formed. Under the conditions used, V was the major product; only a few per cent of VI was formed.

The effect on the photoreactions of removing the air from the solutions was determined using benzene solutions of I, II, and III having concentrations of 4.6×10^{-5} *M*, 4.3×10^{-5} *M*, and 8.8×10^{-5} *M*, respectively. The solutions, in 14-mm. test tubes, were swept with benzene-saturated nitrogen (Linde, 99.9%) for 5 min. prior to and during irradiation. Source No. 1 was used as follows: for I, 1.5 min. at 9.75 in.; for II, 7 min. at 6 in.; for III, 5 min. at 16 in. For comparison, duplicate experiments were run using air in place of nitrogen. Results are given in Table I.

The Synthesis of Derivatives of α-Mercaptoamidines[1,2]

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General syntheses of α-amidinium thiosulfates (Bunte salts) and N,N′-diaryl-α-(acetylmercapto)acetamidines as potential antiradiation drugs are described.

With the discovery by Patt[3] in 1950 that mice could be protected by cysteine against otherwise lethal doses of radiation by X-rays, a new field of investigation was opened. In 1951, Bacq[4] showed that both 2-mercaptoethylamine and 3-mercaptopropylamine are more effective radioprotective agents than cysteine. A large number of analogs and functional derivatives of the above amino thiols have since been tested[5] for this activity. In the most promising compounds, the salient features appeared to be a basic functional group separated from a thiol, or potential thiol group, by two or three carbon atoms. It had been shown that when the thiol group in these amino thiols was replaced by a thiosulfate (Bunte salt) or an isothiuronium group, the activity equalled that of the parent, but these derivatives were much less toxic.

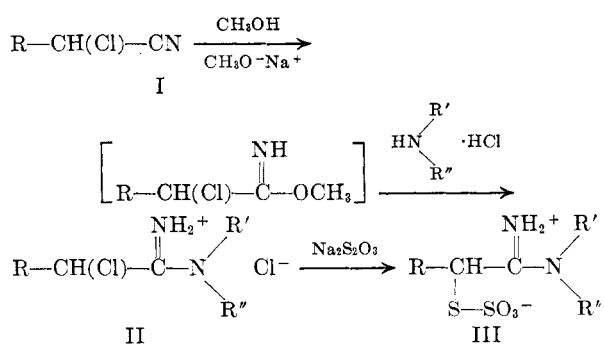
In designing potential antiradiation drugs which adhered to the above criteria, we turned our attention to the synthesis of α-mercaptoamidines and functional derivatives thereof. In these molecules the amidine is the basic group located in the vicinity of a group capable of releasing a thiol group. Three sulfur-containing groups which we considered for incorporation in the molecules were those which are hydrolyzed readily to thiols, such as the thiosulfate (Bunte salt), thiol ester, and isothiuronium groups.

Thus, this paper describes the synthesis of α-amidinium thiosulfates, III (always presented as the zwitterion), α-(acetylmercapto)acetamidines, VI, and that of an α-isothiuronium amidinium salt, VII.

In exploring synthetic routes to these amidines, it was planned to introduce the sulfur-bearing functional group as the last step. The ideal intermediates for the synthesis of all of these compounds was found to be the α-haloamidines.

The reaction scheme which proved most versatile was that leading to α-amidinium thiosulfates (Bunte salts) III. The starting materials for their synthesis were α-chloronitriles, I. When these nitriles were treated with methanol and sodium methoxide, the methyl α-chloroimidate[6] was formed but not isolated and reacted immediately with ammonium chloride or an amine hydrochloride to furnish the α-chloroamidine hydrochloride, II.

These salts were, in general, crystalline, water-soluble solids but proved to be potent vesicants which were difficult to purify. However, it was found that the impure salts were satisfactory for use in the next step.



The reaction of II with sodium thiosulfate provided highly crystalline Bunte salts, III, which were readily purified. Although contact with the latter produced most objectionable skin-rashes, they could be handled much more easily than the chloroamidines. This reaction scheme lent itself to the preparation of α-thiosulfate derivatives of acet-, propion-, and phenylacetamidines, III. Ammonia and aliphatic primary and second-

(1) This work was sponsored by a Research Contract (DA-49-193-MD-2047) from the Office of the Surgeon General, United States Army Medical Research and Development Command.

(2) From a thesis submitted by Thomas L. Welsh to the Graduate College of the University of Illinois in partial fulfillment of the requirements of the degree of Doctor of Philosophy. The preliminary findings were presented before the Anti-Radiation Drug Symposium sponsored by the Medicinal Section of the American Chemical Society in Washington, D. C., on March 29, 1962.

(3) H. M. Patt, *et al.*, *Proc. Soc. Exp. Biol. Med.*, **73**, 18 (1950).

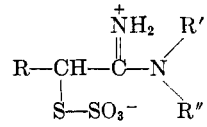
(4) Z. M. Bacq, *et al.*, *Arch. Int. Physiol.*, **59**, 442 (1951).

(5) A. Pihl and L. Eldjarn, *Pharmacol. Rev.*, **10**, 437 (1958).

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

TABLE I

AMIDINIUM THIOSULFATES (BUNTE SALTS)

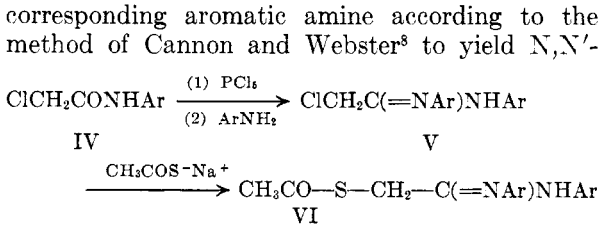


R	R′	R″	Method of prep.	Yield, %	M.p., °C. (dec.)	Molecular formula	Mol. weight		C, %	H, %	N, %	S, %
H	H	H	A	82	157–159	$C_2H_6N_2O_3S_2$	170.2	Calcd.	14.11	3.55	16.46	37.28
								Found	14.02	3.50	16.24	37.53
H	H	CH_3	A	61	154–156	$C_3H_8N_2O_3S_2$	184.2	Calcd.	19.56	4.38	15.21	
								Found	19.95	4.35	15.30	
H	H	C_2H_5	A	97	164–165	$C_4H_{10}N_2O_3S_2$	198.3	Calcd.	24.23	5.08	14.13	
								Found	24.41	5.19	13.71	
H	H	n-C_5H_{11}	B	55	140–142[a]	$C_7H_{16}N_2O_3S_2$	240.3	Calcd.	34.98	6.71	11.66	
								Found	34.93	6.69	11.20	
H	H	$C_6H_5CH_2$	A	81	154–156	$C_9H_{12}N_2O_3S_2$	260.3	Calcd.	41.52	4.65	10.76	
								Found	41.76	4.64	10.38	
H	H	$C_6H_5(CH_2)_2$	B	65	145–148[a]	$C_{10}H_{14}N_2O_3S_2$	274.4	Calcd.	43.77	5.14	10.21	
								Found	43.70	4.92	10.08	
H	CH_3	CH_3	A	82	174–175	$C_4H_{10}N_2O_3S_2$	198.3	Calcd.	24.23	5.08	14.13	
								Found	24.07	5.25	14.15	
H	—$(CH_2)_5$—		A	83	172–173	$C_7H_{14}N_2O_3S_2$	238.3	Calcd.	35.27	5.92	11.76	
								Found	35.37	6.11	11.34	
CH_3	H	H	A	92	161–163	$C_3H_8N_2O_3S_2$	184.2	Calcd.	19.56	4.38	15.21	34.81
								Found	19.72	4.39	15.22	34.93
CH_3	CH_3	CH_3	A	87	195–197	$C_5H_{12}N_2O_3S_2$	212.3	Calcd.	28.29	5.70	13.19	
								Found	28.36	5.77	12.95	
CH_3	H	$C_6H_5CH_2$	B	71	158–159	$C_{10}H_{14}N_2O_3S_2$	274.4	Calcd.	43.77	5.14	10.21	
								Found	43.83	5.25	9.95	
C_6H_5	H	H	B	44	182–183	$C_8H_{10}N_2O_3S_2$	246.3	Calcd.	39.01	4.09	11.37	
								Found	39.15	4.06	11.64	

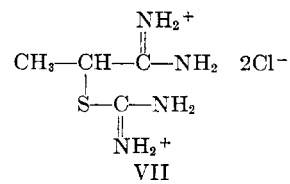
[a] Recrystallized from 30% aqueous ethanol.

ary amines afforded the requisite α-chloroamidine hydrochlorides, II, but aniline and other aromatic amines failed to give crystalline products. The amidinium thiosulfates which were synthesized as described above are listed in Table I. Attempts to hydrolyze several of the Bunte salts, III, with hydrochloric acid to the corresponding mercaptan[7] proved abortive and no recognizable products could be isolated.

A different series of derivatives of α-mercaptoamidines which was synthesized were the α-(acetylmercapto)-N,N′-diarylacetamidines, VI. This sequence of reactions commenced with chloroacetanilides, IV, which were readily prepared by the Schotten-Bauman technique from chloroacetyl chloride and the corresponding aromatic amine. These amides were treated first with phosphorus pentachloride and then with the corresponding aromatic amine according to the method of Cannon and Webster[8] to yield N,N′-diaryl-α-chloroacetamidines, V. The best yields of V were about 40% and it was essential to purify these amidines prior to the next step. Recrystallization was carried out best from hydrocarbons as these compounds polymerized in hydroxylic solvents. On prolonged storage (three to six months), these amidines decomposed and the best results were obtained when they were utilized immediately. Nucleophilic displacement by thiolacetate ion converted V to the thiolesters, VI. Again, the recrystallization of VI was achieved best from hydrocarbon solvents. Three such α-(acetylmercapto)amidines were made in this manner, when Ar is phenyl, *p*-methoxy, and *p*-ethoxyphenyl.



A third class of compounds was explored briefly. The reaction of α-chloropropionamidine hydrochloride (II. R = CH_3, R′ = R″ = H) with thiourea



VII

furnished the α-isothiuronium amidinium dihydrochloride, VII. However, a similar reaction with chloroacetamidine hydrochloride (II. R = R′ = R″ = H) did not yield the analogous product and this reaction is receiving further attention.

(7) For the acid hydrolysis of Bunte salts to mercaptans see E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. I, Chemical Publishing Co., Inc., New York, N.Y., 1958, p. 32, 328.

(8) J. Cannon and G. L. Webster, *J. Am. Pharm. Assoc. (Sci. Ed.)*, **42**, 740 (1953).

Experimental[9]

Extreme caution must be exercised in handling chloronitriles, chloroamidine salts and amidinium thiosulfates as the authors have found that these compounds cause blisters which tend to resist normal healing processes!

Starting Materials.—Chloroacetonitrile was purchased from Distillation Products Industries, Eastman Kodak Company. α-Chloropropionitrile was prepared[10] from lactonitrile[11]; α-chlorophenylacetonitrile was synthesized from benzaldehyde.[12] The amine hydrochlorides, when not available commercially, were made by the addition of a slight excess of the amine to 12 *N* hydrochloric acid with stirring at 0–10°. Evaporation to dryness *in vacuo* followed by trituration with reagent acetone gave products of excellent purity.

General Procedure for the Conversion of α-Chloronitriles to Amidinium Thiosulfates.—In some instances, the intermediate α-chloroamidine hydrochloride was isolated (Method A) in others (Method B) was converted immediately to the corresponding Bunte salt. All yields, physical constants and elemental analyses are collected in Table I.

The compounds crystallized from water unless otherwise specified in the footnote to the table.

The yields of Method A are based upon the isolated crystalline α-chloroamidine hydrochloride, and those of Method B upon the starting α-chloronitrile.

Synthesis of α-Chloroamidine Hydrochlorides.—The method of Schaefer and Peters[6] was used to synthesize these salts from α-chloronitriles. The intermediate methyl α-chloroimidate was not isolated but converted to the amidine hydrochloride. This conversion is illustrated by a typical example which afforded a crystalline salt which was isolated prior to use in the next step.

N-Benzylchloroacetamidine Hydrochloride.—Chloroacetonitrile (7.55 g.; 0.1 mole) was added dropwise to a cold stirred solution of sodium methoxide prepared by dissolving sodium (0.23 g.; 0.01 mole) in dry methanol (75 ml.). The solution was stirred at room temperature for 1 hr. Then, benzylamine hydrochloride (15.8 g.; 0.11 mole) was added and the mixture stirred at room temperature for 16 hr. The mixture was filtered to remove salt and evaporated to dryness *in vacuo*. The residue was triturated with acetone and ether to remove unchanged nitrile, filtered, and dried. The *salt* (19.6 g.; 93%) was recrystallized from isobutyl alcohol m.p. 141–142°.

Anal. Calcd. for $C_9H_{12}N_2Cl_2$ (219.1): C, 49.33; H, 5.52; N, 12.78. Found: C, 49.48; H, 4.67; N, 12.60.

In this fashion, the following α-chloroamidine hydrochlorides were prepared and crystallized from isobutyl alcohol:

N,N-Dimethylchloroacetamidine hydrochloride (84%) m.p. 176–179°.

Anal. Calcd. for $C_4H_{10}N_2Cl_2$ (157.1): C, 30.59; H, 6.42; N, 17.84. Found: C, 30.40; H, 6.52; N, 17.35.

N,N-Dimethyl-α-chloropropionamidine hydrochloride (76%), m.p. 155–158°.

Anal. Calcd. for $C_5H_{12}N_2Cl_2$ (171.1): C, 35.10; H, 7.07; N, 16.38. Found: C, 34.95; H, 7.08; N, 15.85.

This method was also used to prepare the known chloroacetamidine hydrochloride, m.p. 95–97° (lit. m.p. 99–100°[6] or 103–104°[13]), α-chloropropionamidine hydrochloride (83%) m.p. 134°; lit. m.p. 130–131°[6] and N,N-(pentamethylene)-chloroacetamidine hydrochloride, m.p. 182–184°, lit. m.p. 176°.[13]

Method A.—For these experiments the crystalline chloroamidine hydrochloride was converted to the corresponding Bunte salt. A typical experimental is described.

α-Carboxamidinomethanethiosulfuric Acid (III. R=R'=R''=H).—A solution of chloroacetamidine hydrochloride (12.9 g.; 0.1 mole) and sodium thiosulfate pentahydrate (24.8 g., 0.1 mole) in water (50 ml.) was heated at 100° for 1 hr. On cooling in an ice bath, the product crystallized and was purified (see Table I).

Method B.—Because of the vesicant properties of α-chloronitriles and α-chloroamidine hydrochlorides, the minimum amount of handling of these compounds was exercised. Furthermore, purification of the impure, water-soluble, and frequently hygroscopic α-chloroamidine hydrochlorides was very tedious, particularly when it was found that purification of the less soluble amidinium thiosulfates, III, was considerably easier. Thus, in most instances, the sirup obtained after the methanol had been removed was triturated with dry ether (two 50-ml. portions) and used in the next step.

The sirupy α-chloroamidine hydrochloride (in a typical preparation described above from 0.1 mole of α-chloronitrile) was treated with sodium thiosulfate pentahydrate (24.8 g., 0.1 mole) as described in Method A. The only modification to this procedure was that 100 ml. of water was used for those preparations when the mixture consisted of two phases at 100°.

Chloroacetanilides, IV.—The following general procedure was found to be a considerable improvement over the methods described in the literature. It was imperative to start with pure amides for the amidine synthesis.

A stirred solution of 400 ml. of 10% sodium carbonate solution and 200 ml. of benzene containing 0.4 mole of the amine was cooled to 0–5°. Chloroacetyl chloride (0.4 mole) was added dropwise over a period of 1 hr. during which the mixture was kept cool. The anilides (which were sparingly soluble in benzene) were collected and triturated with 5% hydrochloric acid solution (300 ml.) to remove unchanged amine. One recrystallization of the anilides afforded pure products. Table II summarizes our results.

TABLE II

IV. Ar =	Yield, %	Solvent for crystallization	M.p., °C.	Lit. m.p., °C.
C_6H_5	83	50% aq. ethanol	137	134–135[a]
p-$CH_3OC_6H_4$	89	50% aq. ethanol	122	121.5–122.5[b]
p-$C_2H_5OC_6H_4$	64	Benzene	145	145–146[c]
p-BrC_6H_4	65	95% ethanol	179–180	179[d]

[a] O. Dimroth, *Ber.*, **35**, 4041 (1902). [b] W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 103 (1915). [c] A. Bistrzycki and F. Ulffers, *Ber.*, **31**, 2783 (1898). [d] H. Ferichs, *Chem. Zentr.*, **74**, 103 (1903).

N-Ethylchloroacetamidine hydrochloride (73%), m.p. 114–117°.

Anal. Calcd. for $C_4H_{10}N_2Cl_2$ (157.1): C, 30.59; H, 6.42; N, 17.84. Found: C, 30.45; H, 6.50; N, 18.18.

All of these anilides are skin irritants and must be handled with great care. In particular, these solids must be confined to closed vessels as their dust proved to be a great source of irritation.

N,N-Diphenylchloroacetamidine.—Phosphorus pentachloride (4.5 g.; 0.022 mole) was digested in 50 ml. of

(9) Melting points are uncorrected. Microanalyses were determined by Dr. Kurt Eder, Geneva, Switzerland, and by Micro-Tech Laboratories, Skokie, Ill. Several nitrogen analyses were performed here on a Coleman Nitrogen Analyzer, Model 29.

(10) W. Davies and J. A. Maclaren, *J. Chem. Soc.*, 2595 (1951).

(11) Kindly supplied by the American Cyanamid Company.

(12) B. H. Ingha, *J. Chem. Soc.*, 695 (1927).

(13) W. Klarer and W. E. Ulrich, *Helv. chim. acta.*, **27**, 1762 (1944).

sodium-dried benzene for 0.5 hr. The solution was cooled and chloroacetanilide (4.25 g.; 0.025 mole) was added and the mixture heated under reflux for 1.25 hr. The mixture was then cooled and a solution of aniline (2.33 g., 0.025 mole) in benzene (10 ml.) was added. The mixture was refluxed for 1 hr. longer and then volatile solvents were removed at 50 mm. pressure; to the residue was added 50 ml. of additional benzene and evaporated once more to dryness at 50 mm. The dark residue was dissolved in cold absolute ethanol (75 ml.) and the solution cooled to 0°. Ice-cold 10% sodium hydroxide was added until the solution was strongly basic. The *amidine* could be induced to crystallize on scratching and then ice-cold water was added in small portions until all the amidine had precipitated (the final volume was then 225 ml.). The product was filtered and dried *in vacuo*. The *amidine* was purified by continuous extraction with petroleum ether (b.p. 30–60°). (Soxhlet apparatus). The yield was 2.37 g. (39%) m.p. 84–85°. Recrystallization from petroleum ether (b.p. 30–60°) and on cooling to −10° afforded the *amidine* as yellow plates, m.p. 86–88°.

Anal. Calcd. for $C_{14}H_{13}ClN_2$ (244.7): C, 68.71; H, 5.36; N, 11.44. Found: C, 68.63; H, 5.37; N, 11.48.

N,N′-Di(*p*-methoxyphenyl)chloroacetamidine, m.p. 78–80°, was synthesized in 43% yield from chloroaceto-*p*-anisidide by the above method.

Anal. Calcd. for $C_{16}H_{17}ClN_2O_2$ (304.8): C, 63.05; H, 5.62; N, 9.19. Found: C, 63.28; H, 5.59; N, 9.34.

N,N′-Di(*p*-ethoxyphenyl)chloroacetamidine was prepared from chloroacet-*p*-phenetidide as above in 48% yield. It melted at 81°, lit.,[14] m.p. 83°.

N,N′-Di(*p*-bromophenyl)chloroacetamidine was prepared in 10% yield, m.p. 131–133°.

Anal. Calcd. for $C_{14}H_{11}Br_2ClN_2$ (402.5): C, 41.77; H, 2.75; N, 6.96. Found: C, 41.87; H, 2.96; N, 7.06.

N,N′-Diphenyl-α-(acetylmercapto)acetamidine.—To suspension of sodium hydride (1.5 g.) in tetrahydrofuran (150 ml.) was added thiolacetic acid (2.28 g.; 0.03 mole). After the evolution of hydrogen had ceased, to mark the end of the formation of the sodium salt, a solution of N,N′-diphenylchloroacetamidine (7.35 g., 0.03 mole) in tetrahydrofuran (20 ml.) was added. The mixture was refluxed for 3 hr. and filtered while hot. The filtrate was evaporated *in vacuo* and the residue recrystallized from cyclohexane, filtered, and dried. It weighed 5.50 g. and represents a 73% yield, m.p. 115–117°. Recrystallization from cyclohexane raised the m.p. to 120–122°.

Anal. Calcd. for $C_{16}H_{16}N_2OS$ (284.4): C, 67.57; H, 5.67; N, 9.85; S, 11.28. Found: C, 67.57; H, 5.69; N, 10.00; S, 11.37.

Similarly, N,N′-Di(*p*-methoxyphenyl)chloroacetamidine formed the *thiol ester* in 75% yield, m.p. 138–139°.

Calcd. for $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13; S, 9.31. Found: C, 62.79; H, 6.01; H, 8.25; S, 9.19.

N,N′-Di(*p*-ethoxyphenyl)chloroacetamidine was converted to the thiol ester in 54% yield, m.p. 112–114° and was crystallized from cyclohexane.

Anal. Calcd. for $C_{20}H_{24}N_2O_3S$ (372.5): C, 64.49; H, 6.50; N, 7.52. Found: C, 64.45; H, 6.49; N, 7.62.

S-[α-(Carboxamidino)ethyl]isothiourea Dihydrochloride, VII.—A suspension of thiourea (3.4 g., 0.05 mole) and α-chloropropionamidine hydrochloride (7.15 g., 0.05 mole) in tetrahydrofuran (50 ml.) was boiled under reflux for 48 hr. The solid was filtered off, m.p. 230–235° (with decomp.). Recrystallization from absolute methanol did not materially effect the m.p., 232–235° (with decomp.). The yield was almost quantitative.

Anal. Calcd. for $C_4H_{12}N_4Cl_2S$ (219.1): C, 21.92; H, 5.52; N, 25.57; S, 14.63. Found: C, 21.69; H, 5.45; N, 25.66; S, 14.71.

Acknowledgement.—The authors would like to thank Mr. Richard Egan for his fine technical assistance in this work, during the summers of 1961 and 1962.

(14) H. P. Kaufmann, *et al.*, *Ber.*, **75**, 1585 (1942).

Ortho Substitution–Rearrangement of 2-(α-Hydroxybenzyl)benzyltrimethylammonium Ion and a Related Quaternary Ion–Alcohol by Excess Potassium Amide[1]

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In contrast to the 2-benzylbenzyltrimethylammonium ion which undergoes an elimination reaction to form polymeric hydrocarbon material, the 2-(α-hydroxybenzyl)benzyltrimethylammonium ion exhibits the *ortho* substitution–rearrangement with excess potassium amide in liquid ammonia. The success of this rearrangement appears to be dependent on deactivation of the benzylic hydrogen of the 2-α-hydroxybenzyl group by the negative charge on the adjacent oxygen atom in anion intermediates. The resulting 2-methyl-3-dimethylaminomethylbenzhydrol was obtained in yields of 60–79%. Besides this rearranged amino alcohol small amounts of the cleavage products, benzaldehyde and 2-methylbenzyldimethylamine, were isolated. Similarly the 2-(α-hydroxy-α-phenylbenzyl)benzyltrimethylammonium ion afforded 2-methyl-3-dimethylaminomethyltriphenylcarbinol in 75% yield.

It has previously been shown that the benzyltrimethylammonium ion[3] and a number of 2-, 3-, and 4-substituted benzyltrimethylammonium ions[4,5] undergo the *ortho* substitution–rearrangement with sodium amide or potassium amide in liquid ammonia. For example, the 2-ethyl quaternary ion I exhibits this type of rearrangement to form tertiary amine II in 90% yield.[4]

However, the 2- and 4-benzylbenzyltrimethylammonium ions, which have relatively active benzyl hydrogens in the 2- and 4-benzyl groups

(1) Supported in part by the National Institutes of Health Grant No. CA-04-455-04.

(2) National Science Foundation Fellow, 1961–1962.

(3) S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, **73**, 4122 (1951).

(4) C. R. Hauser and A. J. Weinheimer, *ibid.*, **76**, 1264 (1954).

(5) W. Q. Beard, Jr., and C. R. Hauser, *J. Org. Chem.*, **25**, 334 (1960).