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OXETANE FORMATION IN HYPOIODITE REACTION OF 3β- and 3α-HYDROXY-Δ^5-STEROIDS. OXIDOMETHYLENE-3α,5α-A-NOR-CHOLESTANE. (1)

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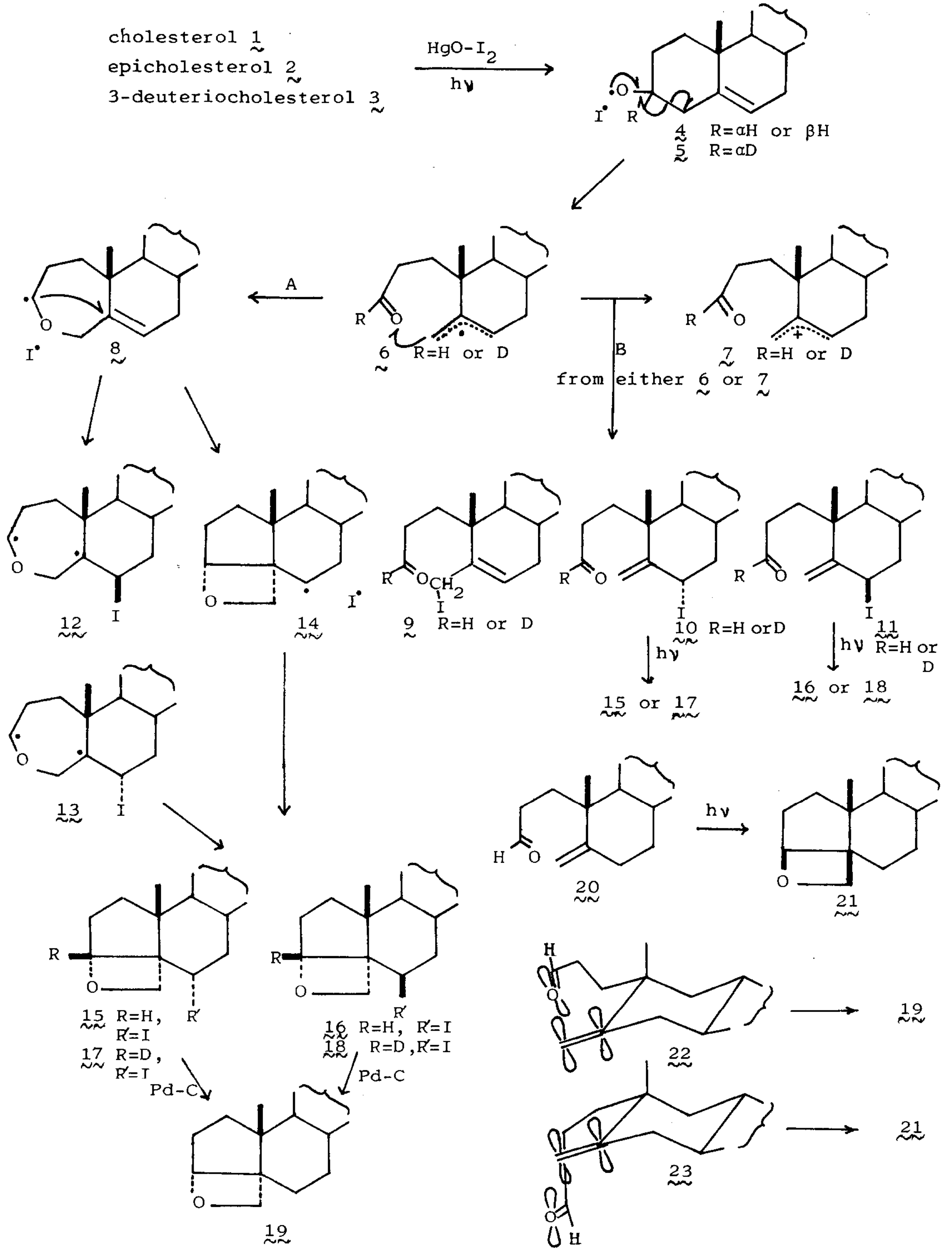
It was briefly mentioned that the hypoiodite reaction of 3β-hydroxy-Δ^5-steroids affords a mixture of aldehydes. (2)

We examined the products from the hypoiodite reaction of cholesterol and epicholesterol in some detail and found that besides the expected iodine-containing aldehyde, oxetanes are formed in substantial amounts.

Cholesterol **1** (1 g) in benzene (150 ml) in the presence of HgO and I_2 (each 3 equivalents) was irradiated through pyrex for 6 hr by a 100-W high pressure Hg arc lamp while argon was bubbled. Four products, an amorphous **9** (25-34%), a crystalline **15**, (8-11%), m.p. 141-143°C, an amorphous **16** (8-11%) and a fourth compound of still unknown structure (4%), m.p. 239-241°C, were obtained by the preparative tlc. The hypoiodite reaction of epicholesterol **2** or 3-deuteriocholesterol **3**, (3) by the same procedure afforded the same series of compounds. (**9**, **17**, **18** and a fourth compound).

9, **15** and **16** all contained iodine in the molecules and it was immediately apparent that **9** was the expected 3,4-seco-4-iodo-cholest-5-en-3-al due to the β-cleavage of the 3β-O-radical **4** from its nmr and ir spectra (nmr, (100 MHz, $CDCl_3$) τ9.33, 18-H, τ9.01, 19-H, τ5.36 (1H)d, τ5.51 (1H)d, (J=12.0 Hz), C-4-methylene protons, τ4.12 (1H)d, (J=6.0 Hz), C-6-H, τ1.90 (1H) s, C-3-formyl proton; ir, (neat) 1731 cm^{-1}, CHO).

The structures of **15** and **16** were confirmed to be 6α-iodo-oxidomethylene-3α,5α-A-nor-cholestane and the isomeric 6β-iodo-oxidomethylene-3α,5α-A-nor-cholestane in the following way. Catalytic hydrogenolysis of either **15** or **16** in a


cholesterol 1
epicholesterol 2
3-deuteriocholesterol 3
HgO-I2
hν
I•
R
4 R=αH or βH
5 R=αD
A
B
from either 6 or 7
6 R=H or D
7 R=H or D
8
12
13
14
9 R=H or D
10 R=H or D
11 R=H or D
hν
15 or 17
16 or 18
20
21
15 R=H, R′=I
17 R=D, R′=I
16 R=H, R′=I
18 R=D, R′=I
Pd-C
19
22
23
H
O
I

mixed solvent of benzene and ethanol (5:8 in vol.) with Pd-C for 36 hr led to the identical iodine-free compound 19, indicating that 15 and 16 are isomeric to each other. The n.m.r. spectra of 15, 16, and 19 all showed a pair of doublets of AB system from τ5.8 to τ6.9. One of the doublets of each pair collapsed to a singlet on double irradiation at the resonance frequencies of the centre of another doublet, and each pair of doublets is assignable to isolated methylene protons attached to oxygen-bearing carbon. There was another one-proton broad singlet around τ4.5 in 15, 16, and 19. These are assignable to protons attached to oxygen-bearing carbon at the C-3, since they are not present in the nmr spectra of products 17 and 18 from 3-deuteriocholesterol. Moreover, these compounds all revealed ir bands due to ethereal linkage at around 1100 cm^{-1}. These

Nmr signals of 15, 16, and 19 (τ,Hz) (100 MHz, $CDCl_3$)

	$18\text{-}CH_3$	$19\text{-}CH_3$	C-3βH	C-4-methylene	C-6-H
15	9.35	9.10	4.48 $W_H=4.1$	5.82,d and 6.28,d ($J_{AB}=7.5$)	5.45,q ($J^{ap}_{AX}=6.0, J^{ap}_{BX}=12.0$)
16	9.28	8.67	4.40 $W_H=3.7$	5.77,d and 6.68,d ($J_{AB}=8.1$)	5.78, t
19	9.36	9.13	4.53 $W_H=4.1$	5.89,d and 6.85,d ($J_{AB}=7.6$)	———

results together with considerations of the probable mode of the formation of 15 and 16 and the reaction of 19 suggested that the framework of 15 and 16 is a hitherto undescribed oxidomethylene-3,5-A-nor-cholestane. The configurations of the oxetane rings should be 3α,5α since the C-3H appeared as a broad singlet (4) and the reported spectral data of oxidomethylene-3β,5β-A-nor-cholestane 21 (5) were different from those of 19. Besides the above signals the nmr spectrum of 15 showed one-proton quartet and that of 16 showed one-proton triplet each assignable to protons attached to iodine-bearing carbon since in the nmr spectrum of 19 these signals vanished (Table). The spin-spin coupling pattern and the coupling constants of these signals together with the results of spin decoupling require that the above protons in 15 and 16 must be positioned at the 6β and the 6α in the chair form B-ring. This assignment is consistent with the fact that the $19\text{-}CH_3$ of 16 is considerably deshielded by virtue of the 6-axial iodine when compared with that of 15 (Δ=0.43 ppm).

The observed regio- (6) and stereoselectivity shown by the exclusive formation of oxetanes with 3β,5β-configuration would provide us with some clues in our speculations on the reaction pathways which are depicted as in the Scheme.

There will be two probable major pathways A and B for the formations of **15** and **16** from the intermediate **6**. It has already been shown that the product of the Paterno-Büchi reaction of 3,4-seco-cholest-4-en-3-al **20** was solely 3β,5β-oxetane **21** (5). This stereo- and regio-selectivity is understandable by considering the approach of the excited electrophilic oxygen (7) from the α-side rather than β-side of the olefinic double bond as shown in **22** and **23** in the Scheme since the transition state **22** would be less stable due to the presence of the 19-methyl group. If **15** and **16** are formed via the Paterno-Büchi reaction of preformed olefins **10** and **11**, the stereochemistry of oxetane formation would be governed by the analogous stereoelectronic effect to the case of **20** to form solely 3β,5β-isomers. The observed exclusive formation of 3α,5α-isomer, therefore, would preclude the pathway B and would make the pathway A more plausible. The pathway A is considered to involve either successive radical cyclization (8) (e.g., **6**→**8**→**14**) to form more stable 3α,5α-oxetane **14** followed by the radical combination to form **15** and **16**, or the formation of oxetane **14** via attack of electrophilic oxygen of the excited **6** on the allyl radical moiety. We consider the former is more likely.

REFERENCES AND NOTES

1) Photoinduced Transformations. XXIV, paper XXIII, H. Suginome and T. Uchida, *Bull. Chem. Soc. Japan*, in press.
2) K. Heusler and J. Kalvoda, *Angew. Chem.*, 76, 518 (1964).
3) R. S. Rosenfeld, D. K. Fukushima, L. Hellman, and T. F. Gallagher, *J. Biol. Chem.*, 211, 301 (1954).
4) Anomalously small $J_{3H,2\alpha H}$ and $J_{3H,2\beta H}$ should be mainly ascribable to the orientation of the α and β bonds at C_3 with respect to the oxetane ring oxygen atom. D. H. Williams and N. S. Bhacca, *J. Amer. Chem. Soc.*, 86, 2742 (1964). H. Booth, *Tetrahedron Letters*, 411 (1965).
5) Y. Kondo, J. A. Waters, B. Witkop, G. Guenard, and R. Beugelmans, *Tetrahedron*, 28, 797 (1972). J. A. Marshall and J. P. Arrington, *J. Org. Chem.*, 36, 214 (1971).
6) A. Hassner, *J. Org. Chem.*, 33, 2684 (1968).
7) N. J. Turro, J. C. Dalton, K. Dawes, G. Farrington, R. Hautala, D. Morton, M. Niemczyk, and N. Schore, *Accounts Chem. Res.*, 5, 92 (1972).
8) H. G. Kuivila and E. J. Walsh, Jr., *J. Amer. Chem. Soc.*, 88, 571 (1965).

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