Faculty of Pharmacy,
Kanazawa University,
13 Takara-machi, Kanazawa

Yoshio Arata (荒田義雄)
Tsutomu Ohashi (大橋 力)

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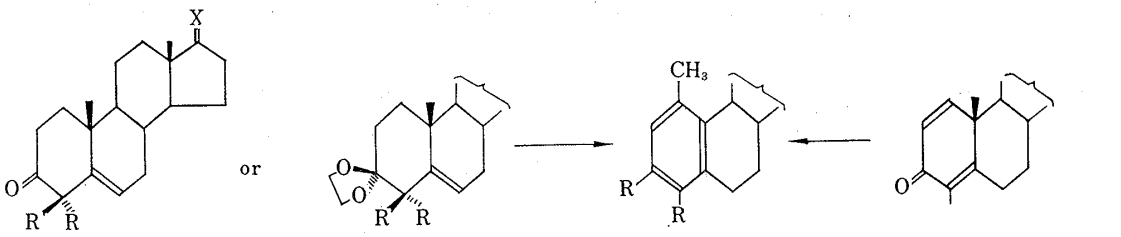
Rearrangement Reaction of 4,4-Dialkyl-5-en-3-one Steroids to A-Ring Aromatic Systems

We wish to report a new rearrangement reaction of 4,4-dialkyl-5-en-3-one steroids to 1-methyl-3,4-dialkyl A-ring aromatic systems.

Treatment of 4,4-dimethylcholest-5-en-3-one[1] (Ia) or its ketal (IIa) with *p*-toluenesulfonic acid in ethylene glycol, mesitylene, xylene or toluene at their reflux temperatures gave an oil (IIIa) as a major product, UV : λ_{max}^{EtOH} mμ (log ε) : (271) 2.80). IR ν_{max} cm^{-1}: very weak bands in a region 1770~1660; 1598 and 1560 (weak bands) and 863 (CH out-of-plane deformation), $[\alpha]_D^{15}$ +113° (c=0.2, $CHCl_3$), NMR*1 : 2.04, 2.15, and 2.21 p.p.m.(three methyls on an aromatic system) and 6.70 p.p.m. as a singlet (one aromatic hydrogen).

Structural proof of IIIa as 1,3,4-trimethyl-19-norcholesta-1,3,5(10)-triene, which would be produced as a result of both migrations of two methyl groups at 4- and 10-positions and a dehydration, was readily performed by direct synthesis. Methylation of 4-methylcholesta-1,4-dien-3-one[2] (IVa) with methylmagnesium iodide, followed by hydrochloric acid treatment in ethanol yielded an A-ring aromatic product,[3] whose infrared and nuclear magnetic resonance spectra and gas liquid chromatographic behavior were identical with that of IIIa. The same rearrangement to yield an oily aromatic hydrocarbon (IIIb) was also observed by the treatment of 4,4-diethylcholest-5-en-3-one[4] (Ib) with *p*-toluenesulfonic acid in boiling ethylene glycol.



Ia : R=CH_3, X=C_8H_{17} (H) ; b : R=C_2H_5, X=C_8H_{17} (H)

IIa : R=CH_3, X=C_8H_{17} (H) ; b : R=CH_3, X=$C_2H_4O_2$

IIIa : R=CH_3, X=C_8H_{17} (H) ; b : R=C_2H_5, X=C_8H_{17} (H) ; c : R=CH_3, X=$C_2H_4O_2$

IVa : X=C_8H_{17} (H) ; b : X=OAc (H)

*1 NMR spectra were measured at 60 Mc./sec. for deutrochloroform solution and calibrated against internal tetramethylsilane. Chemical shifts are given in δ-values.

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In the cholestane series, it was shown that the A-ring aromatic hydrocarbons produced by the rearrangement reaction unfortunately resulted in oily products. Accordingly, repetition of this rearrangement reaction was conducted on an androstane series, which would give rise to a crystalline product, in order to establish a further structural proof. 4,4-Dimethylandrost-5-ene-3,17-dione 3,17-bis cyclic ethylene ketal (IIb) was treated with *p*-toluenesulfonic acid in ethylene glycol. From the reaction there was obtained a mixture, readily separable by column chromatography. An aromatic product, m.p. 139°, $[\alpha]_D^{15}$ +100° (c=0.2, $CHCl_3$), for which the elemental analysis agreed with the empirical formula $C_{23}H_{32}O_2$, was assigned to be 1,3,4-trimethylestra-1,3,5(10)-trien-17-one cyclic ethylene ketal by IR ν_{max} cm^{-1} : 1743, 1716, 1691, 1598, and 1560 (weak bands); 864 (C-H out-of-plane deformation), UV : λ_{max}^{EtOH} mμ (log ε) : 271 (2.52), and NMR data : 0.90 (18-methyl); 2.10, 2.21, and 2.30 (three methyls on A-ring); 3.91 (ethylenedioxy); 6.84 (one aromatic hydrogen).

The structure of an aromatic compound was confirmed to be 1,3,4-trimethylestra-1,3,5(10)-trien-17-one cyclic ethylene ketal (IIIc) by the following synthesis. Reaction of 17β-acetoxy-4-methylandrosta-1,4-dien-3-one (IVb) with methyl Grignard reagent, followed by hydrochloric acid treatment, chromium trioxide oxidation, and ketalization with ethylene glycol gave a crystalline, m.p, 139°, which was identical in all respects with the sample obtained by the above aromatization (IIb→IIIc).

Institute of Applied Microbiology,
University of Tokyo,
Yayoi-cho, Bunkyo-ku, Tokyo

Yoshihiro Sato (佐藤良博)
Akiko Mizuguchi (水口昭子)
Sayoko Tanaka (田仲小夜子)
Kyosuke Tsuda (津田恭介)

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Reduction of Acid Amides to Amines with Sodium Borohydride

The preparation of amines from various acid amides is one of the most important reactions, and the reduction of acid amides with lithium aluminum hydride has been widely studied.[1,2] Complex borohydride, sodium trialkoxyborohydride ($NaBH(OR)_3$)[3] which reacts as medium reducing agent converts acid amides into the corresponding amines in some cases,[4] the reduction of secondary and tertiary amides with lithium borohydride or sodium borohydride-lithium chloride has also been reported,[5~7] the combination of sodium borohydride and aluminum chloride has also been applied successfully to the conversion of amides and lactams to the corresponding amines.[8~10]

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