A Synthetic Approach to Some Steroidal Alkaloids

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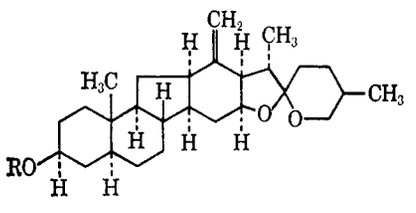
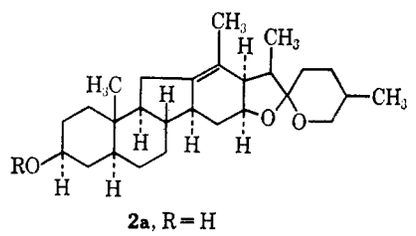
In an effort to prepare model compounds for the synthesis of cevine and veratramine, various reactions of C-nor-D-homosapogenins have been examined. The 3β-tetrahydropyranyl ether of $\Delta^{17a(18)}$-22a,5α-C-nor-D-homospirostene gave the 17aα,18 glycol with osmium tetroxide. Attempted oxidation to the hydroxy aldehyde gave only the 17α,18-nor ketone. Treatment of the $\Delta^{17a(18)}$ olefin with per acid gave a mixture of the 17aα,18- and 17aβ,18-oxides, which afforded the 18-aldehyde in low yield on rearrangement with acid. Conversion of this aldehyde into the 18-amine, *via* the oxime, and the attempted rearrangement of this amine to a pentacyclic cevine precursor are discussed. In an approach to veratramine, the aromatization of the D ring of $\Delta^{13(17a)}$-22a,5α-C-nor-D-homospirostan-3β-ol was attempted. These experiments gave either the 3-ketone or an aromatized ψ-sapogenin. The stereochemistry and spectral properties of these compounds are discussed.

The C-nor-D-homo steroids derived from hecogenin (**1a, 2a**)[3,4] appear to be readily available and attractive starting materials for the partial synthesis of alkaloids of the cevine, jervine, and veratramine groups since the spiro ketal side chain with oxygen atoms attached at C-22 and C-26 would seem to permit a relatively simple approach to the E and F rings of a cevine model or the E ring of veratramine.

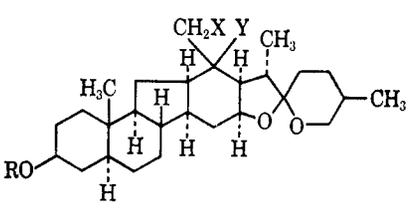


1a, R = H
b, R = C_5H_9O



2a, R = H
b, R = C_5H_9O

The initial goal in the proposed synthesis of the cevine nucleus was the conversion of exocyclic olefin **1** into a compound bearing a nitrogen atom at C-18 (**3a**). It was then planned that advantage could be taken of the "masked" carbonyl group at C-22 to form a pentacyclic Schiff base which could, hopefully, be converted into a deoxygenated cevine alkaloid derivative.



3a, X = NH_2; Y = H
b, X = OH; Y = OH; R = C_5H_9O
c, X = NH_2; Y = OH; R = C_5H_9O

Although the preparation of **1a** by the method developed by the Merck group[3a] proceeded well on a small scale, considerable difficulty was encountered in carrying out this preparation on larger quantities. Consequently, this procedure was modified by first forming the tetrahydropyranyl ether of hecogenin and reducing this to the rockogenin (12β-ol) derivative with lithium–liquid ammonia or sodium–1-propanol.[5] Conversion of rockogenin 3-tetrahydropyranyl ether into the methanesulfonate and reaction with potassium *t*-butoxide to give a mixture of **1b** and **2b** proceeded smoothly. The structure of **1b** was proven by conversion into the 3 acetate, which was identical with material prepared *via* the published procedure,[3a] whereas that of **2b** was confirmed by analysis and the similarity of the nmr spectrum to that reported for **2a**.[3b]

Attempted hydroboration of **1b** with either diborane generated *in situ*[6] or by externally generated diborane[7] gave complex mixtures of products. Although the successful hydroboration of a sapogenin has been reported,[8] repeated attempts to effect the hydroboration of this olefin gave only products in which the spiro ketal side chain has apparently been reduced.

Oxidation of **1b** with osmium tetroxide gave the 17aα,-18-diol. The stereochemistry at C-17a in this compound was tentatively assigned on the basis of a study of models of **1b**, and following the completion of our work, was confirmed by Coxon, *et al.*[9] Although analytical data (see Experimental Section) indicated that chromic acid–pyridine oxidation of this glycol gave the corresponding hydroxy aldehyde, which was then converted through the oxime into a compound which appeared to be an amino alcohol (**3c**), it was subsequently found that osmium tetroxide–hydrogen peroxide oxidation[10] of **1b** gave the same "hydroxy aldehyde." Since periodate

(1) Abstracted from the Ph.D. Dissertations of D. M. Alabran (1965) and A. C. Ruggles (1966), Clemson University, Clemson, S.C., presented in part at the Southeastern Regional Meeting of the American Chemical Society, Louisville, Ky., Oct 1966.

(2) NASA Fellow, 1965–1966.

(3) (a) R. Hirschmann, C. S. Snoddy, C. F. Hiskey, and N. L. Wendler, *J. Amer. Chem. Soc.*, **76**, 4013 (1954); (b) J. M. Coxon, M. P. Hartshorn, and D. N. Kirk [*Tetrahedron Lett.*, 119 (1965)] have recently revised the structure of tetrasubstituted olefin (**2a**).

(4) W. F. Johns [*J. Org. Chem.*, **29**, 2545 (1964)] and Y. Shimizu [*Tetrahedron*, **19**, 1027 (1963)] have also explored this synthetic route to the C-nor-D-homo steroidal alkaloids.

(5) J. W. Huffman, D. M. Alabran, T. W. Bethea, and A. C. Ruggles, *J. Org. Chem.* **29**, 2963 (1964). W. F. Johns[4] has accomplished much the same results through the use of rockogenin-3-pivalate. The Merck procedure suffers from first, the nonstereospecific lithium aluminum hydride reduction of hecogenin, and second, the partial formation of a 3β,12β-disuccinate in addition to the 3β ester.

(6) H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **78**, 5695 (1956).

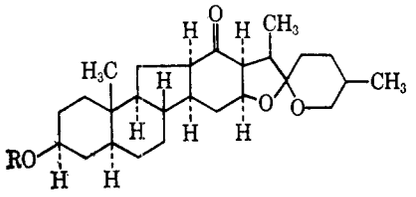
(7) H. C. Brown and B. C. Subba Rao, *ibid.*, **81**, 6428 (1959).

(8) M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **29**, 1120 (1964).

(9) J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, **21**, 2489 (1965).

(10) R. Daniels and J. L. Fischer, *J. Org. Chem.*, **28**, 320 (1963).

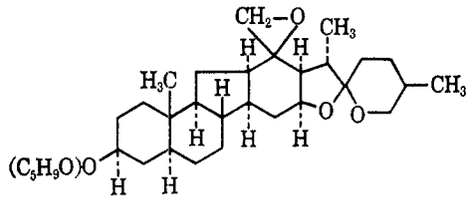
oxidation of **3b** also gave this compound, and reduction with sodium borohydride did not regenerate the diol but gave one of the stereoisomeric 17a alcohols, it is apparent that the "hydroxy aldehyde" is in fact the 18-nor ketone **4a**. Conversion of **4a** into the corresponding



4a, R = C_5H_9O
b, R = C_2H_3O

3β acetate **4b** gave material identical with that prepared by the Merck group.[3a,11] Attempted conversion of **3b** into the 18-methanesulfonate or tosylate also failed, giving only intractable material.

Since the route *via* the 17a,18 glycol did not appear promising, an attempt was made to obtain compounds similar to **3** through the 17a,18 oxides (**5**). Peracid



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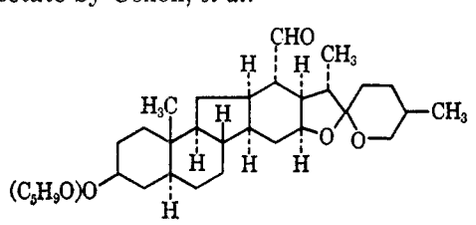
oxidation of **1a** (as the acetate) has been reported to give a mixture of two epoxides in a ratio of *ca.* 3:1.[3a] Although reaction of **1b** with *m*-chloroperbenzoic acid gave a solid of the correct formula and having a sharp melting point, it was subsequently found that this material was actually a mixture of two compounds (see Experimental Section). Attempted separation by chromatography failed, and when a larger quantity of alumina was employed, one stereoisomer was recovered, while the other was converted into a structural isomer. This compound showed a carbonyl peak at 5.79 μ and the absorption at 3.70 μ associated with an aldehyde. On the basis of these data, it was assumed that rearrangement of one of the epoxides had occurred to give the 18α-aldehyde (**6**) whereas the other was unaffected by chromatography. The stereochemistry at C-17a in **6** is assigned by analogy to that suggested for the corresponding 3-acetate by Coxon, *et al.*[9]



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On the basis of the relative amounts of the products from these experiments it was assumed that the major epoxide, that which was recovered unchanged, was the 17aβ oxide, while the isomer which was converted into the aldehyde was the 17aα isomer.[12] While this work was in progress a detailed account of the reactions of various compounds in this series appeared,[9] and this assumption was confirmed, not only on the basis of the course of the rearrangement, but on the position of the chemical shift of the C-18 protons, both of the recovered β epoxide and the α isomer, observed in the mixture.[9] The 18-aldehyde could be obtained preparatively by treating the original mixture of epoxides with aqueous perchloric acid which converts the α oxide into the aldehyde and the β isomer presumably to the allylic $\Delta^{13(17a)}$-18 alcohol,[9] which was not isolated.

Though the total amount of aldehyde which could be prepared by this route was small, owing principally to the unfavorable product ratio in the per acid oxidation of **1b**, sufficient material was obtained to investigate the conversion of **6** into the 18-amino compound. Although the oxime of **6** was obtained readily, this compound was apparently a mixture of *syn* and *anti* isomers which resisted purification. Reduction of the oxime with lithium aluminum hydride gave a noncrystalline material, assumed to be the 18-amine (**3a**, R = C_5H_9O) on the basis of its spectral properties. It is assumed that the aminomethyl group is α in this compound and that no isomerization occurred during the preparation of the oxime and reduction to the amine. A number of attempts to isomerize this material to the corresponding pentacyclic Schiff base gave either recovered starting material or the products of gross decomposition.

In view of the above difficulties encountered in isomerizing **3a** to a pentacyclic cevine precursor, and the unfavorable ratio of products obtained in the oxidation of the exocyclic olefin, this particular approach to the cevine alkaloids was abandoned.

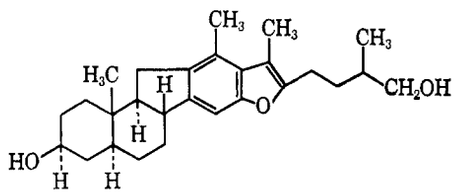
The somewhat less structurally complex steroid alkaloids of the jervine and veratramine group also contain a C-nor-D-homo steroid skeleton. It would appear that a rather simple dehydrogenation sequence based on the $\Delta^{13(17a)}$ olefin **2** could lead to a 22-oxo compound, which could in turn be converted into veratrine. Oxidation of **2a**, prepared by the Bamford–Stevens reaction of hecogenin tosylhydrazone,[3,4] with 2,3-dichloro-5,6-dicyanobenzoquinone or *o*-chloranil gave only the 3 ketone derived from **2a**. This compound could also be obtained by the chromic acid oxidation of **2a**. When the $\Delta^{13(17a)}$-3-tetrahydropyranyl ether (**2b**) was subjected to oxidation by either of the above quinones, only starting material was recovered. However, dehydrogenation of **2a** with selenium dioxide in acetic acid[13] followed by basic hydrolysis gave a compound $C_{27}H_{38}O_3$ in reasonable yield. The infrared spectrum of this material showed hydroxyl and aromatic absorption and the ultraviolet spectrum was that of a complex aromatic system. This compound formed a diacetate, the nmr spectrum of which showed three three-proton singlets (plus the acetate methyls) at δ 0.97, 2.30, and 2.52, and a single aromatic proton at δ 6.92. The rather characteristic resonances associated with the hydrogens adjacent to the spiro ketal oxygens (C_{16},C_{26}) were replaced by a multiplet at δ 3.96 and there were a considerable number of protons centered about 2.67, with a corresponding decrease in size of the high-field envelope. On the basis of

(11) The authors wish to thank Dr. Ralph F. Hirschmann of Merck Sharp and Dohme for a sample of 3β-acetoxy-17a-keto-22a-5α-C-nor-D-homo-18-norspirostene.

(12) J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Aust. J. Chem.*, **18**, 759 (1965).

(13) W. M. Hoehn and C. R. Dorn, *J. Org. Chem.*, **30**, 316 (1965).

these data, it seemed probable that these compounds were C-nor-D-homo-5α-furostan-12,14,16,20(22)-tetraene-3β,26-diol (**7**) and its diacetate.[14] Since compound



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7 and its derivatives did not appear to be particularly attractive materials for a synthesis of veratramine, this approach to these alkaloids was also abandoned.[15]

The stereochemical assignments for the compounds in the C-nor-D-homo steroid series are largely due to the work of Coxon, *et al.*[9,12] These workers, as well as the Merck group,[3a] have attempted to explain the reactions of these compounds in terms of a ring-D boat conformation.[16] It has, however, been recently noted that ring D of jervine and its derivatives may exist in a distorted chair rather than a boat,[17] and a similar course of reasoning may be applicable to the C-nor-D homosapogenin. Coxon, *et al.*, have examined the rotatory dispersion curve of the 18-nor ketone (**4a**), which shows a negative Cotton effect, as expected for a compound with all substituents on the D ring in the β orientation.[12] The moderate amplitude of this Cotton effect ($a = -29$) is as consistent with a flattened chair conformation for ring D as for the boat form.[18] The lack of adequate model compounds for **4** make any definite conclusions regarding the conformation of this compound hazardous, however, the amplitude of the Cotton effect is well within the normal range for cyclohexanones and may tend to indicate that ring D is not a boat in this compound.

In an effort to prepare a simpler 18-nor-C-nor-D-homo ketone, the tetrahydropyranyl ether of 3α-hydroxypregnan-12-one[5] was reduced with sodium–1-propanol to the 12β alcohol. The stereochemistry of this compound was proven by conversion into the known 3α,12β-pregnanediol.[5] Conversion of this compound into the 12β-methanesulfonate, followed by treatment with potassium–*t*-butoxide[3a] gave material which, though nonpolar, did not show the absorption in the infrared around 6 and 11.2 μ associated with a terminal olefin. Tlc of this nonpolar material indicated that it was a mixture of two quite similar compounds, presumably the $\Delta^{13(17a)}$ olefin and an isomer. All attempts to separate these compounds or characterize them more fully failed.

(14) Following the completion of this work, W. F. Johns and L. Laos [*J. Org. Chem.*, **30**, 4220 (1965)] reported the preparation of this compound by an alternate route and studied its reactions in some detail.

(15) It seems probable that the driving force to form the ψ-sapogenin system is far greater than that to simply open the spiro ketal, forming an acyclic hydroxy ketone. Virtually the only success in utilizing the masked carbonyl of a sapogenin for the synthesis of steroid alkaloid is the synthesis of solasodine from diosgenin reported by F. C. Uhle [*ibid.*, **27**, 656 (1962)].

(16) From a study of Dreiding models the *cis* fused C and E rings of these compounds hold the D ring in a rigid boat rather than a twist conformation with a variety of pseudo-rotational forms.

(17) T. Masumune, N. Sato, K. Kobayashi, I. Yamazaki, and Y. Mori, *Tetrahedron*, **23**, 1591 (1967).

(18) P. Crabbe, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1965, pp 88–89, and references cited therein.

Additional insight into the conformation of ring D in these compounds may be obtained from the nmr spectra of the compounds in this series. In particular, the chemical shifts of the C-18 methyl protons in the two stereiosiomeric 17a-hydroxy-22a,5α-C-nor-D-homospirostan-3β-ols are of interest.[9,12] In both the C-18 methyl protons appear at δ 1.15. If the D ring were in either a boat or an undistorted chair conformation it would be expected that the chemical shifts for the protons in the isomer with the axial or "flagpole" methyl group would show a downfield shift. Since there is no difference in chemical shift, it seems probable that the D ring in these compounds also exists as a flattened chair. Although the reactions of all these compounds are most conveniently interpreted in terms of a boat form D ring, a study of models with this ring as a flattened chair indicates that this conformation will also give the reaction products observed by Coxon, *et al.*[9,12]

The nmr spectra of the compounds prepared in the course of this work are unexceptional and are summarized in Table I. It should be noted that the use of the

TABLE I

CHEMICAL SHIFTS OF SELECTED PROTONS IN THE C-NOR-D-HOMOSAPOGENINS[a]

Compd	C-18 protons	C-19 methyl	C-21 methyl (doublet)
1b	4.78 (m)[b]	0.80	1.09 (J = 7)
2b	1.70	0.80	1.18 (J = 7)
17aα,18-Diol	3.68 (m)	0.81	1.03 (J = 7)
4a		0.80	1.19 (J = 8)
5 (α oxide)	2.76 (d, J = 1)	0.77	0.98 (J = 7)
5 (β oxide)	2.42 (d, J = 1)	0.77	0.98 (J = 7)
3a (R = C_5H_9O)	2.08 (d, J = 3)	0.78	0.82 (J = 7)

[a] All spectra were run in deuteriochloroform using tetramethylsilane as internal standard. Signals are given in parts per million relative to this standard (δ). [b] Partially obscured by the signal from the 2 proton of the tetrahydropyran ring.

3-tetrahydropyranyl group as a blocking group complicates the nmr spectra to the point where it is very difficult to assign rigorously the peaks in the δ 3–5 region. The 2 proton in the tetrahydropyran ring appears as a multiplet centered about δ 5.7 and the protons at the 5 position of the tetrahydropyran and C-3, C-16, and C-26 of the sapogenin appear as an envelope from δ 3.2 to 4.2.

Experimental Section[19]

Rockogenin 3-Tetrahydropyranyl Ether 12-Methanesulfonate.—To a stirred solution of 1.0 g of the 3-tetrahydropyranyl ether of rockogenin[5] in 12 ml of dry pyridine was added 0.7 ml of methansulfonyl chloride. The resulting red solution was allowed to stand at room temperature 24 hr, poured slowly into ice water, and the light brown precipitate collected. Recrystallization from acetone gave 0.75 g (70%) of white crystals, mp 132–134° dec.

Anal. Calcd for $C_{33}H_{54}O_7S$: C, 66.63; H, 9.15. Found: C, 66.57; H, 9.16.

$\Delta^{17a(18)}$-22a,5α-C-Nor-D-homospirostene 3β-Tetrahydropyranyl Ether (1b).—To a stirred solution of potassium *t*-butoxide (from 0.34 g of potassium in 31 ml of *t*-butyl alcohol) was added 1.0 g

(19) Melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were run as potassium bromide pellets, using a Perkin-Elmer Model 137 spectrophotometer. Ultraviolet spectra were obtained on a Perkin-Elmer Model 202 spectrophotometer. Nuclear magnetic resonance spectra were run in deuteriochloroform solution using a Varian A-60 spectrometer. Specific rotations were determined in chloroform, employing a Rudolph Model 70 polarimeter. Optical rotatory dispersion data were obtained using a JASCO Model ORD/UV-5 spectropolarimeter. Analyses were performed by Galbraith Laboratories, Knowville, Tenn.

of the above methanesulfonate. The solution was heated at reflux under nitrogen for 18 hr, during which time five additional ml of *t*-butyl alcohol were added. The reaction mixture was cooled, diluted with 2 ml of water, 7.5 ml of tetrahydrofuran, and 15 ml of methanol and heated under reflux for 2 hr more. The solvents were removed at reduced pressure; water was added and the precipitated solid collected and washed free of base, leaving a white solid, mp 142–149°. Recrystallization from acetone gave 83% of the exocyclic olefin: mp 186–187°, $[\alpha]^{27}D$ −63° (*c* 1.05).

Anal. Calcd for $C_{32}H_{50}O_4$: C, 77.06; H, 10.10. Found: C, 77.03; H, 10.23.

There was also obtained from the mother liquors a small quantity of a second compound, mp 161–164°, which did not show the infrared absorption at 11.2 μ typical of exocyclic olefins. The combined mother liquors from several runs gave a larger quantity of this material, the $\Delta^{13(17)}$ isomer **2b**, which crystallized from acetone as small needles: mp 184–186°; $[\alpha]^{27}D$ −58 (*c* 0.601).

Anal. Calcd for $C_{32}H_{50}O_4$; C, 77.06; H, 10.10. Found: C, 77.34; H, 10.27.

Treatment of the 3-tetrahydropyranyl ether of the exocyclic olefin with acetic acid gave the 3 acetate,[3a] mp and mmp 221–225°.

3-Tetrahydropyranyl Ether of 3β,17aα,18-Trihydroxy-22a,5α-C-nor-D-homospirostane (3b).—To a solution of 1.0 g of the exocyclic olefin **1b** in 27 ml of dry pyridine was added 1.0 g of osmium tetroxide. The brown solution was maintained at room temperature and stirred constantly. After 36 hr, 30 ml of water, 2.0 g of sodium bisulfite, and 12 ml of pyridine were added and the stirring was continued for 2 hr. The reaction mixture was extracted with chloroform. The chloroform extracts were washed with water and dried and the solvent removed *in vacuo* leaving a black oil. This oil was dissolved in 200 ml of ethanol, 3.4 g of sodium sulfite and 77 ml of water were added, and the mixture was heated under reflux. After 2 hr, 3 ml of 30% sodium hydroxide was added, and heating continued 2 hr. The mixture was evaporated to dryness, the residue dissolved in ether, washed with water, dried, and the solvent removed at the water pump. The resulting yellow oil was dissolved in hot acetone, water was added to turbidity, and following cooling, there was obtained 92% of glycol, mp 158–160°.

Anal. Calcd for $C_{32}H_{52}O_6$: C, 72.14; H, 9.84. Found: C, 72.24; H, 9.60.

3-Tetrahydropyranyl Ether of 3β-Hydroxy-17a-keto-22a,5α-C-nor-D-homo-18-norspirostane. A.—To 100 ml of slowly stirred pyridine was added 10 g of chromic oxide, followed by 0.5 g of glycol **3b**, and the mixture stirred at room temperature for 16 hr. Water was added, the mixture extracted with ether, the ether layer washed with several portions of water and dried, and the solvent removed at reduced pressure. The residue was recrystallized from acetone and water to give 81% yield of white solid, mp 186–188°, which showed carbonyl absorption at 5.84 μ.

Anal. Calcd for $C_{31}H_{45}O_5$: C, 74.36; H, 9.66. Found:[20] C, 74.01; H, 9.84.

B.—To a solution of 0.725 g of the 17a,18 glycol **3b** in 52 ml of ethanol was added 0.336 g of periodic acid dihydrate in 3 ml of water, and ethanol was added until the solution became homogeneous. The reaction mixture was allowed to stand overnight at room temperature, the solvent removed *in vacuo* at room temperature and the residue taken up in ether. The ethereal solution was washed with 5% sodium bicarbonate and water and dried, and the solvent removed at aspirator pressure to leave a white solid. Recrystallization from acetone and water gave material identical with that obtained in part A.

C.—To solution of 0.1 g of exocyclic olefin **1b** in 199 ml of *t*-butyl alcohol and 25 ml of 30% hydrogen peroxide was added 3 ml of 0.02 *M* osmium tetroxide in *t*-butyl alcohol.[10] The reaction mixture was stirred at room temperature for 48 hr and concentrated at reduced pressure and the residue dissolved in ether. The ethereal solution was washed with water and 5% sodium bicarbonate and dried and the solvent removed at reduced pressure. Recrystallization from acetone and water gave 0.075 g (74%) of nor ketone, mp and mmp 186–188°.

3β-Acetoxy-17a-keto-22a,5α-C-nor-D-homo-18-norspirostane 4b.—A solution of 0.045 g of the 3-tetrahydropyranyl ether 17a-ketone **4a** in 5 ml of acetic acid was heated at reflux for 24 hr, the solvent removed at reduced pressure and the residue dissolved in methylene chloride. After washing with 5% aqueous sodium bicarbonate and water, the solution was dried and the solvent removed leaving a yellow glass. Recrystallization from acetone–water gave 0.030 (67%) of white crystals, mp 220–222°. A sample of this compound supplied by Dr. R. F. Hirschmann of Merck Sharp and Dohme had mp 229–230°. The infrared spectra of the two samples were identical and a mixture melting point was 227–230°. The difference in melting point is apparently due to differences in crystal structure. The Merck sample exists as small needles, while that prepared in this laboratory is thin plates. The ORD curve (methanol) of this compound shows the following values: $[\alpha]_{500}$ −34°, $[\alpha]_{301}$ −480 and $[\alpha]_{268}$ +840. Coxon, *et al.*, reported $[\alpha]_{298}$ −645 and $[\alpha]_{263}$ +20.

3-Tetrahydropyranyl Ether of 3β,17aξ-Dihydroxy-22a,5α-C-nor-D-homo-18-norspirostane.—To a solution of 0.05 g of the nor ketone **4a** in the minimum amount of methanol was added 0.1 g of sodium borohydride and the mixture heated at reflux for 1 hr. The reaction mixture was diluted with water, acidified with concentrated hydrochloric acid, and extracted with methylene chloride. The organic layer was washed with water and dried and the solvent removed *in vacuo* to give 0.04 g (80%) of solid material. Recrystallization from acetone gave the alcohol, mp 216–218°.

Anal. Calcd for $C_{31}H_{50}O_5$: C, 74.06, H, 10.02. Found: C, 73.81; H, 9.94.

3-Tetrahydropyranyl Ether of 3β-Hydroxy-17a-oximino-22a,-5α-C-nor-D-homo-18-norspirostane.—To a solution of 0.2 g of the 18-nor ketone **4a** in 2 ml of 10% sodium hydroxide, 2 ml of water, and sufficient ethanol to make the solution homogeneous was added 0.5 g of hydroxylamine hydrochloride. The reaction mixture was heated at reflux for 3 hr, concentrated at reduced pressure and diluted with water. The oxime separated as an oil which resisted purification and was used as isolated for the next step.

3-Tetrahydropyranyl Ether of 3β-Hydroxy-17ξ-amino-22a,5α-C-nor-D-homo-18-norspirostane.—To a solution of 0.5 g of the oxime in 20 ml of dry ether–tetrahydrofuran (1:1) was added 1.0 g of lithium aluminum hydride and the mixture stirred at room temperature for 1 hr. The excess lithium aluminum hydride was decomposed with water, the layers separated, the ethereal solution dried, and the solvent removed at reduced pressure to give 0.5 g of brown oil. The oil was taken up in chloroform and chromatographed on neutral alumina. Elution with methanol gave 0.35 g (70%) of white solid, mp 149–151°, after recrystallization from methanol.

Anal. Calcd for $C_{31}H_{51}NO_4 \cdot CH_3OH$: C, 72.27; H, 10.05; N, 2.63. Found: C, 72.15; H, 10.00; N, 2.90.

Per Acid Oxidation of $\Delta^{17a(18)}$-22a,5α-C-Nor-D-homospirostene 3-Tetrahydropyranyl Ether.—To a solution of 0.25 g of the olefin **1b** in the minimum amount of chloroform was added dropwise a solution of 0.11 g of *m*-chloroperbenzoic acid also in the minimum amount of chloroform. The reaction mixture was stirred at room temperature for 45 min and then 1.0 g of sodium sulfite in 9 ml of water was added with vigorous stirring. The reaction mixture was diluted with chloroform, washed with successive portions of water and 5% sodium bicarbonate and dried and the solvent removed leaving a colorless solid. Recrystallization from acetone gave 0.13 g (52%) of white solid, mp 176–177°.

Anal. Calcd for $C_{32}H_{50}O_5$: C, 74.67; H, 9.79. Found: C, 74.59; H, 9.68.

Although this material was sharp melting and appeared homogeneous, tlc (silica gel G) showed that it actually consisted of two compounds. When 2.20 g of this material was dissolved in 1:1 hexane–benzene and chromatographed on 200 g of Merck acid-washed alumina, elution with the hexane–benzene mixture gave first a trace of unoxidized olefin, then 1.5 g of homogeneous (tlc) 17aβ,18 epoxide **5**, mp 182–183°, after recrystallization from acetone.

Anal. Calcd for $C_{32}H_{50}O_5$: C, 74.67; H, 9.79. Found: C, 74.53; H, 9.91.

Elution with benzene gave 0.5 g of 17aα-formyl-22a,5α-C-nor-D-homospirostane 3-tetrahydropyranyl ether **6**, mp 158–159°, after recrystallization from hexane.

Anal. Calcd for $C_{32}H_{50}O_5$: C, 74.67; H, 9.78. Found: C, 74.40; H, 9.98.

When a smaller ratio of alumina to compound was employed, the mixture of α and β epoxides was recovered unchanged and the

(20) Satisfactory analytical data could not be obtained for this compound. The original analysis gave C, 72.45; H, 9.43 (calcd for $C_{32}H_{50}O_6$: C, 72.64; H, 9.64). These data led to the incorrect conclusion that this material was the 17a-formyl-17a-hydroxy compound.

use of either BioRad neutral alumina or basic Merck alumina gave results similar to that observed with the acid-washed absorbent.

The acid-catalyzed rearrangement of the mixed 17aα and 17β 18 epoxides was accomplished by treating a solution of 1 g of mixed epoxides in 60 ml of methylene chloride and 120 ml of acetone with 1 ml of 1.5 *M* aqueous perchloric acid. The solution was allowed to stand at 20° for 10 min, water was added, and the product was extracted into methylene chloride and dried over magnesium sulfate. Evaporation of the solvent gave an oil which was taken up in benzene and chromatographed on Merck alumina. Elution with benzene and recrystallization from hexane gave 0.15 g of aldehyde **6**, mp 158–159°, identical with that obtained above from chromatography of the mixed epoxides.

18-Oximino-22a,5α,17β-C-nor-D-homospirostane 3β-Tetrahydropyranyl Ether.—A solution of 0.20 g of the 18-aldehyde **6**, 0.40 g of hydroxylamine hydrochloride, and 0.80 g of sodium acetate in 80 ml of methanol was heated at reflux for 16 hr. The solution was cooled, 80 ml of water added, and the solid product collected. Recrystallization from methanol gave 0.21 g of white solid, mp 155–165°. Repeated recrystallization from a variety of solvents failed to give sharp melting material and tlc showed two components, presumably the *syn* and *anti* oxime, having rather similar R_f values. The infrared spectrum showed absorption at 3.05 and 6.20 μ and the absence of a carbonyl band.

18-Amino-22a,5α,17β-C-nor-D-homospirostane 3β-Tetrahydropyranyl Ether 3c.—To a suspension of 0.10 g of the oxime in 30 ml of ether was added 0.075 g of lithium aluminum hydride and the reaction mixture stirred at room temperature overnight. The excess hydride was destroyed by the dropwise addition of water. The precipitated salts were filtered off, and the ethereal solution was dried and the solvent removed at reduced pressure leaving 0.018 g of oil. Although this material was essentially homogeneous by tlc it could not be induced to crystallize. The infrared spectrum showed absorption at 3.10 and weak absorption in the 6.1–6.3-μ region indicative of a primary amine.

Attempted Rearrangement of 22a,5α,17β-C-nor-D-homospirostan-18-amino-3β-tetrahydropyranyl Ether (3c). A.—A solution of 0.010 g of the 18-amine was heated in ether containing 1 drop of perchloric acid for 10 min. Evaporation of the solvent gave an oil which was shown to be starting material. This procedure was repeated using the reaction times of 30 min, 2 hr, and overnight. Starting material was obtained in each reaction.

B.—To a solution of 0.01 g of 18-amine **3c** in 1 ml of methylene chloride was added 1 drop of boron trifluoride etherate. The solution was allowed to stand overnight. The solution was neutralized with sodium hydroxide solution and the methylene chloride fraction separated and dried over magnesium sulfate. Evaporation of the solvent gave an intractable black gum.

C.—A solution of 0.050 g of 18-amine **3c** in 6 ml of acetic acid and 1 drop of perchloric acid was heated on a steam bath for 2 hr. The solution was cooled and neutralized with aqueous sodium hydroxide. The solution was extracted with ether and evaporation of the ether yielded a yellow glass. The infrared spectrum of the glass showed a carbonyl peak at 5.76 and bands at 8.04, 11.11 and 11.57 μ indicating that the spiro ketal was intact and the tetrahydropyranyl ether had been replaced by an acetate group.

Attempted Aromatizations of 3β-Hydroxy-$\Delta^{17(17a)}$-22a,5α-C-nor-D-homospirostene (2a). A.—A solution of 0.47 g of the olefin **2a** and 0.25 g of *p*-chloranil in 2 ml of *p*-xylene was heated at reflux for 20 hr. After cooling the mixture was diluted with hexane and chromatographed on an alumina column. Elution with various solvents gave a yellow oil which could not be crystallized.

B.—A solution of 0.47 g of the olefin **2a** and 0.23 g of 2,3-dichloro-5,6-dicyanobenzoquinone in 2 ml of xylene was heated at reflux for 20 hr. The reaction mixture was cooled, extracted with hexane and evaporated to dryness leaving a yellow solid. The product, $\Delta^{13(17a)}$-22a,5α-C-nor-D-homospirostene-3-one, was crystallized from acetone giving 0.15 g (32%) of pale yellow crystals, mp 205–210°, raised to 208–210° upon further recrystallization. The infrared spectrum of the product showed carbonyl absorption at 5.86 μ.

Anal. Calcd for $C_{27}H_{40}O_3$: C, 78.60; H, 9.77. Found: C, 78.36; H, 9.86.

C.—When the reaction was repeated using *o*-chloranil, the same product was obtained in low yield.

$\Delta^{13(17a)}$-22a,5α-C-Nor-D-homospirosten-3-on.—A solution of 0.2 g of hydroxyolefin **2a** in 2.0 ml of acetone was treated dropwise with Kiliani's reagent until a slight permanent orange color was obtained. The solution was allowed to stand for 5 min at room temperature, several drops of water were added and the solution was filtered. The filtrate was treated with 0.1 ml of 1 *N* sodium hydroxide and 8 ml of water, the solid mass collected and recrystallized from acetone to give 0.12 g (60%) of ketone, mp 208–210°. The infrared spectrum was identical with the spectrum of both attempted aromatization products and the mixture melting point was 208–210°.

C-Nor-D-homo-5α-furostan-12,14,16,20(22)-tetraene-3β,26-diol.—To a solution of 1.0 g of endocyclic olefin in 20 ml of 90% acetic acid at 90°, 1.8 g of selenium dioxide was added. The dark solution was stirred and heated at 100–110° for 4 hr. The solution was then cooled to 80° and 1.3 g of finely powdered zinc was added. The mixture was heated to 90°, stirred for 4 hr, and filtered while hot, and the cake washed with 40 ml of hot acetic acid. The acetic acid was removed *in vacuo*. The residue was dissolved in 50 ml of 1 *N* methanolic potassium hydroxide solution and refluxed for 2 hr. Water was added and the red oil obtained was taken up in methylene chloride. Evaporation of the solvent gave 0.5 g of crystals of **7** which were collected and recrystallized from methanol, mp 192–195°. The analytical sample, mp 198–200°, was crystallized from methylene chloride. Johns[14] reports mp 202–203°.

Anal. Calcd for $C_{27}H_{38}O_3$: C, 78.98; H, 9.33. Found: C, 78.98; H, 9.51.

Chromatography of 1.49 g of the residue remaining from the crystallization of the furostantetraene on 60 g of Merck acid-washed alumina, deactivated with 5 ml of water, gave 0.49 g of unoxidized olefin **2a**, eluted with benzene. Elution with methylene chloride gave an additional 0.49 g of tetraene, mp 193–196°.

Since the tetraene was quite insoluble in common solvents, 0.08 g was heated for 20 hr on the steam bath in 5 ml of acetic anhydride and 5 ml of pyridine. The reaction mixture was poured into water and extracted with methylene chloride; the extracts were washed with water and dilute hydrochloric acid. Drying and removing the solvent gave an off-white solid, which on recrystallization from aqueous methanol gave the 3β,26 diacetate, mp 132–133° (lit.[14] mp 139–140°).

Anal. Calcd for $C_{31}H_{42}O_5$: C, 75.27; H, 8.56. Found: C, 75.45; H, 8.67.

The nmr spectrum of this compound showed the following peaks in addition to the saturated aliphatic envelope: δ 0.97 (s, C-19 methyl), 1.02 (d, J = 6, C-27 methyl), 2.04 (s, acetate methyls), 2.30 (s, C-18 methyl), 2.51 (s, C-21 methyl), multiplet centered about 2.67 (benzylic protons at C-8, C-11, and C-22), 3.96 (C-26, X_2 portion of an AX_2 pattern), 4.72 (C-3, CH–O, broad multiplet), and 6.92 (broadened s, C-14). The ultraviolet spectrum (CH_3OH) showed λ_{max} 256 mμ (log ε 4.25), 263 (4.24), 284 (3.84), 291 (3.81), 296 (3.83).

Tetrahydropyranyl Ether of 3α-Hyroxy-5β-pregnan-12-one.—To a suspension of 2.0 g of 3α-hydroxy-5β-pregnan-12-one[5] in 20 ml of dihydropyran was added 5 drops of phosphorus oxychloride with vigorous shaking after each drop. The reaction mixture was allowed to stand at 25–30° for 2 hr, 8 ml of 5% potassium hydroxide in methanol was added, and the mixture was poured into 40 ml of 25% aqueous methanol. The product was collected and after washing with 25% aqueous methanol was recrystallized from methanol to give 1 g (41%) of the tetrahydropyranyl ether as white crystals, mp 175–177°.

Anal. Calcd for $C_{26}H_{42}O_3$: C, 77.56; H, 10.51. Found: C, 77.74; H, 10.56.

3-Tetrahydropyranyl Ether of 5β-Pregnane-3α,12β-diol.—To a solution of 1 g of the 3α-tetrahydropyranyl ether in 130 ml of *n*-propyl alcohol was added 10 g of sodium. The solution was heated at reflux for 1 hr, diluted with water, acidified with dilute hydrochloric acid, and extracted with methylene chloride. Upon evaporation of the methylene chloride a dark brown solid was obtained. Recrystallization from acetone gave 0.47 g (47%) of a white solid, mp 167–168°.

Anal. Calcd for $C_{26}H_{44}O_3$: C, 77.18; H, 10.96. Found: C, 77.43; H, 10.93.

5β-Pregnane-3α,12β-diol.—A solution of 0.4 g of tetrahydropyranyl ether from the sodium–alcohol reduction was heated at reflux in 5 ml of acetic acid for 24 hr, then evaporated to dryness *in vacuo*. The residue was dissolved in ether, washed with saturated sodium carbonate solution, dried, and the solvent removed leaving a colorless oil. Hydrolysis of the product by

heating in 5 ml of 1 N potassium hydroxide in methanol for 3 hr gave 0.22 g (53%) of 5β-pregnane-3α,12β-diol,[5] mp and mmp 165–168°.

3-Tetrahydropyranyl Ether of 3α-Hydroxy-12β-methanesulfonoxy-5β-pregnane.—To a chilled (0°) solution of 0.10 g of the 3-tetrahydropyranyl ether of the pregnan-12β-ol in 2 ml of pyridine was added slowly a chilled solution of 0.20 ml of methanesulfonyl chloride in 2 ml of pyridine. The reaction mixture was allowed to warm slowly to room temperature, and then to stand at room temperature for 18 hr. The pale brown solution was poured into ice water, then extracted with two portions of methylene chloride. The extracts were combined and washed with successive portions of water, dilute hydrochloric acid, and water. After drying the solvent was removed *in vacuo* with gentle warming to yield 0.11 g of pale yellow glass. This material is very unstable, both thermally and in solution, and decomposed on attempted purification. When 0.10 g was treated with potassium *t*-butoxide (from 0.10 g of potassium) in 10 ml of *t*-butyl alcohol, in the manner described for the rearrangement of the rockogenin derivative (see above), there was obtained 0.030 g of pale yellow, nonpolar (eluted with hexane–benzene 2:1 from alumina) material. Tlc (silica gel G) showed that this material was a mixture of two compounds in approximately equal amounts, and with very similar R_f values. The infrared spectrum did not show the peaks at 6.1 and 11.2 μ associated with a $\Delta^{17a,18}$ olefin.

Registry No.—**1b,** 15539-07-8; **2a** (3-one) (mp 208–210°), 15538-94-0; **2b,** 15538-95-1; **3a,** 15538-96-2; **3b,** 15538-97-3; **4a,** 15538-98-4; **4b,** 15538-99-5; **5** (17aα-oxide), 15622-67-0; **5** (17aβ-oxide), 15539-00-1; **6,** 15656-71-0; **7,** 4653-71-8; **7** diacetate, 4866-48-2; 3-tetrahydropyranyl ether of 3β,17aξ-dihydroxy-22a,5α-D-nor-D-homo-18-norspirostane, 15539-03-4; 3-tetrahydropyranyl ether of 3β-hydroxy-17aξ-amino-22a,5α-C-nor-D-homo-18-norspirostane, 15539-04-5; 3-tetrahydropyranyl ether of 3α-hydroxy-5β-pregnan-12-one, 15539-05-6; 3-tetrahydropyranyl ether of 5β-pregnane-3α,12β-diol, 15539-06-7; rockogenin-3-tetrahydropyranyl ether 12-methanesulfonate, 11040-86-1.

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The Thermal Decomposition of Tri-*sec*-butyl Phosphate[1]

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Organic phosphorus compounds containing *sec*-butyl groups are of practical importance in the solvent extraction technology of uranium.[2] No information has apparently been published as to their thermal stabilities; it therefore seemed of interest to compare the thermal stability of a secondary isomer with that of its normal counterpart.

The faster thermal dealkylation rate of tri-*sec*-butyl phosphate (TsBP) in comparison with tri-*n*-butyl phosphate (TBP) was qualitatively observed in earlier work.[3] Substantially faster thermal decomposition rates have been reported by Emerson, Craig, and Potts[4] for sulfoxides having both primary and secondary alkyl groups than for those containing only primary groups. A comparison of gaseous products from pyrolysis of the partial esters di-*sec*-butyl phosphoric acid (HDsBP) and di-*n*-butyl phosphoric acid (HDBP) has been made by Hanneman and Porter.[5] Our work, reported here, compares the thermal decomposition rates of, and isomeric olefin yields from, TsBP with those of TBP.[6,7]

The composition of butenes produced when TsBP was isothermally decomposed until no more gas evolved is shown in Table I. The reaction was run in the temperature range 180–241°. Very little variation in composition was found: butene-1 comprised 14–17% of the mixture, *trans*-butene-2, 44–48%, and *cis*-butene-2, 38–40%. Only 0.1% isobutylene was formed.

TABLE I

COMPOSITION OF BUTENES FROM COMPLETE PYROLYSIS OF TRI-*sec*-BUTYL PHOSPHATE (TsBP) AT VARIOUS TEMPERATURES

Temp, ±1°	Time, hr	Yield, %	Isomeric abundance, % Butene-1	Iso-butylene	*trans*-Butene-2	*cis*-Butene-2
180	6.8	96	13.8	...	48.0	38.2
200	1.4	88	15.6	...	45.2	39.2
212	0.6	90	17.3	...	44.5	37.8
241	0.05	90	15.1	0.1	44.3	40.5

Under similar conditions TBP yielded 54–55% butene-1, 25–26% *trans*-butene-2, 19–20% *cis*-butene-2, and 0.4% isobutylene.[7] Reaction time was considerably shortened at higher temperatures. At 180° nearly 7 hr were required for complete decomposition (cessation of gas evolution) but at 241° only 2–3 min were required. At this latter temperature, by comparison, TBP took about 2.5 hr to decompose completely.[7]

The composition of the butenes varied greatly from beginning to end of the pyrolysis (Table II). When only 2.5% of the TsBP had decomposed, half of the gas formed was butene-1 and the remainder was distributed between *cis*- and *trans*-butene-2. As the percentage of pyrolytically formed acid in the reaction mixture increased, the amount of butene-1 formed decreased. The last 10% of gas evolved contained only 8.6% butene-1. The latter stage in the pyrolysis was also the only one in which isobutylene was produced (0.2%).

The rates of formation of HDsBP by thermal action on TsBP at several temperatures are shown in Table III. At comparable temperatures the rates are over

(1) Research sponsored by the U. S. Atomic Energy Commission under contract with the Union Carbide Corp.

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