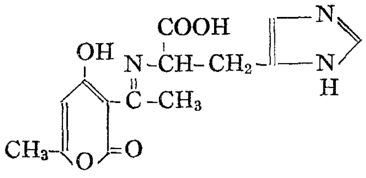
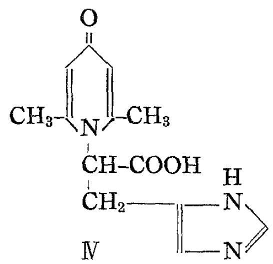
The former was identified as 3-{1-[[1-carboxy-2-(4-imidazolyl)]-ethylimino]ethyl}-4-hydroxy-6-methyl-2*H*-2-pyrone, m.p, 209~210° (decomp.), and the latter α-[(4-imidazolyl)-methyl]-4-oxo-2,6-dimethyl-1,4-dihydro-1-pyridineacetic acid, m.p. 170~175° (decomp.), from the data of an elemental analysis and the absorption spectra.



III



IV

In addition to the fact mentioned above, a primary bioactive amine histamine also reacted with DHA and readily transformed into 2,6-dimethyl-4(1*H*)-pyridone derivative *via* Schiff's base and 2,6-(dihistamyl-2,5-heptadien-4-one as was expected,

Furthermore, we tried to investigate the reaction of DHA with the other amino acids such as lysine and arginine, and found that the basic amino acid is generally more active than the acidic one; the reactivity depends on the basicity of amino acids.

This experiment has aimed to clear the reactivity of DHA with amino acids, especially the ease which DHA was transformed into 2,6-dimethyl-4(1*H*)-pyridone even under a mild condition. Detail of this work will be reported in the near future.

In the paper chromatograhy, Dragendorff's reagent was used as a spraying reagent and BuOH-AcOH-H_2O (4:1:5) system as the developing solvent.

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The Polyphosphoric Acid-Catalyzed Ring Opening of 4,5-Epoxy-3-oxo Steroids : The Synthesis of 4-Alkylthio-4-en-3-oxo Steroids and their Analogs

A number of studies[1] on the ring opening or rearrangement of steroidal α-epoxyketones, mainly of 4,5-epoxy-3-oxo and 16,17-epoxy-20-oxo steroids, have sofar been accumulated in connection with a view to synthesizing modified steroid hormones. However, the reaction still represents a promising method for the synthesis of potential steroids with desired biological activity separated from other actions of the natural hormones, and also for the exploration of complex stereochemical aspects in steroidal

1) References cited in C. Djerassi : "Steroidal Reactions" (1962). Holden-Day Inc., San Fransisco.

reactions. The present communication deals with some examples of the elegant and efficient catalytic action of polyphosphoric acid (referred to PPA hereinafter) for both normal and abnormal ring opening of 4,5-epoxy-3-oxo steroids with suitable nucleophilic reagents and also the first convenient synthesis of 4-alkylthio-4-en-3-oxo steroids and their analogs.

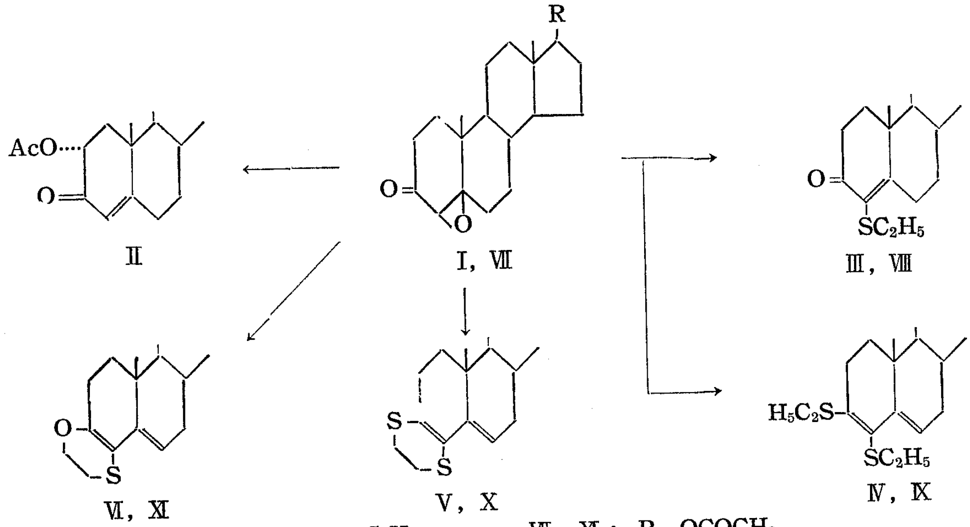
PPA-catalyzed ring opening*1 of 4β,5-epoxy-5β-cholestan-3-one (I)[2] in acetic acid afforded 2α-acetoxycholest-4-en-3-one (II)[3] (m.p. 139~141° *2 (45%). *Anal.* Calcd. for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.87; H, 10.30. $[\alpha]_D^{30}$ +69°. UV λ_{max} mμ (ε): 243 (14,600). IR ν_{max} cm^{-1}: 1736 (s), 1678 (s), 1.610 (m)) as the sole and abnormal product.

PPA-catalyzed ring opening of the epoxide (I) with ethanethiol in dioxane, in marked contrast, did result in a smooth normal epoxide fission affording 4-ethylthiocholest-4-en-3-one (III) (m.p. 129.5~130.5° (71%). *Anal.* Calcd. for $C_{29}H_{48}OS$: C, 78.31; H, 10.87; S, 7.21. Found: C, 78.13; H, 10.69; S, 7.38. $[\alpha]_D^{16}$ +131°. UV λ_{max} mμ (ε): 248 (12800), 316 (2000). IR ν_{max} cm^{-1}: 1668 (s), 1554 (m)), and 3,4-bis(ethylthio)cholesta-3,5-diene (IV) (m.p. 175~175.5° (7.5%). *Anal.* Calcd. for $C_{31}H_{52}S_2$: C, 76.16; H, 10.72; S, 13.09. Found: C, 76.12; H, 10.72; S, 13.23. $[\alpha]_D^{10}$ −186°. UV λ_{max}^{hexane} mμ (ε): 292 (14800). IR ν_{max} cm^{-1}: 1552 (m)).

The structure of these new thiosteroids could be established by their characteristic optical and spectroscopic[4] properties coupled with the following evidence: firstly, III, on treatment with deactivated Raney-nickel in acetone, afforded cholest-4-en-3-one[5] (m.p. 79~80° (69%). $[\alpha]_D^{15}$ +88°. UV λ_{max} mμ (ε): 243 (17500). IR ν_{max} cm^{-1}: 1672 (s), 1612 (m)).

Secondly, further treatment of III with ethanethiol in PPA-dioxane afforded IV in a good yield. And thirdly, IV was in turn hydrolyzed to III by treatment with hydrochloric acid in chloroform.

Here it was reasonably anticipated that ethanedithiol might react first with one end at C-4, accompanied by a spontaneous intramolecular cyclization with another end at C-3. This was exactly the case and cholesta-3,5-dieno[3,4-*b*]dithiane (V)[4] (m.p.



I~VI: R=C_8H_{17} VII~XI: R=$OCOCH_3$

*1 Ring opening of epoxides reported in this communication was conducted at room temperature.

*2 M.p.s were taken on a Kofler block. α Refers to chloroform, ultraviolet absorption spectra to 95% ethanol, and infrared spectra to nujol unless otherwise stated.

2) P.A. Plattner, H. Heusser, A. B. Kulkarni: Helv. Chim. Acta, **31**, 1822 (1948).
3) F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez, G. Rosenkranz: J. Am. Chem. Soc., **75**, 4712 (1953).
4) L.F. Fieser, C. Yuan, T. Goto: *Ibid.* **82**, 1996 (1960).
5) J.F. Eastham, R. Teranishi: Org. Syntheses, **35**, 39 (1955).

161~162.5° (40%). *Anal.* Calcd. for $C_{29}H_{46}S_2$: C, 75.95; H, 10.11; S, 13.98. Found : C, 76.28; H, 10.30; S, 13.58. $[\alpha]_D^{21}$ −131°. UV λ_{max}^{hexane} mμ (ε): 240 (11900), 292 (13900). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1575 (w)), was obtained; no thioketalization was observed. Further confirmation of the 3,5-diene structure for V was supported by the fact that the diene (V) was recovered unchanged after treatment with hydrogen chloride-chloroform,*3 and that desulfurization of V with deactivated Raney-nickel in acetone afforded cholesta-3,5-diene[6] (m.p. 74° (37%). UV λ_{max} mμ (ε) : 228 (16600), 236 (18000), 244 (11600). IR ν_{max} cm^{-1}:1544 (w)).

A further interesting observation was that 2-mercaptoethanol reacted smoothly with I in PPA-dioxane affording cholesta-3,5-dieno[3,4-*b*]oxathiane (VI)[4] (m.p. 152.5~153.5° (40%). *Anal.* Calcd. for $C_{29}H_{46}OS$: C, 78.68; H, 10.47; S, 7.24. Found : C, 78.68; H, 10.65; S, 7.34. $[\alpha]_D^{30}$ −162°. UV λ_{max}^{hexane} mμ (ε) : 223 (9300), 270 (8800). IR ν_{max} $cm.^{-1}$: 1630 (w), 1613 (m)).

This technique of introduction of a thio-function into the steroid nucleus, observed in the cholestane series, was applied with success to 17β-acetoxy-4,5-epoxyandrostan-3-one (VII)[7] affording the following compounds : 17β-acetoxy-4-ethylthioandrost-4-en-3-one (VIII) (m.p. 135~137°. *Anal.* Calcd. for $C_{23}H_{34}O_3S$: C, 70.72; H, 8.77; S, 8.20. Found: C, 70.59; H, 9.00; S, 7.97. $[\alpha]_D^{27.5}$ +96°. UV λ_{max} mμ (ε) : 247 (13900). IR ν_{max} cm^{-1} : 1730 (s), 1672 (s), 1560 (m)). 17β-Acetoxy-3,4-bis(ethylthio)androsta-3,5-diene (IX) (m.p. 130~132°. *Anal.* Calcd. for $C_{25}H_{38}O_2S_2$: C, 69.07; H, 8.81; S, 14.75. Found : C, 69.34; H, 8.92; S, 14.95. $[\alpha]_D^{27}$ −227°. UV λ_{max} mμ (ε) : 292 (17500). IR ν_{max} cm^{-1} : 1735 (s), 1545 (w)). 17β-Acetoxyandrosta-3,5-dieno[3,4-*b*]dithiane (X) (m.p. 201.5~203°. *Anal.* Calcd. for $C_{23}H_{32}O_2S_2$: C, 68.36; H, 7.97; S, 15.85. Found : C, 68.38; H, 8.29; S, 15.91. $[\alpha]_D^{25}$ −188°. UV λ_{max}^{hexane} mμ (ε) : 240 (12800), 294 (14500). IR ν_{max} cm^{-1} : 1718 (s), 1565 (w)). 17β-Acetoxyandrosta-3,5-dieno[3,4-*b*]oxathiane (XI) (m.p. 213~215°. *Anal.* Calcd. for $C_{23}H_{32}O_3S$: C, 71.09; H, 8.30; S, 8.25. Found : C, 71.17; H, 8.71; S, 8.01. $[\alpha]_D^{22}$ −185°. UV λ_{max}^{hexane} mμ (ε) : 222 (9100), 270 (8500). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1718 (s), 1638 (w)).

Further work on the line presented in this communication is at present in progress and the result together with the stereochemical consideration on the cleancut nature of the reaction will be published as a full paper at a late date.

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〔Added in Proof〕 After this Communication had been submitted for publication, a paper (J.M. Krämer, K. Brückner, K. Irmscher, and Karl-Heinz Bork : Chem. Ber., **96**, 2803 (1963)) was published, in which the synthesis of some 4-thiosubstituted testosterones by the base-catalyzed ring opening of 17β-hydroxy-4,5-epoxyandrostan-3-one, was described.

*3 Steroidal 2, 4-dienes are known to isomerize to 3, 5-diene systems under such acidic condition.[8]
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*5 Present address : Nikka Chemical Industrial Co., Ltd., Fukui.

6) H.E. Stavely, W. Bergmann : J. Org. Chem., **1**, 567 (1936).
7) P.L. Julian, V. Georgian, H.C. Printy : U.S. Pat. 2,910,487 (1959).
8) P.N. Rao, H.R. Gollberg : Tetrahedron, **18**, 1251 (1962).