and extracted with ether. The ethereal solution was concentrated under reduced pressure and the resulting oil crystallized and was recrystallized from 95% ethanol; 0.75 g. (26%), m.p. 93–94°; λ_{max} 248 mμ (ε 11,800), 310 mμ (ε 11,300), λ_{min} 286 mμ (ε 1,540).

Anal. Calcd. for $C_{25}H_{25}NO_2$: C, 80.44; H, 6.16. Found: C, 80.21; H, 6.03.

This compound spontaneously decomposed slowly at room temperature and gave an oil. All attempts to prepare another solid derivative were unsuccessful.

Attempted hydrations of this compound XIV by dilute hydrochloric acid at 60° and at 80° were unsuccessful.

Lithium Aluminum Hydride Reduction of 4-Benzyl-5,6-diphenyl-2-hydroxy-2,3-dihydro-1,4-oxazine (XIV).—A solution of 5.0 g. (0.015 mole) of the hydroxydihydroöxazine XIV in 100 ml. of absolute ether was added with constant stirring over a period of 30 minutes to a solution of 0.57 g. of lithium aluminum hydride in 250 ml. of absolute ether. The mixture was stirred for an additional hour, hydrolyzed with water and 10% sodium hydroxide, and extracted with ether. The ethereal solution was concentrated under reduced pressure and the residue was poured into ice-water. The precipitate was crystallized from 95% ethanol; m.p. 102.5–104.5°. A mixture melting point with 4-benzyl-2,3-diphenyl-2-hydroxymorpholine (XXI)[7a] showed no depression.

Anal.[7a] Calcd. for $C_{25}H_{23}NO_2$: C, 79.97; H, 6.71. Found: C, 80.17; H, 6.45.

***erythro*-2-(N-2,2-Diethoxyethyl-N-benzylamino)-1,2-diphenylethanol Hydrochloride (XIXa).**—A mixture of 10.0 g. (0.045 mole) of benzylaminoacetal (VII) and 5.1 g. (0.022 mole) of *trans*-stilbene chlorohydrin[17] was heated on a water-bath for four hours, cooled, and treated with absolute ether. The precipitated benzylaminoacetal hydrochloride was removed by filtration; 5.2 g. (91%). The ethereal filtrate was dried over sodium sulfate, decanted and treated with ethereal hydrogen chloride. The precipitated hydrochloride was crystallized from an absolute ethanol-ether mixture; m.p. 194–196°.

Anal. Calcd. for $C_{27}H_{33}NO_3 \cdot HCl$: C, 71.11; H, 7.52. Found: C, 70.91; H, 7.38.

The **free base** was liberated by treatment of a sample of the hydrochloride with ether and 10% aqueous sodium carbonate. The ethereal layer was concentrated and the residual pale red oil crystallized from petroleum ether; m.p. 138–139°.

Anal. Calcd. for $C_{27}H_{33}NO_3$: C, 77.29; H, 7.93. Found: C, 77.19; H, 8.01.

This compound was also prepared from the diethyl acetal VIIIa by reduction with lithium aluminum hydride and aluminum isopropoxide under the usual conditions.

***threo*-2-[N-2,2-Diethoxyethyl-N-benzylamino]-1,2-diphenyl Ethanol (XXa).**—A mixture of 10.0 g. (0.045 mole) of benzylaminoacetal and 5.9 g. (0.03 mole) of *cis*-stilbene oxide[18] was heated for 12 hours at 100°. The reaction mixture was taken up in ether, dried over sodium sulfate and concentrated under reduced pressure. The residue was crystallized from ethanol; 11.0 g. (88%), m.p. 120–122°.

Anal. Calcd. for $C_{27}H_{33}NO_3$: C, 77.29; H, 7.93; OC_2H_5, 21.48. Found: C, 77.44; H, 7.85; OC_2H_5, 21.01.

The **hydrochloride** was prepared by treating an ethereal solution of the free base with ethereal hydrogen chloride and recrystallization of the precipitate from an ethanol–ether mixture; m.p. 186–187°.

Anal. Calcd. for $C_{27}H_{33}NO_3 \cdot HCl$: C, 71.11; H, 7.52. Found: C, 71.28; H, 7.71.

Lithium Aluminum Hydride Reduction of 4-Benzyl-5,6-diphenyl-2-hydroxymorpholine (XXI).—A solution of 5.0 g. (0.014 mole) of the hydroxymorpholine in 100 ml. of absolute ether was added over a period of 20 minutes to a solution of 0.53 g. of lithium aluminum hydride in 200 ml. of absolute ether. The mixture was stirred for one hour and hydrolyzed with water and 20% sodium hydroxide. The ether layer was dried over sodium sulfate and concentrated; the residue was recrystallized from 95% ethanol, 3.6 g. (74%), m.p. 132–133°, and identified by mixture melting point as *erythro*-1,2-diphenyl-2-benzylethanolaminoethanol[7a] (XVIII).

α-(N-Benzyl-N-acetalamino)-acetophenone Hydrochloride[5] (V).—A solution of 10.0 g. (0.05 mole) of phenacyl bromide in 50 ml. of absolute ether was added with stirring to a solution of 10.0 g. (0.045 mole) of benzylaminoacetal (VII) and 5.0 g. (0.05 mole) of triethylamine in 50 ml. of absolute ether. After standing for 12 hours the solution was filtered to remove precipitated triethylamine hydrobromide; the ethereal filtrate was washed with dilute sodium carbonate, dried over sodium sulfate and treated with ethereal hydrogen chloride to precipitate the hydrochloride; 6.5 g. (34%); m.p. 123–124°. Recrystallization from an ethanol-ether mixture raised the melting point to 124.5–125°. The compound underwent spontaneous decomposition at room temperature and was converted to a dark oil.

Anal. Calcd. for $C_{21}H_{27}NO_3 \cdot HCl$: C, 66.73; H, 7.20. Found: C, 66.44; H, 7.37.

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[17] R. E. Lutz, R. L. Wayland and H. G. France, THIS JOURNAL, **72**, 5511 (1950).

[18] T. W. J. Taylor and C. E. J. Crawford, *J. Chem. Soc.*, 1130 (1934).

[CONTRIBUTION FROM SCHOOL OF MEDICINE, UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Unsaturated Fatty Acids. III. Preparation of 1-C^{14}-Linoleic Acid[1]

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A method has been devised by which linoleic acid isolated from natural sources may be used as a starting material for the preparation of the substance labeled with isotopic carbon in the carboxyl group. In essence, the original carboxyl group is replaced by a bromine atom *via* the silver salt degradation of Borodin and the process reversed *via* the Grignard reaction, the sensitive and synthetically-imposing *cis,cis*-1,4-diene moiety being protected in steps where this is necessary by bromination.

Studies designed to elucidate details of the anabolism of the physiologically important arachidonic acid in mammalian tissues[2] have made the availability of C^{14}-labeled linoleic acid highly desirable, particularly in view of the wealth of deductive evidence that linoleic is an essential exogenous precursor of arachidonic acid. Several recently devised total syntheses of linoleic acid[3] have provided possible routes to such a substance, but the low over-all yields realized in these complex procedures provided incentive for a search for other approaches to the problem.

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[1] This paper is based on work performed under Contract AT-04-I-GEN-12 between the Atomic Energy Commission and the University of California at Los Angeles. Certain aspects of this study were discussed before the Organic Division of the American Chemical Society in Buffalo, N. Y., March, 1952; and in an earlier Communication published in THIS JOURNAL, **74**, 1109 (1952).

[2] *Cf.* J. F. Mead, G. Steinberg and D. R. Howton, *J. Biol. Chem.*, **205**, 683 (1953), and J. F. Mead, *et al.*, work in press and in progress.

[3] (a) R. A. Raphael and F. Sondheimer, *J. Chem. Soc.*, 2100 (1950); (b) H. M. Walborsky, R. H. Davis and D. R. Howton, THIS JOURNAL, **73**, 2590 (1951); (c) W. J. Gensler and G. R. Thomas, *ibid.*, **73**, 4601 (1951).

In the superficially similar problem presented by certain physiologically interesting but structurally complicated steroids, Turner[4] devised an elegant solution involving partial degradation of such substances isolated from natural sources, followed by reconstruction with C^{14}-labeled reagents.

A process resembling this in principle and involving decarboxylation and reconstitution of the fatty acid has now, as described and discussed in detail below, been employed to prepare 1-C^{14}-linoleic acid.[5]

Linoleic acid has for many years been isolated routinely from seed oils rich in this fatty acid by saponification followed by bromination of the fatty acid mixture thus obtained[6]; the resulting readily-purified, petroleum-ether-insoluble bromine adduct of linoleic acid (9,10,12,13-tetrabromostearic acid (I), m.p. 115°)

$$C_5H_{11}(CHBr)_2CH_2(CHBr)_2(CH_2)_7COOH \quad \text{I}$$

is employed as starting material. In addition to the fact that linoleic acid is isolated almost invariably from its natural sources *via* I, bromination serves to protect the sensitive *cis,cis*-1,4-diene system in subsequent steps involving incompatible conditions.[7]

Although Bergström and co-workers[8] have recently described the use of rather bizarre conditions necessitated by low water solubilities of substances involved in the preparation of the silver salt of I, this salt (II) is obtained

$$C_5H_{11}(CHBr)_2CH_2(CHBr)_2(CH_2)_7COOAg \quad \text{II}$$

simply and in excellent yield by addition of an absolute methanol solution of silver nitrate to another of the ammonium salt of I in the same solvent. As indicated by the inertness of the methyl ester of I toward alcoholic silver nitrate, the bromine substituents in these substances are very resistant to nucleophilic displacement.

Treatment of dry II with bromine[9] in carbon tetrachloride solution results in loss of carbon dioxide and formation of a mixture of products of which 1,8,9,11,12-pentabromoheptadecane (III)[11,12] is the principal but not the only neutral component.

$$C_5H_{11}(CHBr)_2CH_2(CHBr)_2(CH_2)_7Br \quad \text{III}$$

Extensive studies[13] of the Borodin degradation of stearic acid have shown that, in addition to the desired bromide (RBr) and regenerated acid (RCOOH), appreciable amounts of the Simonini-type ester (RCOOR) are also formed. Whereas the conventional aqueous alkali extraction of the carbon tetrachloride solution of the reaction products leads to troublesome emulsions and fails to separate the bromide from the small amounts of ester present, chromatography on silicic acid[14] permits clean separation of products accounting for 96–99% of the starting material (II) as the crystalline pentabromide III (70–71%), more-strongly-adsorbed neutral material of presumed ester nature (6–7%), and regenerated acid I (20–21%).

The action of metallic zinc on III results in regeneration[15] of the 1,4-diene moiety; the isolated terminal bromine substituent is unaffected.[16] The resulting 8,11-heptadecadienyl bromide (V) is a brilliant, colorless oil which is readily distillable

$$C_5H_{11}CH{=}CHCH_2CH{=}CH(CH_2)_7Br \quad \text{V}$$

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[4] R. B. Turner, This Journal, **72**, 579 (1950).

[5] Except for the possibility that the low solubility of more highly brominated fatty acids used as starting materials might interpose insurmountable difficulties, there would appear to be no unlikelihood that the same procedure is applicable to the carboxyl-labeling of other unsaturated fatty acids; 1-C^{14}-oleic acid has recently been prepared in this way (D. R. Howton and J. C. Nevenzel, unpublished).

[6] *Cf.* J. W. McCutcheon in *Org. Syntheses*, **22**, 75 (1942).

[7] S. Bergström, K. Pääbo and M. Rottenberg (*Acta chem. Scand.*, **6**, 1127 (1952)) have reported a preparation of 1-C^{14}-oleic acid by a method closely resembling that presently described, but involving preservation of the original and potential double bond as a vicinal diacetoxy moiety; the authors are indebted to Prof. Bergström for access to a manuscript of this study prior to its publication.

[8] S. Bergström, K. Pääbo and M. Rottenberg, *ibid.*, **7**, 1001 (1953).

[9] Although the reaction of silver carboxylates with bromine was studied extensively by the Hunsdieckers[10] and has been called the Hunsdieckerre action (or, more non-committally, the silver salt degradation), an instance of the transformation was reported much earlier and, to the best of our knowledge, for the first time by Borodin (*Ann.*, **119**, 123 (1861)), whose clear recognition of the nature of the reaction provides strong justification for use of his name in connection with it.

[10] *Cf.* H. Hunsdiecker and C. Hunsdiecker, *Ber.*, **75**, 291 (1942), and prior literature cited there.

[11] The closely related preparation of 1-bromo-8,9-dichloroheptadecane by the action of bromine on the silver salt of the dichlorostearic acid produced by addition of chlorine to oleic acid is reported in the patent literature (H. Hunsdiecker and C. Hunsdiecker, British Patent 456,565 (*C. A.*, **31**, 2233^{6} (1937))).

[12] At first thought it might seem that, from the standpoint of simplicity, the preparation of III directly from silver linoleate, addition of bromine and decarboxylation being concomitant, would be advantageous. It should be borne in mind, however, that the facile purification of I serves to eliminate small amounts of contaminating substances produced by non-stereospecific (*i.e.*, non-*trans*) addition of bromine or by substitution (evolution of hydrogen bromide, indicative of substitution, is invariably observed during the bromination of linoleic acid and related substances). Moreover, the physical properties of silver linoleate make it ill-suited to simple efficient preparation and to conversion to a form employable in the Borodin reaction.

[13] J. C. Nevenzel and D. R. Howton, unpublished.

[14] Earlier attempts to employ alumina to effect this separation disclosed the fact that the basicity of this adsorbent results in the conversion of appreciable amounts of III to a higher-melting, more-strongly-adsorbed substance later identified as 8,9,11,12-tetrabromoheptadecanol-1, $C_5H_{11}(CHBr)_2CH_2(CHBr)_2(CH_2)_7OH$ (IV). Here again the comparative inertness of the secondary bromine substituents of this series of compounds toward nucleophilic displacement is demonstrated.

[15] Retention of geometric configuration of monoölefinic substances submitted to the bromination–zinc–debromination cycle has been shown to be very nearly complete, (*cf.* B. H. Nicolet, This Journal, **43**, 2122 (1921); D. Holde and A. Gorgas, *Z. angew. Chem.*, **39**, 1443 (1926); and H. J. Lucas, M. J. Schlatter and R. C. Jones, This Journal, **63**, 22 (1941)). However, J. B. Brown and his associates (*cf.* N. L. Mathews, W. R. Brode and J. B. Brown, *ibid.*, **63**, 1064 (1941)) have presented strong evidence that the stereospecificity of this series of reactions is considerably less when applied to the 1,4-diene system of linoleic acid. By means of infrared spectroscopy, it is now easy to demonstrate that linoleic acid isolated or purified *via* the tetrabromide (I)—as have, almost without exception, all samples of this substance employed in chemical and physiological studies in the past—contains about 15% of one or both of the *cis,trans* isomeric acids. The 1-C^{14}-linoleic acid, its methyl ester, and the precursive dienyl bromide (V), preparations of which are presently described, are similarly inhomogeneous with respect to geometric configuration.

[16] Related instances in which the action of zinc on various polybromides has resulted in the removal of vicinal and retention of isolated bromine substituents have been reported recently (H. Hunsdiecker, *Ber.*, **76**, 142 (1943); A. T. Blomquist and R. W. Holley, This Journal, **70**, 36 (1948); H. Silberman and S. Silberman-Martyncewa, *J. Org. Chem.*, **13**, 709 (1948)). At the time plans for the work described in the present paper were being made, Dr. E. R. Buchman (California Institute of Technology) called our attention to the fact that von Braun and his students (*Ber.*, **44**, 1046, 3704 (1911); **51**, 95 (1918); **52**, 1716 (1919)) prepared a number of unsaturated fatty acids from aliphatic tribromides in which two of the bromine atoms were vicinal by successive treatment with magnesium and carbon dioxide. The volatility of V permitting a seemingly advantageous purification by distillation, direct conversion of III to the dienyl Grignard reagent was not attempted.

(b.p. 120° at 0.1 mm.) without appreciable loss or alteration. Although ultraviolet spectroscopy shows freshly-distilled V to be free of conjugated polyene contamination, its infrared absorption in the 10.3-μ region of the spectrum discloses the presence of about 18% *trans* isomer.[15]

Conversion of V to the corresponding Grignard reagent is complicated by the Wurtz-type coupling side reaction

$$2\,V + Mg \longrightarrow MgBr_2 + C_5H_{11}CH{=}CHCH_2CH{=}CH(CH_2)_{14}CH{=}CHCH_2CH{=}CHC_5H_{11}$$

which is known[17] to become increasingly important as higher aliphatic halides are involved and may, under certain conditions, determine the fate of 70–80% of the halide.[18] The sluggishness with which long-chain halides (such as V) react with magnesium makes carrying out the reaction at high concentration and with all the halide in contact with the metal from the start seem advantageous; to the contrary, however, such conditions favor the undesired coupling reaction strongly.[19] Intensive study of the conversion of V to the Grignard reagent[20] has demonstrated that good yields are obtained only at high dilution or when the bromide, despite its inertness, is added slowly to the magnesium. The consequently sluggish reaction is effectively expedited by the inclusion of small amounts of methyl iodide in the mixture.[21]

The high-vacuum technique which has become conventional in such cases[22] was employed to bring about the reaction of the Grignard with carbon dioxide. Identification of the product as linoleic acid was established by its infrared absorption spectrum, which was sensibly identical with that of the substance isolated from poppy seed oil *via* the bromination–zinc–debromination procedure,[6,15] and by conversion to the characteristic tetrabromide I, m.p. 114–115°, undepressed by admixture with authentic I; experience has shown that a good yield of this derivative (as was obtained in this instance) is perhaps the most reliable indication of high linoleic acid content. The linoleic acid obtained using $C^{14}O_2$ was converted by treatment with diazomethane to methyl 1-C^{14}-linoleate. The 250-mg. sample of ester thus prepared contained about 0.5 mc. of C^{14}; its use in studies of its metabolism will be reported elsewhere.[2]

Experimental

Unless indicated to the contrary, all melting points are corrected and represent data obtained using a Hershberg-type apparatus heated electrically in such a way that the rate of heating at the melting point was 0.5°/min. We are indebted to Dr. A. Elek (Elek Microanalytical Laboratories, Los Angeles) for the unfailing excellence of his analyses; to Miss Fillerup for ultraviolet and to Dr. R. E. Nusbaum and his staff for infrared spectroscopic measurements; and to Dr. J. F. Mead and W. H. Slaton (all at this Laboratory) for radioactivity determinations.

115°—9,10,12,13-Tetrabromostearic acid (I) was prepared essentially as indicated by McCutcheon[6] from poppy seed oil supplied by the Amend Drug and Chemical Co., New York.

The methyl ester of I, prepared by the action of diazomethane on a sample of I melting at 114.4–115.2°, formed clusters of short needles from methanol, m.p. 61.1–61.7°; samples of this substance obtained by classical methods have been reported[23] to melt anywhere from 56 to 63°.

Anal. Calcd. for $C_{19}H_{34}O_2Br_4$: C, 37.15; H, 5.58; Br, 52.06. Found: C, 37.19; H, 5.57; Br, 52.01.

Mixing ethanol solutions of this ester and of silver nitrate at room temperature leads to no discernible formation of silver bromide for at least 15 hours.

Silver Tetrabromostearate (II).—Preparation of II in high yield and in a high state of purity requires a solvent in which II is insoluble and I and its ammonium salt are soluble; the presence of even small amounts of water markedly depresses the solubility of both the latter, in addition to complicating realization of the prerequisite that II to be employed in the Borodin degradation be anhydrous. A stirred solution of 6.00 g. (0.01 mole) of I in 155 ml. of absolute methanol containing 1.6 ml. (0.01 mole) of a 6.3 *N* solution of anhydrous ammonia in the same solvent was treated with 50 ml. of methanol containing 1.70 g. (0.01 mole) of silver nitrate. The resulting voluminous white precipitate was filtered off and dried to constant weight *in vacuo* over concentrated sulfuric acid, giving 6.75 g. (95.5%) of II. (II is very light-sensitive, especially when moist, and rapidly darkens on exposure to the diffuse light of the laboratory.) Like other silver salts of carboxylic acids,[24] II is soluble in ammonium hydroxide; excesses of ammonia must therefore be avoided in its preparation. Thus a 0.07-mole run in which a 35% excess of ammonia was employed gave a 79.3% yield of II; this material (analysis of which is given below) sintered at 114°, the pale brown melt remaining opaque to at least 145°. In another larger-scale (0.52 mole) preparation a 65% excess of ammonia was employed and the yield of II was only 67%.

Anal. Calcd. for $C_{18}H_{31}O_2Br_4Ag$: Ag, 15.27. Found: Ag, 15.22.

The 1,8,9,11,12-Pentabromoheptadecane (III).—Under strictly anhydrous conditions, 21.1 g. (0.02 mole) of a 15.2 weight per cent. solution of bromine in carbon tetrachloride was added over a one-hour period to a stirred slurry of 14.14 g. (0.02 mole) of II in 100 ml. of boiling carbon tetrachloride. Filtration of the cooled reaction mixture gave 3.72 g. (theory 3.76 g.) of silver bromide. Residual bromine in the filtrate (less than equimolar amounts of bromine are involved in the formation of Simonini ester and in the regeneration of I) was destroyed with aqueous sodium bisulfite and the organic phase dried ($MgSO_4$) and freed of solvent, leaving a pale yellow-brown solid residue weighing 12.1 g. Titration of a small aliquot of this crude product indicated the presence of 2.42 g. (20.2%) of regenerated I.

The bulk of the reaction product mixture was resolved by fractional elution from a dry-packed 20 × 7.5-cm. column of silicic acid activated *in situ* by successive prewashing with acetone, ether, and 60–70° petroleum ether.[25] The mixture (11.4 g.) was run into the column with 50 ml. of carbon tetrachloride and the column developed sequentially with 2.5 l. of petroleum ether, 1.5 l. of a 2:3 mixture (by volume) of benzene and petroleum ether and 2 l. of ether.

Evaporation of the petroleum ether eluate gave 8.34 g.

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[17] *Cf.* J. W. H. Oldham and A. R. Ubbelohde, *J. Chem. Soc.*, 201 (1938).

[18] P. A. Levene, C. J. West and J. van der Scheer, *J. Biol. Chem.*, **20**, 521 (1915).

[19] *Cf.* H. Gilman, E. A. Zoellner and J. B. Dickey, THIS JOURNAL, **51**, 1583 (1929); H. Gilman, E. A. Zoellner, W. M. Selby and C. Boatner, *Rec. trav. chim.*, **54**, 584 (1935); and F. C. Gzemski and M. Kilpatrick, *J. Org. Chem.*, **5**, 264 (1940).

[20] The well-known alkali-conjugatability of 1,4-diene systems would seem to be a reasonable basis for concern that exchange of the type $RMgBr + {-}CH{=}CHCH_2CH{=}CH{-} \rightarrow RH + {-}CH{=}CH{-}CH{=}CH{-}CH(MgBr){-}$ might occur to an appreciable extent. Observations made during reaction of CH_3MgI with methyl linoleate indicate that such an exchange, if it occurs, takes place very slowly. Ultraviolet absorption of one sample of reconstituted linoleic acid disclosed the presence of slightly more conjugated diene than was present in the precursive V, but autoxidation cannot be excluded as the cause of this additional isomerization of the diene moiety.

[21] *Cf.* V. Grignard, *Compt. rend.*, **198**, 625 (1934).

[22] *Cf.* M. Calvin, C. Heidelberger, J. C. Reid, B. M. Tolbert and P. F. Yankwich, "Isotopic Carbon," John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 140–142.

[23] I. Santos and A. P. West, *Phil. J. Sci.*, **34**, 199 (1927) (*C. A.*, **22**, 761 (1928)); R. D. Haworth, *J. Chem. Soc.*, 1456 (1929); W. C. Smit, *Rec. trav. chim.*, **49**, 539 (1930).

[24] *Cf.* J. W. H. Oldham, *J. Chem. Soc.*, 100 (1950).

[25] *Cf.* W. A. Schroeder, *Ann. N. Y. Acad. Sci.*, **49**, 204 (1948); and K. N. Trueblood and E. W. Malmberg, *Anal. Chem.*, **21**, 1055 (1948).

(71.3%) of white crystalline solid III from which 6.57 g. (m.p. 62.9–63.8°, employed in the zinc-debromination described below) was obtained by two recrystallizations from methanol–acetone. By additional recrystallization the melting point of III became constant at 64.1–64.6°; Bergström, *et al.*,[8] have recently reported m.p. 66–67° for this substance.

Anal. Calcd. for $C_{17}H_{31}Br_5$: C, 32.15; H, 4.92; Br, 62.93. Found: C, 32.22; H, 4.89; Br, 62.90.

The benzene-petroleum ether eluates yielded 0.68 g. of pale yellow, viscous oil presumed from its chromatographic behavior and in analogy with results of studies of the products of other Borodin degradations to consist principally of the Simonini ester, **tetrabromoheptadecyl tetrabromostearate**. Analytical results given by a rechromatographed sample, however, were in poor agreement with values calculated for this substance.

Anal. Calcd. for $C_{35}H_{62}O_2Br_8$: C, 36.42; H, 5.41; Br, 55.39. Found: C, 38.14; H, 6.41; Br, 52.76.

An attempt to reduce this material to the known heptadecyl stearate was unsuccessful (see below).

Material eluted rapidly by diethyl ether but slowly if at all by the benzene–petroleum ether mixture represents I, the total amount recovered being in excellent agreement with that indicated by titration of an aliquot of the intact reaction mixture (see above).

8,9,11,12-Tetrabromoheptadecanol-1 (IV) was encountered in early experiments concerned with the behavior of III on an alumina chromatographic column. Chromatography of a 0.50-g. sample of III (purified previously only by recrystallization) on a 14 × 2 cm. column of alumina (Harshaw activated, powdered, catalyst grade, reground to −200 mesh through courtesy of R. Schiffman and Co., Los Angeles) resulted in the following observations: petroleum ether (150 ml.) eluted 55 mg. of ill-characterized oily material distributed fairly evenly among the six 25-ml. fractions involved; on changing to diethyl ether (dried over sodium wire), fractions containing 100, then 75 mg. of III were obtained, two subsequent ether fractions containing only traces of solute; acetone (50 ml.) next eluted 240 mg. of IV, crude m.p. 77–80°. Recrystallization of the acetone-eluted material from small amounts of the same solvent at 0° gave clusters of colorless thin blades, m.p. 87.8–88.3° (Bergström, *et al.*,[8] report IV to melt at 76–78°).

Anal. Calcd. for $C_{17}H_{32}OBr_4$: C, 35.69; H, 5.64; Br, 55.88. Found: C, 35.93; H, 5.83; Br, 56.52.

Also in agreement with its postulated structure, the infrared spectrum of IV shows strong absorption at 2.96 μ, characteristic of the hydroxyl group. Final confirmation of this identification was afforded by conversion to the known heptadecanol-1 (see below). That the IV thus found was not originally present in the crude III was shown by rechromatography of unaltered III recovered from an alumina column, additional amounts of IV being formed.

Catalytic Hydrogenation of IV.—Considering the potential utility of the transformation $-CHBrCHBr- \rightarrow -CH_2CH_2-$, very little study has apparently been devoted to this subject.[26] Exploratory experiments in this Laboratory[27] on the catalytic hydrogenation of tetrabromostearic acid (I) have shown that reduction at room temperature and atmospheric pressure over palladium-on-charcoal (American Platinum Works, 10%) is initially rapid but stops short of the theoretical uptake of hydrogen, giving material which still contains bromine. When sufficient KOH to neutralize all HBr anticipated is present at the beginning of the hydrogenation, however, the reaction proceeds rapidly to completion, the theoretical amount of hydrogen is taken up, and stearic acid of high purity is obtained. The same procedure was equally successfully applied to the reduction of IV. On shaking 230 mg. of IV, 110 mg. (theory for four equivalents 106 mg.) of 85% KOH, 300 mg. of 10% palladium-on-charcoal and 20 ml. of absolute ethanol with moist hydrogen, approximately four equivalents of the gas was taken up in 22 min. and the rate of uptake was negligible thereafter. The white crystalline solid, m.p. 51.9–52.3°, recovered conventionally from the hydrogenation mixture, weighed 88 mg. (theory 103); after admixture with an authentic sample of heptadecanol-1 (m.p. 52.6–52.9°, prepared by lithium aluminum hydride reduction of margaric acid), the melting point was 52.0–52.6°.

Catalytic Hydrogenation of Ester Fraction.—Application of the same hydrogenation procedure to this fraction (presumably consisting largely of Simonini ester) was complicated by the low solubility of the material in absolute ethanol; extensive saponification of the ester evidently occurred during the relatively long period of time required to complete the hydrogenation. A mixture of 280 mg. of the material, 128 mg. of KOH (85% pellet, 8 equivalents), 300 mg. of 10% palladium-on-charcoal and 20 ml. of absolute ethanol shaken with moist hydrogen as before for 2.5 hours, let stand overnight, then shaken for an additional 5 hours gave an apparent uptake of about 61 ml. (theory 55.3 ml.). Working up the resulting reaction mixture gave 65 mg. of neutral (partially crystalline) material which was not investigated further and 20 mg. of acidic substance identified after recrystallization from acetonitrile as stearic acid (m.p. and mixed m.p.). Since the chromatographically purified starting material could hardly have contained any appreciable amounts of free acid (*e.g.*, I), the isolation of stearic acid provides good evidence for the original presence of I in an esterified form.

8,11-Heptadecadienyl bromide (V) was prepared by the action of zinc on III under conditions patterned after those employed in a somewhat analogous situation by Silberman and Silberman-Martyncewa.[16] Zinc dust (Baker and Adamson 90% powder, 2.9 g., 0.04 mole) was activated by boiling for a few minutes with 9 ml. of 95% ethanol and 0.36 ml. of 48% aqueous hydrobromic acid. After the mixture had cooled somewhat 5.76 g. (0.0091 mole) of chromatographically-purified and twice-recrystallized III (see above) dissolved in 7 ml. of C.P. benzene was added fairly rapidly and the resulting mixture refluxed for one hour. Excess zinc was then filtered out and 25 ml. each of water and 60–70° petroleum ether added to the filtrate. The organic phase was washed, dried and distilled, yielding 2.53 g. (88.5%) of V, b.p. 118–122° at 0.1 mm., n^{25}D 1.4782. In substantiation of the comments of Bergström, *et al.*,[8] other runs involving essentially identical conditions gave yields of product ranging down to as low as 50%. A sample from another preparative experiment was characterized as follows: b.p. 131° at 0.15 mm., n^{25}D 1.4810, $d^{25.5}$ 1.0215, M^{25}D 87.86 (theory 87.56).

Anal. Calcd. for $C_{17}H_{31}Br$: C, 64.75; H, 9.91; Br, 25.34. Found: C, 64.87; H, 9.91; Br, 25.17.

Shortly after being redistilled, the ultraviolet absorption spectrum of V (run in isoöctane) showed no evidence of conjugation; however, repetition of this determination after the material had stood at 0° (and presumably protected from contact with air) for about a year showed the presence of about 2.5% conjugated diene and 0.8% conjugated triene. The infrared spectrum of a freshly-distilled sample of V showed little significant absorption aside from peaks associated with C–H bending and stretching frequencies and another at 10.3 μ, intensity of which indicated the presence of about 18% *trans* disubstituted olefin content.[15]

1-C^{14}-Linoleic Acid and Methyl 1-C^{14}-Linoleate.—Employing conditions evolved during exploratory studies with *n*-heptadecyl bromide and simpler model compounds,[13] V was converted to linoleic acid in the following way (a high vacuum system patterned after that described by Calvin, *et al.*,[22] was used). Magnesium turnings (80.7 mg., 3.32 mmoles) were treated with 983.8 mg. (3.12 mmoles) of V dissolved in 20 ml. of rigorously dried diethyl ether; 3 ml. of the solution was added initially and stirred with the metal for 1.5 hours. At the end of this time, the mixture having acquired a gray-black color, the bulk of the dienyl bromide solution was introduced over a period of 3.75 hours; stirring was finally continued for an additional 1.75 hours. After the reaction mixture had stood overnight at room temperature, a 0.25-ml. aliquot of it (total volume 10.0 ± 0.3 ml.) was removed by pipet and titrated according to Gilman[28] to reveal an apparent Grignard reagent content of 2.44 mmoles (78%) in the total preparation.[29] Carbon

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[26] See, however, D. R. Howton, THIS JOURNAL, **69**, 2555 (1947).

[27] The assistance of Mr. Gunther Steinberg in these orienting studies is gratefully acknowledged.

[28] *Cf.* L. F. Fieser, "Experiments in Organic Chemistry," Part II, 2nd Ed., D. C. Heath and Co., New York, N. Y., 1941, p. 407.

[29] From the amounts of unreacted carbon dioxide recovered after reaction with this preparation, it would seem that the actual Grignard content is considerably lower than is indicated by this titration procedure; similar observations have been made during cold runs of this and analogous reactions carried out in this Laboratory.

dioxide liberated in the usual way from barium carbonate (638.5 mg., 3.23 mmoles, containing 2.007 mc. of C^{14}) was then added to the Grignard solution (frozen in liquid nitrogen) and allowed to react at −20° for 80 minutes and overnight at room temperature. Unreacted carbon dioxide (1.39 mmoles 43%) was recovered by sweeping the apparatus with nitrogen led finally through traps containing aqueous sodium hydroxide. Note that although 43% was recovered, the excess of carbon dioxide over titration-determined Grignard was only 26.3% of the total introduced.[29] The reaction mixture was treated with 6 *N* HCl (contact of the reaction product with air was avoided in this and in all subsequent operations) and acidic and neutral products were separated by conventional methods. Titration of an aliquot of the acidic product indicated a 40% yield (based on Grignard,[29] 31% based on V, 29.3% based on barium C^{14}-carbonate) of crude 1-C^{14}-linoleic acid. Although the low yield based on unrecovered carbon dioxide might be attributed to reaction with two or three equivalents of Grignard (giving neutral materials of ketonic or tertiary alcoholic nature), assay of the neutral products (365 mg.) of the reaction for radiactivity showed them to contain only 0.12% of that originally present in the barium carbonate. Infrared absorption spectra of neutral materials formed in the analogous reconstitution of stearic acid[13] also demonstrate the essential absence of ketonic and alcoholic products.

Crude reconstituted linoleic acid from a "cold run" conducted in the same manner was a pale yellow oil which crystallized readily on standing in a refrigerator. The neutralization equivalent of this product was 298 (theory 280), indicating the presence of about 6% neutral material. The ultraviolet absorption spectrum of this crude "cold" linoleic acid indicated the presence of 3.9% conjugated diene[20] and 0.7% conjugated triene. The origin of the triene contaminant is obscure; samples of linoleic acid as ordinarily prepared by the action of zinc on the 115° tetrabromostearic acid (I) also frequently contain small amounts of such materials. The infrared absorption spectrum of this reconstituted linoleic acid was essentially identical with that[3b] of the authentic (zinc regenerated) substance, absorption at 10.3 μ indicating the presence of about 15% *trans* isomer. A stream of nitrogen was employed to pass a slight excess of bromine into a solution of 0.29 g. of reconstituted linoleic acid in 10 ml. of 60–70° petroleum ether at 0°, precipitating crude I. Washed twice with 5-ml. portions of ice-cold petroleum ether and dried *in vacuo*, the precipitate weighed 0.175 g. (60% yield)[30] and melted at 110–113°; recrystallization from ethylene chloride raised the melting point to 114–115°, mixed melting point with authentic I (m.p. 115–116°) 115–116°.

Esterification of the acidic products of the "hot run" was accomplished by treatment with an ethereal solution of diazomethane. Solvent and excess diazomethane were removed *in vacuo* and the residual crude ester passed with 60–70° petroleum ether through a 10 × 2 cm. column of 1:1 (by weight) alumina–Celite prewashed with the same solvent. Under these conditions the desired ester is eluted rapidly (collected in about 200 ml. of eluate) while autoxidation products and traces of acidic material are retained on the adsorbent. Removal of solvent from the eluate gave 250 mg. of methyl 1-C^{14}-linoleate (90% based on crude linoleic acid found by titration). On a superficial mass yield basis, this quantity of ester is calculated to contain 0.529 mc. of C^{14}. Direct counting[31] of a small sample highly diluted with corn oil indicated the presence of 0.462 mc. in the total material; combustion of another aliquot followed by count of barium carbonate from the carbon dioxide thus formed showed a 0.501-mc. content.

Acknowledgment.—The authors are indebted to Dr. Harry M. Walborsky for assistance in preliminary investigation of the conversion of III to V; and to Dr. Edwin R. Buchman for his encouragement and wise counsel while this approach to the carboxyl-labeling of unsaturated fatty acids was being planned.

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[30] *I.e.*, 60% of the theoretical 50% yield of the petroleum ether insoluble isomer.

[31] The method of C. Entenman, S. R. Lerner, I. L. Chaikoff and W. G. Dauben (*Proc. Soc. Exp. Biol. and Med.*, **70**, 364 (1949)) was employed.

LOS ANGELES, CALIFORNIA

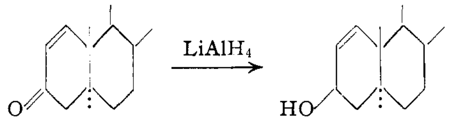
NOTES

Δ^1-Cholesten-3β-ol[1]

BY W. BERGMANN, M. KITA AND D. J. GIANCOLA

RECEIVED APRIL 22, 1954

In view of a recent publication[2] we wish to report the preparation of Δ^1-cholesten-3β-ol (II) which was carried out in this Laboratory some time ago in connection with our studies on the synthesis and photoöxidation of steroid dienes.[3] The new isomer of cholesterol is obtained readily by reduction of the well-known Δ^1-cholesten-3-one (I) with lithium aluminum hydride. As in the case of other cholestenones,[4] the reaction is predominantly, if not exclusively, stereospecific. The reduction product is precipitated quantitatively by digitonin; the sterol recovered from the digitonide[5] does not differ significantly from the product not so purified. The β-configuration of the hydroxyl group was definitely established by hydrogenation of the stenol to 3β-cholestanol.



I II

Experimental

All melting points are corrected. All optical rotations were measured in a 1-dm. tube, the sample being dissolved in 2 ml. of chloroform.

Δ^1-Cholesten-3β-ol (II).—A solution of 1.9 g. of Δ^1-cholesten-3-one (I) (m.p. 99.5°, $[\alpha]^{20}\text{D}$ +60.0° $\lambda^{\text{alc}}_{\text{max}}$ 230 mμ (10.800).) in 30 ml. of anhydrous ether was added dropwise and with vigorous stirring to a solution of 0.2 g. of lithium aluminum hydride in 20 ml. of anhydrous ether. The mixture was stirred for two hours; thereafter the reaction-flask was cooled in ice, and the reduction complex and excess hydride were decomposed with cold, dilute sulfuric acid. More ether was added to the mixture, the ethereal layer separated, washed with water, aqueous sodium bicarbonate solution, water and dried. After evaporation of the solvent, the residue (1.7 g.) was recrystallized from methanol; fine needles, m.p. 131°, $[\alpha]^{25}\text{D}$ +53.6°. A portion (0.209

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[1] The investigation was supported by a grant from the National Institutes of Health, U. S. Public Health Service.

[2] H. B. Henbest, G. D. Meakins and G. W. Woods, *J. Chem. Soc.*, 800 (1954).

[3] R. T. Conca and W. Bergmann, *J. Org. Chem.*, **18**, 1104 (1953).

[4] L. F. Fieser, M. Fieser and R. N. Charkavarti, THIS JOURNAL, **71**, 2226 (1949); W. G. Dauben, R. A. Micheli and J. F. Eastham, *ibid.*, **74**, 3852 (1952); Shoppee and Summers, *J. Chem. Soc.*, 687 (1950).

[5] W. Bergmann, *J. Biol. Chem.*, **132**, 471 (1940).