shown. More evidence was obtained by thin layer chromatography of the "triacetate" mixture, using a benzene–diethylamine–formamide solvent system to develop the chromatogram. Two distinct fractions were observed, but when each fraction was eluted from the plates for determination of pmr spectra, we found that they had reverted to the original mixture of **7** and **9**. Reexamination of the two individual fractions from the first chromatogram showed that each contained the same two distinct zones on the chromatographic plates.

These novel transformations raise interesting questions concerning the conformational properties of highly substituted five-membered rings. It is generally agreed that five-membered rings are not planar, but the pyrrolidine ring has to be severely buckled in order for the transformation **7** → **9** to occur, and the transition state for this reaction requires that two of the three-substituent groups assume a *quasi*-axial configuration. Further studies of this phenomenon are in progress.

Experimental Section

Preparations and physical properties of the following compounds were described in a previous communication:[2] anisomycin (2-*p*-methoxyphenylmethyl-3-acetoxy-4-hydroxypyrrolidine (**1**), deacetylanisomycin (2-*p*-methoxyphenylmethyl-3,4-dihydroxypyrrolidine (**3**), N-acetylanisomycin (2-*p*-methoxyphenylmethyl-3-acetoxy-1-acetyl-4-hydroxypyrrolidine (**5**), N,O-diacetylanisomycin (2-*p*-methoxyphenylmethyl-3,4-diacetoxy-1-acetylpyrrolidine (**7**), 2-*p*-methoxyphenylmethylpyrrolidine 3,4-epoxide (**8**), isoanisomycin (2-*p*-methoxyphenylmethyl-3-*trans*-hydroxy-4-acetoxypyrrolidine (**2**), and N-acetyldeacetylanisomycin (2-*p*-methoxyphenylmethyl-3,4-dihydroxy-1-acetylpyrrolidine (**11**).

2-*p*-Methoxyphenylmethyl-3-acetoxy-4-hydroxy-1-benzylcarbamylpyrrolidine (**4**).—Anisomycin (30 g) was dissolved in a mixture of chloroform (250 ml) and triethylamine (36 ml) at 0°. Benzyl chloroformate (25 ml) was slowly added to the solution with stirring, and the mixture was allowed to warm to room temperature, The chloroform solution was washed with dilute HCl and then with saturated K_2HCO_3 and evaporated to a colorless oil which was crystallized from ether–hexane mixtures (21 g, 46%): mp 69–71°, R_f (tlc) 0.2 (7:3, hexane–ethyl acetate).

Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.31; H, 6.26; N, 3.55.

Preparation of ^{14}C-Labeled Anisomycin (2-*p*-Methoxyphenylmethyl-3-1′-^{14}C-acetoxy-4-hydroxypyrrolidine).—The benzylcarbamyl derivative **4** (5.0 g) was dissolved in freshly distilled dihydropyran (50 ml) and concentrated HCl (0.5 ml) was added to the solution, which was then stirred at room temperature for 24 hr. Ether (250 ml) was added and the mixture was twice extracted with 2 *N* sodium hydroxide solution. Evaporation of the solvent gave the product as a pale yellow gum which could not be crystallized, R_f (tlc) 0.43 (7:3, hexane–ethyl acetate). The product was not characterized but from a study of its chemical reactions, it was deduced to be *2-p-methoxyphenylmethyl-3-acetoxy-H-2′-tetrahydropyranyloxy-1-benzylcarbamylpyrrolidine* (**11**).

Treatment of the tetrapyranyl derivative (**11**) with dilute HCl in ethanol gave a quantitative yield of the starting benzylcarbamyl compound **4**.

The tetrahydropyramyl derivative was treated with a 1 *N* solution of KOH in ethanol at room temperature for 24 hr. Solvent was removed by evaporation under reduced pressure and the residue was dissolved in water, extracted with ethyl acetate which was then dried with Na_2SO_4 and evaporated to a gum, R_f (tlc) 0.05 (7:3, hexane–ethyl acetate), which lacked ester carbonyl absorption in the infrared spectrum. This substance could not be crystallized, but was reesterified by reaction with 1-^{14}C-acetic anhydride in pyridine at room temperature for 16 hr. Evaporation of the solvent provided a radioactive ester, identical in all respects with 2-*p*-methoxyphenylmethyl-3-acetoxy-H-2′-tetrahydropyranyloxy-1-benzylcarbamylpyrrolidine (**11**) previously prepared from the benzylcarbamyl derivative **4**.

The radioactive ester was dissolved in ethanol (100 ml) and hydrogenated (100 mg of 10% Pd–C; H_2, 50 psi) for 18 hr. *p*-Toluenesulfonic acid monohydrate (540 mg) was added to the filtered mixture which was warmed to provide a clear solution and then evaporated to dryness. A solution of the residue in chloroform was washed with water made basic by addition of Na_2CO_3 solution to pH 10, and the chloroform was dried (Na_2SO_4) and evaporated to yield 1-^{14}C-acetate-labeled anisomycin (mp 145–146° from ethyl acetate), 850 mg (40% yield over-all) identical in every respect with the natural material. Liquid scintillation counts showed the product to contain 7.85–7.91 μc/mmol.

Reaction of ^{14}C-Labeled Anisomycin with Acetic Anhydride.—Radioactive anisomycin (85 mg) labeled in the ester function (7.9 μc/mmol) was converted into N,O-diacetylanisomycin (**7**) by the method previously described. Nmr spectra showed the product to be identical with an authentic sample. The N,O-diacetyl derivative was dissolved in methanol containing 10% of saturated aqueous ammonia, the mixture was stirred at 50° for 1 hr and evaporated to provide N-acetyldeacetylanisomycin (**12**), mp 143–145°.[1] Liquid scintillation counts showed this material to contain 2.36 μc/mmol indicating a 30% transfer of the ^{14}C-acetate from **1** to the nitrogen of **12**.

A repeat of this experiment gave radioactive N-acetyldeacetylanisomycin containing 2.2 μc/mmol (27% retention of radioactivity).

Reaction of 1′-^{14}C-Acetate-labeled Isoanisomycin with Acetic Anhydride.—Radioactive isoanisomycin (2-*p*-methoxyphenylmethyl-3-*trans*-hydroxy-4-1′,^{14}C-acetoxypyrrolidine (**2**) was obtained from the epoxide **8**, and labeled acetic acid.[1] Liquid scintillation counts showed it to contain 11.1 μc/mmol.

This isoanisomycin (100 mg) was subjected to the same treatment described above for anisomycin. The N-acetyldeacetylanisomycin (65 mg) obtained after hydrolysis of the acetylation product contained 0.76 μc/mmol (7% retention of radioactivity).

Reaction of Labeled N-Acetyldeacetylanisomycin with Acetic Anhydride.—2-*p*-Methoxyphenyl-3,4-dihydroxy-1-1′-^{14}C-acetylpyrrolidine (100 mg, 13.7 μc/mmol was dissolved in pyridine (2 ml) and acetic anhydride (0.5 ml). After 10 hr the mixture was worked up by the described procedure to yield N,O-diacetylanisomycin (80 mg, 61%), mp 85–88° (13.6 μc/mmol) identical in all respects with authentic material. Hydrolysis of the product by aqueous ammonia in methanol gave N-acetyldeacetylanisomycin (50 mg, 82%), mp 143–144° (13.75 μc/mmol)

Registry No.—**1**, 2322-08-9; **2**, 15815-58-4; **4**, 15815-59-5; ^{14}C-labeled anicomycin, 16165-20-1; N,O-diacetylanisomycin, 15815-61-9; N-acetyl-deacetylanisomycin, 15815-62-0.

Acknowledgment.—We wish to express our appreciation to Mr. D. K. Pirie for technical assistance and to Professor R. B. Woodward who first proposed the cyclic *o*-acetate structure **9**.

Partial Asymmetric Synthesis in the Simmons–Smith Reaction. II[1]

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The accelerating and directing influence of the hydroxyl group on the steric course of addition of the Simmons–Smith reagent has been pointed out in some

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TABLE I

SIMMONS-SMITH REACTION OF ACHIRAL OLEFINS IN THE PRESENCE OF (−)-MENTHOL

Run	Olefin	Cyclopropane product	Yield, %	$[\alpha]^{25}D$ (neat), deg	Optical yield, %	Abs config[b]
1	Methyl crotonate	*trans*-2-Methylcyclopropanecarboxylic acid (**1**)	6.0	−1.2	1.9	*R*:*R*
2	Methyl cinnamate	*trans*-2-Phenylcyclopropanecarboxylic acid (**2**)	7.0	−2.0	0.7	*R*:*R*
3	Dimethyl fumarate	*trans*-Cyclopropane-1,2-dicarboxylic acid (**3**)	5.0	−6.8 (MeOH)	3.4	*R*:*R*
4	Dimethyl dimethylfumarate	*trans*-1,2-Dimethylcyclopropane-1,2-dicarboxylic acid (**4**)	9.0	−2.3 (MeOH)	1.1	*R*:*R*[c]
5	*trans*-β-Methylstyrene	*trans*-1-Phenyl-2-methylcyclopropane (**5**)	12.0	−3.2	*a*	*R*:*R*[d]
6	*trans*-Stilbene	*trans*-1,2-Diphenylcyclopropane (**6**)	18.0	−0.3	*a*	*R*:*R*[e]
7	1,1-Diphenyl-1-propene	1,1-Diphenyl-2-methylcyclopropane (**7**)	12.0	−0.28	0.3	*R*[f]
8	Methyl senecioate	2,2-Dimethylcyclopropanecarboxylic acid (**8**)	18.0	−0.2	*a*	*R*
9	Mesityl oxide	1-Acetyl-2,2-dimethylcyclopropane (**9**)	15.0	−0.7	*a*	*R*

[a] Maximum rotation is unknown. [b] For the absolute configurations assigned to these compounds, see part I of this series. [c] Y. Inouye, *Tetrahedron*, in press. [d] T. Sugita and Y. Inouye, *Bull. Chem. Soc. Jap.*, **39**, 1075 (1966). [e] I. Tömösközi, *Chem. Ind.* (London), 689 (1965). [f] See ref 5 in the text.

TABLE II

PHYSICAL PROPERTIES AND ANALYTICAL DATA OF CYCLOPROPANES[a]

Cyclopropane	Bp, °C (mm)	$n^{25}D$	Mp, °C	Molecular formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
4			220	$C_7H_{10}O_4$	53.16	6.37	52.94	6.47
5	95 (17)	1.5142		$C_{10}H_{12}$	90.85	9.15	89.12	10.33
6	99–100 (0.1)	1.5980		$C_{15}H_{14}$	92.74	7.26	92.47	7.53
7	104–105 (0.1)	1.5764		$C_{16}H_{16}$	92.26	7.74	92.51	7.70

[a] For the other cyclopropanes **1**, **2**, **3** and **8**, data were given in part I. Compound **9** was identified by infrared spectrum and also by the conversion with sodium hypochlorite oxidation into the known compound **8**.

cases[2] and it has been proved that in the reaction of olefinic alcohols, transfer of methylene occurs intramolecularly through an intermediate zincate complex so that the addition is only possible from the side of the double bond nearest the oxygen atom.

In this connection, it seemed of interest to undertake the Simmons–Smith reaction of olefins in the presence of free (−)-menthol, in expectation of possible asymmetric synthesis of cyclopropanes. In accordance with expectation, the Simmons–Smith reaction of various achiral olefins in the presence of 0.3 mol equiv of free (−)-menthol under the standardized conditions afforded the corresponding cyclopropane products with optical activity.

The achievement of partial asymmetric synthesis in the present systems obviously corroborates a stereochemically effective participation of the chiral moiety in the transition state complex leading to cyclopropane products. The mechanistic requirement that (−)-menthyl group must be so accommodated in the transition state as to exert a chiral influence on the steric course of the reaction can be met only by the one-step methylene transfer mechanism involving a three-center intermediate and not by the two-step mechanism.[3]

It thus seems likely that a prior reaction of (−)-menthol with the Simmons–Smith reagent occurs to form iodomethylzinc (−)-menthoxylate as has been indicated[2] and then the latter reacts with olefin to form a three-center transition complex incorporating the chiral moiety, which collapses eventually to yield optically active cyclopropane products.

Both reaction and optical yields in the present systems were found rather poor, amounting to 18 and 3.4%, respectively, at most but the sign of rotation found for cyclopropane products of fully substantiated structures is decisive for the absolute assignment of configuration. As can be seen from the data in Table I, the present Simmons–Smith reaction afforded levorotatory cyclopropanes of the *R* and *R*:*R* configurations. Although the transition state geometry with (−)-menthyl group incorporated has not been elucidated as yet, the present data seem to permit one to formulate an empirical correlation between the absolute configuration of (−)-(3*R*)-menthol employed here and those of the resulting substituted cyclopropane products. This may provide one with a useful means of determining absolute configuration of cyclopropanes in general.

Attempted asymmetric synthesis in the Simmons–Smith reaction in a chiral medium, (−)-menthyl methyl ether, was doomed to failure since the reagent can only be formed with great difficulty in this solvent and furthermore the cyclopropane products obtained in poor yields exhibited no measurable optical activity even on a precision spectropolarimeter.

Experimental Section

Partial asymmetric synthesis of cyclopropanes by the Simmons–Smith reaction of achiral olefins in the presence of (−)-menthol is illustrated by a typical run for (−)-(*R*)-1,1-diphenyl-2-methylcyclopropane (**7**). Identical procedure was followed for other runs with the substrate olefin varied (Table II).

(−)-(*R*)-1,1-Diphenyl-2-methylcyclopropane (7).—Zinc–copper couple (13 g, 0.2 atom, in powder) and methylene iodide (27 g, 0.1 mol) in 150 ml of absolute ether were stirred for 30 min and then (−)-menthol (5 g, 0.03 mol) in 20 ml of ether was added to the preformed solution of the Simmons–Smith reagent, when a mild exothermic reaction took place. After the reaction ceased, 1,1-diphenyl-1-propene (bp 100–105° (0.5 mm), $n^{25}D$

(2) (a) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **80**, 5323 (1958); *ibid.*, **81**, 4256 (1959); *ibid.*, **86**, 1337, 1347 (1964); (b) S. Winstein, T. Sonnenberg, and L. deVries, *ibid.*, **81**, 6523 (1959); (c) W. G. Dauben and D. G. Berezin *ibid.*, **85**, 468 (1963); (d) E. J. Corey and E. Uda, *ibid.*, **85**, 1778 (1963); E. J. Corey and R. L. Dauson, *ibid.*, 1782 (1963).

(3) The successful partial asymmetric synthesis with 1,1-diphenyl-1-propene, methyl senecioate, and mesityl oxide (runs 7, 8, and 9) excludes the operation of the two-step mechanism. According to this mechanism, the addition to the substrate double bond of iodomethylzinc (−)-menthoxylate first formed can not be the asymmetric synthesis step in these cases and the subsequent cyclization (intramolecular nucleophilic displacement) also would proceed under no significant influence of zinc (−)-menthoxylate cation, so that asymmetric induction would not be expected.

1.5990, mp 45.5–50°,[4] 10 g 0.05 mol) in 20 ml of ether was added together with a few drops of boron trifluoride etherate. The reaction mixture was refluxed for 30 hr and then was decomposed with dilute hydrochloric acid. The organic layer was separated, washed several times with aqueous sodium thiosulfate, and dried over anhydrous sodium sulfate. After removal of ether, the residue was ozonized in carbon tetrachloride solution to remove the unreacted olefin. After usual work-up of the ozonide, the neutral fraction was chromatographed on a neutral alumina column (3 × 210 cm) to give pure (−)-(*R*)-1,1-diphenyl-2-methylcyclopropane (**7**), completely free from (−)-menthol and benzophenone as indicated by the ir spectrum and vpc analysis. The ir spectrum was identical in every respect with that of the authentic specimen: bp 104–105° (0.1 mm); $n^{25}D$ 1.5764;[5] $[\alpha]^{25}D$ −0.28° (neat) on a Yanagimoto spectropolarimeter, Model ORD-3; yield 1.2 g.

Registry No.—**4**, 16118-44-8; **5**, 10488-06-9; **6**, 3471-09-8; **7**, 14275-48-0.

Acknowledgment.—The authors are indebted to Professor M. Ohno for his interest in this work.

(4) A. M. van Leusen and J F. Arens, *Rec. Trav. Chim. Pays-Bas*, **78**, 551 (1959).

(5) H. M. Walborsky, C. G. Pitt, *J. Amer. Chem. Soc.*, **84**, 4831 (1962).

Steroids. CCCXI.[1] The Degradation of Stigmasterol to 3β,5α,6β-Trihydroxy-23,24-bisnorcholan-22-oic Acid

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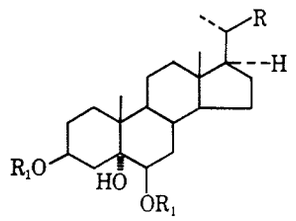
In connection with the synthesis of the insect moulting hormone Ecdysone, recently reported from these laboratories,[2] the preparation of large quantities of 3β,5α,6β-trihydroxy-23,24-bisnorcholan-22-oic acid (**1d**) became necessary.

The degradation of the stigmasterol side chain reported by Fernholz[3a] *via* selective bromination of the nuclear double bond affords 3-hydroxy-23,24-bisnorchol-5-en-22-oic acid in only 20% yield. A modified procedure reported by Smith and Wallis,[3b] which uses iodobenzene dichloride as the selective chlorinating agent, proved to be unsatisfactory for large-scale operation. Thus the approach outlined below was investigated.

Selective epoxidation of the nuclear double bond of stigmasterol acetate was achieved in high yield with *m*-chloroperbenzoic acid in chloroform solution at −80°. The total crude products, consisting mainly of 5α,6α and 5β,6β oxides, were heated on the steam bath with formic acid to yield, after saponification and purification, 72.5% of 24-ethyl-cholest-22-ene-3β,5α,6β-triol[3c] (**1a**). Acetylation of this compound with acetic anhydride in pyridine yielded the diacetate **1b**. Ozonolysis of this diacetate in ethyl acetate solution at



1a, R_1 = H; R = C_8H_{15}
b, R_1 = Ac; R = C_8H_{15}
c, R_1 = Ac; R = CO_2H
d, R_1 = H; R = CO_2H
e, R_1 = H; R = CO_2CH_3

−80° followed by peracetic acid oxidation afforded 3β,5α,6β-trihydroxy-23,24-bisnorcholan-22-oic acid 3,6-diacetate (**1c**). The crude product was saponified to the triol (**1d**) in an over-all yield of 52% from stigmasterol. Formation of the methyl ester (**1e**) of this acid with diazomethane proceeds in quantitative yield.[2a] However, for large scale preparations, other procedures were examined. Esterification of the acid **1d** in the presence of methanol containing 2% w/w of sulfuric acid yielded the methyl ester (**1e**) in only 53.6% yield.

A brief report[4] describing the use of methyl iodide in dimethyl acetamide with sodium bicarbonate as a superior method to esterify acids, prompted us to try these conditions. The reaction proceeds slowly at room temperature, but the transformation is practically quantitative.

Experimental Section[5]

24-Ethylcholest-22-ene-3β,5α,6β-triol (**1a**).—A suspension of 2 kg of stigmasterol in a mixture of 4 l. of pyridine and 2 l. of acetic anhydride was heated under anhydrous conditions with mechanical stirring on the steam bath for 2 hr. The resulting solution of stigmasterol acetate that began to crystallize on cooling, was poured into 60 l. of water and stirred for *ca.* 1 hr to hydrolize the excess acetic anhydride. The crude stigmasterol acetate was collected by filtration, washed with water, and dried at 80° *in vacuo* to yield 2.392 kg of crude product. This material was dissolved in 24 l. of chloroform, cooled to −80° with an external acetone–Dry Ice bath under anhydrous conditions. The mixture was stirred mechanically while a solution of 1.115 kg of *m*-chloroperbenzoic acid in 9 l. of chloroform was added over a period of 3 hr. The reaction temperature was kept at −80° for an additional 3 hr. The acetone–Dry Ice bath was removed and the mixture was allowed to come to room temperature in 24 hr. Stirring was continued for 72 hr and the reaction mixture was washed with a 5% sodium bicarbonate solution until alkaline and then with water until neutral.

The resulting solution was distilled to dryness under reduced pressure, and the residue was heated with 17 l. of 85% aqueous formic acid for 2 hr on the steam bath and then stirred without heating overnight. The crystalline product thus obtained was collected by filtration, washed with formic acid and then with water, and sucked as dry as possible on the filter.

This solid was dissolved in 20 l. of methanol under reflux and a solution of 1.2 kg of potassium hydroxide in 4 l. of methanol was added. The reaction mixture was kept under reflux and with mechanical stirring for 2 hr, cooled to room temperature and poured into 150 l. of water. The crystalline precipitate thus obtained was collected by filtration, washed with water, and dried

(1) Steroids. CCCX: L. Gyermek, J. Iriarte, and P. Crabbé, *J. Med. Chem.*, **11**, 117 (1968).

(2) (a) J. B. Siddall, J. P. Marshall, A. Bowers, A. D. Cross, J. A. Edwards, and J. H. Fried, *J. Amer. Chem. Soc.*, **88**, 379 (1966); (b) J. B. Siddall, A. D. Cross and J. H. Fried, *ibid.*, **88**, 862 (1966).

(3) (a) E. Fernholz, *Ann.*, **507**, 128 (1933). (b) H. Q. Smith and E. S. Wallis, *J. Org. Chem.*, **19**, 1628 (1954). (c) E. Fernholz, *Ann.*, **508**, 215 (1934).

(4) R. A. Raphael, E. C. Taylor, and H. Wynberg, "Advances in Organic Chemistry," Vol. 5, Interscience Publishers, Inc., New York, N. Y., 1965, p 37.

(5) Melting points are corrected, optical rotations are for chloroform solutions. Infrared spectra were determined in potassium bromide disks. Microanalyses were performed either by Mid-West Micro Laboratories, Indianapolis, Ind., or by Dr. A. Bernhardt Mulheim (Ruhr), Germany. Nmr spectra were recorded on a Varian A-60 spectrometer using deuteriochloroform as a solvent and tetramethylsilane as an internal reference standard.