A general procedure for the esterification of diethylene glycol with fatty acids is as follows: One mole of the acid and 1 to 12 moles of diethylene glycol were placed in a flask with about 7.5 to 15 g. of a sulfonated polystyrene resin (Amberlite IR-120) per 100 g. of acid and 200–300 ml. of toluene. The mixture was refluxed from 4 to 18 hours with the removal of water, as the toluene azeotrope, as fast as formed. In most cases the reflux time was 10 to 18 hours. The pot temperature for these esterifications remained at 130 to 150°. At the end of the reflux period the resin was removed by filtration and the esters separated by fractional distillation at reduced pressure. The purity of the esters was checked by the determination of the saponification and hydroxyl numbers.

For example, the observed saponification value for diethylene glycol monolaurate was 274 compared with a calculated value of 288. The hydroxyl value was 6.0 compared with a calculated value of 5.9. The purity of the trichlorophenoxyacetic ester also was checked by a determination of the chlorine content (calcd. Cl, 31.0; found Cl, 31.2).

Discussion of Results

The experimental data are summarized in Table I. In all cases, significantly better yields of monoesters were obtained than when sulfuric or toluenesulfonic acids were used as catalysts. Thus, when a 1-to-1 mole ratio of lauric acid and diethylene glycol was used, a 24% yield of the monoester was obtained. However, when toluenesulfonic acid was substituted for the resin, with all other conditions held the same, the maximum yield of monoester was a little less than 10%. Excellent conversions to monoesters were obtained with a mole ratio of glycol to acid of 6 to 1. Essentially quantitative conversions of the monoester were obtained with mole ratios of 12 to 1.

TABLE I

CATION EXCHANGE RESIN CATALYZED ESTERIFICATIONS OF DIETHYLENE GLYCOL

Acid	Moles glycol per mole acid	Catalyst[a] g. per 100 g. acid	Temp., °C.	Reacn., time, hr.	Conversion of acid to Mono-ester	Di-ester
Lauric	1	7.5	140	18	24	71
Lauric	4	15.5	130	10	71	21
Lauric[b]	4	12.5	180	1.5	67	33
Lauric	6	7.5	140	18	86	11
Lauric	12	15.0	132	18	Quant.	..
Oleic	12	10.6	140	18	Quant.	..
Stearic	12	8.9	150	18	Quant.	..
2,4,5-Trichlorophenoxyacetic	12	13.7	130	4.5	70	..
Benzoic	2	24.6	140	4	75	..

[a] Amberlite IR-120. [b] High-boiling petroleum naphtha used as a solvent. In all other cases toluene was used.

Although most of the esterifications were carried out for 18 hours, essentially as good conversions can be obtained in shorter time. This is indicated in the first three experiments in Table I in which the reaction time was decreased to 1.5 hours by changing the amount of catalyst or the reaction temperature without appreciably changing the total conversion. The resins were used for successive reactions and no loss in the reactivity was observed even at temperatures of 180°. Temperatures of 130–140° are to be preferred, however, because the resins are known to lose their activity slowly at temperatures not much higher than 180°. It was observed that when a petroleum naphtha was used as a solvent, higher temperatures were achieved and the ratio of mono- to diester was somewhat less favorable.

In addition to increasing the yield of monoesters relative to the diesters, the use of cation exchange resins as catalyst offers some other advantages over conventional acid catalysts. The resins can be removed by filtration or decantation so that there is no problem of neutralization or otherwise removing the acid catalyst before working up the product. Sulfuric acid, when used as a catalyst, tends to form colored substances which are difficult to remove, so that it is difficult to obtain a clear, water-white product. No color is produced when cation exchange resins are used as the catalyst. The cation exchange resins can be re-used and might lend themselves to continuous operations in which the reactions could be carried out in packed columns.

Some work has been done using other glycols and glycerol which indicates that the increased yields of monoesters is possible with all dihydric and polyhydric alcohols.

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Derived Steroids. V. 3-β-Alkyl-5-cholestenes[1,2]

BY ROBERT H. BAKER, L. SHERWOOD MINCKLER AND QUENTIN R. PETERSEN[3]

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Previous papers from this Laboratory[2] have demonstrated the high stereospecificity of the reactions of cholesteryl Grignard reagents with compounds containing the carbonyl group. Although in the last paper of this series we assigned the α-configuration to these products, subsequent work by Corey[4] and by Shoppee[5,6] show this assignment to be erroneous.

With the one exception of oxygen[6,7] the only reagents previously studied in reactions with cholesteryl Grignard reagents have been those containing carbonyl groups. The non-stereospecificity of the oxygenation reaction is unique and it was of interest to study other reagents which contain no carbonyl groups.

Some of the reagents we worked with, ethylene oxide and O-methylhydroxylamine, gave little or no products; others, iodine and sulfur, gave somewhat better but still unsatisfactory yields and the only identifiable products were of β-configurations. Cholesterylmagnesium chloride upon treatment with iodine in ether gave a product which appeared to be a mixture of iodides, but successive stages of purification produced crystals which slowly liberated iodine until in the end the properties approached those of the 3-β-iodide. The same Grig-

(1) This work was supported by a grant from the Abbott Fund of Northwestern University.

(2) For paper IV and previous references, see R. H. Baker and Q. R. Petersen, THIS JOURNAL, **73**, 4080 (1951).

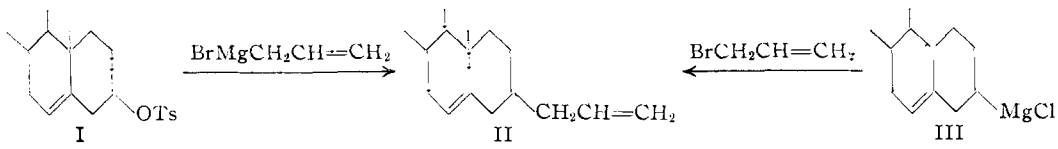
(3) Research Fellow, National Institutes of Health, 1951–1952.

(4) E. J. Corey and R. A. Sneen, THIS JOURNAL, **75**, 6234 (1953).

(5) C. W. Shoppee and R. J. Stephenson, *J. Chem. Soc.*, 2230 (1954).

(6) G. Roberts and C. W. Shoppee, *ibid.*, 3418 (1954).

(7) R. E. Marker, T. S. Oakwood and H. M. Crooks, THIS JOURNAL, **58**, 481 (1936); R. E. Marker, O. Kamm, T. S. Oakwood and J. F. Laucius, *ibid.*, **58**, 1948 (1936).



I II III

nard reagent with sulfur in benzene, or in dry pyridine in which it is notably more soluble, gave a trisulfide, a disulfide and a sulfide but no mercaptan. The disulfide, m.p. 141–143°, was reduced by lithium aluminum hydride to the known 3-β-cholesteryl mercaptan.

Allyl bromide reacted rapidly with the Grignard reagent to produce in moderate yield 3-β-allyl-5-cholestene (II). While the initial product was not of high purity, only one isomer could be identified. It is of interest that this same isomer could be produced, though in poorer yield by reaction of allylmagnesium bromide with 3-β-cholesteryl tosylate (I). While the latter reaction would seem to be sufficient proof of the structure of the hydrocarbon, we have gone further and have related it by stereospecific reactions to 3-β-cholesterylcarboxylic acid (IV). Ethyl cholesteryl ketone (V) related to the acid was reduced *via* the alcohol and its tosylate to propylcholestene. Catalytic hydrogenation of either this or of allylcholestene produced the same propylcholestane VI.

Some years ago Farmer and Kon[8] isolated in small quantity, from selenium dehydrogenation experiments on 3-methyl-3-cholestanol, a methylcholestane, m.p. 96–97, of unknown configuration. It seems reasonable to assume this product was formed *via* a dehydration to olefin followed by disproportionation, most of the olefin being dehydrogenated to the aromatic system but a small amount being reduced. In the light of our present knowledge of the stability of 3-β-derivatives it would be assumed that regardless of the mode of the reduction, surface or gas phase, the product should have been of the β-configuration. This configuration has been confirmed by the sequence of reactions IV to IX: 3-β-carboxylic acid → 3-β-carbinol → 3-β-carbinyl tosylate → 3-β-methyl-5-cholestene → 3-β-methylcholestane, m.p. 97–98°.

Experimental[9]

3-β-Allyl-5-cholestene (II). First Method.—A Grignard solution was made from 20 g. (50 millimoles) of cholesteryl chloride, and the bicholesteryl, 2.1 g., was removed by filtration.[10] To the filtered solution there was added gradually 16 ml. of freshly distilled allyl bromide. After the vigorous reaction subsided the mixture was refluxed for four hours. The mixture was treated with dilute hydrochloric acid and the ether phase was removed and dried over potassium hydroxide. Evaporation of the ether left an oily solid which was crystallized from acetone to give a first fraction of 8 g., m.p. 90–100°. Chromatography over alumina did not markedly purify the material, but repeated crystallization from ethanol–ether and, better, from propanol gave material with little loss which melted at 113–114°, $[\alpha]^{26}D$ −25°.

Anal. Calcd. for $C_{30}H_{50}$: C, 87.73; H, 12.27. Found: C, 88.17; H, 12.27.

3-β-Allyl-5-cholestene. Second Method.—A Grignard solution in ether made from 7 g. (58 millimoles) of allyl bromide and 10 g. (0.4 mole) of magnesium was filtered and added to 1.1 g. (2 millimoles) of cholesteryl *p*-toluenesulfonate. The stirred solution was refluxed for one hour and was allowed to remain at room temperature for 20 hours. Hydrolysis by acid followed by evaporation and crystallization from ethanol–ether gave 0.18 g., m.p. 97–104°. Crystallization from propanol and three recrystallizations from acetic acid left 0.057 g., m.p. 113–114°, $[\alpha]^{26}D$ −27°. The infrared spectrum was identical to the material made by the first method and there was no depression of m.p.

Anal. Calcd. for $C_{30}H_{50}$: C, 87.73; H, 12.27. Found: C, 87.43, H, 12.29.

When allylmagnesium bromide was treated with cholesteryl iodide the latter was recovered in 80% yield.

Ethyl-3-β-cholesterylcarbinol.—To 0.5 g. (13 millimoles) of lithium aluminum hydride in dry ether was added an ether solution containing 1.87 g. (0.44 millimole) of ethyl 3-β-cholesteryl ketone.[11] After one hour at reflux the product was recovered by water hydrolysis, extraction and crystallization from hexane. Three crops of white crystals, 1.54 g. (83%), were obtained. The last crop had m.p. 143–146°, and the purest 146–147°, $[\alpha]^{26}D$ −28°.

Anal. Calcd. for $C_{30}H_{52}O$: C, 84.04; H, 12.23. Found: C, 84.52; H, 12.18.

Ethyl-3-β-cholesterylcarbinyl *p*-Toluenesulfonate.—This was made in the usual way in pyridine at 55° during two hours. Upon pouring into water the gummy solid could not be filtered until it had stood in contact with water several hours. Crystals from hexane gave m.p. 103–105°,[12] $[\alpha]^{25}D$ −8.3°.

Anal. Calcd. for $C_{37}H_{58}O_3S$: C, 76.24; H, 10.03. Found: C, 76.72; H, 10.40.

3-β-Propyl-5-cholestene.—An ether solution of the above tosylate, 0.65 g. (1.1 millimoles), and lithium aluminum hydride, 0.5 g. (13 millimoles), was refluxed for five hours and allowed to stand 12 hours. After hydrolysis with 1 ml. of water and filtration the ether was evaporated to give 0.5 g. of impure white solid, m.p. 131–136°. Crystallization from ether–ethanol gave 0.3 g. of white plates, m.p. 127–129°. Two more crystallizations gave 0.21 g., 48%, of the hydrocarbon, m.p. 123°, $[\alpha]^{27}D$ −31°. It is of note that mixtures of the carbinol and hydrocarbon melted at temperatures between those of the pure compounds.

Anal. Calcd. for $C_{30}H_{52}$: C, 87.30; H, 12.70. Found: C, 86.96; H, 12.80.

Propylmagnesium bromide and cholesteryl tosylate failed to give this hydrocarbon but gave instead β-cholesteryl bromide in 75% yield.

3-β-Propylcholestane (VI).—This was made by the hydrogenation, one atmosphere, of 100-mg. samples of either allyl or propylcholestene in acetic acid, 20 and 60 ml., respectively, over 40 mg. of 10% palladium-on-charcoal. It was necessary to operate at about 75° to avoid precipitation of product. In about two hours, two and one mole, respectively, of hydrogen was added. After removal of catalyst and concentration to 20 ml. the solutions upon cooling deposited 60–82 mg. of needles, m.p. 91°, $[\alpha]^{27}D$ +25°, +24°. Infrared spectra were identical.

Anal. Calcd. for $C_{30}H_{54}$: C, 86.88; H, 13.12. Found (respectively): C, 87.39, 87.34; H, 13.21, 13.10.

3-β-Methyl-5-cholestene (VIII).—To 1 g. (1.8 millimoles) of 3-β-cholesterylcarbinyl tosylate[13] in dry ether was added

(8) S. N. Farmer and G. A. R. Kon, *J. Chem. Soc.*, 414 (1937).

(9) Microanalyses by Mrs. C. White and Miss H. Beck. Specific rotations were taken in chloroform at *c* approximately 1.0.

(10) R. H. Baker and E. N. Squire, THIS JOURNAL, **70**, 1487 (1948).

(11) This was prepared from cholesterylcarboxylic acid now known to be β (references 4, 5 and 6) using Dr. Squire's method (reference 10) of treating the acid chloride with diethylcadmium. The stereospecificity of this reaction is attested by both our work and that of Dr. Corey.

(12) Above 105° the material decomposed to a red liquid as has been observed with the tosylate of epicholesterol by L. C. King and J. Bigelow, THIS JOURNAL, **74**, 6238 (1952).

(13) Prepared by Dr. Petersen's method, reference 2, and referred to therein as the α-isomer.

0.2 g. (5 millimoles) of lithium aluminum hydride. The solution was refluxed 12 hours, and produced a crude solid which was crystallized twice from ethanol to give 0.6 g., 88%, of needles or plates, m.p. 87°. Two forms were observable, plates and somewhat opaque needles. The former sintered slightly below 87° but resolidified and remelted at 87°, $[\alpha]^{26}D$ −34°.

Anal. Calcd. for $C_{28}H_{48}$: C, 87.42; H, 12.58. Found: C, 87.64; H, 12.42.

3-β-Methylcholestane (IX).—Hydrogenation at one atm. of 0.20 g. of the methylcholestene in 80 ml. of acetic acid over 60 mg. of 10% palladium on charcoal at 80° required two hours. After filtering hot and reducing the volume of solvent to 20 ml. and cooling, 0.170 g. of crystals m.p. 97–98° separated. A second crop 0.02 g. was obtained, yield 95%. Crystallization from ethanol, 12 ml., did not change the m.p., lit.[8] 96–97°. Two crystalline forms were again observed. About 5° below the m.p. the plates changed to a needle form $[\alpha]^{25}D$ +11°.

Anal. Calcd. for $C_{28}H_{50}$: C, 86.97; H, 13.03. Found: C, 87.43; H, 12.94.

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The Identification of Sagittol as Eudesmol

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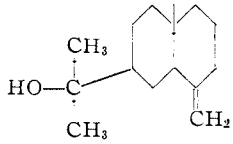
Twenty-five years ago, Yanovsky[1] reported the isolation of a $C_{15}H_{26}O$ alcohol from the steam-distillable portion of the root-cortex of *Balsamorrhiza sagittata* (Pursh) Nutt to which he assigned the name sagittol. His evidence for the hydroxyl function consisted of the formation of an acetate derivative upon refluxing the alcohol with sodium acetate in acetic anhydride.

The structure determination of this nature product was undertaken in these laboratories and a parallel of the chemistry of it with that of eudesmol[2] (I) soon became apparent. Hydrogenation to a di-



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hydro derivative (m.p. 85–86°) and dehydrogenation with palladium–charcoal to eudaline (identified as the picrate) indicated it to be a bicyclic unsaturated alcohol. The similarity of physical constants of these compounds with those in the eudesmol series prompted a comparison with authentic material[3] which established the identity of dihydrosagittol as dihydroeudesmol. The acetate of sagittol was prepared and although its purification was somewhat troublesome its properties corresponded satisfactorily with those reported for both sagittol acetate[1] and eudesmol acetate.[1,2] The specific rotation of sagittol previously reported[1] differed significantly from the value found in the present study and rigorous purification of a sample made the comparison even less satisfactory. Several crystallizations from different solvents did not appreciably alter the melting point although subsequent fractional sublimation of a sample proved the presence of a small amount of a more volatile oily contaminant. The melting point of material thus prepared was not changed but the specific rotation was altered. This second fraction, although too small to permit an investigation, was more negative in specific rotation than sagittol.

The suggestion has been made[4] that sagittol may be identical with cryptomeridol.[5] This is necessarily so in light of the identity established here and that established between cryptomeridol and machilol[6] and between machilol and eudesmol.[7] Thus, it would appear that *Balsamorrhiza sagittata* is another of the many sources of eudesmol. Difficulty in the purification of eudesmol is evidenced by the variance in specific rotations reported on material isolated from its various sources (see Experimental section).

One striking dissimilarity with previous work noted in this study was the product resulting from an attempted dehydration of sagittol to the diolefin (eudesmene) using formic acid. Analytical data indicated it to be the formate ester.

Experimental

Isolation of Sagittol.—Sixty pounds of the damp root-cortex[8] was broken into small pieces and steam-distilled in four batches. The first organic material obtained consisted of a light oil which was followed immediately by crude saggitol as a cotton-like solid. The distillation of each batch was discontinued after a total of 20 l. of water had been collected. Material so obtained (70 g., m.p. 75–78°) was purified by one crystallization from petroleum ether (30–40°) to give 51 g. of colorless solid, m.p. 79–80°. Two additional crystallizations from methanol and water and two from petroleum ether did not change the melting point. Fractional sublimation of this material at 40° (0.3 mm.) afforded a very small amount of light oil mixed with some solid, $[\alpha]^{20}D$ +5.2°. Later fractions were beautifully crystalline, m.p. 79–80°, $[\alpha]^{20}D$ +37.2° (2.31% in ethanol). Constants previously reported for this substance: sagittol,[1] m.p. 77–78°, $[\alpha]^{20}D$ +25.8°; machilol,[9] m.p. 79–80°, $[\alpha]^{25}D$ +30.08°; cryptomeridol,[4,6] m.p. 84°, 79–80°, $[\alpha]^{19}D$ +19.78°, +24.2°; eudesmol,[7] m.p. 82–83°, $[\alpha]D$ +31°.

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.02, H, 11.79. Found: C, 80.91; H, 11.84.

Conversion to Eudaline.—A 2.0-g. sample of purified sagittol was heated at 300° with 1.0 g. of palladium–charcoal[10] for 4 hr. in a nitrogen atmosphere. Isolation in the usual manner followed by treatment of the resulting liquid with picric acid gave 0.91 g. of eudaline picrate, m.p. 92–93° (lit.[11] 90–91°).

Dihydrosagittol.—Some difficulty was encountered in the reduction in that it was too slow to be practical in ethanol or methanol and was accompanied by hydrogenolysis in acetic acid as a solvent. The following represents the most satisfactory conditions found.

A 5.0-g. sample of highly purified sagittol dissolved in 35 ml. of methanol and 5 ml. of acetic acid was shaken at room temperature with 0.10 g. of platinum oxide under one at-

(1) E. Yanovsky, THIS JOURNAL, **52**, 3446 (1930).

(2) L. Ruzicka, A. H. Wind and D. R. Koolhaas, *Helv. Chim. Acta*, **14**, 1132 (1931).

(3) We are indebted to Professor O. Jeger who kindly provided an authentic sample of dihydroeudesmol, m.p. 84–85°.

(4) J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, London, 1952, p. 192.

(5) H. Wienhaus and H. Scholz, *Ber. Schimmel & Co., Akt.-Ges.*, 269 (1929); *C. A.*, **24**, 1933 (1930).

(6) Y. Sugii and T. Sengoku, *J. Pharm. Soc. Japan*, **51**, 196 (1931); *C. A.*, **25**, 2989 (1931).

(7) L. Ruzicka, D. R. Koolhaas and A. H. Wind, *Helv. Chim. Acta*, **14**, 1178 (1931).

(8) Plants were collected in Salt Lake Valley, Utah, in June, 1954.

(9) S. Takagi, *J. Pharm. Soc. Japan*, **473**, 565 (1921); *C. A.*, **16**, 1578 (1922).

(10) N. D. Zelinsky and M. B. Turowa-Pollak, *Ber.*, **58**, 1295 (1925).

(11) L. Ruzicka, J. Meyer and M. Mingazzini, *Helv. Chim. Acta*, **5**, 345 (1922).