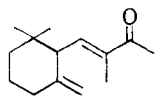
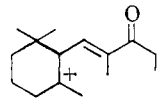


I

I is undoubtedly formed during the cyclization from the intermediate carbonium ion, II.

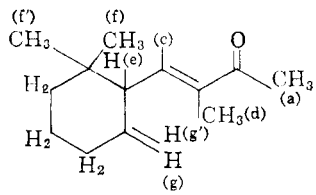


II

It has been our experience that even with the most exacting distillation techniques, γ-isomethylionone is not completely separable from the alpha and beta isomers derived from II.

The isolation of I was accomplished by preparative vapor phase chromatography. I and its alpha iso isomer were found to be separable on a polar column.

The n.m.r. spectrum of I firmly supports the proposed structure and has the following analysis.[2]



TAU VALUES

a	c	d	e	f and f[1]		g and g[1]	
7.83	3.38	8.38	7.17	9.16	9.10	5.56	5.32

($J_{c,e}$ = 9.6 c.p.s.) ($J_{e,c}$ = 10.8 c.p.s.)

This work completes the characterization of all the ionones, *n*-methylionones and isomethylionones derivable from the corresponding carbonium ion precursors.

Experimental

Commercial methylionone[3] was chromatographed through a 9-ft. 1/2-in. o.d. column packed with 15% Carbowax 20M on 60/80 mesh silane treated Celite at 170°, 120 ml. of helium per minute carrier gas, 10 p.s.i. inlet pressure. Numerous repetitive chromatograms were required, collecting only the "tail" portion of the α-isomethyl peak (the major constituent).

The collected trappings were retrapped *via* the same column. At this point n.m.r. showed approximately 10% β-isomethylionone remaining.

The latter was eliminated by trapping from a nonpolar column. (A 10-ft. 1/4-in. o.d. column, packed with Dow Corning 710 on 60/80 mesh Chromosorb, column temperature 150°, 50 ml./min. carrier gas, and 30 p.s.i. helium inlet pressure.) A complete separation of I was thus obtained.

The pure I obtained, b.p. 76°/0.3 mm., had a molecular weight of 206, as determined by the mass spectrometer[4] and analyzed as follows[5]: Calcd. C, 81.50; H, 10.75; found C, 81.78; H, 10.75; isooctane 228; ε 13,380; infrared, 1680 cm.$^{-1}$ (conjugated carbonyl); 892 cm.$^{-1}$ (vinylidene methylene).

I in glacial acetic acid with Adams platinum oxide catalyst, at atmospheric pressure, absorbed 3.0 moles of hydrogen. Chromic acid oxidation of the tetrahydroisomethylionol thus formed, gave on work-up a ketone whose semicarbazone had a m.p. of 168–171° after several recrystallizations from ethanol. Admixture with the semicarbazone of tetrahydroisomethylionone[6] showed no melting point depression.

(2) N.m.r. spectra were measured on a Varian High Resolution spectrometer, HR60. Samples were dissolved in carbon tetrachloride in 7–10% concentration (by volume). The magnetic field strength was 14,092 gauss and the oscillating frequency 60 Mc./s. Tetramethylsilane (1/4%) was used as the standard, as described by G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(3) A number of commercially available methylionones rich in α-isomethylionone were examined. All contained small amounts of I.

(4) Molecular weights were determined by the low-ionization, parent-ion technique on a Consolidated Electrodynamics Model 21-103C mass spectrometer. See, for example, F. H. Field and S. H. Hastings, *Anal. Chem.*, **28**, 1248 (1956).

(5) Microanalyses by the Schwarzkopf Microanalytical Laboratory, Woodside 77, New York.

(6) Pure tetrahydroisomethylionone was prepared by hydrogenating pure α-isomethylionone using Adams' catalyst (3 mole equivalents of hydrogen were absorbed). The resulting tetrahydroionol was subjected to chromic acid oxidation in order to obtain the tetrahydroisomethylionone.

Conversion of Dihydroquercetin to Eriodictyol

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In the original paper[1] on the isolation of dihydroquercetin (3,3′,4′,5,7-pentahydroxyflavanone) from Douglas-fir heartwood, the conversion of this substance to eriodictyol (3′,4′,5,7-tetrahydroxyflavanone) in good yield was described. This was accomplished by reducing it in alcoholic solution with zinc dust and concentrated hydrochloric acid. Wheeler[2] confirmed the reaction, and then Hergert and Kurth[3] prepared eriodictyol in this manner. Wender,[4] however, made several unsuccessful attempts to use the method and finally resorted to other means for preparing eriodictyol. Later Murray[5] reported failure.

The author secured a sample of Murray's starting material (exact history unknown) and confirmed Murray's results. This dihydroquercetin had the previously described[1] melting point and color reactions but had a specific rotation of only +11° (*c*, 4 in equal volumes of acetone and water) instead of +46°. It was presumed to have been largely racemized, possibly by the use of an alkaline isolation method. This alone could not explain the failure to yield eriodictyol since, in the original work, racemic dihydroquercetin was shown to

(1) J. C. Pew, *J. Am. Chem. Soc.*, **70**, 3031 (1948).

(2) L. M. Wheeler, private communication, 1949.

(3) H. L. Hergert and E. F. Kurth, *J. Am. Chem. Soc.*, **75**, 1622 (1953).

(4) S. L. Wender, private communication, 1953.

(5) C. W. Murray, private communication, 1956.

react. When the nonreactive dihydroquercetin was first boiled in water or heated in an oven (two days at 110° or, better, twenty-four hours at 160°) it then reacted to give yields of 20% or more of eriodictyol. Some kind of isomerism seemed to be indicated, and it was decided to explore the matter further at a later date.

After several months, the problem was taken up again; but the recalcitrant dihydroquercetin was then found to give normal yields of eriodictyol, and Murray reported a similar experience. Many attempts were made to convert +46° dihydroquercetin into a product failing to give the eriodictyol reaction or having an altered infrared spectra. These efforts were unsuccessful, and the problem was again laid aside.

Recently Barton[6] experienced difficulty with the reaction. A sample of his starting material with a reported rotation of +32° (*c*, 2.5 in equal volumes of acetone and water) was obtained, and this gave only a small amount of eriodictyol on reduction. A plausible explanation is that two isomers are involved. They would not appear to be molecular isomers such as might result from a keto-enol shift involving the 3 and 4 carbon atoms, since the ultraviolet spectra of the two substances are identical. More likely, it is a case of stereoisomers comparable with the catechol–epicatechol pair. Mahesh and Seshadri[7] have reported such isomerism to occur with 3-hydroxynaringenin, the two pairs of isomers behaving differently in certain chemical reactions. Perhaps a *cis* form of dihydroquercetin is sometimes isolated which then readily changes to a stable *trans* form[8] after isolation. The two samples of dihydroquercetin in question, however, had practically identical infrared spectra in acetone solution.

In order to assure a good yield of eriodictyol, it is best first to racemize the dihydroquercetin with hot alkali. This changes any nonreactive component to the reactive state. Moreover, the resulting optically inactive eriodictyol is more insoluble than the active form, a property which aids in isolation and purification. Substitution of 10% aqueous hydrochloric acid for the concentrated acid is also an improvement. Even dihydroquercetin that fails to give eriodictyol with concentrated acid gives some product with dilute acid. Possibly isomerization accompanies the addition of the more dilute acid. With alkaline racemization, yields of over 50% are readily obtained under a variety of experimental conditions.

During this work the conversion of +46° dihydroquercetin to an optically active form of eriodictyol, as suggested in the previous paper,[1] was confirmed. The material is unstable under the reaction conditions and is, therefore, difficult to prepare in 100% purity. By minimizing the time the product was in contact with acidic medium, material with a specific rotation of −21° (*c*, 4 in acetone) was obtained and is believed to be substantially pure. As before, a stable active tetraacetate, m.p. 120–122°, was prepared. This has now been found to have a rotation of +11° (*c*, 4 in chloroform).

The author is unable to pursue this peculiar behavior of dihydroquercetin further but hopes the above will be of interest to others working in this field.

Experimental[9]

Racemization of Dihydroquercetin.—A solution of 4.00 g. of dihydroquercetin in 40 ml. of 0.1 *N* sodium hydroxide was boiled 30 min.; then 40 ml. water, 20 ml. acetone, and 40 ml. 0.1 *N* hydrochloric acid were added. The solution was allowed to cool, and crystals containing 1.5 moles of water were filtered after several hr. The yield on a dry basis was 3.38 g. The material showed no optical activity.

Eriodictyol from Racemic Dihydroquercetin.—With vigorous mechanical agitation, 20 ml. of 10% aqueous hydrochloric acid was added in 1.5-ml. portions at 5-min. intervals to 10 ml. of ethanol containing 1.00 g. of dihydroquercetin in solution and 2.0 g. of zinc dust in suspension. Agitation was continued another hour and the eriodictyol suspension decanted from the residual zinc. The zinc was washed with a little ethanol, and the washings were added to the decanted liquid. Water (100 ml.) was added and the suspension allowed to stand in the refrigerator overnight. The ariodictyol was filtered, washed with water, and dried. The yield was 0.72 g., m.p. 263–267° dec. Recrystallization from aqueous ethanol gave a product with m.p. 272–274° dec. (reported[10] 267°).

Anal. Calcd. for $C_{15}H_{12}O_6$: C, 62.50; H, 4.17. Found: C, 62.49; H, 4.28.

Tetraacetate from Racemic Eriodictyol.—The above material acetylated with acetic anhydride and pyridine gave a product devoid of optical activity, m.p. 140–142° (reported[11] 137–141°).

Anal. Calcd. for $C_{23}H_{20}O_{10}$: C, 60.52; H, 4.42; CH_3CO, 37.72. Found: C, 60.69; H, 4.58; CH_3CO, 37.54.

Eriodictyol from Optically Active Dihydroquercetin.—To a vigorously stirred solution of 2.00 g. of optically active dihydroquercetin ($[\alpha]^{25}D$ +46°, *c*, 4 in equal volumes of acetone and water) in 20 ml. of methanol 4.0 g. of zinc dust was added, and then 10 ml. of conc. hydrochloric acid, 3 drops at a time, waiting until the purple red color disappeared from the solution before adding the next portion. After 30 min. the acid was added at a rate of 0.5 ml. every 5 min. and after another 30 min. the portion was increased to 1.0 ml. The eriodictyol suspension was decanted from the residual zinc, the zinc washed with a little methanol, and the decanted liquid and washings diluted with cold water to 150 ml. The mixture was rapidly cooled and allowed to stand in the refrigerator 1 hr. The eriodictyol was recovered by filtration, washed with water, immediately dissolved in 50% aqueous acetone, filtered, the filtrate diluted with an equal volume of water, and placed in the refrigerator to effect crystallization. The eriodictyol was recrystallized again in the same manner and the crystals dried in a vacuum desiccator over magnesium perchlorate.

(6) G. M. Barton, private communication, 1960.

(7) V. B. Mahesh and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **41A**, 210 (1955).

(8) J. W. Clark-Lewis and W. Korytnyk, *Chem. Ind.* (London), 1418 (1957).

(9) All melting points were made in Pyrex capillaries and are corrected.

(10) F. Mayer, "The Chemistry of the Natural Coloring Matters," A.C.S. Monograph No. 89, 1943, p. 188.

(11) Y. Kimura, *Yagaku Zasshi*, **58**, 415 (1938).

The yield was 0.65 g., m.p. 269–271 dec., $[\alpha]^{25}D$ −21° (*c*, 4 in acetone). The infrared spectrum was slightly different from that of the racemic material when potassium bromide discs were used, but with acetone solutions the spectra were identical.

Anal. Calcd. for $C_{15}H_{12}O_6$: C, 62.50; H, 4.17. Found: C, 62.50; H, 4.31.

Tetraacetate from Optically Active Eriodictyol.—The above eriodictyol (0.200 g.) was dissolved in a mixture of 2.5 ml. of acetic anhydride and 1.0 ml. of pyridine and the solution allowed to stand 16 hr. It was then poured into water and allowed to stand overnight in the refrigerator. The crystals of eriodictyol tetraacetate which were recovered in nearly quantitative yield melted at 113–117°. Two crystallizations from ethanol yielded 0.230 g. of colorless needles, m.p. 120–122°, $[\alpha]^{25}D$ +11° (*c*, 4 in chloroform).

Bromination of 17-Oxo Steroids with Cupric Bromide[1]

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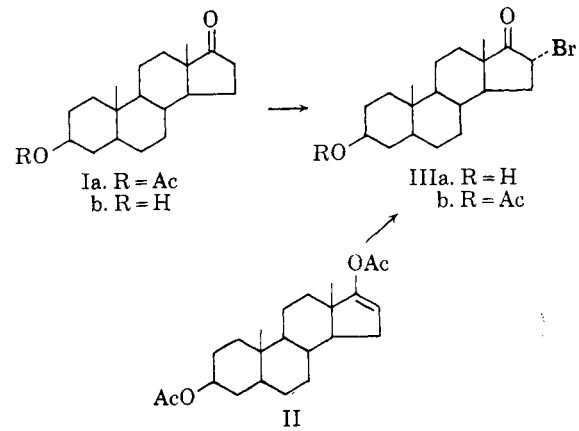
Formation of 16α-bromo-17-oxo-androstanes has been best achieved by bromination of the 17-enol acetates[2,3] since direct bromination of the 17-ketone has generally given poor results.[2,4] Kochi[5] has shown that aliphatic ketones can be halogenated with cupric halides. More recently, cupric bromide was reported to give excellent yields of α-bromocyclohexanones[6] and α-bromo aliphatic aldehydes.[7] In view of these results, it was felt that direct bromination of 17-ketosteroids might be readily achieved by the use of this reagent. This result has been attained, with some measure of success, in the formation of 16α-bromo-17-oxoandrostanes either directly from the 17-ketone or indirectly from the 17-enol acetate.

From 3β-acetoxy-5α-androstan-17-one (Ia) or 3β,17-diacetoxy-5α-androst-16-ene (II), 3β-hydroxy-16α-bromo-5α-androstan-17-one (IIIa) could be obtained in yields of 48% and 60%, respectively. Bromination of 3β-hydroxy-5α-androstan-17-one (Ib) was achieved to yield 59% of IIIa.

Saponification of the 3β-acetoxy group could be avoided by addition of a small amount of pyridine to the reaction. In this way, 3β-acetoxy-16α-bromo-5α-androstan-17-one (IIIb) was obtained from the 17-enol acetate, but the product was not easily purified nor was the yield large. An attempt



to prepare IIIb, retaining the 3β-acetoxy group, from Ia by using pyridine in the reaction was not successful. The infrared spectrum of the product after chromatography on silica gel indicated that there was no saponification, but even after recrystallization only a mixture was obtained. Fajkos[2] has shown that under the basic conditions of sodium borohydride reduction of 16α-bromo-17-ketones, epimerization of bromine occurs. It is possible that mixtures of the 16-epimers are being obtained under the mildly basic conditions in the presence of pyridine.

An attempt was made to form the 16,16-dibromo-17-ketone by using a larger amount of cupric bromide, but the only compound which could be isolated after chromatography was the monobromo ketone IIIa.

Experimental[8]

1. 3β-Hydroxy-16α-bromo-5α-androstan-17-one (IIIa).—A. 3β-Acetoxy-5α-androstan-17-one (Ia) (1.66 g., 0.005 mole) and cupric bromide (2.24 g., 0.01 mole) were dissolved in 250 ml. of methanol and the solution was refluxed for 24 hr. During this time a white precipitate formed and the solution lightened in color. The reaction mixture, after filtration, was evaporated *in vacuo* to a brown paste. To the paste were added 200 ml. of chloroform and 400 ml. of water, which mixture on shaking became almost colorless. The chloroform was separated and the aqueous layer was extracted twice more with 100-ml. portions of chloroform. The combined organic layers were dried over anhydrous magnesium sulfate and then evaporated *in vacuo* to yield white crystals. After two recrystallizations from acetone–heptane, there was obtained 800 mg. (48%) of IIIa as white needles, m.p. 155–156.5°; $[\alpha]^{27}D$ +60° (*c* 2.26) [reported values[9]: m.p. 164–165°; $[\alpha]^{20}D$ +52° (*c* 2.18)]. The infrared spectrum had bands at 3500 and 1740 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{29}BrO_2$: C, 61.78; H, 7.79; Br, 21.64. Found: C, 61.56, 61.53; H, 7.78, 7.90; Br, 21.97, 22.19.

B. 3β-Hydroxy-5α-androstan-17-one (Ib) (2.90 g., 0.01 mole) and cupric bromide (4.48 g., 0.02 mole) were put into 400 ml. of methanol and the solution was refluxed for 24

(1) This work was supported by a grant from G. D. Searle & Co., Chicago, Illinois.

(2) J. Fajkos, *Collection Czech. Chem. Commun.*, **20**, 312 (1955).

(3) J. Fajkos and F. Sorm, *ibid.*, **24**, 766 (1959).

(4) Donnenberg, thesis, Danzig, p. 33 (1938); "Elsevier Encyclopedia of Organic Chemistry," Vol. 14, F. Radt, ed., Springer Verlag, Berlin, 1959, p. 2706s.

(5) J. K. Kochi, *J. Am. Chem. Soc.*, **77**, 5274 (1955).

(6) A. W. Fort, *J. Org. Chem.*, **26**, 765 (1961).

(7) C. E. Castro, *ibid.*, **26**, 4183 (1961).

(8) Melting points were taken on a Kofler block and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord 137 in chloroform solution. Optical rotations were measured in chloroform solution. The silica gel used for chromatography was grade 923 obtained from Davison Chemical Corp., Baltimore, Maryland. Elemental analyses were by Weiler & Strauss, Oxford, England.

(9) J. Fajkos, *Collection Czech. Chem. Commun.*, **23**, 1559 (1958).