Steroids and related products. XXV.[1] Cardiotonic steroids. II.[2] The synthesis of 17β-substituted 14(15)-unsaturated steroids of the A/B-cis series. Part I[3]

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The synthesis, from smilagenin, progesterone, and pregnenolone, of Δ^{14}-3β-hydroxy-5β-etienic acid and some of its ester derivatives, as well as of β-anhydrodigitoxigenin acetate, is described. Since these 14-unsaturated products have served as starting materials for our previously published syntheses of 3β,14β-dihydroxy-5β-etianic acid and of digitoxigenin, the present work establishes that these 17β-substituted 14β-hydroxylated products are available from readily accessible materials and that the syntheses of these 14β-hydroxylated products must be regarded, from a formal point of view, as total syntheses. We have thus elaborated a general pathway from common steroids—also available by total synthesis—to 14β-hydroxylated derivatives, in particular to steroid cardiotonics.

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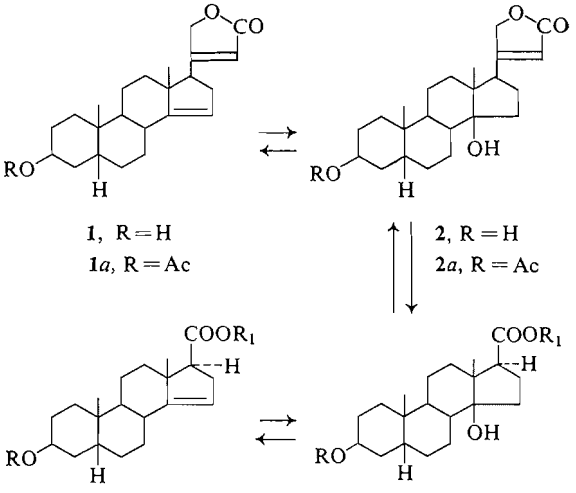
It is well known that one of the major problems of the synthesis of cardiotonic steroids is that of the preparation of 14β-hydroxylated products with a 17β-side chain—an arrangement which is thermodynamically not favored. Whereas another important problem of cardiotonic synthesis, the elaboration of a butenolide ring system attached to position 17 had been solved in various ways and for some time,[4] and whereas Sondheimer and his collaborators (4) had more recently succeeded in solving the delicate problem of elaborating the butenolide structure of cardenolides in the presence of a labile 14β-hydroxyl group, without epimerization in position 17, no general and truly useful method for the introduction of the 14β-hydroxy function into 17β-substituted steroids was known until the development of such a procedure in our laboratory (2).[5] It is well known that the previously described method (7) is lengthy, that its yields are unsatisfactory, and that it cannot be applied to the introduction of a 14β-hydroxy function into a steroid already bearing a 17β-butenolide or α-pyrone substituent.

In our general method for the introduction of the 14β-hydroxy group into 17β-substituted steroids, 14,15-unsaturated products serve as starting materials. In our previous paper on cardiotonic steroids (2), we described, as examples of our procedure, the synthesis of digitoxigenin (**2**) from β-anhydrodigitoxigenin acetate (**1***a*), and of methyl 3β-acetoxy-14β-hydroxy-5β-etianate (**4***c*) —which can be converted by Sondheimer's method (4) to digitoxigenin (**2**)—from methyl $\Delta^{14(15)}$-3β-acetoxy-5β-etianate (**3***c*). The 14-unsaturated products which we had used as the



1, R = H
1*a*, R = Ac
2, R = H
2*a*, R = Ac

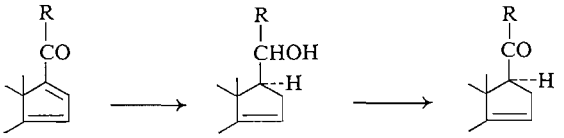
3, R = R₁ = H
3*a*, R = Ac, R₁ = H
3*b*, R = H, R₁ = CH_3
3*c*, R = Ac, R₁ = CH_3

4, R = R₁ = H
4*a*, R = Ac, R₁ = H
4*b*, R = H, R₁ = CH_3
4*c*, R = Ac, R₁ = CH_3

[1]For the previous paper of this series see ref. 1.
[2]For the communication: "Cardiotonic Steroids. I", see ref. 2.
[3]The results reported in this paper are part of the D.Sc. thesis of G. Bach, accepted by the School of Graduate Studies of Laval University, in September 1965; they were presented at the 49th Annual Conference of the Chemical Institute of Canada, in Saskatoon, June 1966.
[4]For general literature references concerning syntheses in the field of cardiotonics we refer to the quotations contained in ref. 2 of this paper. Very recently, Ferland *et al.* (3) have reported a new and interesting approach to the construction of the butenolide ring of cardenolides.
[5]The first report on this procedure and on our synthesis of digitoxigenin was given at the 46th Annual Conference of the Chemical Institute of Canada, June 1963 (compare ref. 5). The synthesis of periplogenin by Deghenghi *et al.* (6), also started from a 14-unsaturated steroid with a 17β-side chain.

starting materials had been prepared previously from natural cardiotonics (8, 9) and we indicated in our publication (2), in a summary fashion, possible pathways to these products from abundant steroids. In the present paper, we wish to report in detail their synthesis from such readily available steroids as pregnenolone (**9**), progesterone (**10**), and smilagenin (**5**), products which themselves are available also by total synthesis.

Although a number of routes to the desired 14-unsaturated steroids can be envisaged, we limit ourselves in this paper to the description of syntheses using for the introduction of the unsaturation in positions-14,15 the general method elaborated by Heusser and his collaborators (10) in which a 14,16-dien-20-one of type *i* is converted by dissolving metal reduction to a 14-unsaturated 20-alcohol, or a mixture of epimeric 14-unsaturated 20-alcohols of type *ii*, which is then reoxidized to a 14-unsaturated 20-ketone of type *iii*.



i *ii* *iii*

We chose for our first synthesis of β-anhydrodigitogenin (**1**) a pathway in which the other 14-unsaturated steroids which we wished to synthesize—Δ^{14}-3β-acetoxy-5β-etianic acid (**3***a*) and its methyl ester **3***c*—could be used as intermediates. At a later date we shall describe a more direct route.

Since $\Delta^{14,16}$-diunsaturated 20-ketones of type *i* are conveniently prepared from the corresponding 16-mono-unsaturated 20-ketones (see below), Δ^{16}-3β-acetoxy-5β-pregnen-20-one (**6***a*) seemed a logical intermediate in the proposed synthesis. In one series of experiments we prepared this product in 61% yield from smilagenin (**5**) by the use of Marker's sapogenin degradation procedure (11), as modified by Dr. M. E. Wall.[6] In this procedure, as in one published earlier by Hewett (12), methylamine hydrochloride is used as catalyst for the preparation of the pseudosapogenin.[7] In another series of experiments, we prepared the 16-unsaturated 20-ketone **6***a* in 81% yield from 3β-acetoxy-5β-pregnan-20-one (**7***a*) by bromination with *N*-bromosuccinimide (14, *cf.* also 15, 16) and dehydrobromination of the resulting 17α-bromide **8**[8] with lithium chloride in dimethylformamide (17, cf. also 16).

The 3β-acetoxy-5β-pregnan-20-one (**7***a*) used in this reaction was synthesized from Δ^5-pregnenolone (**9**) and progesterone (**10**). We transformed the 20-ethylene ketal **9***b* of pregnenolone (18) by Oppenauer oxidation with tertiary aluminium butylate and cyclohexanone to the 20-ethylene ketal **10***a* of progesterone (18). Reduction with palladium on calcium carbonate gave in 93% yield the 20-ethylene ketal **12***a* of 5β-pregnane-3,20-dione, which can be readily converted to the free 3,20-dione **12**. The reduction with the same reagents of free progesterone (**10**) was less stereoselective: the 5β-pregnane-3,20-dione (**12**) could be isolated only in 65% yield and 16% of the pure 5α-isomer **11** was obtained.

Since in our hands—in contrast to an earlier report by Butenandt and Müller (19)—the catalytic reduction of 3-ketones of the 5β-series led, even in acid media, predominantly to the equatorial 3α-alcohols (20), we investigated in one series the deliberate formation of the 3α-alcohol and its "inversion", *via* its tosylate, to the 3β-alcohol.

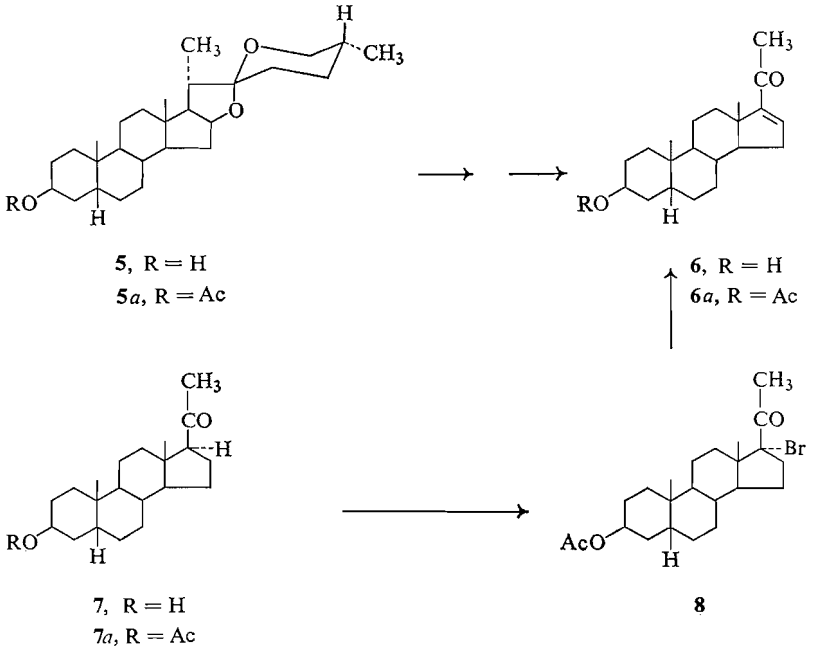
Lithium aluminium hydride reduction of the keto acetal **12***a* gave indeed in 74% yield the 3α-hydroxy 20-ketal **14** and in less than 10% yield the 3β-epimer **13**. Also, the formation of the tosylate **14***a* was almost quantitative but treatment of this product with dimethyl formamide (21), followed by saponification of the intermediate formate with methanolic potassium hydroxide, gave the desired 3β-hydroxy-5β-pregnan-20-one (**7**) in only 18% yield; the 3α-hydroxy derivative **15** was isolated in 13% yield. The deketalization had occurred during the formylation reaction.

The application of Djerassi's method (22) for

[6]We express our sincerest thanks to Dr. M. E. Wall for very kindly communicating the details of the procedure to us, and also for providing us with smilagenin.

[7]Recently, Pettit and Piatak (13) reported the degradation of smilagenin, using one of Dr. Wall's earlier methods (11*f*), but without recording the yields.

[8]It is known that a free-radical bromination of a 20-ketone affords the same stereoisomer as an acid-catalyzed bromination (cf. ref. 16, p. 706, and the references quoted in that publication).

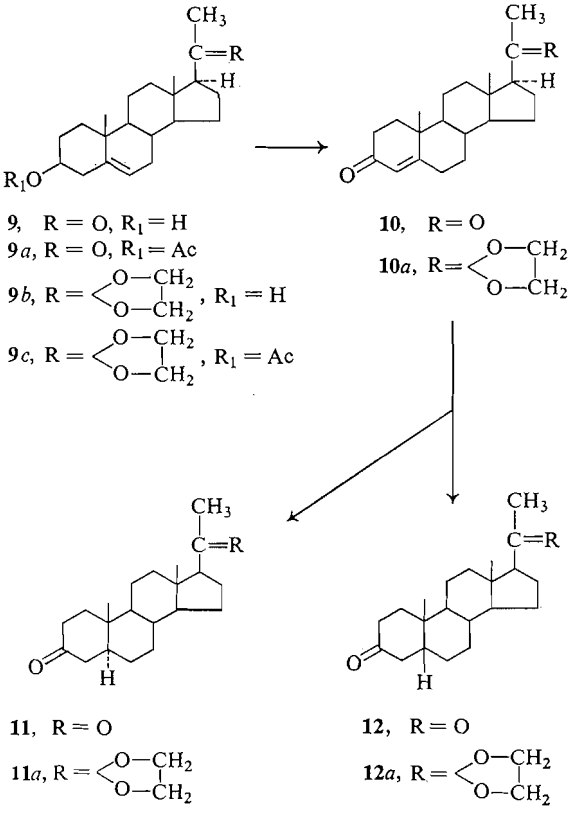


5, R = H
5*a*, R = Ac

6, R = H
6*a*, R = Ac

7, R = H
7*a*, R = Ac

8



9, R = O, R_1 = H
9*a*, R = O, R_1 = Ac
9*b*, R = ethylenedioxy, R_1 = H
9*c*, R = ethylenedioxy, R_1 = Ac

10, R = O
10*a*, R = ethylenedioxy

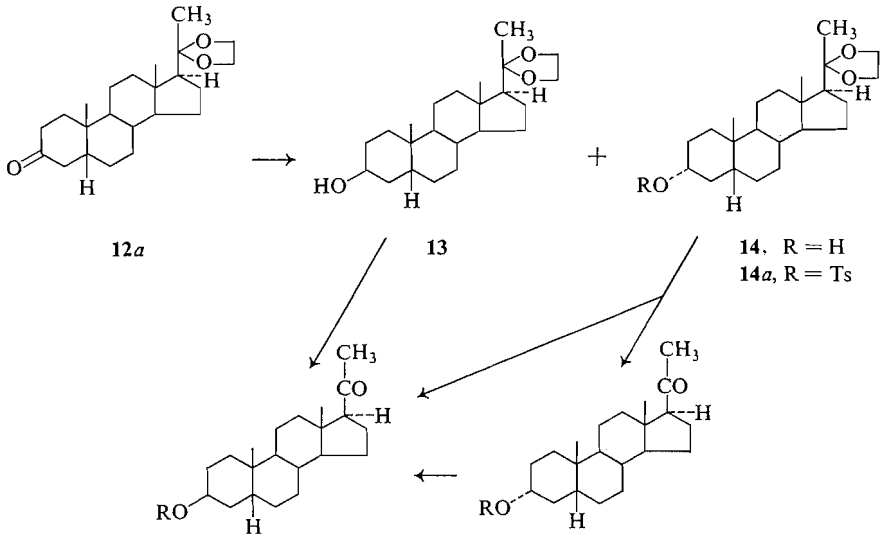
11, R = O
11*a*, R = ethylenedioxy

12, R = O
12*a*, R = ethylenedioxy

the preferential reduction of steroid ketones to axial alcohols with aged Raney nickel (cf. also 23) to the reduction of the 20-ketal **12***a* represented an improvement, but in that case the equatorial alcohol (**14**) still predominated: it was obtained in 62% yield while the 3β-alcohol **13** could be isolated only in 32% yield.

The most satisfactory results were obtained by the use of a method developed in our laboratory (24), by which the axial 3β-alcohols of the 5β-pregnane series are obtained as the major reaction products from the corresponding 3-keto derivatives by a Meerwein–Pondorf reduction, the salient feature of the procedure being the limitation of the reaction time to very short periods. The reaction of the ethylenedioxy ketone **12***a* with *sec*-butanol and aluminium *t*-butoxide for 20 min gave, after deketalization with acetone and *p*-toluenesulfonic acid (25), the desired 3β-hydroxy-5β-pregnan-20-one (**7**) in 52% yield and its epimer **15** in 40% yield. A single recyclization of the still ketalized 3α-hydroxy derivative (**14**) by oxidation with Jones' reagent (26) and another Meerwein–Pondorf reduction raises the yield of the 3β-epimer to 75%.[9]

[9]This experiment was carried out in collaboration with Mr. R. Bouchard of this laboratory.



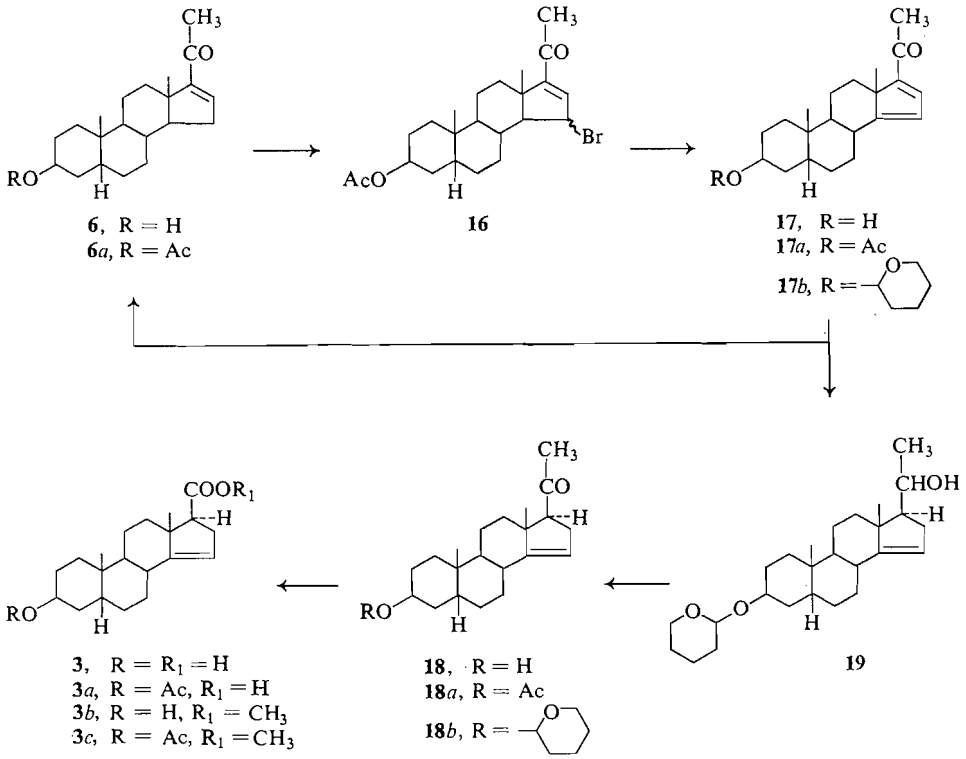
For the reduction of 5β-pregnane-3,20-dione (**12**), unprotected in position-20, this method can, of course, not be used. In this case the best method remained reduction with Raney nickel which gave a 39% yield of the desired 3β-hydroxy derivative **7** and a 32% yield of its epimer **15**.[10]

We have thus prepared, as well from smilagenin (**5**) as from pregnenolone (**9**) and progesterone (**10**), the 16-unsaturated ketone ***6a*** which had now to be transformed into a 14,16-dien-20-one and hence to a 14-mono-unsaturated 20-oxygenated derivative. For the introduction of the unsaturation in position-14, we followed essentially the general pathway elaborated by Ruzicka, Plattner, Heusser, and their co-workers (27–30), which consists in allylic bromination with *N*-bromosuccinimide and dehydrobromination of the mixture of allylic bromides (compare **16**) (cf. also 31) which contains, as already pointed out by the Swiss authors, some dienone (compare ***17a***). The dehydrobromination was performed in our case with dimethyl formamide and lithium chloride (17). As already observed by the Swiss workers (cf. 29, 30, and also 32), the isolation of pure pregnadienones of type ***17a*** presents considerable difficulties because of the contamination of the products with starting material and secondary reaction products (cf. 31). Very recently, Pettit and Piatak (13) prepared the dienone ***17a*** from the mono-unsaturated ketone, following also essentially the method of the Swiss workers but using sodium iodide in acetone for the dehydrobromination reaction; they were able to isolate the pure product only in minute yields (approximately 5%), after complicated, lengthy, and from a preparative point of view, not satisfactory purification procedures. We found that the dienone could be isolated advantageously in the form of the free hydroxydienone **17**, which we used, as will be shown, in any event for the following reactions and which was obtained by treatment of the crude reaction product with methanolic perchloric acid (33).[11] However, we found it more useful not to purify the hydroxy dienone at all and to subject the crude product to the following reduction.

We obtained the best results in the preferential reduction of the 16-double bond of the 14,16-

[10]It may be noted that the inversion of the 3α-hydroxy 20-ketone **15** to the 3β-hydroxy ketone **7** *via* the tosylate ***15a*** and the formate ***7b*** proceeded in a somewhat better yield (29%) than the analogous series of reactions applied to the ethylenedioxy derivative **14**; this sequence of reactions is, however, still less attractive than the Raney nickel reduction.

[11]Although this compound was, according to spectral analysis, free from the mono-unsaturated starting material, the results of its microanalysis did not reach our usual standards.

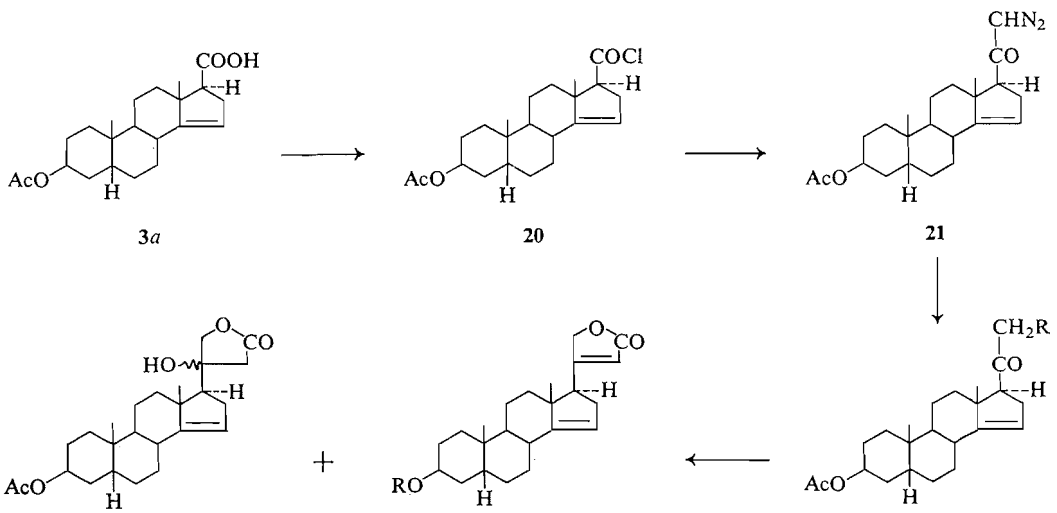


dien-20-one system with sodium and *n*-propanol, as recommended by Heusser *et al.* (10). Since the reaction results also in the reduction of the 20-keto group and would be accompanied by hydrolysis of an ester group in position-3, the 3-hydroxy group of the free dienone **17** was protected prior to reduction by the formation (in 97% yield) of the tetrahydropyranyl ether **17***b* (cf. 34–38, in particular 36), so that the reduction product (**19**) could be re-oxidized with Jones' reagent (26) to the keto ether **18***b*, which gave with *p*-toluenesulfonic acid in ethanol (34) Δ^{14}-3β-hydroxy-5β-pregnen-20-one (**18**). The yield from the hydroxydienone **17** amounted to 31% and the yield from the 16-unsaturated ketone **6** to 8%. As intimated, a considerable improvement in yields was achieved when none of the intermediates between the Δ^{16}-3β-hydroxy-5β-pregnen-20-one (**6**) and the Δ^{14}-3β-hydroxy-5β-pregnen-20-one (**18**) was purified; thus, the total yield of compound **18** from ketone **6** was raised from 8 to 33%.

We also investigated the Birch reduction of the hydroxydienone **17** with lithium in liquid ammonia, in the absence of an alcohol, but in the presence of ammonium chloride as a proton source. Using such a system, described by Stork and co-workers (39), Schaub and Weiss (40) had reduced 6-dehydrotestosterone to the 5-mono-unsaturated 3-ketone, whereas the Birch reduction of this product under classical conditions (lithium in liquid ammonia in the presence of ether and ethanol) gives the α,β-unsaturated Δ^4-3-ketone (41). We considered that in our case the reduction under Schaub's conditions could possibly lead also to the γ,δ-unsaturated Δ^{14}-20-ketone **18**. This was indeed the case[12] but the product could be obtained only in 26% yield and was accompanied by unreacted starting material (**17**) and by a further product which was not completely purified but to which we may assign, according to its spectral characteristics, the structure of the α,β-unsaturated Δ^{16}-20-ketone **6**.[13]

[12]Ether was used as solvent, as described by Barton (42).

[13]The structure of the mono-unsaturated ketone **18** thus prepared was not only confirmed by its comparison with the product obtained by reduction with sodium and *n*-propanol but also by its transformation into authentic methyl Δ^{14}-3β-hydroxy-5β-etianate (**3***b*) obtained from digitoxigenin (**2**) (see below).



The transformation of the 14-unsaturated 20-ketone **18** to Δ^{14}-3β-hydroxy-5β-etienic acid (**3**), and its ester derivatives and thence to β-anhydrodigitoxigenin (**1**), followed classical lines. A haloform degradation of the 3-acetylated 20-ketone **18***a*, according to the procedure of Djerassi and Staunton (43), gave in approximately 85% yield the desired 14-unsaturated 3β-hydroxy acid **3** which was readily acetylated to the acetoxy acid **3***a* (cf. 43), and methylated with diazomethane to the methyl ester **3***b*, which in turn gave under the usual conditions the acetoxy ester **3***c*. The structure of ester **3***c* was not only confirmed by microanalysis, the determination of the usual physical constants, and by ultraviolet and infrared spectroscopy, but also by comparison with an authentic sample prepared from natural digitoxigenin (**2**)[14]. For that purpose, digitoxigenin acetate (**2***a*) was transformed in 85% yield, according to Reichstein's method (44), by ozonolysis and hydrolysis of the resulting glyoxylic ester, into the 21-hydroxy 20-ketone and thence by periodic acid degradation, followed by methylation, to the 14β-hydroxyetianate **4***c* which was dehydrated in 85% yield with thionyl chloride, using Darzens' method (45, compare also 8*d*), to methyl Δ^{14}-3β-acetoxy-5β-etienate (**3***c*) (9). This product proved in every respect identical with the one prepared from smilagenin (**5**), progesterone (**10**), and pregnenolone (**9**), as described above.

The conversion of the 14-unsaturated etioester **3***c* to the 3β,14β-dihydroxyetianic acid **4** and its ester derivatives **4***a–c* was previously described by us (2). The conversion of methyl ester **4***c* to digitoxigenin was reported, as already mentioned, by Sondheimer and his collaborators (4).

For the transformation of the 14-unsaturated acid **3** into β-anhydrodigitoxigenin (**1**) we prepared, according to Reichstein's modification (46) of the method of Adams–Wilds (47), from the acetoxy acid **3***a* the acid chloride **20** which we converted with diazomethane to the diazoketone **21**. In one series of experiments the crude diazoketone was directly transformed into the 21-acetoxy derivative **23***b* with acetic acid (cf. 47*b*, 48, 49), in another, *via* the chloride **23** and the iodide **23***a*, prepared according to the experimental conditions usually employed in this laboratory (50), the replacement of the iodine substituent by an acetoxy group being carried out with potassium bicarbonate and glacial acetic acid (51). The yields of both pathways amounted to 68%, calculated from acid **3***a*. Finally, the diacetoxy ketone **23***b* was subjected to the classical Reformatsky reaction (cf. 52, 53); this led in 26% yield to the desired β-anhydrodigitoxigenin acetate (**1***a*) (8), accompanied by a secondary reaction product which was not fur-

[14]We sincerely thank Dr. J. Renz from Sandoz S.A., Basle, for kindly providing us with this valuable material.

ther investigated but which probably represents the 20-hydroxycardenolide **22**. The structure of β-anhydrodigitoxigenin acetate (**1***a*) was established by the determination of the usual physical constants, microanalysis, ultraviolet and infrared spectroscopy, and by comparison with an authentic sample prepared by dehydration with thionyl chloride in pyridine (45, 8*d*) of digitoxigenin acetate (**2***a*) from natural sources.

This synthesis of the 14-unsaturated 5β-etienic acid **3** and of the 14-unsaturated cardadienolide **1***a* from smilagenin (**5**), progesterone (**10**), and pregnenolone (**9**), establishes the accessibility from readily available materials of 3β,14β-dihydroxyetianic acid and digitoxigenin—previously synthesized in our laboratory from the 14-unsaturated precursors (2). Furthermore, our previously described syntheses of the 14β-hydroxylated products can now be considered to represent—from a formal point of view—total syntheses.

Experimental[15–17]

3β-Hydroxy-20-ethylenedioxy-5-pregnene (9b)

(a) From Pregnenolone Acetate (9a)

Following the procedure of Allen *et al.* (54), 5.003 g of 3β-acetoxy-5-pregnen-20-one (**9***a*) was heated for 8 h at reduced pressure (2–3 mm Hg) with 202 mg of *p*-toluenesulfonic acid in 210 ml of ethylene glycol until 85 ml of the solvent was removed by distillation. The usual working-up gave 5.589 g (99.5% yield) of crystalline *3β-acetoxy-20-ethylenedioxy-5-pregnene* (**9***c*), m.p. 153–156°. One recrystallization from methanol gave 4.85 g (86.3%) of pure ketal **9***c*. The identity of this product with an authentic sample, previously prepared in this laboratory (16), was established by the determination of a mixture melting point and the comparison of the infrared spectra.

The solution of the product in 853 ml of methanol was refluxed for 4 h with a solution of 20.5 g of potassium carbonate in 153 ml of water. After cooling, the product was poured into 800 ml of cold water and the mixture was extracted with ether. The organic solution was washed with water and dried over sodium sulfate. Removal of the solvent gave 4.431 g of an amorphous residue which gave, upon crystallization from methanol, 4.337 g (99.8% yield) of *3β-hydroxy-20-ethylenedioxy-5-pregnene* (**9***b*), m.p. 165–167° [lit. (18), m.p. 163–166°]. The identity with an authentic sample previously prepared in this laboratory was established by the determination of a mixture melting point and the comparison of the infrared spectra.

(b) From Pregnenolone (9)

A quantity of 999 mg of 3β-hydroxy-5-pregnen-20-one (**9**) was added to 45 ml of freshly distilled ethylene glycol, containing 40 mg of *p*-toluenesulfonic acid. From this mixture ethylene glycol was removed by slow distillation in the course of 8 h under a vacuum of 0.5–1 mm Hg, the temperature of the oil bath being maintained at approximately 80°. Agitation was provided with a magnetic stirrer. After cooling, the reaction mixture was poured into 700 ml of a saturated potassium bicarbonate solution at 0°. The crystalline precipitate was filtered and the filtrate was washed with water until neutral and dried. Thus there was obtained 1.16 g (quantitative yield) of 3β-hydroxy-20-ethylenedioxy-5-pregnene (**9***b*), m.p. 160–163°. The product was purified by chromatography on aluminium oxide to give 918 mg (80%) of pure ketal **9***b*, eluted with a benzene–ether mixture (9:1), m.p. 163–166°, and 52 mg (4.5%) of a product of lesser purity, eluted with a benzene–ether mixture (4:1), m.p. 158–161°. The material was found in every respect identical to the one described under *(a)*.

20-Ethylenedioxy-4-pregnen-3-one (10a)

A mixture of 46.845 g of 3β-hydroxy-20-ethylenedioxy-5-pregnene (**9***b*), m.p. 158–163°, 47.164 g of aluminium *t*-butylate and 115 ml of absolute cyclohexanone in 910 ml of absolute benzene was refluxed for 18 h with exclusion of moisture. After cooling, the product was extracted with ether and the organic phase was washed with a cold dilute sulfuric acid solution, with an iced potassium bicarbonate solution, and with water and was dried over sodium sulfate. Removal of the solvent left 123.466 g of an amorphous residue which was chromatographed on 1.82 kg of aluminium oxide. Elutions with petroleum ether – benzene mixtures (9:1, 4:1, and 1:1), with pure benzene and with a (9:1) benzene–ether mixture gave 37.271 g (80% yield) of *20-ethylenedioxy-4-pregnen-3-one* (**10***a*), m.p. 170–192°. Recrystallization from methanol gave 28.141 g (60.3% yield) of the pure progesterone ketal **10***a*, m.p. 187–192.5° [lit. (18), m.p. 189–190°]. A sample was recrystallized twice from methanol and once from ether–hexane for analysis; m.p. 194.5–195°; $[\alpha]_D^{22}$ +112.6° (*c*, 1.000 in $CHCl_3$).

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.14; H, 9.52.

20-Ethylenedioxy-5β-pregnan-3-one (12a)

A quantity of 26.32 g of 20-ethylenedioxy-4-pregnen-3-one (**10***a*), m.p. 187–194°, was dissolved in 1.644 l of dioxane and 1.25 l of ethanol and hydrogenated at atmospheric pressure with 2.362 g of a 4% palladium on calcium carbonate catalyst in the presence of 4.73 g of potassium hydroxide in 5 ml of water. Within 40 min, 1.8 l of hydrogen was taken up (theoretical quantity: 1.79 l). The catalyst was removed by filtration and washed with methylene chloride. The filtrate and the washings were combined and reduced *in vacuo* and the product was precipitated in ice water. The organic material was extracted with ether, the ethereal solution was washed with water and dried over sodium sulfate. The evaporation of the solvent left 26.43 g of a crystalline product, m.p. 162–165°. Recrystallization from methylene chloride – hexane

[15]The melting points were taken in evacuated capillaries and the temperatures were corrected.

[16]If not otherwise stated, Woelm's non-alkaline aluminium oxide, activity III, and Davison's silica gel No. 923 were used for chromatography.

[17]The microanalyses were performed by Dr. C. Daesslé, Montreal, and Mr. A. Bernhardt, Max Planck Institute for Coal Research, in Mülheim, Germany. We express to them and their associates our sincere appreciation.

gave 25.26 g (95.4% yield) of *20-ethylenedioxy-5β-pregnan-3-one* (**12***a*), m.p. 168–173°, and 996 mg of the same substance of lesser purity, melting between 154 and 158° (total yield 99.1%). A sample was recrystallized twice from methylene chloride – hexane for analysis; m.p. 172.5–173°; $[\alpha]_D^{27}$ +37.1° (*c* 1.124 in $CHCl_3$) [lit. (55), m.p. 169.8–172.8°; $[\alpha]_D$+32.0°]; ν_{max} (KBr) 1722 cm^{-1} (3-ketone), 1069 and 1052 cm^{-1} (ketal doublet).

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.81; H, 10.12.

5β-Pregnane-3,20-dione (12)

A quantity of 1 g of progesterone (**10**), m.p. 127.5–128°, was dissolved in 110 ml of dioxane and 100 ml of ethanol and hydrogenated at atmospheric pressure with 100 mg of a 4% palladium on calcium carbonate catalyst, in the presence of 150 mg of potassium hydroxide in 0.4 ml of water. After 25 min, 76 ml of hydrogen was taken up (theoretical quantity: 77 ml). The catalyst was removed by filtration and washed with methylene chloride. The filtrate was combined with the washings and concentrated at reduced pressure. The mixture was poured into ice water and the precipitate was extracted with ether. The organic solution was washed with water and dried over sodium sulfate. The evaporation of the solvent gave 1.01 g of a partly crystalline product which was chromatographed on 30 g of aluminium oxide. Elutions with petroleum ether and with mixtures of petroleum ether – benzene (4:1 and 1:1) gave a crystalline material which was recrystallized from acetone – hexane. Thus there was obtained 645 mg of *5β-pregnane-3,20-dione* (**12**), m.p. 112–116° (64.1% yield). A sample was recrystallized 3 times from acetone–hexane for analysis; m.p. 118–119° [lit. (56*a*), 123°, (56*b*), 120–122°]; $[\alpha]_D^{26}$ +118° (*c*, 1.063 in $CHCl_3$) [lit. (56*b*), 111°]; ν_{max} (KBr) 1722 cm^{-1} (3-ketone), 1705 cm^{-1} (shoulder, 20-ketone).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.98; H, 10.19. Found: C, 79.73; H, 10.09.

Two of the first petroleum ether chromatogram fractions gave by recrystallization from acetone–hexane 160 mg (16%) of *5α-pregnane-3,20-dione* (**11**), m.p. 194–198°; a sample was recrystallized from acetone–hexane for analysis; m.p. 197–198° [lit. 200.5° (57*a*), 203–205° (57*b*)]; $[\alpha]_D^{28}$ +121° (*c*, 1.038 in $CHCl_3$) [lit. 126.9° (57*a*), 108.5 ± 4° (57*b*), 121° (57*c*)]; ν_{max} (KBr) 1719 cm^{-1} (3-ketone), 1700 cm^{-1} (shoulder, 20-ketone).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.98; H, 10.19. Found: C, 79.91; H, 10.15.

Reduction of 20-Ethylenedioxy-5β-pregnan-3-one (12a) with Lithium Aluminium Hydride

In the course of 30 min, a solution of 15.2 g of 20-ethylenedioxy-5β-pregnan-3-one (**12***a*), m.p. 168–173°, in 500 ml of tetrahydrofuran, was added with stirring to a suspension of 17.2 g of lithium aluminium hydride in 1.25 l of tetrahydrofuran. The mixture was refluxed with stirring for 1 h and then left for 16 h at room temperature. The excess reagent was decomposed in the cold with 80 ml of ethyl acetate and with ice and there was added 20 ml of a 10% ammonium chloride solution. The mixture was extracted with ether, the organic phase was washed with a dilute ammonium chloride solution and with water, and was dried over sodium sulfate. The evaporation of the solvent gave 15 g of an amorphous product. Crystallization from methanol yielded 6.8 g (44.5%) of *3α-hydroxy-20-ethylenedioxy-5β-pregnane* (**14**), m.p. 146–147°. A sample was recrystallized twice from methanol for analysis; needles, m.p. 150–151° [lit. 147–149° (55), 149–151° (58)]; $[\alpha]_D^{22}$ +27.0° (*c*, 1.04 in $CHCl_3$) [lit. (55), +28.5°]; ν_{max} (KBr) 3300 cm^{-1} (3α-hydroxyl), 1069 cm^{-1} (doublet), and 1046 cm^{-1} (large band) (ethylenedioxy bands).

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.14; H, 10.48.

The mother liquors (8.2 g) of the crystallization which had yielded the 3α-hydroxy ketal **14** were chromatographed on 225 g of aluminium oxide. Elutions with petroleum ether – benzene (4:1) gave 975 mg (6.4%) of *3β-hydroxy-20-ethylenedioxy-5β-pregnane* (**13**), m.p. 149–157°. A sample was recrystallized twice from methanol for analysis; colorless plates; m.p. 160–161°; $[\alpha]_D^{22}$ +58° (*c*, 1.00 in $CHCl_3$); ν_{max} (KBr) 3420 cm^{-1} (3β-hydroxyl), 1049, and 1035 cm^{-1} (doublet, ethylenedioxy absorption).

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.34; H, 10.47.

Further elutions in the above-described chromatogram with pure benzene and with a benzene – ether mixture (9:1) gave another 4.52 g (29.6%) of the 3α-hydroxy ketal **14**, m.p. 137–150° (total yield of the 3α-hydroxy derivative **14**: 74%).

Reduction of 20-Ethylenedioxy-5β-pregnan-3-one (12a) with Raney Nickel

(a) A quantity of 1 g of 20-ethylenedioxy-5β-pregnan-3-one (**12***a*), m.p. 164–165°, was dissolved in 150 ml of dioxan and reduced at atmospheric pressure with hydrogen in the presence of 5 g of three-year-old "sponge nickel catalyst" from Davison & Co., for a period of 20 h. The catalyst was removed by filtration and was washed with methylene chloride. Evaporation of the solvent from the filtrate and the washings gave 1.01 g of an amorphous reaction product which was chromatographed on 30 g of aluminium oxide. The first fractions, eluted with pure petroleum ether and with a petroleum ether – benzene mixture (9:1), gave 245 mg of starting material **12***a*, m.p. 164–172°. The following fractions, eluted with petroleum ether – benzene mixtures (9:1, 4:1, and 1:1), gave 244 mg of *3β-hydroxy-20-ethylenedioxy-5β-pregnane* (**13**), m.p. 145–156° (32.2% yield). The product was identified by comparison with an authentic sample (see above) through a mixture melting point determination and infrared analysis.

Further elutions with petroleum ether – benzene (1:1 and 1:4) gave 475 mg of *3α-hydroxy-20-ethylenedioxy-5β-pregnane* (**14**), m.p. 144–148° (62.2% yield). The product was identified by comparison with an authentic sample (see above) through a mixture melting point determination and infrared analysis.

(*b*) In another experiment, 6.6 g of the keto ketal **12***a* was reduced under the conditions described under (*a*) for 2 h. No starting material was isolated. The yield of the 3β-hydroxy ketal **13**, m.p. 141–158°, was 2.017 g (30.4%), that of the 3α-hydroxy epimer **14**, m.p. 133–148°, 4.5 g (67.8%).

(*c*) In a third experiment, 1 g of the keto ketal **12***a* was reduced with Raney nickel, freshly prepared from a nickel–aluminium alloy. The reduction time was 1 h. Chromatography of the reaction product afforded 187

mg (18.7%) of 3β-hydroxy-20-ethylenedioxy-5β-pregnane (**13**), m.p. 146–154°, and 769 mg (76.8%) of the 3α-hydroxy derivative **14**, m.p. 144–148°.

Reduction of 5β-Pregnane-3,20-dione (12) with Raney Nickel

A quantity of 450 mg of 5β-pregnane-3,20-dione (**12**), m.p. 113–115°, was dissolved in 75 ml of dioxane and hydrogenated at atmospheric pressure in the presence of 2.5 g of aged Raney nickel (see above). After 11 min, 35 ml of hydrogen was absorbed (theoretical quantity: 34.7 ml). The product was worked up as described before in the case of the reduction of the keto ketal **12***a*. The crude product (460 mg) was amorphous and was chromatographed on 15 g of aluminium oxide. The first fractions eluted with pure petroleum ether and with petroleum ether – benzene mixtures (9:1 and 4:1) gave 254 mg (56.6%) of starting material **12**, m.p. 109–119°. The following fractions, eluted with a petroleum ether – benzene mixture (1:1), gave 112 mg of a crystalline product, m.p. 108–139°. Recrystallization from ether–hexane and rechromatography of the mother liquors gave 60 mg (30.5%) of *3β-hydroxy-5β-pregnan-20-one* (**7**), m.p. 132–135°, as well as 16 mg of the same product of lesser purity, m.p. 110–116° (total yield: 38.6%). Three recrystallizations for analysis from ether–hexane gave fine needles, m.p. 143–143.5° [lit. (19), 142–143°]; $[\alpha]_D^{24}$ +100.6° (*c* 0.976 in $CHCl_3$) [lit. (19), 101° (EtOH)]; ν_{max} (KBr) 3350 cm^{-1} (3β-hydroxyl), 1707 cm^{-1} (20-ketone), 1031 cm^{-1} (alcohol).

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.15; H, 10.63.

Further elutions in the first chromatogram described above (which had yielded the crude 3β-hydroxy 20-ketone **7**) with pure benzene and with a mixture of benzene and ether (4:1) gave 63 mg (32%) of *3α-hydroxy-5β-pregnan-20-one* (**15**), m.p. 135–149°. A sample was recrystallized from dichloromethane–hexane for analysis; needles, m.p. 150–151° [lit. (19), 148–149°]; $[\alpha]_D^{23}$ +104.6° (*c* 1.000 in $CHCl_3$) [lit. (57*b*), +109.5° ±4°]; ν_{max} (KBr) 3380 cm^{-1} (3α-hydroxyl), 1706 cm^{-1} (20-ketone), 1038 cm^{-1} (hydroxyl).

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.22; H, 10.77.

3α-Hydroxy-5β-pregnan-20-one (15) from 3α-Hydroxy-20-ethylenedioxy-5β-pregnane (14)

A solution of 520 mg of 3α-hydroxy-20-ethylenedioxy-5β-pregnane (**14**), m.p. 136–138°, and of 60 mg of *p*-toluenesulfonic acid in 50 ml of absolute acetone was kept at room temperature for 48 h. The mixture was poured into ice water and the precipitate was extracted with ether. The organic phase was washed with water and dried over sodium sulfate. The evaporation of the solvent gave 450 mg of crystalline *3α-hydroxy-5β-pregnan-20-one* (**15**), m.p. 146–148° (98.6% yield). The identity of the product with an authentic sample (see above) was established by the determination of a mixture melting point and the comparison of the infrared spectra.

3β-Hydroxy-5β-pregnan-20-one (7) from 3β-Hydroxy-20-ethylenedioxy-5β-pregnane (13)

A quantity of 9.9 g of 3β-hydroxy-20-ethylenedioxy-5β-pregnane (**13**), m.p. 155–161°, was treated with 1 l of absolute acetone and 1.24 g of *p*-toluenesulfonic acid and the reaction mixture was worked up as described above for the analogous reaction of the 3α-hydroxy derivative (**14**). The crude crystalline 3β-hydroxy-5β-pregnan-20-one (**7**), m.p. 135–137°, was obtained in 98% yield (8.45 g). Recrystallization from ether gave the following batches of pure product: 3.39 g, m.p. 143–143.5°; 2.809 g, m.p. 142–143°; 1.421 g, m.p. 141–142°; and 236 mg, m.p. 140–141° (yield of purified product: 90%). The identity of the product with the one prepared from 5β-pregnane-3,20-dione (**12**) (see above) was established by the determination of a mixture melting point and by infrared analysis.

3β-Hydroxy-5β-pregnan-20-one (7) from 3α-Hydroxy-20-ethylenedioxy-5β-pregnane (14)

A solution of 1.5 g of 3α-hydroxy-20-ethylenedioxy-5β-pregnane (**14**), m.p. 150–151°, in 25 ml of pyridine was treated for 20 h with 1.6 g of *p*-toluenesulfonyl chloride which had previously been dissolved in 6.4 ml of pyridine. The mixture was poured into ice water and the precipitate was extracted with ether. The ethereal solution was washed with water, iced dilute hydrochloric acid, a cold sodium bicarbonate solution, and with water and was dried over sodium sulfate. Evaporation of the solvent gave 2.13 g (99.6%) of *3α-tosyloxy-20-ethylenedioxy-5β-pregnane* (**14***a*), m.p. 160–161°. A sample was recrystallized five times from methylene chloride – ether for analysis; needles, m.p. 162.5–163°, $[\alpha]_D^{25}$ +37.7° (*c* 0.937 in $CHCl_3$); λ_{max} (EtOH) 200 mμ (log ε 3.88), 224 mμ (log ε 4.05), 262 mμ (log ε 2.84); ν_{max} (KBr) 1600 cm^{-1} (aromatic substituent), 1054 and 1034 cm^{-1} (ketal).

Anal. Calcd. for $C_{30}H_{44}O_5S$: C, 69.73; H, 8.58; S, 6.21. Found: C, 69.92; H, 8.63; S, 6.44.

A portion of 1.48 g of the above-described 3α-tosyloxy-20-ethylenedioxy-5β-pregnane (**14***a*), m.p. 158–161°, was dissolved in 86 ml of dimethyl formamide and the solution was refluxed for 105 h, cooled and poured into ice water. The precipitate was extracted with ether and the ethereal solution was washed with water and dried over sodium sulfate. Removal of the solvent gave 1.02 g of crude amorphous *3β-formoxy-5β-pregnan-20-one* (**7***b*), ν_{max} ($CHCl_3$) 1720 cm^{-1} (shoulder) (formate), 1708 cm^{-1} (20-ketone), 1198 cm^{-1} (large band) (formate); this product showed in the ultraviolet no maximum in the region of 222–230 mμ typical of a tosylate function (59). This crude product was treated for 24 h with a solution of 9 g of potassium hydroxide in 175 ml of methanol and 2 ml of water. The solution was concentrated under reduced pressure and poured into ice water. The ethereal extract was washed with water and dried over sodium sulfate. Evaporation of the solvent gave 900 mg of an oil, ν_{max} ($CHCl_3$) 3420 cm^{-1} (large band) (hydroxyl), 1708 cm^{-1} (20-ketone), 1670 cm^{-1} (weak absorption) (double bond), 1032 cm^{-1} (hydroxyl). The product was chromatographed on 28 g of aluminium oxide. Elutions with petroleum ether gave 345 mg of a crystalline unsaturated material, m.p. 114–128°, ν_{max} (KBr) 1707 cm^{-1} (20-ketone), 1672 cm^{-1} (double bond); this material, the formation of which must be due to an elimination reaction, was not further investigated. Elutions with petroleum ether – benzene (1:1) gave 168 mg (18.4%) of *3β-hydroxy-5β-pregnan-20-one* (**7**), m.p. 127–139°. Recrystallization from ether–hexane raised the melting point to 143–143.5°. The identification of the material with an authentic

product, the preparation of which was described above, was effected by a mixture melting point determination and by infrared analysis.

Further elutions in the above-described chromatogram with pure benzene and with a benzene–ether mixture (4:1) gave 122 mg (13.4%) of *3α-hydroxy-5β-pregnan-20-one* (**15**), m.p. 127–138°. Recrystallization from dichloromethane–hexane raised the melting point to 150–151°. The product was identified by a mixture melting point determination and by infrared analysis with authentic material, the preparation of which was described above.

3β-Hydroxy-5β-pregnan-20-one (7) from 3α-Hydroxy-5β-pregnan-20-one (15)

To a solution of 450 mg of 3α-hydroxy-5β-pregnan-20-one (**15**), m.p. 146–148°, in 4.5 ml of pyridine was added 480 mg of *p*-toluenesulfonyl chloride in 2 ml of pyridine and the mixture was stored for 20 h at room temperature, cooled and poured into ice water. Extraction with ether and the usual working-up (see above) gave 670 mg of a partly crystalline product which was recrystallized from methylene chloride – ether to give 528 mg (79.2%) of *3α-tosyloxy-5β-pregnan-20-one* (**15***a*), m.p. 143–151°; recrystallization of the mother liquors gave another 82 mg of the same product of lesser purity, m.p. 137–138° (total yield: 91.3%). A sample was recrystallized 3 times from methylene chloride – ether for analysis; fine needles, m.p. 154–154.5°; $[\alpha]_D^{24}$ +100.1° (*c*, 0.950 in $CHCl_3$); λ_{max} (EtOH) 206 mμ (log ε 3.88), 224 mμ (log ε 4.07), 262 mμ (log ε 2.80); ν_{max} (KBr) 1700 cm^{-1} (20-ketone), 1600 cm^{-1} (aromatic absorption).

Anal. Calcd. for $C_{28}H_{44}O_5S$: C, 71.15; H, 8.53; S, 6.78. Found: C, 71.07; H, 8.47; S, 6.62.

A portion of 450 mg of the above-described 3α-tosyloxy-5β-pregnan-20-one (**15***a*), m.p. 143–151°, was dissolved in 26 ml of dimethyl formamide. The solution was refluxed for four days, cooled and poured into ice water. Extraction with ether and the usual working-up (see above) gave 310 mg of an amorphous product which yielded upon crystallization from methanol–hexane 133 mg (40.3%) of *3β-formoxy-5β-pregnan-20-one* (7*b*), m.p. 107–114°. A sample was recrystallized twice from methanol–hexane for analysis; prisms, m.p. 126–126.5°; $[\alpha]_D^{24}$ +104.1° (*c* 1.038 in $CHCl_3$); ν_{max} (KBr) 1730 cm^{-1} (formate), 1708 cm^{-1} (shoulder) (20-ketone), 1119 cm^{-1} (formate). The product showed no ultraviolet maximum between 222–230 mμ.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.38; H, 9.77.

The filtration of the mother liquors (160 mg) from the crystallization of the formate **7***b* through an aluminium oxide column with an ether–hexane mixture gave 31 mg (10.2%) of *3α-hydroxy-5β-pregnan-20-one* (**15**), m.p. 142–143°, identified by a mixture melting point determination with an authentic sample and by infrared analysis.

A portion of 118 mg of the above-described formate **7***b*, m.p. 107–114°, and of 132 mg of mother liquors representing the same formate, were treated for 16 h at room temperature with 2.5 g of potassium hydroxide in 50 ml of methanol and 2 ml of water. The usual working-up (see above) gave 222 mg of an oil; ν_{max} ($CHCl_3$) 3600 cm^{-1} (sharp band) and 3400 cm^{-1} (wide band) (hydroxyl), 1704 cm^{-1} (20-ketone), 1030 cm^{-1} (hydroxyl). This product was chromatographed on 8 g of aluminium oxide. Elutions with petroleum ether gave 46 mg of the dehydration product, crystallizing in prisms, m.p. 119–128°; ν_{max} (KBr) 2970 cm^{-1} (vinylic hydrogens), 1699 cm^{-1} (20-ketone), 1658 cm^{-1} (double bond), 679 and 665 cm^{-1} (vinylic hydrogen doublet). Elutions with petroleum ether – benzene (9:1, 4:1, and 1:1) gave 93 mg (30.7%) of *3β-hydroxy-5β-pregnan-20-one* (7), m.p. 130–141°, identified by a mixture melting point determination with an authentic sample and by infrared analysis. Elutions with a benzene–ether mixture (4:1) gave 10 mg (3.3%) of *3α-hydroxy-5β-pregnan-20-one* (**15**), m.p. 142–146°, identified in the usual way by comparison with an authentic sample. Taking into account the recovery of starting material, the yield of 3β-hydroxy-5β-pregnan-20-one (**7**) from 3α-hydroxy-5β-pregnan-20-one (**15**) amounted to 22.7%.

3β-Hydroxy-5β-pregnan-20-one (7) by Meerwein–Pondorf Reduction of 20-Ethylenedioxy-5β-pregnan-3-one (12a) and Subsequent Deketalization

To a solution of 136 mg of 20-ethylenedioxy-5β-pregnan-3-one (**12***a*) in 0.75 ml of absolute benzene, 3.8 ml of *sec*-butyl alcohol and 136 mg of aluminium *t*-butylate were added at room temperature. The mixture was refluxed for 20 min and during that time 0.5 ml of absolute benzene was added. Subsequently the product was poured into ice water and the precipitate was extracted with a (3:1) ether – methylene chloride mixture. The organic solution was washed with an iced ammonium chloride solution and was dried over sodium sulfate. Removal of the solvent gave a crystalline product (146 mg), representing a crude mixture of *3β-hydroxy-20-ethylenedioxy-5β-pregnane* (**13**) and of *3α-hydroxy-20-ethylenedioxy-5β-pregnane* (**14**) which was dissolved in 15 ml of absolute acetone. The solution was treated with 18 mg of *p*-toluenesulfonic acid at room temperature for 48 h and poured into ice water. The precipitate was extracted with ether, the ethereal solution was washed with water and dried over sodium sulfate. The removal of the solvent gave 148 mg of a partly crystalline product which was chromatographed on 9 g of aluminium oxide. Elutions with petroleum ether – benzene mixtures (4:1 and 1:1) gave 58 mg (53%) of *3β-hydroxy-5β-pregnan-20-one* (7), m.p. 143.5–144.5°, identified by infrared analysis and by a mixture melting point determination with an authentic sample. Elutions with a (1:4) petroleum ether – benzene mixture, pure benzene, and a (4:1) benzene – ether mixture gave 49 mg (45% yield) of *3α-hydroxy-5β-pregnan-20-one* (**15**), m.p. 146–147°, identified by spectral analysis and by the determination of a mixture melting point with an authentic sample.

17α-Bromo-3β-acetoxy-5β-pregnan-20-one (8)

A quantity of 7.8 g of 3β-hydroxy-5β-pregnan-20-one (7), m.p. 140–143°, was acetylated in the usual fashion, at room temperature, with 35 ml of acetic anhydride in 70 ml of pyridine. The usual working-up gave 8.788 g (99.4%) of crystalline *3β-acetoxy-5β-pregnan-20-one* (7*a*), m.p. 114.5–115°. Two recrystallizations from ether–hexane raised the melting point of the crystalline pellets to 116–117° [lit. (19), 116.5°]; $[\alpha]_D^{24}$ +79.2° (*c*, 0.963 in $CHCl_3$), [lit. (19), +68° (EtOH)]; ν_{max} (KBr) 1743 cm^{-1} (acetate), 1704 cm^{-1} (20-ketone), 1251 and 1230 cm^{-1} (acetate).

A portion of 6.9 g of the above-described 3β-acetoxy-5β-pregnan-20-one (7*a*), m.p. 114–115°, was dissolved in

70 ml of absolute carbon tetrachloride. To this solution was added under vigorous stirring and at reflux temperature 4.25 g of *N*-bromosuccinimide and the mixture was irradiated for 8 min with a 660 W lamp. As the reaction proceeded, the bromosuccinimide at the bottom of the flask disappeared and a light flocculating material was raised to the surface of the yellow solution. The cooled solution was filtered, the precipitate was rinsed with carbon tetrachloride, and the combined solutions were washed with a dilute sodium bisulfite solution and with water, and dried over sodium sulfate. Evaporation of the solvent at reduced pressure gave 8.41 g of foamy material, representing crude *17α-bromo-3β-acetoxy-5β-pregnan-20-one* (**8**), ν_{max} (KBr) 1742 cm^{-1} (acetate), 1706 cm^{-1} (20-ketone), 1251 and 1236 cm^{-1} (acetate), 670 cm^{-1} (17α-bromine substituent). A sample of the crude product was analyzed for bromine.

Anal. Calcd. for $C_{23}H_{35}O_3Br$: Br, 18.19. Found: Br, 18.57.

Crystallization of the crude product from ether–hexane gave 7.668 g (91% yield) of crystalline *17α-bromo-3β-acetoxy-5β-pregnan-20-one* (**8**), m.p. (decomp.) 144–157°. A sample was recrystallized twice from ether–hexane for analysis; prisms, m.p. (decomp.) 158–159°, $[\alpha]_D^{24}$ −46.7° (*c*, 1.200 in $CHCl_3$); ν_{max} (KBr) 1745 cm^{-1} (acetate), 1708 cm^{-1} (20-ketone), 1251 and 1239 cm^{-1} (acetate).

Anal. Calcd. for $C_{23}H_{35}O_3Br$: C, 62.86; H, 8.03; Br, 18.19. Found: C, 62.57; H, 7.97; Br, 18.33.

Δ^{16}-3β-Acetoxy-5β-pregnen-20-one (6a)

(a) From 17α-Bromo-3β-acetoxy-5β-pregnan-20-one (8)

A solution of 2.06 g of 17α-bromo-3β-acetoxy-5β-pregnan-20-one (**8**), m.p. (decomp.) 155–157°, and of 420 mg of lithium chloride in 520 ml of dimethyl formamide was refluxed in a nitrogen atmosphere for 1 h. The mixture was cooled and poured into ice water and the precipitate was extracted with ether. The ethereal solution was washed with an iced dilute hydrochloric acid solution, with a cold sodium bicarbonate solution, and with water and was dried over sodium sulfate. Evaporation of the solvent gave 1.68 g of *Δ^{16}-3β-acetoxy-5β-pregnen-20-one* (*6a*), m.p. 135–136° (quantitative yield). One recrystallization from ether–hexane gave 1.405 g (88%) of pure Δ^{16}-pregnenolone acetate (*6a*), m.p. 136–141°. A sample was recrystallized twice from ether–hexane for analysis; prisms, m.p. 144–144.5°, $[\alpha]_D^{22}$ −48.6° (*c*, 1.000 in $CHCl_3$); λ_{max} (EtOH) 239 mμ (log ε 3.97); ν_{max} (KBr) 3010 cm^{-1} (vinylic hydrogen), 1740 cm^{-1} (acetate), 1658 and 1583 cm^{-1} (Δ^{16}-20-keto doublet), 1252 and 1231 cm^{-1} (acetate).

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.32; H, 9.40.

(b) From Smilagenin Acetate (5a)[18]

To a warm solution of 25 g of smilagenin acetate (25-iso-sarsasapogenin acetate) (*5a*), m.p. 136–142°, in 50 ml of acetic anhydride and 25 ml of pyridine, 8.5 g of methylamine hydrochloride was added, the mixture was refluxed for 2 h, cooled, and poured into ice water. The precipitate was extracted with methylene chloride, the organic solution was washed with water and dried over sodium sulfate. Removal of the solvent at reduced pressure gave 25.6 g of *pseudosmilagenin acetate* which was used without further purification. The product was dissolved in 125 ml of acetic acid and 125 ml of dichloroethane and cooled to −8°. There was added, under vigorous stirring, a cold solution of 12.5 g of chromic acid in 125 ml of acetic acid. Subsequently, there was added slowly to the stirred mixture, at −5°, a solution of 12.5 g of sodium metabisulfite in 38 ml of water. The product was extracted with ether and the organic phase was washed with cold water, an iced sodium bicarbonate solution and with water and was dried over sodium sulfate. Evaporation of the solvent at reduced pressure gave 24.8 g of *3β-acetoxy-16β-hydroxy-5β-pregnan-20-one 16-(δ-acetoxy-γ-methylvalerate)* in the crude state. This product was dissolved in 150 ml of glacial acetic acid and the solution was refluxed for 2 h, cooled, and poured into ice water. The precipitate was extracted with methylene chloride, the organic solution was washed with an iced sodium bicarbonate solution and with water, and was dried over sodium sulfate. The removal of the solvent left 26.2 g of an amorphous product which was chromatographed on 700 g of aluminium oxide. Elutions with petroleum ether and with petroleum ether – benzene mixtures (9:1 and 4:1) gave 12.6 g (64.4%) of *Δ^{16}-3β-acetoxy-5β-pregnen-20-one* (*6a*), m.p. 121–138°. Recrystallization from ether–hexane gave 11.883 g (60.7%) of the pure pregnenolone acetate *6a*, m.p. 139–140°, the identity of which with the product prepared as described under (*a*) was established by the determination of a mixture melting point and by the comparison of the infrared spectra.

$\Delta^{14,16}$-3β-Hydroxy-5β-pregnadien-20-one (17)

A quantity of 5.4 g of Δ^{16}-3β-acetoxy-5β-pregnen-20-one (*6a*), m.p. 137–140°, was brominated in 54 ml of carbon tetrachloride with 3.24 g of *N*-bromosuccinimide as described above for the preparation of the 17-bromide **8**. The usual working-up (see above) gave 6.66 g of an amorphous product, representing crude *Δ^{16}-3β-acetoxy-15ξ-bromo-5β-pregnen-20-one* (**16**); λ_{max} (EtOH) 237 mμ (log ε 3.61), 308 mμ (log ε 2.96); ν_{max} (KBr) 1740 cm^{-1} (acetate), 1678 cm^{-1} (γ-halogenated α,β-unsaturated 20-ketone), 1655 cm^{-1} (α,β,γ,δ-unsaturated 20-ketone), 1585 and 1525 cm^{-1} (weak bands due to the presence of diene **17***a*), 1251 and 1235 cm^{-1} (acetate). A sample of the crude product was analyzed for its bromine contents.

Anal. Calcd. for $C_{23}H_{33}O_3Br$: Br, 18.27. Found: Br, 18.37.

The majority of the crude product (6.63 g) which, according to the spectral data, already contained some diene **17***a*, was dissolved with 1.32 g of lithium chloride in 1.5 l of dimethylformamide and dehydrobrominated as described above for the preparation of the pregnenolone acetate *6a*. There was obtained 5.1 g of a product which, according to the ultraviolet spectrum, represented an approximate (2:3) mixture of the unsaturated bromoketone **16** and the dienone **17***a*; λ_{max} (EtOH) 238 mμ (log ε 3.6), 308 mμ (log ε 3.8); ν_{max} (KBr) 3040 cm^{-1} (shoulder, vinylic hydrogen), 1742 cm^{-1} (acetate), 1670 cm^{-1} (α,β-unsaturated 20-ketone), 1653 cm^{-1}(α,β,γ, δ di-unsaturated 20-ketone), 1590 and 1530 cm^{-1} (weak band) (conjugated double bond), 1252 and 1234 cm^{-1} (acetate). The isolation of pure $\Delta^{14,16}$-3β-acetoxy-5β-pregnadien-20-one

[18]According to a procedure kindly provided by Dr. M. E. Wall.

(**17***a*) by chromatography on aluminium oxide was unsuccessful. The purest fractions obtained, eluted with petroleum ether – benzene (1:1) (459 mg), m.p. 116–119°, still contained some mono-unsaturated product (approximately 10%); λ_{max} (EtOH) 237 mμ (log ε 2.9), 308 mμ (log ε 4.1); ν_{max} (KBr) 3040 cm^{-1} (vinylic hydrogen), 1741 cm^{-1} (acetate), 1642 cm^{-1} (14,16-di-unsaturated 20-ketone), 1526 cm^{-1} (conjugated double bond), 1252 and 1238 cm^{-1} (acetate). No further purification could be achieved by crystallization and sublimation under high vacuum.

A portion of 5.05 g of crude dehydrobromination product was dissolved in 800 ml of methanol containing 2.5% of perchloric acid. The solution was kept for 22 h at room temperature and poured into ice water. The precipitate was extracted with ether, the ethereal solution was washed with a saturated sodium bicarbonate solution and with water, and was dried over sodium sulfate. Removal of the solvent left 4.5 g of an amorphous product which was absorbed on 290 g of aluminium oxide. Elutions with a petroleum ether – benzene mixture (1:1) gave 924 mg of crystalline material, m.p. 135–139°, still containing 30% of mono-unsaturated product, 720 mg of material melting between 142 and 150°, containing approximately 20% of mono-unsaturated material, and 1.205 g melting between 150 and 163°, containing approximately 10% of mono-unsaturated product. Recrystallization of the various fractions in methanol–hexane gave 1.255 g of $\Delta^{14,16}$-3β-*hydroxy-5β-pregnadien-20-one* (**17**), m.p. 152–160°, the ultraviolet spectrum of which showed no mono-unsaturated product (yield from pregnenolone acetate **6***a*: 23.4%). A sample was recrystallized four times from methanol–hexane and sublimed twice in high *vacuo* at 105–110°; pellets, m.p. 173–174°; $[\alpha]_D^{21}$ +453° (*c*, 1.010 in $CHCl_3$); λ_{max} (EtOH) 308 mμ (log ε 4.04); ν_{max} (KBr) 3440 cm^{-1} (hydroxyl), 3040 cm^{-1} (vinylic hydrogen), 1630 and 1523 cm^{-1} ($\Delta^{14,16}$-20-keto doublet), 1034 cm^{-1} (hydroxyl).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.98; H, 9.16.[19]

For the following reaction, crystalline material melting between 152 and 161° was used.

*Δ^{14}-3β-Hydroxy-5β-pregnen-20-one (**18**)*

*(a) From $\Delta^{14,16}$-3β-Hydroxy-5β-pregnadien-20-one (**17**) by Reduction with Lithium and Ammonia*

In the course of 4 min, a solution of 100 mg of $\Delta^{14,16}$-3β-hydroxy-5β-pregnadien-20-one (**17**), m.p. 158–161°, in 6.7 ml of absolute ether was added to a well-stirred solution of 100 mg of lithium and 50 ml of ammonia at −70°. After a further 4 min of stirring, the dark-blue color started to fade and 500 mg of ammonium chloride was added which resulted in complete discoloration. In the course of 3.6 h, the ammonia was evaporated in a nitrogen current and the volume of the liquid was maintained by addition of absolute ether. The mixture was poured into ice water and the precipitate was extracted with ether. The ethereal solution was washed with water and dried over sodium sulfate. Evaporation of the solvent gave 99 mg of an amorphous product which was chromatographed on 4 g of aluminium oxide. The petroleum ether – benzene fractions (4:1 and 1:1) gave 26 mg of Δ^{14}-3β-*hydroxy-5β-pregnen-20-one* (**18**), m.p. 140–159° (25.8% yield). The product was recrystallized three times from ether–hexane for analysis; needles, m.p. 164–164.5°; $[\alpha]_D^{26}$ +66.5° (*c*, 1.000 in $CHCl_3$); λ_{max} (cyclohexane) 194 mμ (log ε 2.17); ν_{max} (KBr) 3485 cm^{-1} (hydroxyl), 3040 cm^{-1} (vinylic hydrogen), 1702 cm^{-1} (20-ketone), 1649 cm^{-1} (double bond), 1135 cm^{-1} (hydroxyl).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.64; H, 10.19. Found: C, 79.46; H, 10.02.

Elutions with petroleum ether – benzene (1:1) gave 10 mg of $\Delta^{14,16}$-3β-*hydroxy-5β-pregnadien-20-one* (**17**), m.p. 151–154°, identified by a mixture melting point, and thin-layer, ultraviolet, and infrared analyses. Taking the recovery of this material into consideration, the yield of the Δ^{14}-pregnenolone **18** amounted to 28.7%.

Benzene and a benzene–ether mixture (4:1) eluted 40 mg of a partly crystalline product, m.p. 148–167°; λ_{max} (EtOH) 231 mμ (log ε ~ 4); ν_{max} (KBr) 3480 cm^{-1} (hydroxyl), 1685 and 1610 cm^{-1} (α,β-unsaturated keto doublet). This product was not further investigated.

*(b) From $\Delta^{14,16}$-3β-Hydroxy-5β-pregnadien-20-one (**17**) by Reduction with Sodium and n-Propanol and Subsequent Oxidation*

From a solution of 800 mg of $\Delta^{14,16}$-3β-hydroxy-5β-pregnadien-20-one (**17**), m.p. 152–160°, in 50 ml of absolute benzene and 1.68 ml of dihydropyran, 25 ml of benzene was removed by distillation, and 32 mg of *p*-toluenesulfonic acid was added at room temperature. After 3.5 days, the mixture was poured into ice water and the precipitate was extracted with ether. The organic phase was washed with a saturated sodium bicarbonate solution and with water, and was dried over sodium sulfate. Evaporation of the solvent gave 1.06 g of an amorphous product which was chromatographed on 50 g of aluminium oxide. Elutions with petroleum ether and with petroleum ether – benzene mixtures (9:1 and 4:1) gave 987 mg (97.4%) of $\Delta^{14,16}$-3β-*(2′-tetrahydropyranyloxy)-5β-pregnadien-20-one* (**17***b*), m.p. 110–132°; λ_{max} (EtOH) 309 mμ (log ε 4.13); ν_{max} (KBr) 3040 cm^{-1} (vinylic hydrogen), 1644 and 1521 cm^{-1} ($\Delta^{14,16}$-20-keto doublet), 1129, 1110, 1015, and 990 cm^{-1} (tetrahydropyranyl ether). This product was employed without further purification in the next step.

A portion of 480 mg of the crude $\Delta^{14,16}$-di-unsaturated tetrahydropyranyl ether **17***b*, m.p. 114–136°, was dissolved in 100 ml of absolute *n*-propanol. At reflux temperature, in the course of 30 min, 1.5 g of metallic sodium was added portionwise to this solution; after 1 h, the sodium was completely dissolved. The crude mixture was diluted with water and neutralized with a 2 *N* hydrochloric acid solution, concentrated at reduced pressure and extracted with ether. The ethereal solution was washed with a sodium bicarbonate solution and with water, and was dried over sodium sulfate. Removal of the solvent gave 500 mg of amorphous Δ^{14}-3β-*(2′-tetrahydropyranyloxy)-20ξ-hydroxy-5β-pregnene* (**19**); ν_{max} ($CHCl_3$) 3620, 3470 cm^{-1} (20-hydroxyl), 3040 cm^{-1} (vinylic hydrogen), 1652 cm^{-1} (double bond), 1131, 1111, 1021, and 997 cm^{-1} (tetrahydropyranyl ether). This product was used without further purification in the next step.

The 14-unsaturated 20-hydroxy ether **19** (500 mg) was dissolved in 50 ml of absolute acetone and the solution

[19]No better analytical results could be obtained.

was cooled to 0°. To this solution was added 0.5 ml of Jones' reagent, prepared by dissolving 267 g of chromic acid in 230 ml of concentrated sulfuric acid and 770 ml of water. After 8 min, the product was poured into ice water and extracted with ether. The organic solution was washed with a saturated sodium bicarbonate solution and with water, and dried over sodium sulfate. The removal of the solvent left 505 mg of an amorphous product, representing crude Δ^{14}-*3β-(2'-tetrahydropyranyloxy)-5β-pregnen-20-one* (**18***b*); ν_{max} (CCl_4) 3040 cm^{-1} (vinylic hydrogen), 1712 cm^{-1} (20-ketone), 1651 cm^{-1} (double bond), 1132, 1112, 1022, and 998 cm^{-1} (tetrahydropyranyl ether). This product was used without purification in the next step.

A portion of 500 mg of the above-described Δ^{14}-pregnenolone ether **18***b* was dissolved in 5 ml of ethanol and heated at reflux temperature for 1 h with 29 mg of *p*-toluenesulfonic acid. The solution was concentrated to half of its volume and extracted with ether. The ethereal solution was washed with a saturated potassium bicarbonate solution and with water, and was dried over sodium sulfate. Removal of the solvent gave 376 mg of a crude product which was chromatographed on 15 g of aluminium oxide. Elutions with petroleum ether – benzene (3:2 and 1:1) gave 123 mg of Δ^{14}-*3β-hydroxy-5β-pregnen-20-one* (**18**), m.p. 150–158° (yield from the tetrahydropyranyloxy diene **17***b*: 32.2%). The identity of the product with the one prepared as described under (*a*) was established by the comparison of the infrared spectra and the determination of a mixture melting point.

(c) From Δ^{16}-3β-Acetoxy-5β-pregnen-20-one (6a) without Isolation of Intermediates

A quantity of 14.9 g of Δ^{16}-3β-acetoxy-5β-pregnen-20-one (**6***a*), m.p. 139–142°, was treated with 8.55 g of *N*-bromosuccinimide in 150 ml of carbon tetrachloride as described above. The amorphous halogenated reaction product (19.2 g) (compare **16**) was dissolved in 4 l of dimethylformamide and the solution was refluxed for 1 h under nitrogen with 3.85 g of lithium chloride. The usual working-up gave 12.5 g of crude dienone **17***a* which was treated for 22 h with 1.6 l of methanol and 40 ml of perchloric acid as described above. The crude reaction product (11.6 g) was filtered through a column of 350 g of aluminium oxide to yield 10.8 g of a clear oil. This product was treated for 110 h in 338 ml of benzene with 21 ml of dihydropyran and 410 mg of *p*-toluenesulfonic acid at room temperature. The resulting product was filtered through a column of 380 g of aluminium oxide and thus gave 14.5 g of crude tetrahydropyranyl ether **17***b* which was treated with 43.5 g of sodium in 2.9 l of *n*-propanol for 2.25 h, as described above. This gave 13.2 g of the crude 14-unsaturated 20-hydroxy ether **19** which was oxidized with 11.5 ml of Jones' reagent. The resulting 20-keto tetrahydropyranyl ether **18***b* (13.46 g) was dissolved in 1.35 l of ethanol and the solution was refluxed for 1 h with 758 mg of *p*-toluenesulfonic acid. The usual working-up gave 12.83 g of amorphous product which was chromatographed on 350 g of aluminium oxide. Petroleum ether – benzene mixtures (4:1 and 1:1) gave 4.371 g of Δ^{14}-*3β-hydroxy-5β-pregnen-20-one* (**18**), m.p. 138–147° (yield from the Δ^{16}-pregnenolone acetate **6***a*: 33.2%). The identity of the material with the products prepared as described under (*a*) and (*b*) was determined by infrared analysis and the determination of mixture melting points.

Δ^{14}-3β-Hydroxy-5β-etianic Acid (3) from Δ^{14}-3β-Hydroxy-5β-pregnen-20-one (18)

A quantity of 3.11 g of Δ^{14}-3β-hydroxy-5β-pregnen-20-one (**18**), m.p. 138–147°, was acetylated in the usual fashion with 18 ml of acetic anhydride in 36 ml of pyridine. Thus was obtained 3.52 g of crude Δ^{14}-*3β-acetoxy-5β-pregnen-20-one* (**18***a*); ν_{max} (CCl_4) 3040 cm^{-1} (vinylic hydrogen), 1740 cm^{-1} (acetate), 1713 cm^{-1} (20-ketone), 1651 cm^{-1} (double bond), 1246 and 1233 cm^{-1} (acetate). This product was dissolved in 130 ml of dioxane and 36.5 ml of water. To this solution was added, in the course of 45 min, with stirring, a sodium hypobromite solution prepared by adding at first 6.64 g of bromine and then 28 ml of dioxane to a cold solution of 4.85 g of sodium hydroxide in 41.6 ml of water. The reaction mixture containing the oxidizing solution and the steroid was stirred at room temperature until the yellow color disappeared, which took 3 h. A few drops of a sodium bisulfite solution was added and the mixture was acidified to pH 3 and poured into ice water. By filtration, 543 mg (17%) of Δ^{14}-*3β-hydroxy-5β-etianic acid* (**3**), m.p. 170–172°, was isolated; $[\alpha]_D^{25}$ +32.7° (*c*, 1.025 in $CHCl_3$); ν_{max} (KBr) 3400 cm^{-1} (large, associated hydroxyl band), 3025 cm^{-1} (vinylic hydrogen), 1707 cm^{-1} (carboxyl), 1646 cm^{-1} (double bond). The mother liquors were extracted with ether and the ethereal solution was washed with a dilute sodium bisulfite solution, with a dilute sulfuric acid solution and with water, and was dried over sodium sulfate. The solvent was evaporated, the residue was dissolved in a few ml of methanol and precipitated with ice water. Thus, another 2.1 g of the 3β-hydroxy Δ^{14}-acid **3**, m.p. 162–174°, was obtained (total yield: 84.4%). The product was characterized completely in the form of its 3-acetoxy methyl ester (see below).

Methyl Δ^{14}-3β-Acetoxy-5β-etianate (3c) (7a, 9, 60)

(a) From the Hydroxyetianic Acid 3 Prepared from Pregnenolone (9), Progesterone (10), and Smilagenin (5)

A quantity of 19 mg of the above-described Δ^{14}-3β-hydroxy-5β-etianic acid (**3**), m.p. 169–170°, was dissolved in 3 ml of absolute methanol and 1.5 ml of absolute ether and treated at 0° with 3.3 ml of a 0.8% ethereal diazomethane solution. After 16 h the product was worked up in the usual way and 20 mg of crude *methyl Δ^{14}-3β-hydroxy-5β-etianate* (**3***b*) was isolated. This product was dissolved without further purification in 0.2 ml of pyridine and acetylated in the usual fashion at room temperature with 0.1 ml of acetic anhydride. Thus, 22 mg of *methyl Δ^{14}-3β-acetoxy-5β-etianate* (**3***c*), m.p. 115–116°, was obtained (yield from the hydroxy acid **3**: 98.4%). A sample was recrystallized once from methanol for analysis; small plates, m.p. 126–126.5°, $[\alpha]_D^{27}$ +37.5° (*c* 1.000 in $CHCl_3$) [lit. (9), m.p. 116–119°, $[\alpha]_D^{24}$ +34.7° ±2° ($CHCl_3$)]; λ_{max} (cyclohexane) 180 mμ (log ε 2.72); ν_{max} (KBr) 3040 cm^{-1} (vinylic hydrogen), 1729 cm^{-1} (acetate), 1722 cm^{-1} (methyl ester), 1648 cm^{-1} (double bond), 1259 and 1234 cm^{-1} (acetate), 1154 cm^{-1} (methyl ester).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.82; H, 9.30.

(b) From Digitoxigenin (2)

A quantity of 1 g of digitoxigenin (**2**), m.p. 249–250°, was acetylated in the usual fashion at room temperature with 4.4 ml of acetic anhydride in 8.8 ml of pyridine. There was obtained 1.11 g (99.8%) of *digitoxigenin acetate* (**2***a*), m.p. 219–220°. One recrystallization from acetone–hexane gave 1.08 g (97.2%) of a product melting between 232 and 235°. A sample was recrystallized three times from acetone–hexane for analysis; prisms, m.p. 224–225°; $[\alpha]_D^{26}$ +21.1° (*c*, 0.991 in $CHCl_3$) [lit. (61), m.p. 222/227°; $[\alpha]_D^{17}$ +19.2°, 21.4° ($CHCl_3$)]; λ_{max} (EtOH) 216 mμ (log ε 4.05); ν_{max} (KBr) 3500 cm^{-1} (14-hydroxyl), 1780 and 1752 cm^{-1} (butenolide), 1740 cm^{-1} (acetate), 1625 cm^{-1} (20(22)-double bond), 1258 and 1238 cm^{-1} (acetate).

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.92; H, 8.85.

Through a solution of 2.2 g of digitoxigenin acetate (**2***a*), m.p. 224–226°, in 120 ml of ethyl acetate, there was passed, at −80°, in the course of 62 min, an oxygen current containing 4.5% of ozone at a rate of 71.3 ml per min. The pale-blue solution was left for 20 min at −80°. The solvent was removed at reduced pressure and the residue dissolved in 18 ml of glacial acetic acid; zinc dust was added portionwise until the solution showed no more reaction with starch and potassium iodide. The mixture was filtered and the residue was washed with chloroform, the filtrate and washings were diluted with chloroform, washed with an iced potassium bicarbonate solution and with water, and dried over sodium sulfate. Evaporation of the solvent gave 2.7 g of amorphous *3β-acetoxy-14β-hydroxy-21-glyoxyloxy-5β-pregnan-20-one*, which was treated in 130 ml of methanol for 20 h at room temperature with a solution 1.75 g of potassium bicarbonate in 55 ml of water. After concentration, the product was extracted with a mixture of chloroform and ether (1:3). The organic solution was washed with water, dried over sodium sulfate, and taken to dryness. There was obtained 2.1 g of crude *3β-acetoxy-14β,21-dihydroxy-5β-pregnan-20-one*; ν_{max} (KBr) 3450 cm^{-1} (hydroxyls), 1742 cm^{-1} (acetate), 1718 cm^{-1} (shoulder) (20-ketone), 1259 and 1238 cm^{-1} (acetate). A quantity of 1.98 g of this product was treated at room temperature for 20 h in 56 ml of methanol with a solution of 3.3 g of periodic acid in 11.2 ml of water. The chloroform extract of the product was washed with water, an iced sodium bicarbonate solution, and with water, and was dried over sodium sulfate. Evaporation of the solvent gave 1.125 g of a *neutral product*. The bicarbonate washings were acidified with sulfuric acid and extracted with chloroform to give 880 mg of an *acid fraction*.

The *neutral fraction* was acetylated in the usual way with 5.25 ml of acetic anhydride in 10.5 ml of pyridine to give 1.064 g of an amorphous product which, upon crystallization from methylene chloride – ether, gave 259 mg of *methyl 3β-acetoxy-14β-hydroxy-5β-etianate* (**4***c*), m.p. 150–153°. The mother liquors of the crystallization were filtered through an aluminium oxide column and thus gave another 559 mg of hydroxyetianate **4***c*, m.p. 150–153° (yield of product from the neutral fraction: 41.9%). A sample was recrystallized three times from ether–hexane; m.p. 155–156°, $[\alpha]_D^{27}$ +38.0° (*c* 1.000 in $CHCl_3$) [lit. (9); m.p. 154–157°; $[\alpha]_D^{25}$ +30.7° ±2° (in $CHCl_3$)]. The product proved identical in every respect with the one prepared in this laboratory from methyl Δ^{14}-3β-acetoxy-5β-etienate (**3***c*) (2).

The *acid fraction* (880 mg) was methylated in the usual fashion in 25 ml of absolute methanol and 7 ml of absolute ether with 54 ml of a 0.7% ethereal diazomethane solution to give 850 mg (43.5%) of *methyl 3β-acetoxy-14β-hydroxy-5β-etianate* (**4***c*), m.p. 147–150° (total yield of this product from digitoxigenin acetate (**2***a*): 85.4%).

A portion of 600 mg of this product, m.p. 148–154°, was dissolved in 6 ml of absolute pyridine; the solution was cooled to 0° and there was added 0.6 ml of thionyl chloride. The mixture was sealed and left for 11 h at 0° and for 1 h at 20°, and was then poured into ice water. The precipitate was extracted with a mixture of chloroform and ether (1:3). The organic layer was washed with iced dilute hydrochloric acid, with a cold potassium bicarbonate solution and with water, and was dried over sodium sulfate. Evaporation of the solvent gave 700 mg of an amorphous product which was chromatographed on 10 g of aluminium oxide (activity II). Elutions with petroleum ether gave 492 mg of *methyl Δ^{14}-3β-acetoxy-5β-etianate* (**3***c*), m.p. 115–120° (yield from the hydroxy ester **4***c*: 85.9%). A sample was recrystallized three times from methanol; m.p. 126–126.5°. The product was found identical with that prepared as described under (*a*) by the comparison of the infrared and ultraviolet spectra and by the determination of a mixture melting point.

Δ^{14}-21-Diazo-3β-acetoxy-5β-pregnen-20-one (21)

A quantity of 810 mg of Δ^{14}-3β-hydroxy-5β-etianic acid (**3**), m.p. 170–172°, was dissolved in 4 ml of pyridine and treated for 16 h with 1.5 ml of acetic anhydride. Subsequently, 1.5 ml of water was added and the mixture was refluxed for 1 h. After cooling, 25 ml of ice water was added and the precipitate was filtered, washed with an iced dilute hydrochloric acid solution and with water, and was dried *in vacuo*. Thus, 800 mg (87.3%) of crude *Δ^{14}-3β-acetoxy-5β-etianic acid* (**3***a*), m.p. 163–164°, was obtained; ν_{max} (KBr) 3400 cm^{-1} (large, associated hydroxyl band), 1738 cm^{-1} (acetate), 1704 cm^{-1} (carboxylic acid), 1648 cm^{-1} (double bond), 1255 (shoulder) and 1234 cm^{-1} (acetate). This product was used without further purification in the following reaction.

A suspension of this product in 42 ml of absolute benzene was cooled to 5°. With repeated shaking, 5.6 ml of oxalyl chloride in 20 ml of absolute benzene was added in the course of 2 min. The mixture was shaken repeatedly and allowed to reach room temperature. After 30 min, the acid was completely dissolved. The solvent was evaporated 1.3 h after the end of the addition of the oxalyl chloride, the product was dried by being dissolved in absolute benzene and by being taken to dryness repeatedly, with exclusion of moisture. There was obtained 822 mg of partly crystalline *Δ^{14}-3β-acetoxy-5β-etianic acid chloride* (**20**), which was used without further purification in the next step.

The acid chloride **20** was dissolved in 30 ml of absolute benzene. To this solution was added at −10°, in the course of 3 min, 20 ml of a 2.9% ethereal diazomethane solution and the mixture was left at 0° for 18 h and at 25° for 25 min. The evaporation of the solvent under reduced pressure, at 22°, gave 890 mg of crude, amorphous *Δ^{14}-21-diazo-3β-acetoxy-5β-pregnen-20-one* (**21**); ν_{max} (CCl_4)

3080 cm^{-1} (vinylic hydrogen), 2100 cm^{-1} (sharp diazo band), 1742 cm^{-1} (acetate), 1650 cm^{-1} (large diazo band), 1260 and 1238 cm^{-1} (acetate). This product was used without purification in the following reaction (see below).

β-*Anhydrodigitoxigenin Acetate (1a)*

(a) From Δ^{14}*-21-Diazo-3*β*-acetoxy-5*β*-pregnen-20-one (21) through* Δ^{14}*-21-Chloro-3*β*-acetoxy-5*β*-pregnen-20-one(23) and* Δ^{14}*-3*β*,21-Diacetoxy-5*β*-pregnen-20-one (23b)*

To a solution of 890 mg of crude Δ^{14}-21-diazo-3β-acetoxy-5β-pregnen-20-one (**21**) in 30 ml of absolute benzene there was added in the course of 4 min, dropwise and with stirring, a solution of 435 mg of anhydrous hydrogen chloride in 5.5 ml of absolute ether. The mixture was stirred for another 40 min at room temperature, poured into ice water and extracted with ether. The organic solution was washed repeatedly with water and was dried over sodium sulfate. The evaporation of the solvent under reduced pressure gave 906 mg of crude, amorphous Δ^{14}*-21-chloro-3*β*-acetoxy-5*β*-pregnen-20-one* (**23**); ν_{max} (KBr) 1738 cm^{-1} (acetate), 1651 cm^{-1} (double bond), 1258 and 1234 cm^{-1} (acetate) which gave a positive Beilstein test and which was used without further purification in the next step.

A solution of the crude chloride **23** (904 mg) in 35 ml of absolute acetone was refluxed under nitrogen with 703 mg of sodium iodide for 45 min. The product was extracted with ether and the ethereal solution was washed with water, a small quantity of iced 0.8% sodium hydroxide solution, again with water, and was dried over sodium sulfate. The evaporation of the solvent gave 937 mg of an oil, representing crude Δ^{14}*-21-iodo-3*β*-acetoxy-5*β*-pregnen-20-one* (**23a**), which was dissolved in 37 ml of absolute acetone and refluxed for 12 h with 4.3 g of potassium bicarbonate in 2.4 ml of glacial acetic acid. The mixture was diluted with ice water and the precipitate was filtered, washed and dried *in vacuo* to give 809 mg of a partly crystalline product. Recrystallization from methanol gave 625 mg of crude crystalline Δ^{14}*-3*β*,21-diacetoxy-5*β*-pregnen-20-one* (**23b**), m.p. 98–106°; ν_{max} (KBr) 1745 cm^{-1} (shoulder, 20-oxo-21-acetate and 3β-acetate), 1728 cm^{-1} (21-acetoxy-20-ketone); (yield from Δ^{14}-3β-hydroxy-5β-etianic acid (**3**): 68.3%). This product which is recrystallized only with difficulty was used without further purification in the next reaction.

A portion of 495 mg of the above-described Δ^{14}-diacetoxypregnenone **23***b*, m.p. 98–106°, was dried with absolute benzene and dissolved in 15 ml of absolute benzene and 15 ml of absolute ether. There was added 1.2 g of granulated zinc, activated with iodine, and 17 ml of solvent was removed by distillation. Freshly distilled ethyl bromoacetate (1.64 ml) was added and 1 ml of solvent was again removed by distillation. The thus initiated vigorous reaction lost its intensity after 3 min and the mixture was heated to ebullition for another 15 min. Absolute dioxane (2.1 ml) was added and the mixture was heated for 30 min, cooled, and acidified with iced dilute hydrochloric acid. The product was extracted with ether, the organic layer was washed with an iced saturated potassium bicarbonate solution and with water and was dried over sodium sulfate. Evaporation of the solvent gave 850 mg of an oil which was acetylated in the usual fashion with 3 ml of acetic anhydride in 6 ml of pyridine to give 640 mg of an amorphous residue which was chromatographed on 30 g of aluminium oxide. Elutions with petroleum ether – benzene (1:1) gave 121 mg 25.5% yield from Δ^{14}-3β,21-diacetoxypregnenone **23***b* of 3β-acetoxy-5β-carda-14(15),20(22)-dienolide (β-anhydrodigitoxigenin acetate) (**1***a*), m.p. 179–185° (yield from the Δ^{14}-3β-hydroxyetianic acid **3**: 17.4%). A sample was recrystallized three times from acetone–hexane for analysis; needles, m.p. 190–192°; $[\alpha]_D^{26}$ −18.2° (*c*, 0.810 in $CHCl_3$) [lit. (8*b*, 8*c*, 62*a*, 62*b*); m.p. 185°; $[\alpha]_D$ −18° ($CHCl_3$)]; λ_{max} (EtOH) 212 mμ (log ε 4.11); ν_{max} (KBr) 1783 and 1752 cm^{-1} (butenolide), 1738 cm^{-1} (acetate), 1645 cm^{-1} (shoulder, 14-double bond), 1630 cm^{-1} (20(22)-double bond), 1250 and 1234 cm^{-1} (large acetate band).

Anal. Calcd. for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.02; H, 8.46.

Elutions in the above-mentioned chromatogram with benzene–ether (9:1) gave 100 mg (20%) of an amorphous product; ν_{max} (KBr) 3430 cm^{-1} (20-hydroxyl), 1782 cm^{-1} (γ-lactone), 1740 cm^{-1} (acetate), 1663 cm^{-1} (double bond), 1245 cm^{-1} (large acetate band), which was not further investigated but to which we assign tentatively the structure of Δ^{14}*-3*β*-acetoxy-20*ξ*-hydroxy-5*β*-cardenolide* (**22**).

(b) From Δ^{14}*-21-Diazo-3*β*-acetoxy-5*β*-pregnen-20-one (21) Directly through* Δ^{14}*-3*β*,21-Diacetoxy-5*β*-pregnen-20-one (23b)*

A solution of 1.342 g of crude Δ^{14}-21-diazo-3β-acetoxy-5β-pregnen-20-one (**21**) in 90 ml of glacial acetic acid was placed in an oil bath preheated to 135° and was heated for 10 min (total reaction time: 20 min). The acetic acid was removed *in vacuo* and the residue was dried repeatedly with absolute ethanol and absolute ether. The product, representing crude Δ^{14}*-3*β*,21-diacetoxy-5*β*-pregnen-20-one* (**23***b*), was purified as described above to give 989 mg of crystalline diacetate **23***b* (68.3%) and 88 mg (6%) of a less pure, only partly crystalline material.

Both purified fractions of the diacetate **23***b* (1.077 g) were subjected under the conditions described above to the Reformatsky reaction to give, after chromatography of the crude reaction product, 258 mg (25.7% from the diacetate **23***b*) of β-*anhydrodigitoxigenin acetate* (**1***a*), m.p. 181–184°. The identity of the product with the one described under (*a*) was established by comparison of the ultraviolet and infrared spectra and by the determination of a mixture melting point.

(c) From Digitoxigenin Acetate (2a)

To a solution of 500 mg of digitoxigenin acetate (**2***a*), m.p. 224–225°, in 5 ml of absolute pyridine, there was added at 0°, 0.5 ml of thionyl chloride and the mixture was transferred into an ampulla which was sealed. The product was kept for 16 h at 0° and for 1 h at room temperature and then poured into ice water. The precipitate was extracted with a mixture of chloroform and ether (1:3) and the organic layer was washed with cold dilute hydrochloric acid, with an iced saturated potassium bicarbonate solution, and with water and was dried over sodium sulfate. Evaporation of the solvent gave 500 mg of a product which was recrystallized from acetone–hexane to give 465 mg (97.2%) of *3*β*-acetoxy-5*β*-carda-14(15), 20-(22)-dienolide (*β*-anhydrodigitoxigenin acetate)* (**1***a*), m.p. 180–183°. Two recrystallizations from dichloromethane–

ether raised the melting point to 190–192°. The identity of this product with the materials synthesized according to (*a*) and (*b*) was established by the comparison of the infrared and ultraviolet spectra and by the determination of mixture melting points.

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