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BICYCLO[3.3.1]NONANES

A NEW SYNTHESIS OF 2-BICYCLO[3.3.1]NONANONE[1]

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Abstract—An investigation of the internal enolate alkylation process as a route to bicyclo[3.3.1]-nonanes has been made. Application of the method to 4-(3-hydroxypropyl)cyclohexanone has been found to provide an economical synthesis for 2-bicyclo[3.3.1]nonanone.

THE bicyclo[3.3.1]nonanes were the subject of sporadic investigation up to about 1922.[3] Interest in molecules with this ring system waned but a recent revival of interest stemmed from two sources. In 1954 Barton *et al.*[4] showed that clovene, an isomerization product of caryophyllene, possessed such a skeleton. Thus the attention of some natural product chemists was drawn to this ring system. During the same era Cope and Prelog[5] were unveiling the chemical consequences of the conformationally-enforced proximity of non-bonded atoms. The bicyclo[3.3.1]nonane ring with an undistorted chair–chair C_3–C_7 distance of 2·5 Å caught the eyes of investigators concerned with studying these consequences in greater detail. While interest was thus aroused, enthusiasm was moderated by the often monumental labor of preparing appropriate bicyclo[3.3.1]nonanes. We turned our attention, therefore, to an exploration of alternate routes to this carbon skeleton.

A survey of the literature revealed that the traditional syntheses of bicyclo[3.3.1]-nonanes utilized either aldol or Claisen condensations to effect ring closure of properly substituted propylcyclohexanes.[6] Less widely utilized were the addition of a carbonium ion to a double bond,[7] or ring closure of a 1,3-disubstituted cyclohexane by means of Dieckmann-type reactions.[8,9] Low yields, presence of bridgehead substituents or the necessity of using selective reactions made most of these methods unattractive for our purposes.

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[2a] American Chemical Society Petroleum Research Fellow 1963–64; [b] American Chemical Society Petroleum Research Fellow 1962–63.

[3] See for example, H. Meerwein, F. Kiel, G. Klogen and E. Schoh, *J. Prakt. Chem.* **[2]104**, 161 (1922) and Refs therein.

[4] A. Aebi, D. H. R. Barton, A. W. Burgstahler and A. S. Lindsay, *J. Chem. Soc.* 4660 (1954).

[5] For a good review of the early work, see V. Prelog, *J. Chem. Soc.* 420 (1950).

[6] For examples and Refs see the following: [a] A. C. Cope and D. M. Gale, *J. Amer. Chem. Soc.* **85**, 3743 (1963); [b] A. C. Cope and M. E. Synerholm, *Ibid.* **72**, 5228 (1950); [c] S. Julia, *Bull. Soc. Chim. Fr.* 780 (1954); [d] D. J. Braisted and J. S. Whitehurst, *J. Chem. Soc.* 4089 (1961); [e] V. Prelog and R. Seiwerth, *Ber. Dtsch. Chem. Ges.* **74**, 1644 (1941); [f] P. Rabe and M. Jahr, *Liebigs Ann.* **360**, 276 (1908); [g] H. Stetter, O.-E. Bänder and W. Neumann, *Chem. Ber.* **89**, 1922 (1956).

[7] G. Büchi, K. Biemann, B. Vittimberger and M. Stoll, *J. Amer. Chem. Soc.* **78**, 2622 (1956); M. Stoll, B. Willhelm and G. Büchi, *Helv. Chim. Acta* **38**, 1573 (1955).

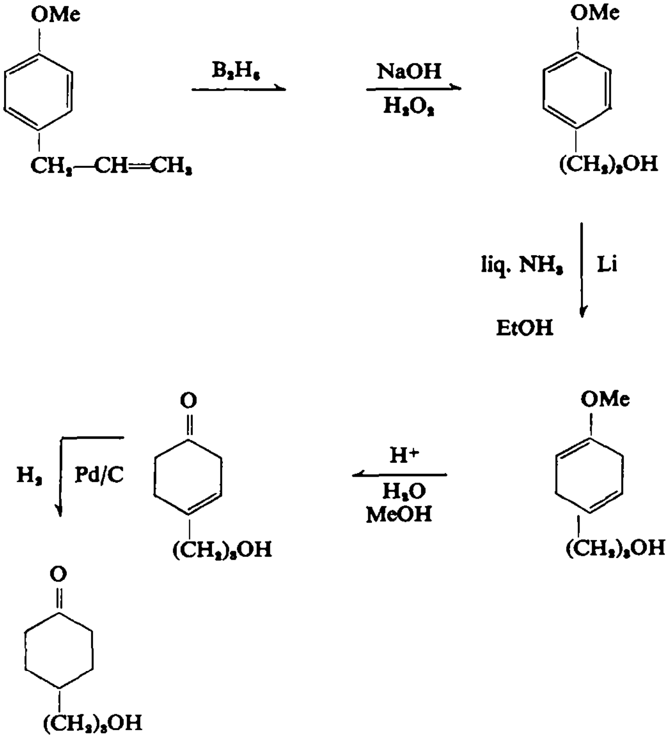
[8] J. P. Ferris and N. C. Miller, *J. Amer. Chem. Soc.* **85**, 1325 (1963).

[9] H. K. Hall, Jr., *J. Org. Chem.* **28**, 3213 (1963).

Two tactical problems dominate the choice of a synthetic route. Any bicyclo[3.3.1]-nonane with saturated carbons at C_3 and C_7 will be seriously strained, and its synthesis will be favored by an irreversible reaction. The group or groups involved in formation of the final ring must be axial on the cyclohexane ring already present. It is energetically more costly to bring two groups to a 1,3-diaxial orientation than to get a single group into an axial position. Therefore, the favored route should proceed via a kinetically-controlled reaction of an appropriately substituted propylcyclohexane. Our initial choice for study was the internal substitution of the enolate of 4-(γ-tosyloxypropyl)cyclohexanone.

Preparation of the intermediate 4-(γ-hydroxypropyl)cyclohexanone was accomplished by two separate routes (schemes A and B). In scheme A 4-(γ-hydroxypropyl) cyclohexanone is synthesized in four steps from *p*-allylanisole. Hydroboration and subsequent oxidation[10] gave mainly the primary alcohol. Though the amount of secondary alcohol present was not determined, allylbenzene gives a 90/10 mixture of primary to secondary alcohol.[10] Birch reduction and subsequent hydrolysis gave 4-(γ-hydroxypropyl)-3-cyclohexenone. This structure was assigned on the basis of the spectral properties of the molecule and its absorption of one mole of hydrogen to give the desired 4-(γ-hydroxypropyl)cyclohexanone. A group of derivative compounds were prepared which testify to the structure of the Birch reduction product (Experimental). The overall yield in this process was about 25% and a large scale would be expensive so we decided to explore an alternate route.

SCHEME A



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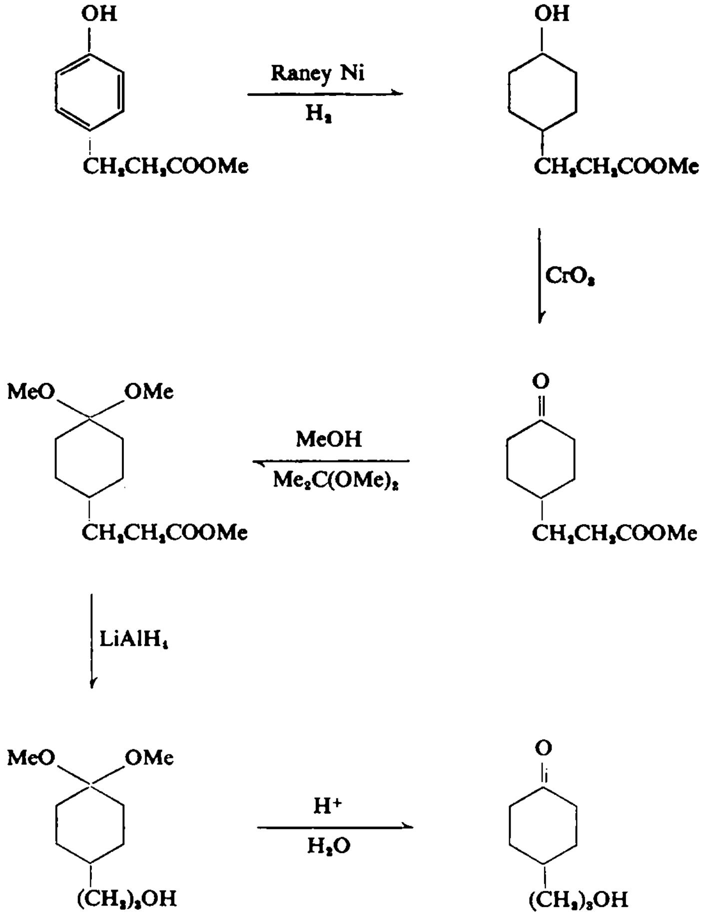
[10] H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.* **82**, 4708 (1960).

SCHEME B



In the second preparation the three carbon chain was introduced via cyanoethylation of phenol.[11] Hydrolysis and esterification gave methyl β-(p-hydroxyphenyl)propionate in good yield. Reduction of the ring was accomplished in nearly quantitative yield. The secondary alcohol was oxidized to a ketone in 80% yield, and after protection of the ketone (methyl ketal) the ester was reduced. The ketal was hydrolyzed readily with the last three steps being carried out without isolation of intermediates in 87% yield. An overall yield of 62% is achieved from p-hydroxyhydrocinnamic acid. Each step can be run conveniently on a large scale. The 4-(γ-hydroxypropyl)cyclohexanone was clearly identified by its spectral properties and dual mode of formation.

Preparation of the tosylate of this alcohol by a conventional procedure[12] gave an oil which would not crystallize. Unless the reaction was carried out at 0° a large portion of the product was converted to 4-(γ-chloropropyl)cyclohexanone, though at 0° contamination of the tosylate by chloride did nor exceed 5–8% (NMR analysis). The crude tosylate showed no hydroxyl and the presence of the sulfonate group was

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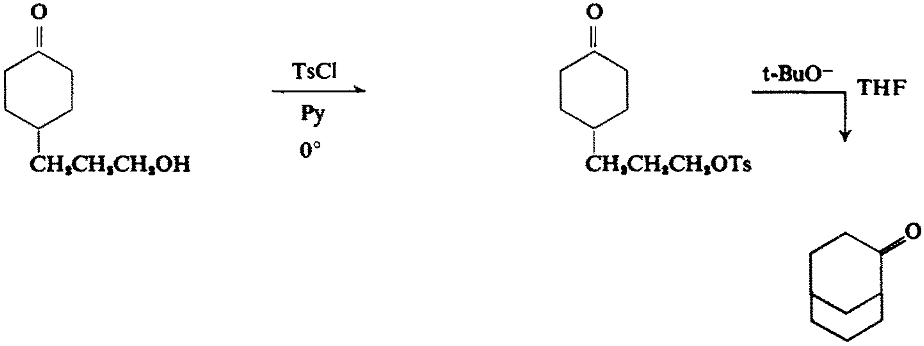
[11] H. W. Johnston and F. J. Gross, *J. Org. Chem.* **22**, 1264 (1957).

[12] R. S. Tipson, *J. Org. Chem.* **9**, 235 (1944).

indicated by strong bands 1355, 1170 and 940 cm^{-1}.[13] The crude material was used directly.

An attempt to bring about ring closure using sodium hydride in anhydrous tetrahydrofuran[14] failed, since after 72 hr only a few per cent of the tosylate had reacted. Addition of a small amount of t-butyl alcohol speeded the reaction. A second attempt using potassium t-butoxide as catalyst proved more successful. Gas chromatography showed that the ring closure proceeds in about 60% yield. Isolation of a pure crystalline product has been accomplished in 42% yield.

This route is an effective method for the preparation of bicyclo[3.3.1]nonanes on a large scale. The only useful alternative presently available is the adaptation of Stork and Landesman's[15] preparation of 2-pyrrolidinobicyclo[3.3.1]nonan-9-one made by Woodward and Foote[16] and applied by Cope and Gale.[6a] This latter process is adapted to the synthesis of 9-bicyclo[3.3.1]nonanone or 2-bicyclo[3.3.1]nonene, but not to the preparation of 2-bicyclo[3.3.1]nonanone or its derivative alcohols. The synthesis reported here provides an effective complement to the (modified) Stork procedure.



EXPERIMENTAL[17]

Methyl β-(p-hydroxyphenyl)propionate. A sample, 127 g (0·77 mole), of β-(*p*-hydroxyphenyl)-propionic acid[18] prepared from phenol via cyanoethylation[11] and subsequent hydrolysis, was heated at reflux for 6 hr with 300 ml dry MeOH, 700 ml ethylene chloride and 4 ml conc H_2SO_4. The solution was washed with $NaHCO_3$aq and water and then dried. After removal of the solvent, the crude product (m.p. 37–40°) was purified by distillation, b.p. 110° (0·05 mm), m.p. 39–40·5°, 123 g (89%). A m.p. of 40–41° has been reported for this ester.[19]

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[13] K. Nakanishi, *Infrared Absorption Spectroscopy*, pp. 54–55. Holden-Day, San Francisco, California (1962).

[14] J. H. Fassnacht and N. A. Nelson, *J. Org. Chem.* **27**, 1885 (1962).

[15] G. Stork and H. K. Landesman, *J. Amer. Chem. Soc.* **78**, 5129 (1956).

[16] C. S. Foote, Ph.D. Thesis, Harvard University (1961).

[17] M.ps are corrected. Analyses by Bernhardt Mikroanalytisches Laboratorium, Mulheim, Germany, or Galbraith Laboratories, Knoxville, Tennessee. IR spectra were run on a Perkin–Elmer Model 21 or Beckmann IR-8 spectrometers. All NMR spectra were run in solution in CCl_4 using a Varian A-60 spectrometer. We are indebted to the National Science Foundation for financial assistance in the purchase of this latter instrument.

[18] T. C. Bruice, *J. Org. Chem.* **19**, 333 (1954).

[19] I. M. Heilbron and H. M. Bunbury, *Dictionary of Organic Compounds* Vol. III; p. 470. Oxford University Press, New York, N.Y. (1938).

Methyl β-(4-hydroxycyclohexyl)propionate. The above ester was hydrogenated over W-4 Raney Ni in abs MeOH at 155–200° and 1400 p.s.i. initial H_2 press. The reduced material was isolated by removal of catalyst and solvent followed by distillation, b.p. 80–90° (0·11 mm), n_D^{20} 1·4700, $\tilde{\nu} = 3450$, 1730, 1050 cm^{-1}, as a colorless liquid in 98% yield. (Found: C, 64·04; H, 9·45; $C_{10}H_{18}O_3$ requires: C, 64·48; H, 9·74%.)

Methyl β-(4-oxocyclohexyl)propionate. To a well-stirred solution of 123·9 g (0·67 mole) methyl β-(4-hydroxycyclohexyl)propionate in 1500 ml acetone cooled in an ice bath was added 85 g chromium trioxide dissolved in 360 ml of 30% H_2SO_4aq.[20] Addition required 1·5 hr. After the solution had stood 10 hr at 0° enough KOH was added to neutralize the acid, and $NaHCO_3$ to make the solution slightly alkaline. Acetone was removed under red. press. and the residue extracted twice with ether. The ether extracts were combined, washed with sat. Na_2SO_4aq and dried. Distillation of the product through a short Fenske column gave 98–99 g (80%) of liquid, b.p. 75–80° (0·07–0·09 mm) $n_D^{20\cdot 2}$ 1·4651, $\tilde{\nu} = 1735$, 1710 cm^{-1}.

A 2,4-*dinitrophenylhydrazone* prepared by the method of Shine[21] melted at 130·9–131·8°. (Found: C, 53·02; H, 5·78; $C_{16}H_{20}N_4O_6$ requires: C, 52·76; H, 5·50%.)

A small amount of β-(4-oxocyclohexyl)propionic acid, m.p. 62–65°, was isolated from the water layer. A m.p. of 60–65° has been reported[22] for this acid.

4-(3-*Hydroxypropyl*)*cyclohexanone.* A mixture of 94 g (0·51 mole) methyl β-(4-oxocyclohexyl)-propionate, 252 g (2·43 moles) 2,2-dimethoxypropane, 300 ml MeOH and 0·375 g *p*-toluenesulfonic acid was allowed to stand at room temp overnight. Solvent was removed until the distillation temp reached 65°, at which point the residue was cooled and 15 drops of 10% KOHaq and 300 ml ether were added. This was shaken with 60 ml sat. Na_2SO_4aq, the aqueous layer extracted with ether, and the organic layers combined and dried. Removal of the solvent gave 117 g (99%) light yellow liquid, $\tilde{\nu} = 1735$, 1110, 1052 cm^{-1}. Attempted distillation of this ketal led to loss of MeOH and formation of methyl β-(4-methoxy-3-cyclohexenyl)propionate, b.p. 87–89° (0·07 mm), $n_D^{20\cdot 2}$ 1·4699, $\tilde{\nu} = 1735$, 1660, 1210, 1170 cm^{-1}.

Either the ketal or enol ether (0·5 mole) in 200 ml anhydrous ethyl ether was added to 0·25 mole (1 equiv.) LAH in 900 ml ether over a 2 hr period. The reaction mixture was heated at reflux for 9 hr. An excess of 5% H_2SO_4aq was added and the mixture stirred vigorously for 6 hr. The ether layer was separated, the aqueous layer extracted several times with ether, all extracts combined and washed with $NaHCO_3$aq. The product was isolated by distillation b.p. 115–116° (0·05 mm), $n_D^{20\cdot 2}$ 1·4816, $\tilde{\nu} = 3430$, 1712, 1057 cm^{-1}, 68 g (87%). The NMR spectrum shows a singlet at 3·69 ppm (OH), a triplet at 3·53 ppm, J = 9 c/s 2 protons (CH_2O), and a complex pattern lying between 1·0 and 2·5 ppm.

A sample of the same material was obtained by hydrogenation of 4-(3)hydroxypropyl)-3-cyclohexenone. A mixture of 0·40 g (2·6 mmoles) of this ketone in 30 ml abs EtOH and 50 mg 5% Pd–C was hydrogenated at 20°. The product distilled from an alembic at a bath temp of 85° at 0·05 mm, n_D^{20} 1·4810. (Found: C, 69·29; H, 10·22; $C_9H_{16}O_2$ requires: C, 69·19; H, 10·33%.)

A 2,4-*dinitrophenylhydrazone* prepared by the method of Shine[18] melted at 135·5–137°. (Found: C, 53·81; H, 5·75; N, 16·82; $C_{15}H_{20}N_4O_5$ requires: C, 53·56; H, 5·99; N, 16·66%.)

4-(3-*Tosyloxypropyl*)*cyclohexanone.* A solution of 5·0 g (32 mmoles) 4-(3-hydroxypropyl)-cyclohexanone in 15 ml anhydrous pyridine was added to a cold (0°) solution of 7·6 g *p*-toluenesulfonyl chloride in 20 ml anhydrous pyridine. The solution was stirred at 0° for 24 hr, 2–3 ml water added and stirring continued for 30 min longer. The reaction mixture was diluted with 200 ml ether and the solution washed with water, dil H_2SO_4aq, $NaHCO_3$aq and dried. Removal of the solvent gave 9·3 g (94%) of a viscous oil which would not crystallize. The crude product showed no band in the IR at 3400 cm^{-1}, had strong bands at 1355, 1170, and 940 cm^{-1} and was used without further purification.

2-*Bicyclo*[3.3.1]*nonanone.* Using scrupulously dried equipment flushed with prepurified N_2 dried over P_2O_5, a slurry of 10·0 g (0·09 mole) potassium t-butoxide was prepared in 1300 ml anhydrous tetrahydrofuran (distilled from NaH directly into the reaction vessel). To this was added during 1 hr a solution of 26·4 g (0·085 mole) of the above tosylate in 250 ml tetrahydrofuran. This mixture was stirred at 43–45° for 22 hr under dry N_2. The reaction mixture was filtered, 150 ml water added to

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

[21] H. J. Shine, *J. Org. Chem.* **24**, 252 (1959).

[22] E. Bowden and H. Adkins, *J. Amer. Chem. Soc.* **62**, 2422 (1940).

the filtrate and the solvent removed. The residue was extracted several times with pentane, the extracts washed with sat Na_2SO_4aq and dried. After removal of the solvent there remained 11·40 g (97%) of a light yellow partly solid product.

Chromatography of the crude product over activity II–III alumina gave 7·4 g (65%) of the material in an early fraction eluted with hexane. The remainder, 4·0 g, was eluted later with ether. Distillation of the smaller fraction gave 1·68 g (12·7%) of recovered 4-(γ-hydroxypropyl)cyclohexanone. Sublimation of the larger fraction (hexane eluate) gave 4·95 g (42% or 48% based on unrecovered alcohol) white crystals, m.p. 134–137° (lit.[8] 135–137), $\bar{\nu}$ = 2920, 2860, 1711, 1455 cm^{-1}, NMR—a series of bands between 90 and 155 c/s. A semicarbazone, m.p. 176–178° (lit.[8] m.p. 179–181°) was prepared.

3-(p-*Anisyl*)-1-*propanol*. A solution containing 18·3 g (0·129 mole) of freshly distilled BF_3-etherate in 25 ml diglyme was added dropwise to a cold solution containing 45·3 g (0·306 mole) *p*-allylanisole and 3·38 g (0·084 mole) $NaBH_4$ in 140 ml diglyme. After addition was complete the solution was stirred at room temp for 1 hr. To this was added 22 ml water and 40 ml 3N NaOH followed by dropwise addition of 43 ml (0·379 mole) 30% H_2O_2. The reaction mixture was poured into 500 ml ice water, and extracted 3 times with ether. The combined ether layers were washed with water, dried, and the ether removed by evaporation. Distillation gave 40·6 g (80%) of a clear liquid, b.p. 107° (1·7 mm), n_D^{20} 1·5275, $\bar{\nu}$ = 3400, 1600, 1235 cm^{-1}. A n_D^{20} 1·5305 has been reported[23] for this compound. The phenylurethane melts at 64–65° and has been reported[24] to melt at 64–65°.

1-*Methoxy*-4-(3-*hydroxypropyl*)-1,4-*cyclohexadiene*. To a mixture of 10·3 g (0·06 mole) 3-(*p*-anisyl)-1-propanol, 200 ml abs EtOH and 800 ml liquid ammonia, 10 g (1·44 g-atoms) Li was added in small pieces. After the blue color had disappeared, 78·6 g (1·47 moles) NH_4Cl was added in small portions and the ammonia allowed to evaporate. The residual moist solid was triturated with anhydrous ether and the slurry filtered (celite added). The ether was evaporated and the moist solid so obtained again treated with ether, the suspension filtered and the ether removed. The process was repeated until no further solid was carried in the ether. Distillation of the residual oil gave 7·09 g (68%) of a colorless liquid, b.p. 100–106° (0·05 mm), n_D^{20} 1·4900–1·5011, $\bar{\nu}$ = 3400, 1705(w), 1665, only end absorption in the UV. (Found: C, 72·13; H, 9·78; $C_{10}H_{16}O_2$ requires: C, 71·39; H, 9·59%.)

4-(3-*Hydroxypropyl*)-3-*cyclohexenone*. A solution of 1·04 g (6·2 mmoles) 1-methoxy-4-(3-hydroxypropyl)-1,4-cyclohexadiene in 100 ml EtOH containing 1 ml water and two drops conc HCl was allowed to stand at room temp for 10 min. Solid $NaHCO_3$ was added until gas evolution ceased. About 15 ml benzene was added, the solvents distilled and the residual oil distilled from an alembic at 0·05 mm and 120° bath temp, 0·6 g (63%), $\bar{\nu}$ = 3400, 1705, 1050 cm^{-1}. (Found: C, 69·95; H, 9·01; $C_9H_{14}O_2$ requires: C, 70·10; H, 9·15%.)

1-*Methoxy*-4-(3-*acetoxypropyl*)-1,4-*cyclohexadiene*. A mixture of 5·81 g (35 mmoles) 1-methoxy-4-(3-hydroxypropyl)-1,4-cyclohexadiene, 50 ml pyridine and 11 ml freshly distilled acetic anhydride was heated 30 min on a steam bath. The solution was diluted with 200 ml benzene, washed thoroughly with water, and the benzene layer was dried. Removal of solvent and distillation gave an oil, b.p. 96° (0·02 mm), n_D^{20} 1·4801, 6·55 g (90%), $\bar{\nu}$ = 1730, 1685, 1655, 1375, 1225 cm^{-1}. (Found: C, 68·73; H, 8·80; $C_{12}H_{18}O_3$ requires: C, 68·54; H, 8·63%.)

4,4-*Dimethoxy*-1-(3-*acetoxypropyl*)*cyclohexene*. A solution of 9·65 g (40 mmoles) 1-methoxy-4-(3-acetoxypropyl)1,4-cyclohexadiene in 60 ml anhydrous methanolic HCl (0·14N) was shaken for 5 min and an excess Na_2CO_3 added. The slurry was diluted with 100 ml benzene, the solids removed by filtration and the solvents evaporated. The residual oil distilled, b.p. 100–104° (0·025 mm), n_D^{20} 1·4671, 9·13 g (82%), $\bar{\nu}$ = 1735, 1115 cm^{-1}. (Found: C, 64·51; H, 9·19; $C_{13}H_{22}O_4$ requires: C, 64·43; H, 9·15%.)

4-(3-*Acetoxypropyl*)-3-*cyclohexenone*. Six grams (29 mmoles) of 1-methoxy-4-(3-acetoxypropyl)-1,4-cyclohexadiene was treated by the procedure described for preparation of 4-(3-hydroxypropyl)-3-cyclohexenone. The product, b.p. 111–112° (0·5 mm), n_D^{20} 1·4725, $\bar{\nu}$ = 1730, 1710, was obtained in 75% (4·19 g) yield. (Found: C, 67·45; H, 8·40; $C_{11}H_{16}O_3$ requires: C, 67·32; H, 8·22%.)

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[23] A. W. Fort and J. D. Roberts, *J. Amer. Chem. Soc.* **78**, 584 (1956).

[24] P. Ramart-Lucas and F. Amagat, *C.R. Acad. Sci., Paris* **188**, 640 (1933).