methyl β-bromopropionate gave an extremely viscous material which could not be obtained analytically pure but gave no test with ferric chloride and was presumed to be largely methyl 6,7,8,9-tetrahydro-5H-cycloheptabenzen-5-one-6-carboethoxy-6-propionate. This crude material was treated with methanolic barium hydroxide[5] and the resultant acid, which decomposed on attempted purification by distillation, esterified directly with diazomethane to give methyl 6,7,8,9-tetrahydro-5H-cycloheptabenzen-5-one-6-propionate (III) as a viscous oil in 60% yield from II. Hydrolysis of the crude intermediate diester with a mixture of acetic and hydrochloric acids or with alcoholic potassium hydroxide resulted in lower yields of III and the formation of tarry by-products.

A Reformatsky reaction of III with methyl bromoacetate followed by dehydration of the crude product and then catalytic hydrogenation afforded IV in 28% over-all yield from III. The low yield realized was not unexpected as it has been previously observed[6] that hindered ketones give poor yields in the Reformatsky reaction.

Experimental[7]

Ethyl 6,7,8,9-Tetrahydro-5H-cycloheptabenzen-5-one-6-carboxylate (II).—A solution of 160 g. (1.0 mole) of 6,7,-8,9-tetrahydro-5H-cycloheptabenzen-5-one (I), prepared as previously described,[8] in 300 ml. of di-*n*-butyl ether (dried over sodium hydride) was added dropwise with vigorous stirring over a period of two to three hours to a gently refluxing mixture of 48 g. (2.0 moles) of sodium hydride in 100 ml. of the dry di-*n*-butyl ether and 240 ml. of freshly distilled diethyl carbonate (b.p. 124–126°). After the addition was complete, the mixture was refluxed for six hours, during which time the mixture was kept fluid by the occasional addition of further quantities of dry solvent, and then allowed to stand overnight. After cooling to 10°, unreacted sodium hydride was destroyed by the addition of 100 ml. of alcohol and the cold mixture was then neutralized by the addition of dilute hydrochloric acid under an atmosphere of nitrogen. After separation of the layers and extraction of the aqueous layer several times with ether, the combined organic layers were washed with saturated salt solution until neutral and then dried over sodium sulfate. Distillation gave 166.5 g. (72%) of II as a yellow oil (b.p. 125–134° at 1 mm., $n^{25.5}$D 1.5623) which gave an intense purple color with 5% ferric chloride solution. The ultraviolet absorption spectrum of an ethanolic solution showed maxima in mμ at 246 (ϵ 6500) and 290 (ϵ 13,000).

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.34; H, 7.00. Found: C, 72.41; H, 6.97.

Methyl 6,7,8,9-Tetrahydro-5H-cycloheptabenzen-5-one-6-propionate (III).—A solution of 156.6 g. (0.67 mole) of the aforementioned keto ester (II) in 500 ml. of purified dioxane[9] was added dropwise with stirring over a period of two to three hours to a gently refluxing mixture of 16.1 g. (0.67 mole) of sodium hydride in 100 ml. of purified dioxane. The resultant mixture was refluxed for an additional hour. To this hot mixture was then added dropwise a solution of 112 g. (0.67 mole) of methyl β-bromopropionate in 200 ml. of purified dioxane. After stirring and refluxing overnight, the mixture was cooled and the precipitated sodium bromide separated by filtration. Removal of the volatile substances from the filtrate by distillation under reduced pressure left 273.5 g. of a viscous yellow oil which gave no test with 5% ferric chloride solution but could not be purified by distillation. A mixture of 15.9 g. of this oil, presumed to contain mainly methyl 6,7,8,9-tetrahydro-5H-cycloheptabenzen-5-one-6-carboethoxy-6-propionate, 78 g. of barium hydroxide octahydrate, 260 ml. of water and 125 ml. of methanol was refluxed vigorously for 20 hours.[5] Most of the methanol was then removed by distillation under reduced pressure and the cooled residue was acidified with dilute hydrochloric acid. The yellow oil which separated was dissolved in ether, the solution dried over sodium sulfate, and the solvent evaporated. The extremely viscous acidic yellow oil which remained (11 g.), and which decomposed on attempted purification by distillation, was taken up in 500 ml. of dry ether. This solution was cooled to 0° in an ice-bath and to it was added with stirring a cold solution of approximately 0.15 mole of diazomethane in ether. Excess diazomethane was destroyed by the addition of a few ml. of acetic acid. Distillation gave 8.56 g. (60% from II) of methyl 6,7,8,9-tetrahydro-5H-cycloheptabenzen-5-one-6-propionate (III) as a viscous yellow oil, b.p. 160–170° at 1 mm., $n^{25.5}$D 1.5344.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.39; H, 7.39.

Dimethyl 6,7,8,9-Tetrahydro-5H-cycloheptabenzene-5-acetate-6-propionate (IV).—A mixture of 40 g. of twenty-mesh zinc, 44 g. (0.18 mole) of III, 27.5 g. (0.18 mole) of methyl bromoacetate and a crystal of iodine in 100 ml. of dry toluene was heated under reflux for three hours with the addition of 20 g. of zinc and 9.2 g. of methyl bromoacetate at one-hour intervals. After the last addition, the heating was continued for six more hours. The mixture was cooled to 0° and 100 g. of ice and 15 ml. of acetic acid added. After separation of the layers and extraction of the organic layer several times with ether, the combined organic layers were washed successively with 1% ammonium hydroxide (10–15 times), water, and a saturated sodium chloride solution, and then dried over sodium sulfate. To the brown, viscous oil which remained after removal of the solvents under reduced pressure was added 40 g. of fused, anhydrous potassium bisulfate and the mixture was heated (oil-bath) at 150–160° for one hour. The organic product was extracted from the solid material with ether, the solution dried, and the solvent removed by evaporation. The dark oil which remained was dissolved in 100 ml. of absolute methanol and treated with hydrogen at 30–40 lb. pressure in the presence of 1–2 g. of Raney nickel catalyst. After removal of the catalyst and solvent, distillation *in vacuo* gave 15.5 g. (28% from III) of IV as a viscous yellow oil, b.p. 170–180° at 0.8 mm., $n^{25.5}$D 1.5201.

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 69.86; H, 7.64.

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The Synthesis of C^{14}-Labeled "Squalene"[1]

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RECEIVED APRIL 19, 1952

The present concern in the metabolic fate of polyisoprenoid compounds[2] has revived the interest in the early hypothesis of Robinson[3] on the possibility of a direct conversion of the triterpene squalene (I) to cholesterol (II). A convenient way to test this suggestion would be to employ squalene uniquely labeled with C^{14}. The location of the label in the terpene should be such that if a conversion of the type described by Robinson occurred, the labeled atom could singly and easily be removed

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[5] G. Buchi and O. Jeger, *Helv. Chim. Acta*, **32**, 538 (1949).

[6] E. C. Horning, M. G. Horning and E. J. Platt, THIS JOURNAL, **72**, 2731 (1950).

[7] Melting points and boiling points are uncorrected.

[8] A. G. Anderson, Jr., and H. F. Greef, THIS JOURNAL, **74**, 5124 (1952).

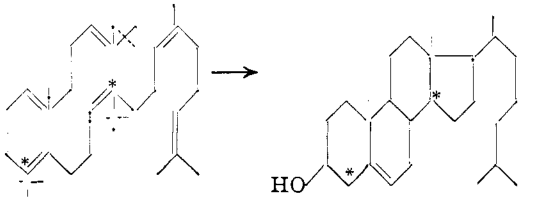
[9] A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1948, p. 175.

[1] The term "squalene" is used to indicate that the product, although a triterpene with six double bonds, is not identical with the naturally occurring compound but is a mixture of double bond isomers (see text).

[2] "Ciba Foundation Conference on Isotopes in Biochemistry," J. and A. Churchill, Ltd., London, 1951, p. 24 ff.; K. Bloch, "Recent Progress in Hormone Research," Vol. VI, Academic Press, Inc., New York, N. Y., p. 111 ff.

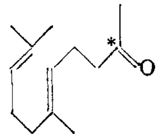
[3] R. Robinson, *J. Chem. Soc. Ind. (London)*, **53**, 1062 (1934).

from the sterol. The placement of the C^{14} at carbon atom four in cholesterol would meet this requirement and such a labeled "squalene" has been prepared. Experimental evidence in support of the postulated conversion has recently been reported by Langdon and Bloch[4] who employed a randomly labeled squalene from natural sources.



I II

The synthesis of squalene has been reported twice. In 1931, Karrer and Helfenstein[5] prepared the compound by allowing farnesyl bromide to react with either magnesium or potassium in a Wurtz reaction and their yield was only 7%. More recently, Schmitt[6] has synthesized squalene in 38%



$+ BrCH_2CH_2CH_2CH_2Br \xrightarrow{Mg} I$

III

yield by means of a Barbier reaction between geranylacetone (dihydropseudoionone), III, and tetramethylene bromide in the presence of magnesium. The method of Karrer and Helfenstein was not investigated because of the low yield in the condensation reaction and the difficulty in preparing pure farnesyl bromide.

The labeled geranylacetone, the required marked intermediate, was prepared by a modification of the method of Carroll[7] using dilute aqueous alcoholic sodium hydroxide for the ketonic cleavage of the labeled ethyl geranylacetoacetate. The usual barium hydroxide method[8] was found to give inconsistent results, whereas the preceding method consistently gave 90% yields. The carbonyl labeled ethyl acetoacetate was prepared by acylation of the magnesium derivative of ethyl *t*-butyl malonate and pyrolysis of the resulting ester.[9] The previously reported procedure of Sakami, Evans and Gurin[10] involving the condensation of ethyl bromoacetate and ethyl acetate in the presence of magnesium was found to proceed erratically. The labeled geranylacetone, prepared above, was allowed to react with tetramethylene bromide and magnesium. When the resulting squalene was isolated directly from the reaction mixture, as described by Schmitt,[5] the infrared spectrum of the distillate showed the presence of a hydroxyl band at 2.92 μ. Treatment of this material with phosphorus tribromide and collidine gave the pure hydrocarbon. The infrared spectrum of the product is shown in Fig. 1. It is of interest to note the presence of bands at both 11.25 and 12.0 μ. Such bands are characteristic of the type of structures[11] $RR'C{=}CH_2$ and $RR'C{=}CHR''$, respectively. A previous report from this Laboratory[12] has shown that natural squalene has only the trialkylethylene structure present but that squalene obtained by purification through the solid hexahydrochloride has both types of structure present. In Fig. 1 it can be seen that the spectra of synthetic and regenerated squalene are identical in all respects. Earlier work[11] has indicated that regenerated squalene has 20–40% of the double bonds present as the unsymmetrical dialkylethylene type and a similar calculation gives about the same result for the C^{14}-labeled material. Thus, synthetic squalene differs from the naturally occurring triterpene in regard to the types of double bonds present.

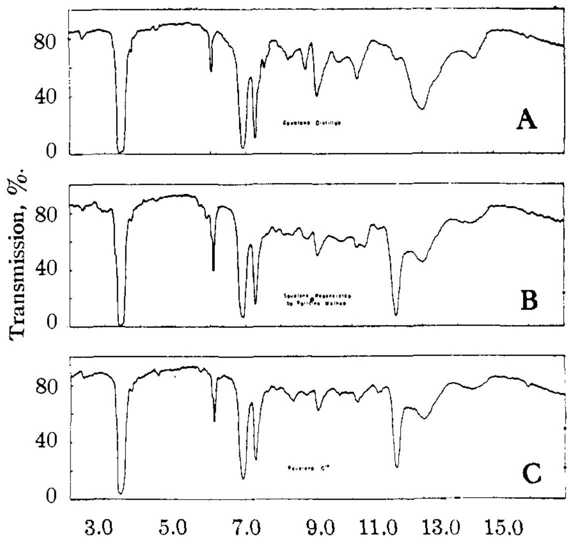


Fig. 1.—Infrared spectra: A, squalene distilled; B, squalene regenerated by pyridine method; C, squalene C^{14}.

It has previously been reported,[12] that squalene can be chromatographed on "Quilon" treated paper using methanol as the developing solvent. It was found that natural squalene gave a single spot with an average R_f value of 0.71 and that regenerated squalene showed two spots, a very strong zone with a value of 0.71 and a second weak one with a value of 0.86. When the C^{14}-labeled material was chromatographed under the same conditions, it also showed two spots with the identical R_f values of the regenerated terpene. Radioautography of the papers showed only two spots and these were identical with those detected by iodine. When the labeled squalene was run together with C^{14}-labeled cholesterol, identical results were obtained as those reported earlier using color tests for identification of the spots.

The authors wish to express their appreciation to Miss Mildred Gee for assistance and to Dr. David

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(4) R. G. Langdon and K. Bloch, THIS JOURNAL, **74**, 1869 (1952).

(5) P. Karrer and A. Helfenstein, *Helv. Chim. Acta*, **14**, 78 (1931).

(6) J. Schmitt, *Ann.*, **547**, 115 (1941).

(7) M. F. Carroll, *J. Chem. Soc.*, 704 (1940).

(8) L. Ruzicka, *Helv. Chim. Acta*, **6**, 492 (1928).

(9) D. S. Breslow, E. Baumgarten and C. R. Hauser, THIS JOURNAL, **66**, 1286 (1944).

(10) W. Sakami, W. E. Evans and S. Gurin, *ibid.*, **69**, 1110 (1947).

(11) H. W. Thompson and D. H. Whiffen, *J. Chem. Soc.*, 1412 (1948).

(12) W. G. Dauben, L. B. Bradlow, N. K. Freeman, D. Kritchersky and M. Kirk, THIS JOURNAL, **74**, 4321 (1952).

Kritchevsky for the determination of the R_f values and to Dr. Keith Freeman for the infrared spectra.

Experimental[13]

Geranyl Chloride.—This preparation was carried out as described by Ruzicka[8] using phosphorus pentachloride and either hexane or ligroin (60–70°) as a diluent. From 90 g. (0.6 mole) of geraniol, 62 g. (60%) of the chloride was obtained, b.p. 93–104° (15 mm.). The thionyl chloride method of Barnard and Bateman[14] was found to be less satisfactory.

Carbonyl-Labeled Ethyl Acetoacetate.—A mixture of 2.87 g. of magnesium, 100 ml. of absolute ethanol, 20 ml. of dry xylene and 2 ml. of carbon tetrachloride was refluxed for 12 hours and then concentrated to dryness under reduced pressure on a steam-bath. Benzene was added twice and removed *in vacuo* to ensure the absence of any alcohol.[15] The residue was heated at 100° under reduced pressure for three hours, cooled, 40 ml. of anhydrous ether added and the mixture stirred vigorously to break up the solid. Ethyl *t*-butyl malonate (22.4 g.) then was added dropwise with stirring and the mixture refluxed until complete solution was obtained. Carboxyl-labeled acetyl chloride, prepared from 10.8 g. of sodium acetate containing 9.9 mc. of C^{14} by distillation from benzoyl chloride, was dissolved in 25 ml. of dry ether and the solution was added dropwise with stirring to the magnesium derivative of the malonic ester. After refluxing for 30 minutes, the reaction mixture was cooled, diluted with water and acidified with dilute sulfuric acid. The aqueous phase was separated and extracted with ether and combined with the above ether. The solvents were distilled, the residue dissolved in 100 ml. of benzene, a small amount of the solvent distilled, 0.75 g. of *p*-toluenesulfonic acid added and the solution refluxed for 90 minutes. The cooled benzene solution was extracted with saturated sodium bicarbonate, saturated sodium chloride and the benzene removed through an 18" column. The residue was distilled, b.p. 180°, yield 12.2 g. (71.3% based upon sodium acetate).

Geranylacetone.—The carbonyl-labeled ethyl acetoacetate (11.53 g.) was diluted with 11.0 g. of non-radioactive ester and the mixture added dropwise with stirring to a cooled solution of 3.46 g. of sodium in 100 ml. of absolute ethanol. After 15 minutes, 26.4 g. of freshly distilled geranyl chloride was added slowly and the resulting mixture heated under reflux for 25 hours. The solution was diluted with 500 ml. of water, extracted with ether and the ether distilled.

The crude product was dissolved in a solution containing 8 g. of sodium hydroxide, 350 ml. of ethanol and 230 ml. of water and refluxed for 48 hours. The reaction was then diluted with 500 ml. of water, extracted twice with 250-ml. portions of ether, the ethereal solution washed with water until neutral, then with saturated sodium chloride solution and dried over sodium sulfate. The product was distilled, b.p. 115° (1 mm.), yield 15 g. (52.5%).

Labeled "Squalene."—A mixture of 15.0 g. of geranylacetone, 10 g. of tetramethylene bromide, 2.3 g. of magnesium and a crystal of iodine was heated on a steam-bath for 30 minutes under an atmosphere of nitrogen. The mixture was then diluted with 45 ml. of dry ether and refluxed for 45 minutes by which time most of the magnesium had dissolved. Another crystal of iodine was added and the solution refluxed overnight. The reaction was decomposed with water and dilute hydrochloric acid, the ethereal layer separated and dried.

The ether was distilled, 30 ml. of dry benzene and 15 ml. of phosphorus tribromide were added and the solution heated on a steam-bath for 12 hours. The cooled mixture was poured into dilute hydrochloric acid and ice-water, the layers separated and the aqueous layer re-extracted with ether. The combined extracts were washed with dilute alkali, water and saturated sodium chloride solution. The solvents were distilled, the residue dissolved in 60 ml. of collidine and heated under reflux for 3 hours. After dilution with aqueous hydrochloric acid, the mixture was extracted four times with ether, the ethereal solution processed in the usual manner and the product distilled, b.p. 210–212° (1.5 mm.), yield 3.1 g. (19.7%).

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(13) All boiling points are uncorrected.

(14) D. Barnard and L. Bateman, *J. Chem. Soc.*, 926 (1950).

(15) B. Riegel and W. M. Lilienfeld, THIS JOURNAL, **67**, 1273 (1945).

The Infrared Spectra of the Isomeric 2-Decalols and their Acetates. The Effects of Stereochemical Configuration

BY WILLIAM G. DAUBEN, EARL HOERGER AND N. K. FREEMAN

RECEIVED MAY 12, 1952

To date, various methods have been employed in the decalols to assign the configuration of the hydroxyl group and the nearest ring juncture hydrogen atom. Originally, Hückel[1] allocated such configurations on the basis of the von Auwer–Skita rule and many of these assignments have been confirmed by the application of the stereospecific elimination reactions[2] in the 1-decalol series and the utilization of conformational analysis[3] in the *trans*-decalols. There is no direct method which is applicable to the *cis*-2-decalols.[4] Last year, Jones, Humphries, Herling and Dobriner[5] reported that in the sterols, a study of the 1200–1260 cm.$^{-1}$ region of the infrared spectrum could aid in the determination of the stereochemical relationship between the C_3-hydroxyl group and the C_5-hydrogen atom. They found that when the acetoxyl group at C_3 and the hydrogen at C_5 were *trans* to each other, only a single strong band occurred in this region. When such a relationship was *cis*, two or three strong bands were observed. Absorption at these frequencies is characteristic of the acetate group in general and these workers suggested that the multiple bands could be due to an equilibrium mixture of unstable rotational isomers. If such were the case, this type of analysis should be applicable to the corresponding acetates of the 2-decalols. These esters have been prepared and their spectra are shown in Fig. 1. Each spectrum was obtained several times with varying operating conditions to verify the spectral details.

The stereochemical configuration assigned to the four 2-decalols at the present time is shown below.[6] If these assigned configurations are correct and if this spectral analysis is applicable, it would be expected that the acetates of I and III should show a single strong band whereas the acetates of II and IV should exhibit a multiple band structure. An examination of the curves shows that the spectrum of the acetates of *cis*-105° decalol (I) does have a single symmetrical band in this region but it was

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(1) W. Hückel, *Ann.*, **441**, 1 (1925); **451**, 109 (1926); **533**, 1 (1938); W. Hückel and C. Kuhn, *Ber.*, **70**, 2479 (1937).

(2) W. Hückel, W. Tappe and G. Legutke, *Ann.*, **543**, 191 (1940); D. H. R. Barton, *J. Chem. Soc.*, 2175 (1949).

(3) D. H. R. Barton, *Experientia*, **6**, 316 (1950).

(4) W. G. Dauben and E. Hoerger (THIS JOURNAL, **73**, 1504 (1951)) have employed an indirect method in which they assign the configuration of a *cis*-decahydro-2-naphthoic acid on the basis of the *cis*-hydrogenation concept of Linstead. The acids obtained were then related to the decalols by the use of stereospecific reactions.

(5) R. N. Jones, P. Humphries, F. Herling and K. Dobriner, *ibid.*, **73**, 3215 (1951).

(6) The positions of the hydrogen atoms are represented in the formulas by black dots, a dot indicating that a hydrogen atom is above the plane of the molecule.