1669-44-9; VIII, 24271-23-6; IX, 33046-75-2; X, 33046-76-3; XI, 33046-77-4; XII, 33046-78-5; XIII, 33046-79-6; XIV, 33046-80-9; XV, 33046-81-0; XVIIa, 33046-82-1; XVIII, 1119-44-4; XIX, 33046-84-3; XX, 6048-08-4; XXI, 24271-22-5; XXII, 3643-55-8; XXIII, 33046-88-7; XXIV, 33046-89-8; XXIVa, 33046-90-1; XXV, 33046-91-2; XXIX, 13891-87-7; XXX, 33046-93-4.

The Synthesis of the A,B and D,E Rings of Medicagenic Acid[1]

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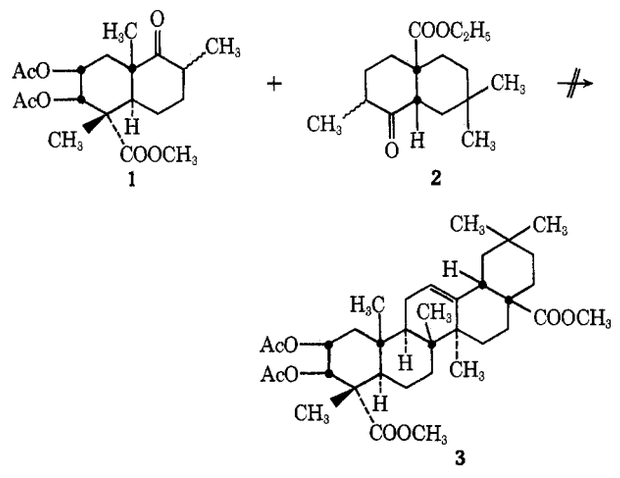
The synthesis of two decalin derivatives to be used in an AB + DE type synthesis of dimethyl diacetoxymedicagenate (**3**) has been accomplished. The A,B segment has a final structure of 1β,6,10β-trimethyl-1α-carbomethoxy-2β,3β-diacetoxy-*trans*-5-decalone (**1**). The D,E portion has a final structure of 10-carbethoxy-2,7,7-trimethyl-*cis*-decal-1-one (**2**). These compounds represent versatile intermediates which will be used in seeking a total synthesis of the sapogenin molecule through annelation of the two fragments.

Interest in medicagenic acid has developed from several studies including its isolation, purification, physiological activity, and biological role in alfalfa forage.[2,3] As reported in earlier communications,[4,5] medicagenic acid was found to be the aglycone in both alfalfa root and blossom saponins, and a pure root saponin was synthesized from the purified natural acid and β-D-glucose.[6]

Our approach to the synthesis focused on an AB + DE sequence in order to avoid the extremely difficult task of building the molecule by attaching each of the five rings with their variety of substituents in successive order. The first half of the study, reported here, required the creation of two stereospecific decalin precursors possessing suitable reaction sites for coupling. A second investigation will be devoted to an examination of different annelation procedures in order to successfully join these two compounds (Scheme I).

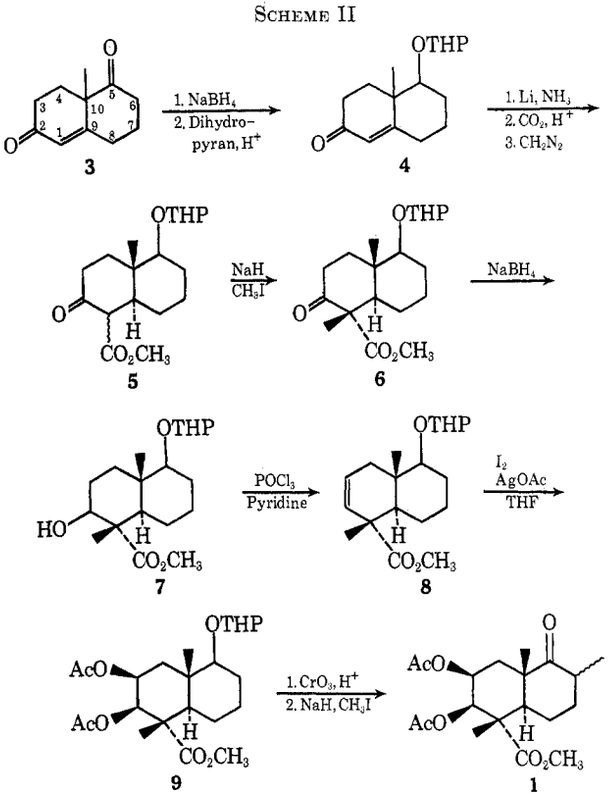
SCHEME I



To allow for flexibility in the synthesis, bicyclic systems were chosen which offer both a high degree of versatility and yet essentially duplicate large portions of the natural molecule. The adaptability of these compounds for the coupling reaction is determined by the variety of reactions which can occur at the ketone groups.

The two compounds will be treated separately, beginning with the synthesis of the A,B ring system (Scheme II). The problems anticipated were essentially threefold: (1) effecting a trans ring juncture; (2) the formation of the correct stereochemistry for the groups at carbon 1; and (3) the introduction of the 2β,3β-diacetoxy group.

SCHEME II



A solution to the first two of these problems was conveniently offered by one series of reactions. Stork

(1) Partial support for this work provided by the University of Nevada, Reno, Agricultural Experiment Station, Journal Series 188 is gratefully acknowledged.

(2) E. D. Walter, G. R. Van Atta, C. R. Thompson, and W. D. Maclay, *J. Amer. Chem. Soc.*, **76**, 2271 (1954).

(3) C. Djerassi, D. B. Thomas, A. L. Livingston, and C. R. Thompson, *ibid.*, **79**, 5292 (1957).

(4) R. J. Morris, W. B. Dye, and P. S. Gisler, *J. Org. Chem.*, **26**, 1241 (1961).

(5) R. J. Morris and E. W. Hussey, *ibid.*, **30**, 166 (1965).

(6) R. J. Morris and D. L. Tankersley, *ibid.*, **28**, 240 (1963).

and his coworkers found that lithium in liquid ammonia specifically reduced 10-methyl-$\Delta^{1(9)}$-octal-2-one and other enones of the same type preferentially to the trans fused compound.[7,8] It should be noted that, in following the general outline of this method, the β-keto acid, resulting from trapping the enolate salt with carbon dioxide, was protected immediately by preparing the methyl ester to avoid rapid decarboxylation. It was also important to introduce the C_1 methyl group in 1,2-dimethoxyethane solvent with methyl iodide as the alkylating agent. Under these conditions, the 1β-methyl compound was prepared almost exclusively over the α epimer.[9] The two epimers were distinguished by an nmr analysis which showed a characteristic chemical shift for the C_1 group.[10] In this manner, **6** was prepared as described by Spencer except that the tetrahydropyranyl ether was not removed.[11,12]

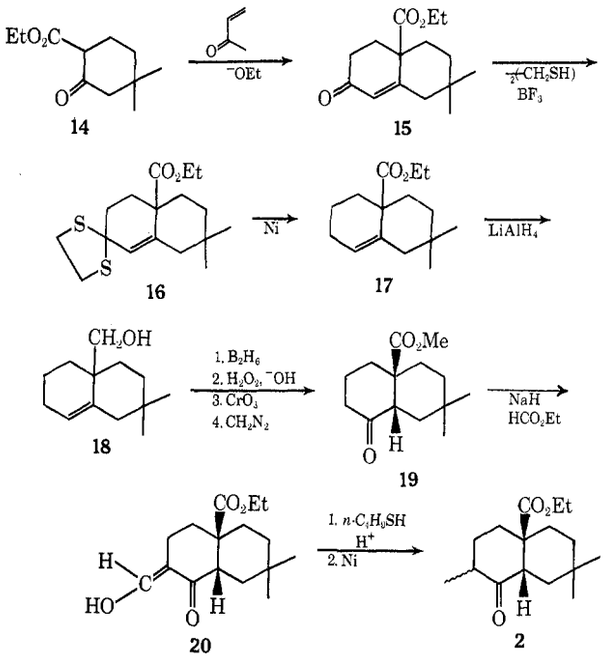
A most difficult problem to solve was the placement of the cis diacetate at carbon atoms 2 and 3. Woodward and colleagues found that iodoacetate would react with olefins to yield cis diacetates, but the conditions of the reaction needed careful control.[13] Although the solvent was not highly critical,[14] it was necessary to maintain 1 equiv of water in the reaction mixture to prepare the cis isomer in good yield. Following Woodward's method, the 2β,3β-diacetoxy group was introduced in the decalin system by the use of the pseudohalogen, iodoacetate.

The final steps of the synthesis were carried out by conventional methods. The tetrahydropyranyloxy group protecting the C_5 position was removed by mild acid hydrolysis and the resultant alcohol was oxidized with the Jones reagent. The C_6 methyl group was introduced using sodium hydride and methyl iodide in dimethoxyethane solution. It was subsequently found in the preparation of **2** that a better α-methylation procedure, resulting in a much cleaner product, employs the use of ethyl formate, followed by butyl mercaptan, with a final reduction by Raney nickel.[15] Work is now in progress to apply this procedure to the A,B ring system reported here.

The remainder of the text will be devoted to the problems associated with the synthesis of the D,E ring system (Scheme III).

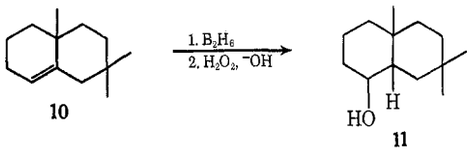
Annelation of **14** with methyl vinyl ketone[16] provided a decalin skeleton upon which three of the five necessary groups had already been positioned. Completion of the sequence consisted of removal of the 2-keto function, introduction of the 1-keto and 2-methyl substituents, and isolation of the cis isomer. It was originally thought that these steps could be accomplished by formation of the thioketal **16** followed by

SCHEME III



desulfurization with Raney nickel,[17] hydroboration of the unsaturated ester,[18] and finally methylation.

Preparation of the thioketal did proceed smoothly and treatment of **16** with Raney nickel in refluxing 95% ethanol for 3 hr provided a single product. Diborane would not react with **17** as expected, even though Sondheimer had reported the hydroxylation of hydrocarbon **10** in good yield.[19] The isomer obtained ex-



clusively in the formation of **11** was that containing a cis ring juncture. This was attributed to the blocking effect of the C_7 methyls to the approach of the diborane from the α side of the molecule. The carbethoxy group in **17** was suspected to be large enough so that now both sides of the olefin **17** would be blocked. Thus, reduction of the ester with lithium aluminum hydride to provide a group at the 10 position comparable in size to methyl was indicated. In addition, this hydroxymethyl function would not affect or be affected by the hydroxylation sequence. The additional step was found to be very beneficial, for the intermediate **18** proved to be easily sublimed and thus provided a convenient method for collecting very pure material midway through the scheme.

The alcohol did react with diborane. The resulting diol was not isolated but was oxidized with chromic acid–acetone solution to the keto acid. The acid was then treated with diazomethane to give *cis*-**19**. This manner of introducing the 1-keto function thus ensured the isolation of **2** exclusively in only one of its possible isomeric forms and eliminated the alternative, re-

(7) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **82**, 1512 (1960).
(8) G. Stork and J. Tsuji, *ibid.*, **83**, 2783 (1961).
(9) E. Wenkert, A. Afonso, J. Bredenberg, C. Kaneko, and A. Tahara, *ibid.*, **86**, 2038 (1964).
(10) K. L. Williamson, T. Howell, and T. A. Spencer, *ibid.*, **88**, 325 (1966).
(11) T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968).
(12) T. A. Spencer, R. J. Friary, W. W. Schmiegel, J. F. Simeone, and D. S. Watt, *ibid.*, **33**, 719 (1968).
(13) R. B. Woodward and F. V. Brutcher, Jr., *J. Amer. Chem. Soc.*, **80**, 209 (1958).
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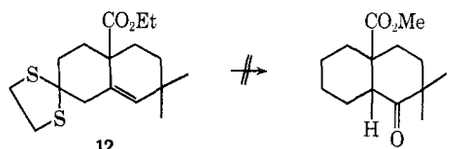
(16) A. S. Hussey, H. P. Liao, and R. H. Baker, *J. Amer. Chem. Soc.*, **75**, 4727 (1953).
(17) G. R. Pettit and E. E. van Tamelen, *Org. React.*, **12**, 356 (1962).
(18) H. C. Brown and K. A. Keblys, *J. Amer. Chem. Soc.*, **86**, 1795 (1964).
(19) F. Sondheimer and S. Wolfe, *Can. J. Chem.*, **37**, 1870 (1959).

quiring the tedious chromatographic separation of isomers.

Methylation of **19** with methyl iodide under a variety of conditions could not be effected. The possibility that the double bond may have migrated into the opposite ring when the thioketal was formed was considered, although this is usually observed only on preparation of the oxygen-containing analogs.[20] All subsequent reactions would then take place in the alternate ring and lead to **13**, which would not be expected



12 **13**

to react readily with methyl iodide since two of the three α positions are already methylated. All analytical methods available to us could not distinguish between the two thioketals or between any of the possible pairs of products in subsequent reactions.

However, when the ketone and 2-furfuraldehyde were allowed to stand in an aqueous methanolic solution, an adduct was formed which had a molecular ion peak at *m/e* 316.[21] Such addition could take place only if the ketone possessed two α hydrogens, and, of the two isomers in question, only **19** does. It seemed that, if **19** would condense with 2-furfuraldehyde, it might also react with ethyl formate and so provide an alternative to direct methylation.

Introduction of an *n*-butylthiomethylene group at the 2 position can be effected by treating the hydroxymethylene derivative of the ketone[22] with *n*-butyl mercaptan.[15] Desulfurization with Raney nickel will lead to the overall insertion of methyl. This three-step sequence has been shown to be compatible with an ester group,[23] and by using sodium hydride as the base the cis ring juncture introduced in the hydroxylation of **18** would not be affected.

The reactions proceeded with ease and provided **2** in good yield.

Experimental Section

General.—Infrared spectra were determined with a Perkin-Elmer Infrared Model 257 recording spectrophotometer. Ultraviolet measurements were obtained from a Beckman Model DB-G spectrometer. Nuclear magnetic resonance spectra were determined using a 60-MHz Varian Associates A-60 spectrometer. All nmr chemical shifts are reported in parts per million from the tetramethylsilane trace used as an internal standard (TMS = 0 ppm). Unless otherwise stated, all samples were neat.

The solvents and analytical reagents for chromatographic separation, ir analyses, and nmr determinations were all of CP grade.

Microanalyses were obtained from Chemalytics Inc., Tempe, Ariz.

Experimental Procedure for the A,B Ring Synthesis. 1β,10β-Dimethyl-1α-carbomethoxy-5β-tetrahydropyranyloxy-*trans*-2-decalone (6) was prepared by the method of Spencer;[11,12] ir (KBr) 1747 (ester C=O), 1725 (C=O), and 1028 cm^{-1} (COC); nmr 3.72 (s, 3, OCH_3), 1.38 (s, 3, bridgehead methyl), and 1.12 ppm (s, 3, C_1 methyl).

Anal. Calcd for $C_{19}H_{30}O_5$: C, 66.64; H, 8.70. Found: C, 66.46; H, 8.60.

The intermediate, 10β-methyl-1α-carbomethoxy-5β-tetrahydropyranyloxy-*trans*-2-decalone, was isolated as a mixture of the two tetrahydropyranyloxy ether isomers, mp 126–130°.

1β,10β-Dimethyl-1α-carbomethoxy-5β-tetrahydropyranyloxy-*trans*-2-decalol (7).—A stirred solution of **6** (3.0 g, 0.0089 mol) in 50 ml of 95% ethanol was cooled in an ice bath and treated dropwise with a solution of sodium borohydride (0.15 g, 0.0040 mol) in 25 ml of 95% ethanol over a 10-min period. The cooling bath was removed, and the reaction was stirred for an additional 1 hr at room temperature.

Glacial acetic acid (3 ml) was added to destroy the excess borohydride, and the mixture was evaporated to a viscous red residue. The residue was taken up in 200 ml of dichloromethane, washed with two 50-ml portions of water and one 50-ml portion of saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated to give 2.9 g of product as a light yellow oil: ir shows absence of the 1725 cm^{-1} peak, broadening of the 1747 cm^{-1} peak due to interaction with the alcohol, and strong absorption of a new peak at 3500 cm^{-1} (OH); nmr 3.90 ppm (s, 1, position varies upon dilution, OH).

1β,10β-Dimethyl-1α-carbomethoxy-5β-tetrahydropyranyloxy-*trans*-Δ²-octalin (8).—While cooling the reaction flask in an ice bath, a stirred solution of **7** (8.0 g, 0.024 mol) in 100 ml of dry, redistilled pyridine was cautiously treated dropwise with phosphorus oxychloride (7.2 g, 0.047 mol). After addition was completed, the reaction mixture was heated on a steam bath for 1 hr and then cooled to room temperature. The reaction mixture was again treated cautiously with cold water to destroy the excess phosphorus oxychloride and then poured into 300 ml of cold water. The mixture was quickly extracted with four 100-ml portions of ether. The combined ethereal fractions were washed with two 100-ml portions of water, two 75-ml portions of 10% HCl, and two 75-ml portions of saturated NaCl. The ethereal solution was dried (Na_2SO_4), filtered, and evaporated. The product, 2.68 g (34.7%), was isolated as a light yellow oil which would rapidly decolorize a 5% bromine–CCl_4 solution, ir 1665 cm^{-1} (C=C), nmr 6.0 ppm (2, vinyls).

1β,10β-Dimethyl-1α-carbomethoxy-5β-tetrahydropyranyloxy-2β,3β-diacetoxy-*trans*-decalin (9).—To a stirred solution of **8** (2.65 g, 0.00823 mol) in 100 ml of dry, redistilled THF was added silver acetate (3.10 g, 0.0185 mol) and finely powdered iodine (2.18 g, 0.00858 mol). The reaction mixture was protected from light and stirred at room temperature for 30 min. Water (0.2 g, 0.009 mol) was added, and the reaction mixture was refluxed for 4 hr, during which time the color deepened. The silver salts were filtered, and the filtrate was treated with sodium acetate (1.5 g, 0.018 mol) and acetic anhydride (2.55 g, 0.0250 mol).

After 12 hr at room temperature the mixture was treated with 100 ml of a saturated NaCl solution to precipitate any residual silver salts and to hydrolyze excess acetic anhydride. The mixture was extracted with three 100-ml portions of ether. The ether portions were combined, dried (Na_2SO_4), filtered, and evaporated. Chromatography of the residue through alumina (50 g) gave 2.4 g (63%) of **9** as a clear, viscous liquid: ir spectrum shows the disappearance of the band at 1665 cm^{-1} and the appearance of a strong peak at 1238 cm^{-1} [O(C=O)CH_3]; nmr exhibits new absorption at 1.95 and 1.90 ppm [s, 3 each, O(C=O)CH_3] which are identical with the acetate absorption values evident in dimethyl diacetoxymedicagenate.

1β,6,10β-Trimethyl-1α-carbomethoxy-2β,3β-diacetoxy-*trans*-5-decalone (1).—The above compound (9) (2.40 g, 0.00544 mol) was dissolved in 100 ml of absolute methanol containing 2 drops of concentrated hydrochloric acid and refluxed for 1 hr. The mixture was concentrated to 50 ml, poured into 100 ml of cold, saturated NaCl solution, and extracted with three 75-ml portions of ether. The ether fractions were combined, dried (Na_2SO_4), filtered, and evaporated to a light yellow solid.

This compound (3.2 g) was dissolved in 50 ml of purified acetone and treated dropwise with Jones reagent (8 *N* chromic acid). The mixture was stirred vigorously for 1 hr at room temperature and then concentrated to 25 ml. The reaction mixture separated into two layers, and the aqueous layer was extracted with two 50-ml portions of ether, dried (Na_2SO_4), filtered, and evaporated to 2.95 g of a light yellow compound.

This residue was dissolved in 100 ml of 1,2-dimethoxyethane and treated with NaH (0.38 g of a 53% dispersion in mineral oil, 0.0083 mol) and 10 drops of dry *tert*-butyl alcohol. After the

(20) C. Djerassi, "Steroid Reactions, An Outline for Organic Chemists," Holden-Day, San Francisco, Calif., 1963, p 22.

(21) The authors are indebted to Dr. G. Doyle Daves of the Oregon Graduate Center for the mass spectral study of **19** and its derivatives.

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evolution of gas had ceased, the mixture was stirred and treated with methyl iodide (11.4 g, 0.0803 mol). The reaction mixture was refluxed for 3 hr and then allowed to stir at room temperature for 12 hr. Several drops of water were added, and the reaction mixture was evaporated. This solid was dissolved in 200 ml of ether, washed with 100 ml of water and 50 ml of saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated to a viscous oily residue.

The resulting product was chromatographed through acid-washed alumina (30 g) and eluted successively with dry hexane, ether, acetone, and absolute methanol. The purified product, 1.82 g, was obtained from the ether fraction: ir 1735 (ester C=O), 1710 (C=O), and 1238 cm^{-1} [O(C=O)CH_3]; nmr 3.62 (s, 3, OCH_3), 2.00 [s, 6, O(C=O)CH_3], and a multiplet from 1.5 to 0.8 ppm corresponding to the different methylene groups. Mass spectral data offers final confirmation of the structure and exact molecular weight of the synthetic A,B ring depicted as compound 1 in Scheme II.

Anal. Calcd for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66. Found: C, 60.84; H, 7.70.

Experimental Procedure for the D,E Ring Synthesis. Materials.—The following compounds, all precursors to **15**, were prepared by methods previously reported.

3-Methyl-Δ^2-cyclohexenone[24] has bp 88–89° (18 mm); $n^{28}D$ 1.4911; 59%.

3,3-Dimethylcyclohexanone[25] has bp 78–80° (28 mm); $n^{26}D$ 1.4451; 63%. Cupric acetate monohydrate (0.02 mol) was substituted in place of cuprous chloride. The Grignard (0.75 mol) was prepared in 500 ml of anhydrous ethyl ether, and 3-methyl-Δ^2-cyclohexenone (0.50 mol) in 200 ml of anhydrous THF was added at −5° in 2.5 hr.

2-Carbethoxy-5,5-dimethylcyclohexanone (**14**)[26] has bp 116–118° (11 mm); $n^{24}D$ 1.4700; 78%.

10-Carbethoxy-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one (15).—A mixture of 2-carbethoxy-5,5-dimethylcyclohexanone (46.9 g, 0.237 mol) and methyl vinyl ketone (15.1 g, 0.216 mol) was added slowly to a solution of sodium ethoxide (0.222 mol prepared from 5.10 g of freshly cut sodium metal and 250 ml of 95% ethanol). The mixture was stirred for 1 hr at 25°, refluxed for 2 hr, and then allowed to stand at room temperature overnight. An additional 15.0 g of methyl vinyl ketone was added and the mixture was refluxed, with stirring, for 4 hr. Ice (*ca.* 100 g) was cautiously introduced followed by 250 ml of dilute HCl. The product, which separated as an orange-red oil, was extracted with three 100-ml portions of ether. The combined ether extracts were washed with 100 ml of 5% aqueous sodium bicarbonate solution and dried (Na_2SO_4). Distillation with a free flame provided 30.3 g (54.6%) of **15**: bp 146–152° (10 mm); ir 1720 (ester C=O), 1680 (C=O), and 1385 and 1365 cm^{-1} (*gem*-dimethyl); nmr (CCl_4) 5.78 (s, 1, vinyl), 4.21 (q, 2, OCH_2CH_3), 1.28 (t, 3, OCH_2CH_3), and 1.04 and 0.89 ppm (s, 3 each, C_7 methyls); uv max (95% ethanol) 239 nm (ϵ 15,500). The bands in the ir spectrum attributed to the *gem*-dimethyl group are very characteristic and appear in the spectra of all subsequent compounds.

Elution of a small sample (50 mg) from activated alumina (8.2 g) with 75 ml of petroleum ether (bp 60–110°) provided a thick, nearly colorless oil which solidified upon refrigeration.

10-Carbethoxy-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one Ethylene Dithioketal (16).—A mixture of **15** (5.00 g, 0.0200 mol) and ethanedithiol (3.80 g, 0.0403 mol) was cooled in ice before 2 ml of freshly distilled boron trifluoride etherate was added dropwise with stirring. After 2 hr at 25°, 5 ml of absolute methanol was added, the top layer was decanted, and the lower layer was evaporated to constant weight under a stream of dry air. The viscous crude material weighed 6.1 g (95%) and was used directly in the following step without further purification.

A sample (70 mg) was chromatographed on activated alumina (8.0 g) and eluted with 75 ml of petroleum ether, providing pure **16**, nmr (CCl_4) 3.27 ppm (m, 4, CH_2S).

Anal. Calcd for $C_{17}H_{26}O_2S_2$: C, 62.54; H, 8.03. Found: C, 62.87; H, 7.95.

10-Carbethoxy-7,7-dimethyl-$\Delta^{1(9)}$-octalin (17).—Raney nickel (type W-2) was prepared according to "Organic Syntheses,"[27] washed free of base, and allowed to stand under distilled water for 3 days in order to partially deactivate the metal and avoid contamination of **17** with the fully saturated analog. It was then washed twice with 95% ethanol just prior to use.

To the Raney nickel (*ca.* 50 g) in 250 ml of 95% ethanol was added **16** (10.0 g, 0.0310 mol) in an equal volume of solvent. The solution, which warmed spontaneously, was allowed to stand for 15 min at 25° and then refluxed for 3 hr. The mixture was filtered, the nickel was washed with 100 ml of 95% ethanol, and the organic material was dried (Na_2SO_4). Concentration of the resulting solution gave 6.61 g (90.3%), bp 78–82° (0.5 mm), $n^{22.5}D$ 1.4841, >95% pure by glpc analysis.

10-Hydroxymethyl-7,7-dimethyl-$\Delta^{1(9)}$-octalin (18).—A suspension of $LiAlH_4$ (2.00 g, 0.0526 mol) in 50 ml of dry ether was cooled to 0° before a solution of **17** (2.36 g, 0.0100 mol) in 50 ml of dry ether was added with stirring over a period of 20 min. After stirring for 1 hr at 25° ethyl acetate (5 ml) was added to decompose the excess hydride. This treatment was followed by the addition of 100 ml of dilute HCl and overnight stirring. The clear, colorless mixture was then separated and the aqueous layer was extracted with two 50-ml portions of ether. The ether extracts were washed with 100 ml of a 5% aqueous sodium bicarbonate solution, the mixture was dried (Na_2SO_4), the solvent was evaporated, and the residue was sublimed at 70° (0.3 mm) giving 1.71 g (88.1%) of a solid, white waxy product, mp 59.5–64.0°.

An analytical sample melting at 61–64.5° was prepared by resubliming the alcohol three times at 155° (0.3 mm): ir (KBr) 3350 (broad, OH) and no appreciable absorption between 1700 and 1800 cm^{-1}; nmr (CCl_4) 5.43 (s, 1, vinyl), 3.48 (s, 2, CH_2OH), and 2.60 ppm (s, 1, position varies upon dilution, OH).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.42. Found: C, 80.31; H, 11.49.

10-Carbomethoxy-7,7-dimethyl-*cis*-decal-1-one (19).—This preparation was carried out without complete purification of the diol or keto acid intermediates.

A.—To **18** (3.88 g, 0.0200 mol) and $LiAlH_4$ (7.60 g, 0.200 mol) in 40 ml of dry ether was added 10 ml of boron trifluoride etherate with stirring and at 0° over a 0.5-hr period. This mixture was stirred at 0° for 1 hr, then at 25° for 24 hr. Ethyl acetate (10 ml) was added followed by 100 ml of dilute HCl. The clear, colorless mixture was separated and the aqueous layer was extracted with 25 ml of ether. The organic material was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was taken up into an ethanolic sodium hydroxide solution prepared from 10 g of sodium hydroxide, 30 ml of water, and 120 ml of 95% ethanol. When the mixture had cooled to room temperature 25 ml of a 20% hydrogen peroxide solution was added dropwise. After stirring at 25° for 5 hr, 100 ml of water and 100 ml of ether were added, the mixture was separated, and the aqueous layer was extracted with three 50-ml portions of ether. Drying (Na_2SO_4) followed by filtration and evaporation of the solvent yielded a residual oil which weighed 4.30 g, nmr (CCl_4) 4.70 (s, 2, position varies upon dilution, OH), no additional absorption downfield from 4.70 ppm.

B.—The diol was dissolved in 150 ml of acetone. With stirring and cooling, Jones reagent[28] was added dropwise until an orange-red color persisted in the acetone layer. Stirring was continued for 0.5 hr, then isopropyl alcohol was added to destroy the excess reagent. To the resulting mixture 100 ml of water and 100 ml of ether were added, the phases were separated, and the aqueous layer was extracted with two 50-ml portions of ether. The ethereal solution was washed with three 100-ml portions of a 15% aqueous sodium carbonate solution, and the combined washings were acidified with dilute HCl and extracted with three 100-ml portions of ether. After drying (Na_2SO_4), filtration, and evaporation of the solvent, 2.08 g of a light yellow solid was obtained: mp 135–142°; ir (KBr) 1720 (acid C=O), 1680 cm^{-1} (C=O); nmr ($CDCl_3$) 10.0 ppm (s, 1, position varies upon dilution, COOH).

C.—The residue was taken up into 50 ml of ether and sufficient diazomethane[29] in an ethereal solution was added at 0° to assure the persistence of the characteristic yellow color. Acetic acid was introduced to destroy the excess reagent and the solution was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude light yellow product weighed 2.02 g, which represented a 42.4% yield from **18**. A portion of this residue (0.92 g) was chromatographed by absorption on activated alumina (25.0 g)

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(25) G. Büchi, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **31**, 241 (1948).
(26) L. Re and H. Schinz, *ibid.*, **41**, 1695 (1958).
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and eluted with 200 ml of dry benzene. Evaporation of the solvent gave 0.47 g of product.

An analytical sample was obtained by rechromatographing the above material on acid-washed alumina (38.0 g). Elution with 100 ml of dry hexane provided pure **19**: ir shows no absorptions above 3000 cm^{-1}; nmr (CCl_4) 3.69 ppm (s, 3, OCH_3).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.35. Found: C, 70.63; H, 9.48.

10-Carbethoxy-7,7-dimethyl-2-hydroxymethylene-*cis*-decal-1-one (20).—To a cold suspension of NaH (0.45 g of a 53% dispersion in mineral oil, 0.010 mol) in 4 ml of dry benzene was added dropwise, over a 10-min period, **19** (0.50 g, 0.0021 mol) and ethyl formate (0.75 g, 0.010 mol, distilled from P_2O_5) in 2 ml of dry benzene. After an initial induction period the reaction began spontaneously at room temperature with a rapid evolution of gas and was complete in 12 hr. Additional ethyl formate (15.0 g, 0.203 mol) was added to ensure the complete conversion to the ethyl ester. After stirring for a total of 24 hr at room temperature, 5 ml of water was added followed by 50 ml of ether. The organic material was extracted with three 25-ml portions of a 2% aqueous sodium hydroxide solution. The aqueous mixture was acidified with dilute HCl and extracted with three 25-ml portions of ether. Drying (Na_2SO_4) and evaporation of the solvent provided 0.37 g of a thick orange-red oil which was used directly in the following step without further purification: nmr (CCl_4) 8.52 (s, CHO), 7.40 ppm (s, vinyl). These two resonance peaks vary in intensity but not in position upon dilution. The integrated area of the two peaks is $^1/_{24}$ of the total resonance signal, equivalent to one proton.

Evaporation of the original ethereal solution led to the recovery of 0.12 g of **19**.

2-*n*-Butylthiomethylene-10-carbethoxy-7,7-dimethyl-*cis*-decal-1-one.—The hydroxymethylene derivative (**20**) prepared as above (0.37 g, 0.0010 mol) and *n*-butyl mercaptan (4.50 g, 0.0500 mol) were refluxed for 6 hr in 30 ml of dry benzene to which had been added 0.1 g of *p*-toluenesulfonic acid. The solution was washed with two 10-ml portions of a 2% sodium hydroxide solution and dried (Na_2SO_4), and the solvent was evaporated under dry air to yield 0.57 g of product: ir 1670 (C=O), 1550 cm^{-1} (C=C); nmr (CCl_4) 7.35 ppm (s, 1, vinyl).

10-Carbethoxy-2,7,7-trimethyl-*cis*-decal-1-one (2).—The unpurified thio compound was dissolved in 25 ml of 95% ethanol. Raney nickel (type W-2, *ca.* 1.0 g) was added, and the suspension was refluxed for 3 hr. Filtration and evaporation of the solvent under dry air yielded 0.28 g of **2**. This represents a 73% yield for the last three steps based on unrecovered **19**: ir and nmr are both very similar to those of **19**, but with nmr integration indicating the presence of three additional methyl protons.

An analytical sample was obtained by absorption of a portion of the material (0.13 g) on acid-washed alumina (5.0 g). Successive 30-ml portions of the following solvents were then run through the column: hexane, benzene, 30% ether–70% benzene, 30% ether–70% benzene, absolute methanol. The purest material was recovered upon evaporation of the first ether–benzene fraction. The sample weighed 0.0213 g.

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.84; H, 9.75.

Registry No.—**1**, 33122-28-0; **2**, 33065-73-5; **6**, 33065-74-6; **7**, 33065-75-7; **8**, 33065-76-8; **9**, 33065-77-9; **15**, 33122-29-1; **16**, 33065-78-0; **17**, 33065-79-1; **18**, 33065-80-4; **18** (keto acid), 33065-81-5; **19**, 33069-12-4; **20**, 33069-13-5; 10β-methyl-1α-carbomethoxy-5β-tetrahydropyranyloxy-*trans*-2-decalone, 7381-72-8; 10β-methyl-1α-carbomethoxy-5α-tetrahydropyranyloxy-*trans*-2-decalone, 33069-15-7; 2-*n*-butylthiomethylene-10-carbethoxy-7,7-dimethyl-*cis*-decal-1-one, 33069-16-8.

Notes

Oxidation of Penicillin and Dihydrocephalosporin Derivatives with Ozone

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A recent publication revealed that ozone under certain conditions is an ideal reagent for converting penicillins into mixtures of *R* and *S* sulfoxides.[1] This communication details the reactions of ozone with various penicillin and cephalosporin derivatives. The results of the oxidation of various penicillin derivatives with ozone are shown in Table I. The determination of the *S* and *R* sulfoxide isomers was accomplished by a study of the nmr chemical shifts.[2,3]

Of particular interest is the high-yielding conversion of 6-aminopenicillanic acid (6-APA) (**1**) into analytically pure, noncrystalline 6-APA sulfoxide having an *S*/*R* ratio of approximately 4/1 as determined from the products formed by acylation with phenoxyacetyl chloride.

Essery, *et al.*, have previously reported the synthesis of 6-APA sulfoxide in 8% yield by oxidation of 6-APA with sodium metaperiodate;[4] the stereochemistry from the latter synthesis, however, has been shown to be *S*, as is the case when various penicillins are oxidized with sodium metaperiodate.[2,5]

Further examination of Table I indicates that the various penicillin compounds exhibit a steric effect on the approach of the ozone molecule which consequently affects the stereochemistry of the resulting sulfoxide. Thus the sulfoxides of the nucleus (**1**) exhibit an *S*/*R* ratio of 4/1 as compared to those of compound **2** with a 1/1 ratio and to the 2-β-acyloxymethyl compound **4** with an *S*/*R* ratio of 1/2. Oxidation of the bulky β-phthalimidopenicillanic acid (**5**) resulted in only the *R* sulfoxide. However, this could possibly result from an *S* to *R* conversion *via* the olefin sulfenic acid, with the driving force being the release of strain between the

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