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THE OXIDATIVE REARRANGEMENT OF 5α-CHOLESTAN-3-ONE

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Abstract—Treatment of 5α-cholestan-3-one (I) with hydrogen peroxide and selenic acid, followed by esterification, leads to 2α-carbomethoxy-A-nor-5α-cholestane (II) as the major product. Two other products also isolated are 3β-carbomethoxy-A-nor-5α-cholestane (IVa) and methyl 2,3-seco-5α-cholestane-2,3-dioate (Va). These facts are discussed in terms of a possible reaction mechanism.

SINCE the discovery that a mixture of selenium dioxide and hydrogen peroxide transforms alicyclic ketones to ring contracted cycloalkanecarboxylic acids,[1] the rearrangement has been extended to acyclic[2,3] and alkylphenyl ketones.[4] Recently, the reaction has been applied to several 3-keto steroids.[5,6]

With 5α-cholestan-3-one[5] (I) a mixture of acids was obtained in 49% yield, which after esterification was separated by chromatography into 2α-carbomethoxy-A-nor-5α-cholestane (II), 25% and 3α-carbomethoxy-A-nor-5α-cholestane (IIIa), 19·5%. In the other study,[6] only a small yield of ring contracted product was obtained from 17β-acetoxy-5α-androstan-3-one; the other products resulted from Baeyer-Villiger oxidation. For the corresponding 5-*beta* analogue, only Baeyer-Villiger products were obtained.[6] Our results on the 5α-cholestan-3-one (I) system, reported here, differ from those previously published in the number of products and, more significantly, in the configuration of the 3-carbomethoxy-A-norcholestane produced.

We have found that reaction of I with selenic acid and 30% hydrogen peroxide in t-butyl alcohol yields a complex mixture of acids. Esterification of the crude product with diazomethane and several recrystallizations from methyl alcohol gave crude 2α-carbomethoxy-A-nor-5α-cholestane (II) in 35% yield. The analytical sample (m.p. 97·2-98°, $[\alpha]^{25}_{D}$ +27°) was identified by comparison of its properties with those reported in the literature,[7,8] elemental analysis, and conversion to the known 2-hydroxymethyl-A-norcholestane.[7] Chromatography of the residue obtained from the mother liquors of crude II on neutral alumina and elution with hexane–benzene gave an oil from which both II and 3β-carbomethoxy-A-nor-5α-cholestane(IVa) were obtained by fractional recrystallization. Compound IIIa was not found, although it has been shown that it can be separated from II by this technique.[8] The yield of IVa (m.p. 75·6–76·7°, $[\alpha]^{29}_{D}$ +1°) was only about 4%. Its identity was shown by elemental analysis, mixture melting point, and comparison of its IR spectrum with

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[1] G. B. Payne and C. W. Smith, *J. Org. Chem.* **22**, 1680 (1957).

[2] H. M. Hellman and A. Rosegay, *Tetrahedron Letters* No. 13, 1 (1959).

[3] N. Sonoda and S. Tsutsumi, *Bull. Chem. Soc., Japan* **32**, 505 (1959).

[4] N. Sonoda and S. Tsutsumi, *Bull. Chem. Soc., Japan* **33**, 1440 (1960).

[5] J. Biellmann and M. Rajic, *Bull. Soc. chim., Fr.* 441 (1962).

[6] E. Caspi and S. N. Balasubrahmanyam, *Tetrahedron Letters* No. 12, 745 (1963).

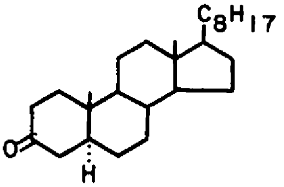
[7] B. B. Smith and H. R. Nace, *J. Amer. Chem. Soc.* **76**, 6119 (1954).

[8] D. E. Evans, A. C. dePaulet, C. W. Shoppee, and F. Winternitz, *J. Chem. Soc.* 1451 (1957).

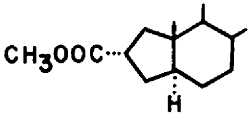
that of an authentic sample.[9] Elution with benzene gave crude methyl 2,3-seco-5α-cholestane-2,3-dioate (Va) in 8% yield. The analytical sample (m.p. 58·6–59·7°, $[\alpha]_D^{28}$ +20°) was identified by elemental analysis and comparison of its physical properties with those reported in the literature.[7] Further elution of the column with more polar solvents produced oils (17% by weight) which are under investigation.

Our isolation of IVa, the epimer of the 3-nor-ester reported by Biellmann and Rajic,[5] justifies questioning the evidence as to the identity of their products. The French workers had identified their ring contracted products by comparison of the physical properties of the methyl esters with those reported for the products obtained from the Favorskii reaction of 2α-bromocholestan-3-one.[7,8] In the case of II, the agreement was good. However, for IIIa, the m.p. 51°, and rotation, $[\alpha]_D$ +11° are between those reported for IIIa (m.p. 45–46°, $[\alpha]_D$ +1°)[8] and Va (m.p. 60–60·3°, $[\alpha]_D$ +19°).[7] Therefore, it is possible that the product assigned structure IIIa by them may actually be Va which we isolated. In the absence of an elemental analysis and other data on their material, this point cannot be rigorously determined.

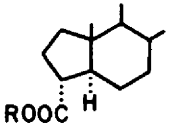
A mechanism has been proposed by Sonoda and Tsutsumi for the rearrangement of desoxybenzoin,[10] in which a peroxyselenious enol ester, VI, is postulated as an intermediate. This then undergoes intramolecular epoxidation to give the enol epoxide VII, which rearranges as shown to give diphenylacetic acid (VIII). Opening of



I

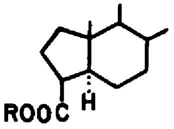


II



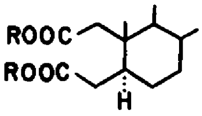
IIIa R=CH_3

IIIb R=H



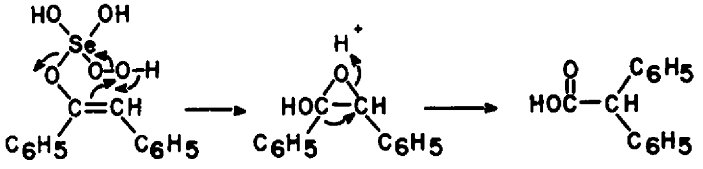
IVa R=CH_3

IVb R=H



Va R=CH_3

Vb R=H



VI VII VIII

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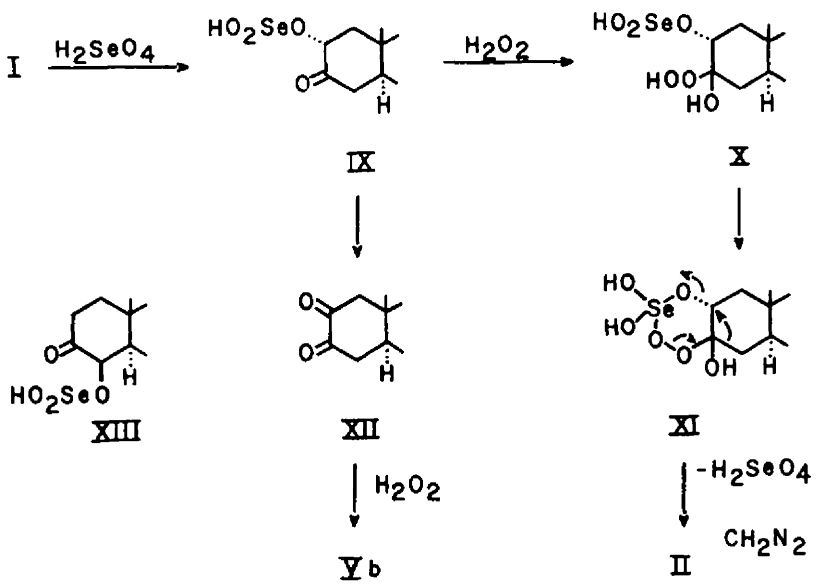
[9] B. Fuchs and H. J. E. Loewenthal, *Tetrahedron* **11**, 199 (1960). The authors wish to thank Dr. Loewenthal, Israel Institute of Technology, Haifa, for supplying them with a sample of 3β-carbomethoxy-A-nor-5α-cholestane.

[10] N. Sonoda and S. Tsutsumi, *Bull. Chem. Soc. Japan.* **34**, 1006 (1961).

epoxide VII in the manner proposed appears unlikely in view of the course of epoxide reactions in acidic solutions.[11]

SCHEME I



Scheme I summarizes our proposed mechanism. All examples of oxidative rearrangement of ketones using hydrogen peroxide and selenic acid or selenium dioxide have involved enolizable ketones. Non-enolizable ketones, even those having *alpha*-hydrogen atoms, fail to give the reaction.[12] Hence, it is plausible to assume that with the steroid ketones also, enolization or enol-ester formation is an essential step. An enol selenite ester, which rearranges to an *alpha*-keto selenium ester, has been proposed by Corey and Schaefer as an intermediate in the selenious acid oxidation of desoxybenzoin.[13] Hence, our first step involves the interaction of ketone with selenic acid to give an *alpha*-keto selenite ester IX. Attack by hydrogen peroxide on the carbonyl group of IX gives X. *alpha*-Substituted hydroxy hydroperoxides such as X have been isolated by Kharasch and Sosnovsky by treatment of *alpha*-bromo and *alpha*-chlorocyclohexanone with hydrogen peroxide.[14] In the absence of a bulky *alpha* group, only dimers were isolated. Cyclization of X gives the peroxide XI, which rearranges as indicated to give product II. A cyclic peroxide has been proposed by Payne to account for the formation of cyclopentanecarboxylic acid from 2-acetylcyclohexanone and hydrogen peroxide.[15] IX can also go to the diketone XII, which can be oxidized by hydrogen peroxide to the 2,3-seco-acid Vb, which we isolated as the methyl ester Va.

[11] R. E. Parker and N. S. Isaacs, *Chem. Revs.* **59**, 737 (1959).

[12] R. A. Jerussi, Ph.D. Diss., New York University, April, 1961.

[13] E. J. Corey and J. P. Schaefer, *J. Amer. Chem. Soc.* **82**, 918 (1960).

[14] M. S. Kharasch and G. Sosnovsky, *J. Org. Chem.* **23**, 1322 (1958).

[15] G. B. Payne, *J. Org. Chem.* **26**, 4793 (1961).

The expected and actually obtained major product of the ring contraction is the 2-isomer, in analogy with other reactions such as bromination, which involve enol intermediates. Our isolation of IVa, though unexpected, can be accounted for by formation of a small proportion of 3-keto-4-selenite ester XIII, which should have the selenite group *beta* in order to produce IVa. In a probably related reaction, the N-bromosuccinimide bromination of the Δ^3 enol ether of 17β-acetoxy-5α-androstan-3-one, the major product was the 4-*alpha*-bromo compound but some of the thermodynamically less stable 4-*beta* isomer was also formed.[16]

Since IVb suffers a 1,3-diaxial methyl-carboxyl interaction, it seems likely that it is thermodynamically less stable than IIIb. Factual information on this point must await epimerization studies of IIIa and IVa.[17]

EXPERIMENTAL[18]

Oxidation of 5α-cholestan-3-one (I). A solution of 5α-cholestan-3-one (I; 1·995 g, 0·00516 mole), t-butyl alcohol (15 ml), 30% aqueous hydrogen peroxide (1·2 ml), and 40% aqueous selenic acid (0·1 ml) was heated under reflux for 15 hr, at which time a negative starch–potassium iodide test was obtained. The solvent was removed under vacuum and the residue treated with 30% potassium carbonate (10 ml), hot water (300 ml), and benzene (200 ml). The mixture was shaken, and the benzene separated and washed with water until clear. All washings were added to the basic solution, acidified with 10% HCl, and continuously extracted with ether for 2 hr. The ether was dried and removed under vacuum to yield 1·652 g of a tan solid, which was esterified with ethereal diazomethane to give 1·612 g of a yellow oil. Two recrystallizations from methyl alcohol produced 0·726 g (35%) crude 2α-carbomethoxy-A-nor-5α-cholestane (II), m.p. 90·3–93·1°. Chromatography of a sample of this material on Florisil and elution with 7:3 hexane–benzene gave a white product, which after 3 recrystallizations from methyl alcohol had m.p. 97·2–98°, $[\alpha]_D^{25}$ +27° (*c* 1·1, $CHCl_3$), λ_{max}^{KBr} 5·82 μ reported[7] m.p. 97·5–98°, $[\alpha]_D$ +29° and[8] m.p. 94–95°, $[\alpha]_D$ +29°), (Found: C, 80·95; H, 11·51. Calc. for $C_{28}H_{48}O_2$: C, 80·71; H, 11·61%).

Reduction of 0·173 g II with 0·480 g $LiAlH_4$ in ether gave 0·152 g solid, m.p. 112·2–117·5°. Chromatography of this material on 8 g Florisil and elution with benzene gave 0·144 g (89%) 2-hydroxymethyl-A-norcholestane, m.p. 116·1–117·7°. Three recrystallizations from methyl alcohol gave m.p. 116·5–119°, $[\alpha]_D^{25}$ +33° (*c* 1·0. $CHCl_3$), (reported[7] m.p. 118–118·5°, $[\alpha]_D$ +32°), (Found: C, 83·95; H, 12·57. Calc. for $C_{27}H_{48}O$: C, 83·44; H, 12·45%.)

The filtrates from the two methyl alcohol recrystallizations of the crude product from diazomethane esterification were combined and the solvent removed to yield 0·863 g of an oil. This was placed on 130 g neutral alumina in hexane.[19] Elution with 85:15 hexane–benzene (20 ml eluates) gave fractions A_1 through A_{27} (265 mg). Fractions A_1 through A_4 (81 mg) were combined and recrystallized from methyl alcohol to yield a solid, m.p. 91·1–95·5°. The IR spectrum of this material was essentially identical with that of an analytical sample of II. Fractions A_6 through A_{27} were combined and fractionally recrystallized from methyl alcohol to yield 3β-carbomethoxy-A-nor-5α-cholestane (IVa), m.p. 75·6–76·7°, $[\alpha]_D^{29}$ +1° ± 1° (*c* 0·5, $CHCl_3$), λ_{max}^{KBr} 5·78 μ (reported[9] m.p. 78·5–79°, $[\alpha]_D$ 0°), and a small amount of II. The NMR spectrum of IVa revealed a singlet at 6·35 Tau (CH_3O—) which integrated for 3 protons. A mixture m.p. of IVa with authentic material

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[16] R. Gardi, P. P. Castelli and A. Ercoli, *Tetrahedron Letters* No. 11 497 (1962).

[17] The configurations of the three A-norcholestane esters discussed in this paper have not been established unambiguously. Shoppee et al.[8] assigned the *alpha* configuration to the 2- and 3-A-norcholestane esters by considering the stereochemistry of the Favorskii rearrangement. Loewenthal[9] assigned the *beta* configuration to his 3-A-norcholestane ester by a combination of chemical evidence and molecular rotation differences. All assignments appear reasonable and consistent.

[18] M.p.s are corrected. Analyses by Schwarzkopf Microanalytical Laboratory, Woodside, New York.

[19] Merck "suitable for chromatographic adsorption" alumina was successively washed with 10% sodium hydroxide solution, warm acetic acid, and distilled water until the washings were neutral; then activated at 200° for 40 hr. To this material was added 3% water by weight.

gave m.p. 75·8–77° and the IR spectra of the two compounds were essentially identical. (Found: C, 80·07; H, 11·48; O, 7·52. Calc. for $C_{28}H_{48}O_2$ C, 80·71; H, 11·61; O, 7·68%).

Elution with benzene (40 ml eluates) gave fractions B_1 through B_7 (178 mg). Fraction B_2 had m.p. 47·5–54°. All B fractions were combined and recrystallized 4 times from methyl alcohol to yield methyl 2,3-seco-5α-cholestane-2,3-dioate (Va) m.p. 58·6–59·7°, $[\alpha]_D^{26}$ +20° (*c* 1·0, $CHCl_3$), $\lambda_{max}^{CCl_4}$ 5·76 μ (reported[7] m.p. 60–60·3°, $[\alpha]_D$ +19°). (Found: C, 75·43; H, 10·87. Calc. for $C_{29}H_{50}O_4$: C, 75·28; H, 10·89%).