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TRANSFORMED STEROIDS.

186. USE OF THE DIACETOXYIODOBENZENE–IODINE SYSTEM FOR THE CONVERSION OF EPIMERIC 17-ETHYNYLANDROST-4-EN-17-OL-3-ONES TO PREGNANES

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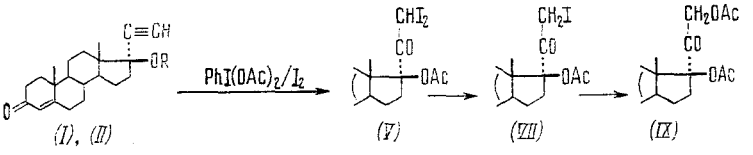
Epimeric 17-acetoxy-17-ethynylandrost-4-en-3-ones react with diacetoxyiodobenzene and iodine in acetic acid or methanol in an unusual manner to give 17-acetoxy-21,21-diiodo-17-pregn-4-en-3,20-diones, which are then converted to 21-monoiodides and 21-acetates. Epimeric 17-hydroxy-17-ethynylandrost-4-en-3-ones are inert under these conditions.

In the framework of our work on the use of hypervalent iodine compounds for the conversion of 17-ethynylcarbinol steroids to 21-substituted 20-ketopregnanes [1, 2], we studied the reaction of epimeric 17-ethynylcarbinols (I) and (III) and their 17-acetates (II) and (IV) under conditions for the iodoacetoxylation of alkynes by acetyl hypoiodide (AcOI) [3-5] generated by the reaction of diacetoxyiodobenzene with iodine in acetic acid [4, 6] or methanol. The reaction of AcOI with alkynes leads to the formation of α-iodoenol-acetates, which are then hydrolyzed to α-hydroxyketones [4, 5]. Contrary to expectation, neither unsaturated products of the addition of AcOI to the acetylenic bond nor products of their possible subsequent stabilization were detected under the conditions studied. 17-Ethynylcarbinols (I) and (III) do not react over 24 h with excess reagent (I_2 + $PhI(OAc)_2$ in acetic acid) at 20°C, while the same reaction with 17-acetates (II) and (IV) proceeds rapidly with an equimolar reagent ratio to give 21,21-diiodoketones (V) and (VI), which crystallize from the reaction medium.



(I), (II) (V) (VII) (IX)

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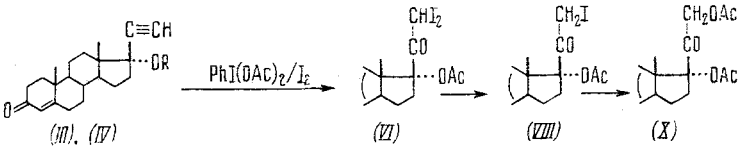
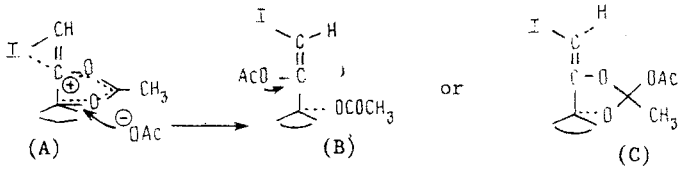


R = H (I), (III); Ac (II), (IV).

A similar result was observed by Nitta et al. [3] in the reaction of 17β-ethynylandrosta-1,4-dien-17α-ol-3-one and its 17α-acetate with AcOI generated on interaction of CH_3CO_3H with I_2. The difference in the reactivities of the 17β-ethynylcarbinol and its 17α-acetate was attributed to intramolecular participation of the 17α-acetoxy group through intermediate A, which is attacked by an acetate ion from the sterically preferred α-side of the molecule to give B or C.



Such an explanation, however, should involve inversion of the stereochemistry of the C^{17} site for any outcome of the reaction, especially in the reaction with 17α-ethynyl-17β-acetate (II), which was not actually observed. Thus, we may assume that the observed activation of the acetylenic bond by the adjacent acetate group in (II) and (IV) is most likely a consequence of the electronic effect of this group. As a result, the rapid regioselective consecutive addition of two AcOI molecules to the triple bond in (II) and to the double bond [6] in intermediate B (with the starting stereochemistry of the C^{17} site) leads to the formation of diiodides (V) and (VI).

21,21-Diodoketones (V) and (VI) are unstable under the reaction conditions and also upon treatment by various solvents. However, these compounds may be stored in the crystalline state for prolonged periods at 0°C. Upon treatment with p-TsOH in acetone at reflux or by a mixture of triethylamine, acetic acid, and acetone, (V) and (VI) are converted into the 21-monoiodides (VII) and (VIII). The prolonged standing of (V) and (VI) in acetic acid, chloroform, methylene chloride, and methanol also leads to elimination of iodine and the formation of (VII) and (VIII). Monoiodides (VII) and (VIII) are stable upon subjection to standard methods for the replacement of the halogen atom by an acetate group [3, 8, 9] and this replacement was accomplished in low yield only upon their reaction with tetramethylammonium acetate in N-methylpyrrolidone. These transformations and the physicochemical indices of 21-iodides (V)-(VIII) are evidence for their structure.

EXPERIMENTAL

The melting points were taken on a Koeffler block. The PMR spectra were taken on Bruker WM-250 and WM-400 spectrometers relative to TMS. The IR spectra were taken on a UR-20 spectrometer for KBr pellets. The chemical ionization mass spectra were taken on a JEOL JMS D-300 mass spectrometer. Silufol and Alugram G/UV_{254} plates were used in analytical thin-layer chromatography with development by a solution of $Ce(SO_4)_2$ in dilute sulfuric acid. Silpearl silica gel was used for preparative separation.

21,21-Diiodo-17β-hydroxy-17α-pregn-4-ene-3,20-dione 17-Acetate (V). a. A sample of 0.38 g powdered $PhI(OAc)_2$ was added to a stirred solution of 0.35 g (II) in 3 ml acetic acid at 20°C and after its complete dissolution, 0.25 g I_2 powder was added in batches over 2.5 h (as the reaction mixture is decolored). Light yellow (V) began to crystallize out of the reaction mixture after 30 min. For complete precipitation of the product, the reaction mixture was left for 3 h at from −5 to 0°C. The precipitate was filtered, washed with anhydrous ether, and dried for 30 min in the air to give 0.5 g (V), which decomposes at 153-155°C. IR spectrum (ν, cm^{-1}): 1255, 1625, 1670, 1725 sh, 1732. PMR spectrum (δ, ppm): 1.05 s (18-Me), 1.22 s (19-Me), 2.14 s (17-OAc), 5.56 s (H^{21}), 5.77 s (H^4). Chemical ionization mass spectrum, m/z: 371 [M + H − I_2].

b. A sample of 0.35 g (II) was added to a stirred solution of 0.38 g $PhI(OAc)_2$ in 3 ml methanol at 20°C and then, 0.25 g powdered I_2 was added in batches over 15-20 min as the reaction mixture was decolorized. Finally, two or three drops of saturated I_2 in methanol was added for the complete consumption of the starting reagent. Crystalline (V) began to precipitate 20 min after the reaction onset. For complete precipitation of the product, the reaction mixture was left for 2-3 h at -10°C. The precipitated product was filtered off and washed consecutively with cold methanol and ether to give 0.45 g (V).

c. A sample of 0.04 g I_2 was added with stirring to a solution of 0.06 g (II) in 2 ml solution of acetic acid in acetic anhydride prepared as described by Chen et al. [10] and maintained for 2 h at 20°C. The reaction mixture was poured into water. The precipitate formed was filtered off, washed with water, and dried to give 0.04 g (V).

21,21-Diodo-17α-hydroxypregn-4-ene-3,20-dione 17-Acetate (VI). A sample of 0.045 g (IV) [1] was added to a stirred suspension of 0.018 g I_2 and 0.024 g $PhI(OAc)_2$ in 0.2 ml glacial acetic acid at 25°C and stirred for 10 min. The precipitate dissolved, the reaction mixture become colorless, and a new precipitate formed. The precipitate was filtered off and washed with ether. The precipitate, which separated from the mother liquor, was also filtered off and combined with the major product to give 0.015 g (VI), which decomposes at 160-163°C. IR spectrum (ν, cm^{-1}): 1258, 1620, 1675, 1730. PMR spectrum (δ, ppm): 0.87 s (18-Me), 1.20 s (19-Me), 2.13 s (17-OAc), 5.51 s (H^{21}), 5.75 s (H^4). Mass spectrum, m/z: 625 $[M + H]^+$, 582 $[M + H - Ac]^+$, 313 $[M - COCH_2I_2 - Me]^+$.

21-Iodo-17β-hydroxy-17α-pregn-4-ene-3,20-dione 17-Acetate (VII). a. A mixture of 0.15 g I_2, 0.42 g $PhI(OAc)_2$), and 0.36 g (II) in 1 ml acetic acid was stirred for 4-5 h and then left at 20°C for 48 h. The precipitate formed was filtered off and washed with ether to give 0.21 g (VII), which decomposes at 137-143°C (crystallized from methanol). IR spectrum (ν, cm^{-1}): 1245, 1618, 1668, 1720, 1740. PMR spectrum (δ, ppm): 1.05 s (18-Me), 1.19 s (19-Me), 2.15 s (17-OAc), 4.02 d and 4.11 d (H^{21}, AB system, J = 13.5 Hz), 5.73 s (H^4). Mass spectrum, m/z: 372 $[M + H - I]^+$. The mother liquor was diluted with water and extracted with chloroform. The extract was washed with aq. $Na_2S_2O_5$ and water and dried over $MgSO_4$. The precipitate was suspended in 2 ml methanol and filtered to give an additional 0.12 g (VII).

b. A solution of 0.05 g (VI) and 0.01 g p-TsOH in 1 ml acetone was heated at reflux for 20 min and evaporated in vacuum. The residue was diluted with water. The precipitate was filtered off, washed with water, and crystallized from methanol to give 0.016 g (VII), which decomposes at 150°C. Thin-layer chromatography of the mother liquor on a silica gel plate with 6:1 benzene–acetone as the eluent gave an additional 0.17 mg (VII).

c. A solution of 0.15 g (V) in a mixture of 0.63 ml Et_3N, 0.4 ml acetic acid, and 3 ml acetone was maintained for 8 h at 20-25°C and evaporated in vacuum. The residue was diluted with water and the precipitate was filtered off and crystallized from aqueous methanol to give 0.1 g (VII).

d. A suspension of 0.03 g (V) in 0.3 ml acetic acid was stirred for 24 h at 20-25°C. Iodine liberation was noted. The reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with aq. $Na_2S_2O_3$ and water and evaporated in vacuum. The residue was subjected to thin-layer chromatography twice on a silica gel plate using 1:3 acetone–petroleum ether as the eluent to give 0.006 g (VII).

21-Iodo-17α-hydroxypregn-4-ene-3,20-dione 17-Acetate (VIII). a. A mixture of 0.05 g (IV), 0.024 g $PhI(OAc)_2$, and 0.018 g I_2 in 0.2 ml acetic acid was stirred for 15 min with isolation of 0.015 g diiodide (VI) as described above. Then, an additional 0.006 g I_2 and 0.008 g $PhI(OAc)_2$ were added to the mother liquor and left overnight. Standard treatment of the reaction mixture with subsequent thin-layer chromatography on silica gel using 3:1 petroleum ether–acetone as the eluent gave 0.021 g (VIII), which decomposes at 123-125°C (crystallized from ether). IR spectrum (ν, cm^{-1}): 1250, 1620, 1680, 1720, 1735. PMR spectrum (δ, ppm): 0.74 s (18-Me), 1.2 s (19-Me), 2.13 s (17-OAc), 3.87 d and 3.97 d (H^{21}, AB system J = 12.7 Hz), 5.7 s (H^4).

b. A mixture of 0.016 g (VI), 0.08 ml Et_3N, 0.05 ml acetic acid, and 0.5 ml acetone was maintained for 24 h at 20-25°C, evaporated in vacuum, and diluted with water. The precipitate formed was filtered off to give 0.008 g (VIII).

17β,21-Dihydroxy-17α-pregn-4-ene-3,20-dione 17,21-Diacetate (IX). a. A mixture of 0.23 g (VII), 0.12 g Bu_4NOAc, and 2.5 ml N-methylpyrrolidone was stirred for 48 h at 20-25°C and then poured into water. The precipitate formed was filtered off, washed with water, dried, and separated by thin-layer chromatography on silica gel using 3:1 petroleum ether–acetone as the eluent to give 0.11 g (IX), mp 164-167°C. IR spectrum (ν, cm^{-1}):

1240, 1260, 1620, 1680, 1740, 1760, 1770. PMR spectrum (δ, ppm): 1.04 s (18-Me), 1.18 s (19-Me), 2.15 s (17-OAc), 2.16 s (21-OAc), 4.78 d.d (H^{21}, AB system J = 17 Hz), 5.71 s (H^4).

b. A solution of 0.015 g 21-acetoxy-17β-hydroxy-17α-pregn-4-ene-3,20-dione [2] in 0.5 ml of a mixture prepared from 0.56 ml 85% phosphoric acid, 3 ml acetic anhydride, 1.6 g anhydrous potassium acetate, and 1 ml acetic acid was heated for 31 h at 70°C, cooled, and diluted with water. The precipitate was filtered off and purified by thin-layer chromatography on silica gel to give 0.003 g of a product consisting of 61% (IX) and 39% starting pregnene as shown by PMR spectral analysis.

17α,21-Dihydroxypregn-4-ene-3,20-dione 17,21-Diacetate (X). A mixture of 0.02 g (VIII), 0.018 g Bu_4NOAc, and 0.2 ml N-methylpyrrolidone maintained for 24 h at 20-25°C, was treated according to the above procedure to give 0.003 g (X), mp 215-220°C, which was identical to an authentic sample.

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ISOMERIZATION OF 14-HYDROXY-17-KETOSTEROIDS: NEW EXAMPLES OF TWO-CENTERED INVERSION OF THE C/D RING FUSION AND X-RAY DIFFRACTION STRUCTURAL ANALYSIS OF d,ℓ-3-METHOXY-14β-HYDROXY-8β,9α-ESTRA-1,3,5(10)-TRIEN-17-ONE

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d,ℓ-3-Methoxy-14β-hydroxy-8α,9β-estra-1,3,5(10)-trien-17-one (I) undergoes two-centered isomerization in alkaline medium to d,ℓ-3-methoxy-14β-hydroxy-8β,9α-estra-1,3,5(10)-trien-17-one (II) in 70% yield. Under analogous conditions, natural isomer (II) is converted into synthetic isomer (I) in 20% yield. The crystalline and molecular structure of isomer (II) was established.

d,ℓ-3-Methoxy-18-methyl-8α,9β-estra-1,3,5(10)-trien-14β-ol-17-one undergoes isomerization in alkaline medium to d,ℓ-3-methoxy-18-methyl-8β,9α-estra-1,3,5(10)-trien-14β-ol-17-one [1] (conversion of trans-anti-cis to trans-syn-cis configuration) through retroaldol cleavage of the C^{13}–C^{14} bond [2]. Conformational calculations by the molecular mechanics

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