Summary

1-Phenyl-5,6-diaminouracil (Ⅸ) or -2-thiouracil (Ⅹ) prepared from 1-phenyl-6-aminouracil (Ⅴ) or 1-phenyl-6-amino-2-thiouracil (Ⅵ) in an usual way was fused with urea or thiourea to yield 3-phenyluric acid and 3-phenylthiouric acid derivatives (ⅩⅡ, ⅩⅢ, XIV and XV), while it was reacted with formamide to afford 3-phenylxanthine derivatives (XX and XXI), and with nitrous acid to give triazolo-derivatives (XXIV and XXV). Acetylation of Ⅸ or Ⅹ resulted in formation of the corresponding 5-acetyl derivatives (XXVII and XXVⅢ) which on heating at 230~240° as the sodium salts were converted into 8-methylpurine derivatives (XXIX and XXX). Preliminary *anti*-cancer testing results of the purine derivatives synthesized were described.

(Received February 8, 1966)

[Chem. Pharm. Bull. 14(12)1370~1377(1966)]

UDC 547.924.07

185. Keiji Yoshida and Tokuo Kubota: Studies on A-Norsteroids. V.[*1] Reaction of Steroidal Diosphenols with Manganese Dioxide.

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In the previous paper,[1] it was reported that treatment of $1\alpha,2\alpha$-dihydroxy-4-en-3-oxo steroids with manganese dioxide resulted in the A-ring contraction giving the respective A-nor-3(5)-ene-1,2-dioxo steroids. During the course of further investigation on this reaction, it has been found that $2,17\beta$-dihydroxyandrosta-1,4-dien-3-one (Ⅱa) was also oxidized with manganese dioxide giving the A-nor-3(5)-ene-1,2-dioxo steroid. The present paper deals with this novel type of ring contraction reaction.

Rao, *et al.*[2] reported that a mixture of androst-4-ene-$2\beta,3\alpha,17\beta$-triol and $2\beta,3\beta,17\beta$-triol was readily oxidized with manganese dioxide in tetrahydrofuran giving $2,17\beta$-dihydroxyandrosta-1,4-dien-3-one (Ⅱa) through 2β-hydroxytestosterone. When 2β-hydroxytestosterone 17-propionate (I) was treated with manganese dioxide in acetone, occurrence of a yellow substance besides the expected diosphenol (Ⅱb) was observed. Prolonged treatment of I with manganese dioxide led to the isolation of yellow crystals, identical with the previously obtained 17β-hydroxy-A-norandrost-3(5)-ene-1,2-dione propionate (Ⅲb). Since it was obvious that the formation of A-norsteroid (Ⅲb) proceeded through further oxidation of the diosphenol (Ⅱb), the reaction with manganese dioxide was investigated on the diosphenol (Ⅱa), which is easily obtainable from testosterone by acetoxylation with lead tetraacetate[3] followed by oxygen oxidation of the crude acetoxylated product in alkali medium.[4]

Although preparation of manganese dioxide followed essentially the procedure of Mancera, *et al.*,[5] the rate of ring contraction of the diosphenol (Ⅱa) varied with a small change in the procedure. Manganese dioxide used in this investigation was prepared as described in the experimental part.

[*1] Part Ⅳ: K. Yoshida, T. Kubota: Tetrahedron, **21**, 759 (1965).

[*2] Fukushima-ku, Osaka (吉田圭治, 久保田徳夫).

[1] T. Kubota, K. Yoshida, F. Hayashi, K. Takeda: This Bulletin, **13**, 50 (1965).

[2] P.N. Rao, L.R. Axelrod: J. Am. Chem. Soc., **82**, 2830 (1960).

[3] F. Sondheimer, K.J. Romo, H. Martinez, G. Rosenkranz: *Ibid.*, **75**, 4712 (1953).

[4] R.L. Clarke: *Ibid.*, **82**, 4629 (1960).

[5] O. Mancera, G. Rosenkranz, F. Sondheimer: J. Chem. Soc., **1953**, 2189.

As mentioned above on the oxidation of I with manganese dioxide, the conversion of the diosphenol (Ⅱa) into the A-norsteroid (Ⅲa) proceeded to a considerable extent at room temperature. Disappearence of the diosphenol (Ⅱa), however, was not completed in this condition and it was difficult to separate the product from the remaining starting material. The optimum condition was treatment with tenfold weight of manganese dioxide in refluxing acetone for 2 hours and there was obtained 33% yield of 17β-hydroxy-A-norandrost-3(5)-ene-1, 2-dione (Ⅲa), which was identical with a specimen previously obtained.[1] Although the yield of this reaction was inferior to 57% yield observed[1] in the oxidation of $1\alpha, 2\alpha, 17\beta$-trihydroxyandrost-4-en-3-one (Va) to Ⅲa, regarding the overall yield from testosterone propionate to Ⅲa, the present method was superior to the previous one because of difficulty in preparation of Va. As described above, acetone was used successfully as the reaction solvent and the reaction proceeded also in chloroform with some delay.

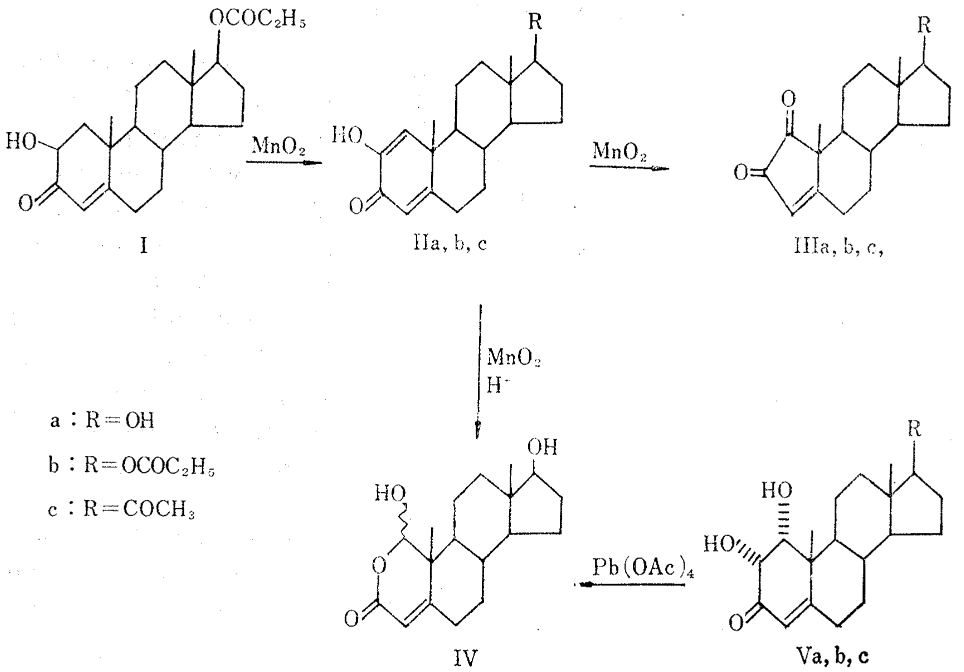

Chart 1.

The same reaction proceeded in the pregnane series and the manganese dioxide oxidation of 2-hydroxypregna-1,4-diene-3,20-dione (Ⅱc), obtained by treatment of 1α, 2α-dihydroxyprogesterone (Vc)[1] with base, yielded A-norpregn-3(5)-ene-1,2,20-trione (Ⅲc).[1]

In the course of attempts to find out a factor accelerating the reaction, it was found that the reaction yielded another product in the presence of acid. The diosphenol (Ⅱa) on treatment with manganese dioxide in acetone containing a small amount of dilute sulfuric acid at 30° for 6 hours gave colorless crystals, $C_{18}H_{26}O_4$, m.p. 247∼249°, in 21% yield, besides 27% recovery of the starting material. The new product could be predicted to be $1\xi, 17\beta$-dihydroxy-2-oxaandrost-4-en-3-one (Ⅳ) arising from oxidative fission of the ring A, based on the analytical result, the UV maximum at 227.5 mμ (ε 14,200) and the IR bands at 3466, 3326, 1690, and 1645 cm^{-1}. The correctness of the assigned structure was confirmed by identification with the authentic lactol (Ⅳ), which was prepared by oxidation of $1\alpha, 2\alpha, 17\beta$-trihydroxyandrost-4-en-3-one (Va) with lead tetraacetate followed by acid treatment in the manner described for analogues of the corticoid series.[6]

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[6] R. Hirschmann, N. G. Steinberg, R. Walker : J. Am. Chem. Soc., 84, 1270 (1962).

In this connection, oxidation of the diosphenol (IIa) was carried out with nickel peroxide,7) which resembles to manganese dioxide in the oxidative feature and is more active than the latter. Treatment of IIa with nickel peroxide afforded the A-norsteroid (IIIa) in 10% yield and the lactol (IV) in 20% yield.

Oxidation with manganese dioxide was extended to an isomer of the diosphenol (IIa), 4,17β-dihydroxyandrosta-1,4-dien-3-one (VI), which was prepared by treatment of 4β,5β,17β-trihydroxyandrost-1-en-3-one (VIIIa)1,8) with base. Treatment of VI with manganese dioxide in acetone at 30° for 6 hours gave a product, m.p. 270~272° (decomp.), in 64% yield. The structure of this compound was inferred to be 5ξ,17β-dihydroxy-4-oxaandrost-1-en-3-one (VII) from the melting point,9) the analytical value and the characteristic absorptions in the IR and UV spectra. Confirmation was made by identification with a sample of the lactol (VII) prepared from oxidative fission of 4β,5β,17β-trihydroxyandrost-1-en-3-one (VIIIa) with lead tetraacetate.

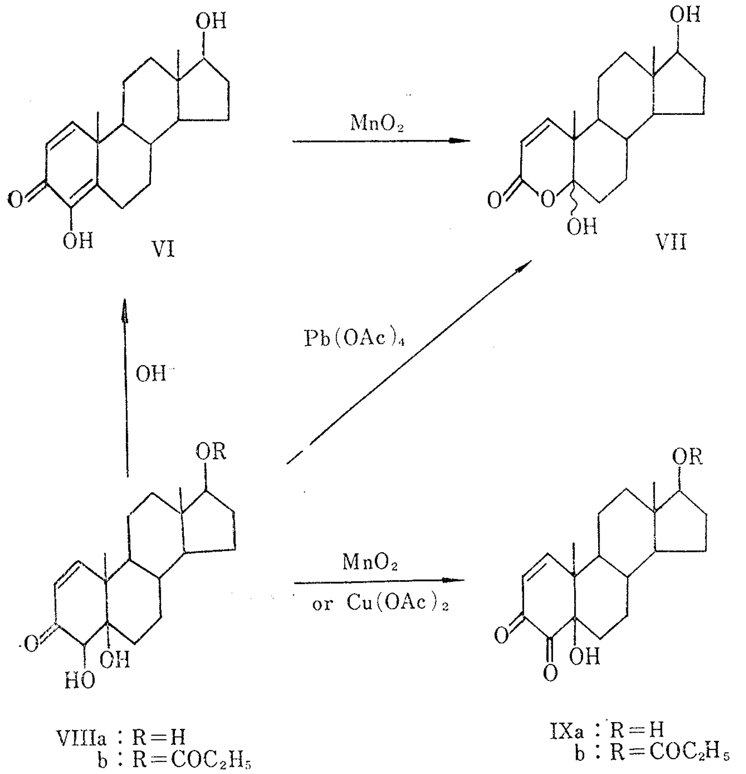

Chart 2.

As mentioned above, the oxidation of the diosphenol (IIa) with manganese dioxide resulted in the ring contraction giving the A-norsteroid (IIIa), whereas the oxidation of IIa in the presence of proton and of VI brought on the ring cleavage giving the corresponding lactol (IV) and (VII). A possible pathway for the ring contraction would be hydroxylation at C_1 in the diosphenol (IIa). Meunier10) and Henbest11) described that the oxidation of alicyclic unsaturated compounds with manganese dioxide gave conjugated ketones through hydroxylation at allylic methylene. In view of this fact, it is supposed that the first step in the oxidation of IIa would probably be the formation of 1ξ-hydroxy-4-ene-2,3-dione (X) involving hydroxylation at the C_1-methylene adjacent to the C_2-carbonyl group in the tautomeric keto form of the diosphenol (IIa). The next step is dehydrogenation of the C_1-hydroxyl group to the carbonyl and the resulting enetrione (XI) may be converted into the A-norsteroid (IIIa) through benzilic acid type rearrangement as suggested previously.12)

In order to postulate a possible mechanism for the ring cleavage leading to the formation of lactols (IV) and (VII), some experiments were carried out. Oxidation of 1α,2α,17β-trihydroxyandrost-4-en-3-one (Va) with manganese dioxide, under the same

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7) K. Nakagawa, R. Konaka, T. Nakata: J. Org. Chem., **27**, 1597 (1962).
8) T. Kubota, K. Yoshida, F. Watanabe: This Bulletin, **14**, 1426 (1966).
9) E. Caspi, B. T. Khan, S. N. Balasubrahmanyam: Tetrahedron, **18**, 1013 (1962).
10) P. Meunier, G. Zwingelstein, J. Jouannetean: Bull. Soc. Chim. Biol., **35**, 495 (1953).
11) H. B. Henbest, E. R. H. Jones, J. C. Owen: J. Chem. Soc., **1957**, 4909.
12) T. Kubota, K. Takeda: Tetrahedron, **10**, 1 (1960).

condition as that obtained the lactol (IV) from IIa, at 30° for 6 hours in acetone containing sulfuric acid gave only the A-nor-3(5)-ene-1,2-dione (IIIa) with the same result as that in absence of the acid1) but the lactol (IV) was not obtained. The result suggested that the formation of the lactol (IV) from IIa does not proceed through the 1-hydroxy-4-ene-2,3-dione (X) postulated above as an intermediate in the ring contraction reaction. On the other hand, when 4β,5β,17β-trihydroxyandrost-1-en-3-one 17-propionate (VIIIb) was treated with manganese dioxide at 30° for 6 hours in the presence or absense of proton, both of the reactions yielded the unchanged starting material and yellow crystals, m.p. 202~204° (decomp.), which was shown to be 5β,17β-dihydroxyandrost-1-ene-3,4-dione 17-propionate (IXb) by the spectral data and the chemical evidences described below. The product (IXb) showed the IR bands at 3410 (OH), 1726 (ester), 1678 and 1612 (unsaturated ketone) cm^{-1}, the UV absorption at 262 mμ (ε 4,800) and the NMR signals at 3.03 τ (J=10.5 c/s) and 3.71 τ (J=10.5 c/s) due to two olefinic protons. Acetylation with acetic anhydride-pyridine did not affect the remaining hydroxyl group and treatment with *o*-phenylenediamine gave a quinoxaline derivative, m.p. 238~239°. Finally, the six-membered enedione (IXb) was identified with the specimen, prepared by oxidation of VIIIb with cupric acetate in methanol. Further treatment of IXb with manganese dioxide at 30° for 6 hours resulted in the recovery of the unchanged starting material and the lactol (VII) could not be found at all. It is, thus, clear that the 5β-hydroxy-1-ene-3,4-dione (IXa) is not an intermediate in the formation of the lactol (VII) from the diosphenol (VI).

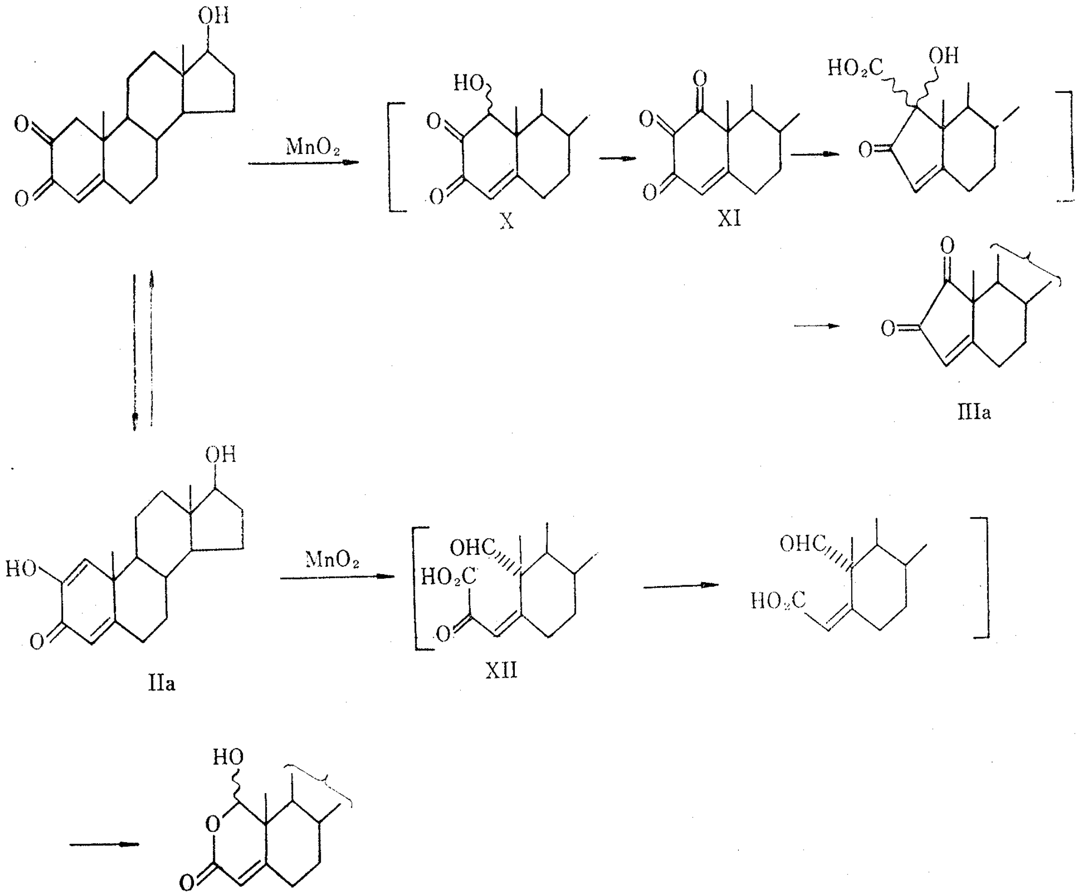

Chart 3.

As the result of the above experiments, the reaction yielding the lactols (Ⅳ) and (Ⅶ) appears to take a different course from that leading the ring contraction, since an earlier stage of the oxidation. Henbest, *et al.*[13] have described that a double bond in enamines or enol ethers was cleaved with manganese dioxide by way of hydroxylation on the double bond and fission of the resulted α-glycol. Although the UV spectrum [λ_{max} 255 mμ (ε 14,100) and 290 mμ (ε 3,200)] of the diosphenol (Ⅱa) in ethyl alcohol was not altered at all with addition of acid, the above facts suggest that the lactol formation would be initiated with oxidative fission of the double bond in the enol form of diosphenol (Ⅱa). It presumably results in the formation of the aldehyde carboxylic acid (Ⅻ), which may be converted into the lactol (Ⅳ) by oxidative decarboxylation followed by cyclization. Nevertheless, attempts to oxidize the diosphenol methyl ether, 2-methoxy-17β-hydroxyandrosta-1,4-dien-3-one,[14] with manganese dioxide in acetone resulted in the complete recovery of the starting materal, in the presence or absence of the acid, and thus some doubts are still remained in the mechanism for the formation of the lactol (Ⅳ).

Experimental

All melting points were uncorrected. Unless otherwise stated, optical rotations were measured in $CHCl_3$ solutions at ca. 25° with a Rudolf Photoelectric Polarimeter Model 200. UV spectra were taken in 95% EtOH solutions with a Hitachi Recording Spectrophotometer EPS-2. IR spectra were recorded on a Koken Infrared Spectrophotometer Model DS 301. NMR spectra were determined at 60 Mc. in $CDCl_3$ solutions containing tetramethylsilane as an internal standard using a Varian A-60 analytical NMR spectrometer.

Preparation of Manganese Dioxide——A solution of $MnSO_4 \cdot 4\sim6H_2O$ (30 g.) of JIS special grade in H_2O (50 ml.) was heated at 90° with stirring. To the solution, a 10% solution of $KMnO_4$ in hot H_2O was added dropwise until the reaction mixture colored pink whereupon about 150 ml. of the $KMnO_4$ solution had been consumed. Stirring at 90° was continued for an additional 15 min., while the coloration had disappeared. The precipitate was collected by filtration and washed thrice with hot H_2O (100 ml. each). After cooling, the MnO_2 was washed with MeOH (100 ml.) and then with ether (100 ml.), and dried at 120～130° for 7 hr. in an oven.

2β-Hydroxytestosterone 17-Propionate (I)——Testosterone propionate was subjected to the same procedure as described by Sondheimer, *et al.*[3] for acetoxylation of testosterone acetate with lead tetraacetate. Repeated recrystallizations of the crude product from MeOH and from AcOEt afforded 2β-acetoxytestosterone 17-propionate,[15] m.p. 187～189°. UV λ_{max} mμ (ε): 244 (15,600). The foregoing product (600 mg.) was treated with KOH in MeOH in the manner described by Rao, *et al.*[2] for partial saponification of 2β-hydroxytestosterone diacetate. Recrystallization of the product from aq. MeOH gave needles (456 mg.) of I, m.p. 129～131°, $[\alpha]_D$ $-99°$ (c=1.05). UV λ_{max} mμ (ε): 244 (14,500). IR ν_{max}^{Nujol} cm^{-1}: 3512, 1734, 1679, 1619 cm^{-1}. *Anal.* Calcd. for $C_{22}H_{32}O_3$: C, 73.30; H, 8.95. Found: C, 73.43; H, 9.06.

Treatment of I with Manganese Dioxide——Progress of the reaction was determined as follows: Small quantities of the reaction mixture were withdrawn at 1 hr. intervals and freed from the MnO_2 and solvent. The samples were examined by thin-layer chromatography (TLC) and by UV spectrum in a EtOH solution.

a) For 2 hr. A mixture of I (100 mg.) and MnO_2 (1.0 g.) in acetone (10 ml.) was stirred at 30～32°. The sample, after 1 hr. stirring, showed the UV maximum at 254 mμ with shoulder at 290 mμ moving from the initial absorption at 240 mμ and exhibited, on TLC, a spot different from that of the starting material. After an additional 1 hr. treatment, no further change was observed on the UV spectrum and on TLC. Filtration of the mixture and evaporation of the filtrate afforded a yellow foam (62 mg.), which on crystallization from aq. MeOH yielded pale yellow needles (36 mg.), m.p. 133～138°. Further recrystallization from aq. MeOH gave needles (25 mg.) of 2,17β-dihydroxyandrosta-1,4-dien-3-one 17-propionate (Ⅱb), m.p. 136～139°, which was still yellowish but sufficient pure for analysis. UV λ_{max} mμ (ε): 254 (14,300), 290 (shoulder, 3,200). IR ν_{max}^{Nujol} cm^{-1}: 3420, 1738, 1683, 1645, 1607. *Anal.* Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.63, H, 8.48.

b) For 6 hr. A mixture of I (160 mg.) and MnO_2 (1.6 g.) in acetone (16 ml.) was stirred at 30～32°. The sample of 5 hr. treatment showed no significant change comparing to the 2 hr. sample on TLC but its

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13) H. B. Henbest, A. Thomas: J. Chem. Soc., **1957**, 3032.

14) J. S. Baran: J. Am. Chem. Soc., **80**, 1687 (1958).

15) K. Kuriyama, E. Kondo, K. Tori: Tetrahedron Letters, **1963**, 1485.

UV spectrum exhibited an absorption maximum at 284 mμ with a lower slope through 255 mμ. The stirring was stopped after 6 hr. and the mixture was filtered. The filtrate was evaporated to give a yellow foam (74 mg.), which was purified by chromatography on silica gel. The eluate (68 mg.) with benzene-$CHCl_3$ (1:1) on recrystallization from acetone-petr. ether afforded yellow plates (44 mg.), m.p. 160~162°, which was identified with a sample of 17β-hydroxy-A-norandrost-4-ene-1,2-dione propionate (IIIb)[1] by the IR spectra and by a mixed m.p. determination.

2,17β-Dihydroxyandrosta-1,4-dien-3-one (IIa)——A mixture of testosterone propionate (40 g.) and $Pb(OAc)_4$ (62 g.) in glacial AcOH (600 ml.) was heated with stirring at 95° for 2.5 hr. Crystals precipitated by addition of H_2O were collected and dissolved in a mixture of ether-$CHCl_3$ (5:1). The solution was washed with 5% $NaHCO_3$ and H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The crystalline residue (42.75 g.) was dissolved in a mixture of EtOH (1.6 L.) and 2.5% KOH (950 ml.) and the solution was stirred at room temperature for 7 hr. while a stream of O_2 was bubbled through it. After acidification with 10% AcOH, the mixture was concentrated to a small volume. The precipitated crystals were filtered and dissolved in ether-$CHCl_3$ (5:1). The solution was washed with 5% $NaHCO_3$ and extracted with 2% NaOH. The enolic fraction was acidified with 20% AcOH and the precipitated crystals were collected, washed with H_2O and dried giving IIa (16.6 g.), m.p. 194~197°, in 47.4% yield. Recrystallization from acetone gave the pure IIa as prisms, m.p. 207~209°, $[\alpha]_D$ −15° (c=1.05). UV $\lambda_{\max}$ mμ (ε): 255 (14,100), 290 (shoulder) (3,200). (reported,[4] m.p. 207~209°, $[\alpha]_D$ −16.2°).

Treatment of 2,17β-Dihydroxyandrosta-1,4-dien-3-one (IIa) with Manganese Dioxide——A mixture of IIa (2.20 g.) and MnO_2 (22 g.) in acetone (220 ml.) was refluxed in a water bath for 2 hr. with stirring. The MnO_2 was filtered and the filtrate was evaporated *in vacuo* leaving a yellow solid (1.27 g.). Recrystallization from acetone gave 17β-hydroxy-A-norandrost-3(5)-ene-1,2-dione (IIIa) (686 mg.) as yellow needles, m.p. 226~230°, in 32.7% yield. Further recrystallization from the same solvent sharpened the m.p. to 228~230°. Identification with an authentic sample obtained previously[1] was established by a mixed melting point and the IR comparison.

2-Hydroxypregna-1,4-diene-3,20-dione (IIc)——A mixture of 1α,2α-dihydroxypregn-4-ene-3,20-dione (Vc)[1] (397 mg.) in MeOH (60 ml.) and 10% KOH (3 ml.) was refluxed for 30 min. in a N_2 atmosphere. The reaction mixture was acidified with AcOH and extracted with ether-$CHCl_3$ (5:1). The organic layer was washed with 5% $NaHCO_3$ and H_2O, dried over Na_2SO_4 and evaporated leaving a crystalline solid (336 mg.). Recrystallization from acetone gave IIc (185 mg.) as plates, m.p. 199~200°, $[\alpha]_D$ +84° (c=0.53). UV $\lambda_{\max}$ mμ (ε): 254.5 (14,500), 290 (shoulder) (3,200). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3256, 1702, 1688 (w), 1673 (w), 1644, 1622. *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.83; H, 8.66.

Treatment of 2-Hydroxypregna-1,4-diene-3,20-dione (IIc) with Manganese Dioxide——A mixture of IIc (110 mg.) and MnO_2 (1.1 g.) in acetone (11 ml.) was refluxed for 9 hr. with stirring. The residue (67 mg.) obtained by removals of the MnO_2 and the solvent, was chromatographed on silica gel (1.2 g.). The fractions (40 mg.) eluted with benzene-$CHCl_3$ (9:1~1:1) were recrystallized from acetone-petr. ether giving yellow needles (21 mg.), m.p. 176~181°. Further recrystallization from acetone afforded A-norpregn-3(5)-ene-1,2,20-trione (IIIc), m.p. 180~181°, identical with an authentic sample obtained previously[1] by a mixed m.p. and the IR comparison.

Treatment of IIa with Manganese Dioxide under a presence of Sulfuric Acid——To a solution of IIa (300 mg.) in acetone (30 ml.) and 10% H_2SO_4 (0.5 ml.) was added MnO_2 (3 g.). The mixture was stirred at 30~32° for 6 hr. The MnO_2 was filtered off and the filtrate was evaporated leaving the residue (256 mg), which was chromatographed on silica gel (5 g.). The fractions (150 mg.) eluted with benzene-$CHCl_3$ (1:1), on recrystallization from acetone, gave plates (80 mg.), m.p. 190~194°, which, after further recrystallization, was identified as the starting material (IIa), m.p. 205~208°. The next fractions (91 mg.) eluted with $CHCl_3$ and $CHCl_3$-MeOH (100:1) were recrystallized from acetone yielding plates (64 mg.), m.p. 247~249°, which was identified with a sample of 1ξ,17β-dihydroxy-2-oxaandrost-4-en-3-one (IV) described below, by a mixed melting point determination and the IR spectra.

1ξ,17β-Dihydroxy-2-oxaandrost-4-en-3-one (IV)——To a solution of 1α,2α,17β-trihydroxyandrost-4-en-3-one (Va)[1] (140 mg.) in dry benzene (10 ml.) and abs. MeOH (20 ml.) was added $Pb(OAc)_4$ (420 mg.) and the solution was allowed to stand at room temperature for 1 hr. After dilution with benzene (30 ml.), the solution was washed with H_2O, dried over Na_2SO_4 and evaporated leaving a gelatinous solid (152 mg.) of the aldehyde-carboxylic acid. The above material was warmed with 50% AcOH (5 ml.) at 100° for 1.5 hr. and extracted with AcOEt. The organic layer was washed with 5% $NaHCO_3$ and H_2O, dried over Na_2SO_4 and evaporated to dryness. The crystalline residue (131 mg.) was recrystallized from acetone giving IV (74 mg.) as plates, m.p. 241~243°. Further recrystallization from the same solvent afforded the analytical sample, m.p. 247~249°, $[\alpha]_D$ +180° (c=0.51). UV $\lambda_{\max}$ mμ (ε): 227.5 (14,200). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3466, 3326, 1690, 1645. *Anal.* Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.30; H, 8.51.

Oxydation of IIa with Nickel Peroxide——To a solution of IIa (300 mg.) in benzene (90 ml.) was added nickel peroxide[7] (3.0 g.). The mixture was stirred at 30~32° for 1 hr. The precipitate was filtered off and the filtrate was evaporated giving a residue (209 mg.), which was chromatographed over silica gel (4 g.). The fractions (66 mg.) eluted with benzene-$CHCl_3$ (1:1) and $CHCl_3$, on recrystallization from acetone, afforded yellow needles (25 mg.), m.p. 226~227°. After further recrystallization from acetone, the product showed m.p. 228~230° and was identified with IIIa.

The next fractions (109 mg.) eluted with $CHCl_3$–MeOH (100:1~50:1), on recrystallization from acetone, afforded plates (60 mg.), m.p. 247~249°, identical with IV obtained in the preceding experiment.

4,17β-Dihydroxyandrosta-1,4-dien-3-one (VI)——A solution of 4β,5β,17β-trihydroxyandrost-1-en-3-one (VIIIa)[1,8] (2.90 g.) in MeOH (145 ml.) and a 1*N* KOH–MnOH solution (29 ml.) was refluxed for 30 min. The reaction mixture was acidified weakly with 10% AcOH and concentrated to a small volume under a reduced pressure. The residue was taken with ether–$CHCl_3$ (4:1) mixture and the organic layer was washed with 2.5% $NaHCO_3$ and H_2O, dried and evaporated giving a residue (2.59 g.). Recrystallization from acetone gave prisms (1.86 g.), melted 205~209° after moistened at 195°. Further recrystallization from acetone afforded pure VI as prisms, m.p. 209~211°, $[\alpha]_D$ +93° (c=1.0). UV λ_{max} mμ (ε): 244 (7,900), 303.5 (5,650). IR ν_{max}^{Nujol} cm^{-1}: 3522, 3417, 1642, 1596, 846. *Anal.* Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.76; H, 8.79.

Treatment of VI with Manganese Dioxide——A mixture of VI (300 mg.) and MnO_2 (3 g.) in acetone (30 ml.) was stirred at 30~32° for 6 hr. Removals of the MnO_2 and the solvent afforded pale yellow crystals (256 mg.), which was chromatographed on silica gel (5 g.). The fractions (14 mg.) eluted with $CHCl_3$, on recrystallization from acetone, gave plates, m.p. 200~202°, identical with the starting material (VI). The next fractions (240 mg.) eluted with $CHCl_3$ and $CHCl_3$–MeOH (100:1) were recrystallized from acetone giving plates (194 mg.), m.p. 270~272° (decomp.), which was identified with a sample of 5ξ,17β-dihydroxy-4-oxa-androst-1-en-3-one (VII) described below.

5ξ,17β-Dihydroxy-4-oxaandrost-1-en-3-one (VII)——A solution of VIIIa (1 g.) and $Pb(OAc)_4$ (4 g.) in benzene (240 ml.) and MeOH (60 ml.) was allowed to stand at room temperature for 20 hr. The reaction mixture was diluted with benzene (30 ml.), washed with 2% NaOH and H_2O, dried over Na_2SO_4 and evaporated leaving a glassy residue (955 mg.). This product was dissolved in a mixture of MeOH (150 ml.) and 1*N* NaOH (9 ml.), and the solution was refluxed for 2.5 hr. in a stream of N_2. After dilution with H_2O and washing with AcOEt, the alkali layer was acidified with 5% HCl. The precipitated crystals were collected, washed with H_2O, dried and recrystallized from acetone giving plates (324 mg.) of VII, m.p. 270~272° (decomp.), $[\alpha]_D$ +166° (c=0.52). UV λ_{max} mμ (ε): 217 (7,740) (reported[9]) m.p. 265~268°, λ_{max}^{MeOH} mμ (ε): 217 (8,000)). IR ν_{max}^{Nujol} cm^{-1}: 3366, 3205, 1695, 1623. *Anal.* Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.48; H, 8.62.

Treatment of 4β,5β,17β-Trihydroxyandrost-1-en-3-one 17-Propionate (VIIIb) with Manganese Dioxide——a) Without acid. A mixture of VIIIb[1,8] (200 mg.) and MnO_2 (2 g.) in acetone (20 ml.) was stirred at 30~32° for 6 hr. The MnO_2 was filtered off and filtrate was evaporated giving a residue (191 mg.), which was separated into two fractions by preparative TLC using silica gel GF plates and developing with benzene–AcOEt (3:1). The easily mobile fraction (75 mg.), on recrystallization from acetone, gave yellow plates (60 mg.), m.p. 202~204° (decomp.), which was identical with a sample of 5β,17β-dihydroxyandrost-1-ene-3,4-dione 17-propionate (IXb) described below in all respects. The less mobile fraction (107 mg.) was recrystallized from acetone yielding plates (88 mg.), m.p. 167~170°, identical with the starting material (VIIIb).

b) In presence of sulfuric acid. A mixture of VIIIb (100 mg.) and MnO_2 (1 g.) in acetone (10 ml.) and 10% H_2SO_4 (0.17 ml.) was processed in the same manner as described in a). The preparative TLC of the crude product afforded the easily mobile fraction (17 mg.) and less mobile one (81 mg.). The respective fractions on recrystallization from acetone gave IXb (12 mg.), m.p. 202~204° (decomp.) and the recovered starting material (VIIIb) (66 mg.), m.p. 167~170°.

Oxidation of 4β,5β,17β-Trihydroxyandrost-1-en-3-one (VIIIa) with Cupric Acetate——A mixture of VIIIa (100 mg.) and $Cu(OAc)_2 \cdot H_2O$ (150 mg.) in MeOH (10 ml.) was refluxed for 1 hr. After dilution with AcOEt, the mixture was washed with H_2O, dried over Na_2SO_4 and evaporated. The yellow residue (97 mg.) was recrystallized from acetone giving 5β,17β-dihydroxyandrost-1-ene-3,4-dione (IXa) (49 mg.) as yellow needles, m.p. 232~234° (decomp.). Concentration of the mother liquor afforded the second crop (20 mg.), m.p. 226~228° (decomp.). The first crop showed the following constants: $[\alpha]_D$ +192° (c=1.06, $CHCl_3$–MeOH, 1:1). UV λ_{max} mμ (ε): 260 (broad) (4,700). IR ν_{max}^{Nujol} cm^{-1}: 3410, 3240, 1733, 1674, 1609. *Anal.* Calcd. for $C_{19}H_{28}O_4$: C, 71.67; H, 8.23. Found: C, 71.64; H, 8.28.

Oxidation of 4β,5β,17β-Trihydroxyandrost-1-en-3-one 17-Propionate (VIIIb) with Cupric Acetate——Treatment of VIIIb (700 mg.) in MeOH (70 ml.) with $Cu(OAc)_2 \cdot H_2O$ (1.05 g.) was carried out in the same manner as the preceding experiment. The crude product (700 mg.) was recrystallized from acetone–*n*-hexane giving 5β,17β-dihydroxyandrost-1-ene-3,4-dione 17-propionate (IXb) (505 mg.) as yellow plates, m.p. 202~204° (decomp.), $[\alpha]_D$ +202 (c=1.06). UV λ_{max} mμ (ε): 262 (broad) (4,800). IR ν_{max}^{Nujol} cm^{-1}: 3410, 1726, 1678, 1612, 1280, 1215. *Anal.* Calcd. for $C_{22}H_{32}O_5$: C, 70.56; H, 8.08. Found: C, 70.47; H, 8.08. NMR (τ): 3.03 (doublet, C_1-proton), 3.71 (doublet, C_2-proton).

Acid Hydrolysis of IXb——To a solution of the foregoing IXb (150 mg.) in MeOH–$CHCl_3$ (3:1) (10 ml.) was added a mixture of conc. HCl (0.5 ml.) and H_2O (0.5 ml.). After standing at room temperature for 72 hr., the solution was diluted with AcOEt, and washed with 5% $NaHCO_3$ and H_2O. The organic layer was dried and evaporated ***in vacuo*** leaving a yellow crystalline residue (130 mg.). Recrystallization from acetone afforded yellow plates (93 mg.), m.p. 230~232° (decomp.), which was identical with the above-mentioned IXa.

Treatment of IXb with *o*-Phenylenediamine——A solution of IXb (100 mg.) and *o*-phenylenediamine (100 mg.) in EtOH (20 ml.) was refluxed for 2 hr. and then concentrated until crystals started separating. After cooling, the crystals (99 mg.), m.p. 237~239°, were collected and recrystallized from $CHCl_3$-EtOH yielding pale yellow needles of the quinoxaline derivative (84 mg.), m.p. 238~239°, $[\alpha]_D$ +230° (c=1.00). UV λ_{max} mμ (ε): 217 (27,700), 223 (26,400), 259 (22,800), 342 (11,500), 358 (10,000). IR ν_{max}^{Nujol} cm^{-1}: 3230, 1737, 1635, 1610 (w), 1556, 1186, 763. *Anal.* Calcd. for $C_{28}H_{34}O_3N_2$: C, 75.30; H, 7.67; N, 6.27. Found: C, 75.24; H, 7.78; N, 6.56.

The authors express their deep gratitude to Dr. Ken'ichi Takeda, Director of this laboratory, for his interest and encouragement during this work.

Summary

Oxidation of 2,17β-dihydroxyandrosta-1,4-dien-3-one (IIa) with manganese dioxide in acetone resulted in the ring contraction giving 17β-hydroxy-A-norandrost-3(5)-ene-1,2-dione (IIIa) whereas the reaction, in the presence of acid, afforded 1ξ,17β-dihydroxy-2-oxaandrost-4-en-3-one (IV). Oxidation of 4,17β-dihydroxyandrosta-1,4-dien-3-one (VI), even in the absence of acid, resulted in the ring cleavage yielding 5ξ,17β-dihydroxy-4-oxaandrost-1-en-3-one (VII). Possible mechanisms for their reactions were discussed.

(Received March 30, 1966)

[Chem. Pharm. Bull. 14(12)1377~1381(1966)]

UDC 547.963.07 : 541.128[546.15]

186. Kin-ichi Imai, Akira Nohara, and Mikio Honjo: Synthesis of Purine Nucleosides Using Iodine as Catalyst.

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The so-called fusion method for the synthesis of purine nucleosides which has been developed by Sato, *et al.*1) involves heating of 1,2,3,5-tetra-O-acyl-D-ribofuranose with various purines in the presence of Lewis acids as catalysts. The method is simple and superior to the conventional method which utilizes heavy metal salts of the bases and halogenosugars to accomplish nucleosides formation.

We have paid our attention to iodine for its catalytic activity in Koenigs-Knorr's reaction2) and the condensation3) of propylene glycol with glucose, and tried this catalyst for the synthesis of nucleosides by the fusion method. This paper deals with a nucleoside synthesis using iodine as a catalyst and detailed studies of the reaction products.

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