of the reaction may be more acceptable except that the absence of a polar solvent makes this proposed equilibration difficult to accept. Consistent with this mechanism, however, is the observation recently reported that methylation of one secondary hydroxyl in simple glucosides increases the acidity of the adjacent group.[53] Whatever the explanation may be, the mechanism of the reaction reported in this work would not be expected to be identical to that of the reaction occurring in a homogeneous methylation in a solution of a quaternary ammonium hydroxide or in a heterogeneous methylation of alkali cellulose using a comparatively highly polar, high boiling reagent like dimethyl sulfate. In these polar solvents the reaction would almost certainly occur exclusively at equilibrated alkoxide ions as predicted by solvent effects[54] in bimolecular ion–molecule reactions. For these reasons, and the steric effects discussed earlier, the results obtained in this investigation and relative rate constants derived therefrom are not expected to be directly applicable to other alkylations of cellulose.

Experimental

Monosodio Cellulose.—Holocellulose, prepared from yellow birch screenings by chlorination and extraction with monoethanolamine,[55] was extracted with 17.5% alkali to obtain the α-cellulose fraction. A 20-g. sample of α-cellulose was dissolved in 600 ml. of cuprammonium hydroxide solution and regenerated by precipitation in 1.5 l. of 6 *N* sulfuric acid. The activated cellulose was treated with sodium hydroxide in boiling butanol-1 by the procedure described by Sugihara and Wolfrom[37] for the preparation of monosodio cellulose. Identical procedures were also used to analyze and methylate the monosodio derivative.

Methyl Monosodio-α-D-glucopyranoside.—The preparation and methylation of methyl monosodio-α-D-glucopyranoside was performed as described by Wolfrom and El-Taraboulsi.[36]

Hydrolysis of Methylcellulose.—A 100 mg. sample of methyl cellulose was stirred into 3 g. of 72% sulfuric acid and allowed to hydrolyze for 15 hours at room temperature. The acid was diluted to approximately 1 *N* by adding 27 ml. of distilled water, and the mixture was refluxed on the steam-bath for 4 hours. After cooling, the solution was transferred to a beaker and Amberlite IR4B was added portionwise under constant stirring at such a rate as to bring the *p*H of the solution up to approximately 4.0 in 30 minutes. The solution was decanted off and reduced in a vacuum oven at 50°.[28]

Hydrolysis of Methylated Methyl α-D-Glucopyranoside.—The sirup obtained on methylating methyl monosodio-α-D-glucopyranoside was refluxed on a steam-bath with 20 ml. of 1 *N* sulfuric acid for 4 hours. The solution was neutralized with Amberlite IR-4B and concentrated as above.

Paper Chromatography.—Quantitative paper chromatography of the neutralized hydrolyzates were performed as described by Lenz and Holmberg.[44] The glucose methyl ethers of different degrees of substitution (*i.e.*, D-glucose, mono-, di- and tri-O-methyl-D-glucose) were separated with the top layer of a 5:1:4 mixture of butanol-1–ethanol–water. The mono-O-methyl-D-glucose isomers were separated with the top layer of a 2:5:5 mixture of 2,4,6-collidine–ethyl acetate–water.

Acknowledgments.—The author wishes to express his appreciation to Professors Conrad Schuerch and Kyosti Sarkanen for helpful criticism in the preparation of this manuscript.

MIDLAND, MICH.

(53) K. Sarkanen and K. Larson, Abstracts of Papers, 135th Meeting American Chemical Society, 8E (1959).

(54) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 134ff.

(55) T. Timell and E. C. Jahn, *Svensk Papperstidn.*, **54**, 831 (1951).

[CONTRIBUTION FROM THE BIOMEDICAL RESEARCH GROUP OF THE LOS ALAMOS SCIENTIFIC LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

Quaternary Salt Formation of Substituted Oxazoles and Thiazoles[1]

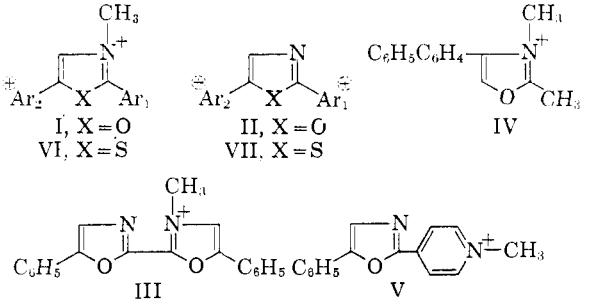
BY VERNON N. KERR, DONALD G. OTT AND F. NEWTON HAYES

RECEIVED MAY 15, 1959

The course of quaternization of a number of oxazoles and thiazoles and various dimethylaminophenyl, pyridyl and quinolyl derivatives has been investigated. The salts have been screened for hypotensive activity.

Until recently, there has been little pharmacological interest in oxazole compounds. After the discovery that certain oxazole quaternary salts produced poikilothermia in mice,[2] there have followed some investigations of other pharmacological properties of these compounds. They have been screened for anti-cancer activity,[3] and they have been found to be active hypotensive agents.[4–7]

In an effort to determine what relationship existed between chemical structure and hypotensive activity, a number of new oxazole quaternary salts and related compounds were synthesized.



Preliminary screening for hypotensive activity has been carried out,[7] both for the compounds reported here (Table I) and those in an earlier paper.[8] The activity of these salts is very de-

(1) Work performed under the auspices of the U. S. Atomic Energy Commission.

(2) C. C. Lushbaugh, *et al.*, *J. Pharm. Exptl. Therap.*, **116**, 366 (1956).

(3) I. U. Boone, V. G. Strang and W. H. Langham, *Cancer Res.*, **18**, No. 8, Part II, 361 (1958).

(4) T. J. Haley, W. G. McCormick and A. M. Flesher, *Arch. Int. Pharm. Therap.*, **59**, 78 (1957).

(5) T. J. Haley, A. M. Flesher and N. Komesu, *J. Am. Pharm. Assoc.*, **47**, No. 6, 401 (1958).

(6) C. H. Tilford, private communication.

(7) J. E. Furchner and L. E. Ellinwood, to be published.

(8) D. G. Ott, F. N. Hayes and V. N. Kerr, THIS JOURNAL, **78**, 1941 (1956).

TABLE I

p-TOLUENESULFONATE SALTS

		M.p., °C.[a]	Formula	Sulfur, % Calcd.	Found	λ_{max1}[b]	$\epsilon_1 \times 10^{-4}$	λ_{max2}	$\epsilon_2 \times 10^{-4}$
Ia	2,3-Dimethyl-5-phenyloxazolium	165–167	$C_{18}H_{19}NO_4S$	9.28	9.23	257	1.49	237s	1.80
b	3-Methyl-2-(*p*-nitrophenyl)-5-phenyl-oxazolium	226–228	$C_{22}H_{20}N_2O_6S$	7.09	7.00	330s	0.20	248	2.14
c	3-Methyl-5-phenyl-2-(2,5-xylyl)-oxazolium	167–168	$C_{25}H_{25}NO_4S$	7.36	7.18	289	1.73	244	1.43
d	3-Methyl-5-(1-naphthyl)-2-phenyl-oxazolium	204–206	$C_{27}H_{23}NO_4S$	7.01	7.11	322	1.28	270	1.28
e	3-Methyl-5-(N,N,N-trimethyl-*p*-aniliniumyl)-2-phenyloxazolium	249–252	$C_{31}H_{36}N_2O_7S_2$	10.07	10.22	290	0.56	236s	2.00
f	3-Methyl-5-(N,N,N-trimethyl-*p*-aniliniumyl)-2-*p*-tolyloxazolium	233–235	$C_{44}H_{38}N_2O_7S_2$	9.85	9.64	305	1.34	237s	1.80
g	2-(*p*-Methoxyphenyl)-3-methyl-5-(N,N,N-trimethyl-*p*-aniliniumyl)-oxazolium	242–244	$C_{34}H_{38}N_2O_8S_2$	9.62	9.90	324	1.72	259s	1.32
h	3-Methyl-5-(N,N,N-trimethyl-*p*-aniliniumyl)-2-(1-naphthyl)-oxazolium	209–212	$C_{37}H_{38}N_2O_7S_2$	9.34	9.13	330	0.77	280	1.22
IIa	N,N,N-Trimethyl-*p*-(5-phenyl-2-oxazolyl)-anilinium	212–213	$C_{26}H_{26}N_2O_4S$	7.12	7.20	384	2.39	317	1.80
b	N,N-Diethyl-N-methyl-*p*-(5-phenyl-2-oxazolyl)-anilinium	136–138	$C_{27}H_{30}N_2O_4S$	6.70	6.68	390	3.60	283	1.48
c	1-Methyl-4-(5-phenyl-2-oxazolyl)-pyridinium[c]	270 subl.	$C_{15}H_{13}ClNO$	13.00[d]	12.65	380	2.26	251	1.32
d	1-Methyl-2-(5-phenyl-2-oxazolyl)-quinolinium	222–224	$C_{26}H_{22}N_2O_4S$	6.99	6.93	320s	0.30	234	2.28
e	1-Methyl-6-(5-phenyl-2-oxazolyl)-quinolinium	228–229	$C_{26}H_{22}N_2O_4S$	6.99	6.83	323	0.54	241	3.08
f	2,5-Oxazolylenebis-(N,N,N-trimethyl-*p*-anilinium . . .)	178–210	$C_{35}H_{44}N_4O_7S_2$	9.43	9.62	394	2.70	340	0.73
g	1-Methyl-3-[5-(N,N,N-trimethyl-*p*-aniliniumyl)-2-oxazolyl]-pyridinium	239–242	$C_{32}H_{35}N_3O_7S_2$	10.06	9.81	321	2.21	257	1.13
III	3-Methyl-5-phenyl-2-(5-phenyl-2-oxazolyl)-oxazolium	264–268	$C_{25}H_{22}N_2O_5S$	6.76	6.86	376	0.70	292	2.02
IV	4-(4-Biphenylyl)-2,3-dimethyl-oxazolium	194–196	$C_{24}H_{23}NO_4S$	7.61	7.49	269	2.42	..	..
V	1-Methyl-4-[5-phenyl-2-(1,3,4-oxadiazolyl)]-pyridinium	209–210	$C_{21}H_{19}N_3O_4S$	7.83	7.72	321	1.95	238	1.33
VIa	2-(*p*-Fluorophenyl)-3-methyl-5 phenylthiazolium	157(168–169)	$C_{23}H_{20}FNO_3S_2$	3.17[e]	3.57	317	1.68	250s	0.84
b	2-(*p*-Chlorophenyl)-3-methyl-5-phenylthiazolium	192–194	$C_{23}H_{20}ClNO_3S_2$	14.00	13.82	322	1.92	..	..
c	2-(*o*-Iodophenyl)-3-methyl-5-phenyl-thiazolium	210–213	$C_{23}H_{20}INO_3S_2$	11.67	11.50	308	1.32	..	..
d	2-(*m*-Iodophenyl)-3-methyl-5-phenyl-thiazolium	172–174	$C_{23}H_{20}INO_3S_2$	2.55[e]	2.87	320	1.49	..	..
e	3-Methyl-5-phenyl-2-styrylthiazolium	90–99	$C_{25}H_{23}NO_3S_2$	14.27	14.06	385	2.36	..	..
f	2-(4-Biphenylyl)-3-methyl-5-phenyl-thiazolium	238–240	$C_{29}H_{25}NO_3S_2$	12.84	12.73	336	2.82	242s	1.84
g	3-Methyl-2-(1-naphthyl)-5-phenyl-thiazolium	151(173–175)	$C_{21}H_{23}NO_3S_2$	13.54	13.30	320	1.32	291s	1.12
h	3-Methyl-5-(2-naphthyl)-2-phenyl-thiazolium	210–212	$C_{27}H_{23}NO_3S_2$	13.54	13.70	333	1.56	284	1.60
i	3-Methyl-5 phenyl-2-(2-thienyl)-thiazolium	173–176	$C_{21}H_{19}NO_3S_3$	22.39	22.11	358	1.64	..	..
j	3-Methyl-2-(N,N,N-trimethyl-*p*-aniliniumyl)-5-phenylthiazolium	238–240	$C_{33}H_{36}N_2O_6S_2$	14.83	14.80	320	1.64	245s	1.22
VIIa	1-Methyl-3-(5-phenyl-2-thiazolyl)-pyridinium	206–209	$C_{22}H_{20}N_2O_3S_2$	15.11	15.34	323	0.70	260s	0.64
b	1-Methyl-4-(5-phenyl-2-thiazolyl)-pyridinium	224–228	$C_{22}H_{20}N_2O_3S_2$	6.60[e]	6.75	384	2.52	250	1.00

[a] All melting points are uncorrected and were taken on a Fischer–Johns melting point block. Microanalyses by Microtech Laboratories, Skokie, Ill. [b] Wave lengths are in mμ; solvent, 95% ethanol. [c] The anion is chloride, rather than tosylate. [d] % Cl. [e] % N.

TABLE II

PHYSICAL PROPERTIES OF FREE BASES

	M.p., °C.[a]	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found	λ_{max}	$\epsilon_1 \times 10^{-4}$
2-Methyl-5-phenyloxazole[b]	.....	.....	...	...	..	..	...	...	276[c]	1.96
4-(4-Biphenylyl)-2-methyloxazole	149–150	$C_{16}H_{13}NO$	81.68	81.52	5.57	5.43	5.95	5.92	280[c]	2.92
4-[5-Phenyl-2-(1,3,4-oxadiazolyl)]-pyridine	143–144	$C_{13}H_9N_3O$	69.94	70.16	4.06	3.98	18.83	18.82	284[c]	2.53
4-(5-Phenyl-2-oxazolyl)-pyridine N-oxide	230–231	$C_{14}H_{10}N_2O_2$	70.58	70.77	4.23	4.46	...	...	352[d]	4.08

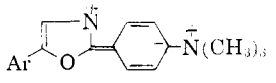
[a] All melting points are uncorrected and were taken on a Fischer–Johns melting point block. Microanalyses by Microtech Laboratories, Skokie, Ill. [b] S. Gabriel, *Ber.*, **43**, 1283 (1910). [c] Solvent, cyclohexane. [d] Solvent, 95% ethanol.

pendent upon specific structure, and no class distinctions could be found; it does not seem to matter whether the quaternary salt is oxazolium, thiazolium, pyridinium or anilinium.

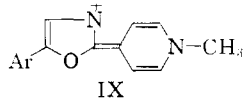
Oxazolium or thiazolium salts were formed quite readily when no substituent held another basic nitrogen. When at least two basic nitrogens were present in the molecule, as with the aminophenyl, pyridyl or quinolyl substituted oxazoles, either a mono or a diquaternary salt may form, depending on the position of the substituent on the five-membered heterocyclic ring. In general, when a group with a basic nitrogen is in the 2-position of the oxazole or thiazole ring, no quaternization takes place with the ring nitrogen, although 2-(*p*-dimethylaminophenyl)-5-phenylthiazole formed the diquaternary salt.

Since the oxazole and thiazole nitrogens are only weakly basic, the nitrogen on the substituent will be quaternized first. In such monoquaternaries, the nitrogen of the oxazole or thiazole ring can accommodate a positive charge in one of the contributing resonance forms (VIII, IX), when the substituent is in the 2-position but not when it is in the 5-position. In addition, any inductive effect would be lessened by the increased distance from the nitrogen of the oxazole or thiazole ring.

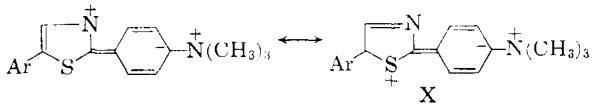
Resonance forms of the charge separation type (VIII) can also contribute to the 3-pyridyl and 6-quinolyl substituted compounds. Resonance forms without the charge separation (IX) probably contribute also to the 2-quinolyl and 2-oxazolyl substituted compounds.



VIII



IX



X

In the case of the thiazole which formed the divalent salt VII, the presence of a sulfur atom rather than an oxygen atom in the heterocyclic structure allows an additional resonance form to assume more importance (X). Also, any inductive effect on the nitrogen would be somewhat offset by the less strongly bound electrons of the sulfur atom *versus* those of an oxygen atom. The strictly analogous oxazole IIa forms only the monoquaternary salt.

The presence of the sulfur atom is not sufficient, however, to allow the thiazole ring nitrogen to quaternize when the 2-substituent is either a 4-pyridyl or a 3-pyridyl group. The effect of the 4-pyridyl group may possibly be ascribed to the difference in resonance forms. Since there is no charge separation involved in a structure such as IX, this resonance form is more stable and thus would be a larger contributor than a form such as VIII.

The blocking effect of the 3-pyridinium group must be due in part to an inductive effect. The resonance form would be one of the same type as VIII and thus should be no more effective than a *p*-aniliniumyl group.

Pharmacological investigation of the oxazolium salts has shown that they are somewhat toxic and thus their value as pharmaceuticals is somewhat lessened.[2,4] One approach to the alteration of the toxicity of compounds which contain basic nitrogen atoms is to form the N-oxide. This has been shown to decrease markedly the toxicity of a number of compounds with little or no change in their pharmacological properties.[9,10]

The closest synthetic procedure which could be used as an analogy for the reaction of the oxazoles was that of Ochiai.[11] The N-oxide of 2,5-dimethylthiazole was formed in good yield with the use of a mixture of glacial acetic acid and hydrogen peroxide. When this procedure was attempted with 2,5-diphenyloxazole, no N-oxide was isolated and only starting material and the degradation products, benzamide and benzoic acid, were recovered. One other attempt was made to secure an N-oxide, this time with 4-(5-phenyl-2-oxazolyl)-pyridine. That the N-oxide which was formed was the pyridine N-oxide is shown by the close resemblance of its absorption spectrum to that of the tosylate salt of the same compound. The long wave length band is at a longer wave length than that expected of an oxazolium compound.[8]

The ultraviolet absorption spectra showed, in addition to the long wave length absorption band, either shoulders or peaks which occurred regularly at *ca.* 223 and 228 mμ. Both of these bands are found with the majority of the compounds listed in Table I. The 1-naphthyl substituted compounds showed neither band.

Experimental

The *p*-toluenesulfonates and chlorides were prepared by a previously described method[8] from compounds reported

(9) H. von Euler and H. Hasselquist, *Arkiv Kemi*, **12**, 559 (1958).

(10) C. C. J. Culvenor, *Rev. Pure Appl. Chem. (Australia)*, **3**, 83 (1953).

(11) E. Ochiai and E. Hayashi, *J. Pharm. Soc. Japan*, **67**, 34 (1947).

earlier.[4,12,13] The physical properties of previously unreported free bases are given in Table II.

4-(4-Biphenylyl)-2-methyloxazole.—Acetamide (7.72 g.) and *p*-phenylphenacyl bromide (35.7 g.) were melted together and heated for 4 hours at 165°. The acetamide was removed from the reaction mixture with water, and the remaining solid was dried and extracted with boiling ethanol. The ethanol solution was taken to dryness, and the solid was triturated with boiling hexane. The product from the hexane was recrystallized twice to give 0.34 g.

4-[5-Phenyl-2-(1,3,4-oxadiazolyl)]-pyridine.—To a solution of 4.1 ml. of benzoyl chloride in pyridine was added 5.1 g. of isonicotinoyl hydrazide. The solution was heated for five minutes on a water-bath, cooled and poured into water. The solid was filtered off, dried (7 g.) and recrystallized from water to give **1-benzoyl-2-isonicotinoylhydrazine**, m.p. 232–234°. *Anal.* Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.77; H, 4.80; N, 17.62.

A solution of 4.9 g. of the hydrazine in 25 ml. of phosphorus oxychloride was refluxed for five hours. The excess phosphorous oxychloride was removed, and the residue was poured into water. The water was taken to *p*H 6 and the solid was filtered off, dried and recrystallized to give 2.8 g.

4-(5-Phenyl-2-oxazolyl)-pyridine N-Oxide.—A mixture of 1 g. of 4-(5-phenyl-2-oxazolyl)-pyridine, 15 ml. of glacial acetic acid and 1.5 ml. of 30% hydrogen peroxide was heated on a water-bath for seven hours. The reaction mixture was taken to dryness and the residue was washed with ether. Recrystallization from acetone gave 0.46 g.

The ultraviolet absorption spectra were taken with a Beckman model DK-1 recording spectrophotometer. The solutions were of 95% ethanol and the concentrations were *ca.* 2.5×10^{-5} mole/l. The infrared absorption spectra of these compounds may be found in the Sadtler Standard Spectra.[14]

Acknowledgments.—The authors wish to express their appreciation to Dr. J. E. Furchner for making available the results of the hypotensive testing, and to Dr. G. H. Daub for valuable discussion. Mrs. R. Lier determined a number of the ultraviolet spectra.

(12) V. N. Kerr, F. N. Hayes, D. G. Ott and E. Hansbury, *J. Org. Chem.*, in press.

(13) V. N. Kerr, F. N. Hayes, D. G. Ott, R. Lier and E. Hansbury, *J. Org. Chem.*, in press.

(14) Samuel P. Sadtler and Son, Inc., Research Laboratories, Philadelphia 2, Pa.

LOS ALAMOS, N. MEX.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BRIGHAM YOUNG UNIVERSITY]

Quinoxalines. I. Preparation and Stereochemistry of Decahydroquinoxalines

BY H. SMITH BROADBENT, EVAN L. ALLRED,[1] LYNN PENDLETON[1] AND CHARLES W. WHITTLE[1]

RECEIVED MAY 26, 1959

The first authentic synthesis of *cis*-decahydroquinoxaline (XI) (m.p. 56–58°) is herein described. It was obtained in high yield by the hydrogenation of quinoxaline (X), or tetrahydroquinoxaline, over 5% rhodium-on-alumina catalyst at 100° and 136 atm. or over freshly prepared Raney nickel W-6 under similar conditions. Evidence is presented supporting the stereochemical assignment and demonstrating that previously reported preparations of decahydroquinoxaline have yielded either tetrahydroquinoxaline (VII), *trans*-decahydroquinoxaline (VIII) or mixtures of the *cis* and *trans* forms.

Decahydroquinoxaline should exist in two geometrically isomeric forms, *cis*- XI and *trans*- VIII depending on the manner of fusion of the cyclohexane and piperazine rings. The presence of the hetero atoms further introduces the possibility of molecular dissymmetry, the *cis* form being *meso* and the *trans* form the racemic (D,L) compound or mixture. Conformational variations involving boat or chair rings and equatorial or axial N–H bonds are also possible.

In the first reported preparation of a decahydroquinoxaline, Mousseron and Combes[2] treated cyclohexene oxide (IV) with 2-aminoethanol followed by chlorination and ammonolytic ring closure. Neither yields nor physical constants were given for the decahydroquinoxaline. An N,N′-dinitroso derivative melting with decomposition at 160° was mentioned. This has now been shown to be N,N′-dinitrosotetrahydroquinoxaline.

Later Beck, Hamlin and Weston[3] prepared a decahydroquinoxaline, m.p. 150–151° (24%), by the action of ethylenediamine on cyclohexene oxide followed by catalytic dehydrative ring closure. Its hydrochloride melted at 365° dec. Neither group discussed the problem of stereoisomerism.

We have now succeeded in the complete hydrogenation of either quinoxaline (X) or of tetrahydroquinoxaline (VII) directly to decahydroquinoxaline by the use of the proper catalytic system, *viz.*, either freshly prepared Raney W-6[4] or 5% rhodium-on-alumina[5] (preferably the latter) at 100° and 136 atm., to give virtually quantitative yields of pure material XII melting at 56–58°. The reaction, however, is extremely sensitive to poisoning of the catalyst. The N,N′-dinitroso derivative was also prepared, m.p. 87–89°.

In view of the known stereochemistry of epoxide ring openings, catalytic hydrogenations and symmetry-physical property considerations, we tentatively assigned the *trans* configuration to the high melting product of Beck, *et al.*, and the *cis* configuration to the low melting, more soluble product we had obtained by hydrogenation. Later work has confirmed this assignment.

Subsequently, Christie, Rohde and Shultz[6] reported the hydrogenation of tetrahydroquinoxalinium ion (VII) in ethanolic hydrogen chloride using platinum oxide at 60° and 50–80 p.s.i.g. Despite a reported crude yield of 90% crude dihydrochloride, the final yield of product melting

(1) Abstracted from the M.S. Thesis, of E. L. A. (1955), C. W. W. (1956) and L. P. (1958).

(2) M. Mousseron and G. Combes, *Bull. soc. chim. France*, 82 (1947).

(3) K. M. Beck, K. E. Hamlin and A. W. Weston, THIS JOURNAL, **74**, 605 (1952).

(4) H. R. Billica and H. Adkins, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 176.

(5) Baker and Co., Inc., "Engelhard Industries News-Letter," January, 1950.

(6) W. Christie, W. Rohde and H. P. Shultz, *J. Org. Chem.*, **21**, 243 (1956).