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TRANSANNULAR CYCLIZATION OF 5β-CHOLESTAN-2α-OL LEADING TO 2α,9α-EPOXY-5β-CHOLESTANE*

Munemitsu Tomoeda and Toshitaka Koga
Faculty of Pharmaceutical Sciences, Kanazawa University
Kanazawa, Japan

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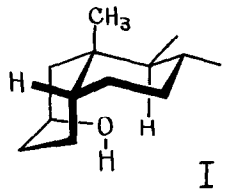
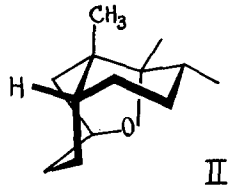
In connection with the general objective of introducing a functional group into an inactivated carbon atom in the steroid nucleus, a number of papers (1,2) have recently appeared which showed that various steroidal alcohols could react with lead tetraacetate in non-polar solvents forming tetrahydrofuran and tetrahydropyran derivatives, cyclization occuring, for instance, in the following directions: 11α→1α, 2β→19, 3α→9α**, 4α→9α**, 4β→19, 6β→19, 11β→18 and →19, and 20→18. To our knowledge, however, no paper has dealt with the cyclization from 2α to 9α positions, although inspection of a Dreiding stereomodel (I) of



I



II

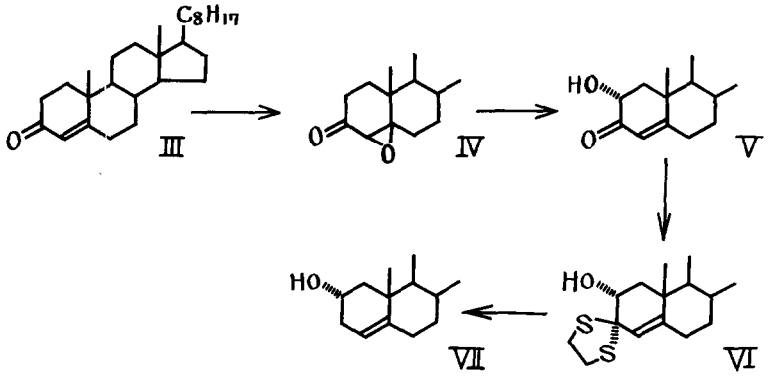
* All new compounds synthesized gave correct analyses.

** These cyclizations occured in the 5β-series.

2α-hydroxy-5β-steroids suggested us that the position of and the distance between the 2α-alcohol and the 9-methine group are favored to ring closure, forming new steroidal tetrahydrofurans (II).

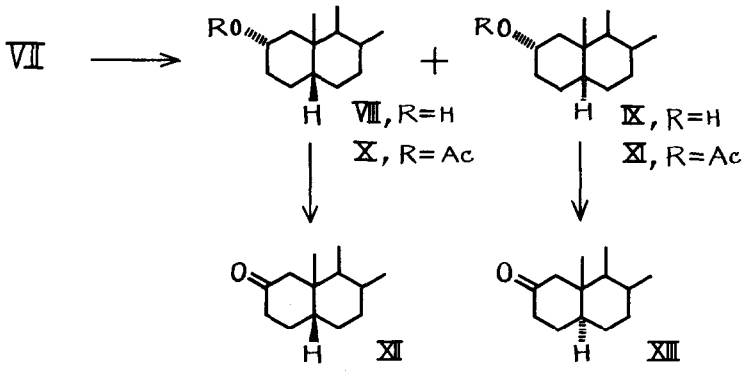
We now wish to report the synthesis of previously unknown 5β-cholestan-2α-ol (VIII) from cholest-4-en-3-one (III) in 15.7% overall yield, and its successful transannular cyclization with lead tetraacetate leading to 2α,9α-epoxy-5β-cholestane (XIV).

Preparation of cholest-4-en-2α-ol (VII) as a key intermediate in the synthesis of VIII was carried out from III in a fashion similar to that reported by Fieser and Romero (3) with some modified steps in a better overall yield of 28.5%. It involved epoxidation (the 4α,5-epoxide (IV), 65.4%) (4), abnormal ring opening in sulfuric acid-aqueous acetone (the 4-en-2α-ol-3-one (V), 61.4%) (5), condensation with ethanedithiol in boron trifluoride etherate-acetic acid (the ethylenethioketal (VI), (86.6%) (3), and desulfurization with Raney Ni (W 2) in methanol



giving VII (81.9%) (3), ν_{max} cm^{-1} (all infrared spectra taken in nujol unless otherwise stated): 3263 (s) (OH), 1657 (w) (-CH=C<), NMR τ (all NMR spectra determined in deuterochloroform at 60 MC): 4.84 (multiplet, one proton) (C_4-H), 6.08 (multiplet, one proton) (C_2 β-H).

Hydrogenation of VII followed firstly the condition of the same authors (3)*, i.e. platinum catalyst in acetic acid, affording on chromatography (silica gel) VIII as colorless needles** (20.9%), m.p. 106-107°, $[\alpha]_D^{18}+29.6°$ (c 0.98, all rotations taken in chloroform), ν_{max} cm^{-1}: 3347 (s) (OH), NMR τ: 5.92 (multiplet, one proton) (C_2 β-H), and its 5α-isomer (IX) (3) as colorless needles (32.8%), m.p. 182.5-183°, $[\alpha]_D^{22}+25.4°$



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* They reported the hydrogenation to give the 5α-isomer (IX) as the sole product.

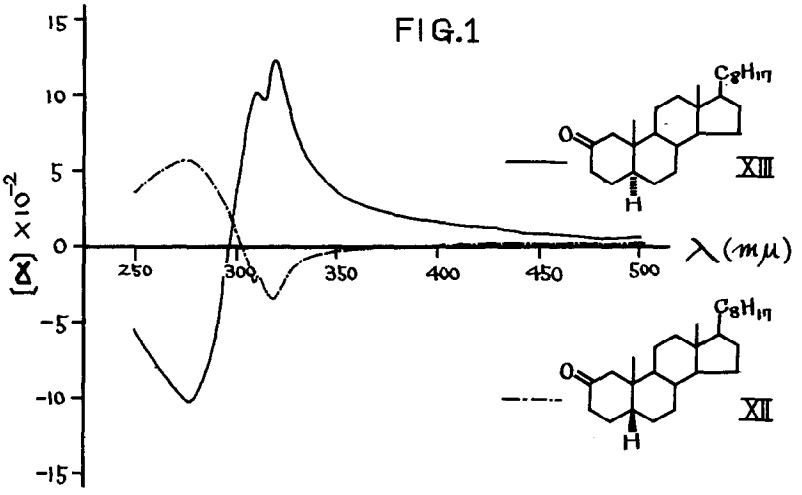
** This alcohol (VIII) is very readily soluble in various solvents of wide range from methanol to petropeum ether, however, it could crystallize from a small amount of 99% ethanol under cooling below -10°.

(c 1.03), ν_{max} cm^{-1}: 3260 (s) (OH), NMR τ: 6.26 (multiplet, one proton) (C_2 β-H). When the hydrogenation was carried out in 99% ethanol, the yield of the 5β-isomer (VIII) was improved to 55.1% and that of the 5α-isomer (IX) dropped to 25.5%.

The NMR information that the signal due to 2β-proton of VIII appears at a lower field as a more narrow multiplet than that of 2β-proton, which is axial, of IX, indicated the equatorial character of 2β-proton (6) and then the β configuration at C-5 of VIII. Further evidence for the structures and configurations at C-5 of the isomeric alcohols, VIII and IX, was obtained that they gave, on acetylation with acetic anhydride-pyridine, their corresponding acetates, 2α-acetoxy-5β-cholestane (X) as colorless needles (91.2%), m.p. 58.5-59.5°, $[\alpha]_D^{25}$+7.9° (c 1.01), ν_{max} cm^{-1}: 1738 (s) ($OCOCH_3$), NMR τ: 4.97 (broad, one proton) (C_2 β-H), 7.94 (singlet, three protons) ($OCOCH_3$), and its 5α-isomer (XI) (7) as colorless needles (96.6%), m.p. 86.5-87.5°, $[\alpha]_D^{24}$ -4.0° (c 1.01), ν_{max} cm^{-1}: 1736 (s) ($OCOCH_3$), NMR τ: 5.17 (multiplet, one proton) (C_2 β-H), 8.01 (singlet, three protons) ($OCOCH_3$), and on oxidation with the Jones reagent, their corresponding 2-oxo derivatives, 5β-cholestan-2-one (XII) as colorless plates (93.5%), m.p. 87.5-88°, $[\alpha]_D^{24.5}$+20.5° (c 0.205 in dioxane)*, RD in dioxane (c 0.201) at 24.5°, $[\alpha]_{317}$ -354° (trough), $[\alpha]_{310}$ -210° (peak), $[\alpha]_{307}$ -234° (trough), λ_{max} mμ (ε) (all UV spectra taken in 95% ethanol): 284 (33) (C=O), ν_{max} cm^{-1}: 1712 (s) (C=O), and its 5α-isomer (XIII) (8) as colorless plates (91.5%), m.p. 131.5-132°, $[\alpha]_D^{24}$+41.8°*

* The measurements were made on a Yanagimoto OR-20 recording spectropolarimeter.

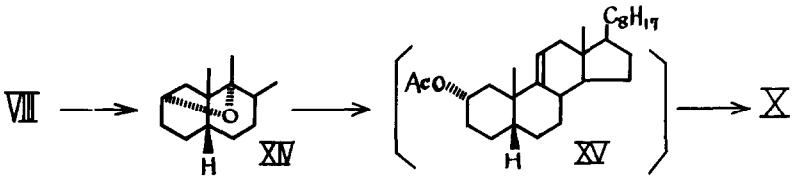
FIG.1



(c 0.199 in dioxane), RD in dioxane (c 0.199) at 24°, $[\alpha]_{318}$ +1220 (peak), $[\alpha]_{312}$ +987 (trough), $[\alpha]_{310}$ +1017 (peak), λ_{max} mμ (ε): 286 (36) (C=O), ν_{max} cm^{-1}: 1709 (s) (C=O). That the ketone (XII) gave a negative cotton effect curve exactly symmetrical to that of the 5α-isomer (XIII) with a positive sign (9) as is shown in Fig. 1, indicated definitely the β configuration at C-5 of XII and then of VIII and X.

It was now found that oxidation of VIII (660 mg., 1.7 mmoles) with lead tetraacetate (1.518 g., 3.4 mmoles) in refluxing benzene (15 ml) for 5 hr. gave on chromatography (silica gel) and crystallization from 99% ethanol the 2α,9α-epoxide (XIV) as colorless needles, m.p. 46-47.5°, $[\alpha]_D^{21}$ -4.0° (c 0.99), (wt. 341 mg., 51.9%).* The structure of the compound (XIV) was

* Oxidation of 17β-acetoxy-5β-androstan-3α-ol with lead tetraacetate was reported to give its 3α,9α-epoxide only in 0.4% yield (10).



characterized by its spectroscopic properties, UV transparent above 210 mμ, IR no hydroxyl absorption but ν_{max} cm^{-1}: 1103 (m) (C-O-C), NMR τ: 5.85 (multiplet, one proton) (C_2 β-H), and was confirmed by its relation to X. The epoxide (XIV) was subjected to ring opening with acetic anhydride-boron trifluoride etherate in benzene (room temperature, 30 min.) giving on chromatography (silica gel) a colorless oil (thin-layer chromatographically homogeneous) characterized as 2α-acetoxy-5β-cholest-9(11)-ene (XV)* (65.1%) by the spectroscopic evidence, $[\alpha]_D^{29}$ +19.2° (c 0.99), λ_{max} mμ (ε): 211.3 (3630) (-CH=C<)**, ν_{max}^{liquid} cm^{-1}: 3049 (m) and 1647 (w) (-CH=C<), 1735 (s) ($OCOCH_3$), NMR τ: 4.61 (broad, one proton) (C_{11}-H), 5.01 (broad, one proton) (C_2 β-H), 7.98 (singlet, three protons) ($OCOCH_3$), which on hydrogenation over platinum catalyst in acetic acid afforded a saturated acetate, m.p. 59-59.5°, alone and on admixture with a sample of X, (62.7%). Their IR spectra were completely superposable.

Attempt at introduction of an oxy-function at C-11 from XIV is at present in progress.

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* Ring openings of steroidal tetrahydrofurans of $-CH_2-O-CH$ type with Ac_2O-BF_3 etherate were reported to give diacetates as major products (11).

** Various steroidal monoenes were reported to show characteristic absorptions in the far-ultra violet region (12).

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References

(1) Ref. cited in C. Djerassi (Ed.), Steroid Reactions, p.327. Holden-Day, Inc., San Francisco (1963).

(2) [a] R. Ledger and J. Mc-Kenna, Chem. Ind. 1662 (1963). [b] K. Heusler and J. Kalvoda, Tetrahedron Letters 1001 (1963). [c] G. Volpp and Ch. Tamm, Helv. Chim. Acta 46, 219 (1963). [d] J. Kalvoda, K. Heusler, G. Anner and A. Wettstein, ibd. 46, 618 (1963). [e] J. Kalvoda, K. Heusler, G. Anner and A. Wettstein, ibd. 46, 1017 (1963). [f] J. Kalvoda, K. Heusler, H. Ueberwasser, G. Anner and A. Wettstein, ibd. 46, 1361 (1963). [g] K. Heusler and J. Kalvoda, ibd. 46, 2020 (1963). [h] K. Heusler and J. Kalvoda, ibd. 46, 2732 (1963). [i] J. Kalvoda, K. Heusler, Ch. Meystre, P. Wieland and G. Anner, Gazz. Chim. Ital. 93, 140 (1963). [j] R. Kwok and M. E. Wolff, J. Org. Chem. 28, 423 (1963). [k] J. F. Bagli, P. E. Morand and R. Gaudry, ibd. 28, 1207 (1963). [l] G. B. Spero, J. L. Thompson, W. P. Schneider and F. Kagan, ibd. 28 2225 (1963). [m] R. M. Moriarty and T. D. D'Silva, ibd. 28, 2445 (1963). [n] D. Hauser, K. Heusler, J. Kalvoda, K. Schaffner and O. Jeger, Helv. Chim. Acta 47, 1961 (1964). [o] M. Akhtar and M. M. Pechet, J. Amer. Chem. Soc. 86, 265 (1964). [p] M. Akhtar and D. H. R. Barton, ibd. 86, 1528 (1964). [q] D. H. R. Barton, A. L. J. Beckwith and A. Goosen, J. Chem. Soc. 181 (1965). [r] R. M. Moriarty and T. D. D'Silva, Tetrahedron 21, 547 (1965).

(3) L. F. Fieser and M. A. Romero, J. Amer. Chem. Soc. 75, 4716 (1953).

(4) P. A. Plattner, H. Heusser and A. B. Kulkarni, Helv. Chim. Acta 31, 1822 (1948).

(5) M. Tomoeda, M. Ishizaki, H. Kobayashi, S. Kanatomo, T. Koga, M. Inuzuka and T. Furuta, Tetrahedron 21, 733 (1965).

(6) L. M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, p. 84. Pergamon Press, London (1959).

(7) A. Fürst and P. A. Plattner, Helv. Chim. Acta 32, 275 (1949).

(8) L. Ruzicka, P. A. Plattner and M. Furrer, ibd. 27, 524 (1944).

(9) C. Djerassi, W. Closson and A. E. Lippman, J. Amer. Chem. Soc. 78, 3163 (1956).

(10) H. Immer, M. Lj. Mihailović, K. Schaffner, D. Arigoni and O. Jeger, Helv. Chim. Acta 45, 753 (1962).

(11) [a] B. Kamber, G. Cainelli, D. Arigoni and O. Jeger, ibd. 43, 347 (1960). [b] K. Heusler, J. Kalvoda, Ch. Meystre, P. Wieland, G. Anner, A. Wettstein, G. Cainelli, D. Arigoni and O. Jeger, ibd. 44, 502 (1961). [c] A. Bowers, E. Denot, L. C. Ibáñez, Ma. E. Cabezas and H. J. Ringold, J. Org. Chem. 27, 1862 (1962).