urated methyl ester, there appear some—much less intense—bands between 2500 and 2800 Å. Whilst no definite statement can be made as to their origin, it is not impossible that they are due to traces of methyl hendeca*trien*oate. Such a substance could be formed by further allylic bromination of methyl 11-bromo-9-hendecenoate in the 8-position and subsequent elimination of two molecules of hydrogen bromide.

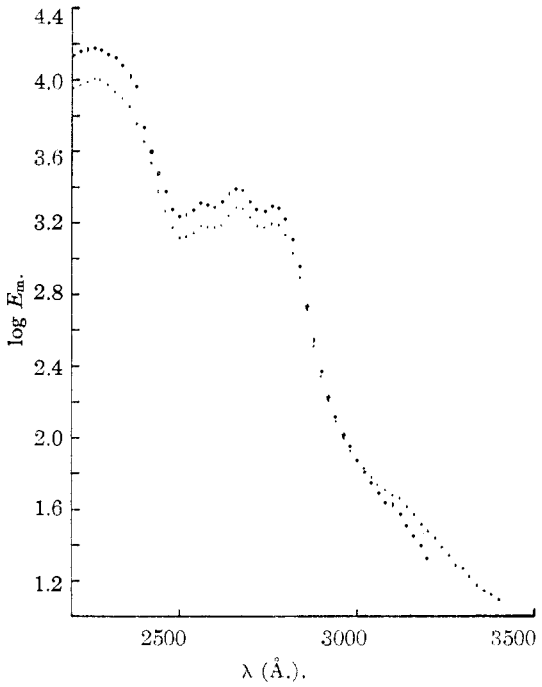

Fig. 1.—Methyl 8,10-hendecadienoate in isoöctane (++++++) and anhydrous ethyl alcohol(. . . . .).

The spectra have been measured by Y. Hirshberg and S. Pinchas, respectively.

Experimental

Methyl 9-Bromo-10-hendecenoate.—When a trace of benzoyl peroxide was added to the mixture of 19.8 g. (0.1 mole) of methyl 10-hendecenoate,[7] 19.5 g. (0.1 mole) of N-bromosuccinimide and 100 cc. of carbon tetrachloride, a strongly exothermic reaction took place after an induction period of a few minutes. The reaction was completed by refluxing the mixture for two hours. The succinimide formed was removed by filtration (8 g.) and the solution distilled *in vacuo*. A small quantity of starting material (b.p. 86–90° (0.05 mm.)) was recovered. The bromo-ester distilled at 110° at 0.05 mm. with slight decomposition; it formed a viscous liquid which did not crystallize even at low temperature (−20°). *Anal.* Calcd. for $C_{12}H_{21}O_2Br$: Br, 28.8. Found: Br, 28.1.

Methyl 8,10-Hendecadienoate.—The bromo-ester was heated for two hours with an equal weight of quinoline at 120–130°. The reaction product was cooled, treated with a slight excess of dilute hydrochloric acid and extracted with ether. The ethereal layer was washed with water, sodium bicarbonate solution and water, dried and distilled; b.p. 80° at 0.5 mm.; yield 8.9 g. (50%); d^{25}_4 0.898; $n^{25}D$ 1.4542; mol. refr., calcd. 58.34 (without exaltation); found, 59.17. *Anal.* Calcd. for $C_{12}H_{20}O_2$: C, 73.5; H, 10.2. Found: C, 73.4; H, 10.2.

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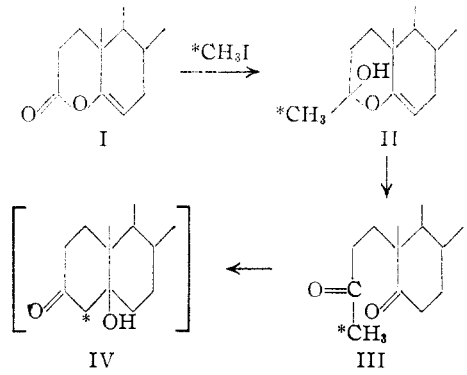
(7) Komppa, *Ber.*, **34**, 895 (1901).

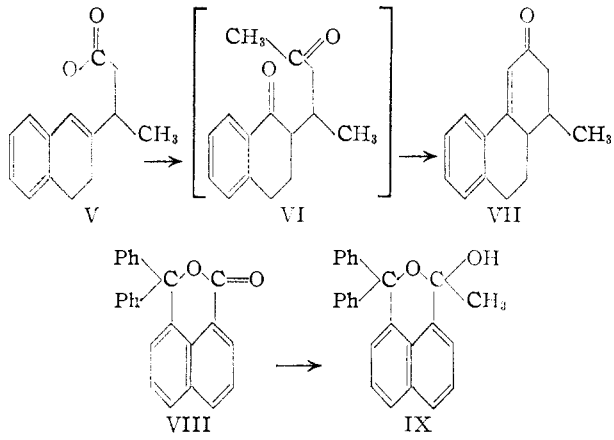
Steroids. IX. An Improved Method of Preparation of Cholestenone-4-C^{14} [1]

BY R. D. H. HEARD AND P. ZIEGLER[2]

Two methods of preparation of cholestenone-3-C^{14} and -4-C^{14} have been described by Turner.[3] As neither procedure proved fully satisfactory in a preparative sense, particularly as regards over-all yield from $C^{14}O_2$, a convenient route to the readily cyclizable methyl diketone III was sought.



A promising approach to III arose from the observation of Belleau,[4] in studies on total synthesis in the doisynolic acid series, that the enol-lactone V with methylmagnesium iodide gave predominantly the α,β-unsaturated ketone VII, after acid hydrolysis. The reaction was assumed to proceed through the intermediate 1,5-diketone VI. On the other hand, with certain other unsaturated lactones, such as coumarin[5] and VIII[6], the end products are the corresponding hemiacetals (*viz.* IX).



The enol-lactone I, with only 1.0 to 1.2 molar proportions of methylmagnesium iodide, was found to give a high yield (70–80%) of product finally identified as the hemiacetal II which separated readily in excellently defined crystalline state but which exhibited a broad melting point range (165–175°) which could not be sharpened with the usual puri-

(1) Aided by grants from the National Cancer Institute, U. S. Public Health Service, the Medical Research Division of the National Research Council (Ottawa), and Charles E. Frosst & Co., Montreal.

(2) Contributed in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) Turner, THIS JOURNAL, **72**, 579 (1950).

(4) Belleau, Thesis, McGill University, 1950.

(5) Willstätter, *et al.*, *Ber.*, **57**, 1938, 1945 (1924).

(6) Geissman and Morris, THIS JOURNAL, **63**, 1111 (1941).

fication procedures. The compound analyzed for $C_{27}H_{46}O_2$, had $[\alpha]^{23}D$ +10°, was positive to tetranitromethane and the Zimmermann reagent, and formed a bisdinitrophenylhydrazone. Treatment with acid, alkali or piperidine, or distillation *in vacuo* at 220–230°, yielded cholestenone quantitatively. These facts were first taken to indicate the 1,5-diketone structure III. However, distillation at a lower temperature (170–180°) yielded a non-crystallizable oil, with markedly altered rotation (+60°), which failed to show a coloration with tetranitromethane. Otherwise its behavior was identical with the Grignard reaction product in that it gave a positive Zimmermann reaction, formed the same bisdinitrophenylhydrazone and rearranged to cholestenone under the same conditions. Infrared spectroscopy[7] (in carbon disulfide) revealed two sharp ketone carbonyl peaks at 1709 and 1722 cm.$^{-1}$ and a weaker but definite band between 3200 and 3300 cm.$^{-1}$ (associated hydroxyl region). The presence of the latter may be due to bonding effects, but could also be explained by contamination with the intermediate hydroxy-ketone IV or the hemiacetal II; in the ultraviolet, the extinction coefficient at 241 mμ indicated cholestenone to the extent of not more than 5%. It is thus concluded that the distillate collected from 170–180° is essentially III. Recently Schmid and Kägi[8] described III (derived through ozonolysis or glycolyzation of $\Delta^{3,5}$-3-methyl-A-nor-cholesten, but also separated by vacuum distillation at 170–180°) as a non-crystalline colorless oil, $[\alpha]^{20}D$ +44°, with a sharp carbonyl band at approximately 1700 cm.$^{-1}$ and a broader strong band at about 2800 cm.$^{-1}$; no derivatives are recorded, but Wolff–Kishner reduction yielded Δ^3- and Δ^4-cholestene and a saturated non-crystalline hydrocarbon which behaved as the expected open ring A normal reduction product. Confirmation of the hemiacetal structure II of the crystalline Grignard reaction product was afforded by the presence of an intense broad associated hydroxyl band between 3200 and 3300 cm.$^{-1}$, with a weak but definite carbonyl band at 1715 cm.$^{-1}$. The ease with which II rearranges through III to cholestenone on pyrolysis or treatment with acid or alkali readily explains its indefinite melting point, the positive Zimmermann reaction, the formation of the bisdinitrophenylhydrazone and the carbonyl absorption in the infrared.

One radioactive run was conducted to give (45%) cholestenone-4-C^{14} counting at 1.52 million/mg./min. The yield was thus lower than that (70%) consistently obtained in inactive preparations, which is ascribed, at least in part, to the fact that the $C^{14}H_3I$ employed was aged and contaminated with decomposition products not removed by preliminary distillation and drying (see experimental).

Comparative yields in the three methods described for the incorporation of isotopic carbon into A of cholestenone, respectively, the phenyl acetate condensation of Turner,[3] the Reformatsky reaction[3] and the Grignard reaction herewith reported, are approximately 45, 30 and 70% (calculated from the ring A keto-acid). Based on economy and utilization of the starting carbon reagent, however, the Grignard method is yet more efficient in that only a slight excess is required; in the same order, the approximate yields are 22%, 10% (each calculated from sodium acetate) and 45–70% (calculated from methyl iodide).

(7) Kindly conducted and interpreted by Dr. K. Dobriner, Sloan-Kettering Institute (New York), and Dr. R. N. Jones, National Research Council (Ottawa).

(8) Schmid and Kägi, *Helv. Chim. Acta*, **33**, 1582 (1950).

Experimental[9,10,11]

4,5-Seco-3,5-oxido-Δ^5-cholesten-3-ol (II).—To I (1.96 g., 5.0 millimoles) in anhydrous benzene (5 ml.) and ether (5 ml.) there was added slowly (15 min.) a solution of the Grignard reagent (5.7 millimoles) prepared from magnesium (0.15 g.) and methyl iodide (0.9 g.) in 12 ml. of absolute ether. The mixture was refluxed one hour, cooled, treated with chilled dilute hydrochloric acid and extracted twice with ether. The combined ether extracts, after three washings each with dilute hydrochloric acid and water, and drying (sodium sulfate), were evaporated and the residue was crystallized from ether–hexane to give 1.42 g. of product II as slender needles melting at 164–175°, $[\alpha]^{23}D$ +10° (chloroform). An additional 0.17 g. (78% total) was recovered from the mother liquor by chromatography (eluted from alumina with benzene–ether, ether and ether–methanol). The melting point could not be sharpened on repeated recrystallization from different solvents.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.65, 80.67; H, 11.43, 11.49.

II gave a distinct yellow coloration with tetranitromethane, a positive Zimmermann reaction, and was transparent in the ultraviolet between 217–450 mμ. Treated with 2,4-dinitrophenylhydrazine in acid–ethanol in the usual manner, a yellow bis-2,4-dinitrophenylhydrazone was formed, m.p. 243–246°.

Anal. Calcd. for $C_{39}H_{54}O_8N_8$: C, 61.40; H, 7.13; N, 14.69. Found: C, 61.37, 61.46; H, 7.04, 7.10; N, 14.65, 14.68.

Cholestenone from II. A. Alkali Treatment.—II (150 mg.) was refluxed (2 hours) in methanolic potassium hydroxide (4%) solution (25 ml.). After evaporation of most of the methanol, water was added and the product collected with ether. The combined ether extracts were washed neutral, dried (sodium sulfate) and evaporated to 140 mg. of oil which crystallized from ether–methanol to yield 125 mg. (88%) of cholestenone, m.p. and admixture m.p. 80–81°, $[\alpha]^{22}D$ +83° (chloroform), log $\epsilon_{max.}$ 4.2 at 242 mμ.

B. Acid Treatment.—II (50 mg.), refluxed (2 hours) in acetic acid (10 ml.), concentrated hydrochloric acid (1 ml.) and water (0.25 ml.), yielded, on processing as described above, 30 mg. of cholestenone, m.p. and admixture m.p. 77–79°.

C. Piperidine Treatment.—A solution of II (200 mg.) in freshly distilled piperidine (7.5 ml.) for 48 hours at room temperature, gave up, on dilution and refrigeration, 150 mg. of crude cholestenone, which, on recrystallization from ether–methanol, had m.p. and admixture m.p. 78–80°, log $\epsilon_{max.}$ 4.2 at 242 mμ.

D. Distillation.—II, distilled *in vacuo* at 0.1 mm. and 220–230° (hot air oven), condensed as an oil which crystallized on standing. Recrystallization (ether–methanol) gave cholestenone, m.p. 77–79°, log $\epsilon_{max.}$ 4.2 at 242 mμ.

4,5-Seco-cholestan-3,5-dione (III).—II (200 mg.) was distilled at 0.1 mm. and 170–180° to yield 190 mg. of a colorless oil (III) which resisted repeated attempts at crystallization. The product gave a positive Zimmermann reaction, no coloration with tetranitromethane, and had $[\alpha]^{19}D$ +60° (chloroform); Schmid and Kägi[8] record $[\alpha]^{20}D$ +44° (chloroform). The optical density measured at 242 mμ indicated the presence of 5% of cholestenone.

The bis-2,4-dinitrophenylhydrazone of III had m.p. 243–245°, with no depression on admixture with that from II.

(9) Melting points were determined under the microscope with the Fisher–Johns apparatus. The values recorded are corrected.

(10) Elementary analyses were carried out by E. Thommen (Basle) and Y. Perron (Montreal).

(11) Counts were ascertained from infinitely thin plates in the windowless flow gas counter (Nuclear Instruments) operating at 40–50% efficiency, and are expressed as disintegrations registered per minute per millimole.

Anal. Calcd. for $C_{39}H_{54}O_8N_8$: N, 14.69. Found: N, 15.24.

Cholestenone from III.—III (50 mg.), refluxed for one hour in 4% methanolic potassium hydroxide (15 ml.), gave a neutral fraction (42 mg.), which crystallized to yield cholestenone, m.p. 78–80°.

Cholestenone-4-C^{14}.—$C^{14}H_3I$ (originally 1.8 millicuries in 266 mg.), which had been stored in the dark for four years but which was deeply pigmented, was distilled through drierite (clear distillate). The system was then flushed with an equal weight of carrier methyl iodide. The Grignard reagent prepared from the combined alkyl halide (3.74 millimoles) reacted, as described above, with 1.2 g. (3.1 millimoles) of the enol-lactone I to furnish, on direct crystallization, 650 mg. (52%) of the hemiacetal II, m.p. 160–175°, count 6.12×10^8. The mother liquors yielded 270 mg. of 3,5-seco-5-keto-cholestan-3-oic acid, m.p. and admixture m.p. 151–154°. This recovery of starting material, not encountered in C^{12} runs with the same molar proportion of methyl iodide, may be due to (a) impurities in the small sample of $C^{14}H_3I$, (b) loss of appreciable total alkyl halide through decomposition on long storage, (c) difference in reaction rate between C^{12} and C^{14}, or a combination of the three factors.

II (650 mg.) was converted by procedure A above to 526 mg. (1.37 millimoles, 45%) of cholestenone-4-C^{14}, m.p. 76–78°, count 6.12×10^8.

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RECEIVED APRIL 5, 1951

Preparation of Acetic-2-C^{14} Acid[1]

BY DANIEL N. HESS

A method has been developed for the preparation of high specific activity acetic-2-C^{14} acid from methanol-C^{14}. The method, which involves the intermediate formation of methyl hydrogen sulfate and acetonitrile, is simpler and is better suited to the synthesis of a product with high specific activity than the conventional method involving carbonation of methyl-C^{14}-magnesium iodide.[2] Yields averaging 87% have been obtained on a 10-millimole scale.

Experimental

A 10.5-millimole portion of crystalline sulfur trioxide was introduced into the reaction flask[3] equipped with a magnetic stirring bar. The flask was quickly attached to a vacuum line, and the 10-ml. bulb was immersed in liquid nitrogen. A 10.06-millimole aliquot of methanol vapor (39.2 millicuries), measured manometrically, was added to the reaction flask. The liquid nitrogen bath was replaced by an ice-bath, and the reaction mixture was stirred. After the initial reaction had subsided, an additional one-half hour at room temperature was allowed for completion of the reaction. Complete reaction was demonstrated by the absence of methanol vapor pressure as determined with a McLeod gage.

The flask was removed from the vacuum line, the bulb was immersed in liquid nitrogen, and 10 ml. of 7.5 *M* potassium cyanide was added dropwise. After the flask was allowed to warm slowly to room temperature with stirring for one-half hour, the acetonitrile solution was distilled into a calibrated 40-ml. flask. Three successive 10-ml. portions of water were added to the reaction flask and distilled to ensure complete transfer of the acetonitrile. Radioactivity assay showed a 96% yield to acetonitrile-2-C^{14}.

The acetonitrile was hydrolyzed by refluxing with 50 millimoles of potassium hydroxide for 24 hours. The radiochemical yield to potassium acetate-2-C^{14}, based on methanol, was 91%.

The alkaline solution of potassium acetate was acidified with 85% phosphoric acid and titrated with a solution of potassium permanganate.[4] The solution was distilled to dryness after the addition of three successive small portions of water. The distillate was titrated with potassium hydroxide, and the water evaporated. The potassium acetate was dried at high vacuum until no pressure greater than 10^{-4} mm. was observed after standing one-half hour under static vacuum at 120°.

The dried salt was covered with phosphoric acid thoroughly saturated with phosphorus pentoxide, the flask was attached to the vacuum line, and the acetic acid was collected in a liquid nitrogen cooled receiver. When the rate of evolution subsided, the flask was gradually heated to 120°, and the temperature maintained until there was no further evolution of acetic-2-C^{14} acid. Thirty-five and two-tenths millicuries of acetic-2-C^{14} acid was obtained, or a yield of 90% based on methanol-C^{14}. In order to determine the purity of the acetic acid prepared by this procedure, the product from a typical run and a purified derivative were analyzed using dilution technique. The radioactivity of the diluted acetic acid was 2.49 μc. per mmole, and the radioactivity of the derivative was 2.52 μc. per mmole. Thus, the product is pure within the limits of the analytical method which has an estimated error of $\pm 1\%$.

Carbon-14 analyses of the methanol, acetonitrile and acetic acid were made on the methyl-3,5-dinitrobenzoate, phloroacetophenone and *p*-nitrobenzyl acetate derivatives, respectively. These derivatives prepared from appropriately diluted samples were converted to carbon dioxide by wet-combustion and assayed for radioactivity by determination of the ion current with a dynamic condenser electrometer. The isotopic dilution method of determining yields[5] and the carbon-14 analysis procedure[6] have been published.

Acknowledgment.—The author wishes to express his indebtedness to Dr. O. K. Neville for his advice and interest in the execution of this project.

(4) This destroyed any cyanide and formate that might be present.

(5) G. A. Ropp, THIS JOURNAL, **72**, 4459 (1950).

(6) O. K. Neville, *ibid.*, **70**, 3499 (1948).

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RECEIVED DECEMBER 8, 1950

Improvements in the Preparation of L-Arabinose from Mesquite Gum[1]

BY C. S. HUDSON

Directions for the preparation of L-arabinose from mesquite gum have been published by Anderson and Sands,[2] by Isbell[3] and recently by White,[4] who has made radical improvements on the older directions. Present knowledge of the structure of mesquite gum, recently reviewed by Jones and Smith,[5] indicates that its graded acid hydrolysis can be expected to liberate principally the L-arabinose moiety as the first step. However, in the earlier methods[2,3] experience showed that it was necessary to continue the acid hydrolysis considerably beyond this first stage in order to be able to control the foaming during subsequent operations. Our experience with the earlier methods[2,3] was not encour-

(1) This document is based upon work performed under Contract Number W-7405, eng. 26 for the Atomic Energy Project at Oak Ridge National Laboratory.

(2) B. M. Tolbert, *J. Biol. Chem.*, **173**, 205 (1948).

(3) The reaction flask consisted of a 25-ml. flask with a 10-ml. bulb sealed onto the bottom. The purpose of the bulb was to contain the small quantities of reagents in the sulfonation phase of the experiment. The larger bulb provided ample volume for subsequent reactions.

(1) Presented at the Portland, Oregon, Meeting of the American Chemical Society in September, 1948.

(2) E. Anderson and Lila Sands, (a) THIS JOURNAL, **48**, 3172 (1926); (b) *Org. Syntheses*, **8**, 18 (1928).

(3) H. S. Isbell in "Polarimetry, Saccharimetry and the Sugars," Circular C440, Natl. Bur. Standards, p. 457 (1942).

(4) E. V. White, THIS JOURNAL, **69**, 622, 715 (1947).

(5) J. K. N. Jones and F. Smith, *Advances in Carbohydrate Chem.*, **4**, 243 (1949).