Synthesis of Substituted Hydrindanes. Part I. Products Arising from the Cyclization of Acetonyl Cyclohexanones and Acetonyl Cyclohexadiones

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The preparation and cyclizations of certain 1,4-diketones have been studied as a route to substituted hydrindan-2-one systems. Other types of products encountered are also described.

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On a étudié la préparation de certaines dicétones-1,4 ainsi que leur cyclisation comme moyen d'arriver au système hydrindanone-2 substitué. On décrit aussi d'autres types de produits qui ont été rencontrés. [Traduit par le journal]

While investigating synthetic routes which could lead to both *Lycopodium* alkaloids possessing the fawcettimine skeleton and certain terpenes we have investigated the preparation of several hydrindan-2-one systems. We were particularly interested in models of type **1** in which R_3 and R_4 would represent either a nine-membered nitrogen containing ring or sidechains susceptible to cyclization to this medium-sized ring.

We decided that cyclohexa-1,3-diones offered certain advantages of reactivity and availability as starting materials and for most of the trial series we chose the readily available dimedone although some sequences have started from dihydroorcinol. Acrylonitrile condenses readily with dimedone in the presence of triethylamine (1) and we have found that by careful adjustment of the p*H* after the reaction, the pure monocyanoethyl derivative **2***a* is obtained directly in yields exceeding 70%. Alkylation of the latter with ethyl β-bromolevulinate in the presence of sodium hydride in dimethoxyethane gave only a poor yield of the triketo ester **3***a*. A similar compound, **3***b* was prepared from 2-allyldihydroorcinol **2***b*, again in low yield but the conditions necessary to cyclize these multifunctional compounds (to give **4***a* and **4***b*) were never achieved. The number of possible reactions of each compound (**3***a* and **3***b*) in reagents normally favoring cyclization, prohibited a meaningful analysis of the products.

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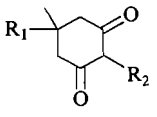

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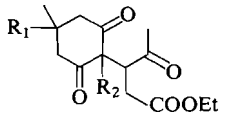
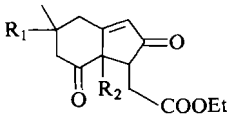


3

a $R_1 = CH_3$; $R_2 = CH_2CH_2CN$
b $R_1 = H$; $R_2 = CH_2CH{=}CH_2$
c $R_1 = CH_3$; $R_2 = CH_2CH{=}CH_2$



4

To further investigate the formation of the five-membered ring, simpler models were sought containing as essential elements the "quaternary" carbon atom and a side chain possessing only one carbonyl residue. Consequently cyanoethyldimedone **2***a* was alkylated in high yield with propargyl bromide to give **5***a*, forming the quaternary center and a less enolizable symmetrical 1,3-diketone. The triple bond was hydrated in virtually quantitative yield to the triketo-

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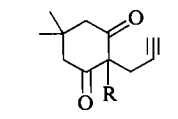
nitrile **6***a* which did not cyclize under basic conditions but afforded only the triketone **6***c* arising from a retro-Michael reaction while acidic conditions tended to open the six-membered ring (retro-Claisen) before effecting the closure, the major product being the cyclopentenone **7**. The analogous allyl-triketone **6***b*, prepared via compound **5***b* (propargylation of **2***c*) and hydration of the triple bond, was more resistant but again the only products isolated in attempted cyclizations were those resulting from expulsion of one of the side chains.

The vulnerability of the β-diketo system to cleavage suggested that internal alkylation might be more rewarding than internal condensation. To convert one of the carbonyl groups in the cyano-diketone **5***a* to a potential leaving group we reduced selectively one of the carbonyl groups and the product (**8***a*) was transformed to both the tosyl and acetyl derivatives (**8***b* and *c*, respectively). Later we found that even under forcing conditions the second carbonyl is quite resistant to sodium borohydride reduction. Since the best method we had found for hydrating the triple bond in the propargyl residue involves a methanolic solution containing a trace of trichloroacetic acid, we felt that it might be possible to isolate the diketone as the corresponding diketal providing the reaction mixture is not decomposed in water. After hydrating the triple bond in the tosyl derivative **8***b*, the volatile products were simply evaporated at or below room temperature *in vacuo* and the crystalline product shows no carbonyl absorption in the i.r. spectrum. Since mild hydrolysis of this material (or just recrystallizing from less than anhydrous solvents) affords the diketone **10***b*, the addition to the triple bond did take place. Elemental analysis of the ketal, with other spectral characterization, showed it to be the cyclic ketal **9**.

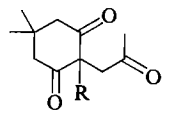
The normal procedure for hydrating the triple bonds in all three compounds **8***a*, *b*, and *c* was without consequence affording the corresponding diketones **10***a*, *b*, and *c*. Attempts to cyclize these compounds gave different results. The alcohol **10***a* suffers ring-opening by retroaldolization under all but the mildest conditions; certainly neither the cyclopentenone **11***a* which could arise by condensation nor the internal alkylation product, cyclopentanone **11***b* was isolated. The tosylate **8***b* cyclizes rapidly at room temperature in methanolic sodium methoxide but forms the (predicted?) substituted cyclopropane **12**. Varying the conditions had no apparent effect on the direction of enolization or carbanion formation and only in one reaction, in *t*-butyl alcohol containing sodium *t*-butoxide, was a different product obtained. We tentatively postulate the latter to be the substituted spiro[4.4.0.$0^{1,7}$]tricyclodecane **13** (see Experimental). The acetyl derivative **8***c* was recovered unchanged from several attempted cyclization reactions, but in one case afforded the spiro[5.4.1]-bicyclodecane system **14**.

One further type of ring closure was tried on molecules containing virtually the same functional groups. Alkylation of cyanoethyldimedone **2***a* with 2,3-dichloropropene afforded the chloro-alkene **15***a* which was reduced to the keto-alcohol **15***b* now suitably functionalized to



5

a R = CH_2CH_2CN
b R = $CH_2CH{=}CH_2$



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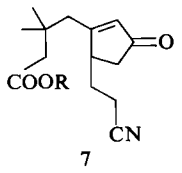
a R = CH_2CH_2CN
b R = $CH_2CH{=}CH_2$
c R = H



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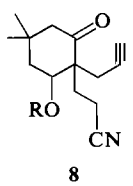
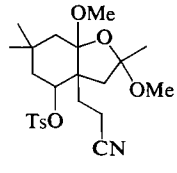


8

a R = H
b R = Ts
c R = Ac



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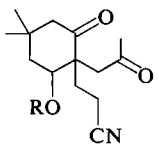
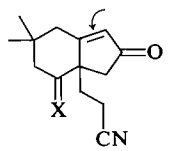


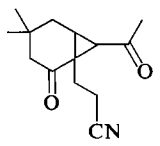
10

a R = H
b R = Ts
c R = Ac



11

a X = H,OH
b X = =O, no double bond (arrow)



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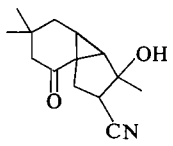


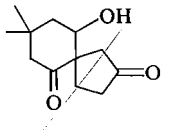
13

attempt cyclization in concentrated acids, as described by Lansbury (2). We had previously failed to prepare enol esters or ethers with the terminal double bond. It was felt that this chloro-alkene (**15***b*) should form the five-membered ring but in cold sulfuric acid the reaction was extremely complex and the nitrile appeared to be the most susceptible function. In refluxing formic acid the molecule (**15***b*) was surprisingly stable affording only the *O*-formyl derivative **15***c*. While this type of cyclization is feasible, most examples in the literature involve benzylic or allylic hydroxyl groups.

The attractiveness of the synthetic route from cyclohexa-1,3-diones lay in the fact that the formation of the quaternary center isolates the two carbonyl groups while preserving a symmetrical molecule: one carbonyl serving as the means to cyclize the five-membered ring while the other is suitably placed for the final synthetic goal or for modifying the six-membered ring. The difficulties encountered in performing the cyclization forced a reassessment of the route. By eliminating one of the two oxygen functions (the hydroxyl in **8***a* for instance) the ring closure should be relatively facile since the competing reactions (retroaldol and retro-Michael) are either impossible or considerably less probable. For certain syntheses, however, an additional problem is introduced, that of reestablishing the oxygen function at the carbon atom adjacent to the quaternary center with acceptable selectivity.

Of several methods tried, the dehydration of the keto-alcohol **8***a* was best accomplished with phosphorus oxychloride in pyridine but the quality of the reagents affects the yield of olefin **16***a* drastically. As in previous series boron trifluoride – trichloroacetic acid catalyzed hydration of the triple bond affords the diketone **16***b*. Cycloaldolization of the latter in methanolic potassium hydroxide is rapid, as is the hydrolysis of the nitrile and the acidic product from the reaction is cyclopentenone **17***a*.

Our first attempt to cyclize the diketo-olefin **16***b* was with sodium hydride in dimethoxyethane (reflecting perhaps previous difficulties) and this reaction had produced three products, the major being an acid isomeric with **17***a* and with quite similar spectral characteristics. We felt at the time that this might be the desired cyclization product and that the smaller quantity of a neutral material from this same reaction was



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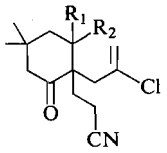
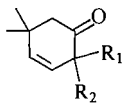


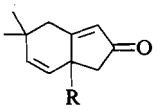
15

a $R_1, R_2 = O$
b $R_1 = H; R_2 = OH$
c $R_1 = H; R_2 = OCHO$



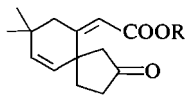
16

a $R_1 = CH_2CH_2CN; R_2 = CH_2C{\equiv}CH$
b $R_1 = CH_2CH_2CN; R_2 = CH_2COCH_3$
c $R_1 = CH_2CH{=}CH_2; R_2 = CH_2C{\equiv}CH$
d $R_1 = CH_2CH{=}CH_2, R_2 = CH_2COCH_3$



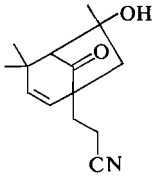
17

a $R = CH_2CH_2COOH$
b $R = CH_2CH_2COOMe$
c $R = CH_2CH_2CN$
d $R = CH_2CH{=}CH_2$

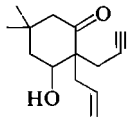


18

a R = H
b R = Me



19



20

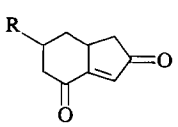
the nitrile **17***c*. When hydrolysis of the nitrile afforded the cyclized acid **17***a*, identical with that from the easier hydroxide cyclization, we were forced to reexamine the anomalous sodium hydride cyclization product. The u.v. spectrum of the latter (λ_{max} 221 nm, ε 6900) suggested an α,β-unsaturated acid rather than a conjugated five-membered ring ketone such as **17***a* (λ_{max} 233 nm, ε 13 000). Other spectral considerations (see Experimental) imply that the anomalous product has the structure **18***a* and its formation can be imagined as combined aldolization and Claisen-type ring closures followed by β-diketone cleavage. The third product from this cyclization was also a nitrile but contained a hydroxyl group. Spectral data, analysis, and con-

sideration of the reactions likely to occur suggest that this new material is the alternate aldolization product **19**.

The analogous series starting with allyl- (**2***c*) rather than cyanoethyldimedone (**2***a*) was also carried through to the cyclized material by the methods already discussed. Thus allyldimedone (**2***c*) is propargylated to afford the diketone **5***b* in which one carbonyl group is then selectively reduced to give the ketol **20**. While we separated the predominant solid isomer in which the hydroxyl group is equatorial both isomers separately or as a mixture are dehydrated to the olefin **16***c*. Hydration of the triple bond affords the diketone **16***d* which cyclizes to the conjugated enone **17***d*. In this compound we assume the three olefinic double bonds (terminal, cyclic, and conjugated) to be sufficiently different to allow selective modification.

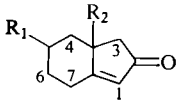
Another approach to compounds of type **1** might be to introduce R_3 and R_4 by a Diels–Alder reaction should enediones such as **1***a* show sufficient reactivity as dienophiles. Not finding products of this nature in the literature, we attempted to prepare them. The fact that hydrindenone **22***a* can be readily prepared from indene (3) prompted a few experiments aimed at functionalizing the allylic methylene group but these failed due to the superior reactivity of the angular methine. To exclude this possibility we synthesized compounds with angular ester functions (**22***c* and *d*). The carbomethoxy groups could be readily eliminated after cyclization (vinylogous β-keto esters) and since synthesis from indene was no longer advantageous we prepared these keto esters from α-carboalkoxycyclohexanones. Alkylation with propargyl bromide (giving **23***a*, *b*, and *c*), hydration of the triple bond (affording **24***a*, *b*, and *c*), and cyclization of the diketo esters lead to the enones **22***c* and *d* in satisfactory yields. Varying the conditions of the ring formation also gave the decarboxylated enones **22***a* and *b*. Our Experimental was adapted from methods described by Raphael (4). The allylic functionalization proved equally unsatisfactory with the angular substituent and a variety of conditions (see Experimental) affecting allylic oxidations afforded starting material as the only tractable product.

One experiment was performed to introduce an angular substituent in compound **22***a* by conjugate addition to the enone system. Treatment



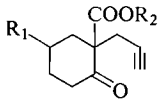
21

a $R = CH_3$
b $R = H$



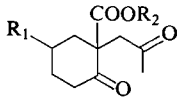
22

a $R_1 = R_2 = H$
b $R_1 = CH_3$; $R_2 = H$
c $R_1 = H$; $R_2 = COOEt$
d $R_1 = CH_3$; $R_2 = COOMe$



23

a $R_1 = H$; $R_2 = Et$
b $R_1 = CH_3$; $R_2 = Et$
c $R_1 = R_2 = CH_3$



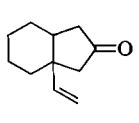
24

a $R_1 = H$; $R_2 = Et$
b $R_1 = CH_3$; $R_2 = Et$
c $R_1 = R_2 = CH_3$

of the latter with tetrakis(iodotri-*n*-butylphosphine) copper and vinyl lithium (5) affords the vinylhydrindanone **25** in modest yield. We hope to use this reaction later in another synthesis.

It had become evident that while the five-membered ring is easily grafted onto the cyclohexanone, the second ketone (perhaps as a latent substituent) would be best introduced at the outset. Arylidene or alkylidene residues, which could later be transformed into carbonyl groups by ozonolysis proved cumbersome and the yields in some steps were extremely poor. Finally the ketone was protected as the dioxalane by the following route.

α-Benzylidene or α-ethylidene cyclohexanones are converted to their spiro-ketals (**26***a* and *b*) and then cleaved by ozonolysis to give the monoketals of the corresponding α-diketones (**27***a* and *b*). Direct alkylation gives largely the dialkylated product **28***a*, the presence of which is easily revealed in the n.m.r. spectrum of the material (**28***b*) arising from the hydrogenation of the triple bonds. By first preparing the hydroxymethylene derivatives then alkylating, the monopropargylated products (**28***e* and *f*) are obtained in satisfactory yield and the hydration of the triple bond can be performed without hydrolysis of the spiro-ketal after slight modification of the conditions. Both diketones **28***g* and *h* were prepared but only the latter was cyclized to the enone **29**, which is a protected form of the desired enedione **21***a*. However, despite numerous attempts to remove the dioxolane moiety



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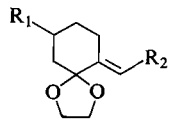
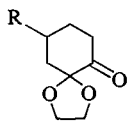


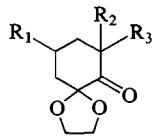
26

a $R_1 = H; R_2 = CH_3$
b $R_1 = CH_3; R_2 = Ph$



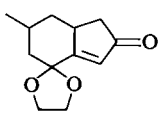
27

a R = H
b R = CH_3

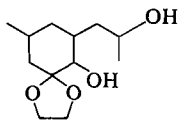


28

a $R_1 = H; R_2 = R_3 = CH_2C{\equiv}CH$
b $R_1 = H; R_2 = R_3 = CH_2CH_2CH_3$
c $R_1 = H; R_2 = R_3 = {=}CHOH$
d $R_1 = CH_3; R_2 = R_3 = {=}CHOH$
e $R_1 = R_2 = H; R_3 = CH_2C{\equiv}CH$
f $R_1 = CH_3; R_2 = H; R_3 = CH_2C{\equiv}CH$
g $R_1 = R_2 = H; R_3 = CH_2COCH_3$
h $R_1 = CH_3; R_2 = H; R_3 = CH_2COCH_3$
i $R_1 = CH_3; R_2 = H; R_3 = CH_2CH{=}CH_2$



29



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none was successful, in most cases hydrolysis destroyed the molecule beyond recognition. The enone spiro-ketal **29** showed great reluctance to undergo Diels–Alder cycloadditions.

As a variant to the method described above and to avoid the hydrolysis of the spiro-ketal during hydration of the triple bond (in **28***e* and *f*) we investigated a parallel route involving allylation of the activated keto-ketal **28***d*. The nature of this product (**28***i*) was confirmed by preparing a sample from the propargyl containing analog **28***f* by hydrogenation over Lindlar catalyst. The hydroxylation of the double bond using mercuric acetate followed by sodium borohydride also reduces the existing ketone moiety to give the diol **30** which is oxidized (Sarett reagent) to the diketo-ketal **28***h*. The latter on reduction with sodium borohydride also affords the diol **30**. This route however offers no advantage, either in yield or ease of manipulation.

Experimental

The normal conditions and instruments for the spectra quoted are: u.v. ethanol solutions, Beckman DK-1A; i.r. Perkin Elmer 457 and Beckman IR 12; n.m.r. Varian A60 and Bruker HX 90, internal TMS standard, coupling constants are given in parentheses; mass spectra, Varian M66. Elemental analyses were performed by Mr. R. Dulude, Chemistry Department, Université Laval and by Dr. F. Pascher, Bonn.

2-Cyanoethyl-5,5-dimethylcyclohexa-1,3-dione (2a)

Dimedone (7 g) is added to a solution of isopropanol (15 ml) and triethylamine (5 ml) in water (15 ml) under nitrogen. Freshly distilled acrylonitrile (3.5 ml) is introduced and the mixture refluxed for 3 h then cooled in ice (*ca.* 2 h) to crystallize the 2,2-bis(2-cyanoethyl)-5,5-dimethylcyclohexa-1,3-dione, m.p. 145° (1.5 g, 12%) (lit. (6) m.p. 146–147°). The filtrate is acidified (dilute hydrochloric acid) to p*H* 6, precipitating the cyanoethyldimedone **2***a* (6.7 g, 70%), m.p. 153–154°; λ_{max} 262 (16 100) and 290 (sh. 7400) nm; ν_{KBr} 2550, 2260, 1640, and 1565 cm^{-1}; δ_{CDCl_3} *gem*-dimethyl s 1.1, $-CH_2CO$ s 2.4, $-CH_2CH_2CN$ m 2.5, and OH (enol) s 8.15.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.3; H, 7.8; N, 7.3. Found: C, 68.5; H, 7.9; N, 7.6.

2-Allyl-5-methylcyclohexa-1,3-dione (2b)

This was prepared following essentially the method of Rosenmund (7), m.p. 135–136°.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.3; H, 8.5. Found: C, 72.1; H, 8.4.

2-Allyl-5,5-dimethylcyclohexa-1,3-dione (2c)

This was prepared by the method of Rosenmund (7), m.p. 145–146° (lit. 145–146°); λ_{max} 262 (13 800) nm; ν_{KBr} 3080, 3010, 2600, 1638, and 1560 cm^{-1}; δ_{CDCl_3} *gem*-dimethyl s 1.07, $-CH_2CO-$ s 2.37, $-CH_2-CH{=}CH_2$ d(6.0) 3.12, m 5.0 and m 5.8; *m/e* 180 (M+), 165, 124, 109, 97, 96, 95, 83 (base), and 81.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.3; H, 8.9. Found: C, 73.4; H, 8.8.

Ethyl 3-[1-(2-Cyanoethyl)-4,4-dimethyl-2,6-dioxocyclohexyl]-4-oxopentanoate (3a)

Sodium hydride (2.35 g) washed free of mineral oil, is suspended in dimethoxyethane (100 ml) under nitrogen. The cyanoethyldimedone **2***a* (4.8 g) is added and after 2 h, ethyl β-bromolevulinate (5.58 g) is introduced dropwise and the mixture is stirred at 48° for 12 h. The reaction mixture is decomposed in water and ether extraction affords a neutral oil (2.5 g) and starting material (3.4 g) from the aqueous phase on acidification. The oil is chromatographed over Florosil. The benzene – 4% ether eluate is the ester **3***a* (0.5 g), m.p. 123–124°; ν_{KBr} 2260, 1740, 1725, 1715, 1695 cm^{-1}; δ_{CDCl_3} *gem*-dimethyl s 0.8, CH_3CH_2O t(7.2) 1.21, and q(7.2) 4.1, CH_3CO s 2.16, $CO-CH-CH_2COOR$ d of d (2.5 and 10.5) 3.70, d of d(8.5 and 10.5) 3.11 and d of d (8.5 and 2.5) 2.51; *m/e* 335 (M+), 290, 262, 248 (base), 220, 207, and 83.

Anal. Calcd. for $C_{18}H_{25}NO_5$: C, 64.5; H, 7.5; N, 4.2. Found: C, 64.3; H, 7.7; N, 4.5.

Ethyl (1-Allyl-4-methyl-2,6-diketocyclohexyl)-4-ketopentanoate (3b)

This is prepared from allyldihydroorcinol **2***b* (8.3 g) as described for **5***a*, except the mixture is heated at 65° for 20 h after standing at room temperature for 4 h. Chromatography affords the ester **3***b* (3.1 g, 20% yield),

m.p. 90–91°; ν_{KBr} 3080, 1735, 1720, 1713, 1690, and 1210 cm^{-1}; δ_{CDCl_3} CH_3CH d(6.8) 1.15, CH_3CH_2O-*t*(7.0) 1.18, and q 4.03, CH_3CO s 2.21, CO—$CHCH_2COOR$ d of d(17.5 and 3.0) 2.65, d of d(17.5 and 8.5) 3.29 and d of d(8.5 and 3.0) 4.18 and the vinyl pattern 4.9 to 6.4; *m/e* 308 (M+), 265, 235.

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.2; H, 7.8. Found: C, 66.1; H, 7.9.

*2-Propargyl-2-(2-cyanoethyl)-5,5-dimethylcyclohexa-1,3-dione (**5a**)*

To potassium (1.02 g) dissolved in *t*-butyl alcohol (50 ml) under nitrogen, is added cyanoethyldimedone **2***a* (4.8 g) followed by propargyl bromide (4.5 ml) dropwise and the mixture is refluxed for 15 h. After cooling and pouring into ice water, the propargyl derivative **5***a* crystallizes (4.7 g, 83%), m.p. 157–158°; λ_{max} 283 (1060) nm; ν_{KBr} 3265, 2260, 2128, 1740, and 1710 cm^{-1}; $\delta_{pyridine\text{-}d_5}$ *gem*-dimethyl s 0.85 and s 0.95, —CH_2—CO s 2.76, H—C≡C—CH_2 t(2.5) 2.86 and d(2.5) 2.95; *m/e* 231 (M+), 191, 163, 147, 84, and 83.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.7; H, 7.4; N, 6.1. Found: C, 72.7; H, 7.6; N, 6.1.

*2-Acetonyl-2-(2-cyanoethyl)-5,5-dimethylcyclohexa-1,3-dione (**6a**)*

To the propargyl derivative **5***a* (4 g) in methanol (150 ml) and ethoxyethanol (5 ml) is added aqueous sulfuric acid (0.3 ml of 1 *N*) and Dowex 50W-X4 resin (0.9 g) charged with mercuric ions (8). The mixture is stirred for 18 h and after neutralizing with ammonia, the resin is filtered and the solvents evaporated. The residue (**6***a*) crystallizes on contact with acetone (4.5 g, quantitative), m.p. 115–116°; ν_{KBr} 2260, 1730, 1705, 1700 cm^{-1}; $\delta_{acetone\text{-}d_6}$ *gem*-dimethyl s 1.17, CH_3COCH_2 s 2.08, and —CH_2CO s 3.08; *m/e* 249 (M+), 234, 207 (base), 206, 190, 179, 178, 167, 164, 109, and 108.

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.4; H, 7.7; N, 5.6. Found: C, 67.2; H, 7.6; N, 5.6.

NOTE: Owing to a certain loss of activity of the treated resin on standing, this hydration is more reproducible using the boron trifluoride – trichloroacetic acid method described later (see **10***c*).

*Cyclization of the Triketonitrile **6a***

(a) With Potassium t-Butoxide (retro-Michael)

Potassium (180 mg) is dissolved in *t*-butyl alcohol (10 ml) under nitrogen and after cooling 2-acetonyl-2-cyanoethyldimedone (**6***a*) (1.4 g) is added and stirring continued for 35 min. The reaction mixture is poured into ice water and acidified with hydrochloric acid (28 ml, 2 *N*). Extraction affords an oil (1.2 g) from which *2-acetonyldimedone* (**6***c*) crystallizes, m.p. 134–135° (lit. (9) 132–133°); λ_{max} 263 (14 400) and λ_{max} (NaOH) 289 (24 600) nm; ν_{KBr} 1723, 1650, and 1570 cm^{-1}; δ_{CDCl_3} *gem*-dimethyl s 1.10, CH_3COCH_2 s 2.17 and s 3.44, ring CH_2CO s 2.35, OH(enol) 9.67.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.3; H, 8.2. Found: C, 67.5; H, 8.2.

(b) With Ethanolic Hydrochloric Acid (retro-Claisen etc.)

To the triketone **6***a* (1.39 g) in dry ethanol (30 ml) is added concentrated hydrochloric acid (1 ml) and the mixture is refluxed for 24 h. After decomposition in ice water, the product (**7**) (1.2 g) is obtained by extraction and purified by molecular distillation (cold finger): λ_{max} 224 (6000) nm; ν_{film} 2260, 1740 (ester), 1705, and 1640 (conjugated cyclopentenone) cm^{-1}; δ_{CCl_4} *gem*-dimethyl s 1.05, CH_3CH_2O t(7.3) 1.26, and q (7.3) 4.15, CH_2COOR s 2.21, =CH—CO broad s 5.97; *m/e* 277 (M+), 247, 231, 189, 164, 163, 149, 148 (base), and 108.

*2-Propargyl-2-(2-cyanoethyl)-3-hydroxy-5,5-dimethylcyclohexanone (**8a**)*

Sodium borohydride (135 mg) is added to a solution of 2-propargyl-2-cyanoethyldimedone (**5***a*) (1.15 g) in methanol (80 ml) and the mixture stirred at room temperature for 4 h. Water (10 ml) is added and the mixture concentrated to about one-third volume before pouring into water and extracting with chloroform. The equatorial hydroxy-ketone **8***a* (1.05 g, 90%) crystallizes from methanol, m.p. 178–179°; ν_{KBr} 3420, 3280, 2260, 1705 cm^{-1}; $\delta_{pyridine\text{-}d_5}$ (90MHz) *gem*-dimethyl two s 0.91 and 1.00, —CHOH d of d(10.0 and 5.5) 4.72 and s 5.0; *m/e* 233, 216, 159, 158 (base), 135, 130, 116, and 101.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.2; N, 6.0. Found: C, 72.2; H, 8.3; N, 6.2.

The hydroxy-ketone gives the *O-tosyl derivative* **8***b* (88% yield) on treatment with tosyl chloride in pyridine. The product crystallizes on pouring the reaction mixture into ice water, m.p. 165° (from methanol); ν_{KBr} 3280, 2260, 1715, 1605, 1195, and 1185 cm^{-1}; δ_{CDCl_3} *gem*-dimethyl two s 0.95 and 1.10, —CH_2CO s 2.27 (broad), tosyl s 2.5 and ABq (J_{AB} = 8.5 Hz) 7.6, C*H*OTs d of d(9.0 and 7.5) 5.30; *m/e* 387 (M+, weak) 216, 215, 200, 188, 173, 159, 158, 155, 133, and 119.

Anal. Calcd. for $C_{21}H_{25}NSO_4$: C, 65.1; H, 6.5; N, 3.6. Found: C, 64.8; H, 6.4; N, 3.7.

Acetylation of hydroxy-ketone **8***a* in acetic anhydride – pyridine on a steam bath for 2 days affords the *O-acetyl derivative* **8***c* (78% after recrystallization), m.p. 129–130°; ν_{KBr} 3310, 2260, 2140, 1735, 1710, 1250, 1240 cm^{-1}; δ_{CDCl_3} *gem*-dimethyl two s 0.99 and 1.11, HC≡C—CH_2—*t*(2) 1.83 and d(2.0) 2.53, CH_3CO s 2.08, C*H*—O—Ac d of d(9.0 and 7.0) 5.63.

Anal. Calcd. for $C_{16}N_{21}NO_3$: C, 69.8; H, 7.7; N, 5.1. Found: C, 69.9; H, 7.7; N, 5.1.

*2-Acetonyl-2-(2-cyanoethyl)-3-hydroxy-5,5-dimethylcyclohexanone (**10a**)*

Hydration of the triple bond was accomplished by the Dowex resin method (see **6***a*) but yields were more reproducible using the following (in all three cases superior to 80%).

The *O*-acetyl derivative **8***c* (420 mg) is dissolved in warm methanol (35 ml) and without cooling mercuric oxide (21 mg), trichloroacetic acid (2 mg), and boron trifluoride etherate (1 ml) are added. After stirring for 2 h and pouring into dilute sulfuric acid, the methyl-ketone **10***c* (358 mg, 80%) was obtained by chloroform extraction.

The hydroxy-ketone **10***a*, m.p. 84–85°; ν_{KBr} 3420, 2260, 1710, and 1705 cm^{-1}; δ_{CDCl_3} *gem*-dimethyl two s 1.03 and 1.08, CH_3CO s 2.21, CHOH d of d(10.0 and 7.0) 4.43 and s 3.2; *m/e* 239 (M+), 208, 194 (base), 191, 164, 148, and 108.

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.9; H, 8.4; N, 5.6. Found: C, 67.0; H, 8.6; N, 5.6.

The tosylate **10***b*, m.p. 135–136°; ν_{KBr} 2260, 1725, 1715,

1605, 1195, 1185 cm^{-1}; δ_{CDCl_3} *gem*-dimethyl two s 0.99 and 1.05, CH_3COCH_2 s 2.05 and ABq (J_{AB} = 18.0 Hz) 2.76, CH_3-aromatic s 2.47, CH—O—Ts d of d(5.32) 5.39, aromatic H ABq (J_{AB} = 8.2 Hz) 7.36.

Anal. Calcd. for $C_{21}H_{27}NSO_5$: C, 62.2; H, 6.7; N, 3.5. Found: C, 62.1; H, 6.9; N, 3.9.

The acetate **10c**, m.p. 143–144°; ν_{KBr} 2260, 1735, 1710, 1700, 1255, 1245 cm^{-1}; δ_{CDCl_3} *gem*-dimethyl two s 1.16 and 1.23, CH_3CO two s 2.12 and 2.29, CHOAc d of d(10.0 and 8.0) 5.77.

Anal. Calcd. for $C_{16}H_{23}NO_4$: C, 65.5; H, 7.9; N, 4.8. Found: C, 65.5; H, 7.9; N, 4.8.

2,8-Dimethoxy-4-tosyloxy-9-cyanoethyl-2-methyl-perhydrobenzfuran (9)

The *O*-tosyl derivative **8b** (3.9 g) is hydrated as above but instead of pouring into dilute acid, the reaction mixture is evaporated *in vacuo* affording a white solid (3.7 g by filtration), m.p. 93–94°; ν_{KBr} 2260, 1605, 1198, and 1185 cm^{-1}; δ_{CDCl_3} *gem*-dimethyl s 1.00, $CH_3C(OCH_3)$ s 1.40, CH_3 aromatic s 2.47, 2 × CH_3O two 2 3.18 and 3.32, CHOTs d of d(10.0 and 7.0) 5.32, aromatic ABq (J_{AB} = 8.5 Hz) 7.70; *m/e* 451 (M+).

Anal. Calcd. for $C_{23}H_{33}O_6SN$: C, 61.2; H, 7.4; N, 3.1. Found: C, 61.3; H, 7.4; N, 3.2.

Cyclizations of Diketo-tosylate 10b

(a) 1-(2-Cyanoethyl)-4,4-dimethyl-7-acetobicyclo-[4.1.0]heptan-2-one (12)

To a methanolic solution of sodium methoxide (sodium (11.5 mg) in methanol (20 ml)), the diketo-tosylate **10b** (202 mg) is added and the mixture stirred at room temperature for 2.5 h. Chloroform extraction, after pouring the mixture into ice water, gives a clear oil (130 mg) which is chromatographed over alumina III. The benzene – 10% ether eluate is the substituted cyclopropane **12** (85 mg, 73%), m.p. 85–86°; λ_{max} 210 (8300) nm; ν_{KBr} 3060, 2260, 1703 (broad) cm^{-1}; δ_{CDCl_3} *gem*-dimethyl two s 0.90 and 1.00, CH_3CO s 2.33, *no* vinyl or aromatic protons; *m/e* 233 (M+), 218, 193, 191, 190, 176, 160, 151, 149, 148 (base). A sample is sublimed for analysis.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.2; N, 6.0. Found: C, 72.0; H, 8.1; N, 6.0.

This same product (**12**) is obtained by refluxing the tosylate **10b** and pyrrolidine in benzene with a Dean–Stark water separator.

(b) 9-Cyano-8-hydroxy-2-oxo-4,4,8-trimethyl-tricyclo[4.4.0.0^{1,7}]decane (13)

To a cold solution of sodium *t*-butoxide (sodium (18.6 mg) in *t*-butyl alcohol (20 ml)), is added the diketo-tosylate **10b** (325 mg) and stirring continued for 3 h at room temperature. The reaction is stopped by pouring into ice water and extracting with ether gives a viscous oil (219 mg) which crystallizes on contact with benzene to afford the spiro compound **13** (175 mg, 75%), m.p. 159–160°; ν_{KBr} 3410, 3045, 2265, 1685 cm^{-1}; δ_{CDCl_3} (90 MHz) *gem*-dimethyl two s 0.90 and 0.97, $CH_3C(OH)$ s 1.46, —CH—CN t (1.5) 2.62, no vinyl or aromatic protons; *m/e* 233 (M+) 218, 190, 177, 176, 134, 125 (base) 107, 106.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.2; N, 6.0. Found: C, 72.1; H, 8.1; N, 5.8.

Cyclization of Diketo-acetate 10c

Potassium (40 mg) is dissolved in *t*-butyl alcohol (30 ml) and to this solution is added the diketo-acetate **10c** (293 mg). After 12 h at 40° the reaction mixture is decomposed in ice water and the neutral products (202 mg) obtained by extraction. Chromatography over alumina III gave a *keto-nitrile* **14** (30 mg), m.p. 141–142°; ν_{KBr} 3390, 1740, and 1710 cm^{-1}; δ_{CDCl_3} *gem*-dimethyl two s 0.92 and 1.13, —CH(OH)— m 4.0 and s (broad) 3.25; *m/e* 210 (M+) 195, 182, 154, 149, 126 (base), 125, 110, and 109.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.5; H, 8.6. Found: C, 68.7; H, 8.7.

Other attempted cyclizations either gave back the starting material or in one case (concentrated hydrochloric acid in ethanol) hydrolyzed the product to the alcohol **10a**.

2-(2-Chloropropen-2-yl)-2-(2-cyanoethyl)-5,5-dimethylcyclohexa 1,3-dione (15a)

To a solution of cyanoethyldimedone **2a** (1.93 g) in dimethylformamide (distilled from sodium hydride) under nitrogen, is added sodium hydride – mineral oil (2 g). After warming at 60° for 17 h, 2,3-dichloropropene (5 ml) is added dropwise and heating continued for 6 h. The crude product obtained by extraction is chromatographed over alumina III affording the crystalline chloroalkene **15a** (1.34 g, 50%), m.p. 116–117° (from ether); ν_{KBr} 3120, 2260, 1730, 1700, 1645, and 900 cm^{-1}; δ_{CDCl_3} *gem*-dimethyl two s 0.84 and 1.21, $—CH_2—CCl=CH_2$ ABq (J_{AB} = 14.5 Hz) 2.74 and two s 5.32 and 5.47; *m/e* 269 and 267 (M+), 232, 231, 229, 227, 218, 201, 199.

Anal. Calcd. for $C_{14}H_{18}NO_2Cl$: C, 62.8; H, 6.8; N, 5.2. Found: C, 63.2; H, 6.7; N, 5.3.

NOTE: vacuum sublimation of **15a** gives the propargyl derivative **5a**.

2-(2-Chloropropen-2-yl)-2-(2-cyanoethyl)-3-hydroxy-5,5-dimethylcyclohexanone (15b)

The diketone **15a** (566 mg) is reduced with sodium borohydride (56 mg) in methanol (50 ml). The colorless oil obtained crystallizes on contact with ether to give the hydroxy-ketone **15b** (505 mg, 90%), m.p. 97–98°; ν_{KBr} 3440, 3010, 2260, 1690, 1645, and 900 cm^{-1}; δ_{CDCl_3} *gem*-dimethyl two s 0.95 and 1.14, $CH_2—CCl=CH_2$ ABq (J_{AB} = 14.5 Hz) 2.87 and s 5.42, —CH(OH)— m 4.35 and s 3.0.

Anal. Calcd. for $C_{14}H_{20}NO_2Cl$: C, 62.3; H, 7.5; N, 5.2. Found: C, 62.7; H, 7.6; N, 5.2.

Cyclizations attempted in concentrated sulfuric acid gave intractable products and refluxing in 97% formic acid afforded the *O-formate* **15c**, m.p. 122–123°; ν_{KBr} 2260, 1730, 1710, 1635, 1180, 1165, and 900 cm^{-1}; δ_{CDCl_3} very similar to **15b** but no OH proton, —OCHO s 8.14; *m/e* 299 and 297 (M+, weak) 262 (base), 211, 209, 190, 174, 134, 133, 132.

Anal. Calcd. for $C_{15}H_{20}O_3NCl$: C, 60.5; H, 6.8; N, 4.7. Found: C, 60.8; H, 6.8; N, 4.7.

2-Propargyl-2-(2-cyanoethyl)-5,5-dimethylcyclohex-3-enone (16a)

The hydroxy-ketone **8a** (2.33 g) is dissolved in pyridine (50 ml, freshly distilled from calcium hydride). After cooling to 0°, fresh phosphorous oxychloride (9 ml) is added and the solution allowed to warm to room temperature and then heated at 60° for 20 h. The reaction

mixture is poured very slowly into stirred ice water affording the crystalline unsaturated ketone **16***a* (1.46 g, 68%), m.p. 86–87°; ν_{KBr} 3260, 3030, 2260, 2120, 1715, and 780 cm^{-1}; δ_{CDCl_3} (90MHz) *gem*-dimethyl two s 1.06 and 1.10 —CH=CH— ABq (J_{AB} = 10.0 Hz) 5.7 (broadened by W coupling); *m/e* 215 (M+), 176, 173, 159, 158, 135 (base), 133, 132, 131, 119, 117, and 105.

Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.1; H, 8.1; N, 6.5. Found: C, 78.1; H, 8.0; N, 6.6.

NOTE: The yield in this elimination varied greatly with the duration of the reaction (19 h, 68%; 23 h, 45%; and 44 h, 20%) and the quality of the reagents. An alternative method employing tosyl chloride in pyridine (65° for 2 days) never gave more than 52% and then only after column chromatography (alumina III).

*2-Acetonyl-2-(2-cyanoethyl)-5,5-dimethylcyclohex-3-enone (**16***b*)

The triple bond in **16***a* (1.36 g) is hydrated as given above for **10***a* affording the methyl-ketone **16***b* (1.05 g, 71%) after column chromatography. Although pure, as shown by t.l.c., this product has never crystallized; ν_{KBr} 3020, 2260, 1715, 1705, and 1365 cm^{-1}; δ_{CDCl_3} (90MHz) *gem*-dimethyl two s 1.06 and 1.14, CH_3-$COCH_2$— s 2.09 and ABq (J_{AB} = 16.5 Hz) 2.75, ring —CH_2CO— ABq (J_{AB} = 14.5 Hz) 2.46, —CH≡CH— ABq (J_{AB} = 10.0 Hz) 5.63. To characterize this product the solid intermediate cyclic acetal is isolated (like **9** but double bond and no *O*-tosyl), m.p. 71–72°; ν_{KBr} 3010, 2260, 1075 cm^{-1}.

Anal. Calcd. for $C_{16}H_{25}O_3N$: C, 68.8; H, 9.0; N, 6.0. Found: C, 69.0; H, 9.0; N, 6.0.

Hydrolysis of this derivative affords the diketone **16***b* quantitatively.

*Cyclization of **19**b*

(a) With Potassium Hydroxide

Under nitrogen, the diketone **16***b* (0.7 g) is boiled in "previously boiled" water and a solution of potassium hydroxide (1.0 g) in "boiled" water (2.7 ml) is added. Refluxing is continued for 12 h and after cooling, diluting with water, salt, and ice the solution is extracted to remove a small quantity of neutral material (23 mg). Acidification of the aqueous solution at 0° and chloroform extraction affords the cyclized acid **17***a* (530 mg, from ether – petroleum ether), m.p. 87–88°; λ_{max} 233 (13 000) nm; ν_{KBr} 3300–2500 (broad), 3010, 1725, 1670, 1620 cm^{-1}; δ_{CHCl_3} 1710, 1688, and 1625 cm^{-1}; δ_{CDCl_3} *gem*-dimethyl two s 0.93 and 1.18, —$COCH_2$— ABq (J_{AB} = 18.0 Hz) 2.27, —CH_2—C(=CH)— s (broad) 2.53 and s (broad) 5.97, —CH=CH— ABq (J_{AB} = 9.5 Hz) 5.50, COOH s (broad) 9.9; *m/e* 234 (M+), 162, 161 (base), 133, 118, 117.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.8; H, 7.8. Found: C, 72.1; H, 7.8.

Treating the acid **17***a* with excess ethereal diazomethane at room temperature gave the *methyl ester* **17***b*, b.p. 97–98° at 0.03 nm; similar properties to the acid: ν_{film} 3010, 1738, 1710, 1625 cm^{-1}; *m/e* 248, 175, 162, 161 (base), 159, 133, 119, 117.

*(b) With Sodium Hydride (**18***a*, **17***c*, *and **19**)*

Under nitrogen, sodium hydride (275 mg; mineral oil suspension) is introduced into dimethoxyethane (50 ml, distilled from sodium hydride). After 20 min, the diketone **16***b* (1.4 g) in dimethoxyethane (15 ml) is added drop by drop. The solution becomes red and is stirred overnight at room temperature. Dilution with ice water and extraction gives a neutral fraction (660 mg) containing several products as shown by t.l.c. (see below). Acidification and extraction of the aqueous phase affords the unsaturated acid **18***a* ([6-(4,4-dimethyl)spiro[5.4]dec-2-en-8-on]ylidene acetic acid) as a yellow solid (541 mg) which is crystallized from petroleum ether – benzene and finally sublimed, m.p. 123–124°; λ_{max} 221(6900) nm; ν_{KBr} 3500–2500 (broad), 3030, 1745, 1690, 1660, 1613, 1268, and 1250 cm^{-1}; δ_{CDCl_3} *gem*-dimethyl two s 1.0 and 1.04, —CH_2—C(=CH—COOH ABq (J_{AB} = 13.0 Hz, allylic coupling 1 Hz) 2.3 and s (broad) 5.80, —CH=CH— ABq (J_{AB} = 9.5 Hz) 5.53; *m/e* 234, 216, 163, 160 (base), 145, 133, 132, 117, and 105.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.8; H, 7.4. Found: C, 71.3; H, 7.7.

The *methyl ester* **18***b* is prepared quantitatively using diazomethane.

The neutral fraction from the reaction above (660 mg) is chromatographed over neutral alumina (II). Elution with benzene gave an unidentified mixture (110 mg) but benzene–ether eluted the *nitrile* **17***c* (118 mg) which could not be induced to crystallize; λ_{max} 232 (13 250) nm: ν_{film} 3020, 2260, 1710, and 1625 cm^{-1}; δ_{CDCl_3} (90MHz) *gem*-dimethyl two s 0.94 and 1.20, —CH_2—CO— ABq 2.26, —CH_2—C(=CH— s (broad) 2.53 and s (broad) 5.98, —CH=CH— ABq (J_{AB} = 10.0 Hz) 5.28. Hydrolysis (6 h in 5% aqueous sodium hydroxide) afforded the acid **17***a*, m.p. 87–88° identical with the sample above.

Further elution (ether–chloroform) gives another *nitrile* **19** m.p. 114–115°; ν_{KBr} 3440, 3030, 2260, 1710, and 785 cm^{-1}; δ_{CDCl_3} *gem*-dimethyl two s 1.02 and 1.06, $CH_3C(OH)$—CH_2— s 1.51 and ABq (J_{AB} = 14.5 Hz) 2.03, —COC*H*—C(—OH s 2.35, —CH=CH— ABq (J_{AB} = 10.0 Hz) 5.73; *m/e* 233, 191 (base), 180, 165, 137, and 109.

Anal. Calcd. for $C_{14}H_{19}O_2N$: C, 72.1; H, 8.2; N, 6.0. Found: C, 72.2; H, 8.2; N, 6.0.

*2-Allyl-2-propargyl-5,5-dimethylcyclohexa-1.3-dione (**5b**)*

Prepared from 2-allyldimedone (**2***c*) (24 g) by essentially the method described above for **5***a*. The propargyl derivative crystallizes from *n*-pentane (25.8 g, 89%), m.p. 58–59°; ν_{KBr} 3290, 3080, 2115, 1718, 1680, 1638 cm^{-1}; δ_{CDCl_3} (90MHz) *gem*-dimethyl two s 0.96 and 1.11, HC≡C—CH_2— t(2.7) 1.92 and d(2.7) 2.62, —CH_2-CH=CH_2 d(7.1) 2.65, q of t(18.0, 8.0, 7.1) 5.55 and m(18.0, 8.0) 5.05; *m/e* 218 (M+), 203, 179, 177, 175, 135, 134 (base), and 121.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.0; H, 8.3. Found: C, 77.1; H, 8.3.

*2-Allyl-2-propargyl-3-hydroxy-5,5-dimethylcyclohexanone (**20**)*

Sodium borohydride (2.02 g) reduction of the diketone **5***b* (16.46 g) in methanol (150 ml) affords the crude hydroxy-ketone **20** (16.4 g, 98%) which from the n.m.r. spectrum and t.l.c. is a mixture of epimeric alcohols but

the equatorial isomer, the major product (4.04 g) crystallizes in part from ether – petroleum ether and the spectral and other characteristics quoted refer to this epimer, m.p. 75–76°; ν_{KBr} 3420, 3250, 2080, 2110, 1700, and 1640 cm^{-1}; δ_{CDCl_3} (90MHz) *gem*-dimethyl two s 0.89 and 1.08, $HC{\equiv}C{-}CH_2{-}$ t(2.5) 2.08 and d(2.5) 2.54, $-CH_2{-}CH{=}CH_2$ d(7) 2.56, q of t(18.0, 9.0, 7.0) 5.45, and m(18.0, 9.0) 5.1, $-CHOH$ d of d(10.5 and 6.5) 4.32; (in the crude product the axial hydroxyl $-CHOH$ gives d of d(6.5 and 6.0) 4.16).

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.3; H, 9.2. Found: C, 76.4; H, 9.3.

The *tosylate* was prepared in pyridine with tosyl chloride, m.p. 112–113° (from ether); ν_{KBr} 3280, 1710, 1640, 1600, 1192, and 1180 cm^{-1}.

Anal. Calcd. for $C_{21}H_{26}O_4S$: C, 67.4; H, 7.0. Found: C, 67.2; H, 7.0.

2-Propargyl-2-allyl-5,5-dimethylcyclohex-3-en-1-one (16c)

The keto-alcohol **20** (500 mg) is dissolved in pyridine (20 ml) and phosphorus oxychloride (2.07 ml) is added with vigorous stirring at room temperature. The mixture is then warmed at 57° for 46 h before cooling and pouring into ice water. After chloroform extraction (and removal of the pyridine by shaking several times with dilute hydrochloric acid, washing and drying) the unsaturated ketone **16c** (352 mg, 77%) is obtained as an oil; ν_{KBr} 3210, 3080, 3020, 1713, and 1640 cm^{-1}; δ_{CDCl_3} *gem*-dimethyl two s 1.03 and 1.09, $HC{\equiv}C$ t(2.7) 2.01, $-CH{=}CH_2$ m 5.6 and m 5.04, $-CH{=}CH-$ ABq (J_{AB} = 9.8 Hz) broadened by W coupling) 5.68.

Semicarbazone, m.p. 164–165° (dec.).

Anal. Calcd. for $C_{15}H_{21}N_3O$: C, 69.5; H, 8.2; N, 16.2. Found: C, 69.6; H, 8.2; N, 16.4.

8-Allyl-5,5-dimethylhydrinda-3,6-dien-2-one (17d) via 16d

The triple bond in **19c** is hydrated as described for **10a** affording the diketone **16d** in yields exceeding 90%; ν_{CHCl_3} 3080, 3005, 1720, 1710, 1360 cm^{-1}; δ_{CDCl_3} (90 MHz) *gem*-dimethyl two s 1.11 and 1.13, $CH_3COCH_2{-}$ s 2.07 and ABq (J_{AB} = 17.0 Hz) 2.44, $CH_2CH{=}CH_2$ d(7.1) 2.28, m 5.55 and m 5.0, ring CH_2CO ABq 2.41, $-CH{=}CH-$ ABq (J_{AB} = 10.0 Hz) 5.65; *m/e* 220 (M+), 205, 178, 177, 163, 162, 147, 138, 137 (base). This product (**16d**) was unstable and was normally cyclized immediately. The diketone **16d** (1.2 g) is refluxed for 15 h in a solution of potassium hydroxide (1.8 g) in water (36 ml) and methanol (10 ml). The clear liquid obtained (1.15 g) is purified by evaporative distillation (76–77° at 0.09 mm); λ_{max} 233 (14 200) nm; ν_{CHCl_3} 3080, 3010, 1705, 1670, and 1625 cm^{-1}; δ_{CDCl_3} (90MHz) *gem*-dimethyl 0.94 and 1.20, $-CH_2CO-$ ABq (J_{AB} = 18.0 Hz) 2.32, $-CH_2CH{=}CH_2$ d(7.0) 2.34, m 5.4 and m 5.0, $-CH_2-C(=CH-CO)$ s(broad, sharpens on irradiation at 5.90) 2.53 and s(broad) 5.90, $-CH{=}CH-$ ABq (J_{AB} = 10.0 Hz) 5.50; *m/e* 202 (M+), 162, 161 (base), 133, 118, 117, and 105.

Anal. Calcd. for $C_{14}H_{18}O$: C, 82.1; H, 9.0. Found: C, 82.4; H, 8.9.

2-Propargyl-2-carboethoxycyclohexanone (23a)

Potassium (4.12 g) is dissolved in *t*-butyl alcohol (150 ml) and to the refluxing solution under nitrogen is added 2-carboethoxycyclohexanone (17 g) and 30 min later propargyl bromide (13.1 g). After 30 min of reflux, the cooled solution is decomposed in ice water and ether extracted. Vacuum distillation gave the alkylated product **23a** (16 g, 77%), b.p. 74–77° at 0.1 mm; ν_{film} 3295 ($C{\equiv}C-H$), 2128 ($C{\equiv}C$), 1740, and 1710 (ester and ketone) cm^{-1}; δ_{CCl_4} CH_3CH_2O- t(7.2) 1.26 and q(7.2) 4.22, $H-C{\equiv}C-CH_2-$ t(2.7) 2.08 and ABq (J_{AB} = 17.3 Hz, split by $\equiv CH$, 2.7) 2.58. *Semicarbazone*, m.p. 152–153° (lit. (4) 152.7–153.5°).

Anal. Calcd. for $C_{13}H_{19}O_3N_3$: C, 58.9; H, 7.2; N, 15.8. Found: C, 59.2; H, 7.3; N, 15.5.

2-Propargyl-2-carboethoxy-4-methylcyclohexanone (23b)

Prepared from α-carboethoxy-4-methylcyclohexanone in 81% yield as described above, b.p. 72–74° at 0.1 mm; ν_{film} 3290, 2128, 1730, 1710, 1210 cm^{-1}; δ_{CCl_4} CH_3CH d(4.9) 1.05, CH_3CH_2O- t(7.2) 1.23 and q(7.2) 4.19, $H-C{\equiv}C-CH_2-$ t(2.5) 2.09 and ABq (J_{AB} = 17.3 Hz, split by $\equiv CH$, 2.5) 2.67.

2-Propargyl-2-carbomethoxy-4-methylcyclohexanone (23c)

The α-carbomethoxy-4-methylcyclohexanone (prepared using dimethylcarbonate (10)) was alkylated as described above affording the product **23c** in 86% yield after distillation, b.p. 94–98° at 0.5 mm; ν_{film} 3295, 2130, 1745, 1720, 1225 cm^{-1}; δ_{CCl_4} CH_3CH d(5.6) 1.07, $H-C{\equiv}C-CH_2-$ t(2.5) 2.04 and ABq (centered at) 2.78, CH_3O- s 3.75.

2-Acetonyl-2-carboethoxycyclohexanone (24a)

To the carboethoxypropargylcyclohexanone **23a** (16.0 g) in methanol (50 ml) is added water (1.5 ml) and concentrated sulfuric acid (0.05 ml). Dowex 50 W-X4 resin, previously treated with mercuric ions (8) (500 mg), is introduced and after warming for a few minutes the mixture is stirred overnight. The filtered solution is neutralized with ammonium hydroxide, dried over sulfate, evaporated, and filtered through a short silica gel column in benzene solution. After distillation (85–90° at 0.1 mm) the yield of methyl-ketone **24a** was 95% (16.5 g); ν_{film} 1733, 1708 cm^{-1}; δ_{CCl_4} CH_3CH_2O- t(7.2) 1.21 and q(7.2) 4.15, CH_3COCH_2- s 2.10 and s 2.79. *Bis-semicarbazone*, m.p. 220–221° (lit. 12) 214° (dec.).

Anal. Calcd. for $C_{14}H_{24}O_4N_6$: C, 49.4; H, 7.1; N, 24.7. Found: C, 49.7; H, 7.3; N, 24.5.

2-Acetonyl-2-carboethoxy-4-methylcyclohexanone (24b)

Prepared in 53% yield using Dowex resin (as above) or in 85% yield following the boron trifluoride – trichloroacetic acid procedure (see **24c** below), b.p. 92–96° at 0.1 mm, on standing the product **24b** finally crystallized, m.p. 64–66° (from pentane); ν_{KBr} 1735, 1708, 1238 cm^{-1}; δ_{CCl_4} CH_3CH d(4.8) 1.00, CH_3CH_2O- t(7.3) 1.21, and q(7.3) 4.12, CH_3COCH_2- s 2.12 and s 2.96.

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 65.0; H, 8.4. Found: C, 65.1; H, 8.4.

2-Acetonyl-2-carbomethoxy-4-methylcyclohexanone (24c)

To red mercuric oxide (7.8 g), anhydrous methanol (16 ml), boron trifluoride etherate (3.1 ml), and trichloro-

acetic acid (156 mg) is added the propargyl-keto ester **23c** (114 g) in methanol (250 ml) at a rate to ensure a mild reflux. The mixture is stirred for 2.5 h before pouring into water (1 l) and acidifying with sulfuric acid. The yellow oil obtained by extraction gave the crystalline product **24c** on standing (109 g, 88%), m.p. 102–103° (from methylene chloride – petroleum ether); ν_{KBr} 1745, 1715 cm^{-1}; δ_{CDCl_3} CH_3CH d(5.0) 1.06, CH_3COCH_2— s 2.23 and s 3.05, CH_3O— s 3.87.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.7; H, 8.0. Found: C, 63.6; H, 8.2.

9-Carboethoxyhydrind-1(8)-en-2-one (22c)

Prepared as described for **22d** in yields up to 70%. After silica gel chromatography: ν_{film} 1740–1700 (ester and ketone), 1625 (conjugated double bond), 850 (double bond) cm^{-1}; δ_{CCl_4} CH_3CH_2O— t(7.0) 1.22 and q(7.0) 4.19, CH_2COCH ABq centered at 2.36 and s 5.93. *Semicarbazone*, m.p. 216–217° (dec.).

Anal. Calcd. for $C_{13}H_{19}O_3N_3$: C, 58.8; H, 7.2; N, 15.8. Found: C, 58.7; H, 7.4; N, 15.4.

5-Methyl-9-carbomethoxyhydrind-1(8)-en-2-one (22d)

To a solution prepared by dissolving potassium (15.6 g) in *t*-butyl alcohol (600 ml) is added at room temperature, the solid powdered diketo ester **4c** (84.6 g) in several portions during 20 min. After stirring for 45 min the mixture is poured into ice water and acidified (p*H* 4) with concentrated hydrochloric acid. Extraction gave a neutral fraction, the enone **22d** (43.9 g) and an acid (24.2 g) arising from ring fission. The enone was distilled, b.p. 98–103° at 0.05 mm; λ_{max} (EtOH) 232 (13 600) nm; ν_{film} 1740–1710 (ester and ketone), 1630 (conjugated double bond) cm^{-1}; δ_{CCl_4} CH_3CH d(7.0) 1.00 (mixture of stereoisomers), CH_3O s 3.72, =CH— s 5.91. *Semicarbazone*, m.p. 205–206° (dec.).

Anal. Calcd. for $C_{13}H_{19}N_3O_3$: C, 58.8; H, 7.2; N, 15.8. Found: C, 58.7; H, 7.3; N, 15.2.

5-Methylhydrind-1(8)-en-2-one (22b)

Cyclization of the diketo ester **23b** (4.8 g) by refluxing with 5% aqueous sodium hydroxide (50 ml) for 6 h under nitrogen affords the unsaturated ketone **22b** (2.6 g, 87%) after extraction and chromatography (silica gel); λ_{max} (EtOH) 231 (16 400) nm; ν_{film} 1709, 1623, and 838 cm^{-1}; δ_{CCl_4} CH_3CH d(7.0) 1.00, =CH— s 5.81. *Semicarbazone*, m.p. 220–221°.

Anal. Calcd. for $C_{11}H_{17}N_3O$: C, 63.7; H, 8.3; N, 20.3. Found: C, 63.5; H, 8.5; N, 19.9.

8-Vinylhydrindan-2-one (5)

To tetrakis[iodo(tri-*n*-butylphosphine)copper(I)] (15.7 g, prepared by the method of Kauffmann (11)) dissolved in tetrahydrofuran (50 ml) and cooled to −78° is added vinyl lithium (0.08 mol) in tetrahydrofuran. After 10 min the enone **22a** (2.72 g) is added in tetrahydrofuran (15 ml) and the temperature allowed to rise to 0°. Stirring is continued for 1 h and the mixture is poured into saturated ammonium chloride solution, ether extracted, and carefully chromatographed (silica gel) to afford the vinylhydrindanone **25** (1.1 g, 34%); ν_{film} 3095 (vinyl), 1740, 1633, 993, and 911 cm^{-1}; δ_{CCl_4} CH_2=CH— d of d(1.5 and 17.3) 5.05, d of d (1.5 and 11.3) 5.10, and d of d(18.5 and 10.0) 5.98. *Semicarbazone*, m.p. 214–215°.

Anal. Calcd. for $C_{12}H_{19}N_3O$: C, 65.1; H, 8.6; N, 19.0. Found: C, 65.4; H, 8.6; N, 18.5.

Cyclohexa-1,2-dione-1-ethyleneketal (27a)

α-Ethylidenecyclohexanone (85 g, lit. (12)), ethylene glycol (80 g), and *p*-toluene sulfonic acid (1.5 g) are dissolved in benzene (400 ml) and refluxed 12 h in a Dean–Stark apparatus. The spiro-ketal **26a** is isolated in the usual manner (92 g, 80%), b.p. 39–42° at 0.1 mm; ν_{film} 1670 cm^{-1}; δ_{CCl_4} CH_3CH= d(7.2) 1.61 and q of t(7.2 and 1.8) 5.65, —OCH_2CH_2O— s 3.88.

The spiro-ketal **26a** (30 g) in pyridine (68 ml) and methylene chloride (136 ml) is cooled to −78° and ozone (~5% in oxygen) is bubbled into the solution until a blue coloration persists. The solution is allowed to warm to ambient and the solvents removed in vacuum. Distillation affords the keto-ketal **27a** (16.1 g), b.p. 45–50° at 0.1 mm; ν_{film} 1735 cm^{-1}; δ_{CDCl_3} —OCH_2CH_2O— s 3.97. *2,4-Dinitrophenylhydrazone*, m.p. 169–170° (lit. (13) 171°).

Anal. Calcd. for $C_{14}H_{16}N_4O_6$: C, 50.0; H, 4.8; N 16.7. Found: C, 49.8; H, 4.9; N, 16.3.

3,3-Dipropargylcyclohexa-1,2-dione-1-ethyleneketal (28a)

To sodium hydride (1.8 g) in benzene (50 ml) is rapidly added the ketal-ketone **27a** (6.24 g) and the mixture refluxed 1 h. After cooling to room temperature, propargyl bromide (4.8 g) is added dropwise and the reaction is allowed to stand overnight. After pouring into ice water and extracting, the mixture (seen by t.l.c.) is chromatographed over alumina III affording the dipropargyl compound **28a** (2.3 g) which eventually crystallized, m.p. 87–88°; ν_{film} 3280, 3270, 2120, 1718, 1200, 1108, and 1092 cm^{-1}; δ_{CCl_4} —CH_2—C≡CH ABq (J_{AB} = 17.0 Hz, split by ≡CH, 2.7) 2.66 and —OCH_2CH_2O— s 4.0.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.4; H, 6.9. Found: C, 72.7; H, 6.9.

Further elution gave mixtures of dipropargyl, monopropargyl, and starting material (600 mg).

Hydrogenation of the dipropargyl derivative **28a** over 10% palladium-on-carbon gave the *3,3-di-n-propylcyclohexa-1,2-dione-1-ethyleneketal* **28b** as a liquid after chromatography: ν_{film} 1715, 1200, 1109, and 1040 cm^{-1}; δ_{CCl_4} CH_3CH_2 m 0.94 (6H) and —OCH_2CH_2O— s 3.96 (4H).

3-Hydroxymethylenecyclohexa-1,2-dione-1-ethyleneketal (28c)

Very dry sodium methoxide (from sodium (16 g) is taken up in benzene (300 ml) and methyl formate (75 ml) is added. The mixture is stirred for 30 min and the addition of more benzene (300 ml) precedes the addition of the ketal-ketone **27a** (41.6 g). After 20 h the mixture is decomposed in ice water and hydroxymethylene **28c** is extracted into iced 2% potassium hydroxide in the usual manner. The distilled product (20.3 g, 41%; b.p. 73–74° at 0.2 mm) crystallized from pentane, m.p. 40–41°; ν_{film} 1715, 1643, 1585 cm^{-1}; δ_{CCl_4} —OCH_2CH_2O— m 4.13, =CHOH s 8.84 and s 13.78 (disappears on adding D_2O).

3-Propargylcyclohexa-1,2-dione-1-ethyleneketal (28e)

The hydroxymethylene **28c** (2.6 g) is added to potas-

sium *t*-butoxide (from potassium (0.55 g) in *t*-butyl alcohol (30 ml)) and after 10 min stirring, propargyl bromide (1.67 g) is added dropwise. The mixture is refluxed 1 h and then cooled, poured into ice cold dilute hydrochloric acid, and ether extracted. The crude product (1.65 g) is chromatographed over alumina III and the fraction eluted with carbon tetrachloride is the product **28***e* (1.01 g, 37%), m.p. 63–64°; ν_{KBr} 3270, 2120, 1725, and 1185, 1085, 1040 cm^{-1}; δ_{CCl_4} —CH—C=O m 2.79 and —OCH_2CH_2O m 3.99.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.3. Found: C, 68.1; H, 7.4.

3-Acetonylcyclohexa-1,2-dione-1-ethyleneketal (28g)

The propargyl derivative **28***e* (2.5 g) is hydrated using the Dowex resin method (see **4***a*) to give the liquid acetonyl-ketone **28***g* (1.5 g, 52%); ν_{film} 1730, 1714, 1195, 1113, and 1040 cm^{-1}; δ_{CCl_4} CH_3CO s 2.13 and —OCH_2-CH_2O— m 3.94. *Bis-semicarbazone*, m.p. 208–209° (dec.).

Anal. Calcd. for $C_{13}H_{22}N_6O_4$: C, 47.8; H, 6.8; N, 25.7. Found: C, 48.1; H, 6.9; N, 25.8.

2-Benzylidene-5-methylcyclohexanone

3-Methylcyclohexanone (13.4 g) and benzaldehyde (10.6 g) are added to a solution of sodium hydroxide (4.0 g) in water. The mixture is refluxed for 3 h and is allowed to stand at room temperature overnight. Extraction with methylene chloride which is washed, dried, and evaporated gives a viscous oil affording the benzylidene derivative (17.9 g, 89%) by distillation (b.p. 108–110° at 0.04 mm). The product crystallizes slowly, m.p. 41–42°; λ_{max} (EtOH) 290 (13 100) nm; ν_{KBr} 3060, 3040, 1685, and 1600 cm^{-1}; δ_{CDCl_3} CH_3CH d(7.2) 0.97, aromatic s (5H) 7.38 and =CH— s 7.50.

Anal. Calcd. for $C_{14}H_{16}O$: C, 84.0; H, 8.1. Found: 83.9; H, 8.1.

The residue from the distillation is taken up in methanol and on cooling affords a small quantity (0.49 g) of the *2,6-bisbenzylidene-3-methylcyclohexanone*, m.p. 118–119°; λ_{max} 316 (11 500) nm; ν_{KBr} 3100, 3020, 1668, 1610, 705, and 695 cm^{-1}; δ_{CDCl_3} CH_3CH d(7.2) 1.28, aromatic s 7.48, =CH— two s 7.70 and 7.83.

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.5; H, 7.0. Found: C, 87.6; H, 7.0.

4-Methylcyclohexa-1,2-dione-2-ethyleneketal (27b)

The benzylidene (from above, 89.5 g) is converted to the spiro-ketal **26***b* (79 g, 72% as described for **26***a*, m.p. 52–53°; λ_{max} 242 (14 250) nm; ν_{KBr} 3040, 1605, 1580, 1200, 1050, and 710 cm^{-1}; δ_{CDCl_3} CH_3CH d(7.2) 0.93, —OCH_2CH_2O— M 4.08, =CH— s 6.78 and aromatic s 7.34.

The benzylidene spiro-ketal **26***b* (24.4 g) in pyridine (100 ml) and methylene chloride (200 ml) is cooled in a Dry Ice – acetone bath and ozone (5% in oxygen) bubbled through the solution until the blue coloration persists (*ca.* 3 h). The solution is allowed to warm to room temperature, washed with 2% hydrochloric acid, sodium bicarbonate, and saturated sodium chloride, and evaporated. Distillation affords the ketal-ketone **27***b* (15.9 g, 93%), b.p. 71–72° at 0.35 mm; n_D^{23} 1.4651; ν_{film} 1735, 1200, 1050 cm^{-1}; δ_{CDCl_3} CH_3CH d(7.2) 1.05 and —OCH_2-CH_2O— m 4.00. The product was characterized as the semicarbazone but the spiro-ketal is also hydrolyzed under these conditions to give: *4-Methylcyclohexa-1,2-dionebis-semicarbazone*, m.p. 251–252°.

Anal. Calcd. for $C_9H_{16}N_6O_2$: C, 45.0; H, 6.7; N, 35.0. Found: C, 44.9; h, 6.8; N, 34.3.

3-Propargyl-5-methylcyclohexa-1,2-dione-1-ethylene-ketal (28f)

The hydroxymethylene **28***d* is prepared as described above (for **28***c*) in 81% yield. The product is normally used directly for the alkylation but a redistilled portion (b.p. 72–74° at 0.15 mm) was characterized: n_D^{27} 1.5095; λ_{max} 282 (8200) nm; ν_{1720}, 1660 and 1595 cm^{-1}; δ_{CDCl_3} CH_3CH d(7.2) 1.07, —OCH_2CH_2O— m 4.13, =CH—OH s 7.31 and s 8.92.

The crude hydroxymethylene **28***d* (46.4 g) is propargylated (as described for **28***c*) affording the alkylated product **28***f* (31.4 g, 76%) by distillation b.p. 85–86° at 0.13 mm, n_D^{24} 1.4879. Cooling affords a solid which is recrystallized from hexane with difficulty, m.p. 42–43°; ν_{KBr} 3300, 2130, 1735, 1200, and 1040 cm^{-1}; δ_{CDCl_3} CH_3CH d(7.2) 1.03, —OCH_2CH_2O— s 3.98.

3-Acetonyl-5-methylcyclohexa-1,2-dione-1-ethylene-ketal (28h)

The propargyl derivative **28***f* (5.2 g) is hydrated as described above for **23***a*. The reaction mixture is poured into ice – 2% sulfuric acid and extracted immediately. The crude product is chromatographed over alumina III to give the acetonyl compound **28***h* (5.2 g, 92%), m.p. 73–74°; ν_{KBr} 1735 (ketone adjacent to ketal), 1720, 1200, 1030 cm^{-1}; δ_{CDCl_3} CH_3CH d(7.2) 1.03, CH_3CO s 2.16, —OCH_2CH_2O— m 3.97.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.7; H, 8.0. Found: C, 63.9; H, 8.1.

6-Methylhydrind-3(9)-en-2,4-dione-4-ethyleneketal (29)

The diketo-ketal **28***h* (8.8 g) in *t*-butyl alcohol (50 ml) is added at room temperature to the solution resulting from dissolving potassium (1.72 g) in *t*-butyl alcohol (75 ml). After stirring for 1 h the reaction mixture is poured into ice water and extracted in the usual manner affording neutral (7.7 g) and acidic products (1.1 g). Chromatography of the former affords the pure enone **29** (4.3 g, 53%), m.p. 53–55°; λ_{max} 234 (13 200) nm; ν_{KBr} 1705, 1630, 1180, 1040 cm^{-1}; δ_{CCl_4} CH_3CH d(7.2) 1.06, —OCH_2CH_2O— s 3.92 and =CH— s 5.75. *Semicarbazone*, m.p. 207–208° (dec.).

Anal. Calcd. for $C_{13}H_{19}N_3O_3$: C, 58.8; H, 7.2; N, 15.8. Found: C, 58.7; H, 7.2; N, 15.9.

Hydrolysis of the ketal was tried using hydrochloric acid in tetrahydrofuran, a trace of perchloric acid in the same solvent, magnesium sulfate in benzene–water, and exchange with acetone catalyzed by *p*-toluene sulfonic acid. The last method afforded starting material and other methods gave no tractable products. Dilute aqueous hydrochloric acid gave the diketo-ketal **28***h* in almost quantitative yield (by hydration and retroaldolization presumably).

3-Allyl-5-methylcyclohexa-1,2-dione-1-ethyleneketal (28i)

The hydroxymethylene **28***d* (9.9 g) is alkylated with allyl bromide (7.5 g) in *t*-butyl alcohol containing potassium *t*-butoxide (as described in the propargylation to give **23***a*). The alkyl-ketone **28***i* (4.9 g, 47%) is obtained

by distillation, 72–76° at 0.04 mm; n_D^{23} 1.4790; ν_{film} 3080, 1645, 895 (=CH_2) and 1735, 1200, 1040 cm^{-1}; δ_{CCl_4} CH_3CH d(7.2) 1.00, —OCH_2CH_2O— m 3.98, CH_2=CH— complex 4.9 to 6.0.

This same compound resulted by hydrogenation of the propargyl derivative **28***f* (5.63 g) in acetone (50 ml) over Lindlar catalyst (800 mg) in the presence of quinoline (100 mg). Distillation gave the allyl compound **28***i* (5.01 g, 88%).

*3(2-Hydroxy-n-propyl)5-methyl-2-hydroxycyclohexanoneethyleneketal (**30**)*

Mercuric acetate (5.35 g) in water (17 ml) is diluted with tetrahydrofuran (17 ml). The allyl ketone **28***i* (3.5 g) is added and the coloration disappears in 15 s. After 5 min stirring, a solution (17 ml) of 0.5 *M* sodium borohydride in 3 *M* aqueous sodium hydroxide is added. The mixture is saturated with sodium chloride and benzene extracted. Evaporation affords the solid diol **30** (3.92 g, 93%), m.p. 131–132° (from acetone – petroleum ether); ν_{KBr} 3340, 1170, 1045 cm^{-1}; ν_{CCl_4} CH_3CH d(7.2) 0.93, CH_3CHOH— d(7.3) 1.24 and s 3.27, —CHOH— s 3.43, O*H* (2H) s 3.12 disappears on adding D_2O), OCH_2CH_2O m 4.10.

Anal. Calcd. for $C_{12}H_{22}O_4$: C, 62.6; H, 9.6. Found: C, 62.4; H, 9.5.

Sodium borohydride reduction of the diketone **28***h* affords this same diol **30** in 98% yield.

*Oxidation of Diol **30***

The ketal-diol **30** (10.7 g) dissolved in pyridine (100 ml) is oxidized with chromium trioxide (18.8 g) in pyridine (200 ml). The mixture is allowed to stand for 24 h and the dione **28***h* (8.4 g, 79%) isolated in the normal manner (identical with **28***h* prepared earlier).

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