Nor Steroids. X. Synthesis of A-Nor Steroids *via* the Dieckmann Condensation[1,2]

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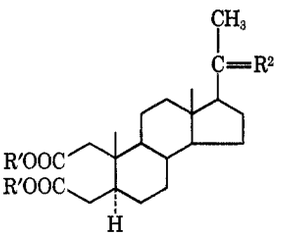
Received December 6, 1972

Dieckmann condensation of dimethyl 2,3-seco-5α-pregnan-20-one-2,3-dioate (Ia) gave an 84% yield of 3α-carbomethoxy-A-nor-5α-pregnane-2,20-dione (IIc). Alkylation of IIc with methyl iodide gave a 91% yield of a 1:1 mixture of the 3α- and 3β-methyl β-keto esters IId,e. Hydrolysis and decarboxylation of the mixture gave a mixture of 3α- and 3β-methyl-A-nor-5α-pregnane-2,20-diones (IIf,g) (80–85% 3α-methyl isomer). The same sequence of reactions in the cholestane series gave the β-keto ester IIIa in 70% yield, and alkylation of this with methyl iodide gave a mixture of the 3-methyl epimers IIIb,c in 69% yield. Hydrolysis and decarboxylation gave a 70% yield of 3α-methyl-A-nor-5α-cholestane-2-one (IIId).

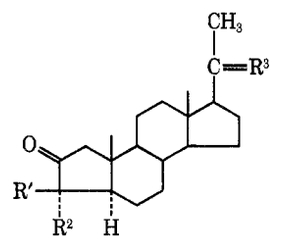
In a previous study[1] the application of the Dieckmann condensation, followed by the methylation of the resulting β-keto ester, to prepare 3-methyl-A-norandrostanes was described. This synthesis has now been extended to the pregnane and cholestane series.

In an earlier investigation[4] the condensation of dimethyl 2,3-seco-5α-pregnan-20-one-2,3-dioate (Ia) using sodium methoxide in benzene gave none of the desired product, but gave a 40% recovery of starting material and a 13% yield of A-nor-5α-pregnane-2,20-dione (IIa), apparently formed by loss of the carbomethoxy group under the conditions of the reaction. Using sodium in toluene, only starting material was recovered.

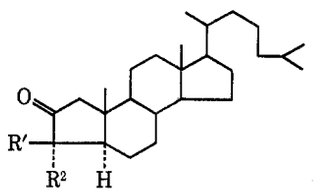
Since it seemed possible that in the earlier study the active hydrogens of the 21-methyl group might be interfering with the condensation, the 20,20-ethylenedioxy derivative (Ib) of the seco ester was prepared,



Ia, R′ = CH_3; R^2 = O
b, R′ = CH_3; R^2 = OCH_2CH_2O
c, R′ = H, R^2 = O



IIa, R′ = R^2 = H; R^3 = O
b, R′ = H; R^2 = CO_2Me; R^3 = OCH_2CH_2O
c, R′ = H; R^2 = CO_2Me; R^3 = O
d, R′ = CH_3; R^2 = CO_2Me; R^3 = O
e, R′ = CO_2Me; R^2 = CH_3; R^3 = O
f, R′ = CH_3, R^2 = H; R^3 = O
g, R′ = H; R^2 = CH_3; R^3 = O



IIIa, R′ = H, R^2 = CO_2Me
b, R′ = CH_3; R^2 = CO_2Me
c, R′ = CO_2Me; R^2 = CH_3
d, R′ = H; R^2 = CH_3

and the Dieckmann condensation was carried out using potassium *tert*-butoxide in benzene and *tert*-butyl alcohol. A 70% yield of the desired A-nor-β-keto ester IIb was obtained, and its structure was established by hydrolysis and decarboxylation to the known A-nor-5α-pregnane-2,20-dione (IIa).

Although this result seemed to substantiate the hypothesis that the 21-methyl group was causing the trouble in the earlier study, the condensation of the seco ester 20 ketone Ia was repeated, but with potassium *tert*-butoxide in place of sodium methoxide. In this instance an 84% yield of the desired 3α-carbomethoxy-A-nor-5α-pregnane-2,20-dione (IIc) was obtained, thus eliminating the interference of the 21-methyl group as the cause of the decarboxylation. The reasons for the lack of success in the earlier experiments are not known.

Although Fuchs and Loewenthal in an earlier study[5] had claimed that the condensation of the seco ester in the cholestane series gave the 3β-carbomethoxy isomer, the nmr data on the β-keto esters in the pregnane series indicated that the carbomethoxy group was α. The C-3 hydrogen appeared as a doublet at δ 3.08 (J = 13 Hz) for the β-keto ester 20-ethylene ketal IIb.

Molecular models indicate that the dihedral angle for the hydrogens at C-3 and C-5 in the 3β-carbomethoxy isomer is approximately 30°, while the angle for the 3α isomer is about 150°. Using the Williamson–Johnson modification[6] of the Karplus equation,[7] the β isomer should show J = 7.5 Hz for the 3α hydrogen, and the α isomer should show J = 13 Hz for the 3β hydrogen. The observed J value of 13 Hz indicates that the condensation product is indeed the 3α-carbomethoxy isomer IIb.

The condensation product from the 20-keto compound IIc showed absorption of the C-3 hydrogen at δ 3.01 (J = 13 Hz), again indicating that the product

(1) For the previous paper in the series see H. R. Nace and J. L. Pyle, *J. Org. Chem.*, **36**, 81 (1971).

(2) Supported in part by the USPHS under Grant No. 5R01 AM 11024-02MCHA.

(3) Abstracted from the Ph.D. Thesis of A. H. S., Brown University, 1968.

(4) D. H. Nelander, Ph.D. Thesis, Brown University, 1963.

(5) B. Fuchs and H. E. Loewenthal, *Tetrahedron*, **11**, 199 (1960).

(6) K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, **83**, 4623 (1961).

(7) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

was the 3α-carbomethoxy isomer. These structures are in accord with those assigned in the androstane series by Nace and Pyle,[1] and in the cholestane series by Paranjape and Pyle[8] and the present authors (see below).

The β-keto ester (20-keto series) IIc was alkylated with potassium *tert*-butoxide and methyl iodide to give a mixture of the 3α- and 3β-methyl β-keto esters IId,e in 91% yield. Integration of the nmr peaks for the 3α- and 3β-$OCOCH_3$ (δ 3.62 and 3.65) indicated that the mixture was 1:1.

The alkylated β-keto ester was hydrolyzed and decarboxylated by heating in a mixture of hydrochloric and acetic acids, to give a mixture of 3α- and 3β-methyl-*A*-nor-5α-pregnane-2,20-diones (IIf,g). The nmr spectral data (see Experimental Section) indicated that the mixture contained 80–85% of the 3α-methyl isomer IIg. Once the β-keto acid is decarboxylated, the 2 ketone can readily equilibrate to give the observed ratio, in which the 3α-methyl compound is the more stable, by analogy with the results obtained for the unalkylated β-keto ester.

In order to clear up any ambiguity about the structure of Fuchs and Loewenthal's β-keto ester,[5] their work was repeated. Dimethyl 2,3-secocholestane-2,3-dioate was treated with potassium *tert*-butoxide to give the β-keto ester IIIa in 70% yield, with physical constants identical with those reported. In the nmr spectrum the C-3 hydrogen appeared at δ 3.08 (J = 13 Hz), indicating that it was β, as discussed above. Accordingly, the carbomethoxy group must be α, contrary to the previous assignment. No change in the J value was observed at 40 MHz.

Alkylation of the β-keto ester with methyl iodide and potassium *tert*-butoxide gave the 3-methyl derivative IIIb,c in 69% yield, as a mixture of isomers epimeric at C-3.

Hydrolysis and decarboxylation proved to be difficult, but prolonged heating with acetic acid and hydrogen bromide gave 3α-methyl-*A*-nor-5α-cholestan-2-one (IIId) in 70% yield. The 100-MHz nmr spectrum showed a doublet at δ 1.03 (J = 7 Hz) for the 3α-methyl group, and there was no indication that any of the 3β isomer was present.

On the basis of these results and those previously reported, the alkylation of *A*-nor-β-keto esters offers an attractive route for introduction of a methyl group into the five-membered ring.

Experimental Section[9]

2,3-Seco-5α-pregnan-20-one-2,3-dioic Acid (Ic).—To a solution of 12.6 g (40.0 mmol) of 5α-pregnane-3,20-dione in 535 ml of 95% acetic acid was added 12.6 g of chromium trioxide, the solution was heated at 60° for 10 hr, then 500 ml of water was added and the mixture was allowed to stand overnight at room temperature. Then it was extracted with 10 × 300 ml of ether, and the extract was washed with water and evaporated to dryness under reduced pressure. The residue was added to 1 l. of 20% K_2CO_3 solution and additional K_2CO_3 was added to pH 9. After washing with 4 × 200 ml of ether the solution was acidified with concentrated HCl and the resulting precipitate was collected, washed with water, and air dried. Recrystallization from acetic acid–water gave 5.46 g (38%) of seco diacid: mp 216–217.5° (lit.[10] mp 218°); $[\alpha]_D$ +91° (*c* 0.48, $CHCl_3$); R_f 0.69 (3:1:1 benzene–ether–acetic acid); ir ($CHCl_3$) 3500–2600 and 1710 cm^{-1}; nmr ($CDCl_3$) δ 0.62 (C-18 CH_3), 0.82 (C-19 CH_3), 2.13 (C-21 CH_3), and 8.38 (COOH); mass spectrum (70 eV) m/e (rel intensity) 364 (0.3) (M^+), 44 (base peak).

Dimethyl 2,3-Seco-5α-pregnan-20-one-2,3-dioate (Ia).—A solution of 1.02 g (2.8 mmol) of 2,3-seco-5α-pregnan-20-one-2,3-dioic acid in 240 ml of a 10% methanolic hydrogen chloride solution was boiled under reflux for 3 hr, allowed to stand overnight at room temperature, and then evaporated to dryness under reduced pressure. Water (100 ml) was added to the residue, then K_2CO_3 to pH 9, and the mixture was extracted with 4 × 50 ml of ether. The extract was washed with saturated brine, dried (Na_2SO_4), and evaporated to give 942 mg (86%) of a colorless oil which could not be crystallized: R_f 1.00; ir ($CHCl_3$) 1735 and 1702 cm^{-1}; $[\alpha]_D$ +71° (*c* 0.9, $CHCl_3$); nmr (CCl_4) δ 0.57 (C-18 CH_3), 0.80 (C-19 CH_3), 2.05 (C-21 CH_3), and 3.63 (s, 6, OCH_3).

Dimethyl 2,3-Seco-20,20-ethylenedioxy-5α-pregnane-2,3-dioate (Ib).—A solution of 1.20 g (3.0 mmol) of the seco diester and 80 mg of *p*-toluenesulfonic acid in 40 ml of benzene and 12.5 ml of ethylene glycol was boiled under reflux with a Dean–Stark trap for 24 hr while 20 ml of distillate was removed. Then 25 ml more of benzene was added and refluxing was continued for 20 hr. The reaction mixture was extracted with 3 × 20 ml of benzene, and the extract was washed with alcoholic KOH, water (2 × 20 ml), and 25 ml of saturated brine, dried (Na_2SO_4), and evaporated to give 1.28 g (94%) of a pale yellow solid. Recrystallization from methanol gave the product as white needles: mp 128–129.5°; ir (CCl_4) 1745 cm^{-1}; $[\alpha]_D$ +63° (*c* 0.96, $CHCl_3$); R_f 1.15; nmr (CCl_4) δ 0.70 (C-18 CH_3), 0.78 (C-19 CH_3), 1.20 (C-21 CH_3), 3.28 (broad, 4, $-OCH_2CH_2O-$), and 3.58 (s, 6, OCH_3); mass spectrum (70 eV) m/e (rel intensity) 421 (1.7) ($M^+ - CH_3$), 87 (base peak).

Anal. Calcd for $C_{25}H_{40}O_6$: C, 68.78; H, 9.23. Found: C, 69.68, 69.95; H, 9.16, 9.33. Further recrystallization and drying did not improve the analytical values, and the high value for carbon is anomalous.

3α-Carbomethoxy-20,20-ethylenedioxy-*A*-nor-5α-pregnan-2-one (IIb).—Under nitrogen, 0.07 g (1.8 mg-atom) of potassium was added to 5 ml of *tert*-butyl alcohol and 5 ml of benzene (solvents dried for 24 hr over calcium hydride and distilled), and after the potassium had reacted, a solution of 150 mg (0.34 mmol) of the seco ester Ib in 10 ml of benzene was added with a syringe with stirring. The solution was then boiled under reflux (nitrogen atmosphere) with a Dean–Stark trap for 17 hr, during which time 5 ml of solvent was removed. The dark orange solution was cooled to room temperature, 15 ml of water, 20 ml of benzene, and 1 ml of dilute HCl were added, the benzene layer was washed with water, 5% $NaHCO_3$, and water (to neutrality) and dried (Na_2SO_4), and the solvent was evaporated to give 97 mg (70%) of white solid. Recrystallization from methanol gave the *A*-nor compound IIb as white needles: mp 177–179°; $[\alpha]_D$ +98° (*c* 1.01, $CHCl_3$); ir ($CHCl_3$) 1755 and 1725 cm^{-1} (an acetone solution gave a green color with ferric chloride); nmr ($CDCl_3$) δ 0.80 (C-18 CH_3), 0.88 (C-19 CH_3), 1.30 (C-21 CH_3), 3.08 (d, J = 13 Hz, C-3 β-H), 3.75 (s, 3, OCH_3), and 3.93 (m, 4, OCH_2CH_2O) (at 40 MHz the 3.08 doublet had J = 12.5 Hz); mass spectrum (70 eV) m/e (rel intensity) 389 (2.3) ($M^+ - CH_3$), 87 (base peak).

(8) B. V. Paranjape and J. L. Pyle, *J. Org. Chem.*, **36**, 1009 (1971).

(9) Melting points were determined with a Herschberg apparatus and Anschutz thermometers and are corrected. Analytical determinations were by Schwarzkopf Microanalytical Laboratory or Midwest Microlab, Inc. Nmr spectra were determined on Varian Models HR-60 and A-60A spectrometers at 60 MHz, unless specified otherwise. TMS was used as internal standard and peak positions are reported in parts per million (δ) downfield from TMS. The authors are indebted to Dr. J. MacReed of the Plastics Department, E. I. du Pont de Nemours and Co., for the two 100-MHz spectra. Mass spectra were obtained with a Hitachi Perkin-Elmer Model RMU-6D mass spectrometer equipped with an MG-150 solid sample direct inlet into the ionization chamber. Thin layer chromatography (tlc) was performed on type K 301 R Eastman chromagram sheets coated with silica gel, the tlc's were developed with 3:1 benzene–ether, and the spots were visualized by spraying with 2,4-dinitrophenylhydrazine in phosphoric acid–ethanol solution, or exposure to iodine vapor. The R_f values were measured relative to 5α-pregnane-3,20-dione. Vapor phase chromatography (vpc) was performed on an Aerograph Model 204 chromatograph, equipped with a flame ionization detector, and a 4-ft column packed with a 1% QF-1 coating on Gas-Chrom Z support. The T_R values refer to retention times relative to that of *A*-nor-5α-pregnane-2,20-dione as the standard at the temperature specified.

(10) R. E. Marker, O. Kamm, and D. M. Jones, *J. Amer. Chem. Soc.*, **59**, 1595 (1937). This procedure consistently gave low yields, *ca.* 15%, in our hands.

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.57; H, 9.24.

Hydrolysis and Decarboxylation of the A-Nor Ketal IIb.—A solution of 100 mg (0.25 mmol) of the above *A*-nor compound in 15 ml of glacial acetic acid and 5 ml of concentrated HCl was boiled under reflux for 70 hr (2 ml of water added after 48 hr) and cooled to room temperature, 20 ml of water was added, and the mixture was extracted with ether. The ether was evaporated, 50 ml of water was added to the residue, K_2CO_3 was added to neutralize acetic acid, and the mixture was extracted with 3 × 20 ml of ether. The extract was washed with water and saturated brine, dried ($MgSO_4$), and evaporated to give 50 mg (67%) of solid which was recrystallized from ethanol–water to give *A*-nor-5α-pregnane-2,20-dione (IIa), mp 174–177° (lit.[11] mp 176–179°). The ir and nmr spectra and R_f were identical with those of an authentic sample; mass spectrum (70 eV) *m/e* (rel intensity) 302 (75.6) (M^+), 43 (base peak).

Dieckmann Condensation of Dimethyl 2,3-Seco-5α-pregnan-20-one-2,3-dioate (Ia).—The ester (450 mg, 1.15 mmol) in 26 ml of benzene was added to 0.15 g of potassium dissolved in 12.5 ml of *tert*-butyl alcohol and 17.5 ml of benzene, heated as above for 17 hr, and worked up as above to give 345 mg (84%) of 3α-carbomethoxy-*A*-nor-5α-pregnane-2,20-dione (IIc). A 240-mg sample was chromatographed on 10 g of silica gel and elution with 5% ether in benzene gave 200 mg of white solid: mp 144–150°; ir ($CHCl_3$) 1755, 1725, and 1700 cm^{-1}; nmr ($CDCl_3$) δ 0.63 (C-18 CH_3), 0.90 (C-19 CH_3), 2.10 (s, 3, C-21 CH_3), 3.01 (d, 1, J = 13 Hz, C-3 β-H), and 3.73 (s, 3, $OCOCH_3$). The addition of 2 drops of D_2O had no effect on the spectrum, but a few crystals of K_2CO_3 caused an immediate decrease in the intensity of the doublet at δ 3.01, and after 5 min the doublet had virtually disappeared. No other change was apparent in the spectrum, even after 24 hr.

Mass spectrum (70 eV) showed *m/e* (rel intensity) 360 (58.6) (M^+), 43 (base peak); $[\alpha]_{589}$ +167°, $[\alpha]_{578}$ +179°, $[\alpha]_{546}$ +205°, $[\alpha]_{436}$ +467°, $[\alpha]_{365}$ +1176° (*c* 0.3, $CHCl_3$). A portion was sublimed at 130° (0.25 mm) to give the analytical sample, mp 147–150°.

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.10; H, 8.93.

Methylation of the A-Nor Ester IIc.—To a solution of 800 mg (2.22 mmol) of 3α-carbomethoxy-*A*-nor-5α-pregnane-2,20-dione (IIc) in 5 ml of benzene was added a solution of 400 mg (2.8 mmol) of potassium *tert*-butoxide in 40 ml of *tert*-butyl alcohol (all carried out in a drybox under nitrogen), and the solution was stirred for 45 min. Then 430 mg of methyl iodide (distilled from zinc dust) was added, and the solution was stirred for 2 hr and then boiled under reflux under nitrogen overnight. After cooling, 10 ml of 6 *N* hydrochloric acid and 100 ml of benzene were added, and the benzene layer was removed, washed with water, K_2CO_3 solution, water again to neutrality, and saturated brine, dried ($MgSO_4$), and evaporated to give 758 mg (91%) of 3-carbomethoxy-3-methyl-*A*-nor-5α-pregnane-2,20-dione (IId,e) as a colorless oil which could not be crystallized: ir ($CHCl_3$) 1750, 1725, and 1700 cm^{-1}; R_f 1.06; nmr ($CDCl_3$) δ 0.67 (C-18 CH_3), 0.92 (broad, shoulder at 0.88, C-19 CH_3), 1.30 and 1.37 (C-3 α- and β-CH_3's), 2.13 (C-21 CH_3), 3.67 and 3.68 (C-3 α- and β-$OCOCH_3$'s); in CCl_4, δ 3.62 and 3.65 (C-3 α- and β-$OCOCH_3$'s, integration indicated a 1:1 mixture).

3-Methyl-*A*-nor-5α-pregnane-2,20-dione (IIf,g).—A solution of 878 mg (2.35 mmol) of the methylated *A*-nor ester in 80 ml of glacial acetic acid and 80 ml of concentrated HCl was heated at 97° for 6 days (20 ml of water was added after the first day), then cooled to room temperature and added to 400 ml of water. Solid K_2CO_3 was added to basicity and the solution was extracted with ether. The extract was washed to neutrality with water, then with saturated brine, dried ($MgSO_4$), and evaporated to give 550 mg of brown solid, which was chromatographed on 40 g of silica gel. Elution with 10% ether in benzene gave 262 mg of a yellow solid, a mixture of 3α- and 3β-methyl-*A*-nor-5α-pregnane-2,20-dione (IIf,g): nmr ($CDCl_3$) δ 0.65 (C-18 CH_3), 0.8–1.18 (m, 7, C-19 and C-3 CH_3's, plus one proton from the steroid nucleus, indicating a mixture of C-3 epimers), and 2.12 (C-21 CH_3).

The 100-MHz spectrum ($CDCl_3$) showed δ 0.64 (s, C-18 CH_3), 0.87 (d, J = 1 Hz, C-19 CH_3), 0.88 (d, J = 6.5 Hz, C-3 CH_3), 1.02 (d, J = 6 Hz, epimeric C-3 CH_3's), and 2.11 (s, C-21 CH_3); in benzene-d_6, δ 0.52 (s, C-18 CH_3) and 1.18 (s, C-21 CH_3). The C-19 CH_3 was shifted upfield to δ 0.54. The larger of the C-3 CH_3 doublets remained relatively unshifted at δ 1.00 (J = 7 Hz) and was assigned to the C-3 α-CH_3. The smaller doublet was shifted upfield to δ 0.62 (J = 7 Hz) and was assigned to the C-3 β-CH_3. Integration of these two doublets indicated a mixture of 80–85% of the α-methyl and 15–20% of the β-methyl epimer, ir ($CHCl_3$) 1735 and 1698 cm^{-1}.

The solid was sublimed at 90° (0.25 mm) to give 190 mg (25%) of the methyl *A*-nor ketone mixture, mp 125–135°, R_f 1.10 (elongated spot). A portion of this material was resublimed at 90° (0.4 mm) to give an analytical sample, mp 126–134°, mass spectrum (70 eV) *m/e* (rel intensity) 316 (49.2) (M^+) and 43 (base peak).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 78.92; H, 10.10.

A second fraction (250 mg) was also eluted from the column with 10% ether in benzene, and the brown solid appeared to be a mixture of two components, R_f 0.61 and 1.17, the latter the epimeric C-3 methyl mixture, based on the nmr spectrum.

Dimethyl 2,3-Secocholestane-2,3-dioate.—A solution of 1.31 g (3.06 mmol) of 2,3-secocholestane-2,3-dioic acid ln 270 ml of 10% methanolic hydrogen chloride was allowed to stand at room temperature for 4 days, and then the solvent was removed under reduced pressure and the residue was triturated with 150 ml of K_2CO_3 solution (pH 10). The mixture was extracted with benzene, and the extract was washed with water and saturated brine, dried ($MgSO_4$), and evaporated to give 1.40 g of white solid. This was chromatographed on 50 g of silica gel and elution with benzene gave 1.35 g (95%) of the dimethyl ester: mp 61–63° (lit.[5] mp 62–64°); ir ($CHCl_3$) 1730 cm^{-1}; R_f 1.56; T_R^{215} 2.03; $[\alpha]_D$ +21° (*c* 0.75, $CHCl_3$); nmr δ 0.65 (C-18 CH_3), 0.78 (C-19 CH_3), 0.88 (side chain CH_3's), and 3.68 (s, 6, OCH_3's).

3α-Carbomethoxy-*A*-nor-5α-cholestan-2-one (IIIa).—A solution of 790 mg (1.5 mmol) of the seco ester in 36 ml of dry benzene was added rapidly to a stirred solution of 0.15 g (3.7 mg-atom) of potassium in 17.5 ml of benzene and 17.5 ml of *tert*-butyl alcohol (both solvents distilled from calcium hydride) and the resulting solution was boiled under reflux (nitrogen atmosphere, Dean–Stark trap) for 17 hr while 25 ml of distillate was collected in the trap. The solution was then cooled to room temperature, 30 ml of water and 10 ml of dilute HCl were added, the water layer was removed, and the organic layer was made up to 150 ml with benzene. It was then washed with water, 5% $NaHCO_3$, and water and dried ($MgSO_4$), and the solvent was removed to give 636 mg of an oil which solidified on standing. Recrystallization from methanol gave 517 mg (70%) of 3α-carbomethoxy-*A*-nor-5α-cholestan-2-one: double mp 109.5–110.5° and 121–123° (lit.[5] mp 110–111° and 120–121°); ir ($CHCl_3$) 1755 and 1725 cm^{-1}; $[\alpha]_D$ +99° (589 nm), +105° (578), +124° (546), +268° (436), and +658° (365) (*c* 0.71, $CHCl_3$) (lit.[5] $[\alpha]_D$ +119°); R_f 1.40; T_R^{215} 1.30; nmr δ 0.67 (C-18 CH_3), 0.80 (C-19 CH_3), 0.85, 0.90 (side chain CH_3's), 2.16 (d, 2, C-1-CH_2), 3.08 (d, 1, J = 13 Hz, C-3 H), and 3.75 (s, 3, OCH_3) (at 40 MHz, the C-3 H appeared as a doublet, J = 12.9 ± 0.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 430 (42) (M^+), 275 (base peak).

3α-Methyl-*A*-nor-5α-cholestan-2-one (IIId).—To a solution of 150 mg (0.35 mmol) of the β-keto ester in 7.5 ml of dry benzene was added a solution of 60 mg (0.42 mmol) of sublimed potassium *tert*-butoxide in 7.5 ml of *tert*-butyl alcohol, the solution was stirred for 0.5 hr, and then 37.5 μl (1.3 equiv) of methyl iodide (distilled from Zn dust) was added, and the solution was stirred for 3 hr. All of the preceding operations were carried out in a dry box under a nitrogen atmosphere. Then 10 ml of dilute HCl and 40 ml of benzene were added, the water layer was removed after shaking, and the organic layer was washed with water, saturated K_2CO_3 solution, and water and then dried ($MgSO_4$) and evaporated to give 113 mg (69%) of 3-carbomethoxy-3-methyl-*A*-nor-5α-cholestan-2-one (IIIb,c) as a colorless oil which solidified to a low-melting solid on standing: ir ($CHCl_3$) 1749 and 1725 cm^{-1}; nmr ($CDCl_3$) δ 0.68 (s, C-18 CH_3), 0.83 and 0.92 with shoulders at 0.90 and 0.95 (C-19 CH_3 and side chain CH_3's), 1.30 and 1.35 (C-3 CH_3), and 3.67 with a shoulder at 3.75 (C-3 $OCOCH_3$); in benzene, δ 0.63 (C-18 CH_3), 0.90, 1.00, 1.05, and 1.10 (C-19 CH_3 and side chain CH_3's), 1.35 (C-3 CH_3), 3.32 with a shoulder at 3.33 (C-3 $OCOCH_3$). The nmr data indicated that two isomers, epimeric at C-3, were present.

(11) H. R. Nace and A. C. Watterson, Jr., *J. Org. Chem.*, **31**, 2109 (1966).

A 100-mg (0.26 mmol) sample of the mixture in 5 ml of glacial acetic acid and 4 ml of concentrated HCl was boiled under reflux for 4 days and poured into 40 ml of water, and the mixture was extracted with benzene (3 × 15 ml). The extract was washed with water until neutral, with 10 ml of saturated K_2CO_3 solution, and with water (4 × 10 ml) and dried ($MgSO_4$), and the solvent was removed to give 88 mg of white solid, nmr (CCl_4) δ 3.60 (C-3 $OCOCH_3$, half the area of the C-18 CH_3 at 0.67, indicating only about 50% hydrolysis). The mixture was taken up in 4 ml of glacial acetic acid and 4 ml of 48% hydrobromic acid and boiled under reflux for 2.5 days. After work-up as above 63 mg (70%) of a white solid was obtained; the nmr spectrum showed no methoxy absorption at δ 3.60. After recrystallization from methanol, 54 mg of 3α-methyl-*A*-nor-5α-cholestan-2-one (IIId) was obtained: double mp 124–125.5° and 131.5–133°; $[\alpha]_{589}$ +110°, $[\alpha]_{578}$ +113°, $[\alpha]_{546}$ +138°, $[\alpha]_{436}$ +296°, $[\alpha]_{365}$ +754° (*c* 0.15, $CHCl_3$); $T_R^{115°}$ 1.26; R_f 1.40; nmr ($CDCl_3$) δ 0.70 (s, C-18 CH_3), 0.83, 0.88, 0.93, and 0.97 (C-19 CH_3 and side chain CH_3's), and a new peak at 1.08 (part of doublet for C-3 CH_3); nmr (100 MHz) ($CDCl_3$) δ 0.70 (s, C-18 CH_3), 0.85, 0.90, 0.92, and 0.95 (s, C-19 CH_3 and side chain CH_3's), and 1.03 (d, J = 7 Hz, C-3 CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 386 (68) (M^+) and 231 (base peak).

Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.65; H, 12.09.

Registry No.—Ia, 39010-42-9; Ib, 39010-43-0; Ic, 26654-59-1; IIb, 39010-45-2; IIc, 39010-46-3; IId, 39010-47-4; IIe, 39010-48-5; IIf, 39010-49-6; IIg, 39010-50-9; IIIa, 27460-19-1; IIIb, 39010-52-1; IIIc, 39010-53-2; IIId, 39010-54-3; 5α-pregnane-3,20-dione, 566-65-4; 2,3-secocholestane-2,3-dioic acid, 1178-00-3; dimethyl 2,3-secocholestane-2,3-dioate, 1180-24-1.

Hydride Reductions of Naphthalic Anhydrides[1]

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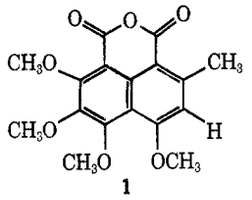
Received December 27, 1972

Diborane reduction, at room temperature, of 1,8-naphthalic anhydrides yields the corresponding cyclic ether (2,1,3-*peri*-naphthopyran) as sole isolable product. Reduction with diborane of 1,8-naphthalide also yields only the *peri*-naphthopyran, but in twice the yield obtained from the anhydride. If both the 2 and 7 positions in the anhydride are occupied, reduction fails to occur. Diborane reduction of 1,2-naphthalic anhydride, or of the adduct from anthracene and maleic anhydride, yields only the corresponding diol. Lithium aluminum hydride reduction, at room temperature, of 1,8-naphthalic anhydride yields no *peri*-naphthopyran, but a mixture of diol and 1,8-naphthalide; 1,2-naphthalic anhydride gives similar results. 2,7-Dimethoxy-1,8-naphthalic anhydride, on lithium aluminum hydride reduction in refluxing tetrahydrofuran, yields no diol but a mixture of naphthalide and cyclic ether, with increase in ratio of cyclic ether as reaction time is increased. The data indicate that the naphthalide (lactone) is a common intermediate for formation of either diol or cyclic ether and that diol is not an intermediate in cyclic ether formation. The first step in the sequence proceeds at a higher rate with lithium aluminum hydride, whereas the second step is faster with diborane. 7-Methyl-2,3,4,5-tetramethoxy-1,8-naphthalic anhydride (**1**), on lithium aluminum hydride reduction, yields only one of the two possible naphthalides; structure **7** has been assigned on the basis of nmr data.

In the course of our earlier investigation[2] of methods for synthesis of substituted 1,8-naphthalic anhydrides, it was discovered that diborane rapidly reduces this type of anhydride, at room temperature, to the corresponding cyclic ether, the 2,1,3-*peri*-naphthopyran. This result was unexpected, since diborane fails to reduce acid chlorides at room temperature,[3] and even sodium borohydride, used by us for preparation of the diborane *in situ*, reduces aromatic acid chlorides only slowly at steam bath temperature.[4] The present investigation is concerned with additional study of reductions with diborane and with lithium aluminum hydride.

1,8-Naphthalic anhydride, as well as 3-methoxy-1,8-naphthalic anhydride, give about the same yield (40%) on reduction at room temperature with diborane, and no other products could be isolated; however, when both the 2 and 7 positions were occupied, reduction failed to occur. Starting material was recovered when there was utilized either 2,7-dimethoxy-1,8-naphthalic anhydride or 7-methyl-2,3,4,5-tetramethoxy-1,8-naphthalic anhydride[5] (**1**). When the same reaction conditions were used for reduction of 1,8-naphthalide (**2**), 2,1,3-*peri*-naphthopyran was again obtained, but in



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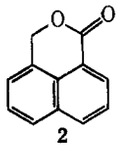

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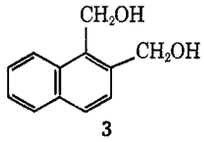
~80% yield.[6] Thus, the intermediacy of **2** in the reduction of 1,8-naphthalic anhydride is suggested.

When 1,2-naphthalic anhydride was subjected to diborane reduction, the sole product isolable from the reaction was the diol, **3**. Similarly, when the adduct of



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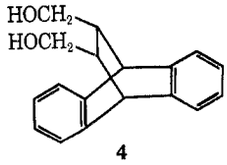

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maleic anhydride and anthracene was reduced, the only product obtained was diol **4**. Thus in absence of the notably stable 2,1,3-*peri*-naphthopyran system, cyclic ether is not formed. Much of the chemistry of the peri-substituted naphthalenes is dominated by the stability of this ring system. For example, 1,8-naphthalic anhydride fails to react with alcohols; indeed,

(1) This investigation was supported in part by a research grant (G-9866) from the National Science Foundation.

(2) J. Cason, A. Weiss, and S. A. Monti, *J. Org. Chem.*, **33**, 3404 (1968).

(3) H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **82**, 681 (1960).

(4) S. W. Chaikin and W. G. Brown, *ibid.*, **71**, 122 (1949).

(5) J. Cason and D. M. Lynch, *J. Org. Chem.*, **31**, 1883 (1966).

(6) There have been several reports of hydride reductions of esters, including lactones, to ethers. The pioneering report of reduction of lactones to tetrahydropyrans by diborane seems to be that of G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, **26**, 4557 (1961).