Tetrahedron Letters No.50, pp. 4487-4493, 1965. Pergamon Press Ltd.
Printed in Great Britain.

CHEMISTRY OF CONJUGATE ANIONS AND ENOLS. VI.[1] THE REACTION OF DIHALOCARBENE WITH ENOLATE ANIONS[2]

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(Received 30 September 1965)

The action of dihalocarbene on non-aromatic enolate anions, which constitutes in theory and in fact a mechanistic parallel to the Reimer-Tiemann reaction, has not been previously reported. The dropwise addition of chloroform to a solution of the stable (1) enolate anion of testosterone (I) in t-butanol containing excess potassium t-butoxide led, after chromatographic separation, to ca. 35% of 6-exochloromethylene-testosterone[3] (IVa) m.p. 198-200°, λ_{max}^{EtOH} 250 mμ, ε 9300, 270 mμ, ε 8200. IR (KBr) 1665, 1570 cm^{-1}. N.m.r. 4.18τ (C-4 H), doublet centered 3.78τ (J 1.5 c.p.s., $=C\begin{smallmatrix}H\\Cl\end{smallmatrix}$ long-range coupled to C-7αH), 8.91τ (C-19 CH_3), 9.21τ (C-18 CH_3). The catalytic reduction of IVa with 10% palladium-carbon in dioxane gave a high yield of 6β-methyldihydrotestosterone (2) while treatment

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[1]Previous paper in this series, S. K. Malhotra and H. J. Ringold, J. Amer. Chem. Soc., 87, 3228 (1965).

[2]Supported in part by grant T-185, American Cancer Society.

[3]Satisfactory elemental analyses were obtained for all new compounds. Molecular weights of VII, VIII, IX and X were confirmed by mass spectroscopy. N.m.r. determinations in $CDCl_3$ with tetramethylsilane internal standard at 60 Mc/S.

with potassium hydroxide in aqueous methanol regenerated testosterone. Although the latter reaction must proceed via the C-6 aldehyde or the tautomeric hydroxymethylene compound, efforts to stop the reaction at that stage were unsuccessful. Compounds of type IV have been postulated (3) as intermediates in the Reimer-Tiemann reaction of phenol although they have never been isolated.

The substitution of bromoform for chloroform gave the corresponding exo-bromomethylene derivative IVb in 27% yield; m.p. 174-176°, λ_{max}^{EtOH} 250 mμ, ε 8700, 270 mμ, ε 9800. IR 1669, 1572 cm^{-1}. N.m.r. 4.17τ (C-4 H), doublet 3.64τ (J 1.5 c.p.s., $=C\begin{smallmatrix}H\\Br\end{smallmatrix}$ long-range coupled to C-7αH), 8.90τ (C-19 CH_3), 9.20τ (C-18 CH_3).

Analogous treatment of the 6-methyl enolate anion (VI) resulted in a 35% yield of an equal mixture of the two isomeric 6-dichloromethyl-6-methyltestosterone (VII and VIII). The precise analogy to the abnormal (4) Reimer-Tiemann reaction is obvious. The higher melting isomer, to which we assign the 6α-dichloromethyl-6β-methyl structure (VII), was separated by its insolubility in benzene; m.p. 250-251°, λ_{max}^{EtOH} 242 mμ, ε 13600, IR 3534 (C-17 OH)[4], 1661, 1587 cm^{-1}, N.m.r. 3.84τ (C-4 H), 3.96τ ($-CHCl_2$), 8.68τ (C-6 and C-19 CH_3, integrated intensity 6 protons) 9.18τ (C-18 CH_3), O.R.D. (dioxane)

[4] 6β-Methyltestosterone exhibits the 17-hydroxyl peak at 3550 cm^{-1} while the hydroxyl of 6α-methyltestosterone appears at 3250 cm^{-1}.

$[\alpha]_{377}$ + 528°, $[\alpha]_{322}$ - 148°.

The 6β-dichloromethyl compound VIII was obtained from the benzene mother liquors. An analytical specimen from ethyl acetate exhibited m.p. 184-186° λ_{max}^{EtOH} 243 mμ, ε 11520, IR 3333 (C-17 OH)[4], 1672, 1587 cm^{-1}, N.m.r. 4.21τ (C-4 H), 4.00τ ($-CHCl_2$), 8.65τ (C-6 CH_3), 8.59τ (C-19 CH_3), 9.17τ (C-18 CH_3); O.R.D. (dioxane) $[\alpha]_{369}$ + 727°, $[\alpha]_{293}$ - 1535°. The stereochemical and proton resonance assignments for VII and VIII are based on the following considerations: (A) the N.m.r. position of the dichloromethyl proton should be essentially the same in the two isomers which allows assignment of the 3.96 and 4.00τ values to that proton in VII and VIII respectively; (B) the greatest deshielding of the C-19 methyl group (8.59τ) should occur in the 6β-dichloromethyl compound VIII; (C) the deshielding of the C-4 proton in VII (3.84τ) is consistent with a bulky 6α-dichloromethyl group; (D) the relative infrared shift of the C-17 hydroxyl (3534 vs. 3333 cm^{-1}) corresponds to the pattern observed with the isomeric 6-methyltestosterones[4].

The treatment of VIII with zinc dust in boiling ethanol smoothly led to the halogen-free 5β,6β-cyclopropyl compound (IX), m.p. 186-188°, no selective absorption in the ultraviolet, IR 1709 cm^{-1}. N.m.r. 8.79τ (C-19 CH_3), 8.98- (C-6 CH_3), 9.29τ (C-18 CH_3), doublets centered at 9.50τ and 10.00τ (J 5 c.p.s., $H \diagdown\!\!\diagup H$).

Similar treatment of VII gave the chlorocyclopropyl

compound X which was unchanged on further zinc reduction; m.p. 139-141°, no selective absorption in the ultraviolet, IR 1715 cm^{-1}. N.m.r. 6.91τ ($_{H}\!\!\times\!\!_{Cl}$)[5], 8.93τ (C-19 CH_3), 8.98τ (C-6 CH_3), 9.24τ (C-18 CH_3). Further reduction of X with lithium in ammonia followed by reoxidation with chromic acid in acetone-sulfuric acid provided the halogen-free 5α,6α-cyclopropano-6β-methylandrostane-3,17-dione (XI), m.p. 113-115°, IR 1736, 1718 cm^{-1}. N.m.r. doublets centered at 10.03τ and 9.43τ (J 5 c.p.s. $_{H}\!\!\times\!\!_{H}$), 9.12τ (C-18 CH_3), 9.02τ (C-6 CH_3), 8.91τ (C-19-CH_3).

The prolonged reaction of the 6β-cyclopropyl derivative IX with anhydrous hydrogen chloride in chloroform[6] gave a 32% yield of 6,6-dimethyltestosterone (XIIa), m.p. 154-156° λ_{max}^{EtOH} 242 mμ, ε 11140. IR 3500, 1667, 1600, 876 cm^{-1} (C-4 proton deformation). N.m.r. 9.19τ (C-18 CH_3), 8.88τ (C-6α CH_3), 8.83 (C-6β CH_3), 8.72τ (C-19 CH_3), 4.08τ (C-4 H). O.R.D. $[\alpha]_{368.5}$ + 248°, $[\alpha]_{238.5}$ - 42°. Oxidation of XIIa with chromic acid gave the 17-ketone XIIb, m.p. 171-174°, IR 1733, 1661 cm^{-1}, which proved to be identical with a product isolated in ca. 15% yield after treatment of the 6α-cyclopropyl compound with hydrogen chloride. Both IX and XI were stable to the

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[5] M. Z. Nazer, J. Org. Chem. 30, 1737 (1965) reported a proton absorption of 6.6τ for an analogous system.

[6] The chloroform contained 0.75% ethanol as preservative. Opening could not be effected in alcohol free anhydrous chloroform.

prolonged action of potassium t-butoxide in boiling t-butanol but X readily underwent opening at room temperature to yield a non-crystalline substance whose infrared and ultraviolet spectra are consistent with a 6α-chloromethyl-6β-methyl-Δ^4-3-ketone structure.

The formation of IV is pictured as proceeding by the attack of dihalocarbene on I to yield the anion II. Exo-protonation of IIa followed by proton abstraction from C-6, or, a direct intramolecular proton transfer from C-6, yields the carbanion III which then expells X(-) (6). The fact that both alkylation and protonation of the anion I occur at C-4 rather than at C-6, and that the reaction of neutral $\Delta^{3,5}$-dienes (7) or $\Delta^{3,5}$-dienol ethers (8) with dihalocarbene yields 3(4)- and 5(6)-cyclopropyl derivatives, indicates that the stability[7] of anion II determines the position of attack in the present case. Although IIb could theoretically undergo ring expansion by halide expulsion, the absence of such products must be due to the very fast protonation of IIa followed by exclusive formation of the more stable enolate anion III and finally halide expulsion from the latter species.

A similar reaction sequence accounts for the formation of VII and VIII except that following exo-protonation, halide elimination can only occur via re-formation of the dichloro-

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[7]Relative to the alternate anion that would be formed by attack at C-4 or C-3,4.

methyl carbanion and ring expansion. The absence of ring-expanded products and the stability of VII and VIII to further base treatment indicates that the dichloromethyl group is not sufficiently acidic to be converted to the carbanion by t-butoxide in t-butanol.

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KO t-Bu
t-BuOH
CHX3
OH(-)
H2
Pd-C
Zn
EtOH
(1) Li-NH3
(2) CrO3
HCl
a. X = Cl
b. X = Br
a. R = H, OH
b. R = O