tifica, Clifton, N. J.; silica gel H for thin layer, E. Merck (Brinkmann Instruments, Westbury, N. Y.); silicic acid, 100 mesh, Mallinckrodt Chemical Works, St. Louis, Mo. Thin layer chromatography (tlc) was carried out on silica gel G (Merck). The plates were prepared with a Desaga applicator set at 0.25 mm. Before the plates were used, they were heated in an oven at 110° for 1 hr. The plates were developed with an ethyl acetate–hexane mixture (1:3) and visualized by spraying with 5% sulfuric acid in ethanol and then charring on a hot plate set at 200°. Spots containing the trityl group were a brilliant yellow. The benzene used to dissolve the trityl ethers was dried over "dri-Na"[19] for at least 24 hr before use. Isopropyl trityl ether was used in the investigation of the parameters affecting detritylation.

Methyl 2,3,4-Tri-*O*-acetyl-α-D-glucopyranoside (I).—To a 2.2 cm × 46 cm column prepared from 100 g of Davison Grade 12 silica gel, activity grade I, was added a solution composed of 1.000 g of methyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-α-D-glucopyranoside[3] in 8 ml of benzene. The column was developed with an additional 170 ml of benzene. After 16 hr at room temperature, the column was eluted with 600 ml of 10% ethyl acetate in benzene. Analysis of eluate by tlc showed triphenylcarbinol and a trace of starting material. The column was then eluted with 600 ml of 25% methanol in ethyl acetate. The solvent was removed on a rotary evaporator and dried in a vacuum desiccator. The residue (553 mg, 98%) was dissolved in a small amount of ether and hexane was added until the solution became cloudy. The solution was cooled overnight in a refrigerator. The long needlelike crystals were filtered and dried to yield 457 mg (81%): mp 109–110°, $[\alpha]^{26}D$ +148 ($CHCl_3$); lit.[11] mp 111°, $[\alpha]^{20.5}D$ +148.8° ($CHCl_3$).

1,2,3,4-Tetra-*O*-acetyl-β-D-glucose (II).—The procedure followed is essentially the same as described above except for the following. Triphenylcarbinol was eluted from the column with 500 ml of 5% ethyl acetate in chloroform; the product was eluted with 500 ml of ethyl acetate and recrystallized by dissolving in a small amount of chloroform and adding ether until the solution was cloudy. The product weighed 515 mg (87%): mp 125–127°, $[\alpha]^{26}D$ +12° ($CHCl_3$); lit.[12] mp 128–129°, $[\alpha]^{20}D$ +12.1° ($CHCl_3$).

Detritylation Activity of Different Silica Gels.—Each sample of silica gel was heated at 300° for 3 hr and then placed in a desiccator to cool. A dry column (2.2 cm o.d.) containing 38 g of silica gel was prepared. A benzene solution (5 ml) containing 250 mg of isopropyl trityl ether was added to the column. It was completely developed with benzene and kept at room temperature for 1 hr. Benzene eluted any remaining starting material and ethyl acetate eluted the triphenylcarbinol. The solvents were evaporated by blowing air over the tared collection beakers. After the residues were dried in a vacuum desiccator, they were weighed and their yields calculated. Melting points and thin layer chromatograms were used for identification and to determine purity (Table I).

Detritylation as Related to Adsorbent Activity.—Davison Grade 12 silica gel was used to evaluate the effect of added water on detritylation activity. Samples having activities II–V were prepared by the addition of water to silica gel activity grade I.[18] A 2.2-cm-o.d. column containing a 100-g sample of silica gel was prepared for each activity grade. A 500-mg sample of isopropyl trityl ether was dissolved in 5 ml of benzene and added to each of the dry columns. The column was completely developed with benzene and then kept at room temperature for 1 hr. Any starting material that remained was eluted with 100 ml of benzene and the product, triphenylcarbinol, was eluted with ethyl acetate (200 ml). The benzene eluate from activity grade IV contained both materials. They were easily separated by triturating the residue with a little cold hexane and then filtering. Triphenylcarbinol is quite insoluble in hexane. The solvents were removed by blowing air over the collection beakers. The residues were then dried in a vacuum desiccator, weighed, and identified by melting point and tlc (Table II).

Registry No.—I, 7432-72-6; II, 13100-46-4.

(19) A granular sodium–lead alloy purchased from J. T. Baker Chemical Co., Phillipsburg, N. J.

Displacement and Elimination Reactions of 5α,6α-Epoxy-3β-cholestanyl *p*-Toluenesulfonate in Dimethylformamide

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Products of the solvolysis of 5α,6α-epoxy-3β-cholestanyl *p*-toluenesulfonate in dimethylformamide containing lithium carbonate and/or lithium chloride have been isolated and characterized. These products appear to be formed by successive displacement and elimination reactions. Convenient preparations of 2,4,6-cholestatriene and 5α,6α-epoxy-3α-cholestanyl formate are described, as well as an example of displacement with over-all retention brought about by successive displacements of chloride.

In the course of our studies on direct displacement and solvolysis reactions of 2,4-cholestadienes substituted at the 6α and 6β positions with appropriate leaving groups, we developed a synthetic route to 6β-(2,6-dichlorobenzoyloxy)-2,4-cholestadiene.[2] The key intermediate in this series of reactions was 5α,6α-epoxy-2-cholestene (**5**), which we prepared by a six-step synthesis from cholesterol (**1a**). In view of the success of Bowers and co-workers[3] in preparing other steroidal 5α,6α-epoxy-2-enes from the corresponding 3β-*p*-toluenesulfonates in refluxing dimethylacetamide containing lithium carbonate, we set out to investigate a similar route to 5α,6α-epoxy-2-cholestene. The reaction proved to be more complex than we had anticipated; therefore we have investigated it in some detail.

Results and Discussion.

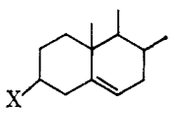
The 5α,6α-epoxy-3β-cholestanyl *p*-toluenesulfonate (**2b**) which was required for our study had been reported by Bourdon and Ranisteano.[4] These workers prepared it by the perbenzoic acid epoxidation of cholesteryl *p*-toluenesulfonate (**1b**). We have repeated their preparation, modified in that *m*-chloroperbenzoic acid was substituted for perbenzoic acid (route A), and we have also employed the alternate route, tosylation of cholesterol α-epoxide (**2a**) (route B). In our hands, route A appears to be preferable in that the product is more readily purified, as discussed below. When the material prepared by route A

(1) Taken in part from the dissertation of G. A. Selter, submitted in partial fulfillment of the requirements for the Ph.D. degree, 1967. This investigation was supported by research funds of Washington State University.

(2) K. D. McMichael and G. A. Selter, *J. Org. Chem.*, **30**, 2549 (1965).

(3) B. Berkoz, A. D. Cross, M. E. Adame, H. Carpio, and A. Bowers, *ibid.*, **28**, 1976 (1963).

(4) R. Bourdon and S. Ranisteano, *Bull. Soc. Chim. France*, 1982 (1960).



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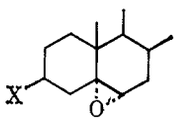
b, X = OTs



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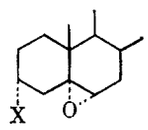
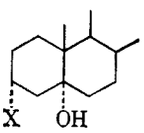
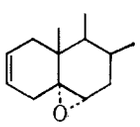
b, X = OTs
c, X = Cl



3a, X = COOH
b, X = OH
c, X = Cl



4a, X = OH
b, X = Cl



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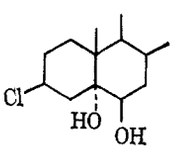

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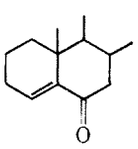

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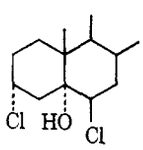

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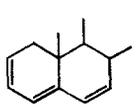

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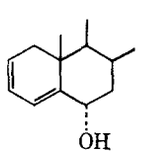

10

was refluxed with boiling dimethylformamide containing lithium carbonate, it afforded 5α,6α-epoxy-2-cholestene (**5**) in moderate (*ca.* 30%) yield. The major product of this reaction, separable from **5** by silicic acid chromatography, was 5α,6α-epoxy-3α-cholestanyl formate (**3a**). The structural assignment was indicated by carbon–oxygen stretching absorptions at 8.42 and 8.67 μ in the infrared, characteristic of formates.[5,6] There was a one-proton singlet at 475 Hz in the nmr, characteristic of the formyl proton.[7] The epoxy ring remained intact in this material, as indicated by the presence of a one-proton doublet at 158 Hz, $J = 3.8$, in the nmr, discussed in more detail later. The ester (**3a**) could not be crystallized from aprotic solvents and decomposed readily in protic solvents. A small amount was obtained as a solid from methanol and analysis of this material was consistent with that of an epoxycholesteryl formate. The 3α configuration was assigned to the formyloxy group in this ester (**3a**) since methanolysis in the presence of potassium hydroxide yielded the known 5α,6α-epxoycholestan-3α-ol (**3b**), identical with an authentic sample.[8] Hydride reduction afforded cholestane-3α,5α-diol (**4a**), also shown to be identical with that reported in the literature.[9] A similar result was reported by Chang and Blickenstaff,[5] who observed the replacement of a 3β-tosyloxy group by a formyloxy group with inversion in the cholestane series. Their mechanism, which appears to explain our results as well, involved displacement of the tosyloxy group by the oxygen of dimethylformamide, followed by hydrolysis of the resulting intermediate, either during the isolation procedure or by traces of water present in the solvent.

When 5α,6α-epoxy-3β-cholestanyl tosylate (**2b**) prepared by route B was subjected to the same conditions, four more compounds were isolated in addition to those described above. In minor amounts we obtained 2,4,6-cholestatriene (**9**) and 4-cholesten-6-one (**7**), discussed in detail below. In considerably greater yield, both 2α- and 3β-chloro-5α,6α-epoxycholestane (**3c** and **2c**) were isolated. The source of the chloride ion required for this reaction appears to be pyridine hydrochloride, incompletely removed from **2b**.[10]

The known 3β-chloro-5α,6α-epoxycholestane (**2c**) was isolated in 14% yield. This compound was shown to be identical with that prepared by Shoppee,[11] who treated cholesteryl chloride with perbenzoic acid. In addition, the epoxide ring could be cleaved smoothly in the presence of an aqueous acetone–periodic acid solution with the formation of the known[11] 3β-chlorocholestane-5α,6β-diol (**12**). Treatment of the 3β-chlorocholestane-5α,6β-diol (**6**) with acetic anhydride afforded the corresponding 6β-monoacetate, identical with that reported by Shoppee.[11]

A second chloro compound, 3α-chloro-5α,6α-epoxycholestane (**3c**), was obtained in 13% yield, having physical properties consistent with those reported by Shiota,[12] whose synthesis consisted of treatment of an ethanolic solution of 3α,6β-dichlorocholestan-5α-ol (**8**) with aqueous sodium hydroxide. Further evidence for the assigned structure was obtained by hydride reduction to 3α-chlorocholestan-5α-ol (**4b**)[8] and by cleavage of the epoxide ring by anhydrous hydrogen chloride with the concomitant formation of the usual *trans*-chlorohydrin,[2,13] 3α,6β-dichlorocholestan-5α-ol (**8**).[12]

Since the formation of 3β-chloro-5α,6α-epoxycholestane in this reaction represents a nucleophilic displacement with retention of configuration, we investigated this process in greater detail. Two types of processes appeared worth initial consideration. First, the intervention of a secondary carbonium ion at C-3 would be compatible with the formation of both 3α- and 3β-chlorine substitution products representing attack on either face of the carbonium ion. Since such an intermediate should also be capable of capture on the β face by other nucleophiles, notably dimethylformamide, we should have observed significant amounts of 5α,6α-epoxy-3β-cholestanyl formate if this route was important. In the absence of such a product, we believe this process is not important, a conclusion which is

(5) F. C. Chang and R. T. Blickenstaff, *J. Am. Chem. Soc.*, **80**, 2906 (1958).

(6) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 189.

(7) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 79.

(8) A. J. Fudge, C. W. Shoppee, and G. H. R. Summers, *J. Chem. Soc.* 985 (1954).

(9) R. B. Clayton, H. B. Henbest, and M. Smith, *ibid.*, 1982 (1957).

(10) Routine microanalysis of a sample of this material indicated a chlorine content of 3.56%, corresponding to a ratio of 1:1.6 of chloride to **2b**, which is adequate to explain the combined yield of 27% of **2c** and **3c**.

(11) C. W. Shoppee, R. J. Bridgewater, D. N. Jones, and G. H. R. Summers, *ibid.*, 2492 (1956).

(12) M. Shiota and T. Toyota, *Bull. Chem. Soc. Japan*, **37**, 891 (1964).

(13) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 194.

reinforced by further experiments described below. Second, the formation of the 3β-substituted product could arise by two successive substitutions, each with inversion. This process requires the intervention of an intermediate having a 3α configuration, formed by displacement of the 3β-tosyloxy group and subsequently destroyed by chloride attack at the 3β position. Two such intermediates appeared reasonable. The intermediate postulated above as important in the formation of the formate ester could be attacked at 3β with the displacement of a dimethylformamide molecule. Alternatively, the 3α-chloro-5α,6α-epoxycholestane (**3c**), presumably formed by direct displacement of the tosyloxy group from **2b**, could serve as the intermediate by a route involving chloride displacement of chloride. Three lines of evidence support the latter hypothesis. First, in solvolysis of **2b** in refluxing dimethylformamide containing a large excess of chloride (supplied as lithium chloride) and lithium carbonate for 2.5 hr, the 3β-chlorine substitution product (**2c**) forms more than 90% of the total chlorine-containing products. Second, if this reaction is repeated with the chloride concentration reduced to 1 equiv and the reaction time is cut to 30 min, chloride attack on the 3α-chloro-5α,6α-epoxycholestane (**3c**)[14] is reduced and it survives to form nearly 60% of the chlorine-containing products. Third, and most directly, the proposed intermediate 3α-chloro-5α,6α-epoxycholestane (**3c**) is converted to 3β-chloro-5α,6α-epoxycholestane (**2c**) and 5α,6α-epoxy-2-cholestene (**5**) by reaction with a tenfold excess of lithium chloride for 2 hr in refluxing dimethylformamide containing lithium carbonate. This displacement of chloride by chloride is another example of the enhanced nucleophilic reactivity of small anions in dipolar aprotic solvents[15] and extends to chloride ion in the observation of similar displacements involving iodide and bromide.[16] In view of these results, caution should be exercised in stereochemical assignments based on the assumption of clean inversion for these or similar systems.

When **2b** is solvolyzed in dimethylformamide without lithium carbonate, a dramatic alteration in the product mixture takes place. Under these conditions, 2,4,6-cholestatriene (**9**) is the major product, isolated in about 60% yield, accompanied by smaller amounts of 4-cholesten-6-one (**7**)[17] and the formate ester **3a**.

The triene (**9**) was identified by its physical properties as well as its characteristic ultraviolet absorption spectrum,[18] which has $\lambda_{max}^{cyclohexane}$ 307 mμ (ε 15,400) with shoulders at 321 mμ (ε 10,080) and 297 (13,400). Upon hydrogenation, the triene (**9**) took up hydrogen in approximately a 3:1 molar ratio to give an inseparable mixture of cholestane and coprostane. On the hypothesis that the triene and conjugated ketone represent products of further transformations of the initially formed materials, we subjected 5α,6α-epoxy-2-cholestene (**5**), 3α-chloro-5α,6α-epoxycholestane (**3c**), and 3β-chloro-5α,6α-epoxycholestane (**2c**) to similar reaction conditions. In the presence of lithium chloride and *p*-toluenesulfonic acid in refluxing dimethylformamide, these compounds were all transformed into the triene **9**. The formation of **9** may be rationalized on the basis of a reaction pathway involving elimination from **2b**, **2c**, or **3c** to give **5**, followed by acid-catalyzed ring opening and loss of a proton to give 2,4-cholestadien-6α-ol (**10**). Acid-catalyzed dehydration of the latter compound (**10**) would then lead to the triene **9**. Support for the last step was obtained by independently preparing **10** and subjecting it to the action of *p*-toluenesulfonic acid in dimethylformamide. The reduction of 2,4-cholestadien-6-one[19] by lithium aluminum hydride afforded an amorphous material which we were not able to characterize completely owing to its rapid decomposition in the presence of air. It was assigned the structure of 2,4-cholestadien-6α-ol on the basis of the spectroscopic behavior of freshly prepared samples (see Experimental Section). The hydroxyl group is assigned the 6α configuration on the basis of similar reduction of **7** to 4-cholesten-6α-ol.[20] Treatment of a freshly prepared sample of **10** with *p*-toluenesulfonic acid and lithium chloride in refluxing dimethylformamide afforded **9** in moderate (51%) yield. It should be noted that the formation of **9** from **2b** represents a three-step synthesis from cholesterol and would appear to be the method of choice for the synthesis of this material.

In addition to triene **9** described above, 4-cholesten-6-one (**7**) was also isolated when 3β- (**2c**) and 3α-chloro-5α,6α-epoxycholestane (**3c**) were treated with *p*-toluenesulfonic acid and lithium chloride in dimethylformamide. Since **7** is not formed from 5α,6α-epoxy-2-cholestene (**5**) under these conditions, it must arise by way of a path not involving **5**. We envision **7** as resulting from an isomerization of 5α,6α-epoxy-3-cholestene, itself a reasonable product of elimination from **2b**, **2c**, or **3c**. Acid-catalyzed opening of the epoxide ring in 5α,6α-epoxy-3-cholestene would afford an allylic carbonium ion which would be transformed into the enol of **7** by loss of a proton from C-6. Ordinary ketonization of the enol would then give **7**.

As indicated in Table I, the nmr absorptions of the 6β protons in the 5α,6α-epoxycholestane derivatives prepared in this work appear as doublets (J = 3.5

TABLE I

NMR FREQUENCIES OF THE ANGULAR METHYL GROUPS, 6β PROTONS, AND 3 PROTONS OF 5α,6α-EPOXYCHOLESTANE DERIVATIVES[a]

Substituent	6-H, Hz	J (6β,7β) Hz	19-CH_3, Hz	18-CH_3, Hz	3-H, Hz
3β-OH	175.0	3.8	64.0	37.2	...
3β-Cl	169.5	3.5	65.0	37.0	...
3α-OH	164.0	3.8	60.0	37.0	230
3α-Cl	158.0	3.5	61.5	37.5	262
3α-Formate	158.0	3.8	62.0	37.0	307
Δ^2	165.0	3.8	59.0	36.0	331
3β-Acetate[b]	174.5–176.5	3.3–4.1	...	...	...
3-Ethylene ketal[b]	169.5–171.5	3.3–4.1	64.4–65.6	...	...

[a] Nmr spectra were obtained with a Varian A-60 instrument at 60 Mc on 10% w/v solutions in CCl_4. Frequencies are in Hertz downfield from the tetramethylsilane reference. [b] Data reported by Cross.[21]

(14) This appears to be the simplest method available for the synthesis of this compound. We have made no attempt to find optimum conditions.

(15) A. J. Parker, *J. Chem. Soc.*, 1328 (1961).

(16) H. B. Henbest and W. R. Jackson, *ibid.*, 954 (1962).

(17) R. B. Turner, *J. Am. Chem. Soc.*, **74**, 5362 (1952).

(18) J. Schmutz, H. Schaltegger, and M. Sanz, *Helv. Chim. Acta*, **34**, 1111 (1951).

(19) H. Reich, F. E. Walker, and R. W. Collins, *J. Org. Chem.*, **16**, 1753 (1951).

(20) D. N. Jones, J. R. Lewis, C. W. Shoppee, and G. H. R. Summers, *J. Chem. Soc.*, 2876 (1955).

Hz), owing to coupling with the 7β proton. This is in agreement with the range of 3.3–4.1 Hz reported for this resonance in other α-epoxides.[21] The position of this resonance is dependent on the configuration and nature of the substituent at C-3. While the data in Table I are too limited to support broad generalization, an electronegative substituent in the 3α position appears to cause an upfield shift of about 10 Hz compared to its 3β epimer. If the 3-ethylene ketal is considered as both a 3α and a 3β substituent, the observed upfield shift of 5 Hz from the resonance in the 3β-acetate or -alcohol would appear to indicate that about half of the 10-Hz shift upfield associated with a 3β to 3α change in configuration is due to introduction of the new 3α substituent and the other half is due to removal of the 3β substituent. This suggests that the observed upfield shifts are due to decreased long-range deshielding as a result of the removal of an electronegative substituent from the 3β position and to added shielding of the 6β proton, perhaps mediated through the epoxide ring, whose electronic environment may be altered by interactions with the α substituents introduced at carbon 3. In any event, the observation of long-range effects on the chemical shift of the 6β proton resonance in these systems indicates that the 6β,7β coupling constant, which appears to be unaffected by long-range effects, is a more reliable criterion of 5,6-epoxide configuration than chemical-shift differences.[21]

Experimental Section[22]

5α,6α-Epoxy-3β-cholestanyl p-Toluenesulfonate (2b). Route A.—A solution of cholesteryl p-toluenesulfonate[23] (19.3 g, 0.035 mole) in 100 ml of chloroform was stirred while m-chloroperbenzoic acid (7.67 g, 0.039 mole of 85% basis) in 150 ml of chloroform was added over 30 min. The mixture was stirred for 1 hr more, when the excess peracid was destroyed by allow addition of 10% aqueous sodium sulfite solution until a negative starch–iodide test was obtained. The organic layer was washed several times with 10% aqueous sodium bicarbonate and dried. Evaporation and recrystallization of the residue from methylene chloride–pentane afforded 8.1 g of material: mp 123.5–125.9° (lit.[4] mp 124°); $[\alpha]^{22}D$ −46° (lit.[4] $[\alpha]^{22}D$ −46°); infrared bands at 6.81 (m), 7.29 (s), 8.41 (s), 8.48 (s), 9.09 (m), 10.46 (s), 11.64 (s), and 15.03 (s) μ.

Route B.—Cholesterol (60.4 g, 0.156 mole) was epoxidized with m-chloroperbenzoic acid (85% 31.0 g, 0.158 mole) according to the procedure described above, affording 58.6 g (93.5%) of cholesteryl α-epoxide whose purity before crystallization was adequate for the subsequent step. A small sample was recrystallized from 5% aqueous acetone, affording colorless needles: mp 141.9–142.9° (lit.[24] mp 141–143°); $[\alpha]^{21}D$ −46.4° (lit.[24] $[\alpha]^{26}D$ −44.5°); infrared band at 2.76 (m) μ.

To a solution of this material (18.0 g, 0.045 mole) in 350 ml of dry pyridine was added p-toluenesulfonyl chloride (9.53 g, 0.049 mole) and the resulting solution was stirred overnight at room temperature. The oily layer produced upon dilution with 350 ml of water was taken up in ether and the remaining mixture was extracted with several portions of ether. The ethereal solutions were combined, washed with water, dried over anhydrous sodium sulfate, and then filtered. The solvent was removed under reduced pressure and the residual syrup crystallized from aqueous ethanol to yield 12.3 g (50%) of a white powder whose infrared spectrum was superimposable on that prepared by route A. A small sample was recrystallized several times from methanol: mp 123.5–124° (lit.[4] mp 124°); $[\alpha]^{22}D$ −46° (lit.[4] $[\alpha]^{22}D$ −46°); infrared bands 8.41 (s), 8.48 (s), and 15.03 (s) μ.

Solvolysis of 5α,6α-Epoxy-3β-cholestanyl p-Toluenesulfonate (Route A) in DMF.—A solution of **2b** (3.20 g, 5.75 mmoles, prepared by route A), in N,N-dimethylformamide (50 ml) containing lithium carbonate (3.20 g) was stirred and refluxed for 2 hr. The reaction mixture was cooled and diluted with ether to precipitate inorganic salts which were removed by filtration. The filtrate was washed with three 100-ml portions of water and the ether layer was dried over sodium sulfate. Evaporation of the solvent left 2.04 g of glassy solid which was chromatographed on 70 g of silicic acid. The hexane–chloroform (3:2) eluates afforded 615 mg of 5α,6α-epoxy-2-cholestene (28%), identified by its infrared spectrum;[25] and the hexane–chloroform (1:4) eluates gave 1.367 g of 5α,6α-epoxy-3α-cholestanyl formate (**3a**) (57%) as a colorless syrup which could not be crystallized from aprotic solvents and which decomposed readily in protic solvents. A small amount was obtained as a white powder from methanol: mp 132–135°; infrared bands at 5.81 (s), 8.40 (s), and 8.66 (m) μ; the nmr spectrum showed a one-proton singlet at 475 Hz (formyl).

Anal. Calcd for $C_{28}H_{47}O_3$: C, 77.91; H, 10.97. Found: C, 77.81; H, 10.76.

Saponification of 5α,6α-Epoxy-3α-cholestanyl Formate (3a).—To a solution of **3a** (270 mg, 0.65 mmole) in 35 ml of methanol was added potassium hydroxide (150 mg, 8.4 mmoles) and the resulting yellow solution was refluxed gently for 30 min. After cooling, the reaction mixture was treated with water and extracted with ether. The ethereal extract was washed with several portions of 5% hydrochloric acid, followed by saturated sodium chloride solution, dried over calcium chloride, and filtered. Removal of the solvent under reduced pressure afforded 210 mg of a yellowish foam. Chromatography over 15 g of silicic acid (60–200 mesh) and elution with chloroform–acetone (99:1) yielded 160 mg (62%) of 5α,6α-epoxycholestan-3α-ol (**3b**) which, after several crystallizations from aqueous acetone, had mp 118–119°. The authentic sample was prepared by the method of Shoppee, *et al.*,[8] and had mp 117.9–118.9° and, after resolidification, mp 117–123° (lit.[8] mp 125–128°), infrared band at 2.80 (s) μ.

Hydride Reduction of 5α,6α-Epoxy-3α-cholestanyl Formate (3a).—A solution **3a** (460 mg) in 10 ml of anhydrous ether was added dropwise to a stirred slurry of lithium aluminum hydride (150 mg) in 10 ml of ether. After stirring at room temperature for 1 hr, the excess hydride was destroyed by slow addition of 15 drops of water, followed by 24 drops of 10% sodium hydroxide solution. After filtration, the solvent was evaporated under reduced pressure to yield 435 mg of a white foam. Chromatography over 50 g of acid-washed alumina and elution with benzene–ether mixtures in proportions of (17:3) to (1:3) afforded small amounts of a white solid, indicating that decomposition was occurring on the column. These fractions gave a combined weight of 112 mg (26%) of a material which was crystallized several times from methanol, affording shiny plates, identified as cholestane-3α,5α-diol (**4b**): mp 201.5–203.5° (lit.[9] mp 202–204°); $[\alpha]^{22}D$ 21° (*c* 1.5, $CHCl_3$) (lit.[8] $[\alpha]D$ 18°); infrared bands at 2.77 and 2.88 μ (*c* 1, $CHCl_3$).

Solvolysis of 2b (Route B) in DMF.—To a solution of **2b** (18.1 g, 32.6 mmoles, prepared by route B) in 250 ml of DMF was added lithium carbonate (18.0 g) and the resulting mixture was kept under reflux for 2.5 hr. The mixture was cooled, added to 500 ml of water, and extracted with ether. The ethereal extracts were washed with several portions of water, dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure, yielding 11.6 g of a gummy residue. Chro-

(21) (a) A. D. Cross, *J. Am. Chem. Soc.*, **84**, 3206 (1962); (b) K. Tori, T. Komeno, and T. Nakagawa, *J. Org. Chem.*, **29**, 1136 (1964).

(22) All melting points were taken on a calibrated Fisher-Johns block and are corrected. Microanalysis and molecular weight determinations were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were obtained on a Beckman IR-8 instrument using 10% w/v solutions in carbon tetrachloride except where otherwise noted. Nuclear magnetic resonance spectra were obtained in 10% w/v solutions in carbon tetrachloride with a Varian Associates A-60 analytical nmr spectrometer. Frequencies are in cycles per second downfield from the tetramethylsilane reference. Ultraviolet spectra were obtained on a Cary Model 14 spectrophotometer in 1-cm quartz cells. Optical rotations were observed on a 2% chloroform solution except where otherwise noted and are accurate to ±2°. The rotatory dispersion data were obtained on a JASCO Model Ord/UV-5 optical rotatory dispersion recorder.

(23) E. S. Wallis, E. Fernholz, and F. T. Gephart, *J. Am. Chem. Soc.*, **59**, 137 (1937).

(24) P. N. Chakravorty and R. H. Levin, *ibid.*, **64**, 2317 (1942).

(25) Samples of this compound prepared in the present work normally melted from 60 to 65°, rather than from 75.1 to 76.1° as reported earlier.[2] They were unequivocally the same compound, however, since both spectroscopic and chemical behavior (in epoxide ring opening reactions reported earlier) were identical. Repetition of the earlier synthesis gave material of mp 60–69°.

matography over 250 g of silicic acid and elution with hexane–chloroform (9:1) afforded 74 mg (0.6%) of 2,4,6-cholestatriene (**9**), identified by its infrared spectrum (see below).

Elution with hexane–chloroform (3:2) gave 1.63 g (12%) of 3β-chloro-5α,6α-epoxycholestane (**2c**) as a crystalline solid, mp 86–87°. An analytical sample was prepared by several recrystallizations from ethanol: mp 90.6–91.2° (lit.[11] mp 89.5–90.5°); $[\alpha]^{22}D$ −54° (lit.[11] $[\alpha]D$ −35.6°); infrared bands (CS_2) at 8.61 (m), 11.52 (m), 12.49 (m), 13.13 (m), and 14.2 (m) μ.

Anal. Calcd for $C_{27}H_{45}OCl$: C, 77.01; H, 10.77; O, 3.80; Cl, 8.42. Found: C, 77.14; H, 11.08; O, 3.94; Cl, 8.18.

Further elution with hexane–chloroform (3:2) afforded 2.2 g (16%) of 5α,6α-epoxy-2-cholestene (**5**) identified by its infrared spectrum. Elution with hexane–chloroform (1:1) afforded 1.45 g (11%) of the crystalline 3α-chloro-5α,6α-epoxycholestane (**3c**). The analytical sample was prepared by several crystallizations from ethanol: mp 166–167° (lit.[12] mp 160–162°); $[\alpha]^{22}D$ −65° (lit.[12] $[\alpha]D$ −37.7°); infrared bands (CS_2) at 7.92 (s), 10.24 (m), 10.72 (m), 12.57 (m), and 13.51 (m) μ.

Anal. Calcd for $C_{27}H_{45}OCl$: C, 77.01; H, 10.77; O, 3.80; Cl, 8.41; mol wt, 421.09. Found: C, 77.19; H, 10.95; O, 4.04; Cl, 8.23; mol wt, 398.

Elution with hexane–chloroform (2:3) gave 0.57 g (5%) of 4-chloesten-6-one (**7**) which, after several crystallizations from methanol, afforded colorless needles: mp 105.2–106.2° (lit.[17] mp 107–108°); molecular rotations, $[\alpha]_{700}$ 32°, $[\alpha]_{589}$ 41°, $[\alpha]_{575-525}$ 48°, $[\alpha]_{359}$ −445° (*c* 0.2, dioxane) (lit.[26] molecular rotation, $[\alpha]_{700}$ 29°, $[\alpha]_{589}$ 40°, $[\alpha]_{575-525}$ 45°, $[\alpha]_{359}$ −435°); infrared bands at 5.94 (s), 6.16 (s), 7.90–7.95 (m), and 8.13 (m) μ; λ_{max}^{EtOH} 242 mμ (ε 7300) [lit.[17] λ_{max}^{EtOH} 641 mμ (ε 7800)]. Elution with hexane–chloroform (1:4) resulted in 6 g (43%) of 5α,6α-epoxy-3α-cholestanyl formate (**3a**) identified as above.

Acid Hydrolysis of 3β-Chloro-5α,6α-epoxycholestane (2c).—To a solution of 3β-chloro-5α,6α-epoxycholestane (**2c**) (420 mg, 1.0 mmole) in 20 ml of acetone was added a solution of periodic acid (228 mg, 1 mmole) in 1 ml of water. The resulting cloudy mixture was refluxed for 40 min, cooled, added to 40 ml of water, and extracted with 40 ml of ether. The ether layer was washed with water, dried over anhydrous magnesium sulfate, and the solvent removed under reduced pressure to yield 421 mg (96%) of 3β-chlorocholestane-5α,6β-diol (**6**) as a clear syrup which crystallized upon addition of a few drops of hexane. The diol (**6**) was recrystallized several times from hexane, affording colorless needles: mp 127.0–127.6° (lit.[11] mp 126°); $[\alpha]^{22}D$ 6° (lit.[11] $[\alpha]D$ −6.3°); infrared band ($CHCl_3$) at 2.76 μ. Upon treatment with acetic anhydride, the diol (**6**) formed the monoacetate, 3β-chlorocholestane-5α,6β-diol 6-acetate, which was crystallized from aqueous acetone, mp 147.5–149° (lit.[11] mp 150–151°).

Reduction of 3α-Chloro-5α,6α-epoxycholestane (3c).—A solution of 3α-chloro-5α,6α-epoxycholestane (**3c**) (50 mg, 0.12 mmole) in 15 ml of anhydrous ether was added to a stirred slurry of lithium aluminum hydride (50 mg, 0.13 mmole) in 5 ml of ether. After stirring at room temperature for 1 hr, a few drops of water were added to destroy the excess hydride. The inorganic salts were removed by filtration and the ether was removed under reduced pressure to yield 27 mg (54%) of 3α-chlorocholestan-5α-ol (**4b**). Recrystallization from methanol afforded colorless crystals, mp 118–119.5°, which gave no depression upon admixture of an authentic sample prepared by the method of Shoppee, *et al.*,[8] and whose infrared spectrum was superimposable with that of the authentic sample.

3α,6β-Dichlorocholestan-5α-ol (8).—A brisk stream of dry hydrogen chloride was passed through a solution of 3α-chloro-5α,6α-epoxycholestane (**3c**) (632 mg, 1.5 mmoles) in 8 ml of chloroform for 15 min. The solvent was then removed under reduced pressure and the solid residue recrystallized several times from aqueous acetone, affording colorless plates: mp 121–122° (lit.[12] mp 118–119°); $[\alpha]^{22}D$ 16°$\frac{1}{4}$ (lit.[12]$\frac{1}{4}$ $[\alpha]D$ 0°); infrared bands at 2.81 (s), 9.98 (m), and 13.9 (m) μ.

Anal. Calcd for $C_{27}H_{46}OCl_2$: C, 70.87; H, 10.13; Cl, 15.50. Found: C, 70.63; H, 9.84; Cl, 15.14.

Solvolysis of 2b in DMF with Excess Lithium Chloride, Unbuffered.—A solution of **2b** (3.2 g, 5.8 mmoles) and lithium chloride (2.44 g, 58 mmoles) in 50 ml of DMF was kept under reflux for 2.5 hr. After cooling to room temperature, the mixture was treated with 75 ml of water and extracted with ether. The ether extract was washed with several portions of water followed by saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and filtered. Removal of the solvent under reduced pressure afforded 1.96 g of an amber syrup which slowly solidified. Chromatography of the residue over 70 g of silicic acid (60–200 mesh) and elution with hexane–chloroform (19:1) gave 1.33 g (62%) of 2,4,6-cholestatriene (**9**) as a colorless syrup which slowly solidified. Crystallization from aqueous acetone yielded long needles: mp 71.5–72.5° (lit.[18] mp 71–72°); $[\alpha]^{22}D$ 7° (lit.[18] $[\alpha]D$ −13.8°); a sample which had been allowed to stand under ordinary laboratory conditions for several days had $[\alpha]^{22}D$ −90°; $\lambda_{max}^{cyclohexane}$ 307 mμ (ε 15,400) with shoulders at 321 mμ (ε 10,080) and 295 mμ; infrared bands at 3.31 (m) and 14.45 (m) μ. Elution with hexane–chloroform (1:4) yielded 320 mg (14%) of 4-chlolesten-6-one (**7**), identified by its infrared spectrum. Elution with chloroform afforded 195 mg (8%) of 5α,6α-epoxy-3α-cholestanyl formate (**3a**), also identified by its infrared spectrum.

Hydrogenation of 2,4,6-Cholestatriene (9).—A solution of 2,4,6-cholestatriene (**9**) (488 mg, 1.32 mmoles) in 25 ml of ethyl acetate was reduced over platinum according to the method of Brown.[13] Upon completion, the reaction mixture had absorbed approximately 3 equiv of hydrogen. After filtration of the reaction mixture and removal of the solvent under reduced pressure, 490 mg of a colorless syrup was obtained. Chromatography over 30 g of alumina and elution with hexane afforded 486 mg (99%) of a mixture of cholestane and coprostane which crystallized as shiny plates upon standing for several days in ethanol containing some ether: mp 69.7–73° (lit.[13] coprostane mp 70°, cholestane mp 80°); the infrared absorptions at 3.3 and 14.35 μ in the starting material (**8**) had disappeared; the nmr showed no absorptions characteristic of vinyl protons; the ultraviolet had no absorptions in the region from 350 to 200 mμ.

Solvolysis of 2b in DMF with Excess Lithium Chloride.—A solution of 5α,6α-epoxy-3β-cholestanyl tosylate (**2b**) (3.2 g, 5.8 mmoles) plus lithium chloride (2.44 g, 58 mmoles) and lithium carbonate (3.2 g) in 50 ml of DMF was refluxed for 2 hr. After cooling to room temperature, the inorganic salts were removed by filtration and washed well with ether. The filtrate and ether washings were combined and worked up as in route B, yielding 2.2 g of a yellow gummy residue. Chromatography over 70 g of alumina and elution with hexane afforded 633 mg (26%) of 3β-chloro-5α,6α-epoxycholestane (**2c**), identified by its infrared spectrum. Elution with hexane–benzene (19:1) gave 482 mg (22%) of 5α,6α-epoxy-2-cholestene (**1**), also identified by its infrared spectrum. Elution with hexane–benzene (7:3) yielded 52 mg (2%) of 3α-chloro-5α,6α-epoxycholestane (**3c**), identical with that described above. No 5α,6α-epoxy-3α-cholestanyl formate (**3a**) was detected in the infrared spectrum of the crude product mixture.

Solvolysis of 2b in DMF with an Equivalent of Lithium Chloride.—A mixture of **2** (4.87 g, 8.75 mmoles, prepared by route A), lithium chloride (370 mg, 8.75 mmoles), and lithium carbonate (4.87 g) was stirred and refluxed in 20 ml of DMF for 30 min. After work-up as above, 3.36 g of semicrystalline solid were obtained. Chromatography over 110 g of alumina as above afforded 3β-chloro-5α,6α-epoxycholestane (843 mg, 23%), 5α,6α-epoxy-2-cholestene (719 mg, 21%), and 3α-chloro-5α,6α-epoxychlolestane (1.165 g, 32%), identified by their infrared spectra. The infrared spectrum of the crude reaction mixture indicated, in addition to the compounds isolated, the presence of *ca.* 15% of 5α,6α-epoxy-3α-cholestanyl formate which was not isolated and was presumably destroyed on the column.

3β-Chloro-5α,6α-epoxycholestane from Its 3α Epimer.—A solution of 3α-chloro-5α,6α-epoxycholestane (848 mg, 2.00 mmoles) in 21 ml of DMF containing lithium chloride (840 mg, 20 mmoles) and lithium carbonate (800 mg) was stirred and refluxed for 3.5 hr. After the usual work-up and chromatographic separation on alumina, there was obtained 3β-chloro-5α,6α-epoxycholestane (222 mg, 26%) and 5α,6α-epoxy-2-cholestene (104 mg, 13%). No 3α-chloro-5α,6α-epoxycholestane was detected. The infrared spectrum of the crude product mixture indicated the presence of minor (5%) amounts of 4-cholesten-6-one and the absence of significant amounts of 5α,6α-epoxy-3α-cholestanyl formate and its ultraviolet spectrum ruled out the presence of more than traces (0.5%) of 2,4,6-cholestatriene.

Solvolysis of 5α,6α-Epoxy-2-cholestene (5) in DMF.—To a solution of 5α,6α-epoxy-2-cholesten (**5**) (190 mg, 0.5 mmole) in 15 ml of DMF was added *p*-toluenesulfonic acid monohydrate (105 mg, 0.5 mmole) plus lithium chloride (100 mg, 2.4 mmoles) and the resulting mixture was refluxed for 2.5 hr. After cooling

(26) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956).

to room temperature, the amber solution was poured into 50 ml of water and extracted with ether. The ethereal extract was washed with water, dried over anhydrous magnesium sulfate, and the solvent removed under reduced pressure, affording 153 mg of an amber syrup. Chromatography over 10 g of acid-washed alumina and elution with hexane gave 52 mg (29%) of 2,4,6-cholestatriene (**9**), identical with that described previously. Elution with hexane–benzene (17:3) yielded 28 mg (15%) of 5α,6α-epoxy-2-cholestene (**5**) as a colorless syrup, identified by its infrared spectrum.

Solvolysis of 3β-Chloro-5α,6α-epoxycholestane (2c).—A solution of 3β-chloro-5α,6α-epoxycholestane (**2c**) (421 mg, 1 mmole) plus *p*-toluenesulfonic acid monohydrate (418 mg, 2 mmoles) and lithium chloride (420 mg, 10 mmoles) in 25 ml of DMF was kept under reflux for 2 hr. After cooling, the yellowish mixture was poured in 75 ml of water and extracted with ether. The ethereal extracts were washed with several portions of water, once with a saturated sodium chloride solution, then dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure to yield 320 mg of a yellowish syrup. Chromatography of this material over 20 g of alumina and elution with hexane afforded 183 mg (50%) of 2,4,6-cholestatriene (**9**), identical with that described previously. Elution with hexane–benzene (1:3) gave 46 mg (12%) of 4-chloesten-6-one (**7**), also identical with that described previously.

Solvolysis of 3α-Chloro-5α,6α-epoxycholestane (3c).—A solution of 3α-chloro-5α,6α-epoxycholestane (**3c**) (421 mg, 1 mmole) plus *p*-toluenesulfonic acid monohydrate (418 mg, 2 mmoles) and lithium chloride (420 mg 10 mmoles) in 50 ml of DMF was kept under reflux for 2.5 hr. The cooled product mixture was then treated in an identical manner with that described for the solvolysis of 3β-chloro-5α,6α-epoxycholestane (**2c** above) under these conditions, yielding 349 mg of a yellowish syrup whose infrared spectrum was superimposable upon that of the aforementioned product mixture. After standing for several days under ordinary laboratory conditions (*i.e.*, atmospheric oxygen), the residue was chromatographed over 20 g of alumina. Elution with hexane afforded 85 mg (23%) of 2,4,6-cholestatriene (**9**), identical with that reported previously. Elution with hexane–benzene (1:3) gave 40 mg (19%) of 4-cholesten-6-one (**7**), identified by its infrared spectrum.

2,4-Cholestadien-6α-ol (10).—A solution of 2,4-cholestadien-6-one[19] (96 mg, 0.25 mmole) in 15 ml of anhydrous ether was cooled in an ice bath under a nitrogen atmosphere, whereupon 2 ml of a 0.4 *M* ethereal solution of lithium aluminum hydride was added dropwise during several minutes. After an additional 15 min at ice-bath temperature, the mixture was allowed to warm to room temperature and the excess hydride was destroyed by addition of 6 drops of water followed by 10 drops of a 10% sodium hydroxide solution. Filtration through anhydrous sodium sulfate and removal of the ether under reduced pressure led to 96 mg of a colorless glass which could not be crystallized and decomposed in the presence of air and light. No carbonyl absorption was observed in the infrared; however, there were peaks at 2.79, 3.30, and 14.32 μ. The ultraviolet absorption, λ_{max}^{EtOH} 265 mμ, and a shoulder at 273 mμ disappeared upon addition of acid with the formation of a new peak, λ_{max}^{EtOH} 238 mμ.

Solvolysis of 2,4-Cholestadien-6α-ol (15) in DMF.—To a solution of freshly prepared 2,4-cholestadien-6α-ol (**15**) (295 mg, 0.8 mmole) in 20 ml of DMF was added *p*-toluenesulfonic acid monohydrate (155 mg, 0.5 mmole) and lithium chloride (150 mg, 3.6 mmoles). The resulting mixture was refluxed for 2.5 hr. After cooling to room temperature, the amber solution was poured into 50 ml of water and extracted with ether. The ether extract was washed with several portions of water, dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield 239 mg of an amber syrup. Chromatography over 15 g of alumina and elution with hexane afforded 146 mg (51%) of 2,4,6-cholestatriene (**9**), whose physical and spectral properties were identical with those reported earlier.

Registry No.—**2a**, 1250-95-9; **2b**, 13095-29-9; **2c**, 13095-30-2; **3a**, 13095-31-3; **3b**, 2953-38-0; **3c**, 13095-33-5; **4a**, 570-96-7; **5**, 13095-35-7; **7**, 13095-36-8; **8**, 13095-37-9; **9**, 13095-38-0; **10**, 13095-39-1; dimethylformamide, 68-12-2.

Alternate Precursors in Biogenetic-Type Syntheses. I. The Synthesis of Cyclohex[*j*]indolo[2,3-*f*]morphan

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cis-Cyclohexindolomorphan was obtained by a Grewe-type synthesis. The *trans* isomer was obtained from 4a-chloro-2,3,4,4a,5,6,7,8-octahydro-1-(indol-3-ylmethyl)-2-methylisoquinoline (**10**) by reduction, intramolecular halogen displacement, and a Plancher rearrangement. The chloro compound **10** arose from the Bischler–Napieralski cyclization of N-[2-(1-cyclohexenyl)ethyl]-N-methylindole-3-acetamide (**9**). Both isomers were degraded to 11-methylbenzo[*a*]carbazole.

The biogenetic-type synthesis of alkaloids, although originally explored by Robinson[1] in 1917, has only recently received widespread attention. The basic philosophy of this approach and some of the syntheses for which it has formed the basis has been the subject of a recent review.[2] A further extension of this work is the preparation of missing alkaloids by insertion of an alternate, biologically feasible precursor at some stage of an established biogenetic-type synthesis. For example, Schöpf[3] has replaced 3,4-dihydro-β-carboline by 6,7-dimethoxy-3,4-dihydroisoquinoline in the scheme for Ruteocarpin and obtained a dimethoxybenzene analog which has not yet been found in nature.

We became intrigued with the possibility of the substitution of tryptophan for one molecule of 3,4-dihydroxyphenylalanine in Robinson's[4] biogenetic scheme for morphine. However, a biogenetic-type synthesis involving the key oxidative coupling step has not yet been accomplished on a preparative basis.[5] Thus far, the closest approach[6] is the cyclization of a benzyloctahydroisoquinoline to tetrahydrodeoxycodeine by Grewe.[7] Therefore, initially, we decided to investigate the Grewe cyclization of the indolylmethyloctahydroisoquinoline **4** to **6**, the indole analog of tetrahydrodeoxycodeine.

(1) R. Robinson, *J. Chem. Soc.*, **111**, 876 (1917).

(2) E. E. van Tamelen, "Progress in the Chemistry of Organic Natural Products," Vol. 19, L. Zechmeister, Ed., Springer-Verlag, Vienna, Austria, 1961, p 242.

(3) C. Schöpf and H. Steuer, *Ann. Chem.*, **558**, 124 (1947).

(4) R. Robinson and S. Sugasawa, *J. Chem. Soc.*, 3163 (1931).

(5) Although D. H. R. Barton, G. W. Kirby, W. Steglich, and G. M. Thomas [*Proc. Chem. Soc.*, 203 (1963)] have accomplished the key oxidation step, the product could not be isolated, but instead was identified by isotopic dilution.

(6) Reference 2, p 259.

(7) R. Grewe, A. Mondon, and E. Nolte, *Ann. Chem.*, **564**, 161 (1949).