is perhaps not particularly surprising when the greater conformational mobility of bicyclo[5.3.0]decanes is taken into account. Moreover, all the compounds listed in Table I contain carbonyl groups other than the lactone carbonyl in the C-7 side chain which must affect the nature of the collision complex.

One other item of interest can be gleaned from the present study. The expected large positive solvent shift associated with a quasiaxial methyl group[8] is not displayed by those compounds having the stereochemistry of helenalin (lactone ring *cis*, C-6 hydroxyl α), *i.e.* **7**, **8**, **9**, **10**, and **13**.[9] In the other two *cis* lactones (C-6 hydroxyl β; **3**, **4**) the C-5 methyl solvent shift is appreciable (0.30 ppm) as it is in the *trans* lactone series, with C-6 hydroxyl β (0.35 ppm). In the two *trans* lactones with C-6 hydroxyl α (**11**, **12**) the solvent shift reaches the very high value of 0.51 ppm. This information may be useful diagnostically in the analysis of other closely related compounds.[10]

Experimental Section

Compounds listed in Table I were available from our sample collection or prepared by the cited literature method. The extent of deuterium incorporation in samples **3a**, **5a**, and **9a** and in 2,3-dideuterioisomexicanin I was evident from the proton count in the nmr spectrum and was checked by mass spectrometry.

(8) N. S. Bhacca and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry," Holden-Day, Inc., 1964, pp 163–165.

(9) The small negative shift in compounds **10** and **13** may be due to the presence of the methoxyl group at C-2.

(10) NOTE ADDED IN PROOF.—E. H. White, S. Eguchi, and J. N. Marx [*Tetrahedron*, **25**, 2009 (1969)] have recently shown that the solvent shift method for the determination of C-11 methyl stereochemistry gave erroneous results when applied to the guaianolides deacetoxymatricarin[11] and achillin.[12]

(11) H. A. Lindo and M. S. Ragab, *Helv. Chim. Acta*, **50**, 1961 (1967).

(12) J. Smolenski, C. L. Bell, and L. Bauer, *Lloydia*, **30**, 144 (1967).

8-Aza Steroids. VI. 21 Hydroxylation[1]

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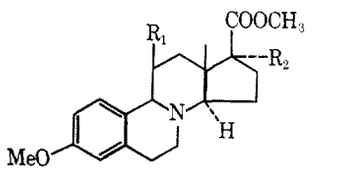
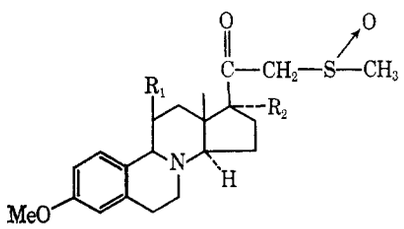
Russell[2] and coworkers recently described the conversion of esters into α-hydroxy ketones by Pummerer reaction on derived β-keto sulfoxides. We independently studied this reaction sequence in the 8-aza steroid series, and in this Note wish to report its application to the elaboration of the corticoid side chain.

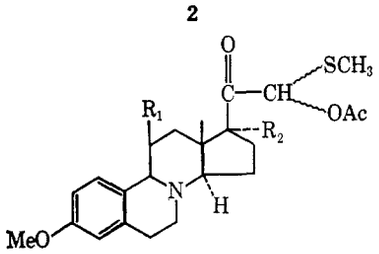
Treatment of esters **1a–1d** with the anion of dimethyl sulfoxide[3] gave β-keto sulfoxides **2a–2d** as epimeric mixtures in yields of 80–100%. When the sulfoxide mixtures were heated in acetic acid for 2 hr at 100°, Pummerer rearrangement to hemimercaptal acetates **3a–3d** took place. These products, also obtained as epimeric mixtures, were formed in crude yields of 70–90%. Since purification of these intermediates proved difficult, the crude products were characterized only by spectral properties and desulfurized directly with Raney nickel. Under these conditions, acetates **4a–4d** were obtained in yields of 50–70% based on sulfoxide **2**.



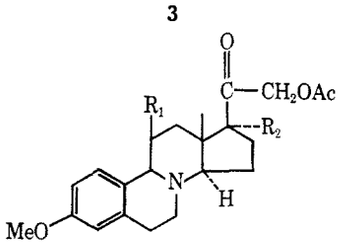
1



2



3



4

a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = OH$
c, $R_1 = OH$; $R_2 = H$
d, $R_1 = R_2 = OH$

Structural assignments were based on microanalysis and spectral data. Thus **3** showed two carbonyl peaks in the ir at 1715 (ketone) and 1755 cm^{-1} (acetate). In the nmr, the acetate methyl and S-methyl signals appeared at 2.13 and 2.00 ppm, respectively, while the C-21 proton resonated as a sharp singlet at 5.9 ppm. For **4**, the spectral data were the same as for **3** except for disappearance of the S-methyl signal and appearance of either a two-proton singlet or AB quartet at 4.65 ppm for the C-21 methylene.

For the dihydroxy ("d") series, the starting ester, **1d**, has not been previously reported, and was prepared by the route previously described.[1] Treatment of ester **5a**[4] sequentially with base followed by bromine, silver nitrate, and potassium borohydride gave **5b**, **5c**, and **1d**, respectively, in yields of 90–100%. This sequence

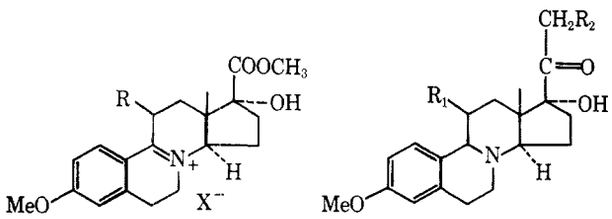
(1) Part V: R. E. Brown, H. V. Hansen, D. M. Lustgarten, R. J. Stanaback, and R. I. Meltzer, *J. Org. Chem.*, **33**, 4180 (1968).

(2) (a) H. D. Becker, G. J. Mikol, and G. A. Russell, *J. Amer. Chem. Soc.*, **85**, 3410 (1963); (b) G. A. Russell, E. Sabourin, and G. J. Mikol, *J. Org. Chem.*, **31**, 2854 (1966); (c) G. A. Russell and G. J. Mikol, *J. Amer. Chem. Soc.*, **88**, 5498 (1966).

(3) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1345 (1965).

(4) R. E. Brown, D. M. Lustgarten, R. J. Stanaback, and R. I. Meltzer, *J. Med. Chem.*, **10**, 451 (1967).

was best carried out without purification of the intermediates; thus **1d** was obtained from **5a** in 83% yield.



5a, R = H; X = ClO_4^-
b, R = Br; X = Br$^-$
c, R = =O; X = ClO_4^-

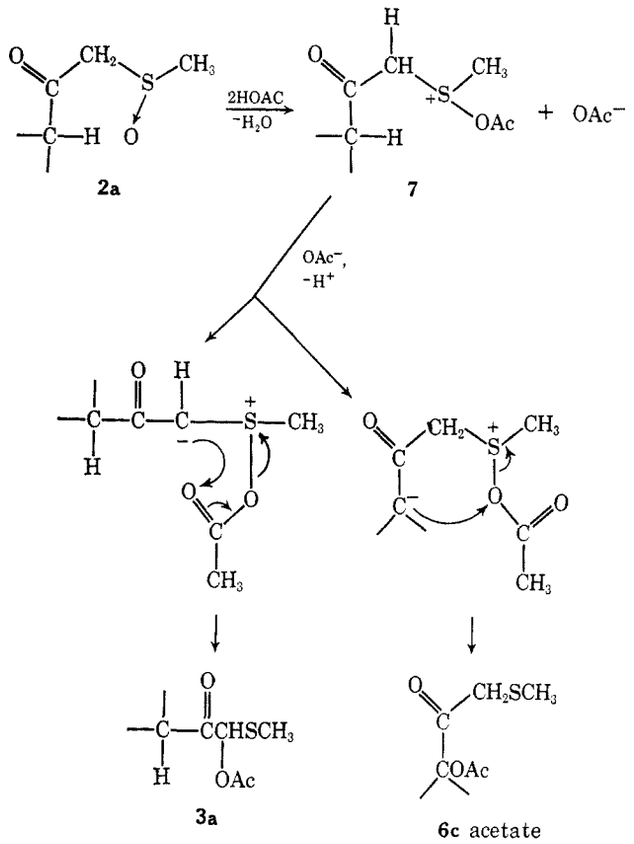
6a, $R_1 = R_2 = H$
b, R_1 = OH; $R_2 = H$
c, $R_1 = H$; $R_2 = SCH_3$

As in the previous work,[1] a single 11β-hydroxy base was obtained.

A by-product isolated in conversion of ester **1a** into acetate **4a** was identified (after hydrolysis of the acetate) as the 17α-hydroxy base **6a**[5,6] by comparison with a previously synthesized sample. We propose that formation of **4a** and **6a** acetate (*via* intermediates **3a** and **6c** acetate, respectively) occurs through five-membered cyclic transition states in which an acetate anion has abstracted a proton from either side of the carbonyl group.[7] The process can be formulated as shown in Scheme I.[8]

A small amount of by-product was similarly isolated from the **2c** to **4c** reaction mixture. Although this material was not examined further, the likelihood exists that it was the 17-acetate of **6b**, formed analogously to **6a** acetate.

SCHEME I



2a **7** **3a** **6c** acetate

Experimental Section[11]

Sulfoxide 2c was prepared from ester **1c**[1] in 86% yield as previously described.[4] The product was recrystallized from acetonitrile: mp 152–154°; ν_{max}^{Nujol} 1700, 3400 cm^{-1}.

Anal. Calcd for $C_{21}H_{29}NO_4S$: C, 64.42; H 7.46; N 3.58; S, 8.19. Found: C, 64.36; H, 7.64; N, 3.58; S, 8.23.

Tlc [methanol–chloroform (20:80)] showed two spots, R_f *ca.* 0.55 and 0.60.

Acetate 4a.—A solution of 24 g of sulfoxide **2a**[4] in 250 ml of acetic acid was heated on the steam bath for 2 hr. The acetic acid was removed and the residue was dissolved in water and made alkaline with 5% sodium hydroxide solution. The oil was extracted with ether. The ether solution was dried (magnesium sulfate) and concentrated to 24.1 g of oil which crystallized (crude **3a**). This was taken up in 2 l. of absolute ethanol and refluxed with stirring for 6 hr with *ca.* 200 g of Raney nickel.[12] The catalyst was filtered and washed well with ethanol. The combined filtrates were concentrated to a semisolid residue. This was triturated with ethanol to give 8.0 g of crystalline **4a**, mp 154–160°. Recrystallization from acetonitrile gave the analytical sample: mp 160–162°; ν_{max}^{Nujol} 1725, 1755 cm^{-1}.

Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 71.36; H, 8.12; N, 4.06.

The mother liquors were chromatographed on 700 g of neutral alumina. After removing 2.1 g of mixed fraction by elution with methylene chloride, subsequent methylene chloride fractions afforded 1.0 g of **6a** acetate, mp 168–172°.

Recrystallization from acetone–water gave the analytical sample: mp 177°; ν_{max}^{Nujol} 1715, 1735 cm^{-1}.

Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 71.51; H, 8.09; N, 4.01.

Hydrolysis of **6a** acetate (1% sodium hydroxide in aqueous methanol) gave alcohol **6a**, mp 198–199°, identical (melting point, mixture melting point, ir, nmr, tlc) with the material previously prepared by a different route.

On tlc (ethanol–chloroform, 15:85) products **4a** and **6a** acetate migrated as single spots of R_f 0.65 and 0.70, respectively.

Acetate 4b.—Ten grams of sulfoxide **2b**[4] were treated with acetic acid and Raney nickel as described for **4a** except that the period of reflux with Raney nickel was reduced to 1 hr. Purification of the crude product was effected by chromatography on Florisil; the product was eluted with anhydrous ether to give 5.0 g, mp 165–167°. Recrystallization from ethyl acetate–hexane gave the analytical sample: mp 166–168°; ν_{max}^{Nujol} 1720–1735, 3480 cm^{-1}.

Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.19; H, 7.54. Found: C, 68.05; H, 7.63.

(5) This proved of importance since it enabled an assignment of the *trans* stereochemistry at the C-D ring junction to be made to the 8-aza-19-norprogesterone series previously described. See ref 4, footnote 10.

(6) Formation of **6a** from **2a** requires the presence of the intermediate **6c** acetate in crude **3a**. Evidence for its presence was observed in the nmr spectrum of crude **3a** which displayed a weak (*ca.* 20% by integration) C-13 methyl signal at 0.95 ppm in addition to the corresponding signal of **3a** at its expected position of 0.86 ppm. The downfield shift of the C-13 methyl group in **6c** acetate relative to the 17-deoxy compound **3a** due to the 17α-acetoxy group is consistent with previous observations.[4]

(7) The cyclic transition states leading to **3a** and **6c** acetate are speculative. The possibility that the two different products result from sulfoxide epimers was considered; unfortunately we did not succeed in attempted separation of the epimers of **2a**.

(8) Formation of intermediate **7** (Scheme I) probably involves attack of the acetyl group of acetic acid on the sulfoxide oxygen followed by protonation and loss of water.[9] However, two alternatives not excluded by the evidence presented here are (1) attack of acetate oxygen on sulfur followed by loss of (doubly protonated) sulfoxide oxygen; (2) protonation of sulfoxide oxygen, loss of a proton from the α carbon, and attack of acetic acid on that carbon to give **4a** directly without intervention of a cyclic intermediate.[2a] A discussion of the scope and mechanism of the Pummerer reaction with leading references has been published.[10]

(9) S. Oae, M. Kise, and M. Yokoyama, *Bull. Chem. Soc. Jap.*, **41**, 1221 (1968).

(10) W. E. Parham and L. D. Edwards, *J. Org. Chem.*, **33**, 4150 (1968).

(11) Melting points were taken on a Fisher-Johns block and are uncorrected. Ultraviolet, infrared, and nmr spectra were determined on Beckman DK-1, Baird Model 455, and Varian A-60 instruments, respectively. Thin layer chromatography was done on Brinkman silica gel F_{254} plates and the spots were visualized with an iodine chamber. All samples for which analytical data are reported showed a single spot unless otherwise indicated. The nmr spectra were run in $CDCl_3$.

(12) Raney Active Nickel Catalyst No. 28 in water was purchased from W. R. Grace & Co., Raney Catalyst Division, Chattanooga, Tenn. It was activated by decanting the water and washing with decantation 15 times with absolute alcohol.

Acetate 4c.—From sulfoxide **2c** as described for **4b**. The crude crystalline product was obtained in 70% yield and showed two spots on tlc. It was recrystallized from ethyl acetate to give an analytical sample, mp 157–160°, which showed one spot and ν_{max}^{Nujol} 1730, 1755, 3600 cm^{-1}.

Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.19; H, 7.54; N, 3.62. Found: C, 68.39; H, 7.78; N, 3.38.

Chromatography of the mother liquors afforded a very small amount of another solid which was not investigated further.

Bromo Salt 5b.—Seventy grams of ester **5a** was converted into its free base and brominated as described previously.[1] Crude salt **5b** was used directly for preparation of **5c**. A sample was recrystallized from methanol for analysis: mp 182–185°; ν_{max}^{Nujol} 1560, 1600, 1610, 1730, 3200 cm^{-1}.

Anal. Calcd for $C_{20}H_{25}NO_4Br_2$: Br, 31.76. Found: Br, 31.94.

Keto Salt 5c.—The crude salt from the above preparation was treated with silver nitrate in acetonitrile as previously described.[1] Crude salt **5c** was used directly for preparation of ester **1d**. A sample was recrystallized from methanol for analysis: mp 140–143°; ν_{max}^{Nujol} 1550, 1590, 1610, 1725, 1740, 3500 cm^{-1}.

Anal. Calcd for $C_{20}H_{24}NO_9Cl$: C, 52.47; H, 5.78; Cl, 7.74. Found: C, 52.33; H, 5.54; Cl, 7.77.

Ester 1d.—The crude salt **5c** from the above preparation was reduced with potassium borohydride as previously described.[1] The crude base **1d** was used directly for preparation of sulfoxide **2d**. A sample was recrystallized from ethyl acetate–hexane for analysis: mp 158–160°; ν_{max}^{Nujol} 1710, 3350, 3475 cm^{-1}.

Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.56; H, 7.70; N, 4.01.

Sulfoxide 2d.—Prepared from ester **1d** in 70% yield. The product was recrystallized from acetonitrile: mp 204–206°; ν_{max}^{Nujol} 1705, 3300, 3600 cm^{-1}.

Anal. Calcd for $C_{21}H_{29}NO_5S$: C, 61.89; H, 7.17; S, 7.87. Found: C, 61.84; H, 7.43; S, 7.79.

Tlc [methanol–chloroform (20:80)] showed two sharp spots of R_f *ca.* 0.6.

Acetate 4d.—Carried out as described for **4c**. The crude residue from the Raney nickel treatment (55%) crystallized readily and was recrystallized from ethyl acetate for analysis: mp 191–193°; ν_{max}^{Nujol} 1730, 1755, 3400, 3450 cm^{-1}.

Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.25; N, 3.47. Found: C, 65.69; H, 7.31; N, 3.76.

Registry No.—**1d**, 21273-53-0; **2c**, 21273-54-1; **2d**, 21273-55-2; **4a**, 21273-56-3; **4b**, 21273-57-4; **4c**, 21273-58-5; **4d**, 21273-59-6; **5b**, 21273-60-9; **5c**, 21273-62-1; **6a** acetate, 21273-61-0.

Acknowledgment.—The authors wish to thank Professor E. L. Eliel for his helpful suggestions. We also thank Mr. A. D. Lewis and the members of his Analytical and Physical Chemical Section, Mrs. Unni Zeek and Mr. R. Puchalski, for the microanalyses and spectra.

Synthesis of 3,5α-Dichloro-3,5-seco-A-norcholestane

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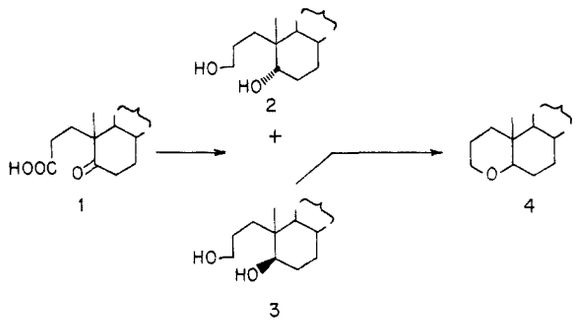
For use as a precursor in the synthesis of organometal substituted steroids, it became necessary to prepare 3,5α-dichloro-3,5-seco-A-norcholestane (**8**). The desired compound has the chlorines in 1,5 positions relative to each other, and possibly could be treated in a number of ways with ring closure to give cholestanes containing a heteroatom in the 4 position.

Reduction of Windaus' keto acid (**1**)[2,3] with lithium aluminum hydride led to a mixture of diols, 3,5-seco-A-norcholestane-3,5α-diol (**2**) and 3,5-seco-A-norcholestane-3,5β-diol (**3**) (Scheme I). These were separated

SCHEME I

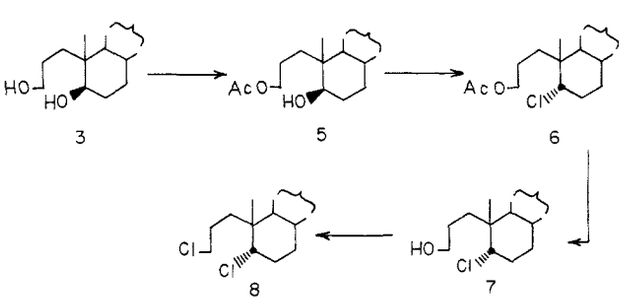


by column chromatography and identified by comparison of their optical rotations with those reported by Edward and Morand[4] for the known epimeric diols.

Initial attempts to react the 3,5α-diol (**2**) with thionyl chloride, a reaction which should proceed with retention of configuration to give the desired 3,5α dichloride, yielded only an oily mixture of unidentified composition. Reactions of the 3,5β-diol (**3**) with (1) phosphorus pentachloride, (2) triphenylphosphine and carbon tetrachloride or carbon tetrabromide,[5] (3) benzenesulfonyl chloride followed by reaction with bromide ion, or (4) phosphorus oxychloride,[6] all which would normally result in inversion of configuration, yielded only the known[7] cyclic ether 4-oxa-5 α-cholestane (**4**).[8,9]

The desired dichloride (**8**) was finally obtained by a sequence of reactions in which the diol monoacetate **5** was converted into the 5α chloride **6** with triphenylphosphine in carbon tetrachloride,[5,11] followed by hydrolysis to the carbinol **7** (Scheme II). Repetition of the chlorination reaction gave 3,5α-dichloro-3,5-seco-A-norcholestane (**8**) in an over-all yield of 32% from the diol **3**.

SCHEME II



(1) Part of Ph.D Thesis of A. B., University of Cincinnati, 1969; Institut für Ökologische Chemie, Birlinghoven, Germany.

(2) A. Windaus, *Ber.*, **39**, 2008 (1906).

(3) J. T. Edward, D. Holder, W. H. Lunn, and I. Puskas, *Can. J. Chem.*, **39**, 599 (1961).

(4) J. T. Edward and P. F. Morand, *ibid.*, **38**, 1325 (1960).

(5) J. Hooz and S. S. Gilani, *Can. J. Chem.*, **46**, 86 (1968).

(6) N. J. Doorenbos and M. T. Wu, *J. Org. Chem.*, **26**, 4550 (1961).

(7) G. R. Pettit and T. R. Kastori, *ibid.*, **26**, 4557 (1961).

(8) For general methods of preparing oxa steroids, see "Steroid Reactions, and Outline for Organic Chemists," C. Djerassi, Ed., Holden-Day, Inc., San Francisco, Calif., 1963, p 490, 492.

(9) An attempt to convert **3** into 3,5-α-dibromo-3,5-seco-A-norcholestane with triphenyldibromophosphorane[10] was unsatisfactory.

(10) G. A. Wiley, R. L. Hershkowitz, D. M. Rein, and B. C. Chung, *J. Amer. Chem. Soc.*, **86**, 964 (1964).

(11) J. B. Lee and I. M. Downie, *Tetrahedron*, **23**, 359 (1967).