0.0006 mol) and LiCl (0.05 g) in 20 ml of DMF was heated at 140° for 10 hr. The crude product was chromatographed on silica gel. Elution with benzene–hexane (4:6) gave 3β-acetoxy-17-methyl-$\Delta^{17(17a)}$-D-homo-5α-androstene (VIa) (0.18 g, 86%), mp 119–120.5°. It showed no depression of its melting point when mixed with the unsaturated product obtained by the reduction of the bromo compounds (IIa and IIIa) with Raney nickel. The ir spectra were also in agreement.

Hydrolysis of compound VIa with 2% methanolic KOH gave the free alcohol (VIb) which was recrystallized from aqueous acetone as plates: mp 128–129°; $[\alpha]^{20}D$ +50.8° (c 0.750). The infrared spectrum showed the hydroxyl bands at 3610 and 1035 cm^{-1}.

Anal. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.33. Found: C, 83.36; H, 11.19.

Registry No.—I, 17182-23-9; IIa, 17182-24-0; IIb, 17182-25-1; IIIa, 17182-26-2; IIIb, 17182-27-3; IVa, 17182-28-4; IVb, 17182-29-5; IVc, 17182-67-1; VIa, 17182-68-2; VIb, 17182-69-3; phosphorus pentabromide, 7789-69-7.

Notes

D-Homoannulation of 3β-Acetoxy-5α-pregnan-20β-ol with Some Chlorinating Agents

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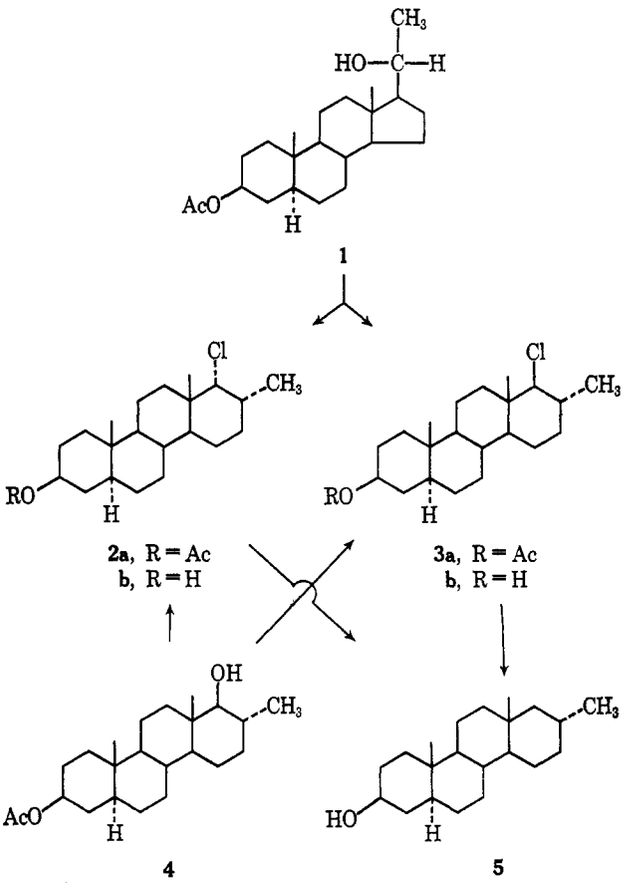
In continuance of our studies of the halogenation of 3β-acetoxy-5α-pregnan-20β-ol[2] (**1**), we wish now to report our observations on the treatment of **1** with several chlorinating agents. We find that chlorination of **1** with phosphorus pentachloride, sulfuryl chloride, or thionyl chloride, under the same conditions described by Adam and Schreiber,[3] leads to D-homoannulation, similar to our previous observation of **1** with phosphorus pentabromide,[2] to afford the two chloro derivatives, 3β-acetoxy-17aα- and -17aβ-chloro-17α-methyl-D-homo-5α-androstanes, **2a** and **3a**, and not 3β-acetoxy-20α- and -20β-chloro-5α-pregnanes[4] as reported.[3]

The halogenation of compound **1** with phosphorus pentachloride or sulfuryl chloride yields predominantly the chloro derivative **2a** (56% PCl_5 and 39% SO_2Cl_2) whereas thionyl chloride affords the chloro compound **3a** as the major product (63%).

The D-homo structure of **2a** and **3a** was established by their synthesis from the reaction of the known 3β-acetoxy-17α-methyl-D-homo-5α-androstan-17aβ-ol (**4**)[5a] with phosphorus pentachloride. The yields of **2a** and **3a** in the reaction were 56 and 18%, respectively. Lithium aluminum hydride reduction of both **2a** and **3a** to 17α-methyl-D-homo-5α-androstan-3β-ol (**5**)[2] further substantiated the D-homo assignment.



The possibility of D-homoannulation occurring on the silica gel column after the reaction, as in the manner reported for 3β-acetoxy-20-chlorobisnorallocholane,[6] is excluded since both **2a** and **3a** are obtained directly from the reaction mixture by crystallization without resort to chromatography.

The difference in the ratios of the rearrangement products obtained in the reaction of **1** with phosphorus pentachloride and thionyl chloride can be rationalized by assuming that, in the reaction with phosphorus

(1) Visiting Fellow, 1966–1968.

(2) R. T. Li and Y. Sato, *J. Org. Chem.*, **33**, 3632 (1968).

(3) G. Adam and K. Schreiber, *Tetrahedron Lett.*, 923 (1965); G. Adam and K. Schreiber, *Tetrahedron*, **22**, 3581 (1966).

(4) We wish to thank Professor K. Schreiber for sending us a sample of their 3β-acetoxy-20α-chloro-5α-pregnane for comparison purposes. The infrared spectrum of their sample is similar to our compound **2a**, but with a slight contamination by compound **3a**. This probably accounts for the discrepancies in melting point and optical rotation of their compounds with those of our samples.

(5) (a) H. Hirschmann, F. B. Hirschmann, and A. P. Zala, *J. Org. Chem.*, **31**, 375 (1966); (b) H. Hirschmann and J. S. Williams, *J. Biol. Chem.*, **238**, 2305 (1963).

(6) M. Uskokovic, M. Gut, and R. I. Dorfman, *J. Amer. Chem. Soc.*, **82**, 3668 (1960).

pentachloride, the initially formed 20β-ester–halide complex rearranges in a concerted manner to the 17aβ-ester–halide complex of 3β-acetoxy-17α-methyl-D-homo-5α-androstane[5]; this is followed by attack of a halide ion (SN2) leading predominantly to the inverted product **2a**. With thionyl chloride, on the other hand, the 17aβ-ester–halide complex probably undergoes an internal displacement reaction (SNi) with retention of configuration[7] to afford **3a** possessing a β-oriented chlorine atom at C-17a.

These assignments of the configuration of the halogen moiety at C-17a were further supported by their nmr spectra. The 17a proton of **2a** occurs at 3.76 ppm (J = 2.5 cps) while that of **3a** appears at 3.30 ppm (J = 10.5 cps). Since the proton in **3a** is more shielded than in **2a**, the assigning of an axial orientation for the C-17a proton is in line with the assignment.[8a,9,10] The greater magnitude of the coupling constant of the proton at C-17a in **3a** than in **2a** is also consistent for the β-chlorine orientation.[2,8b]

In addition, the infrared spectra showed an intense C–Cl stretching band at 702 cm^{-1} in compound **2a** and at 730 cm^{-1} in compound **3a**.[11] The higher frequency of a C–Cl stretching band in **3a** than in its epimer is also in agreement with our assignment.[12]

Experimental Section[13]

3β-Acetoxy-17a-chloro-17α-methyl-D-homo-5α-androstanes (2a and 3a). A. Reaction of 3β-Acetoxy-5α-pregnan-20β-ol (1)[2,14] with Phosphorus Pentachloride.—Anhydrous $CaCO_3$ (1 g) was added to a solution of compound **1** (1 g, 2.8 mmol) in 80 ml of dried $CHCl_3$ and the resulting mixture cooled in an ice–water bath. Phosphorus pentachloride (2.8 g) was added in small portions. After the addition, the mixture was stirred at room temperature for 2 hr, poured into a solution of $NaHCO_3$, acidified with 2 N HCl, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with dilute $NaHCO_3$ and water. After removal of the solvent, the crude product was chromatographed over silica gel. Elution with benzene–hexane (1:3) gave first 3β-acetoxy-17aα-chloro-17α-methyl-D-homo-5α-androstane (**2a**) which was recrystallized from acetone as plates (0.59 g, 56%): mp 169–170°; $[\alpha]D$ −18.8° (c 0.985) {lit.[3] mp 160–165°; $[\alpha]^{22}D$ −5.5° ($CHCl_3$)}; ir, 1734, 1238, 1024 (acetate), 746, 727, and 702 cm^{-1} (C–Cl); nmr, δ 0.80 (s, 3, 19-H), 0.96 (s, 3, 18-H), 0.97 (d, 3, J = 6.5 cps, 17α-CH_3), 2.00 (s, 3, OAc), and 3.76 (d, 1, J = 2.5 cps, 17aβ-H).

Anal. Calcd for $C_{23}H_{37}ClO_2$: C, 72.51; H, 9.79; Cl, 9.31. Found: C, 72.42; H, 9.64; Cl, 9.25.

Further elution with the same solvent afforded the 17aβ-chloro epimer, **3a**. Recrystallization from acetone–water gave rods (0.31 g, 30%): mp 143–144°; $[\alpha]D$ −0.3° (c 1.16) {lit.[3] mp 142–144°; $[\alpha]^{21}D$ +1.7° ($CHCl_3$)}; ir, 1733, 1240, 1025 (acetate), 743, and 730 cm^{-1} (C–Cl); nmr, δ 0.80 (s, 3, 19-H), 0.90 (s, 3, 18-H), 1.04 (d, 3, J = 6.0 cps, 17α-CH_3), 2.01 (s, 3, OAc), and 3.30 (d, 1, J = 10.5 cps, 17aα-H).

Anal. Calcd for $C_{23}H_{37}ClO_2$: C, 72.51; H, 9.79; Cl, 9.31. Found: C, 72.31; H, 9.53; Cl, 9.43.

In another experiment, the crude product was recrystallized from aqueous acetone without resorting to chromatography. The pure product obtained was shown to be identical with **2a** reported above by the determination of melting point, mixture melting point, and infrared spectrum. The mother liquor after repeated recrystallization from aqueous acetone gave another compound which was identified as **3a**.

B. Reaction of Compound 1 with Sulfuryl Chloride in Pyridine.—Compound **1** (1.8 g, 5.04 mmol) was dissolved in 60 ml of pyridine, and the mixture was cooled to 0° in an ice–salt bath. Sulfuryl chloride was then added dropwise and the resulting mixture stirred at 0° for 30 min followed by 1 hour at 20°. The mixture was poured into ice–water and extracted with ether. The ethereal solution after washing successively with dilute HCl, $NaHCO_3$, and water left a residue which was extracted with hexane. The hexane-soluble substance was chromatographed over a silica gel column. Elution with benzene–hexane (7:13) gave first compound **2a** (0.74, 39%) with a melting point of 169–170°, followed by **3a** (0.195 g, 10.3%) of mp 142–144°.

C. Reaction of Compound 1 with Thionyl Chloride.—A mixture of **1** (1 g, 2.8 mmol) and thionyl chloride (12.5 ml) was allowed to stand at 20° for 24 hr. The resulting mixture was poured into ice–water and extracted with $CHCl_3$. The combined extract was washed with $NaHCO_3$ solution and water and evaporated to dryness. The crude product obtained was chromatographed over a silica gel column. Elution with benzene–hexane (1:3) gave first **2a** (0.05 g, 5%) with mp 168–170° and then **3a** (0.66 g, 63%) which melted at 143–144°.

In another experiment, the crude product was recrystallized from aqueous acetone without resorting to chromatography. The pure product obtained showed identical infrared spectrum and melting point with those of **3a** reported above. The mixture melting point gave no depression.

D. Reaction of 3β-Acetoxy-17α-methyl-D-homo-5α-androstan-17aβ-ol (4)[5a] with Phosphorus Pentachloride.—To compound **4** (0.362 g, 1.0 mmol) in 55 ml of $CHCl_3$, anhydrous $CaCO_3$ (0.36 g) was added, and the mixture was cooled in an ice–water bath. Phosphorus pentachloride (2.02 g) was then added in small portions, and the resulting product was worked up as in method A. The crude product was chromatographed on a silica gel column. Elution with benzene–hexane (7:13) gave the 17aα-chloro compound (**2a**) (0.215 g, 56%) with mp 169–170° followed by the 17aβ-chloro compound (**3a**) (0.070 g, 18%), mp 143–144°.

The mixture melting point of the respective samples obtained by these four methods showed no depression. The infrared spectra of the respective samples were also identical.

17aα-Chloro-17α-methyl-D-homo-5α-androstan-3β-ol (2b).—Compound **2a** was hydrolyzed with 2% methanolic KOH to afford compound **2b** which was recrystallized from acetone as needles: mp 214–215°; $[\alpha]D$ −12.2° (c 0.871) {lit.[3] mp 211–215°; $[\alpha]D$ −0.3° ($CHCl_3$)}; ir, 3615, 1034 (OH), 746, 727, and 702 cm^{-1} (C–Cl).

Anal. Calcd for $C_{21}H_{35}ClO$: C, 74.41; H, 10.41; Cl, 10.46. Found: C, 74.61; H, 10.26; Cl, 10.48.

17aβ-Chloro-17α-methyl-D-homo-5α-androstan-3β-ol (3b).—Hydrolysis of **3a** with 2% methanolic KOH gave the free alcohol **3b** which crystallized from acetone as plates: mp 170–170.5°; $[\alpha]D$ +6.5° (c 1.01) {lit.[3] mp 163–165°; $[\alpha]^{22}D$ +9.7° ($CHCl_3$)}; ir, 3615, 1035 (OH), 744, and 730 cm^{-1} (C–Cl).

Anal. Calcd for $C_{21}H_{35}ClO$: C, 74.41; H, 10.41; Cl, 10.46. Found: C, 74.42; H, 10.68; Cl, 10.16.

17α-Methyl-D-homo-5α-androstan-3β-ol (5). A.—Compound **2a** (0.381, 1.0 mmol) was dissolved in 10 ml of THF and added dropwise to the suspension of $LiAlH_4$ (0.912 g) in 15 ml of THF. After refluxing for 8 hr, the mixture was poured into 50 ml of ether. The excess $LiAlH_4$ was decomposed with ice–water and the organic layer was separated. The aqueous layer was extracted repeatedly with ether. After the ethereal extract was dried and evaporated, the crude product left was chromatographed on a silica gel column. Elution with benzene–ether (9:1) gave 17α-methyl-D-homo-5α-androstan-3β-ol (**5**) (0.225 g, 74%) which melted at 141–142°. The mixture melting point with a previous sample[2] showed no depression. The infrared spectrum was also identical with that of a previous sample.[2]

(7) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 392.

(8) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964: (a) p 47; (b) p 51.

(9) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, **80**, 6098 (1958).

(10) J. N. Shoolery and M. T. Rogers, *ibid.*, **80**, 5121 (1958).

(11) Besides these main bands, we also observed bands at 746 and 727 cm^{-1} for **2a** and at 743 cm^{-1} for **3a** which are also probably due to the C–Cl stretching frequency.

(12) D. H. R. Barton, J. E. Page, and C. W. Shoppee, *J. Chem. Soc.*, 331 (1956).

(13) All melting points were taken on a Kofler block and are uncorrected. Rotations were measured in chloroform solution at 20° with a Perkin-Elmer Model 141 polarimeter. Infrared spectra were determined in carbon disulfide solution with a Perkin-Elmer Model 421 spectrophotometer. Nmr spectra were recorded on the Model A-60 Varian Associates spectrometer using deuteriochloroform as solvent and tetramethylsilane as an internal standard (TMS = 0.0 ppm). Microanalysis were performed by the Microanalytical Services Unit of this laboratory.

B.—Compound **3a** (0.15 g, 0.394 mmol) was dissolved in 5 ml of THF and added dropwise to the suspension of $LiAlH_4$ (0.456 g) in 10 ml of THF. The mixture was refluxed for 8 hr and then worked up as in method A. The product (0.07 g, 59%) had a melting point of 141–142°. It showed no depression of its melting point when mixed with a sample obtained by method A. The infrared spectra were also in agreement.

Registry No.—**1**, 17182-23-9; **2a**, 17223-91-5; **2b**, 17223-92-6; **3a**, 17223-93-7; **3b**, 17223-94-8.

The Borane Reduction of Amido Esters

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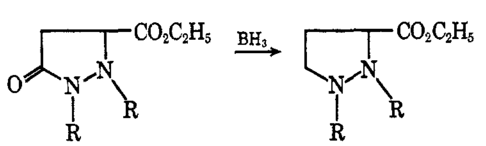
The requirement of various amino ester intermediates for other studies and the ready availability of amido ester precursors has led us to investigate the reduction of amido esters by borane. Our hope was the selective borane reduction of an amide functional group in the presence of an ester group.

The facile borane reduction of simple amides to amines in high yields has been described by Brown and Heim.[1] Borane reduction of fluoroacetamides to fluoroethylamines,[2] trifluoroacetamides to trifluoroethylamines,[3] and N-(2-haloethyl)benzamides to N-(2-haloethyl)benzylamines[4,5] illustrates the selectivity shown by this reagent when both amide and halogen groups are present in the same molecule. Selectivity was also shown in the borane reduction of the carbonyl of a trifluoroacetamido substituent without affecting the carbonyl of a carbamate moiety present in ethyl 4-trifluoroacetylpiperazine-1-carboxylate.[6]

Esters, on the other hand, are only slowly reduced by borane to the alcohol stage.[7,8]

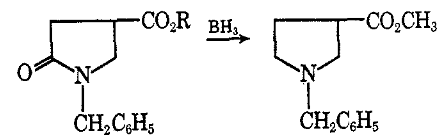
Treatment of 1,2-diethyl-5-ethoxycarbonyl-3-pyrazolidinone (**1b**) with borane in tetrahydrofuran yielded ethyl 1,2-diethylpyrazolidine-3-carboxylate (**2b**, 60%). Similar treatment of 1,2-dimethyl-5-ethoxycarbonyl-3-pyrazolidinone (**1a**) with borane gave ethyl 1,2-dimethylpyrazolidine-3-carboxylate (**2a**, 59%). The structural assignments for these novel heterocycles are based on elemental analyses and infrared and nmr spectra.



1a, R = Me; **b**, R = Et **2a**, R = Me; **b**, R = Et

Several different methods of decomposing excess borane and boron complexes were tried including (1) cold 6 *N* hydrochloric acid, (2) boiling with the alcohol from which the ester is derived, and (3) refluxing with alcoholic hydrogen chloride. The latter method proved to be the best as evidenced by the absence of contamination of reaction products by amino complexed borane.

Borane reduction of 1-benzyl-3-methoxycarbonyl-5-pyrrolidinone (**3a**) gave methyl 1-benzyl-3-pyrrolidinecarboxylate (**4**, 54%). The utility of this synthesis may be realized by comparison with the previous three-step procedure[9] for the preparation of this compound from **3b** in an over-all yield of 28%.



3a, R = Me; **b**, R = Et **4**

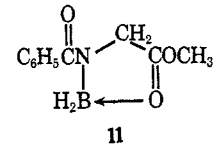
Ethyl N,N-diethylsuccinamate (**5**), upon treatment with borane for 2 hr at room temperature, afforded a mediocre (36%) yield of the selectively reduced product, ethyl 4-diethylaminobutanoate (**6**), which was obtained by distillation. In addition, considerable pot residue remained which was treated with 6 *N* hydrochloric acid and subsequently afforded the corresponding amino alcohol, 4-diethylamino-1-butanol (**7**, 7.3%). The infrared spectrum of **7** was identical with that of a sample of **7** synthesized by the lithium aluminum hydride reduction of **5**.[10] Refluxing **5** with borane for differing periods of time always gave lower yields of **6**.

As examples of compounds in which the amide nitrogen is monosubstituted, the borane reduction of methyl hippurate (**8**) and methyl *p*-acetamidobenzoate (**12**) was explored. Compound **8** gave a mixture of organic products consisting of 2-benzylaminoethanol (**9**, 85%), methyl 2-benzylaminoacetate (**10**, 11%), and an unidentified product (4%). The amino alcohol **9** and the amino ester **10** were identified by comparison with authentic samples. The large proportion of **9**

$$C_6H_5\overset{O}{\overset{\|}{C}}NHCH_2CO_2CH_3 \xrightarrow{BH_3}$$
8

$$C_6H_5CH_2NHCH_2CH_2OH + C_6H_5CH_2NHCH_2CO_2CH_3$$
9 **10**

means that the reduction of the ester grouping is competitive with the reduction of the amide group. Presumably, a cyclic intermediate such as **11** is involved



11

in which the ester carbonyl oxygen forms a coordinate covalent bond with boron and thereby results in an

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(2) Z. B. Papanastassiou and R. J. Bruni, *J. Org. Chem.*, **29**, 2870 (1964).
(3) E. R. Bissell and M. Finger, *ibid.*, **24**, 1256 (1959).
(4) G. R. Pettit, S. K. Gupta, and P. A. Whitehouse, *J. Med. Chem.*, **10**, 692 (1967).
(5) When the halogen is chlorine or bromine, selectivity is observed; however, borane reduction of N-(2-iodoethyl)benzamides results in hydrogenolysis of the carbon–iodine bond in addition to reduction of the amide group.
(6) W. V. Curran and R. B. Angier, *J. Org. Chem.*, **31**, 3867 (1966).
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(9) J. F. Cavalla, *J. Chem. Soc.*, 851 (1959).
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