[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION]

Reactions of Trichloromethyl-Substituted *s*-Triazines in the Presence of Tertiary Amines[1a]

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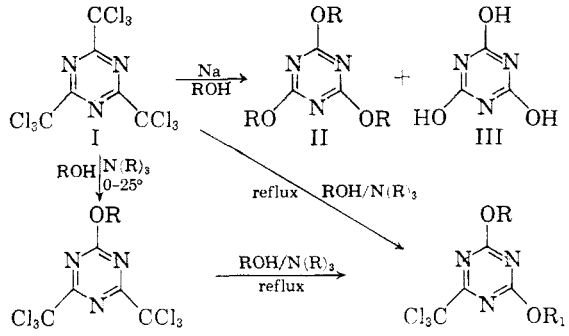
A method has been found which permits the stepwise replacement of one or two trichloromethyl groups attached to a *s*-triazine ring by alkoxy groups. By a variation of this method tertiary amine salts of 2-hydroxy-4,6-bistrichloromethyl-*s*-triazine can be synthesized from 2,4,6-tristrichloromethyl-*s*-triazine.

It is known that trichloromethyl groups attached to *s*-triazine rings can be replaced stepwise by amino or secondary amino groups[2,3]; the reaction involves elimination of trichloromethyl anions[4] which sombine with a proton to form chloroform. Whether one or more trichloromethyl groups are replaced by this reaction depends largely on the reaction temperature. The assumption that the nucleophilic replacement of trichloromethyl groups attached to the *s*-triazine ring would also proceed with other suitable agents, *e.g.*, alcohols was confirmed by the reaction of 2,4,6-tristrichloromethyl-*s*-triazine (I) with ethanol in the presence of three moles of sodium ethoxide or sodium hydroxide which gave 2,4,6-trisethoxy-*s*-triazine (II) and cyanuric acid (III). Stepwise replacement of the trichloromethyl groups, however, could not be achieved by variation of the reaction temperatures. Even when the amount of base was varied from catalytic amounts to two equivalents, the intermediates, 2-ethoxy-4,6-bistrichloromethyl-*s*-triazine (V) and 2,4-bisethoxy-6-trichloromethyl-*s*-triazine (VIII), could not be isolated. If at a given temperature reaction took place at all, the sole reaction products were II and III, indicating that—under the described conditions—the process cannot be stopped after the exchange of one or two trichloromethyl groups.

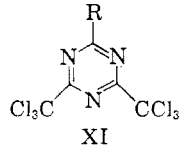
The desired stepwise replacement of trichloromethyl groups by alkoxy groups was accomplished in the presence of aliphatic tertiary amines such as triethylamine. When the reaction of I with alcohols in the presence of triethylamine was carried out between 0° and room temperature, only one trichloromethyl group was replaced by an alkoxy group resulting in 2-alkoxy-4,6-bistrichloromethyl-*s*-triazines (IV-VII), while at reflux temperatures the reaction proceeded to give exclusively 2,4-bisalkoxy-6-trichloromethyl-*s*-triazines (VIII, IX).[5] It was also possible to convert 2-alkoxy-4,6-bistrichloromethyl-*s*-triazines to the 2,4-bisalkoxy-6-trichloromethyl-*s*-triazines by refluxing with the corresponding alcohol in the presence of triethylamine as demonstrated by the conversion of V to VIII and of VII to IX.



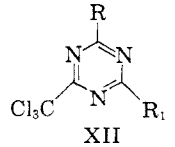
IV. R = CH_3
V. R = C_2H_5
VI. R = $CH(CH_3)_2$
VII. R = n-C_4H_9
VIII. R = C_2H_5; R_1 = C_2H_5
IX. R = n-C_4H_9; R_1 = n-C_4H_9
X. R = CH_3; R_1 = C_2H_5
XXII. R = CH_2CF_3

An attempt to synthesize a 2,4-bisalkoxy-6-trichloromethyl-*s*-triazine bearing two different alkoxy groups was not successful; 2-methoxy-4,6-bistrichloromethyl-*s*-triazine (IV)—upon refluxing with ethanol in the presence of triethylamine—did not give 2-ethoxy-4-methoxy-6-trichloromethyl-*s*-triazine (X) but instead 2,4-bisethoxy-6-trichloromethyl-*s*-triazine (VIII), indicating complete transesterification of the methoxy group by ethanol.

The described method could also be successfully applied for the preparation of *s*-triazine derivatives of type XII from compounds of type XI.



XI



XII

XIII. R = CH_3
XIV. R = C_6H_5
XV. R = CH_3; R_1 = OC_2H_5
XVI. R = CH_3; R_1, = O-n-C_4H_9
XVII. R = C_6H_5; R_1 = OC_2H_5

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(2) A. Weddige, *J. prakt. Chem.*, [2] **33**, 81 (1886).

(3) A. Kreutzberger, *J. Am. Chem. Soc.*, **79**, 2629 (1956).

(4) F. Arndt and B. Eistert, *Ber.*, **68**, 196 (1935).

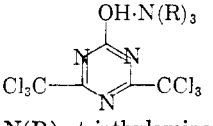
(5) The synthesis of compounds IV–VIII from 2-chloro-4,6-bistrichloromethyl-*s*-triazine by a different procedure has been described recently; H. Schroeder, *J. Am. Chem. Soc.*, **81**, 5658 (1959).

To obtain compounds XV, XVI, and XVII, the starting materials XIII or XIV, respectively, had to be refluxed in the appropriate alcohol in the presence of triethylamine.

The extension of the described method to other tertiary amines as well as to tertiary alcohols or phenols was investigated. From the results obtained we conclude that other aliphatic amines, such as tributylamine, and tertiary heterocyclic *N*-alkylamines, such as *N*-ethylpiperidine and *N*-methylmorpholine, can also be successfully employed for the described method. Reaction, however, could not be achieved in the presence of pyridine or *N*,*N*-dimethylaniline.

Trichloromethyl groups attached to the *s*-triazine ring could not be replaced by tertiary alkoxy or phenoxy groups. When compounds I or XIII were refluxed with tertiary butyl alcohol or phenol, only starting materials were recovered besides small amounts of unidentified products.

Although the conversion of 2,4,6-tristrichloromethyl-*s*-triazine to the desired mono- or dialkoxy substituted trichloromethyl-*s*-triazines occurred in excellent yields, small amounts of solid by-products were isolated. These by-products, only slightly soluble in and not attacked by boiling water and ethanol, had the correct analysis in each case for the tertiary amine salts of 2-hydroxy-4,6-bistrichloromethyl-*s*-triazine (XVIII–XXI), depending on the tertiary amine used for the reaction.



XVIII. $N(R)_3$, triethylamine
XIX. $N(R)_3$, tributylamine
XX. $N(R)_3$, *N*-ethylpiperidine
XXI. $N(R)_3$, *N*-methylmorpholine

The only explanation for the formation of these tertiary amine salts was that traces of water present in the reactants caused a side reaction, which indicated that the tertiary amine salts XVIII–XXI could be prepared exclusively, if water instead of an alcohol were employed in the reaction. This was confirmed by the formation of these salts (XVIII–XXI) when 2,4,6-tristrichloromethyl-*s*-triazine (I) was refluxed in water in the presence of the corresponding tertiary amines. The desired reaction could not be achieved in the presence of *N*,*N*-dimethylaniline or pyridine, although in the latter reaction small amounts of cyanuric acid (III) could be isolated besides unchanged I.

Surprisingly, the tertiary amine salt XVIII was also formed, when 2,4,6-tristrichloromethyl-*s*-triazine (I) was treated with trifluoroethanol in the presence of triethylamine; not even traces of the desired 2-trifluoroethoxy-4,6-bistrichloromethyl-*s*-triazine (XXII) were obtained. Apparently, trifluoroethanol is too acidic and, therefore, the reaction leads to the quantitative formation of XVIII rather than to XXII.

The configuration of the tertiary amine salts XVIII–XXI was confirmed by their reaction with phosphorus oxychloride to give nearly quantitative yields of 2-chloro-4,6-bistrichloromethyl-*s*-triazine (XXIII)[6] and by their hydrogenolysis to give 2-hydroxy-4,6-dimethyl-*s*-triazine (XXIV)[6] directly and not the corresponding tertiary amine salt. This is in contrast to the reported hydrogenolysis of 2-hydroxy-4,6-bis(mono-, di-, or trichloromethyl)-*s*-triazine mono-, di-, or trichloroacetamidine salts which gave in each case the 2-hydroxy-4,6-dimethyl-*s*-triazine acetamidine salt.[6] Apparently, 2-hydroxy-4,6-dimethyl-*s*-triazine (XXIV) is not acidic enough to form salts with tertiary amines. This was confirmed by an experiment in which an ethanolic solution of XXIV and excess triethylamine were allowed to evaporate resulting in the quantitative recovery of XXIV.

Finally, the reaction of trichloromethyl substituted *s*-triazines with mercaptans or hydrogen sulfide in the presence of tertiary amines was investigated. The results of these experiments differ entirely from those obtained with alcohols or water and for this reason will be the subject of further investigations.

EXPERIMENTAL[7]

Reaction of 2,4,6-tristrichloromethyl-s-triazine (I) *with ethanol in the presence of sodium ethoxide or sodium hydroxide.* The reactants were refluxed in ethanol for 30 min. and, after cooling, the solvent removed *in vacuo*. The products obtained from the resulting residue by treatment with ethanol or petroleum ether (b.p. 90–97°) are listed in Table I.

TABLE I

REACTION OF I WITH ETHANOL IN BASE

Base	Mole Equivalents	Compounds Obtained, %			
		I	II[a]	III[b]	Unidentified
C_2H_5ONa	0.1	90	5	5	—
C_2H_5ONa	1	—	62	29	—
C_2H_5ONa	2	—	84	11	—
C_2H_5ONa	3	—	87	9	—
NaOH	1	—	9	35	56

[a] 2,4,6-Trisethoxy-*s*-triazine. [b] Cyanuric acid.

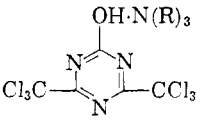
General procedure for the preparation of 2-alkoxy-4,6-bistrichloromethyl-s-triazines. 2-n-Butoxy-4,6-bistrichloromethyl-s-triazine (VII). A 30-g. sample of triethylamine was added at 0°, with stirring, to the solution of 33 g. of 2,4,6-tristrichloromethyl-*s*-triazine (I) in 200 ml. of *n*-butyl alcohol. The reaction mixture was kept overnight between 0° and room temperature. Triethylamine, excess butyl alcohol, and the chloroform formed were removed *in vacuo* at a maximum bath temperature of 20°. The oily residue was dissolved in 250 ml. of petroleum ether (b.p. 30–40°) whereupon a small amount of a solid by-product precipitated.

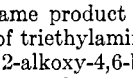
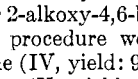
(6) H. Schroeder, *J. Am. Chem. Soc.*, **78**, 2447 (1956).

(7) All melting points were determined with the Fisher-Johns apparatus; microanalyses were by Spang, Microanalytical Laboratory, Ann Arbor, Mich.

TABLE II

TERTIARY AMINE SALTS OF 2-HYDROXY-4,6-BISTRICHLOROMETHYL-*s*-TRIAZINE



Compound	$N(R)_3$	M.P.	Yield, %	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	Cl, % Calcd.	Cl, % Found	N, % Calcd.	N, % Found
XVIII	$N(C_2H_5)_3$	178–180	81.5	$C_{11}H_{16}Cl_6N_4O$	30.51	30.59	3.75	3.77	49.11	47.86	12.94	12.89
XIX	$N(n\text{-}C_4H_9)_3$	106–108	76.5	$C_{17}H_{28}Cl_6N_4O$	39.48	39.63	5.46	5.49	41.14	41.11	10.83	10.73
XX		215–216.5	90.0	$C_{12}H_{16}Cl_6N_4O$	32.38	32.20	3.62	3.94	47.81	47.81	12.59	12.60
XXI		202–204	100	$C_{10}H_{12}Cl_6N_4O_2$	27.74	27.67	2.79	2.92	49.11	49.04	12.94	12.83

The petroleum ether was removed from the filtrate and the remainder distilled *in vacuo*, yielding 20.1 g. (72.5%) of 2-*n*-butoxy-4,6-bistrichloromethyl-*s*-triazine (VII); colorless liquid; b.p. 152–154° (0.7 mm.) (lit.[5] b.p. 146 (0.3 mm.)), n_D^{25} 1.5282 (lit.[5] n_D^{27} 1.5289).

Anal. Calcd. for $C_9H_9Cl_6N_3O$: C, 27.86; H, 2.34; N, 10.83; Cl, 54.84. Found: C, 27.99; H, 2.26; N, 10.89; Cl, 54.69.

The same product was obtained with *N*-ethylpiperidine instead of triethylamine; yield: 66%.

Other 2-alkoxy-4,6-bistrichloromethyl-*s*-triazines prepared by this procedure were 2-methoxy-4,6-bistrichloromethyl-*s*-triazine (IV, yield: 92%), 2-ethoxy-4,6-bistrichloromethyl-*s*-triazine (V, yield: 82.3%), and 2-isopropoxy-4,6-bistrichloromethyl-*s*-triazine (VI, yield: 82.7%). Boiling points and refractive indices of these compounds corresponded closely with those reported in the literature.[5]

General procedures for the preparation of 2,4-bisalkoxy-6-trichloromethyl-s-triazines. 2,4-Bisethoxy-6-trichloromethyl-s-triazine (VIII). (a) The solution of 21.7 g. of tristrichloromethyl-*s*-triazine and 20 g. of triethylamine in 400 ml. of ethanol was refluxed for 8 hr. Then the triethylamine, the excess ethanol, and the chloroform formed were removed by distillation and the oily residue was dissolved in 150 ml. of petroleum ether (b.p. 30–40°) whereupon a small amount of an insoluble by-product precipitated. The petroleum ether was distilled from the filtrate and the remainder distilled *in vacuo*, yielding 11.6 g. (81.3%) of 2,4-bisethoxy-6-trichloromethyl-*s*-triazine (VIII); b.p. 134–135.5° (1.9 mm.) (lit.[5] b.p. 124° (0.1 mm.)), n_D^{25} 1.5111 (lit.[5] n_D^{30} 1.5112). (b) This compound was also obtained by refluxing a solution of 2-ethoxy-4,6-bistrichloromethyl-*s*-triazine (27 g). and triethylamine (31.3 g.) in 150 ml. of ethanol for 7 hr. 2,4-Bisethoxy-6-trichloromethyl-*s*-triazine (VIII) was isolated from the reaction mixture as described above; yield: 88.2%; b.p. 133.5–135.5° (1.9 mm.); n_D^{26} 1.5108.

2,4-Bis-n-butoxy-6-trichloromethyl-s-triazine (IX) was prepared from 2-*n*-butoxy-4,6-bistrichloromethyl-*s*-triazine and *n*-butyl alcohol in the presence of triethylamine by procedure (b) as a colorless oil, b.p. 135–138.5° (0.1 mm.), n_D^{24} 1.5005; yield: 88.5%.

Anal. Calcd. for $C_{12}H_{18}Cl_3N_3O_2$: C, 42.06; H, 5.29; N 12.27. Found: C, 42.24; H, 5.34; N, 12.76.

General procedure for the preparation of 2-alkoxy-4-methyl-6-trichloromethyl-s-triazines. Compounds XV and XVI were obtained by refluxing 2-methyl-4,6-bistrichloromethyl-*s*-triazine (XIII) in the appropriate alcohol in the presence of a tertiary amine for 6–8 hr. The reaction products were isolated in the same manner as described for the 2,4-bisalkoxy-6-trichloromethyl-*s*-triazines.

2-Ethoxy-4-methyl-6-trichloromethyl-s-triazine (XV) was obtained from XIII (33 g.), ethanol (150 ml.), and *N*-ethylpiperidine (30 g.) as a colorless oil, b.p. 94–95° (0.55 mm.); n_D^{23} 1.5177; yield: 56%.

Anal. Calcd. for $C_7H_8Cl_3N_3O$: C, 32.77; H, 3.14; Cl, 41.46; N, 16.38. Found: C, 32.60; H, 3.24; Cl, 41.46; N, 16.36.

2-Butoxy-4-methyl-6-trichloromethyl-s-triazine (XVI) was obtained from XIII (32.6 g.), *n*-butyl alcohol (200 ml.), and *N*-ethylpiperidine (30 g.) as a yellowish oil, b.p. 128–130° (0.6 mm.); n_D^{23} 1.5088; yield: 33.5%.

Anal. Calcd. for $C_9H_{12}Cl_3N_3O$: C, 37.98; H, 4.25; N, 14.77. Found: C, 37.99; H, 4.21; N, 14.81.

General procedure for the preparation of 2-alkoxy-4-phenyl-6-trichloromethyl-s-triazines. 2-Ethoxy-4-phenyl-6-trichloromethyl-s-triazine (XVII). 2-Phenyl-4,6-bistrichloromethyl-*s*-triazine (20 g.) (XIV), ethanol (200 ml.), and triethylamine (39 g.) were refluxed for 8 hr. Triethylamine, excess ethanol, and chloroform were removed by distillation. The remainder solidified at room temperature and was recrystallized from petroleum ether (b.p. 90–97°), resulting in crystals which proved to be 2-ethoxy-4-phenyl-6-trichloromethyl-*s*-triazine (XVII); yield: 14.2 g. or 89%; m.p. 78–79.5°.

Anal. Calcd. for $C_{12}H_{10}Cl_3N_3O$: C, 45.24; H, 3.16; Cl, 33.39; N, 13.19. Found: C, 45.29; H, 3.27; Cl, 32.76; N, 13.14.

General procedure for the preparation of tertiary amine salts of 2-hydroxy-4,6-bistrichloromethyl-s-triazine. Triethylamine salt of 2-hydroxy-4,6-bistrichloromethyl-2-triazine (XVIII). A mixture of 2,4,6-tristrichloromethyl-*s*-triazine, (I, 43.35 g.), triethylamine (42.8 g.), and water (250 ml.) was refluxed, with stirring, for 3 hr. After cooling, the precipitated triethylamine salt of the 2-hydroxy-4,6-bistrichloromethyl-*s*-triazine was filtered, yielding 35.3 g. or 81.5% of product, m.p. 173–177°. After one crystallization from dioxane the salt melted at 178–180°.

According to this procedure other tertiary amine salts were synthesized which are listed in Table II. The tributylamine salt separated from the reaction mixture as an oil. Addition of petroleum ether (b.p. 63–68°) and subsequent evaporation of the solvent resulted in crystallization of the salt. The triethylamine salt XVIII was also obtained, when 2,4,6-tristrichloromethyl-*s*-triazine (35 g.), trifluoroethanol (80 g.), and triethylamine (35 g.) were stirred at 0° for 6 hr. Upon removing the low boiling material between 0° and 20°, 32 g. (92%) of XVIII separated; m.p. 174–178°. A mixed melting point with an authentic sample showed no depression.

2-Chloro-4,6-bistrichloromethyl-s-triazine (XXIII). The triethylamine salt XVIII (30 g.) was stirred and refluxed with phosphorus oxychloride (150 ml.) for 3 hr. The excess phosphorus oxychloride was removed *in vacuo* and the resulting oil slowly added to a mixture of ice and water. The separated 2-chloro-4,6-bistrichloromethyl-*s*-triazine (XXIII)

was taken up with petroleum ether (b.p. 30–40°). After the solution had been concentrated to about 50 ml. and kept at −20° for 5 hr., 11 g. of crystals precipitated.

A further crop of crystals (11.1 g.) was obtained, when the mother liquor was concentrated to about 25 ml. and cooled again to −20°, thus improving the yield of XXIII to 91.4%. The melting point of this compound was 56–57° and showed no depression with an authentic sample.

The tertiary amine salts XX and XXI, respectively, were converted into XXIII by the same procedure; yield: 94.2% and 87%, resp.

2-Hydroxy-4,6-dimethyl-s-triazine (XXIV). A mixture of the triethylamine salt XVIII (8.6 g., 0.02 mole), triethylamine (12.32 g., 0.12 mole), 2% palladium on carbon (12 g.), and methanol (150 ml.) was shaken at room temperature with hydrogen. After the absorption of hydrogen was complete, the catalyst was filtered and a solution of sodium hydroxide (4.8 g., 0.12 mole) in methanol (50 ml.) was added to the filtrate, whereby the triethylamine hydrochloride was converted into triethylamine and sodium chloride. After the precipitated sodium chloride was removed by filtration, the filtrate was evaporated to dryness at reduced pressure. The residue was taken up with absolute ethanol, a further crop of insoluble sodium chloride removed by filtration, and the 2-hydroxy-4,6-dimethyl-*s*-triazine (XXIV) precipitated with ether. The precipitate was sublimed *in vacuo* (bath temperature 160–178° at 0.05–0.02 mm), yielding 2 g. (80%) of pure XXIV; m.p. 236–237° (lit.[6] m.p. 230–231°). A mixed melting point with an authentic sample showed no depression.

By the same procedure, XXIV was obtained from the *N*-ethylpiperidine salt (XX), yield 84%.

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COLUMBUS 10, OHIO

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

Synthesis and Reactions of 5-Bromomethyl- and 5-Chloromethyluracil

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The chlorination of 6-methyl-2-methylmercapto-4-pyrimidinol (I) with *N*-chlorosuccinimide in the presence of benzoyl peroxide gives only the nuclear halogenated product, 5-chloro-6-methyl-2-methylmercapto-4-pyrimidinol (III), and not the isomeric 6-chloromethyl derivative (II) as was previously assumed.[4] 5-Chloromethyluracil (VI) was prepared by the reaction of 5-hydroxymethyluracil (V) with thionyl chloride in the presence of pyridine. Similarly, the treatment of V with hydrogen bromide in glacial acetic acid results in the formation of 5-bromomethyluracil (VII). A few displacement reactions of these compounds are presented, including the preparation of the thiamine analog, 3-(2′,4′-dihydroxy-5′-pyrimidylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium bromide (XI).

The halogenated thymine derivatives, 5-bromomethyluracil (VII) and the corresponding chloro compound (VI), have long been desired as reactive intermediates for the introduction of the thyminyl residue into other molecules.[1] Although Johnson and his coworkers were successful in preparing 5-chloromethyl-6-methyluracil from the reaction of 6-methyluracil with chloromethyl methyl ether, the synthesis of 5-chloromethyluracil by this method was not possible.[1c] These workers apparently did not attempt the direct conversion of 5-hydroxymethyluracil (V) to the corresponding 5-halomethyl derivatives, as the former compound (V) was erroneously thought to be quite unstable, decomposing readily to formaldehyde and uracil.[2] Recent work, however, has shown that 5-hydroxymethyluracil (V) is a reasonably stable compound and may be prepared in good yield from uracil and formaldehyde in alkaline solution.[3]

A compound, obtained by the interaction of *N*-chlorosuccinimide with thymine in chloroform containing benzoyl peroxide, was assigned the 5-chloromethyluracil (VI) structure in 1954.[4] However, this structural assignment seemed to us fairly unlikely, as (1) the chlorine in their compound was stable to boiling ethanol or water, whereas halomethylpyrimidines are notoriously labile compounds,[1c,5] and (2) *N*-chlorosuccinimide is known to be ineffective in producing allylic substitution.[6] We have discovered that the compound of West and Barrett[4] is, in reality, 5-chloro-6-ethoxy-5-methylhydrouracil, a compound previously obtained by Johnson and Sprague[7] from another route. These findings are corroborated by a recent paper,[8] which has appeared since our work was completed.

Because of the above facts, it was desirable to investigate a second allylic chlorination reported in the West and Barrett paper.[4] These workers ob-

(1) (a) D. Riehl and T. B. Johnson, *Rec. trav. chim.*, **59**, 87 (1940); (b) M. M. Endicott and T. B. Johnson, *J. Am. Chem. Soc.*, **63**, 1286 (1941); (c) M. M. Endicott and T. B. Johnson, *J. Am. Chem. Soc.*, **63**, 2063 (1941).

(2) T. B. Johnson and A. Litzinger, *J. Am. Chem. Soc.*, **58**, 1940 (1936).

(3) R. E. Cline, R. M. Fink, and K. Fink, *J. Am. Chem. Soc.*, **81**, 2521 (1959).

(4) R. A. West and H. W. Barrett, *J. Am. Chem. Soc.*, **76**, 3146 (1954).

(5) T. Okuda and C. C. Price, *J. Org. Chem.*, **24**, 14 (1959).

(6) C. Djerassi, *Chem. Revs.*, **43**, 271 (1948).

(7) T. B. Johnson and J. M. Sprague, *J. Am. Chem. Soc.*, **59**, 2436 (1937).

(8) J. H. Burckhalter, R. J. Seiwald, and H. C. Scarborough, *J. Am. Chem. Soc.*, **82**, 991 (1960).