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Summary

In order to find antimicrobial agents, the substitution of 3-acetamido-6-alkoxypyridazine 2-oxide was investigated. As the results obtained, it was made clear that a number of 3-acetamido-6-alkoxypyridazine, 3-amino-6-alkoxypyridazine and their 2-oxides having such a substituent group as nitro, amino, hydroxyamino, azo, hydrazo, chloro, methoxy, methylthio, hydroxy, and mercapto at 5-position of the pyridazine rings, were synthesized. This finding is of use to develop the chemistry of pyridazine.

Among these new compounds, 3-acetamido- and 3-amino-5-nitro-6-alkoxypyridazine 2-oxides were found to exert excellent *in vitro* effects on pathogenic bacteria.

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190. Kikuo Yasuda : Oxidation of 3-Enol Derivatives of 4-En-3-oxo-steroids by *tert*-Butyl Chromate.

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Several works¹⁾ on *t*-butyl chromate oxidation of steroids, especially 3 β -acetoxy- and 3-ethylenedioxy- Δ^5 -steroids to the corresponding 7-ones have been carried out, since Oppenauer and Oberrauch²⁾ reported on the oxidation of cholesteryl acetate. There has been, however, no report on *t*-butyl chromate oxidation of 3-enol derivatives of 4-en-3-oxo-steroids, although Fieser obtained 6 β -hydroxycholest-4-en-3-one by sodium dichromate oxidation of cholest-4-en-3-one enol acetate.³⁾ Some observations on *t*-butyl chromate oxidation of such derivatives are described in the present paper.*²

When testosterone enol diacetate (Ia) was oxidized with *t*-butyl chromate in the presence of acetic anhydride, there was obtained the corresponding 7-one (IIa). The structure of IIa was confirmed because the same substance was given by acetylation of 3,17 β -dihydroxyandrosta-3,5-dien-7-one 17-acetate (Va), which was prepared from 3-ethylenedioxy-17 β -acetoxyandrost-5-en-7-one (VIa) by the method of Marshall and his coworkers.⁴⁾ Their assignment of structure (Va) was based upon analogy to 3-hydroxycholesta-3,5-dien-7-one⁵⁾ for which, however, the possibility of another enolic form, 7-hydroxycholesta-4,6-dien-3-one, was suggested. Now this possibility can be evidently excluded from the above-mentioned observation. IIa (UV : $\lambda_{\max}$ 282 m μ) was treated

*¹ 1604, Shimosakunobe, Kawasaki (安田喜久男).

*² Presented in part at the 14th Annual Meeting of the Pharmaceutical Society of Japan (1961).

1) Most recently : E. Menini, J.K. Norymbergsky : Biochem. J., **84**, 195 (1962) (on 3 β -hydroxy-5-enes and 4-en-3-ones).

2) R. V. Oppenauer, H. Oberrauch : Ann. Asoc. Quim. Argentina, **37**, 246 (1949) (C. A., **44**, 3871 (1950)).

3) L. F. Fieser : J. Am. Chem. Soc., **75**, 4377 (1953).

4) C. W. Marshall, R. E. Ray, I. Laos, B. Riegel : Ibid., **79**, 6303 (1957).

5) a) J. Barnett, B. E. Ryman, F. Smith : J. Chem. Soc., **1946**, 526. b) C. W. Greenhalgh, H. B. Henbest, F. R. H. Jones : Ibid., **1952**, 2375.

with aqueous methanolic sulfuric acid to give the corresponding 3-methyl ether (IIIa) (UV : $\lambda_{\max}$ 311 $m\mu$), which was also obtained by treatment of VIa with the same reagent.

Similar transformations of 3-enol acetates of androst-4-ene-3,17-dione (IVb) and 17 α -acetoxyprogesterone (IVc) were performed.

Enol methyl ethers were oxidized under three different conditions as follows; i) at room temperature without acetic anhydride; ii) at 5~10° without acetic anhydride; iii) at a higher temperature (50~60°) in the presence of acetic anhydride. The 3-enol methyl ethers described below were readily prepared by treatment of the corresponding 4-en-3-ones with methyl orthoformate and *p*-toluenesulfonic acid in dioxane. When 3-methoxyandrosta-3,5-diene-17 β -ol acetate (VIIa) was oxidized at room temperature, the main product was 17 β -acetoxyandrost-4-ene-3,6-dione (VIIIa) (accompanied by a small amount of 17 β -acetoxyandrosta-4,6-dien-3-one), and at 5~10°, 6 β ,17 β -dihydroxyandrost-4-en-3-one 17-acetate (IXa) was obtained as the main crystalline product. These compounds were identified by comparison with the authentic samples.^{6,7)} Similar results were obtained in the oxidation of 3-methoxyandrosta-3,5-dien-17-one (VIIb) and 3-methoxy-17 α -acetoxypregna-3,5-dien-20-one (VIIc) at room temperature. On the oxidation of VIIb and VIIc at 5~10°, attempts to obtain the corresponding 6 β -ols crystalline were unsuccessful, but infrared and ultraviolet spectra of the reaction products showed the presence of considerable amounts of 6 β -ols.

6) H. Mori : This Bulletin, 9, 328 (1961).

7) J. Romo, G. Rosenkranz, C. Djerassi, F. Sondheimer : J. Org. Chem., 19, 1509 (1954).

Treatment of VIIa at a higher temperature in the presence of acetic anhydride afforded 17 β -acetoxyandrost-4,6-dien-3-one (Xa). The corresponding 4,6-dien-3-ones, Xb and Xc, were also obtained by similar oxidation of VIIb and VIIc, respectively. The structures of 4,6-dien-3-ones were approved by ultraviolet spectra and comparison with the authentic samples prepared from the corresponding 4-en-3-ones (IV) by chloranil oxidation.⁸⁾

TABLE I. Ultraviolet (in MeOH) and Infrared (in CHCl₃) Absorptions of XI, II and III

Type of A and B ring	XI				II				III			
Type of D ring	$\nu_{\max} \text{ cm}^{-1}$ $7_{\text{C=O}}$ Δ^3 & Δ^5				$\nu_{\max} \text{ cm}^{-1}$ $7_{\text{C=O}}$ Δ^3 & Δ^5				$\nu_{\max} \text{ cm}^{-1}$ $7_{\text{C=O}}$ Δ^3 & Δ^5			
	$\lambda_{\max} \text{ m}\mu$ ($\epsilon \times 10^4$)				$\lambda_{\max} \text{ m}\mu$ ($\epsilon \times 10^4$)				$\lambda_{\max} \text{ m}\mu$ ($\epsilon \times 10^4$)			
a	1651	1594	1623	279	1639	1598	1660 ^{a)}	282	1604	1561 ^{a)}	1648	311
	(2.33)				(2.44)				(2.63)			
b	1650	1594	1624	279	1639	1600	1660 ^{a)}	282	1608	1560 ^{a)}	1642	311
	(2.17)				(2.34)				(2.73)			
c	1655	1598	1626	279	1640	1600	1661 ^{a)}	282	1608	1561 ^{a)}	1650	311
	(2.06)				(2.33)				(2.55)			
Mean	1652	1595	1626	279	1639	1599	1660 ^{a)}	282	1607	1561 ^{a)}	1648	311
	(2.10)				(2.37)				(2.64)			

a) Inflection

8) a) F.J. Agnello, G.D. Laubach : J. Am. Chem. Soc., **79**, 1257 (1957). b) *Idem* : *Ibid.*, **82**, 4293 (1960). c) J.A. Campbell, J.C. Babcock : *Ibid.*, **81**, 4072 (1959). d) H.J. Ringold, E. Batres, A. Bowers, J. Edwards, J. Zderic : *Ibid.*, **81**, 3485. e) H.J. Ringold, J.P. Ruelas, E. Batres, C. Djerassi : *Ibid.*, **81**, 3715.

As 6-chloro- and 6-methyl-17 α -acetoxypregna-4,6-diene-3,20-dione (XVIIa and XVIIb)⁹ possess surprisingly high progestational activities, it is quite important to establish a practical method of preparation. 3-Methoxy-6-chloro-17 α -acetoxypregna-3,5-dien-20-one (XVIa) was obtained from 6 β -chloro- or 6 α -chloro-17 α -acetoxyprogesterone (XIV or XVa) by the same enolmethylation described above. XVIa was also obtained from 17 α -acetoxy-5 α ,6 β -dichloropregnane-3,20-dione (XVIII)^{*3} by one step of similar treatment (under reflux). XVIa was converted into XVIIa by *t*-butyl chromate oxidation in a considerably high yield. 6 α -Methyl-17 α -acetoxyprogesterone (XVb) was similarly transformed into XVIIb *via* the corresponding 3-enol methyl ether (XVib).

It is reported^{5b,11}) that in the ultraviolet absorption of cholesta-3,5-dien-7-one an acetoxy and a methoxy group at C₃ exert a 6 m μ and a 31 m μ shift, respectively. An analogous relationship was observed in the infrared and ultraviolet spectral data of 3-acetoxy-3,5-dien-7-ones (II), 3-methoxy-3,5-dien-7-ones (III) and 3,5-dien-7-ones (XI)^{*4} (Table I and Fig. 1).

Fig. 1. Schematic Infrared Spectra of XI, II and III (in CHCl₃)

— XI
 --- II
 - · - · - III
 a : 7C=O
 b, c : Δ³ and Δ⁵
 * : Inflection

Experimental^{*7}

General Procedures

1) *t*-Butyl Chromate Oxidation at Room Temperature—To a solution of an enol methyl ether (VII) (1 part) in CCl₄ (10 parts) was dropwise added *t*-butyl chromate in CCl₄ solution¹²⁾ (10 parts) with stirring over a period of 10 min. at room temperature. After 2 hr. oxalic acid (3 parts) in H₂O (20 parts) was added to the reaction mixture. After 1 hr. the whole was extracted with CHCl₃ and the extract was washed with H₂O, dried over anhyd. Na₂SO₄, passed through Florisil and evaporated under reduced pressure. The residue was recrystallized from a suitable solvent.

2) *t*-Butyl Chromate Oxidation in the Presence of Acetic Anhydride—A solution of an enol acetate (I) or an enol methyl ether (VII) (1 part) in CCl₄ (30 parts) was heated with *t*-butyl chromate in CCl₄ solution (10 parts) and Ac₂O (1 part) at 50~60° for 4 hr., and then the reaction mixture was treated as described above.

3) Chloranil Oxidation^{8c)}—A solution of a 4-en-3-one (IV) (1 part) in Me₂CO (20 parts) was refluxed with chloranil (1 part) for 2 hr., then concentrated to about 0.1 volume over a period of 1 hr., diluted with Et₂O, washed with 4% NaOH, H₂O, dried over anhyd. Na₂SO₄ and evaporated. The residue was recrystallized from a suitable solvent.

^{*3} Prepared by Dr. J. Yamada, *et al.* in this Laboratory and will be published elsewhere shortly.

^{*4} Prepared by the method of Marshall, *et al.*¹⁰⁾

^{*7} Melting points are uncorrected. Rotations were measured in CHCl₃ and UV spectra in MeOH.

9) A. Zaffaroni : Acta Endocrinologica, Supplementum, 50 (accompanies Vol., 34), 139 (1960).

10) C.W. Marshall, R.E. Ray, I. Laos, B. Riegel : J. Am. Chem. Soc., 79, 6308 (1957).

11) L. Dorfman : Chem. Revs., 53, 80 (1953).

12) K. Heusler, A. Wettstein : Helv. Chim. Acta, 35, 289 (1952).

4) **Hydrolysis with aq. Methanolic Sulfuric Acid**—A solution of a ketal (VI) or an acetate (II) (1 part) in MeOH (100 parts) was gently refluxed with 10% H₂SO₄ (5 parts) for 30 min., then evaporated without further heating to about 0.1 volume under reduced pressure and poured into H₂O. The precipitates were collected, washed with H₂O, dried and subjected to recrystallization and chromatography, suitably combined.

5) **Acetylation of Dienolones (V)**—To a solution of a dienolone (V) (1 part) in pyridine (5 parts) was added Ac₂O (3 parts) at room temperature. After 1 hr. the reaction mixture was poured into H₂O. The precipitates were collected, washed with H₂O, dried and recrystallized from a suitable solvent.

6) **Enolmethylation**—A mixture of a 4-en-3-one (IV, XIV or XV) (1 part), dry dioxane (5 parts), methyl orthoformate (1 part) and *p*-TsOH·H₂O (0.04 part) was stirred for 1 hr. at 50~60°, then cooled to room temperature and diluted with H₂O (about 10 parts) containing pyridine (about 0.5 part). The precipitates were collected after stirring 1 hr., washed with H₂O, dried and recrystallized from a suitable solvent.

3,17β-Diacetoxyandrosta-3,5-dien-7-one (IIa)

a) **From Ia**—The residue resulting from 650 mg. of Ia by procedure (2) (not at 50~60° but under reflux) was recrystallized from MeOH to 190 mg. of IIa, m.p. 217~220°. Repeated recrystallization from the same solvent afforded an analytical sample as colorless fine needles, m.p. 223~225°. $[\alpha]_D^{20} -238^\circ$ (c=0.66), UV: $\lambda_{\max}$ 282 mμ (ε 23,400). *Anal.* Calcd. for C₂₃H₃₀O₅: C, 71.48; H, 7.82. Found: C, 71.61; H, 7.82.

b) **From Va**—25 mg. of Va was treated by procedure 5). Two recrystallizations of the resulting precipitates from MeOH gave 17 mg. of IIa, m.p. 218~221°, which was identical with the acetate obtained above.

3-Acetoxyandrosta-3,5-dien-7,17-dione (IIb)

a) **From 3-Acetoxyandrosta-3,5-dien-17-one (Ib)**—A mixture of androst-4-ene-3,17-dione (IVb) (10 g.), dry benzene (40 ml.), isopropenyl acetate (10 ml.) and *p*-TsOH·H₂O (0.5 g.) was refluxed for 30 min., then evaporated slowly and finally under reduced pressure almost to dryness and diluted with H₂O. The precipitates were collected, washed with 5% Na₂CO₃, H₂O, dried and recrystallized from MeOH (containing a few drops of pyridine) to 8.3 g. of Ib, m.p. 127~131°. Repeated recrystallization from the same solvent furnished an analytical sample as colorless needles, m.p. 130~133°, $[\alpha]_D^{20} -80^\circ$ (c=0.72), UV: $\lambda_{\max}$ 234 mμ (ε 17,500) (in the lit.,¹³⁾ m.p. 127~129°. *Anal.* Calcd. for C₂₁H₂₈O₃: C, 76.79; H, 8.59. Found: C, 76.68; H, 8.63.

1 g. of Ib (m.p. 127~131°) was treated by procedure (2) (under reflux). The resulting residue was chromatographed on Florisil with benzene to 170 mg. of IIb, m.p. 195~205°, from the earlier eluents. Repeated recrystallization from Me₂CO afforded an analytical sample as colorless scales, m.p. 208~211°, $[\alpha]_D^{20} -245^\circ$ (c=0.99), UV: $\lambda_{\max}$ 282 mμ (ε 24,400). *Anal.* Calcd. for C₂₁H₂₆O₄: C, 73.66; H, 7.66. Found: C, 73.62; H, 7.36.

b) **From 3-Hydroxyandrosta-3,5-diene-7,17-dione (Vb)**—The precipitates obtained from 30 mg. of Vb by procedure (5) were recrystallized from Me₂CO to 230 mg. of IIb, m.p. 204~209°, which was identical with the acetate obtained above.

3,17-Diacetoxypregna-3,5-diene-7,20-dione (IIc)

a) **From 3,17α-Diacetoxypregna-3,3-dien-20-one (Ic)**—The residue resulting from 1.7 g. of Ic (m.p. 198~203°) by procedure (2) (under reflux) was recrystallized from Me₂CO to 510 mg. of bulky yellow needles, m.p. 194~203°, UV: $\lambda_{\max}$ 282 mμ (ε 20,000). Two recrystallizations from Me₂CO gave 240 mg. of IIc, m.p. 217~221°. Further recrystallization afforded an analytical sample as colorless thin plates, m.p. 217.5~219°, $[\alpha]_D^{20} -391^\circ$ (c=0.24), UV: $\lambda_{\max}$ 282 mμ (ε 23,300). *Anal.* Calcd. for C₂₅H₃₂O₆: C, 70.07; H, 7.53. Found: C, 70.46; H, 7.34.

130 mg. of Xc (m.p. 219~221°) was obtained from the mother liquors after laborious recrystallization.

b) **From 3,17α-Dihydroxypregna-3,5-diene-7,17-dione 17-Acetate (Vc)**—33 mg. of Vc was treated by procedure (5). The resulting precipitates were recrystallized from Me₂CO to colorless scales, m.p. 217~219°, which were identical with IIc obtained above.

Oxidation of 3-Methoxyandrosta-3,5-dien-17β-ol Acetate (VIIa)

a) **By Procedure (1)**—The residue resulting from 1 g. of VIIa by procedure (1) was recrystallized from Et₂O to 230 mg. of VIIa as yellow prisms, m.p. 195~200°, which was identical with an authentic sample.⁶⁾ Chromatography of the mother liquors on Florisil afforded a small amount of Xa, m.p. 137~142° (from MeOH), from the earlier eluents with benzene-hexane (1:1).

b) **By Procedure (1) at 5~10°**—1 g. of VIIa was treated by procedure (1) not at room temperature but at 5~10°. Recrystallization of the resulting residue from Me₂CO-hexane gave 200 mg. of IXa as colorless needles, m.p. 204~207°. One more recrystallization from Me₂CO furnished an analytical

13) L. Ruzicka, W.H. Fiescher: *Helv. Chim. Acta*, **19**, 1371 (1936).

sample, UV : $\lambda_{\max}$ 234 $m\mu$ (ϵ 16,100), which was identical with an authentic sample prepared from Ia by the method of Romo, *et al.*⁷⁾

c) **By Procedure (2)**—The residue resulting from 1 g. of VIIa by procedure (2) was recrystallized from MeOH to 250 mg. of Xa as colorless needles, m.p. 135~137°, UV : $\lambda_{\max}$ 283 $m\mu$ (ϵ 24,100), which was identical with an authentic sample prepared from testosterone acetate (IVa) by procedure (3).

Oxidation of 3-Methoxyandrosta-3,5-dien-17-one (VIIb)

a) **By Procedure (1)**—The residue resulting from 1 g. of VIIb by procedure (1) was recrystallized from MeOH to 311 mg. of androst-4-ene-3,6,17-trione (VIIIb) as yellow prisms, m.p. 206~212°. Two recrystallizations from the same solvent afforded an analytical sample, m.p. 218~220°, UV : $\lambda_{\max}$ 252 $m\mu$ (ϵ 10,000), which was identical with an authentic sample.¹⁴⁾ Chromatography of the mother liquors on Florisil with benzene gave a small amount of androsta-4,6-diene-3,17-dione (Xb), but attempts to detect 6 β -hydroxyandrost-4-ene-3,17-dione (IXb) were unsuccessful.

b) **By Procedure (2)**—The residue resulting from 1 g. of VIIb by procedure (2) was recrystallized from MeOH to 190 mg. of Xb, m.p. 166~171°. One more recrystallization from MeOH gave an analytical sample as colorless prisms, m.p. 169~173°, UV : $\lambda_{\max}$ 284 $m\mu$ (ϵ 25,400), which was identical with a sample prepared from androst-4-ene-3,17-dione (IVb) by procedure (3).

Oxidation of 3-Methoxy-17 α -acetoxypregna-3,5-dien-20-one (VIIc)

a) **By Procedure (1)**—The residue resulting from 1 g. of VIIc by procedure (1) was recrystallized from MeOH to 210 mg. of 17 α -acetoxypregn-4-ene-3,6,20-trione (VIIIc) as slightly yellow needles, m.p. 211~215°, which was identical with an authentic sample.⁹⁾

b) **By Procedure (2) under Reflux**—1 g. of VIIc was treated by procedure (2) not at 50~60° but under reflux. Recrystallization of the resulting residue from MeOH gave 260 mg. of Xc, m.p. 208~214°. Repeated recrystallization from the same solvent furnished an analytical sample as colorless prisms, m.p. 220.5~221.5°, $[\alpha]_D^{25} + 12^\circ$ ($c=1.00$), UV : $\lambda_{\max}$ 282~284 $m\mu$ (ϵ 23,400). *Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.27; H, 8.14.

Chloranil Oxidation of IVc—The residue resulting from 5 g. of IVc by procedure (3) was recrystallized from MeOH to 2.4 g. of Xc as slightly yellow prisms, m.p. 214~218°, which was identical with the dienone obtained above.

17 α -Acetoxy-6-chloropregna-4,6-diene-3,20-dione (XVIIa)—5 g. of XVIa was treated by procedure (2) (9 hr. reflux). The resulting residue was stirred with Et_2O (15 ml.) for 1 hr. The precipitates were collected, washed with Et_2O and recrystallized from Me_2CO to 2.1 g. of XVIIa as pale yellow prisms, m.p. 206~209°, UV : $\lambda_{\max}$ 286 $m\mu$ (ϵ 23,500), which was identical with an authentic sample prepared from XVIa by chloranil oxidation in $EtOAc$ with $AcOH$.^{*8,8d)}

6-Methyl-17 α -acetoxypregna-4,6-diene-3,20-dione (XVIIb)—2.5 g. of XVIb was treated by procedure (2) (4.5 hr. reflux). The resulting residue was recrystallized from Me_2CO -hexane to 630 mg. of XVIIb, m.p. 207~212°. Repeated recrystallization gave an analytical sample as colorless cubes, m.p. 215~217°, UV : $\lambda_{\max}$ 288 $m\mu$ (ϵ 21,900), which was identical with an authentic sample prepared from XVIb by chloranil oxidation with $AcOH$.^{8e)}

3-Methoxy-17 β -acetoxyandrosta-3,5-dien-7-one (IIIa)

a) **From VIa**—Recrystallization of the precipitates resulting from 50 mg. of VIa⁴⁾ by procedure (4) gave 15 mg. of IIIa, m.p. 257~260°. Repeated recrystallization from MeOH- Me_2CO afforded an analytical sample as colorless needles, m.p. 263~266°, $[\alpha]_D^{20} - 320^\circ$ ($c=0.50$), UV : $\lambda_{\max}$ 311 $m\mu$ (ϵ 27,300). *Anal.* Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.80; H, 8.06.

b) **From IIa**—The precipitates resulting from 100 mg. of IIa by procedure (4) were recrystallized from MeOH- Me_2CO to 43 mg. of IIIa, m.p. 256~261°, which was identical with the Me_2O obtained above.

3-Methoxyandrosta-3,5-diene-7,17-dione (IIIb)

a) **From 3-Ethylenedioxyandrost-5-ene-7,17-dione (VIb)**—5 g. of 3-ethylenedioxyandrost-4-en-17 β -ol (XIII) was treated by procedure (2). Recrystallization of the resulting residue from Me_2CO gave 3.1 g. of VIb, m.p. 173~183°. Repeated recrystallization from the same solvent afforded an analytical sample as colorless cubes, m.p. 187~189°, $[\alpha]_D^{20} - 16^\circ$ ($c=1.02$), UV : $\lambda_{\max}$ 241 $m\mu$ (ϵ 13,800). *Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.41; H, 8.53.

*⁸ The method of Ringold, *et al.* resulted in a very low yield and attempts to raise the yield were all in vain. Although Agnello and Laubach reported^{8b)} that an enol ether was oxidized more rapidly than the corresponding 4-en-3-one with chloranil, no significant difference was observed in this case.

14) A. Butenandt, B. Riegel: *Ber.*, **69**, 1163 (1936); K. Tsuda, H. Iizuka, Y. Sato, M. Naito: *This Bulletin*, **9**, 925 (1961).

500 mg. of VIb (m.p. 173~183°) was treated by procedure (4). The resulting precipitates were chromatographed on Florisil with benzene to 230 mg. of IIIb, m.p. 202~205°, from the later eluents. Repeated recrystallization from Me₂CO furnished an analytical sample as needles, m.p. 206~207°, UV: $\lambda_{\max}$ 311 m μ (ϵ 26,300), which was identical with an authentic sample.¹⁵⁾ *Anal.* Calcd. for C₂₀H₂₈O₃: C, 76.40; H, 8.34. Found: C, 76.03; H, 8.42.

b) **From IIb**—The precipitates resulting from IIb (50 mg.) by procedure (4) were recrystallized from MeOH to 200 mg. of IIIb, m.p. 205~207°, which was identical with the Me₂O obtained above.

3-Methoxy-17 α -acetoxypregna-3,5-diene-7,20-dione (IIIc)

a) **From 3-Ethylenedioxy-17 α -acetoxypregn-5-ene-7,20-dione (VIc)**—The precipitates resulting from VIc⁴⁾ (300 mg.) by procedure (4) were recrystallized from MeOH to 70 mg. of IIIc, m.p. 249~253°. Two recrystallizations from the same solvent gave an analytical sample as colorless needles, m.p. 252~254°, $[\alpha]_D^{20}$ -357° (c =0.61), UV: $\lambda_{\max}$ 311 m μ (ϵ 25,500). *Anal.* Calcd. for C₂₄H₃₂O₅: C, 71.97; H, 8.05. Found: C, 71.70; H, 7.59.

b) **From IIc**—IIc (50 mg.) was treated by procedure (4). Recrystallization of the resulting precipitates from MeOH gave 17 mg. of IIIc, m.p. 246~251°, which was identical with the Me₂O obtained above.

3-Methoxy-6-chloro-17 α -acetoxypregna-3,5-dien-20-one (XVIa)

a) **From XIV**—A mixture of VII (10 g.), Me₂CO (300 ml.), NaOAc (2 g.) and H₂O (10 ml.) was stirred with NCS (5.5 g., 1.5 mol. equivalent as 100% NCS) at room temperature for 1 hr., and poured into H₂O. The precipitates were collected, washed with H₂O, dried and recrystallized from Me₂CO-hexane to 8.9 g. of crude XIV,^{8d)} m.p. 211~214°.

5 g. of the crude XIV was treated by procedure (6). The resulting precipitates were recrystallized from Me₂CO (containing a few drops of pyridine) to 4.7 g. of XVIa, m.p. 225° (decomp.). Repeated recrystallization from the same solvent afforded an analytical sample as colorless scales, m.p. 232~233° (decomp.), $[\alpha]_D^{28}$ -127° (c =1.65), UV: $\lambda_{\max}$ 251 m μ (ϵ 22,700). *Anal.* Calcd. for C₂₄H₃₃O₄Cl: C, 68.47; H, 7.90. Found: C, 68.55; H, 7.98.

XVa^{8d)} was also converted into XVIa in similar yield by procedure (6).

b) **From XVIII**—A mixture of XVIII³⁾ (m.p. 171~173° (decomp.)) (1 g.), dry dioxane (10 ml.), methyl orthoformate (1 ml.) and *p*-TsOH·H₂O (40 mg.) was refluxed for 1 hr., then cooled to room temperature and poured into H₂O (100 ml., containing 0.5 ml. of pyridine). The precipitates were treated as described above to give 710 mg. of XVIa, m.p. 223° (decomp.), which was identical with the Me₂O obtained above.

Enolmethylations of other 4-en-3-ones, IVa, IVb, IVc and XVb, were listed in Table II.

TABLE II. Enolmethylations of 4-En-3-ones by Procedure (6)

Starting material	Recryst. solvent ^{a)}	Yield of VII	Physic. const. ^{b)} of anal. sample	Analysis		
IVa (10 g.)	Et ₂ O-MeOH	8.8 g. m.p. 173~178°	m.p. 176~180°, $[\alpha]_D^{21}$ -152° (c =1.00) UV: $\lambda_{\max}$ 238 m μ (ϵ 22,800)	Cald. for C ₂₂ H ₃₂ O ₃	C	H
				Found	76.70	9.36
					76.16	9.09
IVb (10 g.)	MeOH	6.3 g. m.p. 161~171°	m.p. 170~174°, $[\alpha]_D^{21}$ -89° (c =1.00) UV: $\lambda_{\max}$ 238 m μ (ϵ 24,000)	Cald. for C ₂₀ H ₂₈ O ₂	C	H
				Found	79.95	9.30
					79.97	9.48
IVc (10 g.)	"	8.5 g. m.p. 190~194°	m.p. 195~198°, $[\alpha]_D^{21}$ -151° (c =1.00) UV: $\lambda_{\max}$ 238 m μ (ϵ 23,200)	Cald. for C ₂₄ H ₃₄ O ₄	C	H
				Found	74.37	8.87
					74.58	8.81
XVb (1.5 g.)	"	1.3 g. m.p. 205~220°	m.p. 217~222°, $[\alpha]_D^{28}$ -176° (c =0.39) UV: $\lambda_{\max}$ 249 m μ (ϵ 18,300)	Cald. for C ₂₅ H ₃₆ O ₄	C	H
				Found	74.96	9.06
					74.71	9.24

a) Containing a few drops of pyridine.

b) Rotations were measured in CHCl₃ containing pyridine⁹⁾ (2 drops/10 ml.).

c) In the most recent lit.,^{d)} m.p. 195~198°, $[\alpha]_D^{25}$ -135° (1% pyridine in CHCl₃), UV: $\lambda_{\max}$ 239 m μ (ϵ 21,000).

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Summary

3-Enol acetates of some 4-en-3-oxo-steroids were oxidized to the corresponding 7-ones with *t*-butyl chromate and 3-enol methyl ethers were to the corresponding 4-ene-3,6-diones, 6 β -hydroxy-4-en-3-ones or 4,6-dien-3-ones according to the reaction conditions. 3-Enol methyl ethers were prepared with methyl orthoformate in dioxane by catalysis of *p*-toluenesulfonic acid. 17 α -Acetoxy-5 α ,6 β -dichloropregnane-3,20-dione was converted into 3-methoxy-6-chloro-17 α -acetoxypregna-3,5-dien-20-one in one step.

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191. Shoji Shibata,^{*1} Akihiro Ohta,^{*2} and Yukio Ogihara^{*1} : Metabolic Products of Fungi. XXI.^{*3} On Ustilaginoidins. (1).^{*4}
The Reactions of Ustilaginoidin A.

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An optically active red coloring matter named ustilaginoidin was isolated from the false smutted ball (*Ustilagoidea virens* (COOKE) TAKAHASHI¹⁾) growing parasitically on spike of rice plant (in Japanese—Inekoji (稲麴)).

Yabuta and Sumiki and their coworkers²⁾ proposed a molecular formula, C₁₉H₁₆O₇, for ustilaginoidin and assumed that it belongs to the anthraquinone pigment mainly on the basis of obtaining anthracene on zinc dust distillation. However, the earlier study of ustilaginoidin was interrupted without providing further evidences for the structure.

In relation to some other studies on the fungal anthraquinones we realized a fact that ustilaginoidin gave no characteristic color reactions of hydroxyanthraquinone, which prompted us to reexamine its chemical structure.

The acetone extracts of the false smutted ball (*Ustilagoidea virens*) collected from the infected rice spikes were separated by CaHPO₄-column chromatography to give three bands. The lowest band which consisted the main portion of the extracts was eluted and recrystallized from dioxan to give a red pigment m.p. >300°, [α]_D -384°, which would correspond to ustilaginoidin of earlier workers and now has been designated ustilaginoidin.

Ustilaginoidin A recrystallized from dioxan gave analytical figures and molecular weight (determined by X-ray crystallographical method) consistent with C₂₈H₁₈O₁₀·2C₄H₈O₂, which lost dioxan on drying at 180° *in vacuo*. It is slightly soluble in bicarbonate solution and soluble in carbonate to form a solution. It gives a red color in conc. H₂SO₄, which turns into green on heating. It shows a green color with FeCl₃ and no remarkable coloration with magnesium acetate in alcohol.

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