Modified Cardenolides. III.[1a] Cyclocardenolides Obtained from 19-Hydroxycardenolides[1b]

MANFRED E. WOLFF AND WINSTON HO

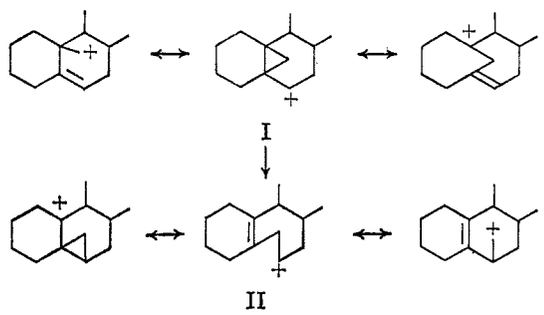
Department of Pharmaceutical Chemistry, School of Pharmacy, University of California at San Francisco, San Francisco, California 94122

Received November 29, 1966

The rearrangements under various conditions of homoallylic cations derived from 3β,14β,19-trihydroxycard-5-enolide 3-acetate or the corresponding 19-tosylate were studied. Solvolysis of the tosylate in presence of sodium acetate gave 5β,10-cyclo-3β,6β,14β-trihydroxycard-20(22)-enolide, 3,6-diacetate, whereas in pyridine the corresponding Δ^6 product was obtained. Treatment of the 19-alcohol with 2-chloro-1,1,2-trifluoro-N,N,N-triethylamine (CTTA) under various conditions produced 3β,14β-dihydroxy-7ξ-fluoro-19-nor-B-homocarda-5(10),20(22)-dienolide 3-acetate, 8β,19-epoxy-3β-hydroxy-14ξ-card-5-enolide acetate, and 3β,19-dihydroxycarda-5,8(14),20(22)-trienolide 3-acetate. The action of CTTA on 14β,19-dihydroxy-3-oxocarda-4,20(22)-dienolide afforded analogous 8,19 epoxides and 8,14 olefins. The formation of these products is discussed in terms of current carbonium ion theory.

In a continuation of our work on modification of cardenolides at C-19,[1a,b] the preparation of analogs modified by homoallylic rearrangements of C-19-substituted aglycones was undertaken.

Rearrangements of cyclopropylcarbinyl cations have been known for some time, and have been explained on the basis of various nonclassical intermediates.[2] The intervention of these ions in rearrangements of 19-substituted Δ^5-steroids[3-10] and related terpenes[11,12] has been postulated. Tadanier[8b] has proposed that the homoallylic rearrangements of C-19-substituted steroids can be explained in terms of the initial formation of the ion I which rearranges at a rapid but finite rate to the ion II. The products of the rearrangement



I

II

depend on the rate of reaction of external nucleophiles with I or II, and the stability of the resulting compounds.

In investigating related reactions of steroidal systems bearing a 14β-hydroxy group, we observed that the presence of this function had a profound effect on the reaction.[13] Solvolysis of **3** with sodium acetate in aqueous dioxane gave a mixture of the 5,10-cyclo derivatives **9** and **10** from which **9** was isolated after acetylation (Scheme I). The presence of the cyclopropane ring in **9** was indicated by an AB system at high field in the nmr spectrum (Table I).

The stereochemistry at C-6 is assigned by the same arguments used[7c,8b] to reverse earlier assignments in the steroid series. The cyclopropyl resonance appears as an AX quartet in which the chemical shift of one proton is in the normal range of 21 cps, whereas the other is at 52 cps. Although the downfield peaks were partially obscured by other peaks when either $CDCl_3$ or benzene was used as solvent, the use of a benzene–$CDCl_3$ mixture allowed observation of all four peaks. The most reasonable explanation for the AX system is that one cyclopropyl proton is deshielded by the 6 substituent, which can only be accomplished by a 6β-acetate function. In contrast to the results obtained in aqueous dioxane containing sodium acetate, solvolysis in pyridine solution in the absence of acetate as a nucleophile gave **14**. The nmr spectrum of **14** shows a one-proton doublet at high field whereas a low-field doublet, due to the C-19 proton deshielded by the 6,7 double bond, is obscured by other peaks. These compounds arise from ion I.

Very different products were formed by the action on **2** of 2-chloro-1,1,2-trifluoro-N,N,N-triethylamine[4,6,14,15] (CTTA) in methylene chloride solution at −20 and 27°. These conditions gave products derived from ion II. Thus, at −20°, 25% of the B-homocardenolide **7** was obtained as the sole isolable product after chromatography. The structure of **7** was assigned on the basis of the nmr and mass spectra. The nmr spectrum computed from time averaging showed two broad peaks of approximately 20-cps half-width which were separated by roughly 50 cps. This

(1) (a) Paper II: M. E. Wolff and W. Ho, *J. Pharm. Sci.*, in press. (b) For a preliminary communication containing a small part of this work, see M. E. Wolff, W. Ho, and B. Katzung, *Chem. Ind.* (London), 1976 (1965). (c) This research was supported in part by a Public Health Service Grant (HE-09578) from the National Heart Institute, U. S. Public Health Service.

(2) For a collection of reprints and commentary, consult P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, Inc., New York, N. Y., 1965.

(3) J. J. Bonet, H. Wehrli, and K. Schaffner, *Helv. Chim. Acta*, **45**, 2615 (1962).

(4) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *Tetrahedron Letters*, 1249 (1962); L. H. Knox, E. Velarde, S. Berger, I. Delfín, R. Grezemkovsky, and A. D. Cross, *J. Org. Chem.*, **30**, 4160 (1965).

(5) J. J. Bonet, H. Wehrli, and K. Schaffner, *Helv. Chim. Acta*, **46**, 1776 (1963).

(6) L. H. Knox, E. Velarde, and A. D. Cross, *J. Am. Chem. Soc.*, **85**, 2533 (1963); **87**, 3727 (1965).

(7) (a) O. Halpern, P. Crabbé, A. D. Cross, I. Delfin, and A. Bowers, *Steroids*, **4**, 1 (1964); (b) H. Carpio, A. Bazán, M. G. T. Medina, and J. A. Edwards, *J. Org. Chem.*, **30**, 4154 (1965); (c) K. Syhora, J. A. Edwards, and A. D. Cross, *ibid.*, **31**, 3411 (1966).

(8) (a) J. Tadanier and W. Cole, *Tetrahedron Letters*, 1345 (1964); (b) J. Tadanier, *Experientia*, **21**, 563 (1965); *J. Org. Chem.*, **31**, 2124 (1966); (c) J. Tadanier, *ibid.*, **31**, 3204 (1966).

(9) J. J. Bonet-Sugrañes, *Afinidad*, **22**, 326 (1965).

(10) M. Akhtar and D. H. R. Barton, *J. Am. Chem. Soc.*, **86**, 1528 (1964).

(11) W. G. Dauben and L. E. Friederich, *Tetrahedron Letters*, 2675 (1964).

(12) Y. Hikino and P. de Mayo, *Chem. Commun.*, 550 (1965).

(13) In all reactions described in this article, thin layer chromatography was used to establish the number and nature of products formed. This technique verified that some reactions took entirely different courses depending on temperature and solvent, and that this is a real effect and not simply the result of the chance isolation of different products from similarly constituted mixtures. In those cases where the obtainment of different products under different conditions is described, tlc studies showed that *none of the other product* was obtained in each case.

(14) D. E. Ayer, *Tetrahedron Letters*, 1065 (1962).

(15) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *J. Org. Chem.*, **29**, 2187 (1964).

SCHEME I

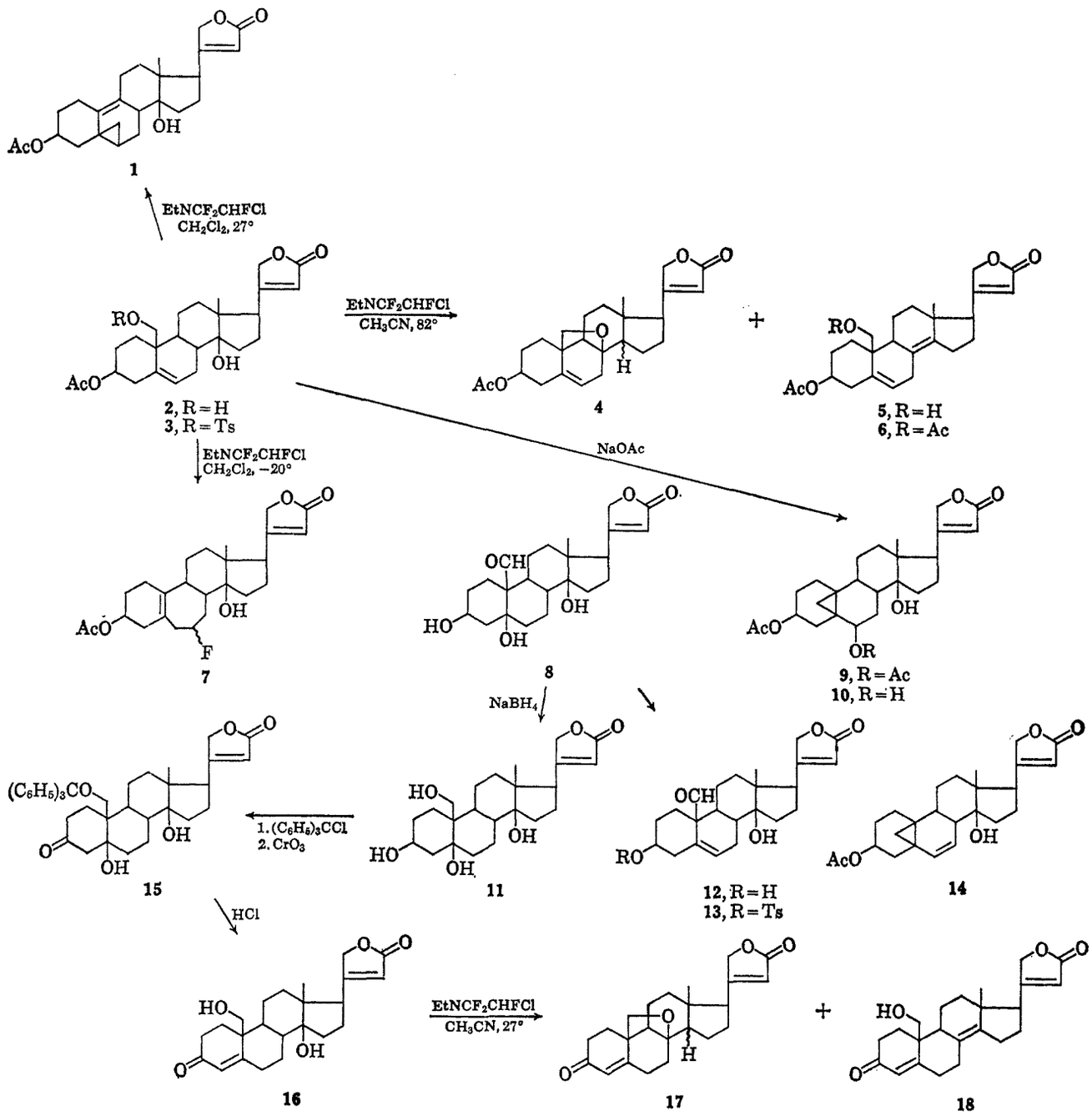


TABLE I

NMR SPECTRA OF MODIFIED CARDENOLIDES

Compd	C-6—H ($W_{1/2}$)	C-7—H	C-18—H	C-19—H δ_A	C-19—H δ_B	J_{AB}, cps	C-21—H	C-22—H
1	...	...	54	20 ⌣ 45 (m)		..	290 (m)	350
2	348 (10)	...	57	215	231	12	293 (m)	353
3	341 (10)	...	48	240	248	11	293 (m)	353
4	314 (8)	...	59	218	234	7	284 (m)	347
5	338 (10)	...	54	219 (s)		..	284 (m)	350
6	333 (11)	...	51	241	249	12	285 (m)	350
7	...	273 (m), 321 (m) ($W_{1/2}$ = 20)	57	...	...	..	294 (m)	354
9	307 (7)	...	53	20	53	6	292 (m)	353
13	353 (6)	...	50	578 (s)		..	292 (m)	353
14	345, 348 (d)	...	53	31, 37 (only visible pair of AB quartet)		6	294 (m)	355
15	...	...	42	202	216	10	290 (m)	350
16	...	...	56	232	241	11	302 (m)	358
17	...	...	62	226	237	9	290, 292 (d)	355
18	...	...	53	235 (s)		..	293 (m)	364

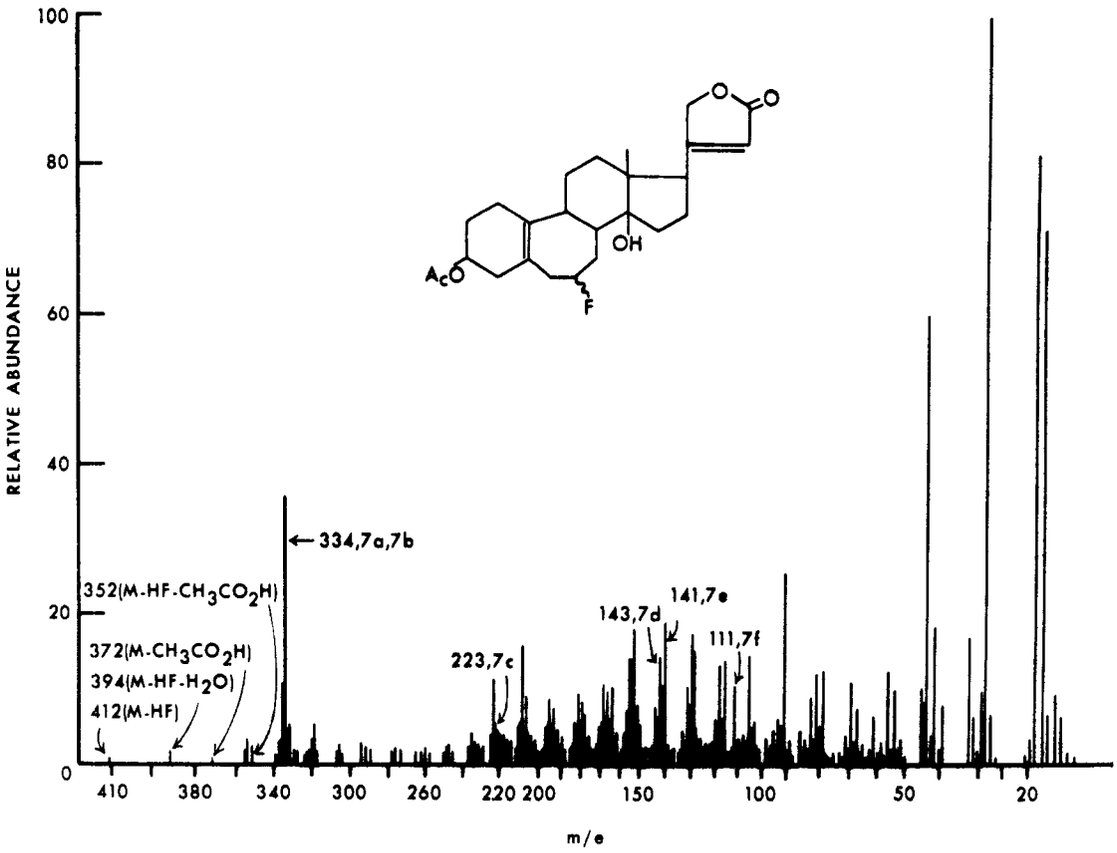
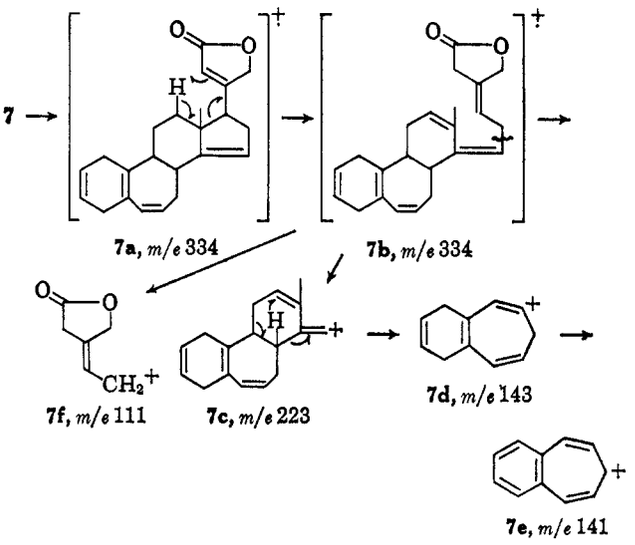


Figure 1.—Mass spectrum of **7**.

would be expected from structure **7** in which the C-7 proton is spin coupled to the fluorine atom and to the flanking methylene groups, and is deshielded by fluorine. Similar nmr results have been described in the steroid series.[4] The mass spectrum (Figure 1) showed unique peaks which can be understood on the basis of the B-homo structure. No molecular ion was seen, owing to facile loss of hydrogen fluoride. Peaks at *m/e* 412, 394, 372, 352, and 334 are readily interpreted in terms of loss of combinations of acetic acid, water, and hydrogen fluoride from the molecular ion. Moreover, the peak at *m/e* 111 to **7f**, is characteristic of the butenolide ring in cardenolides.[16] However, unusual peaks occur at *m/e* 223, 143, and 141. These may be explained in the following way. The ion **7a** undergoes a concerted electron shift giving **7b**, which extrudes 111 mass units to furnish **7c**. Breakage of the 9,14 and 9a,11 bonds by a concerted shift results in the ion **7d**, which aromatizes with loss of two hydrogen radicals giving the benzotropylium cation **7e** derived from the original A- and B-homo rings. (See Scheme II.)

SCHEME II



At 27°, the action of CTTA on **2** gave the 5β,6-cyclocardenolide **1**. The nmr spectrum of **1** shows no olefinic proton other than that in the lactone ring but exhibits λ_{max}^{EtOH} 217 mμ (log ε 4.30). Since this is more intense than the expected absorption of the cardenolide ring [λ_{max}^{EtOH} 217 mμ (log ε 4.16)],[17] the additional absorption at 217 mμ must be due to the vinylcyclopropyl system which is known[7b,18] to absorb in this region [λ_{max}^{EtOH} 216 mμ (log ε 3.95)].

Protons on the cyclopropyl ring form an ABX system because one of the C-19 protons is deshielded by the double bond, and the nmr spectrum is in harmony with this (Table I).

Treatment of **2** with CTTA in refluxing acetonitrile involved other areas of the molecule in these reactions. Thus, **4** and **5** were isolated in good yield in roughly equal amounts under these conditions of elevated temperature. The nmr spectrum of **4** shows an AB quartet arising from protons next to oxygen and a trisubstituted olefinic bond. There was an absence of hydroxyl absorption in the infrared spectrum, and the mass spectrum gave a molecular weight of 412 ($C_{25}H_{32}$-

(16) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 2, Holden-Day, Inc., San Francisco, Calif., 1964, pp 106–108.

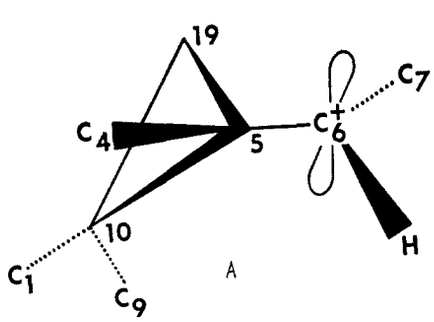
(17) W. D. Paist, E. R. Blout, F. C. Uhle, and R. C. Elderfield, *J. Org. Chem.*, **6**, 273 (1941); L. Ruzicka, P. A. Plattner, and A. Furst, *Helv. Chim. Acta*, **25**, 79 (1942).

(18) J. W. Rowe, A. Melera, D. Arigoni, O. Jeger, and L. Ruzicka, *ibid.*, **40**, 157 (1957).

O_5). These data pointed to structure **4**, in analogy to the 8,19-epoxystrophanthidin derivatives of Ehrenstein.[19] Compound **5** had the same molecular weight (mass spectrometry) as **4**, but the C-19 protons appeared as a broadened singlet[20] in the nmr spectrum, and there was a hydroxyl band in the infrared spectrum. Acetylation gave the diacetate **6**. Compound **5** is formulated with an 8,14 double bond on the basis of nmr and ultraviolet spectra. Only two vinyl protons were seen in the nmr, indicating that an 8,14 or 8,9 double bond is at hand. The ultraviolet extinction of these two chromophores at 210 mμ is quite distinctive,[21] the Δ^8 bond having ϵ_{210} 4400–4500, whereas the $\Delta^{8,14}$ bond has ϵ_{210} 9500–10,500. Since ϵ_{211} for **2** is 18,700, the extinction at 211 mμ for the $\Delta^{8,14}$ formulation can be calculated as approximately 28,700, whereas the value for the Δ^8 compound is 23,150. Compound **5** had $\epsilon_{211\,(max)}$ 28,100, in good agreement with the $\Delta^{8,14}$ structure. Although the formation of **4** might be expected to involve dehydration at C-14 to give **5** followed by addition of the 19-hydroxyl group to the new double bond, this sequence was found not to be operative. Thus, treatment of **2** under the same conditions (CTTA in refluxing acetonitrile) for a shorter period, gave mainly **4** as the first isolable product. When a pure sample of **4** was subjected to similar reaction conditions, the formation of **5** could be established by tlc. On the other hand, when **5** was allowed to react in the same way, no change was observed when tlc was used to monitor the course of the reaction. All of the compounds involved were readily separated on silver nitrate impregnated silica gel tlc plates.

From these data, we conclude that the olefinic linkage at C-14 destabilizes the homoallylic ions I and II by steric and/or inductive effects.

It has been shown recently[22] that in cyclopropylcarbinyl ions, stabilization is secured through overlap of the vacant p orbital of the carbinyl positive ion with the "banana bonds" of the cyclopropane ring. For example, in the present case this would lead to structure A for the ion I. Clearly, major torsional effects



A

would be produced by an 8,14 double bond. The bond angle changes at C-8 can be transmitted readily through *both* C-7 and C-9. These conformational changes apparently preclude the required orbital overlap, and hence the formation of the usual ion. Models show major differences in the geometry of **5** relative to **2**, but it is not possible to specify precisely which deformations are responsible for the destabilization.

It seems clear, moreover, that the ether **4** is formed by some type of concerted process, probably directly from **2**. It is apparent that **1** and **7**, on the one hand, and **4** and **5**, on the other are formed by fundamentally different processes, which are clearly the result of greatly different solvent and temperature conditions. In the absence of studies specifically intended to clarify the nature of these differences, it seems unwarranted to speculate further in this regard. Likewise, we have not assigned the configuration of the 14 proton in **4**.

Rearrangement of a 19-hydroxy-3-oxo-4-ene system was also studied. Reduction of strophanthidin **8** with sodium borohydride gave **11**,[23] and the primary alcohol was protected by tritylation. Oxidation gave **15**, and cleavage of the protecting group proceeded with concomitant elimination of the 5β-hydroxy group to afford **16**.[24] Treatment of **16** with CTTA in acetonitrile at 27° gave **17** and **18**. The infrared, nmr, and mass spectrometric evidence used to establish these structures was similar to that employed for **4** and **5**. It is noteworthy that rather different products, obtained from homoallylic ions, are secured by related reactions in the steroid series.[4] Presumably, the route of formation of **17** and **18** from **16**, as well as the stability of **18** under these conditions, is analogous to the situations described in the case of **2**.

Experimental Section[25]

3β,14β-Dihydroxy-5β,6-methano-19-norcarda-9(10),20(22)-dienolide 3-Acetate (1).—A solution of 0.20 g (0.00046 mole) of **2** and 0.20 g (0.001 mole) of CTTA in 50 ml of dry methylene chloride was stirred at 27° for 16 hr (thin layer chromatography was used to monitor the reaction). The solvent was evaporated under reduced pressure and the oily product was chromatographed on 10 g of Florisil. From the 2% methanol in ether fractions there was obtained 0.06 g of **1**, mp 150–155°. Recrystallization from acetone–petroleum ether (bp 30–60°) gave the analytical sample: mp 157–159°, $[\alpha]^{20}D$ +27° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.23; H, 7.56.

8β,19-Epoxy-3β-hydroxy-14ξ-card-5-enolide Acetate (4).—A solution of 0.20 g (0.00046 mole) of **2** and 0.20 g (0.001 mole) of CTTA in 20 ml of acetonitrile was heated under reflux for 3 hr (thin layer chromatography was used to monitor the reaction). The solvent was evaporated under reduced pressure and the oily residue obtained was solidified when triturated with methanol. It was recrystallized from methanol to give 0.07 g of **4**: mp 178–180°, $[\alpha]^{20}D$ +9° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.67; H, 7.79.

The residue obtained from evaporation of the mother liquor was recrystallized from methanol giving 0.06 g of **3β,19-dihydroxycarda-5,8(14),20(22)-trienolide 3-acetate (5)**: mp 226–228°, $[\alpha]^{20}D$ −68° (*c* 0.6, $CHCl_3$).

(19) K. Otto and M. Ehrenstein, *J. Org. Chem.*, **26**, 2871 (1961).

(20) For a discussion of the nmr spectra of C-19-substituted cardenolides, consult ref 1a.

(21) P. Bladon, H. B. Henbest, and G. W. Wood, *J. Chem. Soc.*, 2737 (1952).

(22) C. V. Pittman, Jr., and G. A. Olah, *J. Am. Chem. Soc.*, **87**, 2998 (1965); H. G. Richey, Jr., and J. M. Ricney, *ibid.*, **88**, 4971 (1966).

(23) E. Rabald and J. Kruas, *Z. Physiol.*, **265**, 39 (1940).

(24) C. Tamm and A. Gubler [*Helv. Chim. Acta*, **42**, 239 (1959)] obtained this material in another way.

(25) Melting points were determined with a Thomas–Hoover apparatus equipped with a corrected thermometer. Infrared spectra were obtained with a Beckman IR-8 or Perkin-Elmer 337 instrument. Microanalyses were performed by the Microanalytical Department, University of California at Berkeley. Optical rotations were obtained in a 0.5-dm tube with a Rudolph photoelectric polarimeter. Nmr spectra were obtained at a field strength of 60 Mcps on samples in deuteriochloroform solution on a Varian A-60 or A-60A instrument, using tetramethylsilane as internal standard. Peak positions of AB quartets were computed with a punch card program on a Wyle calculator. When only small amounts of sample were available, or when the sample was poorly soluble in deuteriochloroform, a Varian C-1024 computer was used for time averaging. Mass spectra were obtained on a Hitachi-Perkin-Elmer RMU-6D instrument by Morgan-Schaffer Corp., Montreal, Quebec, Canada.

Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.56; H, 7.63.

Acetylation of **5** (0.05 g) in pyridine (1.5 ml) with acetic anhydride (0.5 ml) afforded the diacetate **6**. Recrystallization from methanol gave the analytical sample: mp 146–147°, $[\alpha]^{20}D$ −134° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{27}H_{34}O_6$: C, 71.34; H, 7.54. Found: C, 71.59; H, 7.73.

3β,14β-Dihydroxy-7ξ-fluoro-19-nor-B-homocarda-5(10),20(22)-dienolide 3-Acetate (7).—A solution of 0.20 g (0.00046 mole) of **2** and 0.20 g (0.001 mole) of CTTA in 160 ml of dry methylene chloride was kept at −20° for 30 hr. The cold reaction mixture was passed directly through a column of Florisil (15 g) which was eluted with 250 ml of methylene chloride. On evaporation of the methylene chloride no residue was obtained. Further elution with ether, and ether–2% methanol gave 0.05 g of crystalline product, mp 160–175°. Recrystallization from methanol furnished the analytical sample: mp 168–170°, $[\alpha]^{20}D$ +10° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{25}H_{33}FO_5$: C, 69.42; H, 7.69. Found: C, 69.83; H, 7.61.

5β,10-Cyclo-3β,6β,14β-trihydroxycard-20(22)-enolide 3,6-Diacetate (9).—A solution of 0.10 g (0.00017 mole) of **3** and 0.12 g of sodium acetate in 5 ml of dioxane and 3 ml of water was heated under reflux for 2 hr. The solvent was concentrated under reduced pressure and water was added. A gummy residue was obtained which was extracted with ether and the ether layer was washed with water and dried (sodium sulfate). On evaporation of the ether solvent the residue was dissolved in 5 ml of pyridine and 0.1 ml of acetic anhydride was added. The solution was kept at room temperature for 24 hr. It was poured into water and the resulting precipitate was collected, washed with water, and dried. Recrystallization from acetone–petroleum ether once yielded 0.04 g of **9**, mp 185–189°. Further recrystallizations from acetone–petroleum ether gave the analytical sample: mp 187–189°, $[\alpha]^{20}D$ +35° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{27}H_{36}O_7$: C, 68.62; H, 7.68. Found: C, 68.34; H, 7.62.

3β,14β-Dihydroxy-19-oxocarda-5,20(22)-dienolide 3-*p*-Toluenesulfonate (13).—A solution of 0.20 g (0.00051 mole) of anhydrostrophanthidin **12** and 0.2 g of *p*-toluenesulfonyl chloride in 10 ml of pyridine was kept at 27° for 48 hr. The precipitate obtained after concentration under reduced pressure and addition of water was collected and washed with water. Recrystallization from acetonitrile twice gave 0.15 g of product, mp 165–170°. Further recrystallization from the same solvent gave the analytical sample: mp 170–172°, $[\alpha]^{20}D$ −121° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{30}H_{36}O_7S$: C, 66.65; H, 6.71. Found: C, 66.46; H, 6.79.

5β,10-Cyclo-3β,14β-dihydroxycarda-6,20(22)-dienolide 3-Acetate (14).—A solution of 0.25 g (0.0004 mole) of **3** in 10 ml of pyridine was heated under reflux for 2 hr and concentrated under reduced pressure. It was diluted with water and the resulting precipitate was collected and recrystallized from acetonitrile to give 0.12 g of product, mp 220–225°. Further recrystallization from the same solvent gave the analytical sample: mp 224–226°, $[\alpha]^{19}D$ +117° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.90; H, 7.72.

3-Oxo-5β,14β,19-trihydroxycard-20(22)-enolide 19-Triphenylmethyl Ether (15).—A solution of 2.00 g (0.002 mole) of strophanthiodol[23] (**11**) and 3.00 g of chlorotriphenylmethane (0.01 mole) in 40 ml of pyridine was kept at 60° for 24 hr. The solvent was concentrated under reduced pressure, and the residue was poured into water. The resulting precipitate was filtered and washed with water and dried. Without purification it was dissolved in 100 ml of acetone and was oxidized with excess Jones reagent, at 27° for 30 min. The excess chromic acid was decomposed with 2-propanol and the solvent was removed under reduced pressure. The residue was filtered, washed with water, and dried. It was triturated with ether and the insoluble residue was recrystallized from ethyl acetate to give 0.50 g of product, mp 268–270°. The combined ether solution was cooled whereupon an additional 0.30 g of product was recovered. Further recrystallizations from ethyl acetate gave the analytical sample: mp 270–272°, $[\alpha]^{20}D$ −11° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{42}H_{46}O_6$: C, 77.98; H, 7.17. Found: C, 77.71; H, 7.07.

14β,19-Dihydroxy-3-oxocarda-4,20(22)-dienolide (16).—A solution of 0.40 g of **15** in 40 ml of 3% methanolic hydrochloric acid solution and 1 ml of water was heated under reflux for 30 min. The reaction mixture was cooled, water was added, and the resulting precipitate was filtered and discarded (triphenylcarbinol). The filtrate was neutralized with sodium bicarbonate and was extracted with ethyl acetate. After evaporation of the solvent, the residue was recrystallized twice from ethyl acetate to give 0.10 g of product: mp 240–245°, $[\alpha]^{20}D$ +90° (*c* 0.6, methanol) [lit.[24] mp 232–240°, $[\alpha]^{20}D$ +83° ($CHCl_3$)].

Action of CTTA on 16.—A solution of 0.20 g (0.0005 mole) of **16** and 0.20 g (0.001 mole) of CTTA was stirred at 27° for 24 hr. On evaporation of the solvent an oily residue was obtained. The nmr spectrum showed a 1:1 mixture. Preparative thin layer chromatography was used to separate the mixture affording 0.03 g of **8β,19-epoxy-3-oxo-14ξ-carda-4,20(22)-dienolide (17)**, mp 210–215°. Recrystallizations from acetone gave the analytical sample: mp 215–217°, $[\alpha]^{20}D$ −57° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 75.23; H, 7.71.

In a second fraction, 0.02 g of **19-hydroxy-3-oxocarda-4,8(14),-20(22)-trienolide (18)**, mp 202–207°, was obtained. Recrystallization from methanol gave the analytical sample: mp 204–205°, $[\alpha]^{20}D$ −51° (*c* 0.5, $CHCl_3$).

Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.69; H, 7.81.

Registry No.—**1**, 10406-97-0; **2**, 4939-01-9; **3**, 4742-29-4; **4**, 10407-00-8; **5**, 10407-01-9; **6**, 10407-02-0; **7**, 10407-03-1; **9**, 10407-04-2; **13**, 10421-78-0; **14**, 4618-83-1; **15**, 10407-06-4; **16**, 3566-40-3; **17**, 10407-08-6; **18**, 10407-09-7.