Model Studies for Ring C Formation in Pentacyclic Triterpene Synthesis

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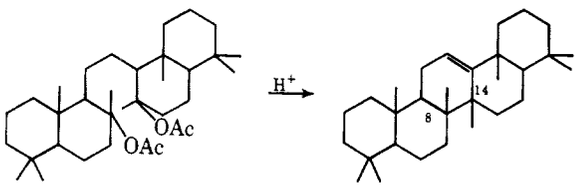
A synthesis of 2,5,6,7,8,8a-hexahydro-2,5,5,8a-tetramethyl-1,3-naphthalenedione (**13**), a potentially useful intermediate in pentacyclic triterpene synthesis, is reported. Reaction of **13** with methyl vinyl ketone leads to 2,5,6,7,8,8a-hexahydro-2,5,5,8a-tetramethyl-2-(3-oxobutyl)-1,3-naphthalenedione (**16**) which undergoes a retro-Michael reaction in preference to cyclization under a variety of basic conditions.

All pentacyclic triterpenoid syntheses reported to date[2] have involved the acid-catalyzed formation of the 8,14 bond in the closure of ring C from a tetracyclic intermediate, a process which may be illustrated by the last step of the synthesis of γ-onocerene (**1**) reported by Corey and Sauers.[2a] Although this step, suggested to be synthetically useful by Halsall and Thomas[2f] on the basis of earlier work, has been extensively used, it is intractable and gives low yields.



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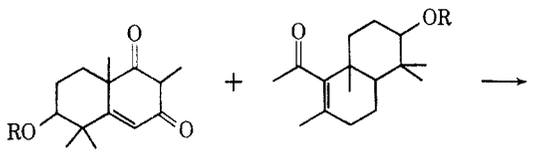
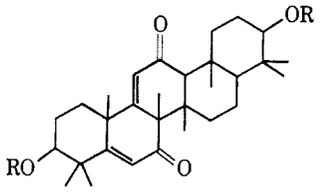
As an attractive alternative we have investigated a variant of the Robinson annelation reaction[3] wherein suitable bicyclic precursors, *e.g.*, **3** and **4**, might be condensed to give the desired skeleton, *e.g.*, **5**. Such



3 **4**



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a pathway would be generally useful if it offered better structural and stereochemical control and improved yields of pentacyclic compounds. The advantage of β-dicarbonyl systems as donors in Michael reactions is well known,[3] while the conjugation of one carbonyl with a double bond (*cf.* **3**) should deactivate this group toward subsequent cyclization. The present study, undertaken to evaluate this route, shows that, while adduct formation is facile, cyclization of the adduct does not compete favorably with retro-Michael reaction under a variety of basic conditions.

Results and Discussion

Two syntheses proceeding from the Wieland–Miescher ketone[4] **6** were used for the preparation of 2,5,6,7,-8,8a-hexahydro-5,5,8a-trimethyl-1,3-naphthalenedione (**7**). Conversion of **6** to the ene ketal **8**[5] was accomplished by ketalization,[6] followed by methylation[7] and Wolff–Kishner reduction. The structure of **8** was confirmed by conversion to the known alcohol **9**.[7] Oxidation of the allylic methylene group of **8** with chromium trioxide in acetic acid[8] gave 5,6,7,8-tetrahydro-4-(2-hydroxyethoxy)-4a,8,8-trimethyl-2(4aH)-naphthalenone in 16–22% yield.[9] Hydrolysis of this compound to **7** proceeded in 84% yield. Owing to the low yield in the oxidation of **8**, an alternative pathway to **7** was explored. Acetylation of **9** prepared from **6** by known procedures[7,10] followed by oxidation of the allylic position,[8] reduction to the 1,3-diol, and oxidation with chromic acid in sulfuric acid[11] gave **7** in low yield.[12] The physical and chemical properties of **7** are consistent with the assigned structure (Scheme I).

The nmr spectrum of compound **7** in deuteriochloroform showed resonances for three singlet methyl groups at δ 1.52, 1.28, and 1.18 ppm, a singlet olefinic proton at δ 6.27, and ring protons and an AB quartet centered at δ 3.52 with a coupling constant of 18 cps assigned to the two nonequivalent protons at C-2 in **7**. These signals disappeared when the solution was shaken with deuterium oxide. This facile exchange indicates the presence of the enols **11** or **12** in low concentration. The infrared spectrum of **7** in chloroform showed no hydroxyl absorptions. In the same solvent the keto form of 5,5-dimethyl-1,3-cyclohexadione was found to predominate slightly over the enol form, although this

(1) University of Illinois Fellow, 1962–1963, 1965–1966; National Science Foundation Fellow, 1963–1965.

(2) (a) E. J. Corey and R. R. Sauers, *J. Am. Chem. Soc.*, **81**, 1739 (1959); (b) E. J. Corey, H. Hess, and S. Proskow, *ibid.*, **85**, 3979 (1963); (c) J. A. Barltrop, J. D. Littlehailes, J. D. Rushton, and N. A. J. Rogers, *Tetrahedron Letters*, 42 (1962); (d) E. Ghera and F. Sondheimer, *ibid.*, 3887 (1964); (e) N. A. J. Rogers and J. A. Barltrop, *Quart. Rev.* (London), **16**, 117 (1962); (f) T. G. Halsall and B. D. Thomas, *J. Chem. Soc.*, 2431 (1956).

(3) (a) E. C. duFeu, F. J. McQuillin, and R. Robinson, *ibid.*, 53 (1937); (b) T. A. Spencer, K. K. Schmiegel, and K. L. Williamson, *J. Am. Chem. Soc.*, **85**, 3785 (1963); (c) S. Swaminathan and M. S. Newman, *Tetrahedron*, **2**, 88 (1958); (d) E. D. Bergman, D. Ginsberg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959); (e) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 210–212.

(4) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **33**, 2215 (1950); A. B. Mekler, S. Ramachandran, S. Swaminathan, and M. S. Newman, *Org. Syn.*, **41**, 38, 56 (1961).

(5) J. Kalvoda and H. Loeffel, *Helv. Chim. Acta*, **40**, 2340 (1957).

(6) E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry, *J. Am. Chem. Soc.*, **86**, 478 (1964).

(7) F. Sondheimer and D. Elad, *ibid.*, **81**, 4429 (1959).

(8) B. R. Davis and T. G. Halsall, *J. Chem. Soc.*, 1833 (1962).

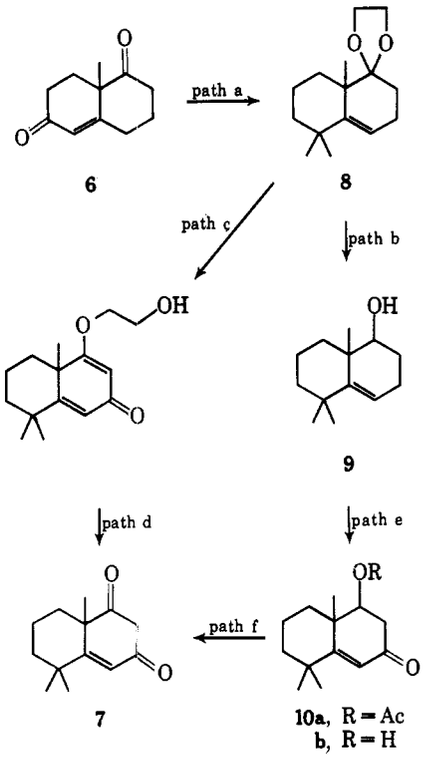
(9) Ring opening of the ketal ring β to the newly formed carbonyl could occur under the reaction or work-up conditions.

(10) C. B. C. Boyce and J. S. Whitehurst, *ibid.*, 2680 (1960).

(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *ibid.*, 39 (1946); N. A. J. Rogers and J. A. Barltrop, *Quart. Rev.* (London), **16**, 81 (1962).

(12) The low yield of the oxidation appears to be due to the fact that the dione **7** is sensitive to the oxidation conditions. However, the use of milder reagents only led to oxidation of the allylic alcohol giving **10b**.

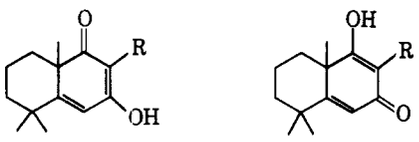
SCHEME I



6 8 9 7 10a, R = Ac b, R = H

path a, $HOCH_2CH_2OH$, H^+; CH_3I, $(CH_3)_3CO^-K^+$; NH_2NH_2, KOH
b, HCl; $LiAlH_4$
c, CrO_3, HOAc
d, $(CH_3)_2CC{=}O$, HCl
e, Ac_2O; CrO_3, HOAc
f, $LiAlH_4$; CrO_3, H_2SO_4

was sensitive to solvent composition.[13] Similar observations have been made by Mangoni and Belardini,[14] in an analogous system. In dimethyl sulfoxide-d_6 the AB quartet is not observed and signals attributable to olefinic protons are seen at δ 5.25 and 5.97. Under these conditions the compound exists in the tautomeric forms **11** and/or **12**.

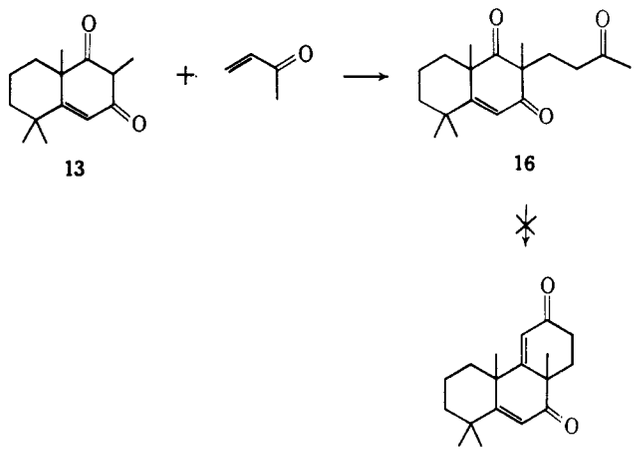


11, R = H; **14**, R = CH_3 **12**, R = H; **15**, R = CH_3

Methylation of **7** proceeded in 50% yield to give 2,5,6,7,8,8a-hexahydro-2,5,5,8a-tetramethyl-1,3-naphthalenedione (**13**). The nmr spectrum of this material in dimethyl sulfoxide-d_6 showed an unsplit resonance at δ 1.63 (relative area 3) attributed to an olefinic methyl group at C-2. The two signals at δ 6.15 (relative area 0.8) and 5.95 (area 0.2) may be ascribed to olefinic protons at C-4 of the tautomers **14** and **15**.

The reaction of **13** with methyl vinyl ketone and a catalytic amount of potassium hydroxide[3c] led to the formation of 2,5,6,7,8,8a-hexahydro-2,5,5,8a-tetramethyl-2-(3-oxobutyl)-1,3-naphthalenedione (**16**) in 92% yield. That this reaction was not stereoselective may be inferred from the nmr spectrum which shows two resonances in a 1:2 ratio at δ 2.12 and 2.08 (combined relative area 3) ascribable to methyl groups adjacent to a carbonyl (Scheme II).

SCHEME II



13 16

The adduct **16** was subjected to a wide variety of bases in attempts to effect cyclization. Conditions used previously on sensitive compounds[3,15] of similar structure either did not cause any change when catalytic amounts of base were used or led to cleavage of the side chain by retro-Michael reaction with formation of **13** when molar amounts of base were added. Since cyclization to the C-3 carbonyl did not occur, the expected deactivation of the C-3 carbonyl has been achieved. However, the C-1 carbonyl is apparently also sufficiently unreactive in intramolecular cyclization[16] that side-chain cleavage predominates. The stability of the anion of **13** certainly contributes a driving force for this cleavage. This suggests that with suitable modification of the different carbonyl groups of **16** the desired cyclization could be achieved, albeit without accomplishing the original goal of a simple one-step procedure.

Experimental Section[17]

3,5,6,7,8,8a-Hexahydro-5,5,8a-trimethyl-1(2H)-naphthalenone Ethylene Ketal[5] (**8**).—Compound **8** was prepared by standard procedures.[6,7] Distillation gave material of bp 87–88° (0.15–0.20 mm); ν_{max} 1570, 1140, 1050 cm^{-1}; δ 5.47 (m, relative area

(13) N. Cyr and L. W. Reeves [*Can. J. Chem.*, **43**, 3057 (1965)] have made a careful study of this type of equilibrium.

(14) L. Mangoni and M. Belardini, *Tetrahedron Letters*, 2643 (1964).

(15) D. Becker and H. J. E. Lowenthal, *J. Chem. Soc.*, 1338 (1965); N. L. Wendler, H. L. Slates, and M. Tishler, *J. Am. Chem. Soc.*, **73**, 3816 (1951).

(16) Presumably this is due to steric hindrance. Similar steric effects appear to inhibit intermolecular carbonyl reactions. For example, 2,2,6,6-tetramethylcyclohexanone does not form a semicarbazone derivative: A. Haller, *Compt. Rend.*, **156**, 1199 (1913).

(17) Melting points were determined in open capillaries on a Büchi melting point apparatus and are corrected. Boiling points are uncorrected. Infrared spectra were recorded either as liquid films relative to air or in chloroform solution relative to chloroform on a Perkin-Elmer Infracord, Model 21, or Model 521 spectrometer. Ultraviolet spectra were measured in 95% ethanol solution relative to 95% ethanol on a Cary 14M or a Perkin-Elmer 202 ultraviolet–visible spectrophotometer. Proton magnetic resonance spectra, reported in δ units, were determined in deuteriochloroform solution on a Varian Associates Model A-60, A-60A, or A-56-60 high resolution spectrometer using tetramethylsilane as an internal standard unless otherwise indicated. Peak areas are assigned relative to the most intense peak in the spectrum unless otherwise indicated. Mass spectra were determined by Mr. J. Wrona on an Atlas CH4 mass spectrometer using a Vac Lock inlet system. Molecular ions for the determination of molecular weights were determined at 11–15 ev. Microanalyses were carried out in the University of Illinois microanalytical laboratory under the direction of Mr. Joseph Nemeth. For chromatography "neutral alumina" refers to Merck neutral alumina (Catalog No. 71707) used as received. Silica gel refers to 0.05–0.20-mm silica gel manufactured by E. Merck Ag, Darmstadt (Germany). The order of elution of petroleum ether (bp 60–68°), ether, chloroform, then ethanol was followed.

1, =C*H*CH$_2$), 3.94 (s, area 4, OC*H*$_2$), 2.30–2.00 (m, area 2, =CHC*H*$_2$), 2.00–1.00 (complex multiplet with sharp peaks at 1.30, 1.12, and 1.08, area 17, C*H*$_2$ and C*H*$_3$).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.08; H, 10.20.

1,2,3,5,6,7,8,8a-Octahydro-5,5,8a-trimethyl-1β-naphthol (9).—Treatment of 2.5 g of **8** with 70 ml of acetone and 2 ml of concentrated hydrochloric acid at reflux for 15 min, followed by isolation of the product with ether and distillation, gave 1.61 g (70%) of 3,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-1(2H)-naphthalenone as a slightly yellow oil: bp 64–66° (0.10–0.15 mm); ν_{max} 1705, 1640 cm^{-1}; δ 5.83 (m, area 1, =C*H*CH$_2$), 2.70–1.00 (complex multiplet with sharp peaks at 1.37, 1.20, and 1.12, area 19, CH$_2$ and CH$_3$). The 2,4-dinitrophenylhydrazone had mp 115–118° (lit.[18] mp 118–122°).

To 576 mg of this ketone in 10 ml of ether 200 mg of lithium aluminum hydride in 15 ml of ether was added and the reaction was stirred for 2 hr. Evaporation of the filtrate after destruction of the excess lithium aluminum hydride by ethyl acetate gave 510 mg (88%) of alcohol **9** as a white solid which was recrystallized from ethanol–water: mp 120–121° (lit.[7,18] mp 122–123°). No depression of melting point was observed upon mixture with material prepared according to the procedure of Sondheimer and Elad.[7]

5,6,7,8-Tetrahydro-4-(2-hydroxyethoxy)-4a,8,8-trimethyl-2-(4aH)-naphthalenone.—Chromium trioxide (4.00 g, 40 mmoles) was slowly added to a stirred mixture of 4.4 g of **8** (18.7 mmoles), 3.28 g of anhydrous sodium acetate (40 mmoles), 3 ml of acetic anhydride, and 110 ml of glacial acetic acid. After stirring at 60° for 4 hr, the mixture was poured into water and extracted three times with methylene chloride. The combined extracts were washed twice with water, dried over sodium sulfate, and evaporated to give 3.8 g of yellow oil which was chromatographed on 110 g of neutral alumina. Elution with 10% ether in petroleum ether gave 1.88 g of a mixture of starting ketal **8** and ketone expected from ketal hydrolysis. Reketalization of this mixture and distillation of the product gave 1.68 g of recovered starting ketal **8**. Elution with ether gave 0.54 g of an unidentified yellow oil. Elution with chloroform gave 0.43 g of a yellow solid which was triturated with petroleum ether–ether, the solvent was removed, and the remaining solid was combined with 0.71 g of yellow solid eluted with absolute ethanol. Recrystallization from heptane gave 0.64 g of a white crystalline solid (22% based on unrecovered starting material): mp 116–117°; λ_{max} 242 mμ (ε 12,300), 277 mμ (ε 4700); ν_{max} 3380, 1640, 1585 cm^{-1}; δ 6.18 and 5.51 (broadened singlets, expanded scale shows J = 1.5 cps, area 1 each, =C*H*CO), 3.97 (s, area 4, OCH$_2$), 3.00 (s, area 1, O*H*), 2.70–1.00 (complex multiplet with sharp peaks at 1.51, 1.30, and 1.21, area 15, CH$_2$ and CH$_3$). The resonance at δ 3.00 disappeared when the solution was shaken with deuterium oxide.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; mol wt, 250. Found: C, 71.95; H, 8.93; mol wt, 250 (mass spectrometric).

2,5,6,7,8,8a-Hexahydro-5,5,8a-trimethyl-1,3-naphthalenedione (7).—A mixture of 257 mg of 5,6,7,8-tetrahydro-4-(2-hydroxyethoxy)-4a,8,8-trimethyl-2(4aH)-naphthalenone, 12 ml of acetone, and 6 ml of 3 *N* hydrochloric acid was heated at reflux for 1.5 hr. The reaction mixture, diluted with 40 ml of water, was extracted twice with ether. The combined ether extracts were extracted with three portions of 2 *N* sodium hydroxide which were combined, acidified with concentrated hydrochloric acid, and extracted twice with ether. Isolation of the product with ether gave 178 mg (84%) of dione **7**, mp 157–159°.

An analytical sample was prepared by recrystallization from acetone: mp 160–161°; λ_{max} 241 mμ (ε 9500), 290 mμ (ε 4400); in ethanol with 2 drops of 2 *N* sodium hydroxide added, strong end absorption below 230 mμ, 329 mμ (ε 7400);[19] ν_{max} 1725, 1665, 1600 cm^{-1}; δ 6.27 (s, area 1, =CHCO), 3.72 and 3.33 (half of an AB quartet, J = 18 cps (area 1 each), COCH$_2$CO), 2.40–1.00 (complex multiplet with sharp peaks at 1.52, 1.28, and 1.18, area 15, CH$_2$ and CH$_3$). The AB quartet at 3.72 and 3.33 disappeared when the solution was shaken with deuterium oxide.

Anal. Calcd for $C_{13}H_{18}O$: C, 75.69; H, 8.80; mol wt, 206. Found: C, 75.49; H, 8.76; mol wt, 206 (mass spectrometric).

4,4a,5,6,7,8-Hexahydro-4β-hydroxy-4a,8,8-trimethyl-2(3H)-naphthalenone Acetate (10a).—1,2,3,5,6,7,8,8a-Octahydro-5,5,8a-trimethyl-1-naphthol (**9**, 3.65 g, 1.88 mmoles) in 120 ml of acetic anhydride containing about 150 mg of anhydrous sodium acetate was heated at reflux for 3.5 hr. The reaction mixture, poured over ice and shaken with water for 0.5 hr, was extracted with two portions of methylene chloride. The combined extracts were washed twice with water and evaporated to give an oil which on distillation gave 4.16 g (96%) of a colorless oil: bp 92–94° (0.4 mm); ν_{max} 1720, 1230 cm^{-1}; δ 5.50 (apparent triplet, area 1, =C*H*CH$_2$), 4.73 (apparent triplet, area 1, OC*H*CH$_2$), 2.40–1.00 [complex multiplet with sharp peaks at 2.09 (COCH$_3$), 1.25, 1.17, and 1.12, area 22, CH$_2$ and CH$_3$].

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24; mol wt, 236.4. Found: C, 75.89; H, 10.23; mol wt, 229.4 (osmetric).

To a stirred mixture of 4.06 g of the above product, 1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1-naphthol acetate (17.2 mmoles), 9.40 g of anhydrous sodium acetate (53.6 mmoles), 9 ml of acetic anhydride, and 86 ml of glacial acetic acid was added 5.36 g of chromium trioxide (53.6 mmoles), and the mixture was stirred at 60° for 5 hr. After dilution with 200 ml of water, the reaction mixture was extracted four times with methylene chloride. The combined extracts were washed twice with water and evaporated to give 4.4 g of yellow oil which was chromatographed on 95 g of silica gel. Elution with 10% ether in petroleum ether gave 208 mg (4%) of unreacted starting material. Elution with 20–30% ether gave 2.80 g (65%) of keto acetate **10a**. An analytical sample was prepared by recrystallization from heptane: mp 84–85°; λ_{max} 239 mμ (ε 13,900); ν_{max} 1730, 1660, 1595, 1240 cm^{-1}; δ 6.04 (s, area 1, =CHCO), 5.05 (m, area 1, OC*H*CH$_2$), 2.62 (m, area 2, CHC*H*$_2$CO), 2.08 (s, area 3, COCH$_3$), 1.95–1.00 (complex multiplet with sharp peaks at 1.36, 1.22, and 1.18, area 15, CH$_2$ and CH$_3$).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; mol wt, 250. Found: C, 72.09; H, 9.18; mol wt, 250 (osmetric).

2,5,6,7,8,8a-Hexahydro-5,5,8a-trimethyl-1,3-naphthalenedione (7).—To 125 mg of **10a** in 15 ml of cooled ether was slowly added 76 mg of lithium aluminum hydride in 25 ml of ether. After stirring at 0° for 0.5 hr, the reaction was worked up in the usual manner. Evaporation of the combined filtrate and washings gave 100 mg of an oil which slowly crystallized on standing: melting range 62–110°; ν_{max} 3600, 3400 cm^{-1}.

Jones reagent[11] (2.85 ml, 11.4 mmoles) was slowly added to a cooled and stirred solution of 1.10 g of the above diol (5.24 mmoles) in 40 ml of acetone. Stirring was continued for several minutes, and then several drops of isopropyl alcohol were added. The reaction mixture was poured into water and the aqueous mixture extracted twice with ether. The combined ether extracts were extracted with two portions of 2 *N* sodium hydroxide solution which were combined, acidified with concentrated hydrochloric acid, and re-extracted with ether. Both ether extracts were then worked up in the usual manner to give 280 mg of acidic material and 567 mg of nonacidic material. The nonacidic material had ν_{max} 3400, 1660, 1590 cm^{-1}. By further Jones reagent oxidation of the nonacidic material it was possible to obtain more of the desired acidic material. Two more oxidations produced an additional 280 mg of acidic material.

The acidic material (560 mg) was chromatographed on 12 g of silica gel. Elution with 1:1 petroleum ether–ether gave 320 mg (30%) of dione **7** as a slightly yellow solid. Recrystallization from acetone gave material identical with that prepared by the alternative route by infrared, ultraviolet, and melting point criteria.

Oxidation of the diol under milder conditions[20] led only to partially oxidized material **10b** as was judged by spectral properties.

2,5,6,7,8,8a-Hexahydro-2,5,5,8a-tetramethyl-1,3-naphthalenedione (13).—A mixture of 206 mg of **7** (1 mmole), 1 ml of 1 *N* sodium hydroxide (1 mmole), 2.1 ml of dioxane containing 68 mg of methyl iodide per milliliter (143 mg, 1 mmole), and 2 ml of water was heated at 100° for 14 hr in a sealed tube. Extractive work-up for acidic and nonacidic products as in the Jones reagent oxidations yielded 122 mg of acidic material as a yellow solid and 96 mg of nonacidic material as a yellow oil.

The acidic material was chromatographed on 4 g of silica gel. Elution with 1:1 petroleum ether–ether gave 109 mg (50%) of diketone **13** as a white, crystalline solid. An analytical sample was prepared by recrystallization from methanol: mp 229.5–231°; λ_{max} end absorption below 211 mμ, 240 mμ (ε 4000), 316 (4600); in ethanol with 2 drops of 2 *N* sodium hydroxide added,

(18) J. D. Cocker and T. G. Halsall, *J. Chem. Soc.*, 3441 (1957).

(19) C. W. Shoppee and R. E. Lack [*ibid.*, 3611 (1964)] reported similar values for a similar chromophore.

(20) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).

intense absorption below 215 mμ, 342 mμ (ε 7600); ν_{max} (KBr) 1715 (m), 1655 (m), 1605 (m), 1550 (s), 1455 (m), 1370 (s), 1250 (m), 1120 cm^{-1} (m); δ (dimethyl sulfoxide-d_6) 6.15 (s, area 0.8, =CH), 5.95 (broad singlet, area 0.2, =CH), 2.30–0.90 (complex multiplet with sharp peaks at 1.63, 1.27, 1.20, and 1.18, area 18, CH_2 and CH_3).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; mol wt, 220. Found: C, 76.07; H, 9.25; mol wt, 220 (mass spectrometric).

2,5,6,7,8,8a-Hexahydro-2,5,5,8a-tetramethyl-2-(3-oxobutyl)-1,3-naphthalenedione (16).—A mixture of 104 mg of **13** (0.47 mmole), 0.47 ml of methanol containing 1 mg of potassium hydroxide per milliliter (0.47 mg), 2.8 ml of methanol, and 0.086 ml of methyl vinyl ketone (72 mg, 1.08 mmoles) was heated at 80° in a sealed tube for 5.5 hr.[4] Extractive work-up with ether followed by evaporation gave 140 mg of yellow oil which was chromatographed on 3 g of silica gel. Elution with 1:1 petroleum ether–ether gave an initial 9 mg of red oil, which was discarded, followed by 127 mg (92%) of light yellow oil. An analytical sample was prepared by distillation in a microsublimation apparatus: λ_{max} 239 mμ (ε 14,300); ν_{max} 1710, 1665, 1610 cm^{-1}; δ 6.23 (broad singlet, area 1, =CHCO), 2.80–1.00 [complex multiplet with sharp peaks at 2.12 and 2.08 ($COCH_3$), 1.47, 1.35, 1.30, and 1.25, area 25, CH_2 and CH_3].

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02; mol wt, 290. Found: C, 74.37; H, 9.04; mol wt, 290 (mass spectrometric).

Attempts were made to carry out the cyclization of **16** with catalytic and molar amounts of sodium methoxide, potassium *t*-butoxide, pyrrolidine, and pyrrolidine acetate under a variety of conditions. With catalytic amounts of base **16** was recovered, while molar or excess base led to recovered **13**.

Registry No.—**7**, 13395-77-2; **8**, 13395-78-3; **9**, 13395-79-4; **10**, 13395-80-7; **10a**, 13395-82-9; **13**, 13428-02-9; **16**, 13395-81-8.

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Dependence of the Rate, Reversibility, and Stereoselectivity of 17-Keto Steroid Alkynylation on the Alkyne and on the Alkali Metal

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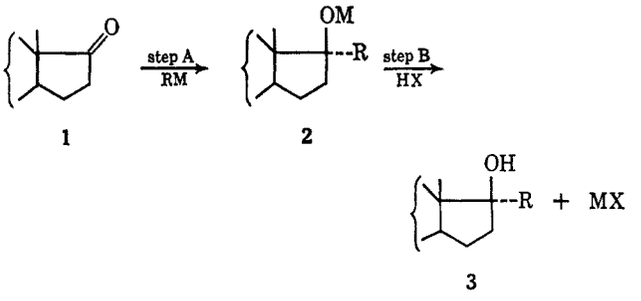
The alkynylation of estrone methyl ether (**4**) with the lithium, sodium, and potassium derivatives of propargyl alcohol, 3-butyn-1-ol, and propargylaldehyde diethyl acetal in pyridine and/or dioxane was studied. Every combination of alkali metal and alkyne tried but one gave the products of highly selective 17α attack of the keto group of **4**. That exception was the alkynylation of **4** with the potassium derivative of propargylaldehyde diethyl acetal in pyridine at room temperature, which produced a mixture containing appreciable amounts of both epimeric 3-methoxy-17-(3-oxo-1-propynyl)estra-1,3-5(10)-trien-17-ol diethyl acetals (**9** and **10**). Nonstereoselectivity in this reaction and high stereoselectivity in the formation of 17-(3-hydroxy-1-propynyl)-3-methoxyestra-1,3,5(10)-trien-17β-ol (**5a**) were both found to be associated with reversibility of the alkynylations of **4** with the *potassium* derivatives of the alkynes. The rate of alkynylation of **4** depended on the structure of the alkyne in the order propargylaldehyde diethyl acetal > 3-butyn-1-ol > propargyl alcohol and on the alkali metal in the order potassium > sodium > lithium. Oxidation of **5a** produced 3-methoxy-17-(3-oxo-1-propynyl)estra-1,3,5(10)-trien-17β-ol (**11**), which was also obtained by hydrolysis of **9**. Hydrolysis of **10** gave the C-17 epimer (**12**) of **11**. Assignment of the configurations at C-17 of **5a** and its epimer **6**, **9** and its epimer **10**, **11** and its epimer **12**, and 17-(4-hydroxy-1-butynyl)-3-methoxyestra-1,3,5(10)-trien-17β-ol (**7**) was made on the basis of their optical rotations.

Alkylations of 17-keto steroids (**1**) by organometallic reagents (RM) generally proceed by attack of the reagent at the sterically less hindered α side of the keto group (17α attack), producing **2**, which after neutralization gives the 17-alkyl steroid 17β-ol **3**.[1] Products resulting from 17β attack have been obtained in small proportion from these alkylations[2,3] and in significant proportion from alkylations with allylic Grignard reagents[4–6] and from alkylations[5] and alkynylations[7,8] in which 17α attack was sterically hindered by nearby α substituents. Concerning alkynylations in particular, little is known about factors other than nearby substituents which affect the rate, reversibility, and stereoselectivity of step A, such as the structure of the alkynyl group R and the metal M. The concern of this paper is several interesting clarifications of these relationships and their synthetic implications arising from a study of the alkynylation of estrone methyl ether (**4**) with the lithium, sodium, and potassium derivatives of propargyl alcohol, 3-butyn-1-ol, and propargylaldehyde diethyl acetal in pyridine and/or dioxane.



Results

The results of these alkynylations are summarized in Tables I–III. They were carried out in two ways. In method A the metal alkyne was prepared by adding the alkyne to a solution of the alkali metal in liquid ammonia. The solvent and **4** were added either as a solution or separately, the ammonia was allowed to evaporate, and the reaction was allowed to proceed

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