[CONTRIBUTION FROM THE DIVISION OF ORGANIC CHEMISTRY OF THE ORTHO RESEARCH FOUNDATION]

The Nef Reaction with α,β-Unsaturated Ketones

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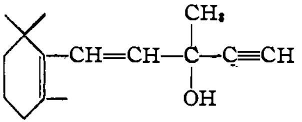
α,β-Unsaturated ketones have been notable for their resistance to conversion to ethynyl carbinols in the Nef reaction. Only six such ketones have been reported successfully condensed and, with one exception, in poor yields. Best results were obtained with sodium acetylide in liquid ammonia.[1,2] Potassium *t*-amylate[3] or sodamide[4] with acetylene have had moderate success while potassium hydroxide with acetylene is stated to fail completely[5] for such ketones.

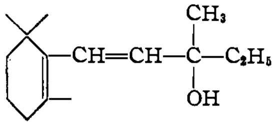
The liquid ammonia–metal acetylide technique appears of greatest versatility for the Nef reaction since it minimizes the destructive effect of highly alkaline reagents, a factor of especial importance when α,β-unsaturated ketones are involved. Since all previous work utilizing this technique on these ketones had been confined to sodium acetylide, it was decided to investigate the action of other metal acetylides in liquid ammonia. A few preliminary experiments indicated that the more reactive potassium acetylide was little better than sodium acetylide. Accordingly, the less reactive calcium[6] and lithium acetylides[7] were investigated. The former gave ethynyl carbinols from eleven α,β-unsaturated ketones in yields of 66 to 96%. Lithium acetylide was likewise superior to sodium acetylide and in some cases to calcium acetylide as well. From saturated ketones, as a rule, poorer yields were realized than with sodium acetylide but interestingly enough, acetophenone and 4-ethoxybutanone-2, which are rather intractable with sodium acetylide, gave good results with calcium and lithium. Isophorone appears to be a very unusual ketone in that it completely resists conversion with sodium,[2] lithium and calcium acetylide. The "inverse" technique, in which the acetylide is formed from the metal amide in liquid ammonia in the presence of the ketone, was found to give generally inferior results.

A new variation of the liquid ammonia–metal acetylide technique, wherein a large excess of sodium acetylide prepared from sodamide is used, has been reported to substantially increase the yields of carbinols from methyl vinyl ketone, ethylidene acetone and mesityl oxide.[2] In the present work this method, using sodium, lithium and calcium, was applied to β-ionone, but no significant benefits were observed.

Some doubt has recently arisen concerning the structure of the ethynyl carbinol of β-ionone. Karrer and Benz[8] reported a product from sodium acetylide in liquid ammonia to which they assigned structure IV, the allylically rearranged product of the normally expected 1,2-adduct, I. The supposed normal carbinol had previously been reported by Gould and Thompson,[3] who found it to be admixed with another product which they tentatively considered a 1:4 adduct. Davies, *et al.*,[4] had also obtained it in good yields by the action of sodamide and acetylene on β-ionone in ether, a reaction which we, like Gould and Thompson, have been unable to effect. From sodium acetylide in liquid ammonia, Rivers[9] obtained a product which analyzed low in carbon and had only one active hydrogen.



I



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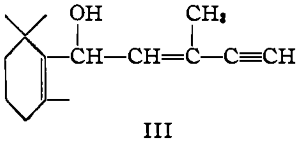

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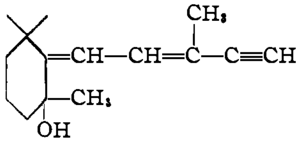

IV

In the present work, no evidence of 1:4 addition was found in the case of β-ionone nor with any other ketone used.[1] The structure of our carbinol was demonstrated as the normal 1,2 adduct, I, by ozonolysis to geronic acid, the presence of two active hydrogens (Zer., 1.98, 2.03), and an absorption curve, $\lambda_{max.}$ 235 mμ (Fig. 1, Curve C) almost identical with those of ethyl-(β-ionol), II, and β-ionol, which contain the same ultraviolet chromophore (Fig. 1, Curves A and B).

Although structure III could conceivably yield geronic acid upon ozonolysis, it was found untenable since, upon absorption of two moles of hydrogen, the ethynyl carbinol yielded the corresponding ethyl carbinol, II, $\lambda_{max.}$ 231 mμ, $\epsilon_{max.}$ 5,600, identical with that obtained by the addition of ethyl lithium to β-ionone. Similar hydrogenation of structure III would have destroyed its ultraviolet chromophore. Structure IV is obviously inapplicable, since it could not yield

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(1) Hennion and Lieb, THIS JOURNAL, **66**, 1289 (1944).

(2) Cymerman, Heilbron and Jones, *J. Chem. Soc.*, 90 (1945).

(3) Gould and Thompson, THIS JOURNAL, **57**, 340 (1935); Clemo and Hoggarth, *J. Chem. Soc.*, 476 (1941), reported a 70% yield from 5-keto-6,9-rubanene by this method.

(4) Davies, Heilbron, Jones and Lowe, *J. Chem. Soc.*, 584 (1935).

(5) Vaughn, United States Patent 2,163,720, June, 1939.

(6) Vaughn and Danehy, *Proc. Indiana Acad. Sci.*, **44**, 144 (1934).

(7) Campbell and Campbell, *ibid.*, **50**, 123 (1940).

(8) Karrer and Benz, *Helv. Chim. Acta*, **31**, 390 (1948).

(9) Rivers, Ph.D. Thesis, M. I. T., 1941.

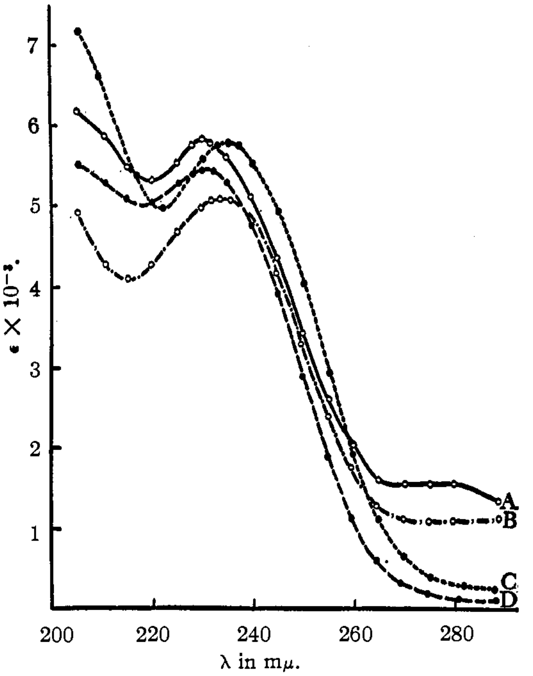
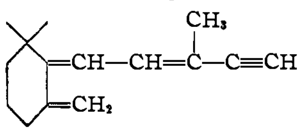


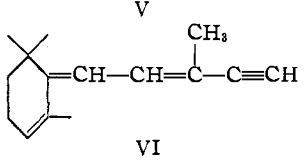
Fig. 1.—Absorption spectra in ethanol of: (A) ethyl-(β-ionol) (II) prepared according to Kipping and Wild; (B) β-ionol; (C) ethynyl carbinol from β-ionone (I); (D) ethyl-(β-ionol) by hydrogenation of I.

geronic acid upon ozonolysis, and being a conjugated dienyne would be expected to have an absorption maximum in the region of 270 mμ rather than 235 mμ.[10]

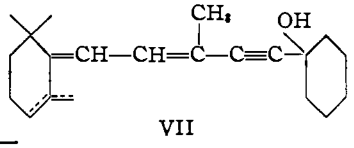
The ethynyl carbinol is extremely sensitive to acids, undergoing almost immediate dehydration even at lowered temperatures. The product, a very labile hydrocarbon, had one active hydrogen and produced no geronic or isogeronic acid upon ozonolysis. Its absorption maximum at 307 mμ (Fig. 2, Curve A) is consistent with that of an alkylated conjugated trienyne.[10] The product must, therefore, have structure V or VI, or is a mixture of both. Although it could not be obtained analytically pure, upon condensation with cyclohexanone through its Grignard derivative it yielded a carbinol with the correct analysis for structure VII, five double bonds, one active hydrogen and an absorption maximum at 311 mμ (Fig. 2, Curve B). The shift of four mμ to the red is that expected for the addition of an alkyl group to a conjugated system.



V



VI



VII

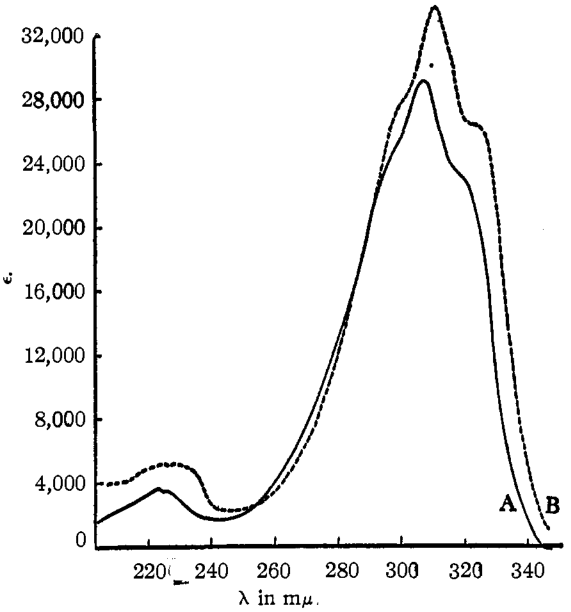


Fig. 2.—Absorption spectra in ethanol of: (A) dehydration product (V–VI) of I; (B) condensation product with cyclohexanone (VII).

The product of Karrer and Benz, since its absorption maximum was at 306 mμ and it possessed little more than one active hydrogen, would appear to have consisted for the most part of the dehydration product V–VI. Such a supposition is rendered even more plausible by the fact that the authors worked up their reaction mixture with dilute sulfuric acid, a treatment which we found invariably contaminated the carbinol with dehydration product.

Experimental

Condensation.—One mole of ketone was added to a liquid-ammonia suspension of 1.1 moles of lithium or calcium acetylide during ten minutes, and the mixture was stirred under a continuing slow stream of acetylene. Where the addition product precipitated as a gummy mass, interfering with stirring, addition of anhydrous ether or diethylamine always overcame this difficulty. The reaction was terminated at the appropriate time by the cautious addition of ammonium chloride, and the ammonia was allowed to evaporate completely. After working up the residue with ether and water and drying over anhydrous potassium carbonate, the product was distilled.

Purification of Products.—Aside from small quantities of undistillable tar, the only impurity found in the product was unreacted starting ketone. This was removed by fractional distillation with a 10″ Vigreux column in the cases of methyl vinyl ketone, ethylidene acetone, and mesityl oxide. In the other cases the entire distillate was dissolved in 85% methanol containing excess semicarbazide base. After adding one cc. of glacial acetic acid, warming

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(10) Braude, *Ann. Rept. Chem. Soc.*, 105 (1945); Heilbron, Jones and Lacey, *J. Chem. Soc.*, 27 (1946).

TABLE I

TABULAR CONSPECTUS OF NEF REACTIONS

Ketone	Acetylide	NH_3(1) l./mole	Temp., °C. below zero	Time, hr.	Conversion[a]	Yield, %[b]	B. p.		$n^{20}D$	Carbon, %		Hydrogen, %	
							°C.	Mm.		Calcd.	Found	Calcd.	Found
α,β-Saturated Ketones													
Acetone	Na	1[c]	60 evap.[d]	1 4	77	77[e]	103–105	760	1.4196				
Acetone	Ca	1	60 evap. to 5[d]	0.67 1	62	62							
Dihydro-β-ionone[f]	Na	2[c]	45	3	90	94[g]	100	1.1	1.4930	81.76	81.79 81.80	10.98	11.04 11.02
Dihydro-β-ionone	Ca	1	50–40	3	41	52							
4-Ethoxybutanone-2[h]	Na	2.5	70–60	5	35	35[ee]	82–85	17	1.4363	67.56	67.95 68.03	9.92	9.60 9.55
4-Ethoxybutanone-2	Li	2.5	70 40–35	1 3.5	64	64							
Acetophenone	Li	1	34 evap. to 5	3	29	82[i]	95 M. p. 48.5–50°	9					
Acetophenone	Ca	1	34 evap. to 5	3	47	77							
α,β-Unsaturated Ketones													
Methyl vinyl ketone[j]	Li	1	40–35	3	68	68[k]	57.5–59	60	1.4448	74.97	74.70	8.39	8.26
Methyl vinyl ketone	Ca	1	55 evap. to 5[d]	0.4 1.4	71	71							
Ethylideneacetone[l]	Li	1	45–35	3	71	79[m]	62	25	1.4541	76.32	76.04	9.15	9.03
Ethylideneacetone	Ca	1	60–34 evap. to 5[d]	1	78	78							
Mesityl oxide	K	1	45–40	3	10.3	42[n]	73–74	26	1.4620	77.37	77.55	9.74	9.66
Mesityl oxide	Li	0.67[c]	60–35 evap. to 30	3 0.5	26	48							
Mesityl oxide	Ca	1	40	3.5	46	75							
Isophorone	Li	0.8	40	3	0	0[o]							
Isophorone	Ca	1	45–34	3	0	0[o]							
Carvone	Li	1[c]	40–35	3	86	88	91	1.5	1.5074	81.78	81.53	9.15	9.13
Carvone	Ca	1	45–35	3	73	73							
Pseudoionone[p]	Li	0.67[c]	40	3	62	65	107–108	0.7	1.5110	82.51	81.97 81.96	10.16	10.02 10.02
Pseudoionone	Ca	1.5	70–60	3	64	66							
Pseudoionone	Ca[q]	1[c]	55–45	3	6.4	14							
α-Ionone[r]	Na	0.67[c]	40–35	3	30	[s]	89	0.55	1.4937	82.51	82.50 82.77	10.16	10.14 10.17
α-Ionone	Li	0.67[c]	40–35	3	67	84[t]							
α-Ionone	Ca	0.8[c]	50–40	3	67	67							
β-Ionone[u]	K	1	45–35	3	6	29[v]	84 M. p. 20.5	0.5	1.5024	82.51	82.42 82.58	10.16	10.19 9.95
β-Ionone	Na	1[c]	45–35	3	27	74							
β-Ionone	Na[w]	1	34	3	15	64							
β-Ionone	Li	0.67[c]	35–34	3	79	95							
β-Ionone	Li[q]	0.67[c]	40–35	2.75	0	0[o]							
β-Ionone	Li[w]	2	34	3	63	94							
β-Ionone	Li[x]	0.7[c]	+25	24	86	86							
β-Ionone	Ca	2	60	4	47	67							
β-Ionone	Ca[q]	2	62	2.5	47	77							
β-Ionone	Ca[w]	1	34	3	61	61							
β-Ionone	Ca[y]	2	60	3	37	73							
Benzalacetone	K	2	70	0.2	40	40[ff]	131 M. p. 50–50.5[aa]	7		83.68	83.53 83.48	7.03	7.07 7.03
Benzalacetone	Li	1.3[z]	40–35	3	71	85							
Benzalacetone	Li[q]	1	40–35	2.75	10	[s]							
Benzalacetone	Ca	1	62–50 50–34	1 0.5	96	96							
Furfuralacetone	Li	1	40–34	2	69	80	97 Freezes >5°	3.5	1.5418	74.05	74.00 74.10	6.22	6.29 6.29
Furfuralacetone	Ca	1	65–55	1.5	75	81							
Chalcone	Li	1	40–34	3	81	81[bb]	109–111	0.002	1.6152	87.15	87.25[cc] 87.21	6.02	6.10 6.21
Chalcone	Ca	1	40	3	60	60[bb]							
Dibenzalacetone	Li	2	40–35	3	3	0[o]	M. p. 88–88.5°			87.67	87.74 87.78	6.20	6.10 6.25
Dibenzalacetone	Ca	2	50–40	3	89	92[dd]							

[a] Yield of purified product based on ketone originally taken. [b] Yield of purified product based on unrecovered ketone. [c] Auxiliary solvent (0.33 l./mole of fresh Merck "absolute" ether) was necessary. [d] Hydrolyzed with ice water directly after ammonia evaporation, rather than with NH_4Cl before evaporation. [e] Yields reported in literature: 86–93% by

NaC_2H in ammonia.[15] [f] By Raney nickel hydrogenation of pure β-ionone (note *u*): b. p. 64° (0.2 mm.), $n^{25}D$ 1.4792. [g] Yields reported in literature: 60–70% by $NaNH_2$–C_2H_2 in ether.[16] [h] Prepared by BF_3-catalyzed addition of ethanol to methyl vinyl ketone: b. p. 52–53.5° (17 mm.), $n^{20}D$ 1.4060. Experiments performed by R. E. Juday. [i] Yields reported in literature: 7%,[17] 50% (crude)[18] by NaC_2H in ammonia; 16%,[19] 2%[20] by $NaNH_2$–C_2H_2 in ether; 29% by BrMgC⋮CMgBr.[21] [j] The commercial azeotrope was treated with Drierite and distilled, collecting at 80–83°. [k] Yields reported in literature: 21% by NaC_2H in ammonia[1]; 40% by large excess of NaC_2H in ammonia.[2] [l] Prepared according to Grignard and Fluchaire, *Ann. chim.* [10] 9, 10 (1928): b. p. 120.5°, $n^{20}D$ 1.4360. [m] Yields reported in literature: 27%[1]; 40%.[2] [n] Yields reported in literature: 24%[1]; 55%.[2] [o] 90–95% of unreacted ketone recovered. [p] Purified through the sodium bisulfite derivative: b. p. 103–107° (1.2 mm.), $n^{20}D$ 1.5316. [q] "Inverse" technique. [r] Purified through the sodium bisulfite derivative: b. p. 79° (0.3 mm.), $n^{25}D$ 1.4966, $\lambda_{max.}$ 228 mμ, $\epsilon_{max.}$ 13,500. [s] No attempt was made to recover semicarbazone. [t] Recovery by hydrolysis of the semicarbazone residue from ethynyl carbinol distillation. [u] Purified by three recrystallizations of the semicarbazone from 95% ethanol, and hydrolysis with 2 *N* H_2SO_4[22]: b. p. 121.5° (7 mm.), $n^{20}D$ 1.5200–1.5205, $\lambda_{max.}$ 296 mμ, $\epsilon_{max.}$ 10,500–10,700. [v] Yields reported in literature: 45% (very impure),[9] 31%[8] by NaC_2H–ammonia; 57% by $NaNH_2$–C_2H_2 in ether[4]; 9% by K *t*-amylate in ether–*t*-AmOH.[3] See discussion in body of paper. [w] Procedure of Cymerman, Heilbron and Jones.[2] [x] Rocked at room temperature in a stainless-steel pressure bomb. [y] Calcium acetylide made from calcium amide. [z] 0.67 l./mole of auxiliary solvent. [aa] Recrystallized from benzene–ligroin. [bb] Purified by acetic acid–catalyzed condensation with phenylhydrazine, the ketone being unrecoverable. [cc] The ketone and the ethynyl carbinol differ little in analysis; of greater significance is the complete disappearance of the positive dinitrophenylhydrazine test after purification. [dd] Purified by ethanol precipitation of unreacted ketone, followed by crystallization from ligroin (b. p. 70–90°) with a little chloroform. [ee] Yields reported in literature: 30–40% by LiC_2H in ammonia.[23] [ff] Yields reported in literature: 20% by NaC_2H in ammonia.[1]

to 50°, and standing overnight at room temperature, the mixture was poured into water and extracted with 700 cc. petroleum ether. Any precipitated semicarbazone is filtered off at this point. The petroleum ether solution was diluted to twice its volume and dried overnight at −5° over anhydrous potassium carbonate, whereupon the semicarbazone usually precipitated. The mixture was filtered, concentrated and distilled. Where the semicarbazone was soluble in petroleum ether (*e. g.*, α-ionone, ψ-ionone) the carbinol was distilled from the semicarbazone, with no trouble except in the case of chalcone. Here phenylhydrazine proved a suitable purifying agent.

Ozonization of the Ethynyl Carbinol of β-Ionone.—Five grams of carbinol in 125 ml. of carbon tetrachloride was ozonized according to Strain[11] using the apparatus of Henne and Perilstein.[12] There was obtained 2.7 g. of the dinitrophenylhydrazone of geronic acid, 34%.

Dehydration of the Ethynyl Carbinol of β-Ionone.—To a solution of 21.8 g. of the carbinol in 300 cc. of dry benzene was added 300 mg. of *p*-toluenesulfonic acid monohydrate and the mixture refluxed under a water separator. After half an hour, the theoretical volume of water had been collected. The cooled solution was washed with alkali, dried, and distilled. The total distillate, 12.4 g., was collected at 60–70° (0.02 mm.); $n^{20}D$ 1.5788; $\lambda_{max.}$ 307 mμ; $\epsilon_{max.}$ 29,100. On redistillation, it boiled at 55° (0.01 mm.), the other constants remaining unchanged (Fig. 2, Curve A). The compound is very unstable and darkens and polymerizes even under nitrogen at 0°.

Anal. Calcd. for $C_{15}H_{20}$: C 89.93; H, 10.06. Found: C, 88.86, 88.47; H, 10.11, 9.95.

Condensation of the Dehydration Product, V-VI, with Cyclohexanone.—A solution of 10.4 g. of freshly distilled trienyne in 250 cc. of anhydrous ether was treated with 10% excess ethylmagnesium bromide and refluxed for twenty-three hours. The formation of this acetylenic Grignard is a very slow reaction. Then 5.5 g. of cyclohexanone in 50 cc. of anhydrous ether was added and the mixture refluxed four hours more. After hydrolysis with ammonium acetate solution, the dried ethereal extract yielded 11.6 g. of an extremely viscous distillate which was collected at 130–135° (0.01 mm.), $\lambda_{max.}$ 311 mμ; $\epsilon_{max.}$ 33,700 (Fig. 2, Curve B). This distillate crystallized upon standing, and after recrystallization from a little hexane melted at 104.5–106.5°. The absorption spectrum remained unchanged. This compound is stable when kept at 0–5°.

Anal. Calcd. for $C_{21}H_{30}O$: C, 84.51; H, 10.13; unsaturation, 5.0 $\models$. Found: C, 84.18, 84.16; H, 9.97, 10.07; unsaturation, 5.1 $\models$.

Ethyl (β-Ionol), II.—A solution of the ethynyl carbinol of β-ionone (10.6 g.) in 100 cc. of methanol was hydrogenated at atmospheric pressure using 5 g. of Raney nickel. Absorption ceased when two equivalents of hydrogen had been consumed. The product (9.0 g.) boiled at 82° (0.2 mm.) or 99° (1.4 mm.), $n^{25}D$ 1.4931; $\lambda_{max.}$ 231 mμ; $\epsilon_{max.}$ 5,550 (Fig. 1, Curve D).

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.09, 80.73; H, 11.74, 11.80.

An authentic specimen was prepared by the method of Kipping and Wild.[13] The product, after semicarbazide purification, boiled at 99–100° (1.4 mm.); $n^{25}D$ 1.4962; $\lambda_{max.}$ 231 mμ; $\epsilon_{max.}$ 5820 (Fig. 1, Curve A).

Anal. Found: C, 80.87, 80.90; H, 11.50, 11.50.

β-Ionol was prepared by Meerwein–Ponndorf reduction of β-ionone according to Kandel.[14] The product, after semicarbazide purification, was fractionated through a 12″ Vigreux column; b. p. 89° (0.7 mm.); $n^{25}D$ 1.5002; $\lambda_{max.}$ 234 mμ; $\epsilon_{max.}$ 5,200 (Fig. 1, Curve B).

Absorption Spectra.—All absorption spectra were determined in 95% ethanol using a Beckman spectrophotometer.

Acknowledgment.—The authors are indebted to Mr. William Häffcke for the ozonizations as well as for technical assistance in carrying out some of the experimental procedures, and to Messrs. Joseph Grodsky and John Cozzolino for the microanalyses.

Summary

A method of general application has been developed for converting α,β-unsaturated ketones into their ethynyl carbinols in very good yields.

Calcium and lithium acetylides have been found to give only 1:2 adducts with α,β-unsaturated ketones.

The structure of the acetylenic adduct of β-ionone has been elucidated.

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(11) Strain, *J. Biol. Chem.*, **102**, 137 (1933).

(12) Henne and Perilstein, THIS JOURNAL, **65**, 2183 (1943).

(13) Kipping and Wild, *J. Chem. Soc.*, 1239 (1940).

(14) Kandel, *Ann. chim.*, **11**, 73 (1939).

(15) Hurd and McPhee, THIS JOURNAL, **69**, 239 (1947).

(16) Ruzicka and Fischer, *Helv. Chim. Acta*, **17**, 633 (1934).

(17) Campbell, Campbell and Eby, THIS JOURNAL, **60**, 2882 (1938).

(18) Macallum, United States Patent 2,125,384 (August, 1938).

(19) Rupe and Giesler, *Helv. Chim. Acta*, **11**, 656 (1928).

(20) Carothers and Coffman, THIS JOURNAL, **54**, 4071 (1932).

(21) Zalkind and Ivanov, *Chem. Abs.*, **36**, 3790 (1942).

(22) Young, Cristol, Andrews and Lindenbaum, THIS JOURNAL, **66**, 855 (1944).

(23) Milas, *et al.*, *ibid.*, **70**, 1602 (1948).