[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Hindered Amines. Preparation and Reactions of Some Secondary Acetylenic Amines[1]

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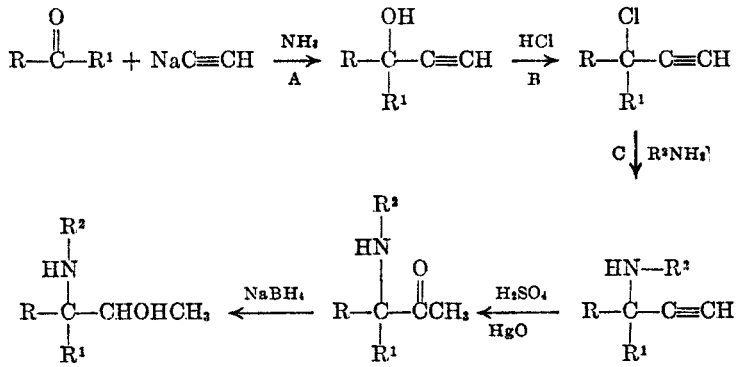
The preparation of additional[4] highly hindered amines and some related ketones and alcohols is reported. The isolation of conjugated Schiff's bases from the α-chloroacetylenes and strong bases is discussed.

The findings by Hennion and Teach[2] that α-chloroacetylenes react with sodamide or sodium acetylide in liquid ammonia to form acetylenic amines was followed by the report[3] that some primary and secondary amines could be used in place of the strong base to give secondary and tertiary acetylenic amines. Further work[4] in this field has shown that a variety of tertiary α-chloroacetylenes and primary amines can be used in this reaction.

This communication reports an extension of this reaction to include many heretofore inaccessible acetylenic amines, their derivatives, and hydrogenation products.

The Hennion procedure for the preparation of these compounds consists of the first three steps of the following reactions:



The work reported previously[2-4] dealt with compounds where R and R^1 were methyl or ethyl or combined as cyclohexyl. This reaction has been extended to include the *n*-propyl, isopropyl, and *t*-butyl groups. However, when these larger groups are present on the tertiary carbon atom, conditions for both reaction B and C must be altered.

Reaction B has been studied extensively.[5a,b] The difficulties reported in purifying the α-chloroacetylene were confirmed; therefore our aminations were carried out with the crude chloride.

When the R and R^1 groups are large, the reaction C is very slow. Even with 3-chloro-3-methyl-1-butyne and *t*-butylamine the reaction time is ten to fourteen days at 20–30°, and when R and R^1 are larger than methyl this time is greatly increased. It has been found[4] that the addition of catalytic amounts of cuprous chloride or copper bronze to the reaction mixture greatly increased the reaction rate. In most cases slow addition of the acetylenic chloride to a mixture of the amine and catalyst must be practiced, or a very vigorous reaction may ensue. The use of dimethylformamide as a solvent gave much better yields in the highly hindered cases (where R or R^1 is isopropyl or *t*-butyl).

When the α-chloroacetylene (IV) was treated with lithium *t*-butylamide, the conjugated Schiff's base VI was isolated in addition to the acetylenic amine. The structure VI was suggested by the similarity of its infrared absorption curve to that obtained from the Schiff's base VII which was prepared from crotonaldehyde and *t*-butylamine. All of these compounds showed sharp, medium to strong bands at 6.00 μ to 6.06 μ (C=N) and 6.16 μ to 6.20 μ (C=C).

The simpler Schiff's base VIII was prepared by the action of lithium *t*-butylamide on 3-chloro-3-methyl-1-butyne. The hydrogenation of VIII over platinum oxide gave isoamyl-*t*-butylamine (IX)

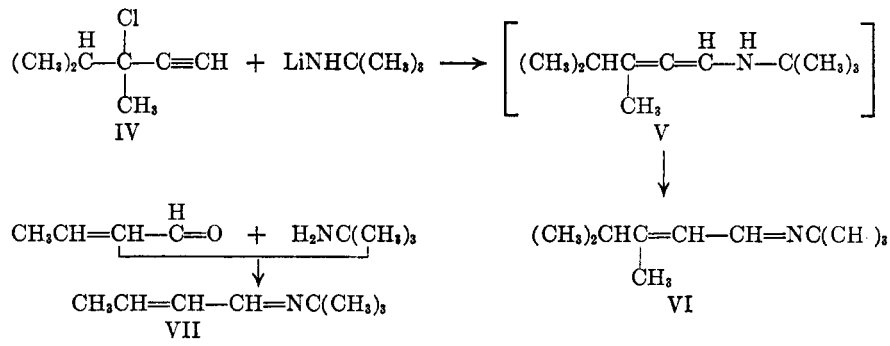
(1) Given in part at the American Chemical Society Meeting, New York City, September 11–16, 1960.

(2) G. F. Hennion and E. G. Teach, *J. Am. Chem. Soc.*, 75, 1653 (1953).

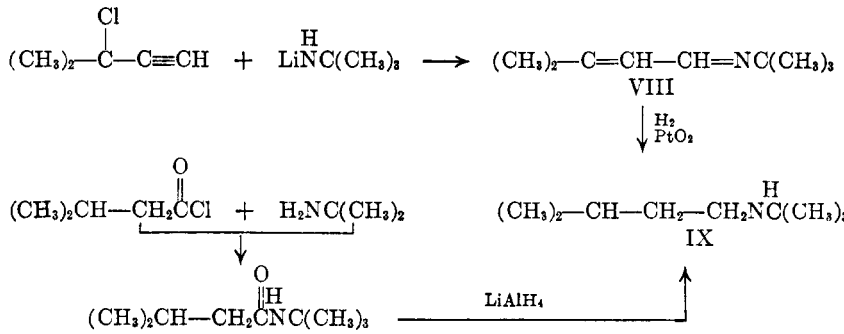
(3) G. F. Hennion and K. W. Nelson, *J. Am. Chem. Soc.*, 79, 2142 (1957).

(4) G. F. Hennion and R. S. Hanzel, *J. Am. Chem. Soc.*, 82, 4908 (1960).

(5)(a) G. F. Hennion, J. J. Sheehan, and D. E. Maloney, *J. Am. Chem. Soc.*, 72, 3542 (1950). (b) G. F. Hennion and A. P. Boisselle, *J. Org. Chem.*, 26, 725 (1961).



A more rigorous proof of structure was obtained in the following manner:



which was also prepared by reduction of *N*-*t*-butylisovalerylamide with lithium aluminum hydride.

The conjugated Schiff's bases (VI and VIII) were unstable and gradually decomposed on standing; they were also unstable in acid solution although the hydrochloride salts could be prepared in nonaqueous media.

Difficulty in hydrogenating some of the more hindered acetylenic amines to the saturated derivatives has been reported.[4] It has now been found that some of these saturated amines may be prepared by hydrogenating the acetylenic amines as the hydrochlorides over platinum oxide.

In a previous communication[6] a method for the direct hydration of primary acetylenic amines to the amino ketones was not developed, although this transformation was accomplished *via* the acetyl derivatives. It has been found that many of the secondary acetylenic amines in this series can be readily hydrated to the corresponding amino ketones by the usual procedure.[7] On treatment with sodium borohydride or lithium aluminum hydride, these ketones can be reduced to the corresponding amino alcohols.

EXPERIMENTAL

Nearly all of the compounds in these series melted with decomposition but without discoloration. Since these decomposition points were easily duplicated, these are listed as the melting points. The melting points are uncorrected.

Because of the impossibilities of calculating yields since the intermediate chlorides were not purified,[5a,d] no yields are given in the Experimental however, since yields of 21% are reported for the preparation of 3-*t*-butylamino-3-ethyl-1-pentyne from purified chloride and the yield of the required α-chloroacetylene is reported[8] to be about 60%, the over-all yield would be about 12%. Since we have found that as R and R^1 increase in size the yields of the α-chloroacetylenes are diminished, we would expect our over-all yields to be below 10%. The amines themselves were not purified but were converted to the hydrochlorides for purification. The purity and structure of the α-amino acetylene were checked by infrared spectra and titration. In general, no attempts to find maximum conditions for optimum yields were made; only a single run for each α-amino acetylene was carried out.

α-Acetylenic amines. To a well-stirred mixture of three equivalents of the amine, one equivalent of water, and 1–2 g. of copper bronze, the α-chloroacetylene (1 eq.) was added slowly. The mixture became warm, and the rate of addition was regulated to keep the temperature below 40°. An ice bath was used when necessary. After all of the chloro compound had been added, the mixture was stirred overnight. Water was added, and the layers were separated. The water layer was extracted with ether and the ether layer added to the organic material. The ether solution was extracted with cold dilute hydrochloric acid, and the water layer was neutralized with sodium hydroxide. The water layer was extracted with ether; and after drying, the ether was removed at reduced pressure, and the remaining oil was distilled. The hydrochloride salts were prepared from the distillates in ether by treatment with anhydrous hydrogen chloride (see Table I).

Preparation of the ketones. To a mixture of 30 g. of concd. sulfuric acid, 22 ml. of methanol, 28 ml. of water, and 1 g. of mercuric oxide, there was added slowly 0.1 mole of the acetylenic amine. The mixture was then refluxed with stirring for 4 hr., and additional 1-g. portions of mercuric oxide were added hourly. The mixture was treated with carbon and filtered. The filtrate was made basic with sodium hydroxide and was extracted with ether. The ether solution was dried over anhydrous magnesium sulfate, and the ether

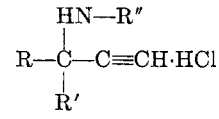
(6) G. F. Hennion and E. G. Teach, *J. Am. Chem. Soc.*, 75, 4297 (1953).

(7) J. D. Rose and B. C. L. Weedon, *J. Chem. Soc.*, 782 (1949).

(8) G. F. Hennion and K. W. Nelson, *J. Am. Chem. Soc.*, 79, 2144 (1957).

TABLE I

ACETYLENIC AMINES

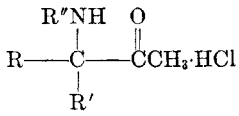


R	R′	R″	M.P.	Formula	Calcd.	Found
CH_3	$CH_2CH_2CH_3$	$CH(CH_3)_2$	167–169	$C_{10}H_{20}NCl$	N 7.38	N 7.37
CH_3	$CH_2CH_2CH_3$	$C(CH_3)_3$	175–176	$C_{11}H_{22}NCl$	N 6.88	N 6.65
CH_3	$CH(CH_3)_2$	$CH(CH_3)_2$	179–180	$C_{10}H_{20}NCl$	N 7.38	N 7.17
					Cl 18.69	Cl 18.71
CH_3	$CH(CH_3)_2$	$C(CH_3)_3$	190–191	$C_{11}H_{22}NCl$	N 6.88	N 6.89
CH_3	$C(CH_3)_3$	$CH(CH_3)_2$	198–199	$C_{11}H_{22}NCl$	N 6.88	N 6.88
CH_3	$C(CH_3)_3$	$C(CH_3)_3$	[a]	$C_{12}H_{24}NCl$	N 6.43	N 6.35
CH_3	CH_3	$C(CH_3)_2(C_2H_5)$	167–169	$C_{10}H_{20}NCl$	N 7.38	N 7.17
CH_3	CH_3	$CH(CH_3)CHC_3H_7$	133–135	$C_{10}H_{20}NCl$	N 7.38	N 7.11
$CH(CH_3)_2$	$CH(CH_3)_2$	C_2H_5	177–179	$C_{11}H_{22}NCl$	C 64.84	C 64.55
					H 10.88	H 11.10
					N 6.88	N 7.03
$CH(CH_3)_2$	$CH(CH_3)_2$	$CH(CH_3)_2$	206–207	$C_{12}H_{24}NCl$	N 6.43	N 6.58
					Cl 16.28	Cl 16.54
CH_3	CH_3	$-C(CH_3)_2-CH_2-C(CH_3)_2-CH_3$	168–169	$C_{13}H_{26}NCl$	N 6.04	N 6.08
CH_3	$(CH_2)_3CH_3$	$C(CH_3)_3$	144–146	$C_{12}H_{24}NCl$	N 6.43	N 6.39
C_2H_5	$CH_2CH_2CH_3$	$C(CH_3)_3$	163–164	$C_{12}H_{24}NCl$	N 6.43	N 6.30
CH_3	$CH(CH_3)CH_2CH_3$	$C(CH_3)_3$	174–175	$C_{12}H_{24}NCl$	N 6.43	N 6.25
CH_3	CH_3	$C(C_2H_5)_3$	172–173	$C_{12}H_{24}NCl$	N 6.43	N 6.65
	$-CH_2-CH_2-CH_2-CH_2-$	$C(CH_3)_3$	234–235	$C_{11}H_{20}NCl$	N 6.94	N 7.14
C_2H_5	$CH(CH_3)_2$	$CH(CH_3)_2$	206–207	$C_{11}H_{22}NCl$	N 6.88	N 6.58
					Cl 17.40	Cl 17.75

[a] Gradually decomposes above 180°.

TABLE II

AMINO KETONES



R	R′	R″	M.P.	Formula	Calcd.	Found
CH_3	$CH(CH_3)_2$	$C(CH_3)_3$	138–140	$C_{11}H_{24}NOCl$	N 6.32	N 6.21
					Cl 15.99	Cl 16.17
CH_3	$CH(CH_3)_2$	$CH(CH_3)_2$	122–124[a]	$C_{14}H_{27}NO_7$[a]	C 52.32	C 52.50
					H 8.47	H 8.70
					N 4.36	N 4.29
CH_3	CH_3	$C(CH_3)_2(C_2H_5)$	123–125	$C_{10}H_{22}NOCl$	N 6.74	N 6.67
					Cl 17.07	Cl 17.43

[a] Isolated as the tartrate.

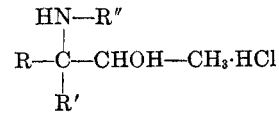
was evaporated. The residue was distilled at reduced pressure. The hydrochlorides were made in the usual manner (see Table II).

Preparation of the alcohols. An excess of sodium borohydride was added to an ethanolic solution of the ketone. The mixture was allowed to stir overnight. The alcohol was distilled at reduced pressure, and water was added to the residue. The mixture was extracted with ether, and the ether solution was dried over magnesium sulfate. The ether solution was filtered, and alcoholic hydrogen chloride was added. The hydrochlorides were recrystallized from an appropriate solvent; usually either ethyl acetate or methyl ethyl ketone was satisfactory (see Table III).

N-t-Butyl-3-methylcrotonaldiimine (VIII). To a mixture of 9.66 g. (1.4 moles) of lithium ribbon in 1 l. of diethyl ether, there was added slowly, with stirring, 92.4 g. (0.6 mole) of bromobenzene. After the addition had been completed, the mixture was filtered through glass wool to remove the excess lithium ribbon. To the resulting solution there was added, dropwise with stirring, 58.4 g. (0.8 mole) of *t*-

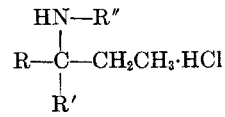
TABLE III

AMINO ALCOHOLS



R	R′	R″	M.P.	Formula	Calcd.	Found
CH_3	$CH(CH_3)_2$	$CH(CH_3)_2$	118–120	$C_{10}H_{24}NOCl$	N 6.68	N 6.84
CH_3	$CH(CH_3)_2$	$C(CH_3)_3$	104–106	$C_{11}H_{26}NOCl$	N 6.26	N 5.96
CH_3	$C(CH_3)_3$	$CH(CH_3)_2$	130–132	$C_{11}H_{26}NOCl$	N 6.26	N 6.13
CH_3	CH_3	$C(CH_3)(C_2H_5)$	72–75	$C_{10}H_{24}NOCl$	N 6.68 Cl 16.90	N 6.42 Cl 17.12

TABLE IV. SATURATED AMINES



R	R′	R″	M.P.	Formula	Calcd.	Found
CH_3	$CH(CH_3)_2$	$CH(CH_3)_2$	183–184	$C_{10}H_{24}NCl$	N 7.23	N 7.53
CH_3	$CH_2CH_2CH_3$	$CH(CH_3)_2$	113–115	$C_{10}H_{24}NCl$	N 7.23	N 7.00
CH_3	$CH_2CH_2CH_3$	$C(CH_3)_3$	142–144	$C_{11}H_{26}NCl$	N 6.74 Cl 17.06	N 7.00 Cl 17.44
CH_3	$C(CH_3)_3$	$CH(CH_3)_2$	182–183	$C_{11}H_{26}NCl$	C 63.58 H 12.61 N 6.74	C 63.74 H 12.57 N 6.72
CH_3	CH_3	$-CH(CH_3)C_2H_5$	137–139	$C_9H_{22}NCl$	N 7.79	N 7.71
CH_3	CH_3	$-C(CH_3)_2C_2H_5$	183–185	$C_{10}H_{24}NCl$	N 7.23	N 7.54
CH_3	CH_3	$-CH(CH_3)C_3H_7$	142–144	$C_{10}H_{24}NCl$	N 7.23	N 7.04
$(CH_3)_2CH$	$CH(CH_3)_2$	C_2H_5	195–196	$C_{11}H_{26}NCl$	C 63.58 H 12.61	C 63.58 H 12.59
C_2H_5	C_2H_5	$C(CH_3)_3$	168	$C_{11}H_{26}NCl$	C 63.58 H 12.61	C 63.24 H 12.48
CH_3	$CH(CH_3)_2$	$C(CH_3)_3$	136–137	$C_{11}H_{26}NBr$[a]	C 52.51 H 10.39 N 5.55	C 52.51 H 10.09 N 5.75
$-(CH_2)_5-$		$C(CH_3)_3$	181–182	$C_{12}H_{26}NCl$	N 6.37	N 6.21

[a] Hydrobromide.

butylamine, and the mixture was then stirred for 0.5 hr. To the cooled and vigorously stirred mixture, 61.5 g. (0.6 mole) of 3-chloro-3-methyl-1-butyne was added dropwise; the stirring was then maintained for 3 hr. at room temperature. One liter of water was added, and the layers were separated; the organic layer was dried over magnesium sulfate and concentrated at reduced pressure. The residue was distilled under reduced pressure. A yield of 8.5 g. of VIII, boiling at 50–54°/10 mm., was obtained. Infrared spectrum in chloroform: 6.00 μ (shoulder); 6.04 μ (C=N); 6.19 μ (C=C); no C=CH; no NH.

t-Butylisoamylamine hydrochloride. Method A. A mixture of 8.5 g. of VIII, dissolved in 300 ml. of ethanol, was hydrogenated with Raney nickel under 40 p.s.i. of hydrogen. The catalyst was filtered, and the filtrate was made acidic with alcoholic hydrogen chloride and concentrated under reduced pressure. The residue was dissolved in water; the solution was made basic with 50% sodium hydroxide and extracted with ether. The ether was dried over magnesium sulfate and concentrated. The product (3.5 g.) was collected at 90°/125 mm., n_D^{25} 1.4119. The hydrochloride was prepared in ether and recrystallized from a mixture of methyl ethyl ketone and ether; it melted at 184–186°.

Anal. Calcd. for $C_9H_{22}NCl$: C, 60.14; H, 12.34. Found: C, 59.98; H, 12.31.

t-Butylisovalerylamide. Isovaleryl chloride was added slowly, with stirring, to an excess of *t*-butylamine. Water was added, and the layers were separated. The water layer was extracted with ether, and the ether layer, combined with the organic layer, was dried over magnesium sulfate and concentrated at reduced pressure. The residue was recrystallized from petroleum ether (b.p. 30–60°), m.p. 92–94°.

Anal. Calcd. for $C_9H_{19}NO$: N, 8.91. Found: N, 8.66.

t-Butylisoamylamine hydrochloride. Method B. The *t*-butylisovalerylamide was reduced with lithium aluminum hydride in ether. The hydrochloride was prepared, and after recrystallization from methyl ethyl ketone and ether, it melted at 185–186°.

Anal. Calcd. for $C_9H_{22}NCl$: N, 7.79; Cl 19.73. Found: N, 7.85; 7.85; Cl, 20.09.

A mixture of the product from Methods A and B melted at 185–186°.

t-Butyl-3,4-dimethylpentylamine. A solution of the Schiff's base V (prepared in a similar manner to III) in ethanol was hydrogenated over Raney nickel under 40 p.s.i. of hydrogen. After filtration the solution was made acidic with alcoholic hydrogen chloride and concentrated at reduced pressure. The residue was crystallized from methyl ethyl ketone. The solid which separated was largely *t*-butylamine hydrochloride. The mother liquors were concentrated, and the solid was recrystallized twice from ethyl acetate, m.p. 177–179°.

Anal. Calcd. for $C_{11}H_{26}NCl$: C, 63.89; H, 12.19; N, 6.77. Found: C, 63.80; H, 12.16; N, 6.42.

α-Acetylenic amines by the dimethylformamide method. 3-Isopropylamino-3,4-dimethyl-1-pentyne. To a mixture of 280 g. (4.65 moles) of isopropylamine, 2 g. of cuprous chloride, 2 g. of copper bronze, and 1 l. of dimethylformamide, there was added, dropwise with stirring, 180 g. (1.38 moles) of 3,4-dimethyl-3-chloropentyne. The mixture was stirred overnight at room temperature, and 1 l. of water was added followed by 1.5 moles of 50% sodium hydroxide. The solution was extracted with ether, and the ether layer was washed with water, dried over magnesium sulfate, and concentrated at reduced pressure. The residue was distilled under vacuum, and the product collected at 45–47°/6 mm. weighed 70 g. (33%), n_D^{25} 1.4315.

Preparation of saturated amines. In addition to the method previously published,[4] the following procedure was used: an alcoholic solution of the amine and two equivalents of hydrogen chloride was hydrogenated over platinum oxide at 40 p.s.i. of hydrogen. The catalyst was filtered and the solution was concentrated at reduced pressure. The hydrochloride was purified by recrystallization or converted to the free base which could be purified by distillation (see Table IV).

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INDIANAPOLIS, IND.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Highly Hindered Aliphatic Tertiary Amines

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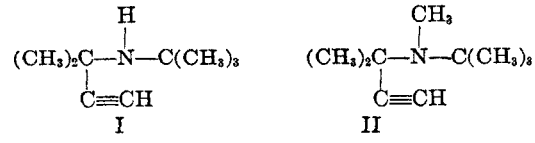
The preparation of a progression of highly hindered aliphatic noncyclic tertiary amines by alkyl sulfate treatment of hindered secondary amines is reported. The yield of tertiary amines is decreased with increased steric hindrance of the nitrogen, and the limitation by steric hindrance is shown. *N*-(*t*-Amyl)-*N*-(*t*-butyl)methylamine has the unusually high pK_a of 11.9 when determined in water.

N-(*t*-Amyl)-*N*-(isopropyl)methylamines form quaternary methyl iodides that are stable at room temperature, but *N*-(*t*-amyl)-*N*-(*t*-butyl)methylamines do not and decomposition products are isolated.

During the past decade, hindered tertiary amines were investigated, among others, by Brown[1] and by Hall,[2] who determined the basic strength of a number of representative compounds. Pharmacologically, it was discovered that certain hindered tertiary amines were effective ganglionic blocking agents.[3] The methods described by Hennion[4] were applied in this laboratory to obtain a series of hindered acetylenic secondary amines[5] of the type



I

II

represented by compound I. Certain of these compounds displayed considerable pharmacological effect, and therefore, the corresponding tertiary compounds—*e.g.*, II—were desired. This paper reports a study of the problem of converting such secondary amines to highly hindered tertiary amines and quaternization studies of the latter.

3-*t*-Butylamino-3-methyl-1-butyne (I) was treated in various ways to study its conversion to the corresponding tertiary amines. The Eschweiler-Clarke method employing formaldehyde–formic acid proved to be sensitive to the amount of formic acid and the time of heating. Excess of formic acid at reflux temperature was accompanied with loss of isobutylene and formation of 3-dimethylamino-3-methyl-1-butyne. However, by running the reaction for a longer period of time at a lower temperature, 3-[*N*-(*t*-butyl)methylamino]-3-methyl-1-butyne (II) was obtained in good yield.[6] This tertiary amine, like others later described, was characterized by a higher refractive index (about 0.02 unit) than the corresponding secondary amine. In addition, *the picrates of the tertiary amines were all found to be relatively insoluble in ethanol*, whereas the picrates of the starting secondary amines were soluble in ethanol. This fact proved helpful in

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(2) H. K. Hall, Jr., *J. Am. Chem. Soc.*, 79, 5444 (1957).

(3) H. Spinks and E. H. P. Young, *Nature*, 181, 1397 (1958).

(4) G. F. Hennion and R. S. Hanzel, *J. Am. Chem. Soc.*, 82, 4908 (1960).

(5) N. R. Easton *et al.*, *J. Org. Chem.*, 26, 3772 (1961).

(6) This method was developed by Wm. L. Garbrecht.