dis.[6] In the present instance compounds I, IV, and V exhibited only a sharp singlet for the C-18 methyl at τ 8.95, 8.99, and 9.00.[7]

Examination of the infrared spectrum[8] of IV demonstrated the presence of both free and hydrogen-bonded hydroxyl at 3609 cm and 3390 cm.$^{-1}$. The latter disappeared after a *ca.* 50-fold dilution, indicating intermolecular hydrogen bonding for this compound. Compound V showed only a single peak at 3589 cm.$^{-1}$. The shift of 20 cm.$^{-1}$ with V compared with IV is in accord with the $\Delta\mu$ of 19 cm.$^{-1}$ observed by Schleyer and West[9] for intermolecular hydrogen bonding with a methanol–*n*-butyl fluoride system.

It is interesting to note that polarities could not be used with confidence for structure determinations in this series. Compounds II and III were not separated by silica gel, thin layer chromatography using ether–benzene (3:2) as the eluent. However, compounds IV and V showed the expected polarities, with IV slightly more polar than V [ΔR_f 0.08 on silica gel using ether–benzene (2:3) as the eluent].

Compounds IV and V were tested in the Merck Institute for Therapeutic Research.[10] Compound IV was 0.5 times as active as 21-chloroethisterone, s.c. (2.5 times ethisterone), in the Clauberg assay.[11] In the pituitary gonadotrophin inhibition test[12] IV was 0.2 times as active as Norlutin, s.c. Compound V was inactive in both assays.

Experimental[13]

16α-Fluoro-17α-chloroethynyl-4-androstene-3β,17β-diol (II) and 16α-Fluoro-17β-chloroethynyl-4-androstene-3β,17α-diol (III).—A solution consisting of 3.84 g. of *cis*-1,2-dichloroethylene in 15 ml. of sodium-dried ether was added to a stirred solution consisting of 7.6 ml. of 1.30 *N* methyllithium in 15 ml. of sodium-dried ether maintained under 1 atm. of nitrogen and cooled by an ice bath. Stirring was continued for an additional 15 min. after removal of the ice bath, followed by the dropwise addition of 500 mg. of 16α-fluoro-Δ^5-androsten-3β-ol-17-one in 45 ml. of sodium-dried ether over a 5-min. period. After an additional 1.7 hr. the reaction mixture was poured into ice–water and ether. The ether layer was separated, washed with water, dried over potassium carbonate, and concentrated *in vacuo* to yield 614 mg. of an off-white foam. Crystallization from ether afforded 308 mg. of 16α-fluoro-17β-chloroethynyl-5-androstene-3β,17α-diol (III), m.p. ~185–238°. A sample for analysis, prepared in an analogous reaction with protection of the C-3β-ol as the tetrahydropyranyl ether, was crystallized several times from methanol, m.p. 255–256°, $[\alpha]_D$ −37°.

Anal. Calcd. for $C_{21}H_{25}ClFO_2$: C, 68.74; H, 7.69; F, 5.18. Found: C, 68.38; H, 7.54; F, 4.94.

Evaporation of the filtrate afforded a yellow gum which on crystallization from cyclohexane with a trace of methylene chloride yielded 225 mg. of 16α-fluoro-17α-chloroethynyl-5-androstene-3β,17β-diol (II), m.p. 100–105°. A sample for analysis was crystallized from benzene, m.p. 100–105°; $[\alpha]_D$ −145°.

Anal. Found: C, 69.28; H, 8.18; F, 4.80.

16α-Fluoro-17α-chloroethynyl-4-androsten-17-β-ol-3-one (IV).—To a stirred solution consisting of 1.0 g. of II in 50 ml. of acetone and maintained under 1 atm. of nitrogen was added 0.63 ml. of 8 *N* Jones[4] reagent. Stirring was continued for 5 min., followed by dilution of the reaction mixture with 200 ml. of ether. The ether suspension was washed with water, saturated aqueous sodium bicarbonate solution, and water, and then dried over potassium carbonate and concentrated *in vacuo* to yield 855 mg. of a colorless foam. The crude 3-keto Δ^5-steroid and 86 mg. of *p*-toluenesulfonic acid were dissolved in 25 ml. of acetone and left at room temperature overnight. The solution was concentrated to about 5 ml. *in vacuo*, diluted with ether, and washed with saturated aqueous sodium bicarbonate solution and water, dried over magnesium sulfate, and concentrated *in vacuo* to yield 825 mg. of a colorless foam. After setting aside 50 mg., the remainder was chromatographed on 47 g. of acid-washed alumina. Elution with benzene–ether (3:1) afforded 289 mg. of 16α-fluoro-17α-chloroethynyl-4-androsten-17β-ol-3-one (IV), double m.p. 100–105°, 166–169°. Three crystallizations from ethyl acetate afforded a sample for analysis: double m.p. 100–105°, 191–193°; $[\alpha]_D$ +47°; ultraviolet spectrum, λ_{max}^{MeOH} 241 mμ (ε 16,600).

Anal. Calcd. for $C_{21}H_{26}ClFO_2$: C, 69.12; H, 7.18; F, 5.21. Found: C, 69.15; H, 6.87; F, 5.36.

16α-Fluoro-17β-chloroethynyl-4-androsten-17α-ol-3-one (V).—Starting with 1.50 g. of III, Jones oxidation and acid-catalyzed isomerization afforded 714 mg. of V. A sample for analysis was crystallized two times from ethyl acetate: m.p. 198–200°; $[\alpha]_D$ +136°; ultraviolet spectrum, λ_{max}^{MeOH} 242 mμ (ε 16,950).

Anal. Found: C, 69.14; H, 7.10; F, 5.10.

(6) A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, **84**, 3784 (1962).

(7) N.m.r. spectra were taken in deuteriochloroform with a Varian HR-60 spectrometer. We are indebted to B. Arison and Dr. N. R. Trenner for these determinations.

(8) Infrared spectra were measured on a Perkin Elmer 421 spectrometer in CCl_4 solution. We are indebted to R. Walker for the infrared analysis.

(9) P. von R. Schleyer and R. West, *J. Am. Chem. Soc.*, **81**, 3164 (1959).

(10) We are indebted to Drs. S. L. Steelman and D. Patanelli for carrying out this determination.

(11) M. K. McPhail, *J. Physiol.* (London), **83**, 145 (1934).

(12) J. A. Epstein, H. S. Kupperman, and A. Cutler, *Ann. N. Y. Acad. Sci.*, **71**, 560 (1958).

(13) Melting points were taken on a micro hot stage and are corrected. Rotations were determined in chloroform at *ca.* 25° at a concentration of 7 mg./ml. We are indebted to A. Kalowski for the ultraviolet spectra and to R. Boos and his associates for the microanalysis herein reported.

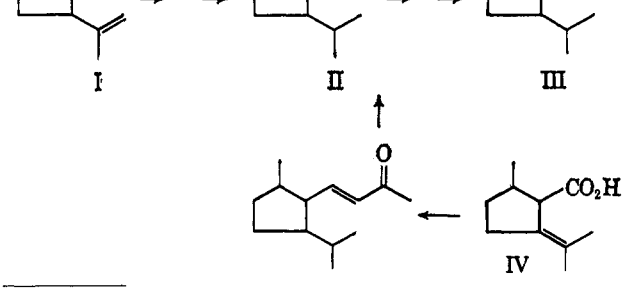
Synthesis of 4-(2-Methyl-5-isopropenyl-1-cyclopenten-1-yl)butan-2-one. A By-Product in the Synthesis of Pseudoionone

JOSEPH WOLINSKY, MICHAEL R. SLABAUGH,[1] AND THOMAS GIBSON

Department of Chemistry, Purdue University, Lafayette, Indiana

Received July 20, 1964

The thermal isomerization of dehydrolinalyl acetoacetate produces, in addition to the commercially valuable pseudoionone, an appreciable amount of a ketone $C_{13}H_{20}O$.[2-5] Kimel[3] and Saucy[5] identified this by-product as ketone I on the basis of a comparison of its degradation products II and III with authentic II and



(1) Participant in the National Science Foundation Undergraduate Research Program, summer, 1963.

(2) P. Teisseire, *Recherches* (Paris), **5**, 3 (1955).

(3) W. Kimel, N. W. Sax, S. Kaiser, G. G. Eichmann, G. O. Chase, and A. Ofner, *J. Org. Chem.*, **23**, 153 (1958).

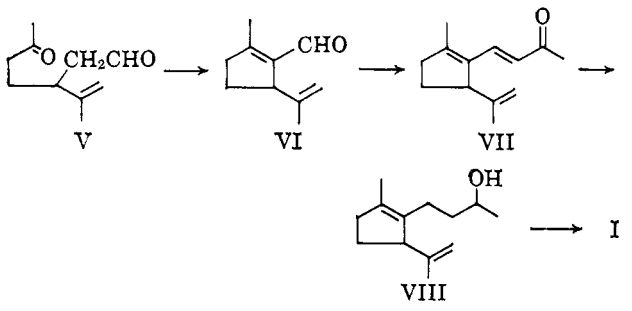
(4) O. Isler, L. H. Chopard, W. Geux, G. Ryser, and G. Saucy, *Chimia* (Aarau), **11**, 103 (1957).

(5) G. Saucy, L. H. Chopard, W. Geux, G. Ryser, and O. Isler, *Helv. Chim. Acta*, **41**, 160 (1958).

III derived from pulegenic acid (IV): The identity of these compounds was indicated by infrared comparison and mixture melting point determinations.

It has recently been demonstrated[6] that the pulegenic acid, produced by the action of sodium methoxide or sodium ethoxide[7,8] on pulegone dibromide, is the *trans* isomer; consequently, II and III derived from pulegenic acid should have the methyl group at C-1 oriented predominantly *trans* to the substituents at C-2.[9] The formation of II and III from ketone I, on the other hand, involved a catalytic hydrogenation step which should proceed largely by *cis* addition of hydrogen to give isomers with the methyl group at C-1 *cis* to the substituents at C-2. Furthermore, we have found it impossible to distinguish between certain isomeric compounds derived from or closely related to pulegenic acid on the basis of their infrared spectra. Thus, the *four* isomeric 2-acetoxymethyl-3-isopropenyl-1-methylcyclopentanes, 2-acetoxymethyl-3-isopropenyl-1-methyl-1-cyclopentene, and 3-(1-acetoxyethyl)-1-isopropenylcyclopentane exhibit essentially identical infrared spectra.[10] We must conclude, therefore, that the structure assigned to ketone I is open to question.

The availability of 2-methyl-5-isopropenyl-1-cyclopentene-1-carboxaldehyde (VI) in connection with another problem suggested its conversion into ketone I according to the scheme outlined below. These



transformations have been accomplished and the structure originally suggested for ketone I has been confirmed.

Aldehyde VI was obtained from the keto aldehyde V[11] by cyclization with piperidine–acetic acid.[12] The aldehyde VI was transformed into the unsaturated ketone VII on treatment with acetone and alkali. Reduction of VII with sodium and ethanol gave the alcohol VIII which on oxidation according to the Jones procedure[13] gave ketone I. The structure of I was fully confirmed by its infrared and n.m.r. spectra (see Experimental). The identity of the synthetic ketone I with that derived from pyrolysis of dehydrolinalyl acetoacetate was established by spectral and gas chromatographic comparison and by the identity of the infrared spectra of their 2,4-dinitrophenylhydrazone derivatives.

(6) J. Wolinsky, H. Wolf, and T. Gibson, *J. Org. Chem.*, **28**, 274 (1963).

(7) H. Rupe and K. Schafer, *Helv. Chim. Acta*, **11**, 466 (1928).

(8) S. A. Achmad and G. W. K. Cavill, *Australian J. Chem.*, **16**, 858 (1963).

(9) Kimel's[8] conversion of IV into II involved a base-catalyzed condensation of 5-isopropenyl-2-methyl-1-cyclopentanecarboxaldehyde with acetone. It is quite possible that base-catalyzed epimerization of the aldehyde at C-1 might have preceeded the aldol condensation. Equilibration of pure *trans*-methyl pulegenate with sodium methoxide in methanol (J. Wolinsky and D. Chan, unpublished results) affords a mixture of 74% *trans*- and 26% *cis*-methyl pulegenates. It seems reasonable to assume that if epimerization of 5-isopropenyl-2-methyl-1-cyclopentanecarboxaldehyde occurred the *trans* isomer would predominate and lead ultimately to II where the substituents at C-1 and C-2 are largely *trans*.

(10) See also C. Djerassi, T. Nakano, A. N. James, L. H. Zalkow, E. J. Eisenbraun, and J. N. Shoolery, *J. Org. Chem.*, **26**, 1192 (1961).

(11) J. Wolinsky and W. Barker, *J. Am. Chem. Soc.*, **82**, 636 (1960).

(12) This cyclization is to be contrasted with the exclusive formation of 1-acetyl-4-isopropenyl-1-cyclopentene when the keto aldehyde V in ether is stirred with aqueous alkali.[11]

(13) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(14) All boiling and melting points are uncorrected. Vapor phase chromatographic analyses and separations were conducted on a Carbowax 20M column. The n.m.r. spectra were obtained with the Varian Associates A-60 spectrometer. The microanalyses were performed by Dr. C. S. Yeh and associates.

Experimental[14]

2-Methyl-5-isopropenyl-1-cyclopentene-1-carboxaldehyde (VI).—To a solution of 61.2 g. (0.36 mole) of 8-*p*-menthene-1,2-diol[11] in 150 ml. of tetrahydrofuran was added 100 g. (0.46 mole) of sodium metaperiodate in 400 ml. of water. The resulting mixture was kept at 0° for 6 days, filtered to remove sodium iodate, and extracted with methylene chloride. Distillation gave the keto aldehyde V, b.p. 80.5–82° (1 mm.), $n^{25.5}$D 1.4580. A solution of 50 g. of crude keto aldehyde V in 300 ml. of benzene containing 3 ml. of piperidine and 3 ml. of acetic acid was heated to reflux for 1 hr. during which time water was removed by use of a Dean–Stark trap. The benzene solution was cooled, washed with dilute hydrochloric acid and dilute sodium carbonate solution, and was then dried. Distillation afforded 29.7 g. (59%) of a colorless oil: b.p. 50–58° (0.5 mm.), n^{20}D 1.5056, $[\alpha]$D +61.5° (*c* 8.01, EtOH); ν_{max} 3.65, 6.10, 6.13, and 11.25 mμ; λ_{max} (EtOH) 250 mμ (ε 11,800); n.m.r. signals at 1.53 (CH_3—C=C), 2.03 (CH_3—C=C—CO—), 3.29 (C=C—CH—C=C), 4.35 (—C=CH_2), and 9.24 (CHO) p.p.m.

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.92; H, 9.71.

The 2,4-dinitrophenylhydrazone derivative of aldehyde VI was recrystallized from ethanol and showed m.p. 173–174°, λ_{max}^{EtOH} 386 mμ (ε 30,400).

Anal. Calcd. for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49. Found: C, 58.21; H, 5.57.

4-(2-Methyl-5-isopropenyl-1-cyclopenten-1-yl)-3-buten-2-one (VII).—To a solution prepared from 25 ml. of 3 *N* sodium hydroxide and 100 ml. of acetone was added dropwise a solution of 10.0 g. (0.07 mole) of aldehyde VI in 100 ml. of acetone. The resulting mixture was kept at room temperature for 15 hr. The organic layer was separated, dried, and distilled to yield 9.0 g. of the unsaturated ketone VII: b.p. 97–98° (0.5 mm.); a v.p.c. purified sample of the ketone VII displayed n^{20}D 1.5495, ν_{max} 6.02, 6.21, 6.32, and 11.25 μ; λ_{max} 297 mμ (ε 12,000); n.m.r. signals at 1.59, 1.97 (2 CH_3—C=C), 2.16 (CH_3—C=O), 3.5 (C=C—CH—C=C), 4.68 (C=CH_2), and 5.85, 6.12, 7.16, 7.43 (—CH=CH—C=O) p.p.m.

The 2,4-dinitrophenylhydrazone derivative of ketone VII exhibited m.p. 156.5–157.5° after it was recrystallized from ethanol.

Anal. Calcd. for $C_{19}H_{22}N_4O_4$: C, 61.61, H, 5.99; N, 15.13. Found: C, 61.86; H, 6.17; N, 15.04.

The semicarbazone derivative of ketone VII was recrystallized from ethanol and showed m.p. 159–160°.

Anal. Calcd. for $C_{14}H_{21}N_3O$: C, 67.98; H, 8.56; N, 16.99. Found: C, 67.96; H, 8.77; N, 16.70.

4-(2-Methyl-5-isopropenyl-1-cyclopenten-1-yl)butan-2-ol (VIII).—Sodium (4.5 g., 0.19 g.-atom) was added in small pieces to a solution of 5.7 g. (0.03 mole) of unsaturated ketone VII in 80 ml. of absolute ethanol. After stirring for 1 hr., 30 ml. of water was added and the resulting solution was extracted with ether. Distillation gave 1.0 g. of forerun, b.p. 68–80 (1 mm.) and 2.0 g. of alcohol VIII, b.p. 80–84° (1 mm.). A redistilled sample of alcohol VIII showed n^{22}D 1.4889; ν_{max} 3.0, 3.29, 6.13, and 11.28 μ; n.m.r. signals at 1.04, 1.15 (CH_3—CH—O), 1.54, 1.68 (2 CH_3—C=C), broad 3.24 (C=C—CH—C=C), a multiplet centered at 3.62 (—CH—O), and 4.64 (C=CH_2) p.p.m.

Anal. Calcd. for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 79.87; H, 11.40.

Ketone I.—To a solution of 2.0 g. of alcohol VIII in 25 ml. of acetone was added dropwise 2.3 ml. of 8 *N* CrO_3 solution.[13] The resulting mixture was filtered and the filtrate was distilled to give 1.5 g. of ketone I, b.p. 77–78° (0.8 mm.). A sample of ketone I purified by v.p.c. showed $n^{23}D$ 1.4815; $[\alpha]D$ +124° (*c*, 0.89, EtOH); ν_{max} 3.28, 5.85, 6.10, and 11.25 μ; n.m.r. signals at 1.56, 1.68 (2 CH_3—C=C), 2.0 (CH_3—C=O), broad 3.22 (C=C—CH—C=C), and 4.66 (C=CH_2) p.p.m. The infrared and n.m.r. spectra were identical with those of a sample of ketone I supplied by Dr. W. Kimel.[15]

The 2,4-dinitrophenylhydrazone of ketone I showed m.p. 68.5–69° after being recrystallized from ethanol. The 2,4-dinitrophenylhydrazone of the optically inactive ketone supplied by Dr. Kimel exhibited m.p. 88–90°, lit.[16] m.p. 88–89°. The infrared spectra of the two derivatives, when measured in chloroform solution, were identical.

(15) The authors wish to express their gratitude to Dr. W. Kimel for providing a generous sample of ketone I isolated from the pyrolysis of dehydrolinalyl acetoacetate.

(16) Y. R. Naves, P. Ardizio, and B. Wolf, *Bull. soc. chim. France*, 1213 (1957).