Isomerization as described under *cis*-1-cyclohexenyl-1-propene gave the *trans* isomer, $n^{20}D$ 1.5021, λ_{max} 233 mμ (ε 23,000), J_{AB} = 16 c.p.s. A value of $n^{20}D$ 1.5028, λ_{max} 234 mμ (ε 23,700), has been reported for this isomer.[17] An analytical sample of the *cis* isomer was prepared by gas chromatography.

Anal. Calcd. for $C_{10}H_{16}$: C, 88.18; H, 11.82. Found: C, 88.24; H, 11.41.

Gas Chromatographic Analyses.—Analyses were performed on a Perkin-Elmer 154B gas chromatograph. The analysis of the products from reduction of 1-ethynylcyclohexene was made on a 6 ft. × 0.25 in. column containing 20% Reoplex 400 on Chromosorb W at 110°. The studies on reduction of 1-cyclohexenyl-1-propyne and 1-cyclohexenyl-1-butyne were made on the same column at 140°. Analysis of the mixture from 1-cyclohexenyl-3-buten-1-yne was carried out on a 6 ft. × 0.25 in. column containing 5% Ucon Polar on firebrick at 164°. All components were identified by comparison with internal standards prepared by synthesis. Helium was used as carrier gas.

1-Alkylcyclohexenes.—A series of 1-alkylcyclohexenes was prepared for internal standards. In each case the necessary Grignard reagent prepared from an alkyl halide and magnesium in ether was allowed to react with cyclohexanone. The distilled alkylcyclohexanols were distilled from anhydrous potassium acid sulfate using the general procedure of Ohloff.[18] The following were prepared in this way.

1-Ethylcyclohexene.—The product was obtained in 42% overall yield: b.p. 54–56° (47 mm.), $n^{20}D$ 1.4564; lit.[19] b.p. 136°, $n^{20}D$ 1.4562.

1-Propylcyclohexene.—This hydrocarbon was obtained in 15% over-all yield as a light oil: b.p. 70–73° (53 mm.), $n^{20}D$ 1.4565; lit.[20] b.p. 154.7–157.7°, $n^{20}D$ 1.4578.

1-Butylcyclohexene.—This olefin was prepared in 34% overall yield: b.p. 65–68° (28 mm.), $n^{20}D$ 1.4606; lit.[20] b.p. 178–179°, $n^{20}D$ 1.4568.

N.m.r. Spectra.—The n.m.r. spectra were run on a Varian A-60 n.m.r. spectrometer[22] in carbon tetrachloride solution using tetramethylsilane as an internal standard.

(17) O. Grummitt and Z. Mandel, *J. Am. Chem. Soc.*, **78**, 1054 (1956).

(18) G. Ohloff, *Ann.*, **627**, 79 (1959).

(19) R. A. Benkeser and J. J. Hazdra, *J. Am. Chem. Soc.*, **81**, 228 (1959). $n^{20}D$ 1.4562.

(20) F. K. Signaigo and P. L. Cramer, *ibid.*, **55**, 3326 (1933).

(21) R. A. Benkeser, C. Arnold, Jr., R. F. Lambert, and O. H. Thomas, *ibid.*, **77**, 6042 (1955).

(22) We are indebted to the National Science Foundation for a grant which provided part of the funds for purchase of this instrument.

Chloromethylation of Estrone Methyl Ether

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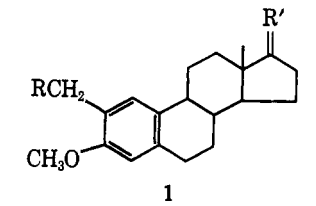
The chloromethylation reaction represents a classical method for the introduction of a functional group into an aromatic system.[1] Its application to the activated A ring of estrone derivatives was explored as a potential route to C-2 and C-4 substituted steroids.[2,3]

The title reaction was seen to proceed smoothly with aqueous formaldehyde and hydrogen chloride, no additional catalyst being necessary. The resultant mixture of chloromethyl compounds was best utilized by displacement of the halogen by acetate ion. Subsequent hydrolysis provided, by direct crystallization, 40% of the 2-hydroxymethyl derivative **1a**. Structural assignment was made on the basis of the infrared absorption (12.0 μ)[4] and the n.m.r. spectrum (two singlets in the aromatic region). The nature of the hydroxyl group was demonstrated by manganese dioxide oxidation to the corresponding aldehyde **4**. In addition, a facile hydrogenolysis over palladium catalyst afforded the 2-methyl derivative **1d**.

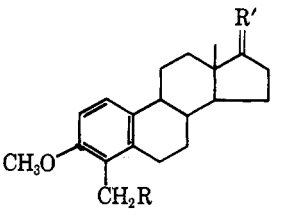
Investigation of the mother liquors revealed as a minor constituent the 4-hydroxymethyl derivative **2a**. The n.m.r. spectrum of this compound showed the AB pattern expected for the vicinal aromatic protons, in accord with the assignment made from the infrared spectrum (12.3 μ). Again, hydrogenolysis afforded the methyl derivative **2d**.

Direct hydrolysis of the chloromethylation mixture in aqueous dioxane containing potassium hydroxide afforded a lower yield of the hydroxymethyl derivatives owing to a competitive formation of dimeric materials such as **3**. When methanol was substituted as solvent the methoxymethyl derivate **1b** was formed as demonstrated by the new methoxyl absorption in the n.m.r. spectrum. Hydrogenolysis of this compound afforded the 2-methyl derivative **1d**, although the rate of reaction was much slower than that seen for hydrogenolysis of the hydroxy derivative **1a**.

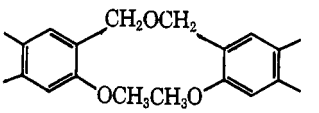
Hydride reduction of the 17-carbonyl groups in **1a**, **1d**, **2a**, and **2d** proceeded normally to furnish the corresponding alcohol derivatives. The derivatives **1d** and **2d** showed especially clearly the infrared distinction due to aromatic protons.[4]



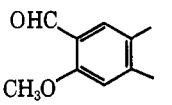
1



2



3



4

a, R = OH; R′ = O
b, R = OCH_3; R′ = O
c, R = R′ = OH
d, R = H; R′ = O
e, R = H; R′ = OH

Experimental Section[5,6]

2-Hydroxymethylestrone 3-Methyl Ether (1a).—A stream of hydrogen chloride was passed through a stirred solution of 15 g. of estrone methyl ether in 150 ml. of ethylene dichloride and 10 ml. of 40% aqueous formaldehyde at 20°. After 2 hr. an additional 10 ml. of aqueous formaldehyde was added. After a total of 6 hr. the solution was diluted with aqueous sodium carbonate and extracted with chloroform. Chromatography of a portion of the resultant crude product failed to yield a crystalline com-

(1) R. C. Fuson and C. H. McKeever, *Org. Reactions*, **1**, 63 (1942).

(2) See W. M. Hoehn and W. F. Johns [U. S. Patent 2,853,501 (1958)] for the initial disclosure of a portion of this work.

(3) More recent work of a similar nature includes the Mannich addition described by T. L. Patton [*J. Org. Chem.*, **25**, 2148 (1960)] and extended by H. Kaneko, M. Hashimoto, and A. Kobayashi [*Chem. Pharm. Bull.* (Tokyo), **12**, 196 (1964)].

(4) Infrared distinction between isolated and adjacent hydrogens on an aromatic ring in steroids has been pointed out by A. S. Dreiding, W. J. Pummer, and A. J. Tomasewki [*J. Am. Chem. Soc.*, **75**, 3159 (1953)].

(5) Infrared spectra were determined as KBr disks, ultraviolet spectra in methanol, rotations in chloroform (1%), and n.m.r. spectra in deuteriochloroform ($\Delta\nu$ = 0 from tetramethylsilane as an internal standard, with a Varian A-60 spectrometer). The spectral and analytical data reported were furnished by Dr. R. T. Dillon and staff.

(6) The chromatography described was carried out by Dr. E. G. Daskalakis and staff, using silica gel as adsorbent.

ponent. The remainder of the material (12.4 g.) and 40 g. of freshly fused sodium acetate in 200 ml. of acetic acid was heated at 100° for 5 hr. The solution was cooled, diluted with water, and extracted with chloroform. The resultant product, 13.1 g. of a halogen-free oil, was saponified in 100 ml. of methanol and 50 ml. of water containing 25 g. of potassium carbonate (1 hr. at reflux). Chloroform extraction of the reaction mixture yielded 10.7 g. of product. Crystallization and recrystallization from acetone afforded 4.08 g. of alcohol **1a**, m.p. 154–157°. Another recrystallization from acetone–cyclohexane afforded the analytical sample: m.p. 163–164°; λ_{max} 2.73, 5.72, 12.0 μ; λ_{max} 280 mμ (log ϵ 3.45), 286 mμ (log ϵ 3.45); $\Delta\nu$ 277 (CH_2OH), 397 (C-4 *H*), 432 (C-1 *H*) c.p.s.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.41; H, 8.13.

The mother liquors were chromatographed on silica. Fractions eluted with 10% ethyl acetate in benzene were combined and recrystallized twice from acetone, yielding 0.80 g. of **4-hydroxymethylestrone 3-methyl ether** (**2a**), m.p. 193–197°. Another recrystallization from acetone afforded the pure material: m.p. 200–202°; λ_{max} 2.84, 5.78, 12.3 μ; λ_{max} 282 mμ (log ϵ 3.37), 288 mμ (log ϵ 3.36); $\Delta\nu$ 282 and 287 (CH_2OH), 401, 410, 431, 440 (C-1 and C-2 *H*) c.p.s. On D_2O exchange the CH_2OH doublet became a singlet at 284 c.p.s.

Anal. Found: C, 76.40; H, 8.62.

When the chloromethylation product was hydrolyzed in aqueous dioxane containing potassium hydroxide, the yields of the two hydroxymethyl compounds (**1a** and **2a**) were lower. An amorphous material (20% of the total, mol. wt. 525) was eluted with 2% ethyl acetate–benzene. A portion crystallized and was recrystallized from acetone to yield a material (**3**): m.p. 208–210°; λ_{max} 5.76 μ; $\Delta\nu$ 275 ($-CH_2O$), 395 (C-4 *H*), 441 (C-1 *H*) c.p.s.; mol. wt. 561.

2-Methoxymethylestrone 3-Methyl Ether (**1b**).—The chloromethylation of 10 g. of estrone methyl ether was carried out as described above. The crude chloromethyl mixture was boiled for 4 hr. in 80 ml. of methanol and 40 ml. of water containing 20 g. of potassium carbonate. The product (11 g. of semicrystalline material) was isolated by ether extraction and chromatographed on silica. The fractions eluted with 5% ethyl acetate–benzene were recrystallized from acetone, yielding 1.32 g. of crystalline material, m.p. 110–118°. An additional recrystallization of this material from acetone–petroleum ether gave the pure ether **1b**: m.p. 123–125°; λ_{max} 5.73 μ; λ_{max} 281 mμ (log ϵ 3.44), 286 mμ (log ϵ 3.44); $\Delta\nu$ 204 (OCH_3), 227 (OCH_3), 267 (CH_2OCH_3), 395 (C-4 *H*), 435 (C-1 *H*) c.p.s.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.52; H, 8.37.

In addition to **1b**, both hydroxymethyl compounds **1a** and **2a** were obtained.

2-Hydroxymethylestradiol 3-Methyl Ether (**1c**).—A solution of 0.46 g. of the hydroxymethyl compound **1a** in 5 ml. of tetrahydrofuran was added to a solution of 0.50 g. of lithium aluminum hydride in 40 ml. of ether. The mixture was stirred at room temperature for 1 hr. and then was diluted slowly with ethyl acetate. Water was added and the product was extracted with ether, yielding 0.42 g. of a crystalline product. Recrystallization from acetone yielded 0.35 g. of the 17-hydroxy compound **1c**, m.p. 195–198°, recrystallized from methanol–ethyl acetate to afford the pure diol, m.p. 198–200°, λ_{max} 3.02 μ.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.86; H, 8.91.

4-Hydroxymethylestradiol methyl ether (**2c**) was prepared by a similar reduction of the ketone **2c**. Recrystallization of the very insoluble product from boiling Cellosolve afforded the pure compound, m.p. 259–263°, λ_{max} 3.04 μ.

Anal. Found: C, 76.04; H, 8.84.

Hydrogenolysis Experiments.[7]—A solution of 1.53 g. of the 2-hydroxymethyl derivative **1a** in 30 ml. of acetic acid and 1.0 g. of 5% palladium-on-carbon catalyst was stirred in an atmosphere of hydrogen. After 45 min., uptake of hydrogen ceased. The mixture was filtered, the solvent was distilled, and the resulting residue was recrystallized from hot petroleum ether (b.p. 60–70°) (Darco) to provide 0.83 g. of 2-methylestrone 3-methyl ether (**1d**): m.p. 152–153°; λ_{max} 5.76, 12.02 μ; $\Delta\nu$ 129 (Ar-CH_3), 392 (C-4 *H*), 422 (C-1 *H*) c.p.s.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.30; H, 8.63.

(7) The hydrogenations were performed by Mr. W. M. Selby and staff.

The same compound was prepared by O-methylation of 2-methylestrone,[8] using methyl iodide–potassium carbonate.

Reduction of 0.20 g. of the methoxy compound **1b** required 18 hr. and afforded 80 mg. of the pure 2-methyl compound **1d**.

The same procedure yielded **4-methylestrone methyl ether** (**2d**) when the hydroxymethyl derivative **2a** was used as substrate. The reduction product was recrystallized from petroleum ether–methanol to give 0.36 g. of the pure 4-methyl derivative **2d**: m.p. 159–160°; λ_{max} 5.78, 12.43 μ; $\Delta\nu$ 127 (ArCH_3) c.p.s.

Anal. Found: C, 80.83; H, 8.71.

Reduction of the 2-hydroxymethyl derivative **1c** during a 15-min. period and recrystallization of the product from petroleum ether yielded 50 mg. of **2-methylestradiol 3-methyl ether** (**1e**): m.p. 139–140°; λ_{max} 2.79, 11.6 μ.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.91; H, 9.66.

The same compound was prepared in good yield by lithium aluminum hydride reduction of the 2-methyl compound **1d**.

4-Methylestradiol 3-methyl ether (**2e**) was obtained by hydrogenolysis of the hydroxymethyl derivative **2c** or preferably by lithium aluminum hydride reduction of the ketone **2d** (procedure given above). The product was purified by recrystallization from petroleum ether to yield the alcohol **2e**: m.p. 170–172; λ_{max} 2.84, 12.42 μ.

Anal. Found: C, 80.04; H, 9.59.

2-Formylestrone 3-Methyl Ether (**4**).—A solution of 0.65 g. of the hydroxymethyl derivative **1a** in 30 ml. of chloroform was stirred with 0.60 g. of manganese dioxide for 72 hr. The solution was filtered through Super-Cel and the filtrate was concentrated, yielding 0.40 g. of crystals, m.p. 155–160°. Recrystallization of this material from acetone–petroleum ether gave the pure aldehyde **4**: m.p. 170–172°; λ_{max} 5.77, 5.98 μ; λ_{max} 224 mμ (log ϵ 4.29), 266 (4.12), 332 (3.69); $\Delta\nu$ 400 (C-4 *H*), 463 (C-1 *H*), 622 (*CH*O) c.p.s.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 77.05; H, 7.66.

(8) Dr. A. Goldkamp of these laboratories kindly furnished this sample which was prepared by the method of Patton.[3]

Citrus Carotenoids. IV. The Isolation and Structure of Sintaxanthin

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In a previous communication,[2] we have described the isolation and characterization of a new carotenoid ketone from the flavedo of the fruit of the trigeneric hybrid, *Sinton citrangequat* (*Citrus sinensis* × *Poncirus trifoliata* × *Fortunella margarita*). This pigment was designated citranaxanthin and shown to be 5,9,14,18-tetramethyl-20-(2,6,6-trimethylcyclohex-1-enyl)eicosa-3,5,7,9,11,13,15,17,19-nonaene-2-one; the unusual feature of citranaxanthin is the terminal methyl ketone grouping in the side chain.

We wish to report herein the isolation and elucidation of the structure of a second carotenoid ketone from the flavedo of the *Sinton citrangequat*. This pigment is similar to citranaxanthin but possessing a nonaenone chromophore. Accordingly, we propose to call this new carotenoid sintaxanthin.

When the crude pigment extract of the flavedo of the *Sinton citrangequat* fruit collected in Feb. 1964 was

(1) A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) H. Yokoyama and M. J. White, *J. Org. Chem.*, **30**, 2481 (1965).