rings.[5] This result contrasts sharply with the minute shift found by Slomp[2] for the homologous 1-methylbenzo[*c*]phenanthrene (Ia) and suggests that structural deformation of the aromatic ring system or the aromatic methyl from planarity due to steric interactions[2] is small or nonexistent in the phenanthrene IIIc, where only *one* "inside" methyl is present. However, from the n.m.r. evidence it is now concluded that the presence of *two* "inside" methyls leads to distortion in the phenanthrene case also.

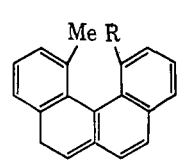
TABLE I
CHEMICAL SHIFTS OF METHYL PROTONS IN SOME AROMATIC SYSTEMS[a]

Compd.	Methyl proton resonances, p.p.m.
Toluene	2.32[b]
1-Methylbenzo[*c*]phenanthrene (Ia)	2.36[b]
1,12-Dimethylbenzo[*c*]phenanthrene (Ib)	1.92[b]
1-Methylestra-1,3,5(10)-trien-17-one (IIa)	2.34[c]
3-Hydroxy-1-methylestra-1,3,5(10)-trien-17-one (IIb)	2.29[c]
6-Methyl-1,2-cyclopentenophenanthrene (IIIa)[d]	2.57
3,6-Dimethyl-1,2-cyclopentenophenanthrene (IIIb)[d]	2.53 (6-Me) 2.43 (3-Me)
7-Hydroxy-3′,3′,5-trimethyl-1,2-cyclopentenophenanthrene (IIIc)[e]	1.33 (*gem*-diMe) 3.00 (5-Me)
9,10-Dihydro-4,5-dimethylphenanthrene (IVa)	2.25[f]
4,5-Dimethylphenanthrene (IVb)	2.57[f]

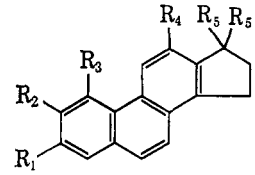
[a] Footnote 4. [b] See ref. 2. [c] See ref. 6. [d] Gift sample kindly supplied by Professor H. Dannenberg, Max Planck Institute for Biochemistry, Munich, Germany. [e] Made available by Dr. S. Kaufmann, Syntex. [f] Spectral data of H. Joshua, Ph.D. Dissertation, New York University, 1964. This information was generously provided, together with a sample of IVa, by Professor K. Mislow, Princeton University. N.m.r. data for IVa has also been published elsewhere.[6]

Mislow and his colleagues recently made a comprehensive comparative study of the ultraviolet and n.m.r. spectra of numerous bridged biphenyls related to, and including, 9,10-dihydro-4,5-dimethylphenanthrene (IVa).[7] They concluded that nonbonded molecular strain in the latter (IVa) is very likely relieved by in-plane and out-of-plane deformations of the methyl groups.

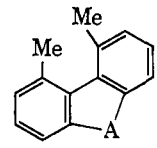
Introduction of a second "inside" methyl group on the fully aromatic phenanthrene nucleus leads to a strong diamagnetic shift of *ca.* 0.4 p.p.m. (*cf.* IIIc and IVb), a value similar to that recorded earlier for introduction of an extra "inside" methyl into benzo[*c*]-phenanthrenes (*cf.* Ia and Ib).[2] A severe methyl–methyl nonbonded interaction leading to reduced deshielding of the methyl groups by the ring currents of the phenanthrene system is indicated. That the integrity of the aromatic system in IVb remains largely



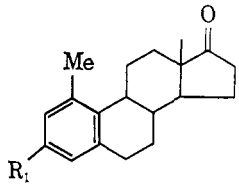
Ia, R = H
b, R = Me



IIIa, $R_1 = R_3 = R_4 = R_5 = H$; R_2 = Me
b, $R_1 = R_3 = R_5 = H$; $R_2 = R_4$ = Me
c, R_1 = OH; $R_2 = R_4 = H$; $R_3 = R_5$ = Me



IVa, A = CH_2—CH_2
b, A = CH=CH



IIa, R_1 = H
b, R_1 = OH

undisturbed has already been deduced from ultraviolet spectral data.[8] Molecular distortion appears to be achieved, therefore, principally by a bending of the C–Me σ bonds out of the plane of the ring system.

No firm evidence for long-range coupling between protons of ring A and C-methyl substituents was derived from these studies.

(5) The additional saturated cyclopentane ring of the phenanthrenes derived from steroids does not affect the aromatic 1- and 2-methyl proton resonances significantly (*cf.* toluene and IIa, Table I). Caspi and coworkers[6] have already shown that for 1-methylestra-1,3,5(10)-trienes a 3-hydroxyl causes a small *diamagnetic* shift of the 1-methyl proton resonance (*cf.* IIa and IIb). The effect of a similar substituent in the phenanthrene IIIc would be expected, therefore, to diminish slightly the paramagnetic shift induced by the aromatic rings B and C.

(6) E. Caspi, T. A. Wittstruck, and P. G. Grover, *Chem. Ind.* (London), 1716 (1962).

(7) K. Mislow, M. A. W. Glass, H. B. Hopps, E. Simon, and G. H. Wahl, *J. Am. Chem. Soc.*, **86**, 1710 (1964).

(8) G. M. Badger, J. E. Campbell, J. W. Cook, R. A. Raphael, and A. I. Scott, *J. Chem. Soc.*, 2326 (1950).

3,5-Cyclo-6-norcholestan-7-one[1]

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Received February 26, 1965

With the view of preparing steroid hormone analogs with a contracted ring B, we turned to a consideration of 3,5-cyclo steroids as intermediates in which the functional integrity of C-3 could be preserved during the rigorous conditions of pyrolysis necessary to bring about the contraction of the ring as envisaged in our synthesis. Because of the low cost of cholesterol and the fact that functional groups are not present elsewhere in the molecule, we chose to carry out model studies in the cholestane series.

For the starting material in our proposed synthesis we employed the previously reported[3] 3,5-cyclo-6,7-secocholestane-6,7-dioic acid (1), which may be pre-

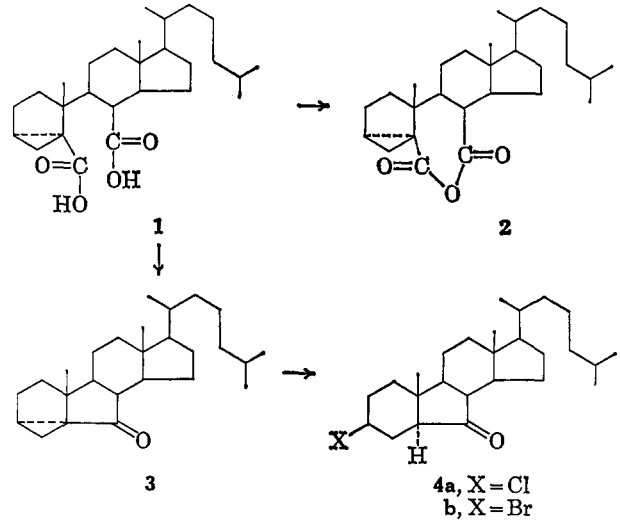
(1) The initial preparation of 3,5-cyclo-6-norcholestan-7-one is described in a thesis presented by W. W. Zorbach to the Faculty of Graduate Studies and Research, McGill University, Montreal, Canada, in partial fulfillment of the requirements for Degree of Doctor of Philosophy in Biochemistry, May 1951.

2) (a) To whom correspondence should be sent: Department of Chemistry, Georgetown University, Washington, D. C. (b) The present study is taken from a thesis submitted by J. Al-Kassir to the Graduate School of Georgetown University in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Chemistry, Dec. 1963. A scholarship for the graduate education of J. Al-Kassir by the Government of Iraq is gratefully acknowledged. (c) Deceased.

(3) K. Ladenburg, P. N. Chakravorty, and E. S. Wallis, *J. Am. Chem. Soc.*, **61**, 3483 (1939).

pared from cholesterol in five steps. The diacid **1**, when heated with acetic anhydride, gave the anhydride **2** instead of the desired product,[4] but when **1** was first converted to its lead salt and pyrolyzed at a high temperature, 3,5-cyclo-6-norcholestan-7-one (**3**) was formed (see Scheme I).[5] The ketone **3** was converted to its oxime, but only under conditions of prolonged refluxing. In accordance with our expectations based on the behavior of 3,5-cyclocholestan-6-one, the cyclopropane ring of **3** was opened readily with hydrogen chloride or with hydrogen bromide, giving 3β-chloro-6-norcholestan-7-one (**4a**) and 3β-bromo-6-norcholestan-7-one (**4b**), respectively.

SCHEME I



The infrared absorption spectrum of 3,5-cyclo-6-norcholestan-7-one (**3**) shows a carbonyl absorption frequency of 1722 cm.$^{-1}$, which reflects simultaneously the pseudoconjugation imposed by the 3,5-cyclopropane ring[6] and the increased strain brought about by contracting ring B.[7] Opening of the cyclopropane ring of **3** with hydrogen halide removes the pseudoconjugation and an increase in the carbonyl absorption is observed. 3β-Chloro-6-norcholestan-7-one (**4a**) shows a carbonyl absorption at 1748 cm.$^{-1}$, while the 3β-bromo analog **4b** absorbs at 1745 cm.$^{-1}$.

For comparison purposes, the known 3β-chlorocholestan-6-one,[8] 3β-bromocholestan-6-one,[8] 3α-chlorocholestan-6-one,[9] and 3α-bromocholestan-6-one[9] were synthesized. Attempts to convert the two latter 3α-halo ketones to the corresponding 6-nor analogs failed, and, when 3α-chlorocholestan-6-one was oxidized to the known 6,7-seco 6,7-diacid,[9] followed by a cyclization procedure previously reported,[4,10] only 3α-chloro-6,7-secocholestane-6,7-dioic acid anhydride could be obtained. Attempts to oxidize 3α-bromocholestan-6-one by the same procedure[9] to give the corresponding 6,7-dioic acid failed to give crystalline material which could be identified as 3α-bromo-6,7-secocholestane-6,7-dioic acid. The reasons for this anomalous result are not clear.

Presented as new data are the carbonyl stretching frequencies for 3β-chlorocholestan-6-one (1720 cm.$^{-1}$), 3α-chlorocholestan-6-one (1715 cm.$^{-1}$), 3β-bromocholestan-6-one (1718 cm.$^{-1}$), and 3α-bromocholestan-6-one (1714 cm.$^{-1}$).

(4) Because ring B is doubly annulated, and contrary to adipic acid, the Blanc rule does not apply. Failure of the rule in this context was first recognized by H. Wieland and E. Dane [*Z. Physiol. Chem.*, **210**, 268 (1932)].

(5) A 3,5-cyclo-6-nor steroid has been reported previously by W. G. Dauben and G. J. Fonken [*J. Am. Chem. Soc.*, **78**, 4736 (1956)] who prepared 7β-methoxy-3,5-cyclo-6-norcholestane.

(6) R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1252 (1954).

(7) C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press Inc., New York, N. Y., 1963, p. 202.

(8) J. H. Benyon, I. M. Heilbron, and F. S. Spring, *J. Chem. Soc.*, 907 (1936).

(9) A. Windaus and A. Stein, *Ber.*, **37**, 3699 (1904).

(10) M. Gut, *J. Am. Chem. Soc.*, **76**, 2261 (1954). In a private communication, Dr. Gut advises that the conditions for anhydride and ketone formation are essentially the same, and that it is not possible to control the cyclization to ensure even partial ketone production. See also L. F. Fieser, *ibid.*, **75**, 4386 (1953).

Experimental

All melting points were determined using a Kofler hot stage. Infrared absorption spectra were prepared using a Perkin-Elmer Model 137B infrared spectrophotometer with sodium chloride cells.

3,5-Cyclo-6,7-secocholestane-6,7-dioic Acid Anhydride (**2**).—A solution of 1 g. of 3,5-cyclo-6,7-secocholestane-6,7-dioic acid (**1**)[8] in 35 ml. of acetic anhydride was refluxed for 2 hr. The mixture was poured over ice and was allowed to stand for 2 hr. The solids were filtered and were recrystallized twice from methanol, giving 0.75 g. (78%) of the anhydride **2**, m.p. 91–92°, $[\alpha]^{25}D$ −15.0° (*c* 1.00, ethanol).

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.44; H, 10.31.

3,5-Cyclo-6-norcholestan-7-one (**3**).—To 4.0 g. of 3,5-cyclo-6,7-secocholestane-6,7-dioic acid (**1**) in 25 ml. of ethanol was added aqueous 1 *N* sodium hydroxide until the solution had pH 7.5. To this was added dropwise, with constant stirring, a warm solution of 3.1 g. of lead nitrate in 22 ml. of water. The precipitate was collected by filtration and was washed with water–ethanol (3:5). It was dried to constant weight at 100° under a reduced pressure of 20 mm.

Ten grams of the lead salt was pyrolyzed in 1-g. lots in bent sealing tubes (10-cm. o.d.) using a sodium nitrite–sodium nitrate bath. The pyrolysis was started at 280°, after which the temperature was elevated gradually over a period of 3 hr. to 340°. The tubes were allowed to cool and were cut. The pale yellow oily distillates were rinsed from the tubes with ether and were combined. The solution was decolorized with Darco G-60, filtered, and evaporated *in vacuo*. The oily residue was dissolved in a small amount of *n*-pentane and was placed on a column of 100 g. of activated alumina (Fischer reagent grade). Elution was started with *n*-hexane and the resulting eluates were discarded. From the benzene–*n*-hexane (5:95 and 10:90) eluates there was obtained 800 mg. of material which, when recrystallized from methanol, gave pure 6-nor ketone **3**: m.p. 77–79°; $[\alpha]^{25}D$ +26.7° (*c* 0.720, ethanol); $\nu_{max}^{CCl_4}$ 1722 (C=O stretching), 1325 (C-3–H bending), 1050 (symmetrical cyclopropane ring vibration), and 865 (asymmetrical cyclopropane ring vibration) cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{42}O$: C, 84.26; H, 11.42. Found: C, 84.14; H, 11.65.

Oxime of 3.—In a 25-ml. round-bottom flask fitted with a reflux condenser were combined 25 mg. of 3,5-cyclo-6-norcholestan-7-one (**3**), 25 mg. of anhydrous sodium acetate, and 25 mg. of hydroxylamine hydrochloride dissolved in 4 ml. of methanol and 1 ml. of water. The solution was refluxed for 7 hr. and, after cooling, the material separated as felted needles which, when recrystallized from methanol, gave pure oxime: m.p. 174.5–175.5°; $\nu_{max}^{CCl_4}$ 3600 (O–H stretching), 3320 (O–H bonding), 1660 (C=N stretching), 1342 (O–H bending), 1325 (C-3–H bending), 1050 (symmetrical cyclopropane ring vibration), 945 (N–OH stretching), and 860 (asymmetrical cyclopropane ring vibration) cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{43}NO$: C, 80.98; H, 11.24; N, 3.63. Found: C, 81.16; H, 11.30; N, 3.52.

3β-Chloro-6-norcholestan-7-one (**4a**).—To a solution of 25 mg. of 3,5-cyclo-6-norcholestan-7-one (**3**) in 5 ml. of acetic acid was added 1 ml. of concentrated aqueous hydrochloric acid. After standing overnight, the solution was dissolved in 200 ml. of ether and was extracted with aqueous sodium bicarbonate and then with water. The ether extract was dried over magnesium sulfate and, after filtering, was evaporated to dryness. Two recrystallizations of the residue from absolute ethanol gave 20 mg. of

chloro ketone **4a**, m.p. 91–92°, $[\alpha]^{25}D$ 0° (*c* 0.200, ethanol), $\nu_{max}^{CCl_4}$ 1748 (C=O stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{43}ClO$: C, 76.71; H, 10.65; Cl, 8.71. Found: C, 76.51; H, 10.51; Cl, 8.40.

3β-Bromo-6-norcholestan-7-one (4b).—To a solution of 100 mg. of 3,5-cyclo-6-norcholestan-7-one (**3**) in 10 ml. of acetic acid was added 1 ml. of 48% aqueous hydrobromic acid. After standing overnight, the separated crystalline material was collected by filtration. Crystallization under refrigeration from a small volume of methanol was slow (2 weeks), and an additional crystallization gave 65 mg. of pure bromo ketone **4b**, m.p. 84–85°, $[\alpha]^{25}D$ −5.3° (*c* 1.00, ethanol), $\nu_{max}^{CCl_4}$ 1745 (C=O stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{43}BrO$: C, 69.16; H, 9.60; Br, 17.70. Found: C, 69.20; H, 9.40; Br, 17.34.

Acknowledgment.—The authors are grateful to Miss Paula M. Parisius, Microanalytical Laboratory (under the direction of Dr. W. C. Alford), National Institutes of Health, Bethesda, Maryland, for the elemental analyses.

Some Steroid Ternary Iminium Salts and Their Conversion to 17β-(N-Pyrrolidinyl) Steroids

RICHARD M. SCRIBNER

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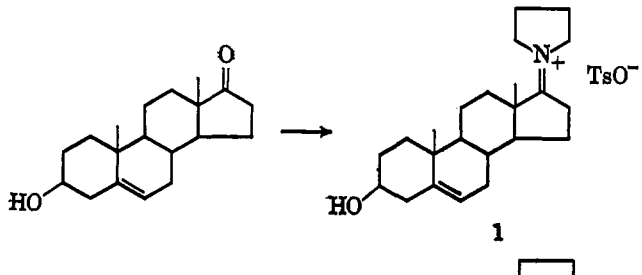
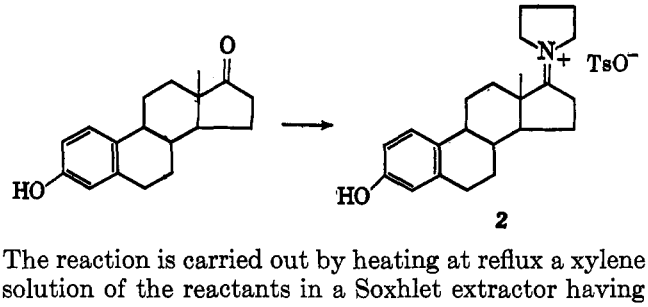
Received April 1, 1965

The enamines of 17-keto steroids, with few exceptions, are notoriously difficult to prepare.[1] By using the high-boiling amine, 4-methylpiperidine, Goldkamp[2] was able to convert several 17-keto steroids to the corresponding enamines, but even under forcing conditions yields were low.

We have found that 17-keto steroids react smoothly with pyrrolidine in the presence of a molar equivalent of *p*-toluenesulfonic acid to afford ternary iminium salts, *i.e.*, protonated enamines,[3] in better than 95% yield.



1

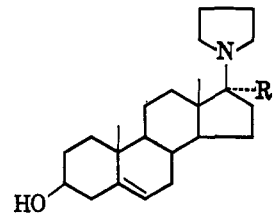


2

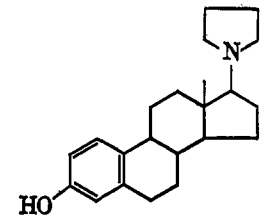
The reaction is carried out by heating at reflux a xylene solution of the reactants in a Soxhlet extractor having calcium carbide in the thimble as a dehydrating agent. After about 10 hr. the insoluble steroid salt is isolated simply by filtration.

The reaction is probably general for most 17-keto steroids,[4] but efforts to extend it to other heterocyclic nitrogen compounds, such as 4-methylpiperidine,[5] N-methylpiperazine, morpholine, hexamethyleneimine, 4-chloropyrazole, and imidazole, have been unsuccessful.

Ternary iminium salts are known to undergo rapid attack by a wide variety of nucleophilic agents.[6] N-(3β-hydroxyandrost-5-en-17-ylidene)pyrrolidinium *p*-toluenesulfonate (**1**), when suspended in ether and treated with lithium aluminum hydride, gives the corresponding 17β-(N-pyrrolidinyl) steroid **3a** in high yield (Table I).[7] Similarly, reduction of an ethereal suspension of the ternary iminium derivative **2** of estrone gives 3-hydroxy-17β-(N-pyrrolidinyl)estra-1,3,5(10)-triene (**4**).



3a, R=H
b, R=CH_3
c, R=C≡N
d, R=C≡CH



4

Methylmagnesium bromide in ether reacts smoothly with **1** to give the 17α-methyl steroid **3b**. Sodium cyanide in acetonitrile reacts to give the 17α-cyano steroid **3c**. Lithium acetylide etyhlenediamine complex or ethynylmagnesium bromide in ether react with **1** to afford the 17α-ethynyl steroid **3d** in low yields, but action of ethynylmagnesium bromide on the nitrile **3c** in tetrahydrofuran gives **3d** in excellent yield. These reactions are analogous to those observed by Lednicer and Babcock[8] for their steroid 17-N,N-dimethyliminium salts.

Oxidation of the 17β-pyrrolidinyl-5-androsten-3β-ols (**3**) to the corresponding Δ^4-3 ketones (**5**) is readily accomplished with cyclohexanone under Oppenauer conditions.

Treatment of 5α-androstane-3,17-dione with excess pyrrolidine and *p*-toluenesulfonic acid under the conditions described earlier for the preparation of **1**, followed by reduction of the crude product with lithium aluminum hydride in ether, gives 3β,17β-bis(N-pyrrolidinyl)-5α-androstane (**6**).[7]

(1) F. W. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, **75**, 1918, 5927 (1953); J. L. Johnson and M. E. Herr, *ibid.*, **78**, 430 (1956).

(2) A. Goldkamp, *J. Med. Pharm. Chem.*, **5**, 1176 (1962).

(3) G. Opitz and A. Griesinger, *Ann.*, **665**, 101 (1963).

(4) Shortly after the completion of this work, N. J. Leonard and J. V. Paukstelis [*J. Org. Chem.*, **28**, 3021 (1963)] reported the direct synthesis of ternary iminium salts by reaction of nonsteroidal ketones or aldehydes with the perchloric acid salts of secondary amines, especially pyrrolidine.

(5) The failure of 4-methylpiperidine to afford even a detectable amount of steroid ternary iminium salt under our forcing conditions, in contrast to the success of Goldkamp in preparing enamines with this amine,[2] suggests that the steroid iminium salts are formed directly (as reported in ref. 4) rather than by preliminary formation of enamine followed by protonation.[3]

(6) For example, see N. J. Leonard and A. S. Hay, *J. Am. Chem. Soc.*, **78**, 1984 (1956); G. Opitz, A. Griesinger, and H. W. Schubert, *Ann.*, **665**, 91 (1963).

(7) M. Davis [U. S. Patent 3,169,093 (1965)] has recently described the preparation of a number of 17β-(N-pyrrolidinyl) steroids, including the compounds designated above as **3a** and **6**, by heating steroid ketones with pyrrolidine and formic acid at about 170°.

(8) D. Lednicer and J. C. Babcock, *J. Org. Chem.*, **27**, 2541 (1962); D. Lednicer, U. S. Patent 3,107,254 (1963).