100° for 2 hr and cooled, and the reaction was quenched with cold 10% hydrochloric acid (120 ml). The phases were separated and the organic layer was extracted with a portion of 10% hydrochloric acid. The combined acid fractions were extracted with four portions of 1:1 benzene–ether (50 ml), then made basic with 20% sodium hydroxide solution. Extraction with methylene chloride (five 75-ml portions) and subsequent distillation gave quinoline (2.2 g, identified by its infrared spectrum), bp 75–85° at 0.2 mm, followed by the major fraction (3.2 g), bp 131–134° at 0.2 mm. The latter was chromatographed on alumina (100 g). Elution with petroleum ether–benzene (9:1, 900 ml) gave 2-butylmercaptoquinoline, 0.5 g. Further elution with petroleum ether–benzene (4:1, 150 ml; 7:3, 900 ml; 3:2, 450 ml; 1:1, 450 ml; 1:3, 450 ml) and benzene (450 ml) gave 3-butylmercaptoquinoline, 2.1 g, bp 132° at 0.1 mm. Its nmr spectrum showed H-2 as a doublet at δ 9.07 ($J_{2,4}$ = 2.5 cps) and the remaining five aromatic protons as a complex multiplet between δ 8.40 and 7.50. The aliphatic protons gave the expected triplet at 3.01 (CH_2S), a multiplet between 1.85 and 1.15 (CH_2 groups), and a triplet at δ 0.90 (CH_3).

Anal. Found: C, 71.89; H, 7.03; N, 6.49.

Continued elution with benzene–ether (99:1, 150 ml; 49:1, 450 ml; 9:1, 450 ml; 3:1, 150 ml) gave 4-butylmercaptoquinoline, 0.4 g. No quinoline 1-oxide could be detected upon elution with ether or methanol.

B. The Ethyl Sulfate Salt.—Quinoline 1-oxide (14.5 g, 0.1 mole) was heated with ethyl sulfate (15.4 g, 0.1 mole) at 100° for 1.5 hr. The mixture was cooled, washed with dry ether, and used without further purification. A suspension of sodium *n*-butylmercaptide in butanethiol was prepared as in A, using 4.6 g (0.1 mole) of sodium hydride dispersion. The gummy quinolinium salt, prepared above, was then added to the suspension of the mercaptide in 1-butanethiol. The mixture was heated at 100° for 2 hr, then worked up as in part A. Distillation of the basic fraction gave quinoline (4.7 g), bp 62–70° at 0.2 mm, and a 2-, 3-, and 4-butylmercaptoquinoline mixture (5.5 g) together with quinoline 1-oxide, bp 131–134° at 0.2 mm. The high-boiling mixture was chromatographed on alumina (90 g). Elution with petroleum ether–benzene (20:1, 300 ml; 10:1, 300 ml) gave 2-butylmercaptoquinoline (0.6 g). Further elution with petroleum ether–benzene (9:1, 150 ml; 3:1, 75 ml) gave a mixture (0.2 g), shown (nmr) to consist of equal parts of 2- and 3-butylmercaptoquinoline. Further elution with petroleum ether–benzene (3:1, 150 ml; 1:1, 600 ml), benzene (600 ml), and benzene–ether (99:1, 150 ml; 20:1, 150 ml; 9:1, 75 ml) gave 3-butylmercaptoquinoline (3.4 g), identified by its nmr spectrum. Continued elution with benzene–ether (1:1, 150 ml) and ether (225 ml) gave 4-butylmercaptoquinoline (0.3 g) and with methanol (150 ml) furnished quinoline 1-oxide (0.21 g).

The Reactions of Quinoline 1-Oxide with 1-Butanethiol. C. In the Presence of Acetic Anhydride.—Quinoline 1-oxide (14.5 g, 0.1 mole) was dissolved in acetic anhydride (100 ml), and 1-butanethiol (32 ml, 0.3 mole) was added slowly. The mixture warmed spontaneously and was then heated under reflux for 2 hr and cooled, and the solvents were removed under reduced pressure. The residue was treated with 10% hydrochloric acid, and the mixture was worked up as under A. The basic fraction was boiled down with several portions of benzene, then chromatographed on alumina (140 g) without prior distillation. Elution with petroleum ether (400 ml) gave 2-butylmercaptoquinoline (4.5 g). Further elution with petroleum ether (150 ml) gave a mixture (0.2 g), shown to be composed of equal amounts of the 2- and 3-butylmercaptoquinolines (nmr). Pure 3-butylmercaptoquinoline (0.5 g) was eluted by petroleum ether (375 ml) and petroleum ether–benzene (9:1, 100 ml). Continued elution with benzene (600 ml) furnished quinoline (3.6 g) and then with methanol (100 ml) to give quinoline 1-oxide (0.9 g).

D. In the Presence of Benzenesulfonyl Chloride.—Benzenesulfonyl chloride (17.7 g, 0.1 mole) was added dropwise to a solution of quinoline 1-oxide (14.5 g, 0.1 mole) in benzene (100 ml). Then 1-butanethiol (32 ml, 0.3 mole) was added and the mixture was heated at 100° for 2.0 hr. The mixture was cooled and worked up as under A. Distillation of the basic fraction gave quinoline (2.6 g), bp 60–70° at 0.4 mm, and another fraction (7.4 g), bp 132–136° at 0.7 mm. A portion (3.7 g) of the latter was chromatographed on alumina (80 g). Elution with petroleum ether (1 l.), petroleum ether–benzene (19:1, 500 ml) and benzene (100 ml) gave 2-butylmercaptoquinoline (2.9 g). Elution with benzene (200 ml) gave a mixture of 3- and 4-butylmercaptoquinoline (0.5 g) in the ratio of 2:3 as determined from its nmr spectrum. Further elution with benzene–ether (19:1, 100 ml) gave 3-butylmercaptoquinoline (0.2 g), and with ether–methanol (1:1, 100 ml) gave quinoline 1-oxide (0.1 g).

2-Azaquinolizinium Oxides[1]

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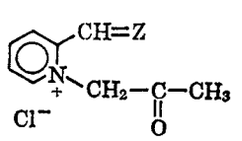
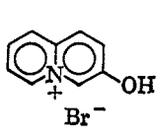
Bromoacetone reacts with picolinaldoxime or with the oxime of 2-acetopyridine to yield 2-azaquinolizinium 2-oxide salts substituted in the 3- or 1,3-positions, respectively. Benzologs of the title system were prepared by reaction of bromoacetone with 1- or 3-oximinomethylisoquinoline. The substitution of chloroacetaldoxime for bromoacetone has made possible the preparation of the parent system. 2-Azaquinolizinium 2-oxide and the 3-methyl homolog have been reduced to known 2-azaquinolizidine derivatives.

Schraufstätter[2] discovered that the salt I, obtained by quaternization of picolinaldehyde diethyl acetal with chloroacetone, readily undergoes hydrolysis and cyclization in boiling 48% hydrobromic acid affording 3-hydoxyquinolizinium ion (II). It seemed possible that through use of commercially available picolinaldoxime a quaternary salt (Ib) capable of undergoing hydrolysis and cyclization might be formed.



Ia, Z = $(OC_2H_5)_2$
b, Z = NOH



II

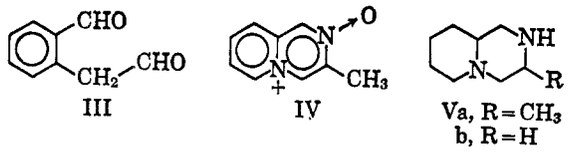
When picolinaldoxime in acetone or tetramethylene sulfone solution was allowed to react with bromoacetone, the resulting salt was unaffected by boiling 48% hydrobromic acid and the ultraviolet absorption spectrum of the salt was more complex than that expected for Ib. Since glutaconic dialdehyde reacts with hydroxylamine to afford pyridine 1-oxide,[3] and homophthaldehyde (III) under the same conditions yields isoquinoline 2-oxide,[4] it seemed likely that the new product was 3-methyl-2-azaquinolizinium 2-oxide

(1) This investigation was supported by Public Health Service Research Grant No. H-2170 of the National Heart Institute.

(2) E. Schraufstätter, *Angew. Chem. Intern. Ed. Engl.*, **1**, 593 (1962).

(3) P. Baumgarten, R. Marlander, and J. Olshausen, *Ber.*, **66**, 1802 (1933).

(4) C. Schöpf, A. Hartmann, and K. Koch, *ibid.*, **69**, 2766 (1936).

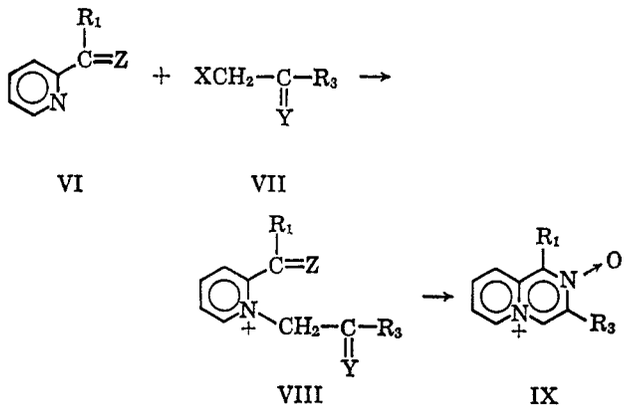


III IV Va, R = CH_3; b, R = H

(IV).[5] Catalytic reduction of the new salt over platinum oxide afforded the known[6] 3-methyl-2-azaquinolizidine (Va).

The new 3-methyl-2-azaquinolizinium oxide (IV) was not affected by phosphorus trichloride or by acetic anhydride.

The reaction of phenacyl bromide (VIIa) with picolinaldoxime (VIa) does not lead to cyclization but affords the uncyclized quaternary salt VIIIa which may be cyclized to IXa in 85% yield by the action of hydrobromic acid.

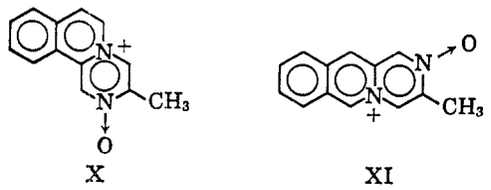


VI VII VIII IX

a, R_1 = H; Z = NOH; X = Br; Y = O; R_3 = C_6H_5
b, R_1 = CH_3; Z = NOH; X = Br; Y = O; R_3 = CH_3
c, R_1 = H; Z = NOH; X = Cl, Y = NOH; R_3 = H
d, R_1 = H; Z = (OCH_2CH_2O); X = Cl; Y = NOH; R_3 = H

The oxime of 2-acetopyridine (VIb) with bromoacetone produces 1,3-dimethyl-2-azaquinolizinium 2-oxide (IXb). The use of chloroacetaldoxime (VIIc) with either picolinaldoxime (VIc) or 2-(1,3-dioxolan-2-yl)pyridine (VId) afforded the expected quaternary salts VIIIc and d, which, on cyclization, gave the parent cation of the series, 2-azaquinolizinium 2-oxide (IXc or d). Reduction of the chloride afforded 2-azaquinolizidine, identified by the melting point of the dipicrate.

Reaction of bromoacetone with 1-oximinomethyl- or 3-oximinomethylisoquinoline yielded the expected benzologs, 3-methyl-2-azabenzo[*h*]quinolizinium 2-oxide (X) and 3-methyl-2-azabenzo[*g*]quinolizinium 2-oxide (XI).



X XI

Experimental Section

Analyses were by Dr. Ing. A. Schoeller, Kronach, Germany, or by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points were determined in capillaries, using a Mel-Temp apparatus. All ultraviolet absorption spectra were measured in 95% ethanol using 1-cm quartz cells with the Cary Model 14 spectrophotometer.

3-Methyl-2-azaquinolizinium Bromide 2-Oxide (IV).—A solution of 1.3 g of 2-pyridinealdoxime and 1.4 g of bromoacetone in 5 ml of acetone was refluxed for 6 hr. The precipitated salt was collected, washed with 5% acetone–ethyl acetate solution, and crystallized from methanol–ethyl acetate as yellow needles: yield 1.3 g (54%); mp 260° dec; λ_{max}, mμ (log ϵ), 228 (4.20), 245 (4.13), 268 (4.02), 276 (3.99), 323 (3.86), 341 (sh) (3.84), 354 (3.88), and 368 (3.87).

Anal. Calcd for $C_9H_9BrN_2O$: C, 44.50; H, 3.89; N, 11.57. Found: C, 44.83; H, 3.76; N, 11.62.

Slightly better results (66% yield) were obtained when the quaternization was carried out in 2 ml of tetramethylene sulfone at room temperature for 6 days.

The **picrate** crystallized from methanol as yellow needles, mp 207–210° dec.

Anal. Calcd for $C_{15}H_{11}N_5O_8$: C, 46.27; H, 2.84; N, 17.99. Found: C, 46.08; H, 2.94; N, 17.86.

3-Methyl-2-azaquinolizidine (Va).—A solution containing 500 mg of 3-methyl-2-azaquinolizinium bromide 2-oxide (IV) in 100 ml of methanol was hydrogenated at atmospheric pressure in the presence of 50 mg of platinum oxide catalyst until the solution became colorless. The catalyst was removed by filtration and the filtrate was concentrated under vacuum. The residue was treated with a dilute solution of sodium carbonate and extracted with ether. Evaporation of the ether gave an oil, bp 90° (1.5 mm).

The infrared spectrum was identical with that of an authentic sample.[6]

Anal. Calcd for $C_9H_{18}N_2$: C, 70.07; H, 11.76; N, 18.16. Found: C, 69.75; H, 11.78; N, 17.77.

The dipicrate crystallized from water as yellow needles, mp 232–245° dec (lit.[6] mp 229–238° dec).

Anal. Calcd for $C_{21}H_{24}N_8O_{14}$: C, 41.17; H, 3.95; N, 18.30. Found: C, 41.37; H, 3.73; N, 18.83.

1-Phenacyl-2-oximinomethylpyridinium Bromide (VIIIa).—A solution of 2.44 g of 2-pyridinealdoxime and 3.98 g of phenacyl bromide (VIIa) in 10 ml of acetone was refluxed for 6 hr. On working up as for IV, a brown precipitate was obtained which crystallized from methanol as brownish yellow needles: yield 2.7 g (45%); mp 202–203° dec; λ_{max}, mμ (log ϵ), 237 (4.05) and 301 (3.89).

Anal. Calcd for $C_{14}H_{13}BrN_2O_2$: C, 52.34; H, 4.07; N, 8.72. Found: C, 52.49; H, 3.93; N, 8.89.

3-Phenyl-2-azaquinolizinium Picrate 2-Oxide (IXa).—A solution of 0.5 g of 1-phenacyl-2-(aldoximinomethyl)pyridinium bromide (VIIIa) and 5 ml of 48% hydrobromic acid was heated on a steam bath for 4 hr. On working up as for IV, a yellow solid was obtained and was crystallized from methanol as yellow needles, yield 0.4 g (85%), mp 262° dec. The bromide was not obtained pure for analysis, but was converted to the picrate which crystallized from methanol in yellow needles, mp 167–168°.

Anal. Calcd for $C_{20}H_{13}N_5O_8$: C, 53.21; H, 2.90; N, 15.51. Found: C, 53.15; H, 2.93; N, 15.46.

1,3-Dimethyl-2-azaquinolizinium Bromide 2-Oxide (IXb).—A solution of 2.2 g of 2-acetylpyridine oxime (VIb) and 2.3 g of bromoacetone in 10 ml of acetone was refluxed for 6 hr. The precipitated salt was collected, washed with 5% acetone–ethyl acetate, and crystallized from methanol as brownish yellow needles: yield 2.0 g (50%); mp 207° dec; λ_{max}, mμ (log ϵ), 228 (4.04), 241 (3.95), 252 (3.94), 272 (3.81), 276 (3.82), 315 (sh) (3.61), 322 (3.62), 342 (3.55), 358 (3.50), and 370 (3.60).

Anal. Calcd for $C_{10}H_{11}BrN_2O \cdot H_2O$: C, 43.96; H, 4.79; N, 10.25. Found: C, 44.00; H, 4.79; N, 11.04.

1-(2-Oximinoethyl)-2-(oximinomethyl)pyridinium Chloride (VIIIc).—A solution of 2-pyridinealdoxime (1.3 g, VIc) and chloroacetaldoxime[7] (1.0 g) in 2 ml of tetramethylene sulfone was left at room temperature for 8 days. The solid mass of salt was broken up and washed thoroughly with ethyl acetate, then crystallized from methanol–ethyl acetate as brownish yellow needles, yield 1.9 g (90%), mp 190° dec.

Anal. Calcd for $C_8H_{10}ClN_3O_2$: C, 44.57; H, 4.67; N, 19.49. Found: C, 44.61; H, 4.83; N, 19.65.

1-(2-Oximinoethyl)-2-(1,3-dioxolan-2-yl)pyridinium Chloride (VIIId).—A solution containing 1.5 g of 2-(1,3-dioxolan-2-yl)-

(5) This structure was first suggested by Dr. J. C. Parham in this laboratory.

(6) K. Winterfeld and G. Gierenz, *Ber.*, **92**, 240 (1959). We are grateful to Professor Winterfeld for supplying us with a sample.

(7) R. W. L. Kimber and J. C. Parham, *J. Org. Chem.*, **28**, 3205 (1963).

pyridine (VId) and 1.0 g of chloroacetaldoxime in 2 ml of tetramethylene sulfone was allowed to react at room temperature for 8 days. On working up as above, a precipitate was obtained which crystallized from methanol–ethyl acetate as pale yellow needles, yield 2.0 g (83%), mp 169–170° dec.

Anal. Calcd for $C_{10}H_{13}ClN_2O_3$: C, 49.08; H, 5.37; N, 11.45. Found: C, 49.07; H, 5.16; N, 11.60.

2-Azaquinolizinium Chloride 2-Oxide (IXc).—A solution of 1.0 g of 1-(2-oximinoethyl)-2-(1,3-dioxolan-2-yl)pyridinium chloride (VIIId) and 10 ml of concentrated hydrochloric acid was heated on a steam bath for 4 hr. The acid was removed under reduced pressure (aspirator) and the residue crystallized from methanol as pale yellow needles, yield 0.6 g (80%). The compound turns dark at 190° and decomposes above 240°.

Anal. Calcd for $C_8H_7ClN_2O$: C, 52.61; H, 3.86; N, 15.34. Found: C, 52.62; H, 3.76; N, 15.55.

Cyclization of 1-(2-oximinoethyl)-2-(oximinomethyl)pyridinium chloride (VIIIc) by the above method yielded the same product.

The **bromide** was obtained by substituting 48% hydrobromic acid for hydrochloric acid in the cyclization procedure. It crystallized from methanol as yellow needles which decompose at 280° with previous darkening: yield 85%; λ_{max}, mμ (log ϵ), 288 (3.99), 258 (sh) (3.63), 265 (sh) (3.59), 275 (sh) (3.52), 308 (sh) (3.50), 320 (3.62), 339 (3.66), and 360 (3.32).

Anal. Calcd for $C_8H_7BrN_2O$: C, 42.31; H, 3.10; N, 12.33. Found: C, 42.09; H, 3.05; N, 12.19.

2-Azaquinolizidine (Vb).—A suspension of 1.0 g of 2-azaquinolizinium chloride 2-oxide (IXc) in 200 ml of methanol was hydrogenated at atmospheric pressure for 2 days in the presence of 0.1 g of platinum oxide catalyst. The colorless solution was concentrated under reduced pressure and the residue was treated with a dilute solution of sodium carbonate and then extracted with ether. Evaporation of the ether gave an oil which distilled at 60° (1 mm).

The dipicrate crystallized from water as yellow needles, mp 251–260° dec (lit.[6] mp 250–260° dec).

Anal. Calcd for $C_{20}H_{22}N_8O_{14}$: C, 40.14; H, 3.70; N, 18.72. Found: C, 40.51; H, 4.00; N, 18.48.

3-Methyl-2-azabenzo[*h*]quinolizinium Bromide 2-Oxide (X).—A mixture of 1.7 g of 1-oximinomethylisoquinoline[8] and 1.4 g of bromoacetone in 20 ml of acetone was refluxed for 6 hr. On working up as usual, the yellow precipitate was crystallized from methanol–ethyl acetate as yellow needles: yield 1.5 g (50%); the compound darkens at 225° and decomposes at 252°; λ_{max}, mμ (log ϵ), 245 (4.26), 251 (4.27), 290 (3.99), 352 (3.78), 367 (3.97), and 388 (4.04).

Anal. Calcd for $C_{13}H_{11}BrN_2O \cdot 0.5H_2O$: C, 52.02; H, 4.03; N, 9.33. Found: C, 51.80; H, 4.13; N, 9.26.

3-Methyl-2-azabenzo[*g*]quinolizinium Bromide 2-Oxide (XI).—A mixture of 1.7 g of 3-oximinomethylisoquinoline[9] and 1.4 g of bromoacetone in 20 ml of acetone was refluxed for 6 hr. The precipitated salt was collected, washed with ethyl acetate, and crystallized from methanol–ethyl acetate as reddish yellow needles, yield 1.65 g (55%); the compound darkens at 190° but does not melt till 405°. The bromide was not obtained pure.

The **picrate** crystallized from methanol as yellow needles, mp 224–225° dec.

Anal. Calcd for $C_{10}H_{13}N_5O_8$: C, 51.94; H, 2.98; N, 15.94. Found: C, 51.71; H, 3.02; N, 15.92.

(8) R. S. Barrows and H. G. Lindwall, *J. Am. Chem. Soc.*, **64**, 2430 (1942).

(9) F. R. Crowne and J. G. Breckenridge, *Can. J. Chem.*, **32**, 641 (1954).

Ketenes. VIII. Some Reactions of 1-(Dimethylamino)-4-methyl-1-penten-3-one[1]

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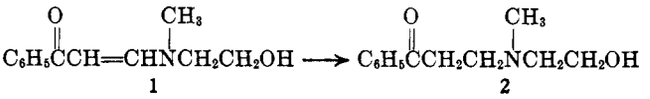
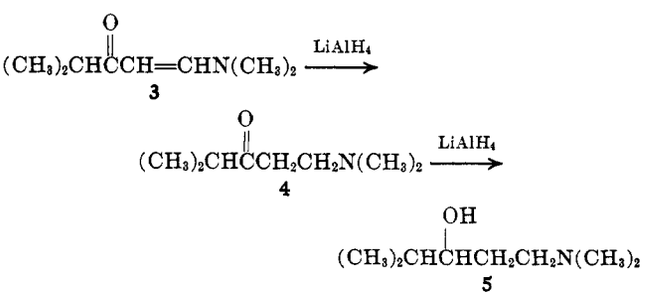
Some new reactions of 1-(dimethylamino)-4-methyl-1-penten-3-one (DMPN), which is prepared from ketene and N,N-dimethylisobutenylamine, are described. In particular, reductions, amine exchange, heterocyclic formation, and addition to dimethylketene are covered.

The recent discovery of a facile synthesis for 1-(dimethylamino)-4-methyl-1-penten-3-one (DMPN) from ketene and N,N-dimethylisobutenylamine[2] prompted us to investigate some reactions of this material. Vinylogous amides, of which DMPN is an example, are a class of materials that have received attention in recent years because of their special properties.[3-6] Because DMPN is an amide vinylog, the field position of the dimethylamino group is at δ 2.86 in the nmr spectrum, which is very close to the position reported for amides, but considerably different from that for amines.[7]

Walker reported that reduction of amide vinylogs with lithium aluminum hydride generally leads to reduction of the carbonyl group not the enamine group. He also reported that the amide vinylog **1** is reduced by lithium aluminum hydride to the saturated amino ketone **2**, and he felt that the hydroxy group contributes



to stopping the reduction at **2** because of the formation of "*noncyclic*, insoluble metallic complex salts of these products, resulting in their precipitation—*i.e.*, removal from the scene where further attack by hydride might progress."[6] In view of the work of deStevens and Halamandaris[8] and of our work with DMPN (**3**), we feel



that the hydroxy group is not necessary for the success of this reduction. DMPN when reduced with lithium aluminum hydride in ether gave 1-(dimethylamino)-4-methyl-3-pentanone (**4**) in 68% yield. This is a 1,4

(1) Paper VII in this series: J. C. Martin and R. H. Meen, *J. Org. Chem.*, **30**, 4311 (1965).

(2) R. H. Hasek and J. C. Martin, *ibid.*, **28**, 1468 (1963).

(3) S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945).

(4) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, *ibid.*, **71**, 3337 (1949).

(5) N. F. Albertson, *ibid.*, **74**, 249 (1952).

(6) G. N. Walker, *J. Org. Chem.*, **27**, 4227 (1962).

(7) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p. 56.

(8) G. deStevens and A. Halamandaris, *J. Org. Chem.*, **26**, 1614 (1961).