amylase is reflected in the lower total nitrogen, 15.92%.

These two animal amylases are in many respects similar in their enzymatic activity and are both activated by chloride. If the clue to this activation is to be found in the amino acid composition, one might expect to find it related to the amino acids which are found in similar quantities. These are, however, found in amounts that are well within the usual range of protein composition. Work on this problem is being continued.

DEPARTMENT OF PHYSIOLOGY
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MASSACHUSETTS

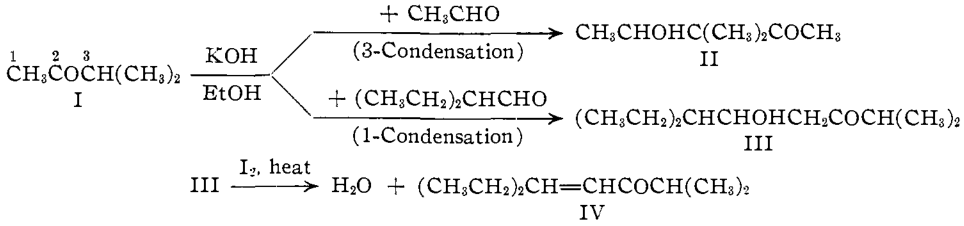
The Base-catalyzed Condensation of Aldehydes with Methyl Isopropyl Ketone[1]

BY ARNOLD T. NIELSEN[2a] AND ELWIN B. W. OVIST[2b,c]

RECEIVED MAY 11, 1954

The base-catalyzed condensations of formaldehyde[3,4] and acetaldehyde[3,5] with methyl isopropyl ketone (I) have been reported to occur on the methylidyne group (3-condensation). On the other hand, several aldehydes have been found to condense on the methyl group of this ketone (1-condensation) including isobutyraldehyde,[6a] citral,[6b] benzaldehyde,[6c,d] salicylaldehyde,[6e] *o*-phthalaldehyde,[6f] and furfural.[6g]

In the present work the acetaldehyde condensation has been repeated using ethanolic potassium hydroxide catalyst. The ketol obtained, 4-hydroxy-3,3-dimethyl-2-pentanone (II), produced only traces of water on attempted dehydration by heating with iodine; thus, 3-condensation was indicated to be the main reaction, as previously reported.[5] (Zalkind[5] obtained II in 32% yield using potassium cyanide catalyst and oxidized it to 3,3-dimethyl-2,4-pentanedione.) However, we have found *n*-butyraldehyde and α-ethylbutyraldehyde to undergo mainly 1-condensation with I.



With α-ethylbutyraldehyde, the unsaturated ketone, 6-ethyl-2-methyl-4-octen-3-one (IV), was obtained as the main product in 47% yield; the structure of IV was confirmed by ozonolysis of it to α-ethylbutyric and isobutyric acids. The ketol, 6-ethyl-5-hydroxy-2-methyl-3-octanone (III), obtained in 6.5% yield, gave a 75% yield of IV when heated with iodine (86% water of dehydration). Thus, in this case, 98% or more of the ketone condensation occurred on the methyl group. In the *n*-butyraldehyde condensation the yields of unsaturated ketone, 2-methyl-4-octen-3-one (V) and ketol (VI) were 12 and 28%, respectively; a 6% yield of 2-ethyl-2-hexenal was also formed by self-condensation of the aldehyde. The structure of V was demonstrated by hydrogenation of it to 2-methyl-3-octanone. The present data do not permit determination of the exact amount of 1-condensation; from the dehydration data it is known to be at least 65%. Since VI gave a negative iodoform test it is likely that the actual value is somewhat higher. Under conditions identical with those found to be favorable for the acetaldehyde and *n*-butyraldehyde condensations, propionaldehyde failed to react with I, most of it being consumed by self-condensation to form propionaldol and 2-methyl-2-pentenal. It would appear from this last observation that the course of these reactions is sensitive to the relative reactivities and concentrations of the various carbanions present as well as to steric factors which are evidently operating.

In the presence of acid catalysts methyl isopropyl ketone reacts with bromine[7] and acetic anhydride[8] to give 76 and 68% 3-condensation, respectively; we have found, incidental to this work, that *n*-butyric anhydride gives 74% 3-condensation using Hauser's procedure.[8] In the acid-catalyzed reactions of I, unlike the base catalyzed, the amount of 3-condensation appears to be reasonably independent of the attacking molecule and to be determined by the concentrations of the reacting enols, at least for the limited number of cases so far studied.

If a general procedure were at hand for oxidizing 1,3-ketols to 1,3-diketones in high yields, a simple analytical method would then be provided for the analysis of ketol mixtures formed by condensing aldehydes with unsymmetrical methyl ketones.[9] Our initial experiments to find such a procedure have been only partly successful. We have found N-bromosuccinimide to oxidize 5-hydroxy-2,4,4-trimethyl-3-octanone to 2,4,4-trimethyl-3,5-octanedione in 81% yield (acid potassium permanganate gave 41%[10]). However, at-

---

[1] Based upon a thesis submitted by Elwin B. W. Ovist in partial fulfilment of the requirements for the degree of Master of Science, University of Idaho, 1951.

[2] Present address: (a) Purdue University, Lafayette, Indiana; (b) Kansas State College, Manhattan, Kansas; (c) Research Corporation Fellow, 1950–1951.

[3] J. E. Dubois, *Ann. chim.* (Paris), **6**, 406 (1951).

[4] J. Decombe, *Compt. rend.*, **203**, 1077 (1936).

[5] J. Zalkind, *J. Russ. Phys. Chem. Soc.*, **37**, 486 (1905); *Chem. Zentr.*, **76**, II, 752 (1905).

[6] (a) H. Thoms and H. Kahre, *Arch. Pharm.*, **263**, 241 (1925); (b) Haarman and Reimer, German Patent 73,089 (April 25, 1893); *Chem. Zentr.*, **73**, I, 235 (1902); (c) K. v. Auwers, *Ber.*, **45**, 2764 (1912); (d) K. v. Auwers and H. Voss, *ibid.*, **42**, 4411 (1909); (e) A. McGookin and D. J. Sinclair, *J. Chem. Soc.*, 1170 (1928); (f) J. Thiele and E. Weitz, *Ann.*, **377**, 1 (1910); (g) I. Kasiwagi, *Bull. Chem. Soc., Japan*, **1**, 90 (1926); *C. A.*, **20**, 3005 (1926).

[7] H. M. E. Cardwell and A. E. Kilner, *J. Chem. Soc.*, 2430 (1951).

[8] C. R. Hauser and J. T. Adams, THIS JOURNAL, **66**, 345 (1944); *ibid.*, **67**, 284 (1945).

[9] Diketones of the type RCOCH2COR and RCOC(R)(R')COR (R' = alkyl or H) may readily be separated quantitatively by the procedure of Hauser and Adams (ref. 8).

[10] A. T. Nielsen, C. Gibbons and C. Zimmerman, THIS JOURNAL, **73**, 4696 (1951).

tempted oxidation of three ketols of the type $RCHOHCH_2COR'$ with a variety of oxidizing agents failed to yield a diketone in isolable amounts.

Experimental[11]

Condensation of Acetaldehyde with Methyl Isopropyl Ketone.—Acetaldehyde, 44 g. (1.0 mole) dissolved in 86 g. (1.0 mole) of methyl isopropyl ketone was added dropwise with stirring to 258 g. (3.0 moles) of the ketone and 100 ml. of *N* ethanolic potassium hydroxide solution during four hours (temp. 10°, nitrogen atmosphere maintained). The mixture was immediately washed several times with water, dried and distilled under nitrogen to yield 4.8 g., b.p. 75–82° (24 mm.), 21 g. (16%) of 3,3-dimethyl-4-hydroxy-2-pentanone, b.p. 89–90° (20 mm.), n^{25}D 1.4330 (lit.[5] b.p. 79–80° (10 mm.)) and 9.8 g. of residue. A 4.5-g. sample of the ketol on heating with iodine gave only traces of water.

The reaction of *n*-heptaldehyde with methyl isopropyl ketone was carried out similarly and found to give a mixture of condensation products which could not be purified by fractional distillation.

α-Ethylbutyraldehyde and Methyl Isopropyl Ketone Condensation.—Employing the above procedure, α-ethylbutyraldehyde (100 g., 1.0 mole) was dissolved in 43 g. (0.5 mole) of methyl isopropyl ketone and added, with cooling below 30°, during one hour to a solution of 215 g. (2.5 moles) of the ketone and 75 ml. of *N* ethanolic potassium hydroxide solution. After standing for 16 hours the mixture was worked up and distilled to yield 79.4 g. (47%) of 6-ethyl-2-methyl-4-octen-3-one, b.p. 99–102° (15 mm.), n^{25}D 1.445 and 12.2 g. (6.5%) of **6-ethyl-5-hydroxy-2-methyl-3-octanone**, b.p. 116–119° (14 mm.), n^{25}D 1.443. When the reaction mixture was allowed to stand for 20 minutes after addition of the aldehyde, the yields of unsaturated ketone and ketol were 30 and 8%, respectively.

On redistillation the ketol had b.p. 116–117° (13 mm.), n^{25}D 1.4424; it gave a negative iodoform test.[12]

Anal. Calcd. for $C_{11}H_{22}O_2$: C, 70.91; H, 11.91. Found: C, 71.28, 71.33; H, 12.17, 12.11.

A 14.7-g. (0.079 mole) sample of the ketol was distilled at 690 mm. with a few crystals of iodine; 1.2 g. (86%) of water was collected. The residue which remained was diluted with ether and washed with sodium bisulfite solution, dried and distilled. After removing the ether there was obtained 10.0 g. (75.5%) of 6-ethyl-2-methyl-4-octen-3-one, b.p. 92–96° (13 mm.), n^{25}D 1.445 and 1.7 g. of residue. The 2,4-dinitrophenylhydrazone derivative, m.p. 62–63°, showed no depression in melting point when mixed with an authentic sample.

Reaction of the ketol with acid potassium permanganate produced the corresponding unsaturated ketone (42% yield). No evidence of diketone formation was observed.

6-Ethyl-2-methyl-4-octen-3-one.—A fraction, b.p. 99–100° (13 mm.), n^{25}D 1.4458, obtained by redistillation of the above unsaturated ketone, was used for analysis.

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.82; H, 12.14.

The **2,4-dinitrophenylhydrazone** derivative, after two recrystallizations from ethanol, melted at 62–63°.

Anal. Calcd. for $C_{17}H_{24}N_4O_4$: C, 58.61; H, 6.94. Found: C, 58.66; H, 7.02.

The **semicarbazone** derivative after three recrystallizations from dilute ethanol melted at 99–100°.

Anal. Calcd. for $C_{12}H_{23}N_3O$: C, 63.97; H, 10.29. Found: C, 65.25; H, 10.41.

Quantitative hydrogenation of a small sample of 6-ethyl-2-methyl-4-octen-3-one in isoamyl alcohol (platinum catalyst, 26°, 695 mm.) resulted in absorption of 1.01 mole equivalents of hydrogen within 30 minutes, after which time hydrogenation ceased. The hydrogenation product, not isolated, is believed to be 6-ethyl-2-methyl-3-octanone.

Ozonolysis of 6-Ethyl-2-methyl-4-octen-3-one.—A 15.1-g. (0.085 mole) sample of the unsaturated ketone dissolved in 20 ml. of carbon tetrachloride was ozonized until absorption of ozone was complete. The solution of the ozonide was then poured slowly into 100 ml. of 6 *N* sodium hydroxide solution; 20 ml. of 30% hydrogen peroxide solution was then added and the mixture heated for two hours on the steam-bath. After cooling, the mixture was extracted with ether; the ether extracts after drying and distilling gave 0.7 g., b.p. 85–93° (14 mm.), n^{25}D 1.430, and 0.55 g. of residue. The aqueous solution was acidified with hydrochloric acid, saturated with ammonium sulfate and extracted with six 50-ml. portions of ether. After drying the combined extracts and distilling the ether, the residue was distilled to yield 4.1 g., mainly isobutyric acid, b.p. 150–165° (690 mm.); 1.9 g., b.p. 80–95° (17 mm.), mainly α-ethylbutyric acid and 0.5 g. of residue. Redistillation of the isobutyric acid fraction gave 1.3 g., b.p. 150–155° (690 mm.), n^{20}D 1.3918, neut. equiv. 86 (calcd. 88), *p*-phenylphenacyl ester derivative, m.p. 88.5° (mixed with an authentic sample gave no depression). A part of the α-ethylbutyric acid fraction, b.p. 87–93° (17 mm.), n^{20}D 1.4123, had neut. equiv. 117 (calcd., 116); *p*-phenylphenacyl derivative, m.p. 76° (mixed with an authentic sample gave no depression).

***n*-Butyraldehyde and Methyl Isopropyl Ketone Condensation.**—*n*-Butyraldehyde (144 g., 2.0 moles) dissolved in 172 g. (2.0 moles) of methyl isopropyl ketone was added to 344 g. (4.0 moles) of the ketone and 100 ml. of *N* ethanolic potassium hydroxide solution during 4.5 hours (temp. 10–15°). After standing 30 minutes, the mixture was worked up to yield on distillation at 14 mm. 7.9 g., mainly 2-ethyl-2-hexenal, b.p. 70–78°; 32.5 g. (11.6%) of 2-methyl-4-octen-3-one, b.p. 80–84°, n^{25}D 1.4479; 89 g. (28.2%) of ketol, b.p. 98–108°, n^{25}D 1.4429; residue, 18.2 g. When the reaction mixture was allowed to stand overnight the yields of unsaturated ketone and ketol were 6 and 17%, respectively.

The 2-ethyl-2-hexenal fraction formed a 2,4-dinitrophenylhydrazone derivative, m.p. 123° (mixed with an authentic sample gave no depression; lit.[13] m.p. 123°).

The ketol fraction on redistillation gave 78.5 g., b.p. 101–104° (14 mm.), n^{25}D 1.4415; this material gave a negative iodoform test[12] and is believed to be mainly 5-hydroxy-2-methyl-3-octanone. *Anal.* Calcd. for $C_9H_{18}O_2$: C, 68.32; H, 11.47. Found: C, 68.31; H, 11.42.

Dehydration of a 15.8-g. sample of the ketol by distilling with a few iodine crystals gave 0.88 g. (50%) of water; 3.4 g., b.p. 55–86° (690 mm.), of a *n*-butyraldehyde and methyl isopropyl ketone mixture; 2.9 g. of 2-methyl-4-octen-3-one, b.p. 66–78° (15 mm.) and 3.1 g. of residue.

Treatment of the ketol with neutral or alkaline potassium permanganate, alkaline or acidic hydrogen peroxide, bismuth trioxide[14] or aluminum *t*-butoxide resulted mainly in recovery of unreacted ketol. Treatment with N-bromosuccinimide in aqueous *t*-butyl alcohol gave a lachrymatory, bromine containing product, b.p. 84–94° (16 mm.), not identified; N-chlorosuccinimide also gave an unidentified product. No evidence of diketone formation was observed in any of these experiments.

A redistilled sample of the **2-methyl-4-octen-3-one**, b.p. 81–82° (14 mm.), n^{25}D 1.4479, was used for analysis.

Anal. Calcd. for $C_9H_{16}O$: C, 77.08; H, 11.50. Found: C, 76.54; H, 11.46.

The **2,4-dinitrophenylhydrazone** derivative after recrystallization from ethanol melted at 76°.

Anal. Calcd. for $C_{15}H_{20}N_4O_4$: C, 56.24; H, 6.29. Found: C, 56.64; H, 6.67.

A sample of 2-methyl-4-octen-3-one dissolved in ethanol was shaken for two hours with hydrogen at three atmospheres in the presence of platinum catalyst. The catalyst was filtered and the filtrate concentrated to 25 ml. From this solution a semicarbazone was prepared, m.p. 69–70°, which when mixed with an authentic sample of 2-methyl-3-octanone semicarbazone, m.p. 71–72°, showed no depression in melting point (lit.[15] m.p. 75°). 2-Methyl-3-octanone, b.p. 168–170° (690 mm.), was prepared in 72% yield by acid potassium permanganate oxidation of 2-methyl-3-octanol; the latter compound, b.p. 180–183° (690 mm.), was prepared in 72% yield from *n*-amylmagnesium bromide and isobutyraldehyde.

Attempted Condensation of Propionaldehyde with Methyl Isopropyl Ketone.—Propionaldehyde (58.1 g., one mole)

---

[11] All melting points are corrected, boiling points are uncorrected.

[12] The quantitative method of G. F. Hennion and C. J. Pillar was used (THIS JOURNAL, **72**, 5318 (1950)); diacetone alcohol was found to give a 97% yield of iodoform with this procedure.

[13] S. G. Powell and D. A. Ballard, *ibid.*, **60**, 1914 (1938).

[14] W. Rigby, *J. Chem. Soc.*, 793 (1951).

[15] P. Karrer, F. Canal, K. Zohner and R. Widmer, *Helv. Chim. Acta*, **11**, 1083 (1928).

and methyl isopropyl ketone were employed under the conditions of the acetaldehyde condensation (50 ml. of ethanolic potassium hydroxide). Products obtained were 2-methyl-2-pentenal, 16.7 g. (34.2%), b.p. 51–56° (50 mm.); propionaldol, 6.3 g. (11%), b.p. 91–93° (18 mm.) and residue, 16.7 g. The 2-methyl-2-pentenal gave a 2,4-dinitrophenylhydrazone derivative, m.p. 162–164°, which when mixed with an authentic sample showed no depression in melting point. The propionaldol on redistillation had b.p. 94° (20 mm.), $n^{25}\text{D}$ 1.4380 (lit.[16] b.p. 84–86° (11 mm.)). On standing 24 hours the aldol became characteristically very viscous, $n^{25}\text{D}$ 1.4500.[16] In another run in which 100 ml. of *N* ethanolic potassium hydroxide was employed the yield of 2-methyl-2-pentenal was 12% and propionaldol, 56%. No evidence for aldehyde–ketone condensation products could be detected.

Condensation of *n*-Butyric Anhydride with Methyl Isopropyl Ketone.—*n*-Butyric anhydride and methyl isopropyl ketone reacted by the procedure of Hauser and Adams[8] to form **3,3-dimethyl-2,4-heptanedione** in 15.8% yield, b.p. 91–94° (20 mm.), $n^{25}\text{D}$ 1.4322; it produced no color in the presence of ethanolic ferric chloride solution.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.89; H, 10.47.

From the same reaction **2-methyl-3,5-octanedione** was also obtained (5.6% yield), b.p. 89° (20 mm.), $n^{25}\text{D}$ 1.4558; it produced a deep red color when treated with ethanolic ferric chloride solution. *Anal.* Found: C, 68.86; H, 10.40.

2,4,4-Trimethyl-3,5-octanedione.—5-Hydroxy-2,4,4-trimethyl-3-octanone,[10] 10 g. (0.054 mole), b.p. 112–113° (14 mm.), $n^{25}\text{D}$ 1.4437, and 28 g. of N-bromosuccinimide were dissolved in 150 ml. of *t*-butyl alcohol and 10 ml. of water.[17] After standing at room temperature for 24 hours, 400 ml. of water was added and then sodium bisulfite solution until the solution became colorless. The solution was extracted with four 100-ml. portions of ether; after drying the extracts and distilling the ether there was obtained 8.1 g. (81%) of 2,4,4-trimethyl-3,5-octanedione, b.p. 100–102° (14 mm.), $n^{25}\text{D}$ 1.4375 (lit.[10] b.p. 103–105° (14 mm.), $n^{25}\text{D}$ 1.4361). In a similar experiment using N-bromoacetamide the yield was 70%, b.p. 100–102° (14 mm.), $n^{25}\text{D}$ 1.4375.

In another experiment attempted oxidation of 5-hydroxy-2,4,4-trimethyl-3-octanone with chromium trioxide in acetic acid resulted in 76% recovery of the ketol. An attempted oxidation with aluminum *t*-butoxide and acetone resulted in quantitative deketolization to diisopropyl ketone and *n*-butyraldehyde.

---

(16) V. Grignard and P. Abelmann, *Bull. soc. chim. France*, [4] **7**, 638 (1910).

(17) L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **72**, 5531 (1950).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF IDAHO
MOSCOW, IDAHO

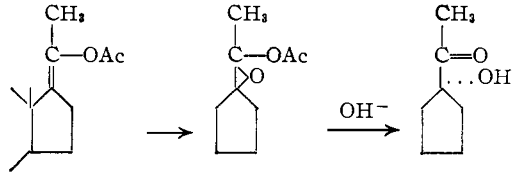
The Preparation of 17α-Hydroxy-20-ketosteroids

BY EUGENE P. OLIVETO AND F. B. HERSHBERG

RECEIVED MAY 26, 1954

The elegant procedure of Gallagher[1] for the preparation of 17α-hydroxy-20-ketosteroids by the reaction of $\Delta^{17(20)}$-enol acetates with peracids unfortunately involves the preparation of perbenzoic or monoperphthalic acid, and this may become troublesome on a large scale. A procedure involving the substitution of the commercially available peracetic acid[2] would therefore be of value. This material has the following average composition: peracetic acid, 40% by wt.; hydrogen peroxide, 5% by wt.; acetic acid, 39% by wt.; sulfuric acid, 1% by wt.; water, 13% by wt.

Recently, the Upjohn research group[3] published a procedure using peracetic acid in which the sulfuric acid had been neutralized by the addition of sodium acetate, and under these conditions it behaves like perbenzoic and monoperphthalic acids



I II III

We have observed, however, that if the sulfuric acid is not neutralized, the intermediate epoxide II cannot be isolated, and the desired 17-hydroxy-20-ketone III can be obtained without resorting to alkaline hydrolysis. Acetate groups in other portions of the molecule are therefore preserved.

Allopregnan-3β-ol-20-one was converted to its enol acetate, then dissolved in benzene and reacted with peracetic acid. After destruction of the excess peracid, the organic layer was concentrated, and crystals of allopregnan-3β,17α-diol-20-one 3-acetate (Compound L 3-acetate) were deposited. Compound L was obtained by alkaline hydrolysis of the benzene mother liquor.

Similarly, pregnan-3α-ol-11,20-dione gave pregnan-3α,17α-diol-11,20-dione and its 3-acetate.

For preparative purposes, in order to obtain the highest possible yields, a complete hydrolysis is probably desirable, because it seems likely that the sulfuric acid, besides hydrolyzing the epoxide II, also may cause partial hydrolysis of the other esters in the molecule.

Experimental[4]

Allopregnan-3β,17α-diol-20-one (Compound L) and Its 3-Acetate.—A solution of 40.0 g. of pregnenolone acetate in 400 ml. of acetic acid was hydrogenated with 10 g. of 5% palladium-on-charcoal. The catalyst was removed by filtration and the filtrate concentrated to a residue under vacuum. This crude allopregnanolone acetate (m.p. 136–141°) was refluxed for 4 hr. in 500 ml. of acetic anhydride containing 6 g. of *p*-toluenesulfonic acid. During this time 400 ml. of distillate was collected, then the rest was removed *in vacuo*. The residue was dissolved in 300 ml. of benzene, the benzene washed with 200 ml. of 20% sodium acetate solution, and water, and then allowed to react at room temperature with 40 ml. of peracetic acid for 140 minutes. A solution of 40 g. of sodium sulfite in 150 ml. of water was then added with cooling, the benzene layer washed with water, dried and concentrated by distillation. When about half the benzene had been removed, crystals began to form. The distillation was stopped, the benzene cooled to *ca.* 20°, and a crop of 5 g. of allopregnan-3β,17α-diol-20-one 3-acetate was removed. Recrystallization from benzene gave 3.6 g., m.p. 184.8–186.8°, $[\alpha]\text{D}$ +17.0° (acetone). The benzene mother liquor was concentrated to a residue, and saponified by refluxing for 15 minutes with 20 g. of sodium hydroxide in 200 ml. of water and 1800 ml. of methanol. Upon concentration and cooling, there was obtained, in two crops, 19 g. of allopregnan-3β,17α-diol-20-one, m.p. 247–253°.

Its 3-acetate, prepared by the action of acetic anhydride in pyridine, was identical with the material obtained from the reaction mixture.

In a similar manner, pregnan-3α-ol-11,20-dione was converted to its enol acetate and reacted with peracetic acid to

---

(1) T. H. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.*, **179**, 507 (1949); B. A. Koechlin, D. L. Garmaise, T. H. Kritchevsky and T. F. Gallagher, THIS JOURNAL, **71**, 3262 (1949); T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, *J. Biol. Chem.*, **74**, 483 (1952).

(2) Buffalo Electro-Chemical Co., Buffalo, N. Y.

(3) H. V. Anderson, E. R. Garrett, F. H. Lincoln, A. H. Nathan and J. A. Hogg, *J. Biol. Chem.*, **76**, 743 (1954).

(4) All m.p.'s are corrected. All rotations were taken in a 1-dcm. tube at a concentration of *ca.* 1%.