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REACTIONS OF PHENOLIC STEROIDS WITH MODERATELY CONCENTRATED SULPHURIC ACID

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While extensive studies relating the colorimetric procedures have been made, little work[1,2] has been reported on the detailed chemistry of the reactions of steroids with strong acids. We report here the reactions of steroidal estrogens with moderately concentrated sulphuric acid. Methylated estradiol, 3-methoxy-estra-1,3,5(10)-trien-17β-ol, was heated with 78% (w/w) sulphuric acid for 20 minutes at 100°. Sulphur dioxide and hydrogen sulphide were detected during the course of the reaction. Dark red resinous products were collected through centrifuging and treated with ethereal diazomethane in methanol. The reaction mixture was promptly diluted with water, extracted with n-hexane, benzene, and chloroform, successively. The following reaction products* were obtained from these extracts through column chromatography on silica gel:

17-Methyl-3-methoxy-18-nor-estra-1,3,5(10)-trienes (I)———: Although the fraction eluted by n-hexane gave a single spot in thin-layer chromatographic analysis under various solvent systems, GC-Mass spectroscopy exhibited the presence of several components differing from 3-methoxyestra-1,3,5(10),16-, 17β-methyl-3-methoxy-18-nor-estra-1,3,5(10),13-tetraene, or 3-methoxyestra-1,3,5(10)-triene. Two components were obtained from this fraction as colorless oils both revealing M^+ peak of 270. The ultra-violet, infra-red and n.m.r. spectra of them were essentially identical. Although each gave a single peak in gaschromatogram on 1.5% SE-30 or 3% OV-17, it was inferred that both of these two components would still be isomeric mixtures since their n.m.r. signals near 9τ were typical for neither rearranged nor original angular methyl group but corresponded with three protons and moreover they were optically inactive. The following data were common to these two substances, unless otherwise stated. $\lambda_{max}^{isooctane}$ mμ (log ε) : 221 (3.60), 278 (3.34), 287 (3.39) (anisole type). ν_{max}^{direct} cm^{-1} : 1610, 1570, 1500, 865, 835. NMR : ($CDCl_3$) τ2.5-3.5 (3 arom. H), 6.25 (s, 3H, OCH_3), 8.8-9.2 (3H). $[\alpha]_D^{16^\circ}=0^\circ$ (C=1.86 in $CHCl_3$) and $[\alpha]_D^{26.5^\circ}=0^\circ$ (C=1.02 in $CHCl_3$) for another one. No reaction was occured with osmium tetroxide; considerable amounts remained intact when treated with sulphuric acid again.

* All compounds had satisfactory elemental analyses and mass spectra consistent with the structures assigned to them.

3'-Methyl-7-methoxy-1,2-cyclopenteno-9,10-dihydrophenanthrene (II)———: m.p. 82-83°. $\lambda_{max}^{isooctane}$ mμ (lɑg ε) : 282 (4.41). ν_{max}^{KBr} cm^{-1} : 1618, 1590, 1570, 1502, 877, 810. NMR ($CDCl_3$) : τ2.2-3.3 (5 arom. H), 6.20 (s,3H, OCH_3), 7.2 (m, 4H, C-9, C-10, $-CH_2-CH_2-$), 8.70 (d, J=7cps. 3H, C-3'-CH_3). $[\alpha]_D^{22}=0^o$ (C=1.31 in $CHCl_3$).

Methyl 3'-methyl-7-methoxy-1,2-cyclopenteno-9,10-dihydrophenanthrene-6-sulphonate (III)———: m.p. 143-143.5°. λ_{max}^{MeOH} mμ : 282.5 (4.40). ν_{max}^{KBr} cm^{-1} : 1608, 1595, 1500, 883, 830, 780 (arom.), 1396, 1184 ($-SO_2-$). NMR ($CDCl_3$) : τ1.82 (s, 1H, C-5-H), 2,45 (d, J=8cps, 1H, C-4-H), 2.92 (d, J=8cps, C-3-H), 3.15 (s, 1H, C-8-H), 6.10 (s, 3H, SO_3CH_3), 6.24 (s, 3H, OCH_3), 7.2 (m, 4H, C-9, C-10, $-CH_2-CH_2-$), 8.71 (d, J=7cps, 3H, C-3'-CH_3). $[\alpha]_D^{20}=0^o$ (C=0.93 in dioxane).

3'-Methyl-7-methoxy-1,2-cyclopentenophenanthrene (IV)———: Mp. 147-9° (lit.[3] 148°) 1,3,5-trinitrobenzene complex 136-137° (lit.[3] 137°). $\lambda_{max}^{isooctane}$ mμ (log ε) : 225 (4.15), 237 (4.17), 255 (4.35), 262 (4.50), 283 (4.15), 292 (4.14), 302 (4.13), 326 (2.93), 341 (3.14), 358 (3.17). ν_{max}^{KBr} cm^{-1} : 1615, 1580, 1530, 855, 810, 800. NMR ($CDCl_3$) : τ2-3 (7 arom. H), 6.00 (s, 3H, OCH_3), 8.60 (d, J=7cps, 3H, C-3'-CH_3). $[\alpha]_D^{21}=0^o$ (C=1.54 in $CHCl_3$). Identical with the authentic specimen prepared by the method of Cohen[3], in m.p., mixed m.p. and IR spectra. On treatment with metallic sodium and isoamyl alcohol, IV gave the dihydrophenanthrene II, which was dehydrogenated to IV with selenium. There were several other components exhibiting UV spectrum of Δ^8-olefin, naphthol- or cyclopentadienophenanthrene-type; the attempts of complete identifications resulted in no success.

Methylated estrone, 3-methoxyestra-1,3,5(10)-trien-17-one, gave the same products as those from estradiol. From 3-methoxyestra-1,3,5(10)-trien-17α-ol on refluxing for 40 min. in formic acid, I and II were obtained instead of the expected $\Delta^{13(17)}$[4] or Δ^8-olefin.

In respect of the reaction mechanism, it seems from these results that one of the features of the reaction with sulphuric acid is the dehydrogenation without opening of ring D, being different from the cases of DDQ[5]- and chloranil[6]-oxidation. In 80 to 100% aqueous sulphuric acid, cyclic aliphatic alcohols and their corresponding olefins disproportionate to produce cycloalkenyl cations and saturated hydrocarbons[7]. The carbonium ions formed can then disproportionate again to yield substituted allylic carbonium ions and the corresponding hydrogenated compounds[8,9]. Various combinations of hydride transfer from olefinic compounds to the cations[10] would be possible in these processes. Sulphuric acid seems also to act as another acceptor of hydride anions[8]. Recently, Jones et al.[2] suggested that one of the Kober-chromogens[11] would be attributed to the resonating tertiary carbonium ion such as V. A plausible explanation on the present reactions is thus shown in the scheme .

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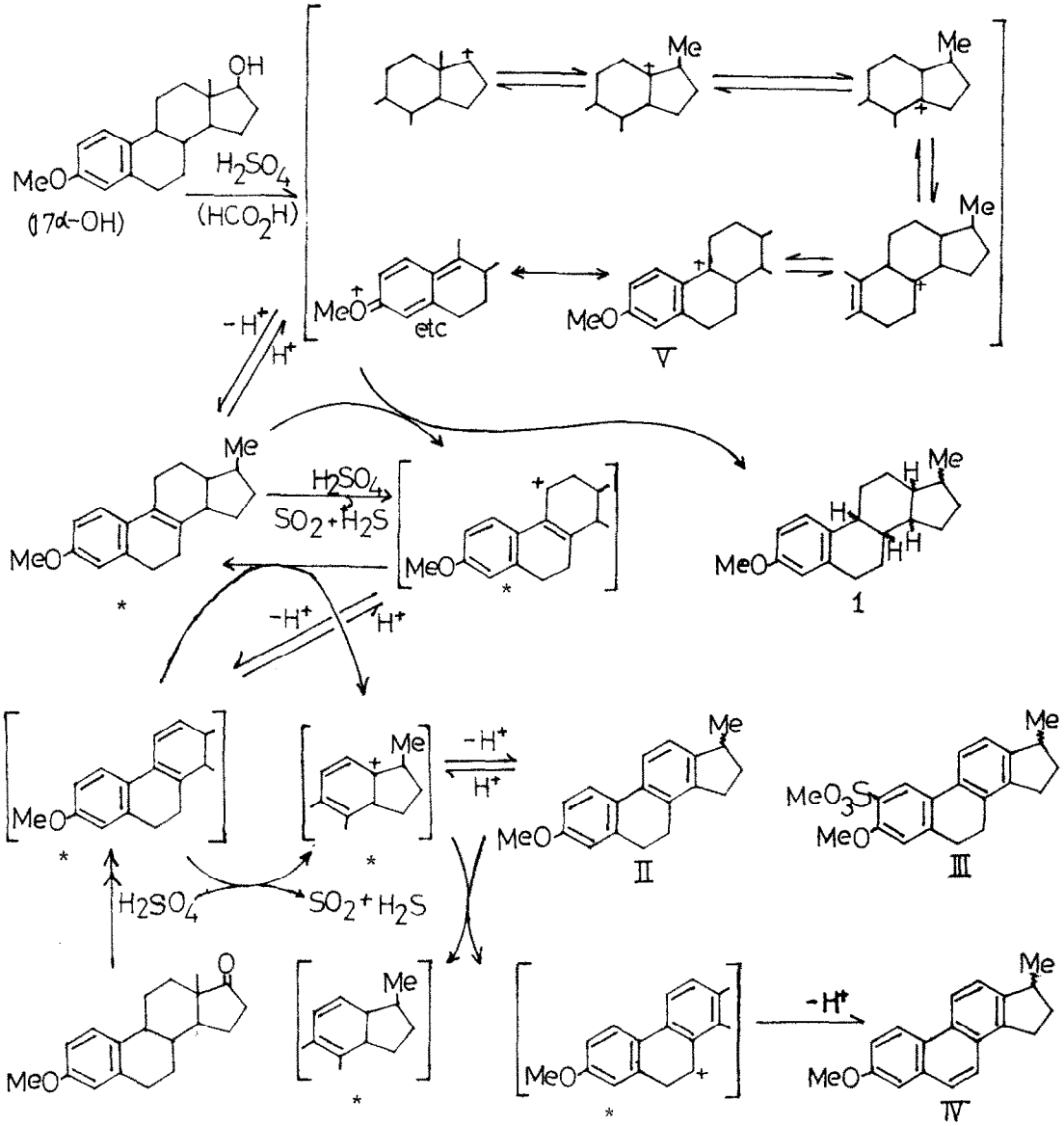

* One of the possible isomeric species is shown.

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