[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

SUBSTITUTED PYRROLIDINES AND PYRROLIDYLETHANOLS[1]

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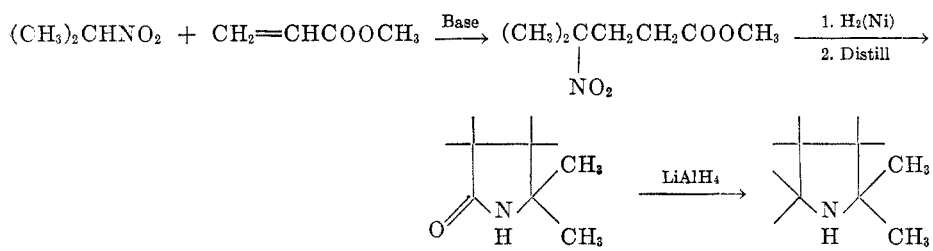
In previous papers from these laboratories (1) a number of pyrrolidyl alkanols were described. The preparation and properties of some additional compounds of this type are herewith reported. Most of the pyrrolidyl alkanols listed in Table I were prepared by the alkylation of the corresponding pyrrolidine with ethylene chlorohydrin. This procedure is illustrated in the experimental part by a detailed description of the preparation of 2-(2,2-dimethyl-1-pyrrolidyl)ethanol. 2,2-Dimethylpyrrolidine was also converted to 2-(2,2-dimethyl-1-pyrrolidyl)-propanol by treatment with ethyl α-bromopropionate followed by reduction of the ester with lithium aluminum hydride.

Many of the requisite pyrrolidines were obtained by lithium aluminum hydride reduction of the corresponding pyrrolidones. This reaction failed to take place under conditions which reduced the N-hydroxyethylpyrrolidones (1), but proceeded smoothly when boiling tetrahydrofuran was used in place of ether.

The pyrrolidones were obtained from the appropriate γ-nitro esters or acids by Raney nickel hydrogenation followed by distillation. Leonard and Beck (2) have reported the high pressure hydrogenation of γ-nitro esters to pyrrolidines using copper chromite catalyst. However, in their procedure the pyrrolidines are alkylated on the nitrogen atom by the alcohol used as solvent or by the alcohol moiety of the ester. 2,2-Dimethylpyrrolidine has been prepared by Buckley and Elliott (3) by the reduction of 5-amino-2,2-dimethylpyrroline-N-oxide or 5-imino-2,2-dimethylpyrrolidine. However, the present series of reactions seems to us to be more convenient.



The addition of nitroparaffins to acrylic esters is described by Bruson (4) and affords excellent results with simple acrylates and methacrylates but fails or gives very poor yields with crotonates, a fact also noted by Leonard and co-workers (5, 6) as well as by Kloetzel (7).

Although 2-nitropropane fails to add to methyl crotonate, it will add to allyl

[1] A portion of this work was reported before the XIIth International Congress of Pure and Applied Chemistry, New York, September 10–13, 1951.

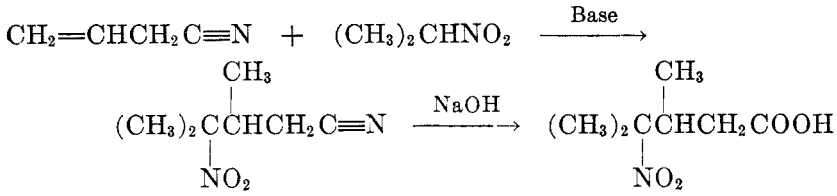
TABLE I

PYRROLIDYL ALKANOLS

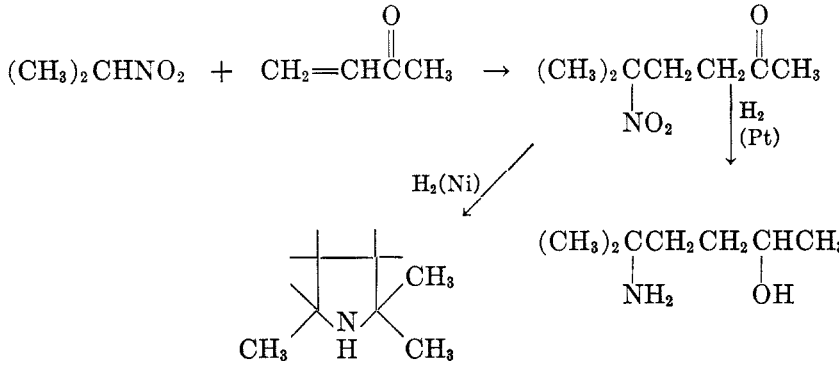
FORMULA	YIELD, %[a]	B.P.,[2] °C.	MM.	n_D^{25}	d_4^{25}	FORMULA	NEUT. EQUIV.		NITROGEN, %	
							Calc'd	Found	Calc'd	Found[2]
$C(CH_3)_2CH_2CH_2CH_2NCH_2CH_2OH$	72.4	90	18	1.4660	0.9454	$C_8H_{17}NO$	143.23	143.1	9.78	9.81
$C(CH_3)_2CH_2CH_2CH_2NCH(CH_3)CH_2OH$[b]	20	94	16	1.4582	.9187	$C_9H_{19}NO$	157.25	—	8.91	8.85
$CH(C_2H_5)CH_2CH_2CH_2NCH_2CH_2OH$[c]	73.7	90	10	1.4680	.9420[d]	$C_8H_{17}NO$	143.23	—	9.78	—
$C(CH_3)_2CH_2CH(CH_3)CH_2NCH_2CH_2OH$	65.6	87	12	1.4581	.9154	$C_9H_{19}NO$	157.25	158.4	8.91	9.02
$C(CH_3)_2CH(CH_3)CH_2CH_2NCH_2CH_2OH$	72.3	98	15	1.4666	.9332	$C_9H_{19}NO$	157.25	—	8.91	9.23
$C(CH_3)_2CH_2CH_2CH(CH_3)NCH_2CH_2OH$	14.6	86	11.5	1.4602	.9206	$C_9H_{19}NO$	157.25	159.4	8.91	8.89
$C(CH_3)(C_2H_5)CH_2CH_2CH_2NCH_2CH_2OH$	45[e]	110	15	1.4590[f]	.9111[f]	$C_9H_{19}NO$	157.25	157.2	8.91	8.81
$CH(CH_3)CH(C_2H_5)CH(CH_3)CH_2NCH_2CH_2OH$	34	104	16	—	—	$C_{10}H_{11}NO$	171.3	—	4.33[g]	4.29[g]

[a] Yield based on the corresponding substituted pyrrolidine unless otherwise indicated. [b] This was prepared by essentially the same procedure used for 2-(1-pyrrolidyl)propanol in our previous work (1). [c] Previously prepared by Normant (14), by a different procedure, who reports b.p. 91–92° (12 mm.) and d^{13} 0.953. [d] d^{13} 0.95085. [e] Yield based on N-(2-hydroxyethyl)-4-methyl-4-aminohexene-1. [f] Index of refraction and density were taken at 20° for this compound. [g] This was analyzed as the cyclopentyl-*n*-propylacetate ester ($C_{20}H_{37}NO_2$), to be reported in a future communication. [2] See footnote 2 in text.

cyanide or crotononitrile (8), giving β,γ-dimethyl-γ-nitrovaleronitrile, which can be hydrolyzed to the corresponding acid.

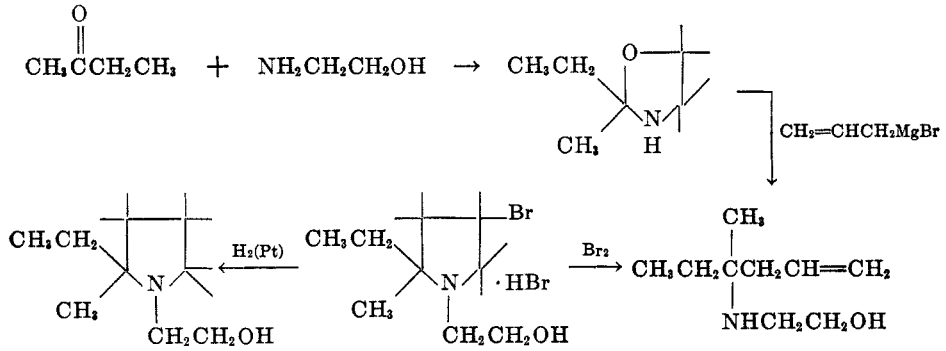


Kohler and co-workers (9–11) and also Kloetzel (12) have studied the addition of nitroparaffins to α,β-unsaturated ketones using various basic catalysts. However, the only completely aliphatic ketone used was mesityl oxide. We have found that 2-nitropropane can be successfully added to methyl vinyl ketone using trimethylbenzylammonium hydroxide or piperidine as a catalyst to give 5-methyl-5-nitrohexanone-2. The more hindered mesityl oxide failed to add either nitroethane or 2-nitropropane, and Kloetzel (12) reports a relatively unfavorable equilibrium with nitromethane.



On hydrogenation of the nitro ketone with platinum oxide the only product isolated was 5-amino-5-methylhexanol-2. However, with Raney nickel catalyst the product was the desired 2,2,5-trimethylpyrrolidine.

2,4-Dimethyl-3-ethylpyrrolidine (13) was prepared by the high pressure hydrogenation of 3-acetyl-2,4-dimethylpyrrole with Raney nickel. 2-(2-Ethyl-2-methyl-1-pyrrolidyl)ethanol was prepared by the following series of reactions.



EXPERIMENTAL[2]

Methyl γ-methyl-γ-nitrovalerate. This was prepared essentially by the method of Bruson (4) except that a slightly higher temperature (85–100°) was found desirable. The product was distilled through a short packed column, b.p. 79° (1 mm.) giving an 86% yield of light blue liquid, n_D^{25} 1.4385.

Methyl α,γ-dimethyl-γ-nitrovalerate. This compound has been prepared by Leonard and Shoemaker (6) and by Kloetzel (7) but only in 33–35% yield. By a procedure similar to that described for the monomethyl compound we obtained a 72% yield from 2-nitropropane and methyl methacrylate; b.p. 79° (1.7 mm.); n_D^{25} 1.4367; d_4^{25} 1.0774.

Anal. Calc'd for $C_8H_{15}NO_4$: N, 7.40. Found: N, 7.45.

β,γ-Dimethyl-γ-nitrovaleric acid. A mixture of 15.6 g. (0.1 mole) of β,γ-dimethyl-γ-nitrovaleronitrile (8) and 100 ml. of 10% aqueous sodium hydroxide was heated under reflux for four hours. Acidification of the cooled solution gave 10.9 g. of crystalline solid which was recrystallized from water containing a little methanol giving 6.4 g. (36.6%) of a white crystalline solid, m.p. 81.5–83°. Recrystallization of a sample from a mixture of carbon tetrachloride and hexane did not raise the melting point.

Anal. Calc'd for $C_7H_{13}NO_4$: C, 47.99; H, 7.50; N, 8.00; Neut. equiv., 175.2.
Found: C, 48.02; H, 7.39; H, 8.07; Neut. equiv., 173.0.

5-Methyl-5-nitrohexanone-2. To a solution of 111 ml. (1.28 moles) of 2-nitropropane and 5 ml. of 40% aqueous trimethylbenzylammonium hydroxide (Triton B) in 100 ml. of absolute ethanol, was slowly added with stirring during one hour 100 ml. (1.28 moles) of methyl vinyl ketone. The temperature spontaneously reached 64°. After stirring under reflux for one hour, the mixture was diluted with ether, washed with dilute hydrochloric acid, then with dilute sodium bicarbonate, and finally with a saturated sodium chloride solution and dried over sodium sulfate. The solvent was removed and the product was distilled through a short column giving 108.9 g. (53.4%) of light yellow liquid, b.p. 119° (11 mm.), n_D^{25} 1.4447, d_4^{25} 1.05644.

Anal. Calc'd for $C_7H_{13}NO_3$: N, 8.80. Found: N, 8.62.

5,5-Dimethylpyrrolidone-2.[3] A solution of 148 g. (0.845 mole) of methyl γ-methyl-γ-nitrovalerate in 500 ml. of absolute ethanol was hydrogenated in the presence of about 25 g. of Raney nickel catalyst at 60° and about 1000 p.s.i. The solution was filtered from the catalyst, the solvent was removed, and the residue was heated to 200° and then distilled under reduced pressure; b.p. 75° (0.05 mm.); yield 82.5 g. (86.2%). It solidified in the receiver and a small sample was recrystallized from pentane, m.p. 37–41°.

Anal. Calc'd for $C_6H_{11}NO$: N, 12.38. Found: N, 11.94.

5-Ethylpyrrolidone-2. This has been reported by Müller and Feld (15). We prepared it from methyl γ-nitrocaproate (16) in 80% yield essentially as described above for 5,5-dimethylpyrrolidone-2; b.p. 136° (12 mm.).

3,5,5-Trimethylpyrrolidone-2.[4] This was prepared in 94% yield from methyl α,γ-dimethyl-γ-nitrovalerate by a procedure similar to that described for 5,5-dimethylpyrrolidone-2; b.p. 122° (11 mm.). A sample was recrystallized from hexane, m.p. 80–82°.

Anal. Calc'd for $C_7H_{13}NO$: N, 11.01. Found: N, 11.09.

4,5,5-Trimethylpyrrolidone-2. This was prepared in 65.3% yield from β,γ-dimethyl-γ-nitrovaleric acid by a procedure similar to that described above for 5,5-dimethylpyrrolidone-2; b.p. 135° (15 mm.); m.p. 45–47°.

Anal. Calc'd for $C_7H_{13}NO$: N, 11.01. Found: N, 11.02.

2,2-Dimethylpyrrolidine. To 38.0 g. (1 mole) of $LiAlH_4$ and 400 ml. of tetrahydrofuran was slowly added with stirring 90.5 g. (0.8 mole) of the above 5,5-dimethylpyrrolidone-2

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[2] Melting points and boiling points are uncorrected. Analyses by Mr. Harold Emerson and Mr. William A. Struck and staff of our Microanalytical Laboratory.

[3] This has been prepared by Buckley and Elliott (3) by the hydrolysis of 5-imino-2,2-dimethylpyrrolidine or by the hydrolytic hydrogenation of 5-amino-2,2-dimethylpyrroline-N-oxide.

in 200 ml. of tetrahydrofuran. After refluxing for eight hours most of the solvent was removed by distillation on a steam-bath and was replaced by carefully adding 300 ml. of ether. Then 30 ml. of water was slowly added followed by 200 ml. of concentrated hydrochloric acid in 300 ml. of water. The aqueous solution was extracted continuously with ether for five hours. The ether extract was discarded and the aqueous solution was made very strongly basic with sodium hydroxide and again extracted continuously with alcohol-free ether for 12 hours. This ether solution was dried over potassium carbonate and distilled through a good column giving 62.5 g. (79%) of colorless liquid, b.p. 103°, n_D^{25} 1.4304, d_4^{25} 0.82114.

Anal. Calc'd for $C_6H_{13}N$: N, 14.13; Neut. equiv., 99.17.

Found: N, 14.12; Neut. equiv., 99.6.

2-Ethylpyrrolidine. This has been prepared by several workers (18–20) by different procedures. We made it in 87% yield by a process similar to that described for 2,2-dimethylpyrrolidine except that after the decomposition of the lithium-aluminum complex with water and hydrochloric acid the mixture was steam-distilled until the boiling point reached 100°. Then it was made strongly basic with 50% sodium hydroxide solution and again steam-distilled until little more basic material was coming over. The steam distillate was extracted continuously with alcohol-free ether which was dried over potassium carbonate and distilled through a packed column, b.p. 116–123°.

2,2,4-Trimethylpyrrolidine.[4] This was prepared in 85% yield by the lithium aluminum hydride reduction of 3,5,5-trimethyl pyrrolidone-2 by the method described for 2-ethylpyrrolidine; b.p. 119°; n_D^{25} 1.4259; d_4^{25} 0.8063.

Anal. Calc'd for $C_7H_{15}N$: N, 12.38; Neut. equiv., 113.20.

Found: N, 12.36; Neut. equiv. 114.6.

2,2,3-Trimethylpyrrolidine. This was prepared in 60.8% yield from 4,5,5-trimethylpyrrolidone-2 as described for 2-ethylpyrrolidine; b.p. 128°; n_D^{20} 1.4400.

Anal. Calc'd for $C_7H_{15}N$: N, 12.38. Found: N, 12.08.

2,2,5-Trimethylpyrrolidine. A solution of 135 g. (0.85 mole) of 5-methyl-5-nitrohexanone-2 in about 450 ml. of absolute ethanol was hydrogenated in the presence of 20 g. of Raney nickel at 60° and 1000 p.s.i. The solution was filtered from catalyst and carefully fractionated through a packed column giving 77 g. (80%) of colorless liquid, b.p. 112°; n_D^{25} 1.4223; d_4^{25} 0.7980.

Anal. Calc'd for $C_7H_{15}N$: N, 12.38; Neut. equiv., 113.20.

Found: N, 12.38; Neut. equiv. 115.2.

5-Amino-5-methylhexanol-2. A solution of 21.6 g. of 5-methyl-5-nitrohexanone-2 in 125 ml. of 95% ethyl alcohol was hydrogenated in the presence of 0.2 g. of platinum oxide at 90° and 50 p.s.i. When about half of the theoretical amount of hydrogen had been absorbed the reaction stopped. A second portion of 0.2 g. of catalyst was added and then the hydrogenation proceeded to completion at room temperature. The total time was 20 hours. The solution was filtered and distilled through a six-inch packed column giving 14.0 g. (66.5%) of colorless liquid; b.p. 100° (12 mm.); n_D^{25} 1.4512; d_4^{25} 0.8968. The infrared absorption spectrum[5] indicated the presence of amino and hydroxyl groups but no ketone.

Anal. Calc'd for $C_7H_{17}NO$: C, 64.07; H, 13.06; N, 10.68; Neut. equiv., 131.22.

Found: C, 64.16; H, 12.43; N, 10.73; Neut. equiv., 133.0.

2-(2,2-Dimethyl-1-pyrrolidyl)ethanol. In a 500-ml. flask, fitted with condenser, stirrer, and thermometer, was placed 59.9 g. (0.6 mole) of 2,2-dimethylpyrrolidine and then 48.4 g. (0.6 mole) of ethylene chlorohydrin was added. The mixture was heated to about 120° to start the reaction. When the initial reaction had subsided, it was heated to 150–160° for five minutes. After cooling 60 ml. of 50% aqueous sodium hydroxide was added and the

[4] Compounds formulated as $C_7H_{13}NO$ and $C_7H_{15}N$ are reported by Weil (17) and are probably 3,5,5-trimethylpyrrolidone-2 and 2,2,4-trimethylpyrrolidine respectively. See also Beilstein's *Handbuch der Organischen Chemie*, Ed. 4, Vol. 20, p. 110, and Vol. 21, p. 575.

[5] Infrared absorption spectra are by Mrs. Agatha R. Johnson of our Physics Department.

product was taken up in ether. After drying over potassium carbonate the ether was removed and the residue was distilled through a short column giving 62.2 g. of colorless liquid with the properties shown in Table I.

2-Methyl-2-ethyloxazolidine. This was prepared essentially by the procedure described by Cope and Hancock (21) for similar compounds. The reaction of 223.5 g. (3.1 moles) of methyl ethyl ketone and 183.3 g. (3.0 moles) of ethanolamine gave 232.9 g. (67.3%) of the oxazolidine, b.p. 59° (30 mm.); n_D^{20} 1.4465; n_D^{25} 1.4440.

Anal. Calc'd for $C_6H_{13}NO$: N, 12.16. Found: N, 12.02, 12.31.

N-(2-Hydroxyethyl)-4-methyl-4-aminohexene-1. Allylmagnesium bromide was prepared from 145.8 g. (6 moles) of magnesium and 242 g. (2 moles) of allyl bromide in 1.5 l. of absolute ether. To this was slowly added 104 g. (0.9 mole) of 2-methyl-2-ethyloxazolidine. The reaction was forced to completion by distilling 1 l. of the ether, adding 1 l. of dry tetrahydrofuran, and then distilling off 1 l. more of the solvent. After standing overnight the reaction mixture was decomposed with water and filtered from the precipitated magnesium hydroxide using a filter aid. The precipitate was washed with ether which was used to continuously extract the aqueous filtrate for five hours. The basic fraction was separated by extraction of the ether with dilute hydrochloric acid. This was made basic with sodium hydroxide and the oil which separated was extracted with several portions of ether. This ether solution was dried over potassium carbonate and distilled, giving 55.6 g. (35.3%) of colorless liquid, b.p. 113° (16 mm.); n_D^{20} 1.470.

Anal. Calc'd for $C_9H_{19}NO$: N, 8.91. Found: N, 8.83.

2-(2-Methyl-2-ethyl-1-pyrrolidyl)ethanol. To 32.5 g. (0.21 mole) of the above aminohexene in 100 ml. of chloroform was slowly added 33.6 g. (0.21 mole) of bromine in 100 ml. of chloroform at a temperature below 40°. Distillation of the chloroform left a residue of crude 2-(2-methyl-2-ethyl-4-bromo-1-pyrrolidyl)ethanol hydrobromide. In order to remove the bromine from the ring this was dissolved in 150 ml. of absolute ethanol and hydrogenated at 60° and 50 p.s.i. in the presence of 0.1 g. of platinum oxide catalyst. After filtering from the catalyst the solvent was distilled. The residue was taken up in water, treated with decolorizing charcoal, and made basic with sodium hydroxide solution. This was extracted with ether in several portions. The extract was dried over potassium carbonate, the solvent removed, and the product was distilled giving 14.8 g. (45%) of colorless liquid with the properties listed in Table I.

2,4-Dimethyl-3-ethylpyrrolidine.[6,7] A solution of 50 g. of 2,4-dimethyl-3-acetylpyrrole (22) in about 125 ml. of dioxane was hydrogenated in the presence of 10 g. of Raney nickel at 190° and 1000 p.s.i. The catalyst was removed and the product was distilled through a packed column, b.p. 151–152°, n_D^{20} 1.4377. A sample was converted to a picrate[6] and crystallized from ether, m.p. 109–110°.

Anal. Calc'd for $C_{14}H_{20}N_4O_7$: N, 15.73. Found: N, 15.51.

SUMMARY

Satisfactory methods for the preparation of substituted pyrrolidines and pyrrolidylethanols from γ-nitrocarbonyl compounds are described.

A number of new pyrrolidyl alcohols have been made by these and other methods.

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REFERENCES

(1) MOFFETT, *J. Org. Chem.*, **14**, 862 (1949).
(2) LEONARD AND BECK, *J. Am. Chem. Soc.*, **70**, 2504 (1948).

[6] Fischer and Höfelmann (13) report no physical constants for this pyrrolidine, but they obtained a picrate, m.p. 135°, crystallized from alcohol.

[7] Prepared under the direction of Dr. William Bradley Reid, Jr. in these laboratories.

(3) BUCKLEY AND ELLIOTT, *J. Chem. Soc.*, 1508 (1947).
(4) BRUSON, U. S. Patent 2,390,918 (1945).
(5) LEONARD AND FELLEY, *J. Am. Chem. Soc.*, **71**, 1758 (1949).
(6) LEONARD AND SHOEMAKER, *J. Am. Chem. Soc.*, **71**, 1760 (1949).
(7) KLOETZEL, *J. Am. Chem. Soc.*, **70**, 3571 (1948).
(8) BUCKLEY, ELLIOTT, HUNT, AND LOWE, *J. Chem. Soc.*, 1505 (1947).
(9) KOHLER, *J. Am. Chem. Soc.*, **38**, 889 (1916).
(10) KOHLER AND RAO, *J. Am. Chem. Soc.*, **41**, 1697 (1919).
(11) KOHLER AND SMITH, *J. Am. Chem. Soc.*, **44**, 624 (1922).
(12) KLOETZEL, *J. Am. Chem. Soc.*, **69**, 2271 (1947).
(13) FISCHER AND HÖFELMANN, *Z. physiol. Chem.*, **251**, 187 (1938).
(14) NORMANT, *Compt. rend.*, **226**, 1734 (1948).
(15) MÜLLER AND FELD, *Monatsh.*, **58**, 22 (1931).
(16) BRUSON, U. S. Patent 2,342,119 (1944).
(17) WEIL, *Ann.*, **232**, 206 (1886).
(18) DEJONG AND WIBAUT, *Rec. trav. chim.*, **49**, 237 (1930).
(19) MÜLLER AND WACHS, *Monatsh.*, **53** and **54**, 420 (1929).
(20) MÜLLER AND FELD, *Monatsh.*, **58**, 12 (1931).
(21) COPE AND HANCOCK, *J. Am. Chem. Soc.*, **64**, 1503 (1942).
(22) RAINEY AND ADKINS, *J. Am. Chem. Soc.*, **61**, 1104 (1939).