[CONTRIBUTION FROM THE BIOCHEMICAL RESEARCH LABORATORY, THE DOW CHEMICAL CO.]

γ-Tetrahydropyranyloxy-α,β-acetylenic Ketones

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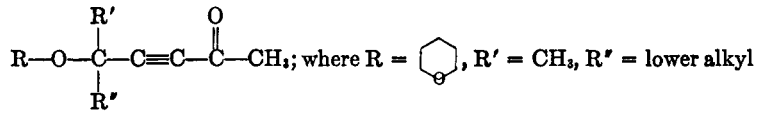
A series of γ-tetrahydropyranyloxy-α,β-acetylenic methyl ketones has been prepared. The general structure is represented by:



(C_1–C_8) and where R' and R'' make up a cycloalkane ring. The ketones were prepared from the tetrahydropyranyl derivatives of tertiary ethynyl alcohols by reaction of acetic anhydride with the Grignard derivatives.

In some recent work on cardiac stimulants[1b] it was found that β-acetylacrylic acid and its esters were active *in vitro*. Although it was postulated that only *cis* isomers of these compounds were active, it was felt that this point should be checked by testing several α,β-acetylenic ketones.

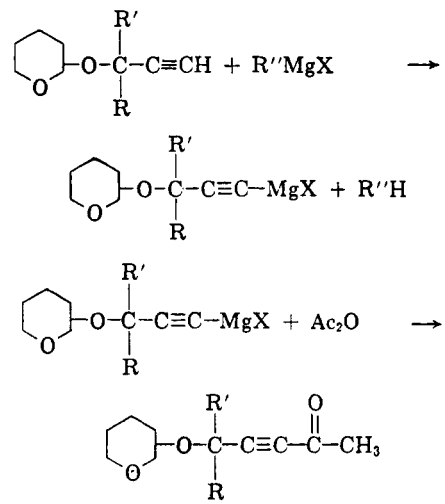
α,β-Acetylenic ketones have been prepared by oxidation of the corresponding secondary alcohols[2] and by treatment of either the Grignard or sodio derivatives with acid anhydrides or acid chlorides at low temperatures.[3]

In the present case, the presence of a free hydroxyl group was undesirable, both because of ester formation with the anhydride or acid chloride to be used and because of the insolubility of the disodio or magnesio derivatives of the ethynyl alcohol to be employed.

Henbest, Jones, and Walls[4] used the dihydropyran adduct of propargyl alcohol in a preparation of γ-hydroxypropiolic acid with good results. The dihydropyran adducts of the ethynyl alcohols required for the present work were readily available[5] and were employed for the synthesis of the ketones. Chromic acid oxidation of the corresponding secondary alcohols was considered to be an impractical method because it would have required an additional step in the synthesis.

The ketones were prepared according to the reaction sequence:

The Grignard reagent (reaction A) was prepared by the method of Henbest, et *al.*[4] from ethylmagnesium bromide. It was found that the magnesium derivatives of the acetylenic compounds were not sufficiently soluble in ether or benzene (used by Henbest, *et al.*[4]) but that they were very soluble in tetrahydrofuran, even at −78°. Tetrahydrofuran was therefore employed throughout this work. Furthermore, a nitrogen atmosphere was found to be essential for the reaction with the anhydride (reaction B) in order to prevent formation of large amounts of high boiling gums.



(A)

(B)

The tetrahydropyranyl grouping is easily removed by aqueous acid, but the products were readily recovered without loss of this group by pouring the mixture into ice cold water followed by rapid separation of the aqueous and organic phases. At 0° acetic anhydride did not hydrolyze rapidly enough to cause extensive removal of the tetrahydropyranyl protecting group.

The analyses (C and H) were all quite good, (See Table I) although the infrared spectrum of each showed a band at 5.75 μ which was interpreted as an ester.[6] It was estimated that this contamination amounted to a range of 2–5% for the various compounds. No acetylenic hydrogen and no free OH was detected.

(1a) Present address: Arapahoe Chemicals, Inc., Boulder, Colo.

(1b) D. R. Bennett, K. S. Anderson, M. V. Anderson, Jr., D. N. Robertson, and M. B. Chenoweth, *J. Pharmacol. Exptl. Therap.*, **123**, 489 (1958).

(2) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

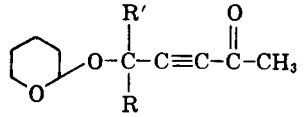
(3) D. Nightingale and F. Wadsworth, *J. Am. Chem. Soc.* **67**, 416 (1945). J. W. Kroeger, J. A. Nieuwland, *J. Am. Chem. Soc.* **58**, 1861 (1936).

(4) H. B. Henbest, E. R. H. Jones, and I. M. S. Walls, *J. Chem. Soc.* 3646 (1950).

(5) D. N. Robertson, *J. Org. Chem.*, **25**, 931 (1960).

(6) A referee has suggested that an exchange of acetyl for tetrahydropyranyl could account for this.

TABLE I

PHYSICAL PROPERTIES OF KETONES PREPARED 

R	R′	B.P.	mm.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	CH_3	83–84	0.6	69.1	68.54	68.13	8.63	8.57
CH_3	CH_3CH_2	69–72	0.01	29.4	69.61	69.70	8.98	8.84
CH_3	$(CH_3)_2CHCH_2$	83–86	0.04	35.2	71.39	71.25	9.59	9.27
CH_3	$CH_3(CH_2)_5$	119	0.06	35.9	72.81	72.74	10.06	9.96
R, R′ = 		100–102	0.15	65.7	71.97	71.72	8.86	8.26

EXPERIMENTAL

γ-Tetrahydropyranyl-α,β-acetylenic ketones. The general procedure employed is exemplified by the preparation of 5-methyl-5-(tetrahydro-2-pyranyloxy)-3-undecyn-2-one.

All tetrahydrofuran was dried by passage through a column of calcium hydride just prior to use. A nitrogen atmosphere was employed throughout all operations up to isolation of the product.

Grignard reagent was prepared from 7.3 g. (0.3 mole) of magnesium and 33 g. (0.3 mole) of ethyl bromide in 200 ml. of tetrahydrofuran. A solution of 71.7 g. (0.3 mole) of 2-(ethynyl-1-methylheptyloxy)tetrahydropyran in 150 ml. of tetrahydrofuran was added at a rate commensurate with ethylene evolution. This addition was conducted at room temperature and the mixture was finally heated to reflux to insure complete exchange.

The resulting solution was chilled in a Dry Ice bath for 0.5 hr. and 102 g. (1.0 mole) of acetic anhydride was then added over a 1-hr. period. The slow addition was primarily to ensure that the low temperature would be maintained. A white precipitate formed during addition of the anhydride. The mixture was held at Dry Ice temperature for 2 hr. after anhydride addition was complete. The mixture was then either worked up at once or placed in a deep-freeze (−17°) overnight with no appreciable difference in the final product.

The sirupy mixture was poured into a large volume of ice and water with vigorous (mechanical) stirring, separated, and the aqueous phase extracted once with ether. The combined organic phases were washed twice with ice water, twice with saturated brine, and dried over sodium sulfate in the refrigerator. Distillation gave 30.6 g. (35.9%) of the ketone, b.p. 115–119° (0.09–0.06 mm.).

Table I lists the ketones prepared.

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[CONTRIBUTION FROM THE MCPHERSON CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

Synthesis of 7-Methyl-2,3,4,5-tetrahydro-1-benzoxepin and 4-Methyl-5,6,7,8-tetrahydronaphthol by Alkaline Cyclizations[1]

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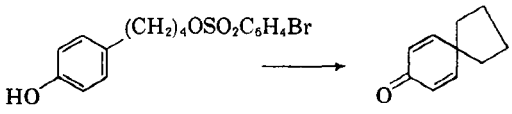
On treatment of 4-(2-hydroxy-5-methylphenyl)-1-butyl bromide, III, with alkaline reagents 7-methyl-2,3,4,5-tetrahydro-1-benzoxepin, V, is formed. On similar treatment 4-(5-hydroxy-2-methylphenyl)-1-butyl bromide, VI, yields 4-methyl-5,6,7,8-tetrahydronaphthol, VIII. In neither case is any cyclohexadienone-type product formed.

The work herein reported was stimulated by the observation that 4-*p*-hydroxyphenyl-1-butyl *p*-bromobenzenesulfonate, I, is cyclized to spiro-[4.5]deca-1,4-diene-3-one, II, on treatment with alkali.[3]

We wished to find out if 4-(2-hydroxy-5-methylphenyl)-1-butyl bromide, III, would yield the



dienone, IV, or the cyclic ether, V, and if 4-(5-hydroxy-2-methylphenyl)-1-butyl bromide, VI, would yield the dienone, VII, or the tetrahydronaphthol, VIII, on treatment with alkaline reagents.

We have found that treatment of III with sodium methoxide in methanol at reflux or with sodium or lithium amide in liquid ammonia affords 7-methyl-2,3,4,5-tetrahydro-1-benzoxepin, V, in 80–85% yields. No trace of dienone, IV, was found. This reaction represents the first synthesis of the tetrahydro-1-benzoxepin ring system.

(1) The material presented herein was taken in part from the Ph.D. thesis of A. B. Mekler, Ohio State University, 1959.

(2) Holder of Charles F. Kettering Fellowship, 1956–57; U. S. Industrial Company Fellowship, 1957–58; and Allied Chemical and Dye Company Fellowship. We are also indebted to the E. I. du Pont de Nemours Company for support of this work.

(3) S. Winstein and R. Baird, *J. Am. Chem. Soc.*, **79**, 756 (1957).