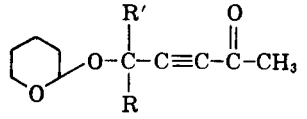
TABLE I

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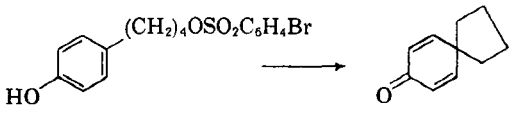
On treatment of 4-(2-hydroxy-5-methylphenyl)-1-butyl bromide, III, with alkaline reagents 7-methyl-2,3,4,5-tetrahydro-1-benzoxepin, V, is formed. On similar treatment 4-(5-hydroxy-2-methylphenyl)-1-butyl bromide, VI, yields 4-methyl-5,6,7,8-tetrahydronaphthol, VIII. In neither case is any cyclohexadienone-type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



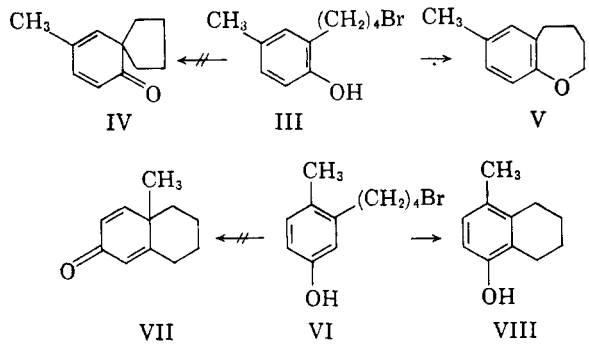
dienone, IV, or the cyclic ether, V, and if 4-(5-hydroxy-2-methylphenyl)-1-butyl bromide, VI, would yield the dienone, VII, or the tetrahydronaphthol, VIII, on treatment with alkaline reagents.

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).



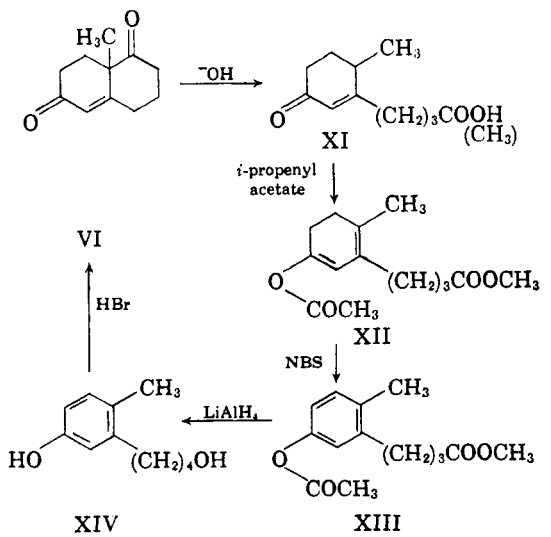
Interestingly, when the alcohol, 4-(2-hydroxy-5-methylphenyl)-1-butanol, X, was treated with 48% hydrobromic acid in a mixture of acetic acid and *sym*-tetrachloroethane at reflux an 86% yield of 4-methyl-5,6,7,8-tetrahydro-1-naphthol, VIII, was obtained. When the acetic acid was omitted from this reaction mixture, the bromide, III, was formed in 96% yield. This effect of solvent on the course of reaction is noteworthy. Thus either the benzoxepin, V, or the naphthol, VIII, can be obtained from the above alcohol, depending on the steps used subsequently.

When VI was treated with similar basic reagents 4-methyl-5,6,7,8-tetrahydronaphthol,[4] VIII, was formed in 67–82% yields but no trace of dienone, VII, was detected. This cyclization represents a new synthesis of VIII.

The bromide, III, was synthesized from *p*-cresol as follows. Succinic anhydride was condensed by the Friedel-Crafts method with *p*-cresol directly to form β-(2-hydroxy-5-methylbenzoyl)propionic acid,[4] IX, in 52% yield. Previously *p*-cresyl methyl ether had been condensed similarly (in unstated yield) and complete demethylation (when 2.5 equivalents of aluminum chloride were used) occurred.[4] The acid, IX, was first reduced to γ-(2-hydroxy-5-methylphenyl)butyric acid;[4] and the latter, as ester, then reduced to 4-(2-hydroxy-5-methylphenyl)-1-butanol, X, with lithium aluminum hydride. Treatment of X with hydrobromic acid yielded III (see above).

The bromide, VI, was prepared as indicated in the chart.

An attempt at cyclization of the phenolic ester corresponding to XIII by refluxing with a solution of sodium methoxide in methanol resulted in recovery of starting phenolic ester.



(4) R. B. Woodward and T. Singh, *J. Am. Chem. Soc.*, **72**, 494 (1950). We thank Dr. Woodward for sending us an authentic sample of VIII.

EXPERIMENTAL[5]

β-(2-Hydroxy-5-methylbenzoyl)propionic acid (IX). To a stirred solution of 100 g. of *p*-cresol and 100 g. of succinic anhydride in 1 l. of purified *sym*-tetrachloroethane[6] at 55° was added 268 g. of aluminum chloride during 3 hr. After most of the aluminum chloride had been added a solid began to separate from the red solution and stirring became difficult. After all of the aluminum chloride had been added the the bath temperature was raised to 135° and the reaction mixture held at this temperature for 2.5 hr. The mixture at first became fluid, then darkened to black, and finally set to a semisolid mass. After cooling the mixture was added to ice and hydrochloric acid and the solvent was removed by steam distillation. The crude acid which was obtained as a solid after cooling was washed and dissolved in warm alkali and this solution clarified with charcoal (Darco G-60). Acidification afforded 99 g. of crude acid, m.p. 134–136.5°. Recrystallization from benzene yielded 94.8 g. (52%) of β-(2-hydroxy-5-methylbenzoyl)propionic acid,[4] IX, m.p. 136–137°.

4-(2-Hydroxy-5-methylphenyl)-1-butanol, X. Acid IX (92 g.) was reduced to γ-(2-hydroxy-5-methylphenyl)butyric acid,[4] m.p. 88–89°, in 93% yield by the modified Clemmensen method[7] (30 hr. of reflux, 5 additions of 100 ml. portions of concd. hydrochloric acid). This acid was esterified with methanol to yield the liquid ester, b.p. 123–124° at 0.5 mm. in 92% yield, and this ester was reduced by lithium aluminum hydride in the usual way to yield 4-(2-hydroxy-5-methylphenyl)-1-butanol, X in 95% yield. Crystallization from ethanol afforded X in colorless crystals, m.p. 82–83°, with little loss.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.0; H, 8.9. Found: C, 73.2; H, 8.7.

When 5.0 g. of X, 60 ml. of *sym*-tetrachloroethane,[6] 60 ml. of 48% hydrobromic acid, and 60 ml. of acetic acid was refluxed for 4 hr., a conventional workup yielded 3.8 g. (83%) of 4-methyl-5,6,7,8-tetrahydronaphthol, VIII, m.p. and mixed m.p. with an authentic sample,[4] 87–88°. Comparison of the x-ray powder diffraction patterns of the two samples showed that they were identical and a satisfactory carbon-hydrogen analysis was obtained with our sample.

4-(2-Hydroxy-5-methylphenyl)-1-butyl bromide, III. A mixture of 10.0 g. of X, 100 ml. of pure *sym*-tetrachloroethane[6] and 100 ml. of 48% hydrobromic acid was refluxed for 2 hr. The organic product, isolated as usual, yielded III as a colorless oil, b.p. 134–135° at 1 mm. in 96% yield.

Anal. Calcd. for $C_{11}H_{15}BrO$: C, 54.3; H, 6.2. Found: C, 54.5; H, 6.2.

(5) All melting points corrected. Microanalyses by Galbraith and Co., Knoxville, Tenn. The term "as usual" means that the organic solvent layer of product was washed with alkali (where non-acidic products were at hand), with saturated sodium chloride solution, filtered through anhydrous magnesium sulfate, and stripped of solvents by distillation.

(6) For purification by sulfuric acid treatment see L. F. Fieser, *Experiments in Organic Chemistry*, D. C. Heath and Co., New York, N. Y., 2nd Ed., 1941, p. 366.

(7) E. L. Martin, *J. Am. Chem. Soc.*, **58**, 1438 (1936).

7-Methyl-2,3,4,5-tetrahydro-1-benzoxepin, V. A solution of sodium methoxide (prepared by dissolving 12.8 g. of sodium in 435 ml. of absolute methanol) and 9.04 g. of III was refluxed for 4 hr. The organic product, isolated in the usual way, yielded 4.87 g. (81%) of V as a colorless oil, b.p. 88–90° at 2–3 mm. An alkaline extract of the crude reaction product afforded no phenolic material.[8]

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.4; H, 8.7. Found: C, 81.3, 81.4; H, 8.5, 8.6.

The benzoxepin, V, did not yield a crystalline tetranitrofluorenone[9] derivative, nor did solution of the two show a marked deepening of color.

When 1.21 g. of III in 15 ml. of dry ether was treated with 1.9 g. of lithium amide in 75 ml. of liquid ammonia for 24 hr. 0.7 g. (86%) of V was obtained which was identical to the V described above. Again, no trace of phenolic material was obtained. Infrared spectra of the entire crude reaction mixture showed no trace of absorption in the carbonyl or hydroxyl regions.

Methyl γ-(4-acetoxy-1-methyl-1,3-cyclohexadien-2-yl)butyrate, XII. The conversion of 1,6-diketo-8a-methyl-1,2,3,4,-6,7,8,8a-octahydronaphthalene[10] to γ-(3-keto-6-methyl-1-cyclohexen-1-yl)butyric acid, XI, was carried out[11] by warming a mixture of 51.3 g. of the octalindione, 110 ml. of 10% sodium hydroxide, and 120 ml. of alcohol for 20 min. after standing at room temperature for 30 min. Acid XI which had the properties described,[10a] was obtained in 91% yield. On esterification by refluxing a solution of 57.0 g. of acid, 40 ml. of methanol, 150 ml. of methylene chloride, and 2 ml. of sulfuric acid into a column so that the azeotrope was removed as formed, there was obtained 59.7 g. (96%) of the methyl ester of XI, b.p. 124–126° at 1 mm., as a pale yellow mobile oil. A solution of 61.6 g. of this ester, 325 ml. of isopropenyl acetate, and 2 ml. of sulfuric acid was distilled under a column for 10 hr., the acetone being removed as formed. After the usual workup there was obtained 68.5 g. (87%) of enol acetate XII as a liquid, b.p. 131–135° at 1 mm. The possibility that the double bonds were not as shown, or that a mixture of isomers was present, is not excluded.

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.6; H, 8.0. Found: C, 66.4; H, 7.4.

Methyl γ-(5-acetoxy-2-methylphenyl)butyrate, XIII. A mixture of 68.3 g. of XII, 45.0 g. of *N*-bromsuccinimide, 1.0 g. of benzoyl peroxide, and 500 ml. of carbon tetrachloride was held at reflux for 2 hr. The resulting mixture was refluxed with stirring for 4 hr. after addition of 100 ml. of collidine. After a conventional workup there was obtained 52.6 g. (77%) of XIII as an almost colorless oil, b.p. 145–150° at 1 mm.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.2; H, 7.2. Found: C, 67.6; H, 7.0.

After refluxing a solution of 16.8 g. of XIII in 75 ml. of methanol and 50 ml. of 3*M* hydrochloric acid for 4 hr., a conventional workup yielded 12.6 g. of distillate, b.p. 115–116° at 0.4 mm., which solidified on standing. Recrystallization from petroleum ether (b.p. 30–60°) gave 11.6 g. (83%) of methyl γ-(5-hydroxy-2-methylphenyl)butyrate, m.p. 81–82°. In another run using 5 ml. of 10% hydrochloric acid in 100 ml. of methanol and 8.7 g. of XIII, after refluxing for 4.5 hr. a 69% yield of a polymorphic form, m.p. 70–71°, was obtained.[12]

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.2; H, 7.7. Found: 82° isomer, C, 69.6; H, 7.4. 71° isomer, C, 69.4; H, 7.8.

After refluxing a solution of 0.81 g. of this phenolic ester in 15 ml. of methanol containing a slight excess of sodium methoxide for 5 hr., 0.72 g. was recovered unchanged.

4-(5-Hydroxy-2-methylphenyl)-1-butanol, XIV. Reduction of 47.4 g. of XIII in ether with excess lithium aluminum hydride at reflux for 4 hr. afforded 29.6 g. (86%) of XIV, m.p. 85–87°. Recrystallization from alcohol afforded the analytical sample, m.p. 87–88°, with little loss.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.3; H, 8.8. Found: C, 73.0; H, 8.7.

4-(5-Hydroxy-2-methylphenyl)-1-butyl bromide, VI. A mixture of 8.0 g. of XIV, 100 ml. of *sym*-tetrachloroethane, and 100 ml. of 48% hydrobromic acid was refluxed for 2 hr. After the usual workup, 8.9 g. (83%) of VI, b.p. 142–143° at 1 mm., was obtained.

Anal. Calcd. for $C_{11}H_{15}BrO$: C, 54.3; H, 6.2. Found: C, 54.2; H, 5.9.

When a mixture of 5.0 g. of XIV, 60 ml. of *sym*-tetrachloroethane,[6] 60 ml. of 48% hydrobromic acid, and 60 ml. of acetic acid was refluxed for 4 hr. and worked up as usual, there was obtained 3.4 g. (74%) of 4-methyl-5,6,7,8-tetrahydronaphthol, VIII, m.p. and mixed m.p. with an authentic sample,[4] 87–88°. Identity was also established by X-ray powder photography.[13]

4-Methyl-5,6,7,8-tetrahydronaphthol, VIII. A solution of 1.1 g. of VI in 60 ml. of absolute methanol containing 0.1 mole of base was refluxed for 4 hr. Treatment as usual afforded a yellow oil, b.p. 107–109° at 0.5 mm., which solidified on standing. Recrystallization from petroleum ether (b.p. 30–60°) yielded 0.41 g. (67%) of VIII, m.p. 87–88°. The identity with authentic VIII[4] was established as described above.[13] A better yield (82%) of VIII was obtained on treatment of 1.15 g. of VI with the sodium amide from 3.9 g. of sodium in 75 ml. of liquid ammonia for 24 hr. Before allowing the ammonia to evaporate 100 ml. of dry ether was added. However, because of the small size of these runs the yield difference may not be significant.

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(8) We are indebted to Dr. D. J. Collins for repetition of this experiment.

(9) M. S. Newman and W. B. Lutz, *J. Am. Chem. Soc.*, **78**, 2469 (1956).

(10) See a. A. L. Wendler, H. L. Slates, and M. Tishler, *J. Am. Chem. Soc.*, **73**, 3816 (1951) and references therein. b. M. S. Newman and A. B. Mekler, *J. Am. Chem. Soc.*, **82**, 4039 (1960).

(11) In reference 10a no yield of XI was mentioned in an experiment on a small scale.

(12) We are indebted to Mr. S. Ramachandran for this run.

(13) We are indebted to Prof. P. M. Harris of this department for this identification.