and XI could be isolated from a number of reactions. Their structure follows from the elemental analysis and consideration of the infrared spectra which show medium bands at 3080 and 3140 cm.$^{-1}$, respectively (NH stretching), and strong bands at 1625 and 1640 cm.$^{-1}$, respectively (C═N stretching in nonresonating systems). No bands at 1550 cm.$^{-1}$[8] and in the 830–900-cm.$^{-1}$ region,[9] characteristic of the *s*-triazine system, were observed. The n.m.r. spectrum of X showed two identical ethyl groups with CH_2 absorption at τ 8.3 (which would correspond to ethyl groups attached to saturated carbon). Similarly, the n.m.r. spectrum of XI showed only one type of CH_2 at low field (τ 7.8) corresponding to vinyl methylene (═C—CH_2—). The remaining *gem*-ethyls and the methyl of the vinylethyl all absorb above τ 8. In both spectra an NH peak was visible at τ 4.94 and in XI the methyl absorption of the enolic methoxyl was located at τ 6.3. Confirmation of these structures follows from the synthesis of compound XI, and other analogous 4-alkoxy-2,2,6-trialkyl-1,2-dihydro-*s*-triazines by a new unequivocal reaction to be reported in another communication.[10]

This investigation suggests that the failure to obtain dialkylhalo-*s*-triazines from Grignard reactions with trichloro-*s*-triazine reported in the previous literature was due to (a) the formation of *gem*-dialkyldihydrotriazines and (b) the formation of insoluble quaternary ammonium salts, both of which result when too strong conditions were used in the Grignard reaction. We were able to demonstrate formation of dihydro-*s*-triazine XI in 76% yield from the reaction of 2-ethyl-4,6-dimethoxy-*s*-triazine with ethylmagnesium chloride under the conditions of run 22; only 11% of polyalkylated *s*-triazines were formed. Likewise, the dihydrotriazine XI was obtained in 42.6% yield from the reaction of 2,4-diethyl-6-methoxy-*s*-triazine (run 23); only 1% of triethyltriazine was formed and a great amount of starting material was recovered (56.4%). *Evidently a stepwise alkylation of alkoxytriazines is not a practical route to dialkyl- or trialkyl-s-triazines.*

Discussion

The immediate consequence of bringing together a Grignard reagent and a basic trisubstituted *s*-triazine should be a formation of a complex. We have found, indeed, that Grignard reagents cannot be detected by the Gilman's test[11] shortly after 1 equiv. of ethylmag-

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(7) It is of interest that, in spite of the treatment of the intermediate complex with methanol, which achieved substitution of chlorines by methoxy groups, it was still necessary to add water in order to free the triazines. Indeed, direct evaporation of the methanol solution gave a solid from which triazines could be liberated only by addition of water.

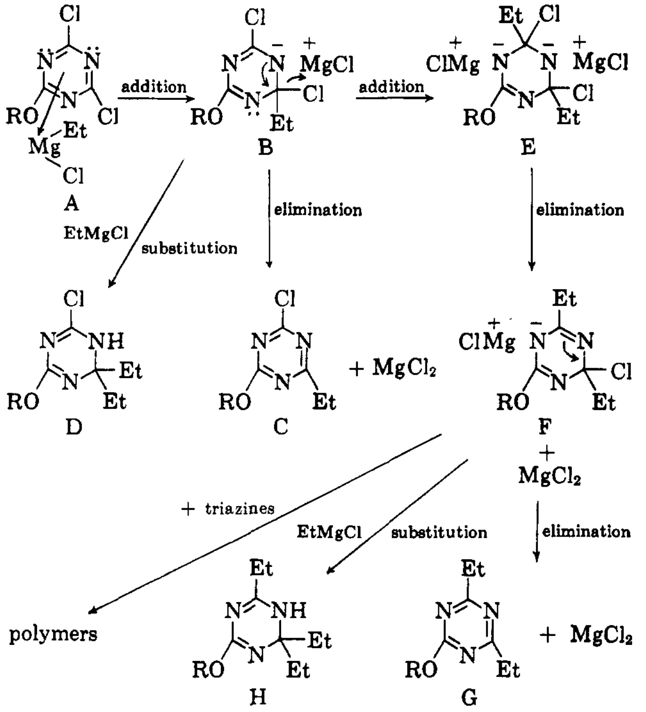
(8) *Cf.* L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 270; also see the infrared data on *s*-triazines in the Experimental section.

(9) F. C. Schaefer [*J. Org. Chem.*, **27**, 3608 (1962)] points to the 750–850-cm.$^{-1}$ region as that containing characteristic bands distinguishing between individual *s*-triazines. The *s*-triazines described in this work possessed their characteristic bands rather in the 830–900-cm.$^{-1}$ region.

(10) H. Bader, *ibid.*, **30**, 930 (1965).

(11) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925); H. Gilman and L. H. Heck, *ibid.*, **52**, 4949 (1930).

CHART I



nesium chloride was added to triethyl-s-triazine in diethyl ether at −15°, although the triazine was quantitatively recovered after hydrolysis. The Roumanian authors[4] found evidence for similar complexes with trimethyl-s-triazine. This tendency of complex formation accounts for the necessity of having 3 to 3.5 moles of a Grignard reagent present to effect dialkylation.

A possible sequence of events is shown in Chart I, using monoalkoxydichloro-s-triazine (A) as the illustration (the species shown in Chart I are understood to be complexed throughout this discussion).

Addition of the Grignard reagent across the C=N bond leads to the nonaromatic structure B in what is probably the slow rate-determining step of the reaction. From this postulated intermediate B, elimination, for instance of Cl^- ion, would lead to the monosubstituted product C. An alternative pathway for a reaction open to the intermediate B is substitution, leading to *gem*-dialkyldihydro-s-triazine D (*cf.* analogous compound X described in the previous section). A third mode of reaction of the intermediate B is a further addition of second molecule of a Grignard reagent to give the tetrahydro derivative E. This intermediate, with its multiple charge, should rapidly collapse to a dihydrotriazine F which, as was indicated in the case of its analog B, could either (a) lose Cl^- to give the final monoalkoxydialkyl-s-triazine G, (b) undergo substitution by another Grignard reagent to give the stable dihydro-s-triazine H, or (c) could react with itself or with another triazine molecule present (such as G, C, D or A) to produce polymeric materials.

We have isolated considerable amounts of *gem*-diethyldihydro-s-triazine H as described in the preceding section (see discussion of runs 22 and 23).

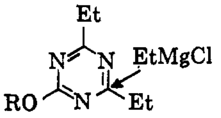
The reaction scheme summarized in Chart I serves to explain most of our observations if the following additional points are considered: (1) the reactivity sequence for the group X—C=N where X is halogen or alkoxy should be in the order halogen > alkoxy; (2) the reactivity of the alkoxy-s-triazines and of the mixed alkoxyalkyl- and alkoxychloro-s-triazines should be affected also by the steric requirements of the alkoxy groups; (3) the relative rates of elimination, further addition, and substitution from B (or F) should be strongly affected by the nature of the group being substituted (halogen in Chart I or alkoxy group in other examples); and (4) the nature of the solvent would be expected to play a role, by affecting the extent of complex formation between the Grignard reagent and the triazine.

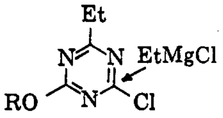
As to point 1, our observations follow the expected reactivity sequence of X—C=N. Halo-s-triazines react much faster than the alkoxy-s-triazines.

(2) The nature of the alkoxy group has a pronounced effect on the reactivity of trialkoxy-s-triazines. The order of reactivity is OMe > OEt ≫ O-*i*-Pr, suggesting the steric effect as the cause.

A steric effect explains the greater reactivity of a methoxy group than of an ethoxy group (and much greater than of an isopropoxy group) in the dichloroalkoxy- and the monochlorodialkoxy-s-triazines. As mentioned in the preceding section, this affords a convenient preparation of dialkylisopropoxy-s-triazines in acceptable yields.

(3) The alkyl-s-triazines present a special problem. They are susceptible to the addition of the Grignard reagent, but this addition cannot be followed by elimination; thus *gem*-dialkyldihydro-s-triazines are the final products. It is interesting to consider the two cases of mixed triazines: the alkylalkoxy-s-triazines and the alkylchloro-s-triazines. As was mentioned in the preceding section, the reaction of 2,4-diethyl-6-methoxy-s-triazine with ethylmagnesium chloride gives 42.6% of the dihydro-s-triazine XI and only 1% of triethyl-s-triazine (run 23, product isolated), indicating that addition to Et—C=N bond is favored over addition to MeO—C=N. On the other hand, 2-ethyl-4-chloro-6-isopropoxy-s-triazine could be further alkylated to 2,4-diethyl-6-isopropoxy-s-triazine in a yield not much lower than that of the diethylated product obtained directly from 2,4-dichloro-6-isopropoxy-s-triazine (*cf.* runs 24 and 21). This would indicate that addition to Cl—C=N bond is easier than that to Et—C=N bond.





(4) The effect of solvent was shown to be opposite in the reactions of halo- and of the alkoxy-s-triazines. The inertness of alkoxy-s-triazines toward Grignard reagents in tetrahydrofuran (run 5) contrasts with the enhanced reactivity of the halotriazines (runs 7, 9, 10, and 13) in the same solvent (both alkoxy- and halotriazines reacted with Grignard reagent in diethyl ether). It seems possible that a complexing between the alkoxy groups and the Grignard reagent is required for the reaction and that such complexing is weakened in the presence of tetrahydrofuran, which presumedly coordinates strongly with the magnesium.

The observation that dialkyl- and trialkyl-s-triazines cannot be made in high yields by stepwise alkylation of either halo- or alkoxytriazines rules out a model consisting of successive additions and eliminations A → B → C (followed by addition and elimination). On the other hand, the model shown in Chart I involving *successive additions* of the Grignard reagent to triazine A and the dihydrotriazine B accounts for these observations. Thus (a) alkylation of monoalkyldialkoxytriazines (analogous to C) gives mostly *gem*-dialkyldihydrotriazines X and XI (*cf.* runs 22–24, Table II, and discussion of them, above), and (b) slow addition of the Grignard reagent, over 2 hr. instead of 20 min. results in markedly decreased yields of dialkyltriazines.

Experimental[12]

Materials.—Cyanuric chloride was purified by recrystallization of a commercial sample from benzene. Trimethyl cyanurate, 2,4-dichloro-6-methoxy-*s*-triazine (XV), and 2-chloro-4,6-dimethoxy-*s*-triazine (XIV) were prepared according to Dudley, *et al.*[13] Triethyl (XII) and triisopropyl (XIII) cyanurates were prepared by the method of Spielman, *et al.*[14] 2,4-Dichloro-6-ethoxy- (XVI) and 6-isopropoxy-*s*-triazine (IV) were obtained in yields of 95% using the procedure of Huemer.[15]

The following infrared absorptions were observed: 2,4-dichloro-6-methoxy-*s*-triazine, 1530 and 1500 (triazine ring stretching) and a set of three bands common to all dichloro-*s*-triazines at 916, 847, and 807 cm.$^{-1}$; similarly, 2,4-dichloro-6-ethoxy-*s*-triazine, 1540, 1500, 880, 841, and 808 cm.$^{-1}$; 2,4-dichloro-6-isopropoxy-*s*-triazine, 1540, 1490, 905, 860, and 808 cm.$^{-1}$; 2-chloro-4,6-dimethoxy-*s*-triazine, 1540 and two strong peaks at 928 and 806 cm.$^{-1}$.

Reactions of Trimethyl Cyanurate with Ethylmagnesium Chloride. A.—A solution of ethylmagnesium chloride (436 ml., 3.2 *N*; 1.4 moles) in diethyl ether was added dropwise over a 30-min. period under a nitrogen atmosphere to a stirred solution of 60.0 g. (0.35 mole) of trimethyl cyanurate in 1500 ml. of methylene chloride at −15°. Stirring was continued for 6 hr. at −15° at which time 200 ml. of water was added dropwise below 10°. The coagulated inorganic precipitate was filtered and washed with methylene chloride. The filtrate was concentrated and the residue was distilled at 115–125° (20 mm.) yielding 43.0 g. (74%) of a mixture of triazines. Analysis and isolation of pure components by g.l.c.[12] showed it to contain V–VII. 2,4,6-Triethyl-*s*-triazine (V) was isolated in 1.0% yield (0.6 g.): n^{29}D 1.4690; identical in retention time and spectra with a sample prepared by Schaefer and Peters[16]; infrared absorption, 1540 (triazine ring stretching), 895, and 840 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{15}N_3$: C, 65.43; H, 9.15; N, 25.44. Found: C, 65.27; H, 8.97; N, 25.44.

2,4-Diethyl-6-methoxy-*s*-triazine (VI) was isolated in 27.8% yield (16.2 g.): n^{27}D 1.4742; identical in retention time and spectra with a sample prepared by the method of Schaefer[17]; $\lambda_{\max}^{\mathrm{EtOH}}$ 236 mμ (ϵ 2200); infrared absorption, 1545 and 1530 (triazine ring stretching), and 928 and 838 cm.$^{-1}$ (characteristic of dialkylalkoxy-*s*-triazines).

Anal. Calcd. for $C_8H_{13}N_3O$: C, 57.46; H, 7.84; N, 25.14. Found: C, 57.82; H, 7.64; N, 25.45.

2-Ethyl-4,6-dimethoxy-*s*-triazine (VII), isolated in 42.0% yield (24.5 g.), was identical with the previously isolated sample (by g.l.c. and infrared).[16] For further data, see below.

Anal. Calcd. for $C_7H_{11}N_3O_2$: C, 49.68; H, 6.55; N, 24.84. Found: C, 49.56; H, 6.43; N, 24.89.

Fractionation through a 20-cm. Fenske column gave (i) a 2:3 mixture of triethyl- and 2,4-diethyl-*s*-triazines, b.p. 80–90° (10 mm.), n^{27}D 1.4681; (ii) 2,4-diethyl-6-methoxy-*s*-triazine, b.p. 90° (10 mm.), n^{27}D 1.4742 [lit.[17] b.p. 58–64° (0.75 mm.), n^{20}D 1.4765]; and (iii) a residue which on crystallization from pentane gave 2-ethyl-4,6-dimethoxy-*s*-triazine in microprisms: m.p. 55.2–55.9°; $\lambda_{\max}^{\mathrm{EtOH}}$ 233 mμ (ϵ 2900); infrared absorption, 1550 and 1530 (triazine ring stretching), 995, 935, and 822 cm.$^{-1}$.

B.—In a similar experiment with a reaction period of 18 hr., the residue from the methylene chloride solution was taken up in pentane and the resulting solution was stored at −20° overnight. An oily solid was separated and crystallized from ether to give 3.2 g. (4.6%) of 2,2,6-triethyl-4-methoxy-1,2-dihydro-*s*-triazine (XI) in long colorless prisms: m.p. 143–145°; $\lambda_{\max}^{\mathrm{EtOH}}$ 273 mμ (ϵ 1750).

Anal. Calcd. for $C_{10}H_{19}N_3O$: C, 60.88; H, 9.71; N, 21.30. Found: C, 61.10; H, 9.71; N, 21.07.

Reactions of Cyanuric Chloride with Ethylmagnesium Chloride. A.—A solution of ethylmagnesium chloride in ether (48 ml., 2.92 *N*; 0.14 moles) was added over a 5-min. period to a stirred solution of 6.45 g. (0.035 mole) of cyanuric chloride in 300 ml. of ethylene chloride at −15°. Stirring was continued at −15° for 3 hr.; then 18 ml. of water was added dropwise while the temperature was maintained below 15°. Anhydrous magnesium sulfate (20 g.) was then added, the resulting cake was filtered and washed with methylene chloride, and the solvent was removed under reduced pressure. The residue was extracted with hot pentane. Evaporation of the extract and distillation of the residue gave 3.0 g. of pale yellow oil, b.p. 77–78° (8 mm.). Analysis by g.l.c. showed it to contain 90% of 2-chloro-4,6-diethyl-*s*-triazine, 9% of 2,4-dichloro-6-ethyl-*s*-triazine, and 1.0% of triethyl-*s*-triazine. A sample of pure 2-chloro-4,6-diethyl-*s*-triazine was isolated *via* g.l.c.: n^{25}D 1.4927; infrared absorption, 1540, 1505, 880–895, 862, and 831 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{10}ClN_3$: C, 48.98; H, 5.87; Cl, 20.65; N, 24.48. Found: C, 48.88; H, 5.88; Cl, 20.67; N, 24.25.

B.—In a similar experiment on a four times larger scale, the reaction mixture was poured into a stirred mixture of 64 g. of anhydrous potassium carbonate in 100 ml. of methanol at 0 to 10°. Stirring was continued for 10 hr. at room temperature; then 56 ml. of water was added dropwise at −10°. The solid cake was separated, the solvent was removed, and the residue was fractionated through a 20-cm. Fenske column, yielding (i) 0.5 g. of triethyl-*s*-triazine, b.p. 145–150° (150 mm.); (ii) 10.3 g. (44.0%) of 2,4-diethyl-6-methoxy-*s*-triazine, b.p. 130° (50 mm.); and (iii) 0.9 g. (3.8%) of 2-ethyl-4,6-dimethoxy-*s*-triazine, b.p. 123–125 (20 mm.).

C.—As an alternate procedure, instead of the treatment with potassium carbonate, a solution of sodium methoxide (from 11.2 g. of sodium) in 150 ml. of methanol was added over a period of 15 min. at −20 to 0°. The yields were not affected.

D.—Under the conditions of procedure A but with only 2 equiv. of ethylmagnesium chloride, evaporation of the methylene chloride solution gave a residue (6.5 g.) which was redissolved in pentane. After storage at −20°, 0.15 g. of 4,6-dichloro-2,2-diethyl-1,2-dihydro-*s*-triazine (XI) separated in yellow crystals: m.p. 121–123°; $\lambda_{\max}^{\mathrm{EtOH}}$ 290 mμ (ϵ 1850). (This by-product was also isolated from a reaction, performed under conditions of procedure B.)

Anal. Calcd. for $C_7H_{11}Cl_2N_3$: C, 40.39; H, 5.33; Cl, 34.07; N, 20.19. Found: C, 40.63; H, 5.85; Cl, 33.81; N, 20.34.

The mother liquors were concentrated and the residue (6.3 g.) was shown by g.l.c. to contain 1% of triethyl-*s*-triazine, 80% of 2,4-dichloro-6-ethyl-*s*-triazine, and 20% of 2-chloro-4,6-diethyl-*s*-triazine. Crystallization from aqueous ethanol at −20° gave crude 2,4-dichloro-6-ethyl-*s*-triazine, m.p. 30–31° (Hirt, *et al*,[2] reported m.p. 35°), which distilled at 110° (40 mm.): $\lambda_{\max}^{\mathrm{cyclohexane}}$ 265 mμ (ϵ 1600); infrared absorption, 1530 and 1490 (triazine ring stretching), and 887, 848, and 817 cm.$^{-1}$, characteristic of dichloro-*s*-triazines (*cf.* dichloroalkoxy-*s*-triazines, above).

Anal. Calcd. for $C_5H_5Cl_2N_3$: Cl, 39.80. Found: Cl, 40.15.

Reactions of 2,4-Dichloro-6-isopropoxy-*s*-triazine (IV) with Ethylmagnesium Chloride. A.—A solution of ethylmagnesium chloride in tetrahydrofuran (96.5 ml., 3.12 *N*; 0.3 moles) was added over a 5-min. period to a stirred soluion of 20.8 g. (10.1 mole) of 2,4-dichloro-6-isopropoxy-*s*-triazine in 150 ml. of methylene chloride at −15°. Stirring was continued at −15° for 10 hr., then 35 ml. of water was added dropwise, followed with 10 g. of anhydrous magnesium sulfate. The suspension was filtered

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(12) All melting points are corrected. The infrared spectra were determined with a Perkin-Elmer Infracord spectrophotometer as liquid film, or, in case of solids, as a Nujol mineral oil mull. Ultraviolet spectra were determined on a Cary Model 12 ultraviolet spectrophotometer. The distilled products were analyzed for individual components by gas–liquid chromatography with a F and M Model 500 instrument using a 6-ft. 20% Carbowax 20,000 (on 60–80 Chromsorb W firebrick) column, obtained from F and M Scientific Corp. In some cases, analytically pure samples of individual components were secured also by g.l.c. separation.

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(14) M. A. Spielman, W. J. Close, and I. J. Wilk, *ibid.*, **73**, 1775 (1951).

(15) H. Huemer, German Patent 854,801 (Nov. 6, 1952).

(16) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 2778 (1961).

(17) F. C. Schaefer, *ibid.*, **27**, 3608 (1962); this method was applied to this particular case by Drs. R. G. Shepherd and W. E. Taft of the Lederle Laboratories Division.

and the solids were washed with methylene chloride. Evaporation of the filtrate gave an oily residue (19.0 g.) which was extracted with pentane. The pentane solution was concentrated and the residue was distilled, yielding 11.6 g. of oil, b.p. 120° (35 mm.). Analysis by g.l.c. showed it to contain (i) 8.6 g. (44.0% yield) of 2,4-diethyl-6-isopropoxy-*s*-triazine (VIII) which could be isolated in various ways, one of which is described below and (ii) 3.1 g. (15.5% yield) of 2-chloro-4-ethyl-6-isopropoxy-*s*-triazine (IX), the sample of which was isolated *via* g.l.c.: $n^{27}\mathrm{D}$ 1.4870; infrared absorption, 1545 and 1505 (triazine ring stretching), and 909, 880, and 825 cm.$^{-1}$ (all three common to chloroalkylalkoxy-*s*-triazines).

Anal. Calcd. for $C_8H_{12}ClN_3O$: C, 47.64; H, 6.00; Cl, 17.58; N, 20.84. Found: C, 47.66; H, 6.15; Cl, 18.35; N, 20.90.

B.[18]—After filtration of the inorganic salts, 20 g. of ethylene glycol and 4.12 g. of 50% sodium hydroxide solution were added to the methylene chloride filtrate and the solvent was distilled at atmosphere pressure to one-eighth of the original volume. A check by g.l.c. indicated complete conversion of 2-chloro-4-ethyl-6-isopropoxy-*s*-triazine to the 2-hydroxyethyl derivative. Water (100 ml.) was added and, after separation of the organic layer, the aqueous layer was re-extracted with methylene chloride. Removal of the solvent from the organic layer and distillation of the residue gave 7.8 g. (40.1%) of 2,4-diethyl-6-isopropoxy-*s*-triazine (VIII): b.p. 125–127° (26 mm.); $n^{30}\mathrm{D}$ 1.4688; λ_{max} 238 mμ (ϵ 2450); infrared absorption, 1555 (shoulder) and 1540 (triazine ring stretching), and 917 and 838 cm.$^{-1}$ (common to other dialkylalkoxy-*s*-triazines).

Anal. Calcd. for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.52; H, 8.55; N, 21.34.

Combined distillation residues yielded, on fractionation, 2-ethyl-4-isopropoxy-6-(2-hydroxyethoxy)-*s*-triazine: b.p. 127–130° (0.1 mm.); $n^{27.5}\mathrm{D}$ 1.4919; λ_{max} 235 mμ (ϵ 2800); infrared absorption, 3350 (OH), 1555 and 1540 (shoulder) (triazine ring), and 908, 885, and 830 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{17}N_3O_3$: C, 52.85; H, 7.54; N, 18.49. Found: C, 52.90; H, 7.71; N, 18.53.

2,4-Diethyl-6-ethoxy-*s*-triazine (XVII) was obtained from run 20. An analytical sample of this compound and of the compounds which follow was secured by g.l.c. separation[12]: $n^{25}\mathrm{D}$ 1.4731; infrared absorption, 1595, 1545, 912, and 840 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.19. Found: C, 59.73; H, 8.51; N, 23.15.

2-Ethyl-4,6-diethoxy-*s*-triazine (XVIII) was obtained from run 15: $n^{25}\mathrm{D}$ 1.4772; infrared absorption, 1560, 1545, 945, 863, and 832 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{15}N_3O_2$: C, 54.80; H, 7.61; N, 21.30. Found: C, 54.65; H, 7.41; N, 21.27.

2-Ethyl-4,6-diisopropoxy-*s*-triazine (XIX) was obtained from run 16: $n^{30}\mathrm{D}$ 1.4688; infrared absorption, 1570, 1550, 968, 908, and 833 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{19}N_3O_2$: C, 58.62; H, 8.50; N, 18.65. Found: C, 58.50; H, 8.35; N, 18.62.

6-Chloro-4-ethyl-6-methoxy-*s*-triazine (XXI) was isolated from run 19: m.p. 38–40°; infrared absorption, 1555, 1520, 924, 873, and 826 cm.$^{-1}$.

Anal. Calcd. for $C_6H_8ClN_3O$: C, 41.51; H, 4.65; Cl, 20.43; N, 24.21. Found: C, 41.47; H, 4.63; Cl, 20.50; N, 24.28.

2-Chloro-4-ethyl-6-ethoxy-*s*-triazine (XXII) from run 20 had $n^{25}\mathrm{D}$ 1.4946 and infrared absorption at 1555, 1545, 1510, 964, 900, and 825 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{10}ClN_3O$: C, 44.82; H, 5.37; Cl, 18.90; N, 22.40. Found: C, 44.66; H, 5.51; Cl, 18.46; N, 22.10.

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[18] With E. O'Bara.

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s-Triazines. IV.[1a] Synthesis of Trisubstituted *s*-Triazines by Reaction of Acylimidates with Amidines

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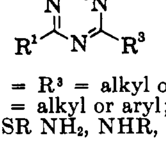
Reaction of acylimidates with amidines at room temperature affords a practical route to hitherto inaccessible trisubstituted *s*-triazines bearing three different substituents. These may be alkyl or aryl groups, or one of them can be an alkoxy, alkylthio, or amino group.

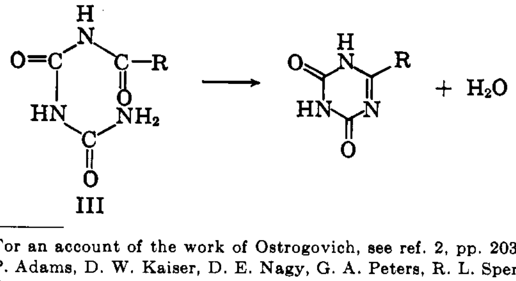
The principal methods of synthesis of alkyl- and aryl-*s*-triazines are based on trimerization or cotrimerization of nitriles, amidines, or imidates.[2,3] Consequently they are suitable for the preparation of *s*-triazines possessing three identical substituents (I) or of those containing two types of substituents (II).



I, $R^1 = R^2 = R^3$ = alkyl or aryl
II, $R^1 = R^2$ = alkyl or aryl; R^3 = alkyl, aryl, OR, SR NH_2, NHR, etc.

This paper describes the first preparative method for *s*-triazines bearing three different alkyl or aryl substituents. One of these can also be an alkoxy, alkylthio, or amino group.

This investigation arose from the consideration of the facile ring closures of acylbiurets (III) to guanamines, first described by Ostrogovich[4] and more recently investigated by Kaiser and co-workers.[5] The latter extended this method to acylcyanoguanidines



III

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[4] For an account of the work of Ostrogovich, see ref. 2, pp. 203–204.

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