STUDIES ON THE SYNTHESES OF HETEROCYCLIC AND NATURAL COMPOUNDS. PART 969.[1] A FACILE CONVERSION OF DEHYDROEPIANDROSTERONE INTO 16α-HYDROXYPREGNENOLONE 3-ACETATE

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Abstract —— Dehydroepiandrosterone (6) was converted into 16α-hydroxypregnenolone 3-acetate (11), employing 1,3-dipolar cycloaddition of nitrile oxide as a key reaction to give the isoxazolines (8 and 9).

Within the last decade intensive researches[2-10] on side-chain synthesis of sterols have brought many fruitful results for the synthesis of various physiologically active compounds. In search of a novel method for a modification of steroidal side-chain, we have investigated a formation of isoxazolines on steroidal D-ring using 1,3-dipolar cycloaddition of nitrile oxide, since this reaction proceeds stereoselectively and a conversion of isoxazoline to β-hydroxyketone by a reductive N-O bond cleavage is well known[11].

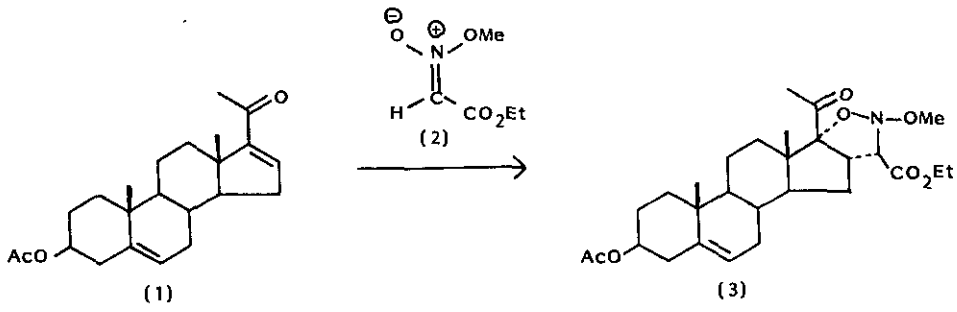
In 1975, Kamernitzky reported[12] the cycloaddition of the nitronic ester (2) with pregn-16-en-20-one (1) to give the isoxazolidine (3) regio- and stereoselectively, however, this reaction proceeded efficiently only under high pressure (14,000 atm), having a large negative activation volume. Moreover, Vekvelsky has published[13] the synthesis of isoxazoline (5) on D-ring by treatment of 17-ketosteroid (4) with formamide and perchloric acid. Here we wish to report a facile conversion of dehydroepiandrosterone to 16α-hydroxypregnenolone 3-acetate and 16-acetylandrostane derivative via an isoxazoline formation followed by a reductive N-O bond cleavage. It has been known that the 16α-hydroxypregnenolone displays an analogous effect as that of cortico-suprarenal hormone.

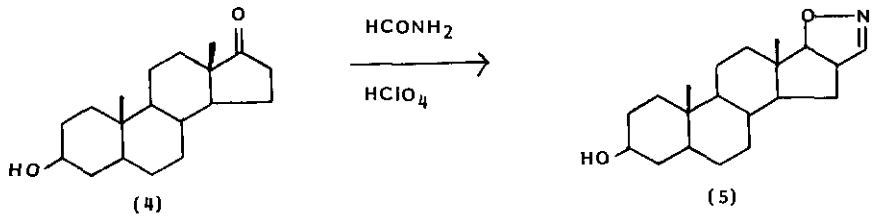
Thus, the starting androsta-5,16-diene-3β-ol 3-acetate (7) was prepared from dehydroepiandrosterone according to Barton's procedure[15]. 1,3-Dipolar cycloaddition of 7 with the nitrile oxide prepared from nitroethane and phenyl isocyanate gave rise to the inseparable isoxazolines (8 and 9) in the ratio of ca. 1 : 3. This ratio was deduced from its nmr data [δ : 0.8 (18-Me) and 1.95 (20-Me) for 9, 0.90 (18-Me) and 1.99 (22-Me) for 8]. A mixture of the isoxazolines (8 and 9) was hydrogenated with W-2 Raney Ni in ethanol and acetic acid under an atmosphere of hydrogen to afford the β-hydroxyketones (11 and 12), which were then separated by silica-gel column chromatography. The structure of the less polar compound was assigned to be 16α-hydroxypregnenolone 3-acetate (11) by direct comparison with the authen-

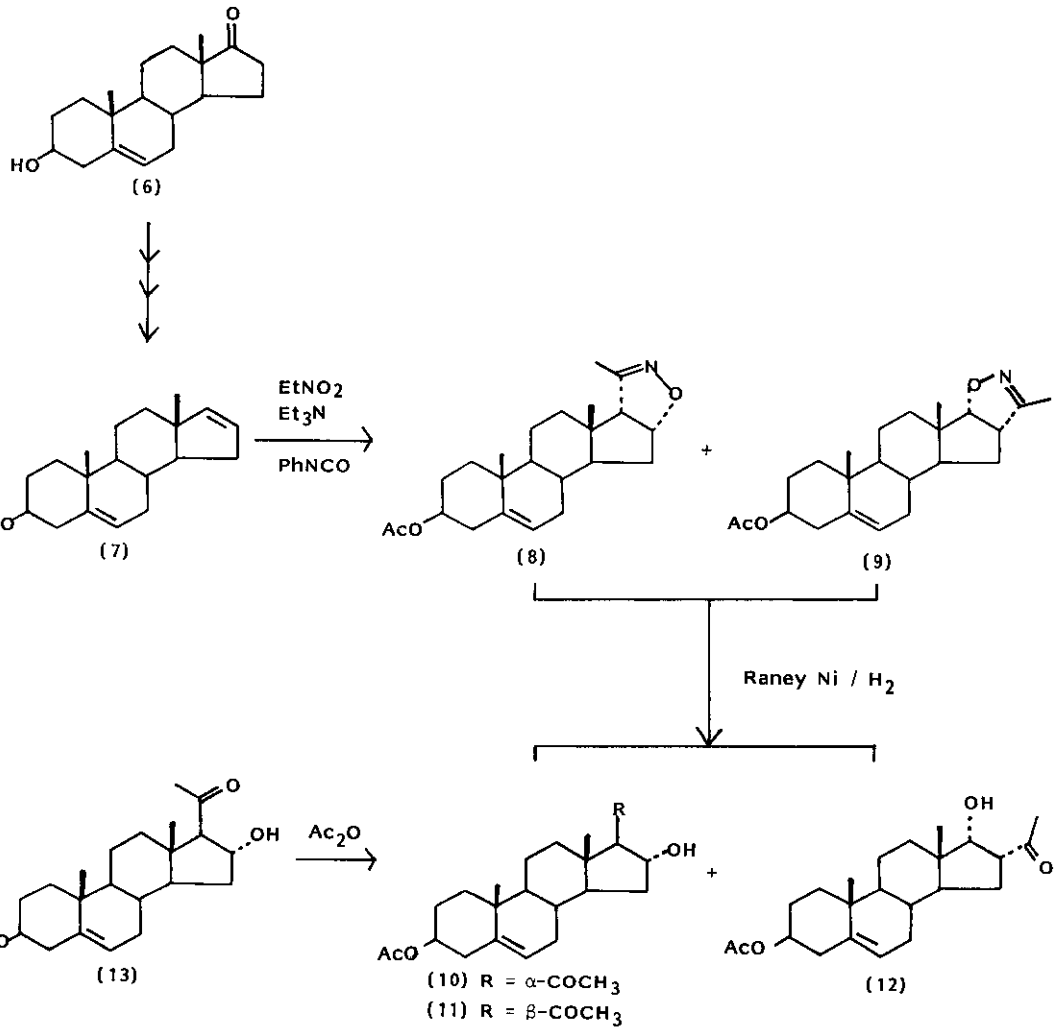
tic sample, derived by acetylation of 16α-hydroxypregnenolone (13)[16]. This fact indicated that 17β-acetyl group of 10 was epimerized to 17α-acetyl compound (11) during the reductive N-O bond cleavage, and this type of epimerization has been sometimes observed in this field[17,18]. On the other hand, the more polar compound was assigned to be 16α-acetyl-17α-hydroxy derivative (12) tentatively.

Thus, a simple conversion of dehydroepiandrosterone to 16α-hydroxypregnenolone 3-acetate was achieved via an isoxazoline formation by using 1,3-dipolar cycloaddition of the nitrile oxide as a key reaction.

In order to extend this strategy, 17(20)-(Z)-ethylidene-steroid (14) was treated with the nitrile oxide derived from ethyl 3-nitropropionate to give the isoxazoline (15), which may lead to bilic acid derivative, however this reaction afforded none of desired product. Various attemped formation of the isozazoline ring for 14 has been unsuccessful unfortunately.






O
HO
(6)
EtNO2
Et3N
PhNCO
AcO
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N
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Raney Ni / H2
O
OH
HO
(13)
Ac2O
R
(10) R = α-COCH3
(11) R = β-COCH3
(12)
(14)
(15)

EXPERIMENTAL SECTION

Ir spectra were measured with a 215 Hitachi grating infrared spectrophotometer, nmr spectra with a JEOL JUN-FX100 spectrometer using tetramethylsilane as an internal reference. Mass spectra were taken with a JEOL JMS-D300 spectrometer.

Formation of the Isoxazolines (8 and 9).—— To a stirred solution of 7 (430 mg) and nitroethane (136 mg) in dry benzene (120 ml) containing triethylamine (3 drops), was added a solution of phenyl isocyanate (500 mg) in dry benzene (5 ml) at 0°C under an atmosphere of nitrogen. After the stirring had been continued at ambient temperature for 42 h, the mixture was refluxed for 4 h. The precipitated insoluble materials were filtered off. The filtrate was washed with saturated aqueous sodium hydrogen carbonate and water and dried (Na_2SO_4). Evaporation of the solvent gave a reddish oil, which was subjected to column chromatography on silica gel. Elution with benzene-ethyl acetate (9 : 1 v/v) afforded the isoxazolines (8 and 9) (330 mg) as a colorless powder in the ratio of ca. 1 : 3, m.p. 138-145°C (methanol); $\nu_{max.}$ ($CHCl_3$) 1700 cm^{-1} (C=O); δ($CDCl_3$) 0.80 (9/4H, s, 18-Me), 1.04 (3H, s, 19-Me), 1.95 (9/4H, s, 20-Me), 1.99 (3/4H, s, 22-Me), 2.04 (3H, s, OAc), 4.45 (3/4H, d, J = 9Hz, 17-C<u>H</u>); <u>m/e</u> 371.2431 (<u>M^+</u>). $C_{23}H_{33}NO_3$ requires 371.2458.

16α-Hydroxypregnenolone 3-Acetate (11) and its Isomer (12).—— To a stirred solution of the isoxazolines (8 and 9) (100 mg) in dry ethanol (3 ml) was added a suspension of W-2 Raney nickel (5 mg) in dry ethanol (0.5 ml) and three drops of glacial acetic acid were then added. The resulting mixture was stirred at room temperature under an atmosphere of hydrogen for 28 h and was then partitioned between saturated aqueous sodium hydrogen carbonate and methylene chloride. The aqueous layer was extracted with methylene chloride. The organic extracts were combined and dried (Na_2SO_4). Removal of the solvent afforded the residue which was subjected to silica-gel column chromatography. Elution with benzene gave the 16α-hydroxypregnenolone 3-acetate (11) (11 mg) as colorless needles, m.p. 166°C (lit.[19], m.p. 165 - 168°C); δ($CDCl_3$) 0.66 (3H, s, 18-Me), 1.02 (3H, s, 19-Me), 2.04 (3H, s, OAc), 5.38 (1H, m, 6-H). Further elution with benzene gave the 17α-hydroxy compound (12) (34 mg) as needles, m.p. 159 - 167°C (methanol); $\nu_{max.}$ ($CHCl_3$) 1710 cm^{-1} (C=O); δ($CDCl_3$) 0.80 (3H, s, 18-Me), 1.03 (3H, s, 19-Me), 2.04 (3H, s, OAc), 5.36 (1H, m, 6-H).

Acetylation of 16α-Hydroxypregnenolone (13).—— A mixture of 13 (1 mg), acetic anhydride (1 drop) and pyridine (2 drops) was allowed to stand at room temperature for 24 h. The mixture was poured into water and extracted with methylene chloride. Evaporation of the solvent gave the 16α-hydroxypregnenolone 3-acetate (11), which was identical with the sample obtained above.

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