STEROIDS AND RELATED NATURAL PRODUCTS

XXX. SELECTIVE REDUCTION OF ESTERS. PART A. BENZOATES[1]

GEORGE R. PETTIT,[2] BRIAN GREEN, GEORGE L. DUNN,[3] PETER HOFER, AND WILLIAM J. EVERS

Department of Chemistry, University of Maine, Orono, Maine, and Department of Chemistry, Arizona State University, Tempe, Arizona

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ABSTRACT

Previously, reagents such as sodium borohydride – boron trifluoride were shown to be capable of reducing typical aliphatic esters and lactones to the corresponding ether derivatives. Under the same reaction conditions, a variety of benzoate esters (*Ib*, *IIb*, III, and V) were essentially unaffected. Resistance to attack was illustrated by conversion, with sodium borohydride – boron trifluoride, of 3-oxo-17β-benzoyloxy-5α-androstane (III) into 3β-hydroxy-17β-benzoyloxy-5α-androstane (IV) and of reserpine (V) into alcohol VI. With aryl–carbon–oxygen bonds of the ketone VII or alcohol IX*a* type, reaction with sodium borohydride – boron trifluoride was shown, in general, to cause reductive fission of the benzyl–oxygen linkage (e.g. X → XI). An exception was noted in the case of tertiary benzyl alcohols containing an available β-hydrogen (e.g. IX*c*). Here, dehydration to yield, for example, olefin XII*b* appears to be the more favorable reaction course. The marked difference in the reactivity of sodium borohydride – boron trifluoride toward benzoyl–oxygen vs. benzyl–oxygen bonds has been demonstrated.

Previous applications of diborane – boron halide[1] reagents for direct conversion of esters into ethers have involved a variety of aliphatic-type esters and lactones. In general, conversion into the ether derivative increased substantially as the alcohol segment of the ester varied from primary to tertiary.[4] Two phenyl esters, however, were found (1) to undergo only hydrogenolysis to the corresponding alcohol derivatives. More recently, Eliel and Daignault (2) have extended the reduction reaction to thiol esters and have obtained good yields of the corresponding thioethers. The present investigation was undertaken to determine whether the mesomeric effect of the aromatic ring in a benzoate-type ester would decrease the basicity[5] of the carbonyl group enough to substantially reduce the rate of reduction, or whether attack would proceed by one or more of the

[1] *For part XXIX in this series, see G. R. Pettit and W. J. Evers, Can. J. Chem., 44, 1097 (1966). The present study is based on part of the Ph.D. dissertation submitted by G. L. Dunn to the Graduate School, University of Maine, Orono, Maine, July 1962.*

[2] *Present address: Department of Chemistry, Arizona State University, Tempe, Arizona.*

[3] *NDEA Predoctorate Fellow, 1960–1962.*

[4] *Dr. J. S. E. Holker and his colleagues have extended the reduction reaction to several steroid ring-D lactones derived from primary alcohols, and have obtained good yields of the corresponding tetrahydropyrans. We are grateful to Dr. Holker for providing us with this information before publication. One unsuccessful attempt to reduce a γ-lactone derived from a tertiary alcohol has also been noted (3a). Interestingly, extended platinum – perchloric acid catalyzed hydrogenation of 3β-acetoxy-5α-lanost-8-ene has been found to yield 3β-ethoxy-5α-lanostane (3b). We thank Professor J. T. Edward for bringing a similar, but unpublished, example to our attention. Both observations seem to be related to the recently reported (3c) preparation of ethers by reductive (platinum-catalyzed) condensation of alcohol–ketone mixtures.*

[5] *The increased π-bond overlap resulting from phenyl–carbonyl conjugation would be expected to inhibit association with boron trifluoride (compare with eq. [i]).*

[i] $$Ar-\overset{\displaystyle O}{\overset{\|}{C}}-OR \xrightarrow{BF_3} Ar-\overset{\displaystyle \ominus OBF_3}{\overset{|}{\underset{\displaystyle \oplus}{C}}}-OR \leftrightarrow Ar-\overset{\displaystyle \ominus OBF_3}{\overset{|}{\underset{\displaystyle \oplus}{C}}}=OR$$

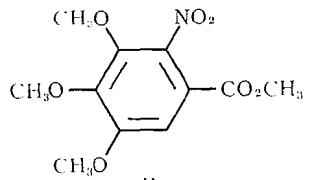
The reaction sequence illustrated in part by eq. [i] is assumed (4) to represent an important step in the reduction of esters to ethers by diborane – boron trihalide reagents.

following pathways: (*a*) reduction to the corresponding benzyl ether, or (*b*) hydrogenolysis to the corresponding alcohol derivatives.[6]

Subjecting 24-benzoyloxy-5β-cholane (I*b*, prepared from alcohol I*a*), in diethylene glycol dimethyl ether (diglyme) containing sodium borohydride, to treatment with boron trifluoride (in tetrahydrofuran) under conditions (1 h at ice-bath temperature and 1 h at room temperature) normally employed[1] in the ester → ether reduction sequence led to unreacted benzoate I*b* (79% recovery) accompanied by alcohol I*a* (20% yield). Extending the same reaction procedure to 3β-benzoyloxy-5α-cholestane (II*b*) gave comparable results: unreacted ester and alcohol II*a*. Under the same conditions 3β-cyclohexylcarbonyloxy-5α-cholestane (II*c*) was easily converted, in reasonable yield (50%), into ether II*d*. Comparing the benzoate and cyclohexanecarboxylate esters of alcohol II*a* provided a vivid illustration of differences in the reaction course.

Reduced reactivity of the benzoate esters toward sodium borohydride – boron trifluoride suggested that other more reactive carbonyl groups might be reduced selectively in their presence. Accordingly, two examples were studied. First, 3-oxo-17β-benzoyloxy-5α-androstane (III) was reduced (68% yield) with sodium borohydride – boron trifluoride to 3β-hydroxy-17β-benzoyloxy-5α-androstane (IV*a*). The remaining reaction product consisted primarily of diol IV*b* (20% yield). Sodium borohydride reduction of ketone III to alcohol IV*a* confirmed the structural and stereochemical assignments. The predominant formation of the C-3 equatorial alcohol when sodium borohydride – boron trifluoride is used is consistent with an earlier observation by Jones (9) involving diborane – boron trifluoride reduction of 4-*t*-butylcyclohexanone.[7] A second example of selective reduction, namely, conversion of reserpine (V) into alcohol VI, was of more practical importance.

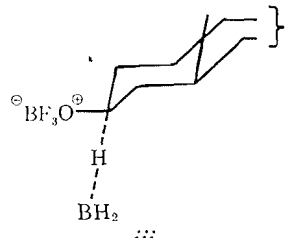
[6]*Brown and Subba Rao reported (5) that reaction between sodium borohydride – boron trifluoride etherate (in diglyme) and ethyl benzoate, as well as two derivatives, proceeded slowly, but the products were not ascertained. During the same period, a similar study with diborane was summarized (6), and a potentially important observation concerning the unreactivity of diborane toward acid halides (5, attributable to the electron-withdrawing effect of the halogen, thereby reducing attack by the Lewis acid diborane) was noted. The amine borane derived from pyridine and diborane, however, appears to resemble a borohydride, and has been shown (7) to reduce benzoyl chloride easily to benzoyl alcohol.*



ii

Again, in 1960, Tarbell and his colleagues reduced methyl benzoate (ii) to the corresponding benzyl alcohol (68% yield) with sodium borohydride – aluminium chloride (known to generate diborane), and the same alcohol was obtained in excellent conversion (93%) from the corresponding carboxylic acid by employing sodium borohydride – boron trifluoride (8).

[7]*Diborane or diborane – boron trifluoride reduction of 4-t-butylcyclohexanone yielded, in each case, approximately 15–16% of the thermodynamically less stable (cis) axial alcohol. Interestingly, trimethylamine borane – boron trifluoride gave 46–52% yields of the axial alcohol. The stereochemical course of ketone reduction by diborane (10) appears, in general, to favor equatorial alcohol formation, and in the case of ketone III may proceed via an intermediate such as iii.*



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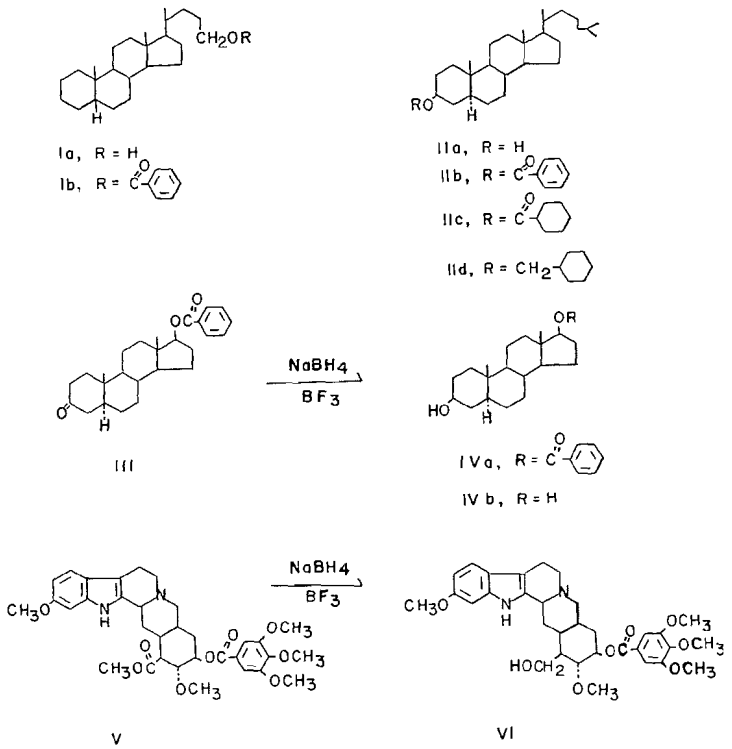


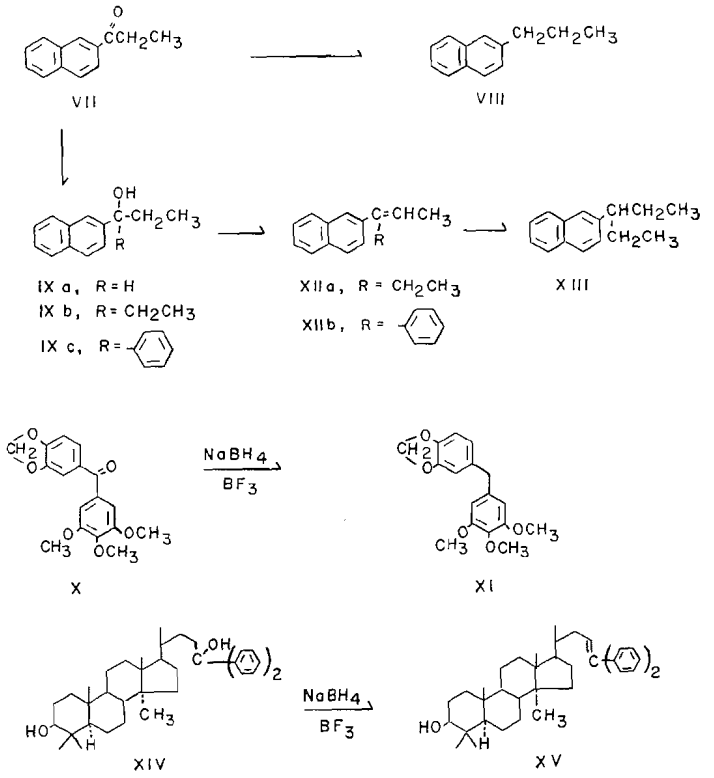
When reduction was attempted, in normal fashion, by adding a mixture of boron trifluoride and the alkaloid to sodium borohydride, a solid boron trifluoride – reserpine adduct separated from solution. Subsequently, a procedure based on adding boron trifluoride etherate to a mixture of reserpine and sodium borohydride provided alcohol VI. The results of infrared spectral and elemental analytical determinations supported structural assignment VI. Preferential reduction at the carbomethoxy group provides, in effect, a new means of further modifying the hypotensive and central nervous system activity of reserpine.[8]

At this point, the investigation was expanded to encompass effects of boron trifluoride – sodium borohydride on other types of benzyl–oxygen linkages.[9] Allowing both 2-naphthylethyl ketone (VII) and the corresponding alcohol (IX*a*) to react with boron trifluoride – sodium borohydride as in the case of, for example, benzoate I*b* yielded (good overall conversion) in both cases the product of complete hydrogenolysis: 2-(*n*-propyl)naphthalene (VIII). Benzyl alcohol IX*a* was obtained by lithium aluminium hydride reduction of ketone VII, and an authentic specimen of hydrocarbon VIII was prepared by catalytic hydrogenation (VII → VIII). Under similar conditions, diaryl ketone X was easily reduced to 3,4-methylenedioxyphenyl-3,4,5-trimethoxyphenylmethane (XI).[10]

[8]*Consult ref. 11 for leading literature citations pertinent to this point.*

[9]*A preliminary account of this study has been summarized in ref. 12. During the same period Venkataraman and his colleagues (13) reported boron trifluoride – sodium borohydride to be useful for the reduction of anthraquinones to anthracenes, and indicated that the reagent was also convenient for the analogous reduction of chromones and chromanones. Longer treatment with diborane was observed to give comparable results. Later, two additional examples (14) of the reaction with respect to chromanones were reported. Proposed mechanisms for this type of reduction reaction have been summarized (13b, 14b).*

[10]*It should be noted that other metal hydride techniques, particularly with aluminium chloride – lithium aluminium hydride, have been employed successfully for reductive cleavage of benzyl–oxygen bonds in various aryl ketones and in benzylic and allylic alcohols (see ref. 15 and footnotes 2 and 3 in ref. 12).*



One limit to the utility of the hydrogenolysis reaction was found during routine extension to several tertiary-type benzylic alcohols. Treating ketone VII with ethylmagnesium bromide provided tertiary alcohol IX*b*. From the reaction between alcohol IX*b* and boron trifluoride – sodium borohydride, only a mixture of *cis* and *trans* olefins corresponding to structure XII*a* was isolated. The olefin mixture was not further characterized, but was instead hydrogenated in the presence of palladium on charcoal to hydrocarbon XIII. The latter compound (XIII) was identical with a specimen prepared in an unequivocal manner (acid-catalyzed dehydration followed by hydrogenation) from alcohol IX*b*. The analogous preparation (VII and phenylmagnesium bromide) of diaryl tertiary alcohol IX*c* and subsequent reaction with the hydride reagent yielded olefin XII*b*. The crystalline hydrocarbon was readily characterized and shown to be identical with a sample prepared by hydrochloric acid catalyzed dehydration of alcohol IX*c*. A reaction course terminating in dehydration was again encountered with tertiary alcohol XIV. Reaction with boron trifluoride – sodium borohydride gave only olefin XV, a substance previously characterized in our laboratory. The possibility of dehydration catalyzed by boron trifluoride taking precedence came into question when a solution of alcohol IX*b* in diglyme (containing sodium borohydride) was slowly treated with boron trifluoride etherate; the same result ensued (production of olefin XII*a*). These experiments also suggest that hydroboration of olefins such as XII and XV is a relatively slow process, or that they (the olefins) arise at a terminal stage.[11] In this regard, boron trifluoride – sodium borohydride reduction

[11]*Olefins are known to arise during lithium aluminium hydride reduction of certain aryl ketones; for example, see ref. 15a.*

of triphenylcarbinol gave, as expected, triphenylmethane; however, no further effort was made to delineate the mechanism (13*b*, 14*b*) of olefin formation.

The preceding experiments served to extend the scope of reduction reactions with boron trifluoride – sodium borohydride to selective reduction in the presence of a benzoate ester, and with certain limitations (tertiary benzyl alcohols bearing an available β-hydrogen substituent) to reductive fission of benzyl–oxygen bonds. Later, carbonate-type esters were found to be similar to benzoates in their resistance to attack by boron trifluoride – sodium borohydride; a summary of these observations will appear in a later paper.

EXPERIMENTAL[12]

24-Benzoyloxy-5β-cholane (Ib)

To a cool (ice bath) solution of 24-hydroxy-5β-cholane (I*a*, 1.2 g) in pyridine (7 ml, distilled from potassium hydroxide) was added benzoyl chloride (1 ml). After 8 h at room temperature, the mixture was poured into water (50 ml) and extracted with diethyl ether. The combined ethereal extracts were washed successively with saturated sodium bicarbonate solution, water, 5% hydrochloric acid, and water. Removal of solvent *in vacuo* yielded a pale-yellow oil (1.7 g), which was dissolved in petroleum ether and chromatographed on a column of acid-washed alumina (30 g). Elution with petroleum ether and 3:1 petroleum ether – benzene gave a colorless oil, 1.4 g, 90%; ν_{max}^{neat} 1 720, 1 600, 1 580, 1 260, and 706 cm^{-1}. Crystallization from methanol – diethyl ether gave 1.35 g of crystals melting at 44–45°. After three recrystallizations from the same solvent mixture, an analytical specimen displayed the same melting point and had $[\alpha]_D^{20}$ +18.5° (*c*, 1.27). A thin-layer chromatogram (10:1 petroleum ether – ethyl acetate as the mobile phase) showed one spot.

Anal. Calcd. for $C_{31}H_{46}O_2$: C, 82.61; H, 10.29. Found: C, 82.25; H, 10.67.

Attempted Sodium Borohydride – Boron Trifluoride Reduction of 24-Benzoyloxy-5β-cholane (Ib)

A solution of ester I*a* (1.0 g) in tetrahydrofuran (20 ml) containing boron trifluoride etherate (7.5 ml) was added to a cool (ice bath) solution of sodium borohydride (0.17 g) in 20 ml of dry diglyme. Stirring was continued for 1 h at ice-bath temperature, and during a second hour while the solution was being heated at reflux. The solution was cooled (ice bath) and cautiously treated with 2 *N* hydrochloric acid, followed by dilution with water and extraction with diethyl ether. The combined ethereal extracts were washed with saturated sodium bicarbonate solution and water, and concentrated *in vacuo* to a colorless oil (1.2 g). A solution of the oily product in petroleum ether was chromatographed on acid-washed alumina (30 g). The petroleum ether and 1:1 petroleum ether – benzene fractions provided 0.79 g, m.p. 44–45°, of ester I*a*.[13] A fraction eluted with chloroform crystallized from methanol as needles (0.15 g, 20%) melting at 127–129°. The latter product proved[13] to be 24-hydroxy-5β-cholane (I*a*).

3β-Benzoyloxy-5β-cholestane (IIb)

Conversion of 3β-hydroxy-5α-cholestane (5.0 g) into benzoate ester II*b* by employing benzoyl chloride (8 ml) in dry pyridine (40 ml) was accomplished essentially as noted with ester I*b*. The crude product recrystallized from diethyl ether – methanol as colorless needles weighing 5.2 g and melting at 137–138° to an opaque liquid which cleared at 158–159° (ref. 17 reports m.p. 133–135° to 152–156°).

Attempted Reduction of 3β-Benzoyloxy-5α-cholestane (IIb)

Method A: Sodium Borohydride – Boron Trifluoride

A 1.0 g sample of ester II*b* was subjected to treatment with sodium borohydride (0.16 g) in the presence of boron trifluoride etherate (7.5 g) as described above for benzoate ester I*b*. A thin-layer chromatogram of the product indicated a two-component mixture. The first substance isolated weighed 0.92 g and proved[13] to be starting material (II*b*). The remaining product was found to contain, on the basis of comparative thin-layer chromatograms, 3β-hydroxy-5α-cholestane. No substance corresponding to ether II*d* was detected.

[12]*Acid-washed alumina refers to a Merck (Rahway) product. The petroleum ether employed was a fraction boiling at 65–70°. A summarized description of other general methods, solvents, reagents, and chromatographic procedures used in the present study appears in an introduction to the Experimental section of part XXVIII in this series (see G. R. Pettit, J. C. Knight, and W. J. Evers, Can. J. Chem., 44, 807 (1966)).*

Melting points reported for analytical specimens were recorded on a Kofler melting point apparatus. All other melting point determinations were performed with open Kimble glass capillaries in a silicone oil bath and are uncorrected. The purity of all analytical samples (colorless in each case) was confirmed by thin-layer chromatography on silica gel G, and the plates were developed with concentrated sulfuric acid.

Proton magnetic resonance (see ref. 16), ultraviolet (ethanol solution, Perkin–Elmer model 400 spectrometer), infrared spectra (potassium bromide, unless otherwise noted) and gas chromatographic data were provided by Dr. R. A. Hill (University of Maine). Specific rotation values (chloroform solution) were determined in the laboratories of Drs. Weiler and Strauss, Oxford, England, and P. Demoen, Janssen Pharmaceutica, Beerse, Belgium. Elemental analytical data was provided by Dr. A. Bernhardt, Max-Planck Institut, Mülheim, Germany.

[13]*The identity of this substance was established by mixture melting point determination and infrared spectral comparison with an authentic sample.*

Method B: Lithium Aluminium Hydride – Boron Trifluoride

The preceding experiment (A) was repeated with lithium aluminium hydride (0.16 g) in place of sodium borohydride and with tetrahydrofuran (40 ml total) as solvent (1). The principal product, 0.80 g, was starting material,[13] and the residual mixture consisted largely of ester II*b* accompanied by a small amount of alcohol II*a*. A thin-layer chromatographic study of the mixture failed to reveal ether II*d*.

3β-Cyclohexylcarbonyloxy-5α-cholestane (IIc)

Method A

Platinum oxide (0.2 g) was added to a solution of commercial cholesteryl benzoate (8.7 g) and 70% perchloric acid (3 drops) in tetrahydrofuran (200 ml), and the mixture was shaken under a slight positive pressure of hydrogen for 2 h. At this time, an aliquot sample displayed a strong tetranitromethane test; thus, another 0.5 g quantity of platinum oxide was added and hydrogenation continued. Five hours later, hydrogen absorption appeared to be complete, and catalyst was removed by filtration. Dilution with water led to a solid which crystallized from chloroform–methanol as colorless needles, 4.2 g, m.p. 161–162°. An additional 0.62 g, m.p. 159–161°, of cyclohexylcarbonyloxy ester II*c* was obtained by recrystallization of the second and third crystal crops.

Method B

The cyclohexylcarbonyloxy ester II*c* of alcohol II*a* (0.5 g) was prepared from the acid chloride (by employing 10 ml of thionyl chloride, reflux for 1.5 h) derivative of cyclohexanecarboxylic acid (1.0 g) in pyridine (5 ml) as summarized with ester I*b*. The pale-yellow solid crystallized from chloroform–methanol as colorless needles, 0.5 g, m.p. 160–161° (ref. 18 reports m.p. 158.5–159°). The identical composition of both esters (obtained by methods A and B) was confirmed.[13]

3β-Cyclohexylmethyleneoxy-5α-cholestane (IId)

Reduction of cyclohexylcarbonyloxy ester II*c* (1.0 g in 50 ml of tetrahydrofuran) with sodium borohydride (0.19 g in 20 ml of diglyme) and boron trifluoride (12 ml) was accomplished by the procedure illustrated with ester I*a*. A petroleum ether solution of crude product was chromatographed on activated alumina (30 g). Elution with the same solvent (400 ml) gave a fraction (0.43 g) which crystallized from chloroform–methanol as colorless blades, 0.40 g, m.p. 157.5–158.5°. Further recrystallization from the same solvent mixture gave an analytical specimen with an unchanged melting point and with $[\alpha]_D^{20}$ +15.2° (*c*, 1.212); ν_{max} 2 900, 1 470, 1 450, 1 380, and 1 120 (broad) cm^{-1}.

Anal. Calcd. for $C_{34}H_{60}O$: C, 84.23; H, 12.47; O, 3.30. Found: C, 84.14; H, 12.39; O, 3.65.

Continued elution with chloroform gave 0.57 g of alcohol II*a*.

3-Oxo-17β-benzoyloxy-5α-androstane (III)

After one recrystallization from methanol, the pale-yellow solid (7.5 g, m.p. 150–160°) obtained from 3-oxo-17β-hydroxy-5α-androstane (7.0 g) and benzoyl chloride (6 ml) in pyridine (40 ml) was dissolved in 1:1 petroleum ether – benzene and chromatographed on acid-washed alumina. An initial fraction (0.45 g, m.p. 150–160°) eluted with the same solvent mixture was discarded, and subsequent fractions through 5:1 benzene–chloroform were collected. The colorless solid weighed 6.3 g (66%) and melted at 196–199°. Four recrystallizations from acetone gave an analytical sample in the form of rods, m.p. 201–202° (ref. 19 reports m.p. 201–202°), $[\alpha]_D^{20}$ +73.1° (*c*, 1.30); ν_{max} 1 710, 1 280, and 720 cm^{-1}.

Anal. Calcd. for $C_{26}H_{34}O_3$: C, 79.14; H, 8.68. Found: C, 79.11; H, 8.33.

3β-Hydroxy-17β-benzoyloxy-5α-androstane (IVa)

Method A

Reduction of ketone III (1.0 g) in diglyme (25 ml) – tetrahydrofuran (25 ml) with sodium borohydride (0.19 g) – boron trifluoride etherate (7.7 ml) was conducted as described for benzoate ester I*b*. The crude viscous oil was chromatographed on acid-washed alumina, and fractions eluted by benzene yielded a solid (0.73 g) melting at 170–180°. One recrystallization from acetone – petroleum ether gave colorless plates weighing 0.68 g (68%, m.p. 201–202°). Further recrystallization from the same solvent mixture gave a pure specimen melting at 202–203°, $[\alpha]_D^{20}$ +53.4° (*c*, 1.25).

Anal. Calcd. for $C_{26}H_{36}O_3$: C, 78.74; H, 9.15. Found: C, 78.99; H, 8.87.

The column was next eluted with chloroform and the resulting fraction allowed to crystallize from benzene – petroleum ether. The specimen of 3β,17β-dihydroxy-5α-androstane (IV*b*) that was obtained weighed 0.15 g (20%) and melted at 164–165° (ref. 20 reports m.p. 164°).

Method B

The preceding experiment (see method A) was repeated, omitting boron trifluoride etherate and tetrahydrofuran. The crude viscous oil (0.95 g) crystallized upon trituration with methanol to yield 0.90 g of crude alcohol IV*a* melting at 175–185°. A 0.10 g sample was purified as described above by column chromatography on acid-washed alumina (3 g). The fraction eluted by 5:1 benzene–chloroform yielded 0.08 g of alcohol IV*a* melting at 202–203°; ν_{max} 3 400, 1 710, 1 280, and 715 cm^{-1}. The specimen of alcohol IV*a* prepared by method B was identical[13] with that obtained by method A.

Sodium Borohydride – Boron Trifluoride Reduction of Reserpine (V)

In a typical experiment, reserpine (15.0 g) was dissolved in hot (100–110°) diglyme (750 ml) and, after the solution was cooled (ice bath), sodium borohydride (5.6 g) was added. Next, a solution composed of boron

trifluoride etherate (190 ml) and tetrahydrofuran (190 ml) was added dropwise over a 30 min period. Before the cool (20°) solution was cautiously treated with 2 *N* hydrochloric acid (250 ml), stirring was continued for 3 h at ice-bath temperature and for 1 h at reflux. The pH of the mixture was adjusted to 8–9 with ammonium hydroxide, and the solution was diluted with water and extracted with chloroform. After removal of solvent the red viscous oil was triturated with diethyl ether, and the yellow solid (10.5 g, giving a green Beilstein test) was collected, dissolved in methanol (475 ml) – concentrated hydrochloric acid (25 ml), and heated at reflux for 30 min. Concentration to a volume of ca. 200 ml and cooling (ice bath) provided 5.0 g of a straw-colored solid, decomposition point 265°, which recrystallized from 95% ethanol as cream-colored plates decomposing at 265°. Two additional recrystallizations from the same solvent did not change the appearance or decomposition point of *alcohol VI hydrochloride*, $[\alpha]_D^{22}$ −76.5° (*c*, 1.2); ν_{max} 3 400, 3 150, 2 600, and 1 708 cm^{-1} (in reserpine, the bands at 1 709 and 1 720 cm^{-1} correspond, respectively, to benzoate and methoxycarbonyl absorption).

Anal. Calcd. for $C_{32}H_{41}O_8N_2Cl$: C, 62.27; H, 7.00; Cl, 5.75; N, 4.54; O, 20.74. Found: C, 61.87; H, 6.58; Cl, 6.01; N, 4.76; O, 21.16.

A suspension of the hydrochloride in water – diethyl ether was shaken with 1 *N* sodium hydroxide. The mixture was diluted with benzene, and the upper phase was washed with water and concentrated. When the concentrate was allowed to stand at room temperature, *alcohol VI* separated from solution as rosettes of colorless needles, decomposition point 134–144° (Kofler block m.p. 144–148°). The free base (VI) was pure as evidenced by a thin-layer chromatogram, but quickly became yellow and impure on exposure to air and light. A pure specimen was preserved in the dark and exhibited $[\alpha]_D^{20}$ −55.7° (*c*, 0.88) and ν_{max} 3 400, 1 709, and 1 130 cm^{-1}.

Anal. Calcd. for $C_{32}H_{40}O_8N_2$: C, 66.20; H, 6.94; N, 4.83; O, 22.05. Found: C, 65.99; H, 6.88; N, 4.93; O, 21.95.

2-(n-Propyl)naphthalene (VIII)

Method A

By using the procedure outlined for the attempted reduction of benzoate *Ib*, a sample of 2-naphthylethyl ketone (3.0 g, VII (21)) was reduced with sodium borohydride (1.3 g) – boron trifluoride etherate (80 g). A solution of the crude product in petroleum ether was chromatographed on activated alumina (80 g). Elution with the same solvent yielded 2.2 g of a colorless mobile oil, b.p. 134° at 20 mm; λ_{max} 225, 276, and 319 mμ (log ε 4.23, 3.90, and 2.73). The ultraviolet spectrum of 2-methylnaphthalene has been reported (22) to be λ_{max} 220, 276, and 319 mμ (log ε 4.02, 3.68, and 2.71). Homogeneity of the hydrocarbon was confirmed by vapor phase chromatography. The *picrate* derivative (prepared in 95% ethyl alcohol) crystallized from ethanol as yellow needles, m.p. 89–91°. Boiling points of 273–274° at 760 mm and 135° at 12 mm have been reported (23) for hydrocarbon VIII, and the *picrate* derivative has been found (23*a*) to melt at 90–92°.

Method B

A solution of 2-naphthylethyl ketone (3.0 g) in tetrahydrofuran (20 ml) was reduced with lithium aluminium hydride (6.0 g) in tetrahydrofuran (50 ml) during 3 h at room temperature. The mixture was cautiously treated with 2 *N* sulfuric acid and extracted with chloroform. Removal of solvent from the combined chloroform extracts gave a nearly quantitative yield of 1-(2-naphthyl)propanol (IX*a*), b.p. 162° at 20 mm, ν_{max}^{neat} 3 480 cm^{-1}. A 0.92 g specimen of alcohol IX*a* was reduced by the sodium borohydride (0.38 g) – boron trifluoride etherate (22 g) technique as noted above in method A. After chromatographic purification, a 0.57 g quantity of 2-(*n*-propyl)naphthalene was isolated. The product (VIII) displayed the same ultraviolet spectrum as material prepared by method A, and both the hydrocarbon (VIII) and alcohol (IX*a*) precursor were pure as evidenced by vapor phase chromatography.

Method C

An authentic specimen of hydrocarbon VIII was prepared by catalytic (0.5 g of 10% palladium on charcoal) hydrogenation (4 h with a slightly positive pressure) of 2-naphthylethyl ketone (3.0 g) in methanol (100 ml). After catalyst and solvent were removed, the pale-yellow oily product was distilled *in vacuo*. The pure sample of hydrocarbon VIII (2.7 g) displayed ultraviolet and infrared (neat) spectra and vapor phase chromatographic behavior identical with those observed for the products from methods A and B. The *picrate* derivative, m.p. 89–91°, was identical[13] with the corresponding derivative described as part of method A.

3,4-Methylenedioxyphenyl-3,4,5-trimethoxyphenylmethane (XI)

Sodium borohydride (0.24 g) – boron trifluoride etherate (16 g) reduction of 3,4-methylenedioxy-3′,4′,5′-trimethoxybenzophenone (X, 1.0 g (12)) was performed as noted above (see VIII, method A). The product (XI, 0.58 g, m.p. 56–58°) crystallized from petroleum ether as colorless plates. Two recrystallizations from the same solvent provided an analytical sample melting at 55.5–56°.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00; O, 26.46. Found: C, 67.89; H, 5.94; O, 26.18.

3-Hydroxy-3-(2-naphthyl)pentane (IXb)

A solution of 2-naphthylethyl ketone (16.3 g) in diethyl ether (125 ml) was added during 30 min to a solution prepared from diethyl ether (35 ml), ethyl bromide (16 g), and magnesium (3.6 g). Twenty minutes later, reaction was complete and the mixture was treated with water (20 ml) followed by 10% aqueous sulfuric acid (100 ml). The ethereal layer was separated and successively washed with water, aqueous

potassium carbonate, and water. After removal of solvent, the residue was distilled through a 6 inch Vigreux column to yield 7.7 g of tertiary alcohol IX*b* boiling at 105–106° (0.08–0.09 mm); ν_{max}^{neat} 3 400, 3 010, 2 950, 2 900, 2 840, 1 598, 1 505, 1 460, 1 375, 1 270, 1 155, 1 132, 965, 915, 900, 860, 820, and 750 cm^{-1}.

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.46; O, 7.14. Found: C, 83.99; H, 8.22; O, 7.63.

3-(2-Naphthyl)pentane (XIII)

Method A

Reaction between 3-hydroxy-3-(2-naphthyl)pentane (2.0 g) and sodium borohydride (0.70 g) – boron trifluoride etherate (30 g) was attempted and the product isolated as was, for example, ketone VII. Again, when the reaction was repeated with a total reaction time of only 20 min, the following results were observed. A thin-layer chromatogram (hexane as the mobile phase) of the crude oily product indicated a major component (assumed to be olefin XII*a*) as a mixture of the two geometrical isomers, accompanied by a number of more polar materials. The presence of starting material was not detected. A solution of the product in hexane was chromatographed on activated alumina. Elution with the same solvent gave 1.14 g of an oily fraction displaying two spots (believed to be the geometrical isomers of olefin IX*a*) on a thin-layer chromatogram (hexane as the mobile phase). The olefin mixture was dissolved in hexane (20 ml) and hydrogenated (under a slightly positive pressure) in the presence of 10% palladium on charcoal (0.05 g). Next, the solution was filtered and chromatographed on activated alumina (35 g). Elution with hexane gave 1.1 g of 3-(2-naphthyl)pentane (XIII); ν_{max}^{neat} 3 010, 2 950, 2 900, 2 840, 1 600, 1 509, 1 460, 1 375, 890, 858, 820, and 750 cm^{-1}; proton magnetic resonance response ($CDCl_3$ solution): triplet (J = 7 c.p.s.) at 0.76 and complex signals at 1.40–1.87, 2.14–2.52, and 6.85–7.53 δ.

Anal. Calcd. for $C_{15}H_{18}$: C, 90.85; H, 9.15. Found: C, 90.81; H, 9.13.

Method B

A solution of alcohol IX*b* (1.6 g) in methanol (15 ml) containing 1 drop of concentrated hydrochloric acid was heated at reflux for 30 min. After dilution with water, the mixture was extracted with diethyl ether. The ethereal extract was washed with water and concentrated to an oily residue. A thin-layer chromatogram (hexane as the mobile phase) of the olefin mixture (XII*a*) displayed two principal spots with R_f values identical with those observed for the olefin described in method A (see above), and a number of lesser and more polar components. The crude olefin was partially purified by column chromatography and the mixture of geometrical isomers subjected to catalytic hydrogenation as described in the preceding experiment (see method A). Final purification was again achieved by column chromatography with hexane as solvent and eluent to yield 0.68 g hydrocarbon XIII as a colorless oil.

Anal. Found: C, 90.88; H, 9.13.

The infrared (neat) and proton magnetic resonance spectra of hydrocarbon VIII prepared by methods A and B were identical.

1-(2-Naphthyl)-1-phenylpropanol (IXc)

Conversion of 2-naphthylethyl ketone (5.0 g) into tertiary alcohol IX*c* was accomplished with the Grignard reagent prepared from magnesium (3.8 g) and bromobenzene (23 g) in tetrahydrofuran solution (80 ml). Except for a 2 h period at reflux and final dilution of the reaction mixture with saturated ammonium chloride solution, the reaction and isolation of crude alcohol were carried out as illustrated in the case of tertiary alcohol IX*a*. A pure specimen of alcohol IX*c* (4.9 g) crystallized from diethyl ether – petroleum ether as prismatic needles melting at 91–92°.

Anal. Calcd. for $C_{19}H_{18}O$: C, 86.98; H, 6.92. Found: C, 87.07; H, 7.04.

1-(2-Naphthyl)-1-phenyl-prop-1-ene (XIIb)

Method A

A sample of 1-(2-naphthyl)-1-phenylpropanol (IX*c*, 1.5 g) was treated with sodium borohydride (0.43 g) – boron trifluoride etherate (24 g) and the product isolated as summarized in the case of alcohol IX*b*. A solution of the crude olefin in hexane was chromatographed on activated alumina (40 g). The fraction eluted with hexane weighed 0.95 g (XII*b*) and crystallized from diethyl ether – petroleum ether as colorless prisms (0.35 g) melting at 104–106°; λ_{max} 239, 248, 276, 286, and 297 mμ (log ϵ 4.67, 4.64, 4.06, and 3.94); ν_{max} 3 000, 2 850, 1 500, 1 490, 1 440, 1 360, 900, 850, 825, 818, 770, 755, and 700 cm^{-1}; proton magnetic resonance response ($CDCl_3$ solution): doublet (J = 7 c.p.s. (CH_3)) at 1.78, quartet (J = 7 c.p.s. (=CH—)) at 6.33, and complex signals from 7.25 to 7.85 (12 aromatic H) δ.

Anal. Calcd. for $C_{19}H_{16}$: C, 93.40; H, 6.60. Found: C, 93.59; H, 6.73.

Method B

The acid-catalyzed dehydration of alcohol IX*c* (1.5 g) in methanol (30 ml) containing concentrated hydrochloric acid (2 ml) and isolation of olefin were executed as described for alcohol IX*b*. Recrystallizing the crude product (1.4 g) from diethyl ether – petroleum ether led to 0.40 g of hydrocarbon XII*b* melting at 104–106°. The ultraviolet spectra of olefin XII*b* prepared by methods A and B were identical, and both specimens were shown[13] to represent the same substance.

3β-Hydroxy-24,24-diphenyl-4,4,14α-trimethyl-5α-23-cholane (XV)

The sodium borohydride (0.008 g) – boron trifluoride etherate (0.46 g) reagent was allowed to react with 3β,24-dihydroxy-24,24-diphenyl-4,4,14α-trimethyl-5α-cholane (0.06 g, XIV) and the product isolated as

summarized for alcohol IXc. Crystallizing the crude material from chloroform–acetone gave 0.045 g of colorless crystals melting at 237–239°. Recrystallization from the same solvent led to a pure sample of olefin XV melting at 244–246° (ref. 24 reports m.p. 244–247°). Olefin XV was identical[13] with an authentic sample.

Triphenylmethane

Triphenylcarbinol (1.0 g) was easily reduced by sodium borohydride (0.29 g) – boron trifluoride etherate (16 g) as noted above for ketone VII. A solution of the crude hydrocarbon in hexane was chromatographed on activated alumina. Elution with the same solvent gave 0.66 g of triphenylmethane, which crystallized from diethyl ether – methanol as colorless needles (0.36 g) melting at 93–94°. The hydrocarbon was identical[13] with an authentic sample.

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REFERENCES

1. G. R. PETTIT and D. M. PIATAK. J. Org. Chem. **27**, 2127 (1962).
2. E. L. ELIEL and R. A. DAIGNAULT. J. Org. Chem. **29**, 1630 (1964).
3. (*a*) S. RAKHIT and M. GUT. J. Org. Chem. **29**, 229 (1964).
   (*b*) J. D. CHANLEY and T. MEZZETTI. J. Org. Chem. **29**, 228 (1964).
   (*c*) M. VERZELE, M. ACKE, and M. ANTEUNIS. J. Chem. Soc. 5598 (1963).
4. G. R. PETTIT and T. R. KASTURI. J. Org. Chem. **26**, 4557 (1961).
5. H. C. BROWN and B. C. SUBBA RAO. J. Am. Chem. Soc. **82**, 681 (1960).
6. H. C. BROWN and W. KORYTNYK. J. Am. Chem. Soc. **82**, 3866 (1960).
7. E. M. FEDNEVA. Zh. Obshch. Khim. **30**, 2818 (1960).
8. K. I. H. WILLIAMS, S. E. CREMER, F. W. KENT, E. J. SEHM, and D. S. TARBELL. J. Am. Chem. Soc. **82**, 3982 (1960).
9. W. M. JONES. J. Am. Chem. Soc. **82**, 2528 (1960).
10. H. C. BROWN and D. B. BIGLEY. J. Am. Chem. Soc. **83**, 3166 (1961). W. M. JONES and H. E. WISE, JR. J. Am. Chem. Soc. **84**, 997 (1962).
11. G. R. PETTIT and A. B. NEILL. Can. J. Chem. **42**, 1764 (1964).
12. G. R. PETTIT, B. GREEN, P. HOFER, D. C. AYRES, and P. J. S. PAUWELS. Proc. Chem. Soc. 357 (1962).
13. (*a*) D. S. BAPAT, B. C. SUBBA RAO, M. K. UNNI, and K. VENKATARAMAN. Tetrahedron Letters, 15 (1960).
   (*b*) C. J. SANCHORAWALA, B. C. SUBBA RAO, M. K. UNNI, and K. VENKATARAMAN. Indian J. Chem. **1** 19 (1963).
14. (*a*) H. B. BHAT and K. VENKATARAMAN. Tetrahedron, **19**, 77 (1963).
   (*b*) W. J. WECHTER. J. Org. Chem. **28**, 2935 (1963).
15. (*a*) K. T. POTTS and D. R. LILJEGREM. J. Org. Chem. **28**, 3202 (1962).
   (*b*) J. H. BREWSTER, H. O. BAYER, and S. F. OSMAN. J. Org. Chem. **29**, 110 (1964).
   (*c*) J. H. BREWSTER and H. O. BAYER. J. Org. Chem. **29**, 116 (1964).
   (*d*) E. L. ELIEL. Record Chem. Progr. Kresge-Hooker Sci. Lib. **22**, 129 (1961).
16. G. R. PETTIT, J. A. SETTEPANI, and R. A. HILL. Can. J. Chem. **43**, 1792 (1965).
17. CH. TAMM and R. ALBRECHT. Helv. Chim. Acta, **42**, 2177 (1959). W. BERGMANN, M. KITA, and D. J. GIANCOLA. J. Am. Chem. Soc. **76**, 4974 (1954).
18. J. W. COOK and M. F. C. PAIGE. J. Chem. Soc. 336 (1944).
19. L. RUZICKA and M. W. GOLDBERG. Helv. Chim. Acta, **19**, 99 (1936).
20. J. FAJKOS. Chem. Listy, **52**, 1780 (1958); Chem. Abstr. **53**, 5344 (1959).
21. C. DJERASSI and G. R. PETTIT. J. Org. Chem. **22**, 393 (1957).
22. R. N. JONES. J. Am. Chem. Soc. **67**, 2127 (1945).
23. (*a*) S. H. MORRELL, G. B. PICKERING, and J. C. SMITH. J. Inst. Petrol. **34**, 677 (1948); Chem. Abstr. **43**, 2608 (1949).
   (*b*) H. KÖLBEL. Brennstoff-Chem. **30**, 73 (1949); Chem. Abstr. **44**, 2217 (1950).
24. G. R. PETTIT, P. HOFER, W. J. BOWYER, T. R. KASTURI, R. C. BANSAL, R. E. KADUNCE, and B. GREEN. Tetrahedron, **19**, 1143 (1963).