on Raroporl 30, 100–120 mesh, 120°) showed that all the **7t** was converted to a single product, assigned the structure **2,3,4,5-tetramethyl-5-vinyl-2-cyclopentenone (8).** Pure **8** was collected by preparative VPC (5 ft × 0.25 in. column, 10% SE-30 on Chromosorb W, 80–100 mesh, 120°): ir ($CCl_4$) 1700 (s), 1650 (w), 1250 (m), 885 $cm^{-1}$ (s); uv $\lambda_{max}$ (MeOH) 237 nm (ε 8820); NMR ($CCl_4$) δ 1.0–1.2 (m, 6 H), 1.63 (q, 3 H, $J$ = 1 Hz), 1.90 (q, 3 H, $J$ = 1 Hz), 2.3 (m, 1 H), 4.6–5.8 (m, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 164 (85), 149 (100), 135 (49), 121 (60), 119 (20), 105 (38), 93 (30), 91 (29), 79 (25), 77 (23), 67 (25), 65 (15), 53 (26).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.47; H, 9.92.

Treatment of **8** (10 mg) with excess sodium methoxide in $CH_3OD$ for 5 hr at room temperature followed by work-up analogous to that used in the preparation of **8** from **7t** gave **8-$d_4$**, whose NMR spectrum consisted of two sharp singlets at δ 1.00 and 1.13 (3 H), a sharp singlet at 1.63 (3 H), and a vinyl proton multiplet at 4.6–5.8 (3 H).

**5-Trideuteriomethyl-2,3-epoxy-2,3,4,6-tetramethyl-4-vinyl-5-cyclohexenone (6*).** To a solution containing 145 mg (0.7 mmol) of a mixture of **6c** and **6t** (as obtained from epoxidation of **5**) in 5 ml of dimethyl sulfoxide-$d_6$ was added, with stirring and under $N_2$, 95 mg (0.85 mmol) of potassium *tert*-butoxide. The mixture was stirred at room temperature for 4.5 hr, then quenched with ice–water and extracted with ether. The combined organic layers were dried ($Na_2SO_4$) and the solvent was evaporated to give a nearly quantitative yield of **6***. The NMR spectrum was identical with that of the starting material, except that the peak at δ 1.67 was decreased in area by 50%.

**Acid-Catalyzed Rearrangement of 6*.** The procedure and work-up were as described for the treatment of **6c** and **6t** with trifluoroacetic acid. The recovered unreacted **6c*** had an NMR spectrum identical with that of pure **6c** except that the signal at δ 1.67 had sharpened and was reduced in area to only 3 H. The major rearrangement product **7t*** had an NMR spectrum identical with that of pure **7t** except that the signal at δ 1.60 was absent, and that at δ 1.67 had sharpened to a singlet. The amount of **7c*** collected was insufficient for an NMR spectrum.

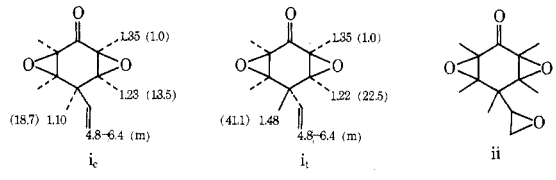
**Acid-Catalyzed Rearrangement of 6c.** A solution of pure **6c** (22 mg, recovered from the treatment of a mixture of **6c** and **6t** with trifluoroacetic acid at room temperature for 1 hr) in 0.5 ml of trifluoroacetic acid was allowed to stand at room temperature for 12 hr. There was no change in the NMR spectrum. The solution was then heated at 60° and the NMR spectrum gradually changed. After 7.5 hr the reaction was essentially complete and the solution was poured into a slurry of aqueous sodium bicarbonate and methylene chloride and worked up (vide supra). VPC (5 ft × 0.25 in. column, 10% SE-30 on Chromosorb W, 80–100 mesh, 135°) gave 15% recovered **6c** and 85% of a mixture (4:1) of **7t** and **7c** whose spectra (ir, NMR) were identical with those described above.

**Acknowledgment.** We are indebted to the National Institutes of Health for a grant (GM-15997) in support of this research.

**Registry No.**—$i_c$, 54277-18-8; $i_t$, 54353-09-2; ii, 54325-80-3; **5**, 54277-19-9; **6c**, 54325-81-4; **6t**, 54353-10-5; **7c**, 54277-20-2; **7t**, 54277-21-3; **8c**, 54277-22-4; **8t**, 54277-23-5.

## References and Notes

(1) H. Hart, I. Huang, and P. Lavrik, *J. Org. Chem.*, **39**, 999 (1974).
(2) For the mechanistic details of the latter process, including deuterium labeling experiments, see ref 1.
(3) H. Hart and M. Nitta, *Tetrahedron Lett.*, 2113 (1974).
(4) When excess *m*-chloroperbenzoic acid was used, di- and triepoxides of **5** were formed. The diepoxides were a mixture of $i_c$ and $i_t$ in which the two epoxide rings are cis to one another and either cis or trans to the vinyl group. There was no detectable amount of the isomer with the two epoxide rings trans to one another. The stereochemistry of the triepoxide ii is not known, though it seems probable that the two epoxide oxygens on the cyclohexanone ring are cis. Spectral properties of i and ii are given in the Experimental Section.



$i_c$ $i_t$ ii

(5) Chemical shifts are in δ units, with relative downfield shifts in the presence of Eu(fod)$_3$ given in parentheses; see D. R. Kelsey, *J. Am. Chem. Soc.*, **94**, 1764 (1972).
(6) H. Hart, M. Verma, and I. Wang, *J. Org. Chem.*, **38**, 3418 (1973).
(7) Insufficient **7c*** was isolated for spectral examination.
(8) NMR spectra were obtained on either a Varian Associates T-60 or HA-100 spectrometer; ir spectra were measured on a Unicam SP-200 spectrophotometer and were calibrated against a polystyrene film, uv spectra on a Unicam SP-800 spectrophotometer, and mass spectra at 70 eV on a Hitachi Perkin-Elmer RMU-6 spectrometer. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich., or Clark Microanalytical Laboratories, Urbana, Ill. Analytical gas chromatography (VPC) was done on a Varian Aerograph Model 1400 (flame ionization detector), and preparative VPC was done with a Varian Aerograph Autoprep Model 700 instrument (thermal conductivity detector).

# Generalized Syntheses of γ Diketones. I. Addition of Dimetalloacetylides to Aldehydes. II. Dialkylation of Bisdithianes[1a]

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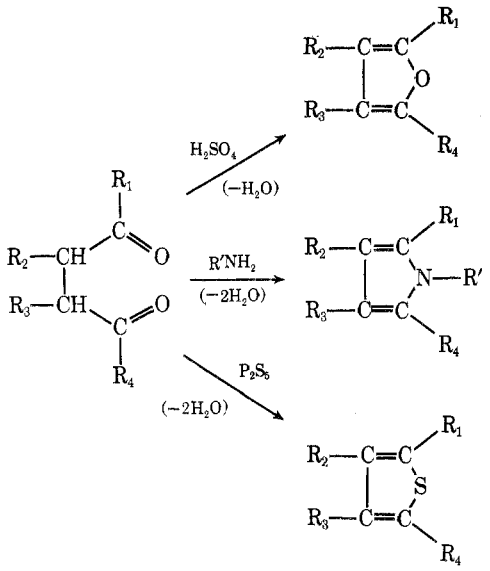
γ diketones are synthetically very useful but not generally accessible. Extensive preliminary studies revealed that the addition of dimetalloacetylides to aldehydes followed by catalytic reduction of the carbon–carbon triple bond and then oxidation of the saturated glycol to the diketone was one of the more promising approaches. The development of this method into a general, preparative procedure yielding a variety of 1,4 diketones in 20–60% overall yields is reported. The generality of application of the Corey–Seebach bisthio carbanions to the preparation of γ diketones via both single-step and stepwise dialkylations has also been examined. For the less reactive primary alkyl derivatives, the single-step approach and, for all other primary alkyl halides, the stepwise approach seem to offer the best general route to the target compounds. Thus this procedure is complementary to the dimetalloacetylide route which is superior when R is secondary or tertiary alkyl, and in which the bisthio carbanion approach generally fails. Many of the compounds made have not been reported heretofore.

γ diketones (1,4-dicarbonyl compounds) have great utility in organic synthesis, e.g., they readily undergo enolic dehydration and Knorr–Paal condensations to form furans, pyrroles, and thiophenes. Work carried out in this laboratory[2] has expanded the application of the Knorr–Paal pyrrole synthesis to produce a number of highly sterically

crowded heterocycles. However, the application of these syntheses is severely limited by the availability of appropriately substituted γ diketones.




Aromatic diketones, in which $R_1$ and $R_4$ are phenyl or substituted phenyl radicals, are fairly readily available by Friedel–Crafts acylation with the corresponding dicarboxylic acid chlorides.[3] However, the only commercially available γ diketone is the simplest possible aliphatic one, 2,5-hexanedione or acetonylacetone. The synthetic utility of the acetoacetic ester process by which this compound is made breaks down when applied to higher homologs. Cyclopentenones become the principal products instead of γ diketones.[4] Various methods have been reported in the literature for making a number of γ diketones, but these methods are usually quite cumbersome, often very limited in scope, and generally give only low yields of the desired products.[4] Therefore the work herein described was undertaken with the purpose of developing more general synthetic procedures for making γ diketones.

Initial efforts were directed toward ketone-forming reactions with dibasic acids, including succinic, fumaric, maleic, and acetylenedicarboxylic acids and their various derivatives.

(1) Addition of organometallic reagents to diesters at low temperature gave only very low yields of diketones in the presence of much unreacted starting material. The use of ferric chloride catalysis gave only slight increases in yield.

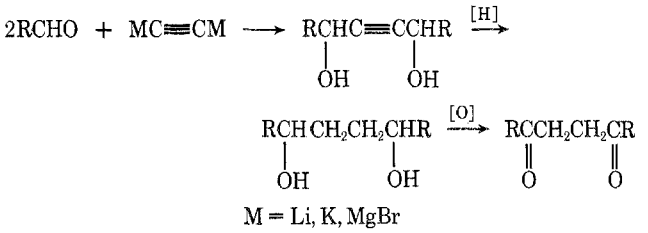
(2) Reaction of organolithium reagents with dicarboxylic acids resulted only in neutralization of the acids. Further reaction may have been prevented owing to insolubility of the intermediate salt.[5]

(3) Addition of organometallic reagents to dinitriles resulted only in formation of tars. No ketonic products could be isolated.

(4) Addition of organometallic reagents to dicarboxylic acid chlorides uder ferric chloride catalysis produces low yields of diketone accompanied by large amounts of lacetone by-product.[6] Isolation of the small amount of the desired product was impractical.

**I. Addition of Dimetalloacetylides to Aldehydes.** A potential, indirect route to γ diketones would be the condensation of acetylene with 2 mol of an aldehyde to give an acetylenic glycol. The glycol might then be hydrogenated to the saturated diol with subsequent oxidation producing the diketone. Only two reports were found in the literature in which this scheme had been tried. The preparation of 2,7-dimethyl-3,6-octanedione via acetylenebismagnesium bromide was reported in 1948 by Deemer, Lutwak, and Strong.[7] The overall yield of diketone was low since the acetylenic glycol was obtained in only 27% yield (purified) and after reduction and oxidation (yields not stated) the product was isolated only as the dioxime derivative. Using a similar procedure, Jones and coworkers[8] have reported a 48% yield of 4,7-decanedione starting with *n*-butyraldehyde. The only other reference to this synthetic scheme is the statement by Hunsdiecker[4] that γ diketones may be made this way but *"nur mit schlechter Ausbeute"*. No specific details were given.

We now report the development of the acetylenic glycol process on a preparative scale and the extension of it to prepare a variety of γ diketones as shown.




After our work was completed there has appeared recently[9] a paper reporting a 1,4-diketone synthesis of comparable generality and in approximately equivalent overall yields from organolithium reagents and *N,N,N'N'*-tetramethyldiamides at −78°. This procedure has the advantage of being a one-step rather than a three-step procedure, but also the disadvantage of requiring less accessible reagents. Furthermore, it is not necessary in the three-step procedure to purify the intermediates.

**Preparation of Acetylenic Glycols.** The preparation of acetylenic glycols from aldehydes and ketones has been discussed in several reviews.[10] Besides the bisbromomagnesium derivative of acetylene, glycols have been made from sodium, lithium, and potassium acetylides. The acetylenebismagnesium bromide reagent was the one used most extensively in our work.

This reagent was prepared by rapidly bubbling purified acetylene through ethereal ethylmagnesium bromide. It separates as a dark, oily, ether-insoluble phase by disproportionation of the initially formed monometallic derivative. The literature[11] suggests a 24–72-hr reaction period, but in our hands a 6–12-hr period gave equivalent results. Furthermore, the reagent could be formed as a gray, insoluble powder in benzene in 3–6 hr.

Dilithium acetylide was prepared by bubbling acetylene through either a solution of butyllithium or a solution of lithium metal in liquid ammonia. In the latter case the acetylide was isolated as a white powder. The dilithium compound is also commercially available from Alfa Chemicals, but only the in situ prepared ether suspension of the acetylide gave a successful reaction with aldehydes in our experience. The use of the isolated samples of the acetylide appeared to result in mostly aldol condensation products. Dipotassium acetylide was prepared by passing acetylene through a fine suspension of potassium hydroxide in diglyme or acetone dimethyl ketal.

The acetylenic glycols prepared according to the general scheme are shown in Table I. In most of the preparations of acetylenic glycols, the major by-products were those resulting from self-condensation of the aldehyde and from monoaddition of the acetylene derivative. The aldol condensation products were especially prominent with the low molecular weight, straight-chain aldehydes. Formation of these by-products may be inhibitable by using even slower rates of addition of the aldehydes, or by using solvents such

**Table I**
**1,4 Diketones via Dimetalloacetylides**

$$2RC{=}O + MC{\equiv}CM^{a-d} \longrightarrow RCHOHC{\equiv}CCHOHR \longrightarrow RCHOHCH_2CH_2CHOHR \longrightarrow RC(=O)CH_2CH_2C(=O)R$$

| R | Acetylenic glycol[e] % yield,[f] physical properties | Hydrogenated glycol[e] % yield,[f] physical properties | Ketone[e] % yield,[f] physical properties |
|---|---|---|---|
| Et | 32,[a,d] 72 (crude);[b] bp 90–95° (0.05 Torr) [lit.[h] bp 90–95° (1 Torr) | 44; bp 80–82° (0.7 Torr) [lit.[h] bp 101–102° (3 Torr) | 80 (18);[g] bp 45–50° (0.25 Torr) [lit.[j] bp 98° (14 Torr)] |
| *n*-Pr | 46;[a] bp 77–95° (0.05 Torr) [lit.[n] bp 113–114° (1 Torr)] | 96 (crude) | 44 (19);[g] mp 22–25° bp 62–64° (0.3 Torr), $N^{20}{}_0$ 1.4230 [lit.[o] bp 53.5° (0.1 Torr), $N^{20}{}_0$ 1.4230] |
| *i*-Pr | 68,[a] 22;[b] two white solid stereomers, mp 65–68°, 104–105° (lit.[k] mp 61–63°, 104–105°) | 97 (crude) | 95 (62);[g] bp 100–102° (9 Torr) [lit.[l] bp 100–102° (10–11 Torr)] |
| *t*-Bu | 31,[a] 22;[c] two white solid stereomers; mp 110.5–111°; 129–131° | 85; mp 160–165° (isomer mixture) | 96 (24);[g] mp 16–19° (lit.[m] mp 16.5–18°) |
| *n*-Hexyl | 50,[a] 38;[d] white, solid mixture of stereomers, mp 47–49° (lit.[p] mp 47–49°) | 99, mp 74–89° (isomer mixture) (lit.[p] mp 85–86° and 105–106°) | 92; mp 67–68° |
| Ph | 35;[a] white solid mixture of stereomers, mp 132–135° (lit.[q] mp 129–130°) | 100; mp 89–99° (isomer mixture) (lit.[r] mp 90° and 113°) | 70 (24);[g] mp 142–143° (lit.[s] mp 143–144°) |
| Cyclohexyl | 32,[a] 31;[d] white, solid mixture of stereomers, mp 102–106°; after separation by recrystallization, mp 100.5–102.5, 126.2–127.2° | 96; two stereomers, mp 149.2–149.8° and 186–186.5° | 95 (29);[g] bp 17–171° (1 Torr) |

[a] BrMgC≡CMgBr (ether). [b] LiC≡CLi. [c] KC≡CK. [d] BrMgC≡CMgBr (benzene). [e] Spectral and analytical data for new compounds are provided in the Experimental Section. [f] Percentage yield in the individual step if the intermediate was isolated. [g] Overall yield without purifying intermediates based on the amount of magnesium originally employed in formation of the ethylmagnesium bromide used in making the acetylide. [h] W. J. Doran and E. M. Van Heyningen, U.S. Patent 2,561,688 (1951). [j] E. E. Blaise, *C. R. Acad. Sci.*, **158**, 504 (1914). [k] Cf. ref 7. [l] A. Spassoff, *Bull. Soc. Chim. Fr.*, 4, 1658 (1937). [m] W. A. Brown and G. T. Wright, *Can. J. Chem.*, **35**, 236 (1957). [n] C. S. Marvel and W. W. Williams, *J. Am. Chem. Soc.*, **61**, 2714 (1939). [o] D. Chakravarti, N. K. Rorp, A. Chakravarti, and V. Sarkar, *J. Indian Chem. Soc.*, **44**, 463 (1967). [p] Y. Zal'kind and V. J. Tzereshkv, *J. Gen. Chem. USSR*, **5**, 1768 (1925); *Chem. Abstr.*, **30**, 3408 (1936). [q] Cf. ref 8. [r] R. E. Lutz and J. S. Gillespie, Jr., *J. Am. Chem. Soc.*, **72**, 344, 2002 (1950). [s] J. B. Conant and R. E. Lutz, *J. Am. Chem. Soc.*, **45**, 1303 (1923).

as chloroform or dichloromethane in which the acetylene-bismagnesium bromide is reported to be soluble. The acetylenic carbinol by-products are probably formed from some of the mono compound, acetylenemagnesium bromide, which did not disproportionate. It should be noted here that care must be exercised in the handling of any acetylenic carbinols since at least two of them, 1-hexyn-3-ol and 4-ethyl-1-octyn-3-ol, are known to be toxic when inhaled or absorbed through the skin.[12]

**Hydrogenation of Acetylenic Glycols.** The triple bonds of the acetylenic glycols were conveniently hydrogenated in the presence of common catalysts such as platinum, palladium, or nickel.

Reduction in ethanol at 60 psi generally took place rapidly and cleanly, giving the desired product after filtration and evaporation of solvent. In the case of the sterically hindered glycol, 2,2,7,7-tetramethyl-4-octyne-3,6-diol, the hydrogenation reaction was somewhat slower and required 2 hr for the theoretical uptake of hydrogen. Also some side reactions were evidenced with some of the lower molecular weight compounds, principally owing to hydrogenolysis. Efforts to reduce this side reaction by hydrogenating the acetylene glycol diacetate gave only marginal improvements.

**Oxidation of γ Dialcohols.** A wide variety of oxidizing agents are known that are capable of converting secondary alcohols to ketones, but not all are applicable to a bifunctional system or a system containing easily oxidizable carbon atoms bearing tertiary hydrogens. Deemer, Lutwak, and Strong[7] used a two-phase system consisting of benzene and an aqueous solution of sodium dichromate, sulfuric acid, and acetic acid for the oxidation of 2,7-dimethyl-3,6-octanediol. We investigated this oxidation procedure, but regularly obtained major amounts of a ketonic by-product of undetermined structure (C=O absorption at 1775 $cm^{-1}$), e.g., reaction of 2,7-dimethyl-3,6-octanediol gave a mixture with diketone to by-product ketone ratio of 1.6:1. The Jones procedure[8] likewise proved to be unsatisfactory, yielding a 2.7:1 ratio of the two products from the same diol.

Ultimately the Sarett procedure[13] as modified by Cornforth[14] and further by Collins[15] proved to be the cleanest even for alcohols containing no tertiary hydrogen, and so it was employed in all cases. The diketones thus obtained are listed in Table I. The low yield of 3,6-octanedione is ascribed to losses due to volatility whereas that of 4,7-decanedione reflects a 50% loss due to hydrogenolysis to 4-decanone in the reduction step.

**Table II**
**1,4-Diketones via Bis(*m*-dithianes)**

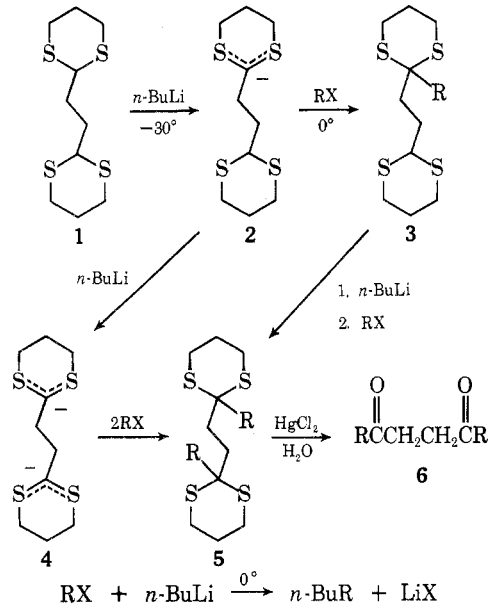
| | R | Dithane (5) Yield (1 → 5), % | Dithane (5) Mp, °C | Diketone (6), overall yield (1 → 6) %, physical properties |
|---|---|---|---|---|
| Single-step dialkylation (1 → 5) and subsequent hydrolysis | Et | 54 | 130–131[c] | 46[d] |
| | *i*-Pr | *a* | *a* | 50[b,d] |
| | *n*-Bu | 54 | 79.5–81[c] | 49 (78[b]), mp 48–49°[c] |
| Stepwise dialkylation (1 → 5) and subsequent hydrolysis | *n*-Pr | 79 | 121.5–123.5[c] | 68[d] |
| | *i*-Pr | 43 | 109–110[c] | 40[d] |
| | $PhCH_2$ | 57 | 133.5–135[c] | 52 mp 63–64° (lit.[e] mp 64–65°) |
| | *i*-Bu | 62 | 84–85.5[c] | 49[f] |
| | *i*-$BuCH_2$ | *a* | *a* | 77[b,c] mp 32–34°[c] |

[a] Solid, purified compound not isolated. [b] Unpurified intermediate hydrolyzed directly. [c] Spectral and analytical data for new compounds are provided in the Experimental Section. [d] Physical properties same as those of material reported in Table I. [e] D. Ivanov and N. Marekov, *Annu. Fac. Sci. Nat. Univ., Skopje, Math. Phys. Chim.*, **47**, 41 (1952); *Chem. Abstr.*, **48**, 10591 (1954); *Chem. Zentr.*, 9087 (1955). [f] Characterized by GC, ir, and NMR. Previously reported by O. Dann, E. Pietschmann, and W. Dimmling, *Arch. Pharm. (Weinheim)*, **292**, 508 (1959).

**II. Dialkylation of Bisdithianes.** In 1965 Corey and Seebach[16] reported a method for thioacetalization of aldehydes with 1,3-propanedithiol. Alkylation of the substituted *m*-dithianes thus obtained followed by hydrolysis led to ketones. That this approach likewise offers promise as a route to diketones was established by the synthesis of 1,4-cycloheptanedione.[17]

We report herein our study on the generality and utility of this approach to the synthesis of symmetrical acyclic γ-diketones via dialkylation of 2,2′-ethylenebis(*m*-dithiane) (**1**), a substance we had already been investigating ourselves in a related connection[18] prior to the appearance of the Corey papers.

Dialkylation might be carried out by successive monoalkylations, each requiring ionization of the intermediate bis(*m*-dithiane) followed by treatment with the alkylating agent (route **1** → **2** → **3** → **5**), or, in an operationally simpler alternative, by adding 2 equiv of the ionizing base (*n*-butyllithium) all at once followed by 2 equiv of alkylating agent (route **1** → (**4**) → **5**). The success of the latter approach would depend, of course, either on the possibility of generating the dianion (**4**) directly, or, more likely, the ability of the excess alkylating agent to survive attack by the second equivalent of ionizing base to form **7** while the first alkylation step on the monoanion (**2**) was in progress. The second alkylation step (**3** → **5**) could then proceed in the same manner as the first.




The progress of the reaction was conveniently followed by NMR spectrometry. The NMR absorption of the two methine protons in 2,2′-ethylenebis(*m*-dithiane) occurs as a multiplet at δ 4.05 whereas methylene protons adjacent to sulfur atoms resonate at δ 2.8 ppm. Thus monoalkylation is accompanied by a decrease in the ratio of methine to the above-mentioned methylene protons from 1:4 to 1:8, and complete dialkylation results in the disappearance of the methine proton resonances altogether.

The deprotonation (metalation) was initially carried out using 2 equiv of *n*-butyllithium at −30°; then 2 equiv of alkyl halide was added at −5° followed by a 3-day period at 0° for completion of the reaction. Under these conditions the results in Table I were obtained from the first three alkyl halides tried. It is evident that single-step dialkylation was successfully accomplished in these instances in preparatively acceptable yields.

However, when the more reactive alkylating agent benzyl bromide was employed under the same conditions, only the monalkylated crystalline intermediate bis(*m*-dithiane) (**3**) could be obtained; none of the dialkylated product (**5**) was found. A significant amount of the side-product, 1-phenylpentane (**7**), was also isolated.

The extent of ionization of **1** under the reaction conditions was then determined by quenching a solution of the anion in deuterium oxide. The NMR spectrum of the recovered product revealed that just one-half of the methine protons had been replaced, indicating that only the monoanion, **2**, had formed in significant amounts. Doubling the amount of *n* butyllithium (4:1 base-substrate ratio) resulted in a 75% deuteration upon quenching, suggesting that the dianion **4** is formed to some extent in the presence of excess *n*-butyllithium.

Therefore, successful single-step dialkylation in the three cases reported in Table II must have occurred, because ionization of the second methine proton and subsequent coupling with the alkyl halide were faster than direct nucleophilic displacement on the halide by *n*-butyllithium, but the converse is true with benzyl bromide.

Accordingly, stepwise dialkylation was employed in the remainder of the reactions studied. Analysis of the initially formed anion demonstrated that **2** was quantitatively formed in the presence of only 1 mol of base.

Stepwise alkylations with isopropyl iodide and benzyl

bromide were carried out for comparison with the single-step approach. In addition three additional stepwise dialkylations were done. The results are recorded in Table II.

All attempts at alkylation with tertiary and secondary halides, including *tert*-butyl chloride, *tert*-butyl bromide, 2-bromobutane, 2-iodooctane, and cyclopentyl iodide, failed with the single exception of isopropyl iodide, presumably owing to precedence of direct β-elimination of HX from the halides.

In summary, the synthesis of γ diketones of the type $RCOCH_2CH_2COR$ via dialkylation of 2,2′-ethylenbis(*m*-dithiane) appears to be preparatively successful for primary alkyl halides and isopropyl halide. Furthermore, overall yields for the same product are superior to those obtained via the dimetalloacetylide procedure while at the same time being more convenient and less time consuming. The bis(*m*-dithiane) approach should also be readily amenable to the synthesis of unsymmetrical diketones via stepwise alkylation.

Finally, it should be noted that the two methods nicely complement each other since the dimetalloacetylide process succeeds when R = aryl, secondary alkyl, and tertiary alkyl whereas the bis(*m*-dithiane) approach does not.

All the dialkylated bis(*m*-dithianes) reported here, four of the intermediate glycols, and four of the γ diketones (5,8-dodecanedione,[19] 2,11-dimethyl-5,8-dodecanedione, 7,10-hexadecanedione, and 1,4-dicyclohexyl-1,4-butanedione) are new compounds. Spectral (ir and NMR) and analytical data were obtained consistent with the assigned structures for all compounds reported.

## Experimental Section

**Starting Materials. Tetrahydrofuran** (THF) was refluxed overnight over excess-powdered $LiAlH_4$ and then distilled off the $LiAlH_4$ just prior to use.[20]

***n*-Butyllithium** (commercial, Foote or Alfa) in hexane solution was used as received.

**Alkyl bromides and iodides** were prepared from the corresponding alcohols using HBr and $H_2SO_4$, constant-boiling HI, or phosphorus and iodine. The Corey and Anderson *o*-phenylene phosphate method[21] proved to be more cumbersome and gave lower yields. The halides were dried over $CaCl_2$ and distilled prior to use.

**2,2′-Ethylenebis(*m*-dithiane) (1)** was prepared basically as described in the literature[17] in 80–90% yields. Carbon tetrachloride was found to be much superior as the recrystallizing solvent to the chloroform–methanol solvent reported, giving a higher purity product, mp 135–136° (lit.[17] 132–135°).

**Preparation of Acetylides. Preparation of Acetylenebismagnesium Bromide.** In a typical run a solution of ethylmagnesium bromide in ether was prepared from 24 g (1.0 g-atom) of magnesium turnings and 109 g of ethyl bromide. The solution was stirred rapidly under nitrogen at room temperature while a stream of purified acetylene[22] was then introduced into the liquid via a long dropper tube. After 6–12 hr of treatment with acetylene (depending upon the rate of addition), the acetylenebismagnesium bromide separated out as a dark, viscous, ether-insoluble oil. Anhydrous ether had to be added periodically to maintain the volume unless a Dry Ice condenser was employed. The addition of acetylene was continued until hydrolysis of an aliquot of the supernatant liquid formed only a negligible amount of base as determined by titration.[23]

In the case in which benzene solvent was used, the ethyl Grignard reagent was prepared in the usual manner, and the bulk of the ether was distilled off. An equal volume of dry benzene was then added, and the acetylene treatment was carried out as described above. The use of benzene cut the reaction time to approximately 3–5 hr. The acetylenebismagnesium bromide separated as a gray, powdery suspension rather than as an oil.

**Preparation of Dilithium Acetylide.** Purified acetylene was bubbled rapidly for 2 hr through a stirred mixture of 100 ml of 1.6 *M* commercial hexane solution of *n*-butyllithium (Alfa) and 150 ml of anhydrous ether, additional ether being added to compensate evaporation losses. During this time the solution turned a milky white. The mixture was stirred for several more hours to complete reaction and to allow for disproportionation of any monolithium acetylide.

**Preparation of Dipotassium Acetylide.** A *p*-dioxane suspension was prepared from KOH and acetylene.[24]

**Preparation of Acetylenic Glycols.** The following example is illustrative. Pivalaldehyde (0.2 mol) in 10 ml of anhydrous ether was added dropwise to an excess of the acetylenebismagnesium bromide prepared as described above and the yellow suspension was allowed to stand for 36 hr at room temperature. Hydrolysis was accomplished by cooling and stirring with 30 ml of saturated aqueous $NH_4Cl$. The ether layer was decanted, the gray precipitate was washed further, and the combined ether portions were evaporated to leave 11.2 g of moist solid. Titration with petroleum ether left 4.8 g of the acetylenic glycol (2,2,7,7-tetramethyloct-4-yne-3,6-diol). Several more crops were obtained by concentrating the mother liquor and chromatography on alumina to give a total yield of 6.15 g (31%) of mixed stereomers: mp 111–118°; ir (KBr) 3240 (s, broad, H-bonded OH), 1120, 1080, 1010 (all s), and 1385, 1360 $cm^{-1}$ (m, *t*-Bu); NMR ($CDCl_3$) δ 4.05 (m, 1, CHOH), 2.63 (m, 1, OH), and 1.00 ppm [s, 9, $C(CH_3)_3$].

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.52; H, 11.46.

**1,4-Dicyclohexyl-2-butyne-1,4-diol** was a mixture of stereomers: mp 102–106°; ir (KBr) 3250 (s, broad, H-bonded OH), 1140 (m), 1070 $cm^{-1}$ (s); NMR ($CDCl_3$) δ 4.19 (m, 1, CH), 3.10 (m, 1, OH), and 1.45 ppm (m, 11, cyclohexyl).

Anal. Calcd for $C_{16}H_{26}O_2$ (higher melting stereomer, mp 126.2–127.2°): C, 76.75; H, 10.47. Found: C, 77.01; H, 10.46.

**Hydrogenation of Acetylenic Glycols.** The general procedure followed is illustrated by the following example. Two grams (0.01 mol) of 2,2,7,7-tetramethyloct-4-yne-3,6-diol (stereomeric mixture) dissolved in 50 ml of 95% EtOH was shaken under 4 atm of $H_2$ until the theoretical uptake was complete (2 hr). (Analysis of an aliquot after 45 min showed the presence of olefinic hydrogen atoms in the NMR spectrum). Crystallization from the filtered solvent yielded 1.7 g (84%) of **2,2,7,7-tetramethyloctane-3,6-diol:** mp 160–165°; ir (KBr) 3340 (s, broad, H-bonded OH), 1075 (s, secondary OH), and 1390, 1355 $cm^{-1}$ (m, *t*-Bu).

Anal. Calcd for $C_{12}H_{26}O_2$: C, 71.23; H, 12.95. Found: C, 71.44; H, 12.79.

**1,4-Dicyclohexyl-1,4-butanediol:** ir (KBr) 3330 (s, broad, H-bonded OH), 1080 (m), 1060, 1040, 985 $cm^{-1}$ (all s).

Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89. Found: C, 75.78; H, 11.62.

**Oxidation of the Saturated Diols.** The following is illustrative of the oxidation reactions. For each 0.1 mol of diol to be oxidized a solution was prepared by adding 62 g of $CrO_3$ dissolved in 62 ml of $H_2O$ to 620 ml of reagent-grade pyridine at 0°. To this solution the alcohol in enough additional pyridine to dissolve it was added with swirling, and the mixture was allowed to stand at room temperature for 1–5 days. The reaction mixture was then poured into a threefold volume of water and extracted several times with ether. After concentrating the extract by evaporation, it was washed with dilute aqueous HCl until no further reaction, then dried and evaporated. In a specific instance 4.0 g (0.016 mol) of 1,4-dicyclohexyl-1,4-butanediol in 60 ml of pyridine was oxidized in 3.5 days to produce 3.7 g (95%) of **1,4-dicyclohexyl-1,4-butanedione:** bp 170–171° (1 Torr); ir (film) 1700 $cm^{-1}$ (ketonic C=O, no evidence of lactone); NMR ($CCl_4$) δ 2.7 (s, 4, $CH_2C{=}O$), 2.4 (m, 2, CH), and 1.5 ppm (m, 20, cyclohexyl $CH_2$).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 77.03; H, 10.50

**7,10-Hexadecanedione:** mp 68.2–69°; musty, slightly sweet odor; ir (KBr) 1690 $cm^{-1}$ (s, C=O); NMR ($CCl_4$) δ 2.55 (s, 2, $-COCH_2CH_2CO-$), 2.4 (t, 2, $-COCH_2CH_CH_2CH-$), 1.3 (m, 8, $CH_2-$), 0.9 ppm (t, 3, $CH_3$).

Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89. Found: C, 75.65; H, 11.95.

**Single-Step Dialkylation (1 → 5). General Procedure.** In a typical reaction 6.1 g (0.023 mol) of 2,2′-ethylenebis(*m*-dithiane) dissolved in 150 ml of THF was placed under dry nitrogen atmosphere in a stirred reaction flask and cooled to −30° with a Dry Ice–isopropyl alcohol bath. Then 2 molar equiv (35 ml, a sight excess) of 1.6 *M n*-butyllithium in hexane was added dropwise from a syringe over a 10-min period. Stirring was continued for 3 hr at −20 to −30°, during which time a deep orange solution formed.

The temperature was then allowed to rise to −5° and 0.055 mol of the halide dissolved in 50 ml of THF was added dropwise at that temperature, during which time the solution color changed to light

yellow. After allowing the reaction mixture to stand at 0° in a refrigerator for 3 days, it was quenched with several milliliters of water, concentrated to ca. 50 ml, diluted with 150 ml of water, and extracted three times with ether, pentane, or $CH_2Cl_2$. The combined extract was washed with saturated aqueous NaCl, dried over anhydrous $K_2CO_3$, and evaporated. The product, usually obtained as an off-white solid or slowly crystallizing oil, was further purified by trituration with ether or recyrstallization from acetone or $CCl_4$.

**2,2'-Ethylenebis(2-ethyl-*m*-dithiane):** NMR ($CCl_4$) $\delta$ 2.80 (m, 4, $SCH_2$), 1.90 (m, 6, $SCCH_2$), and 1.01 ppm (t, 3, $CH_3$).

Anal. Calcd for $C_{14}H_{26}S_4$: C, 52.12; H, 8.12. Found: C, 52.02; H, 8.19.

**2,2'-Ethylenebis(2-*n*-butyl-*m*-dithiane):** NMR ($CDCl_3$) $\delta$ 2.80 (m, 4, $SCH_2O$, 1.67 (m, 10), and 0.93 ppm (t, 3, $CH_3$).

Anal. Calcd for $C_{18}H_{34}S_4$: C, 57.09; H, 9.05. Found: C, 57.21; H, 9.28.

**Stepwise Dialkylation (1 → 2 → 3 → 5). General Procedure.** A solution of the monanion, 2-lithio-2,2'-ethylenebis(*m*-dithiane), was prepared following the same procedure given above except that only 1 molar equiv of *n*-butyllithium was used. After a 3-hr period at −20 to −30° the mixture was allowed to warm to −5°, and a solution of 1 molar equiv of alkyl halide in THF was added. The solution was stirred for 1 hr at 0°, then cooled again to −30° and the sequence repeated with another molar equivalent of base and halide. After storing the mixture for 3 days at 0°, it was worked up as in the procedure above.

**2,2'-Ethylenebis(2-*n*-propyl-*m*-dithiane):** analytical sample mp 123.9–124.4°; NMR ($CDCl_3$) $\delta$ 2.87 (m, 4, $SCH_2$), 2.12 (s, 2 $SCCH_2CH_2CS$), 1.73 (m, 6), and 0.95 ppm (t, 3, $CH_3$).

Anal. Calcd for $C_{16}H_{30}S_4$: C, 54.80; H, 8.62. Found: C, 54.84; H, 8.62.

**2,2'-Ethylenebis(2-isopropyl-*m*-dithiane):** NMR ($CDCl_3$) $\delta$ 2.8 (m, 4, $SCH_2$), 2.25 (s, 2, $SCCH_2CH_2CS$), 2.0 (m, 3, SCCH, secondary and primary), and 1.15 ppm [d, 6, $-CH(CH_3)_2$].

Anal. Calcd for $C_{16}H_{30}S_4$: C, 54.80; H, 8.62. Found: C, 54.67; H, 8.61.

**2,2'-Ethylenebis(2-isobutyl-*m*-dithiane):** mp 86.8–87.9° (analytical sample); NMR ($CDCl_3$) $\delta$ 2.83 (m, 4, $SCH_2$), 2.18 (s, 2, $SCCH_2CH_2CS$), 1.90 (m, 5), and 1.04 ppm [d, 6, $CH(CH_3)_2$].

Anal. Calcd for $C_{18}H_{34}S_4$: C, 57.09; H, 9.05. Found: C, 57.00; H, 9.15.

**2,2'-Ethylenebis(2-benzyl-*m*-dithiane):** mp 137.2–137.8° (analytical sample); NMR ($CDCl_3$) $\delta$ 7.26 (s, 5, $C_6H_5$), 3.10 (s, 2, $PhCH_2$), 2.83 (m, 4, $SCH_2$), 2.18 (s, 2, $SCCH_2CH_2CS$), and 1.92 ppm (m, 2, $SCCH_2$).

Anal. Calcd for $C_{24}H_{30}S_4$: C, 64.52; H, 6.77. Found: C, 64.79; H, 6.85.

**Hydrolysis of 2,2'-Ethylenebis(2-alkyl-*m*-dithianes) (5). General Procedure.** Following essentially the procedure of Seeach, Jones, and Corey[17] a mixture of 1.16 g of $HgCl_2$, 0.36 g of HgO, 1.5 ml of $H_2O$, and 25 ml of MeOH for each millimole of substrate was refluxed for 4–5 hr while vigorously stirring with a Vibro Mixer (Chemie-Apparatebau, Zurich). After cooling, filtering, and concentrating the organic phase, it was diluted with water, extracted with $CH_2Cl_2$, dried, and evaporated to yield the desired diketone, which could be used as such in Knorr–Paal type procedures or further purified by crystallization.

**5,8-Dodecanedione:** ir (KBr) 1695 $cm^{-1}$ (s, C=O); NMR ($CDCl_3$) $\delta$ 2.57 (s, 2, $O{=}CCH_2CH_2C{=}O$), 2.40 (t, 2, $COCH_2CH_2C$), 1.43 (m, 4, $CH_2$), and 0.9 ppm (t, 3, $CH_3$).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.93; H, 11.42.

**2,11-Dimethyl-5,8-dodecanedione:** bp 92° (0.3 Torr); ir 1705 $cm^{-1}$ (s, C=O); NMR ($CDCl_3$) $\delta$ 2.67 (s, 2, $COCH_2CH_2CO$), 2.43 (t, 2, $COCH_2$), 1.50 (m, 3, $-CH_2CH<$), and 0.9 ppm [d, 6, $CH(CH_3)_2$].

Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.13; H, 11.31.

**Registry No.**—1, 14947-53-6; **5** (R = Et), 54276-92-5; **5** (R = *n*-Bu), 54276-93-6; **5** (R = *n*-Pr), 54276-94-7; **5** (R = *i*-Pr), 54276-95-8; **5** (R = *i*-Bu), 54276-96-9; **5** (R = $PhCH_2$), 54276-97-0; **5** (R = *i*-$BuCH_2$), 54325-79-0; **6** (R = *n*-Bu), 15982-65-7; **6** (R = *i*-$BuCH_2$), 54276-98-1; **6** (R = Et), 2955-65-9; **6** (R = *i*-Pr), 51513-41-8; **6** (R = *n*-Pr), 22633-21-2; **6** (R = $PhCH_2$), 54276-99-2; **6** (R = *i*-Bu), 54277-00-8; **6** (R = *t*-Bu), 27610-88-4; **6** (R = hexyl), 54277-01-9; **6** (R = Ph), 495-71-6; **6** (R = cyclohexyl), 18986-63-5; propionaldehyde, 123-38-6; butyraldehyde, 123-72-8; isobutyraldehyde, 78-84-2; pivalaldehyde, 630-19-3; heptanal, 111-71-7; benzaldehyde, 100-52-7; cyclohexanecarboxaldehyde, 2043-61-0; 4-octyne-3,6-diol, 24434-07-9; 5-decyne-4,7-diol, 1070-40-2; *meso*-2,7-dimethyl-4-octyne-3,6-diol, 54277-02-0; *dl*-2,7-dimethyl-4-octyne-3,6-diol, 54277-03-1; *meso*-2,2,7,7-tetramethyl-4-octyne-3,6-diol, 54277-04-2; *dl*-2,2,7,7-tetrimethyl-4-octyne-3,6-diol, 54277-05-3; *meso*-8-hexadecyne-7,10-diol, 54277-06-4; *dl*-8-hexadecyne-7,10-diol, 54277-07-5; *meso*-1,4-diphenyl-2-butyne-1,4-diol, 54277-08-6; *dl*-diphenyl-2-butyne-1,4-diol, 54277-09-7; *meso*-1,4-dicyclohexyl-2-butyne-1,4-diol, 54277-10-0; *dl*-1,4-dicyclohexyl-2-butyne-1,4-diol, 54277-11-1; 3,6-octanediol, 24434-09-1; 4,7-decanediol, 4469-89-0; 2,7-dimethyl-3,6-octanediol, 31206-61-8; *meso*-2,2,7,7-tetramethyloctane-3,6-diol, 54277-12-2; *dl*-2,2,7,7-tetramethyloctane-3,6-diol, 54277-13-3; *meso*-7,10-hexadecanediol, 54277-14-4; *dl*-7,10-hexadecanediol, 54277-15-5; *meso*-1,4-diphenylbutane-1,4-diol, 13401-42-8; *dl*-1,4-diphenylbutane-1,4-diol, 13401-43-9; *meso*-1,4-dicyclohexyl-1,4-butanediol, 54277-16-6; *dl*-1,4-dicyclohexyl-1,4-butanediol, 54277-17-7; acetylenebismagnesium bromide, 4301-15-9; ethyl bromide, 74-96-4; acetylene, 74-86-2; dilithium acetylide, 1070-75-3; dipotassium acetylide, 22754-96-7.

## References and Notes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