

[Chem. Pharm. Bull.]
14(3) 301~303 (1966)

UDC 547.91.07 : 547.292-38 : 546.819

Hiroshi Mitsuhashi, Kazunori Shibata, and Namio Uehara :
Lead Tetraacetate Cleavage of 20-Hydroxyspirostan.(Faculty of Pharmaceutical Sciences, Hokkaido University*¹)

Marker, Wagner, and co-workers¹⁾ oxidized hecogenin with chromic acid in acetic acid and isolated a supposed "5 α -pregn-16-ene-3,12,20-trione hydrate." Wall and Walens²⁾ oxidized cyclopseudosapogenins with chromic acid and also isolated a similar product. Subsequently, Callow and James³⁾ characterized the substance prepared from hecogenin as a 3,12-dion-20-ol (20-hydroxyspirostan) by preparing the same product from pseudohecogenin with peracid. It is suspected that the spiroketal side chain of sapogenins, generally, prefer an open chain configuration in acid medium as shown in Chart 1-A, and this possibility is observed in the bromination at position 23, the Clemmensen reduction of 22-carbonyl group,¹⁾ and the Baeyer-Villiger oxidation of spiroketal side chain.⁴⁾ According, it appears that 20-hydroxyspirostan also assume an α -ketol configuration under the same conditions as shown in Chart 1-B.

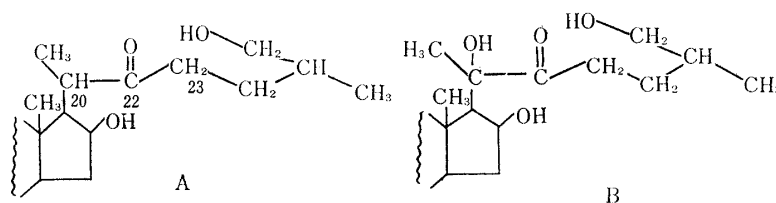


Chart 1.

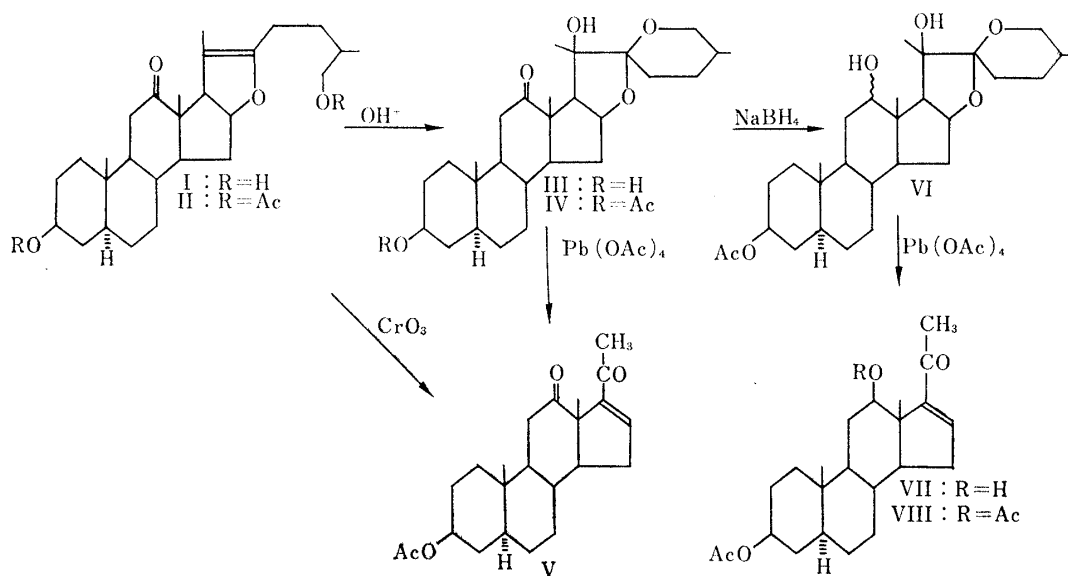


Chart 2.

*¹ Nishi 7-Chome, Kita-15-jo, Sapporo (三橋 博, 柴田和則, 上原南男).

- 1) R.E. Marker, R.B. Wagner, P.R. Ulshafer, E.L. Wittbecker, D.P.J. Goldsmith, C. H. Ruof : J. Am. Chem. Soc., **69**, 2167 (1947).
- 2) M.E. Wall, H.A. Walens : *Ibid.*, **77**, 5661 (1955); **80**, 1984 (1958).
- 3) R.K. Callow, V.H.T. James : Chem. & Ind.(London), **1956**, 112.
- 4) R.E. Marker, E. Rohrmann, H.M. Crooks, E.L. Wittle, E.M. Jones, D.L. Turner : J. Am. Chem. Soc., **62**, 525 (1940).

If this is correct, it seemed reasonable that a 20-hydroxyspirostan would be cleaved by lead tetraacetate and this method would be suitable for degradation of a spirostan to a pregnane without protection of other functional groups. Pseudohecogenin (I) was treated with monoperphthalic acid in dioxane-ether for a week to give the 20-hydroxyspirostan (III) in 73% yield. These compounds (III, IV, V) are rather difficult to purify and wide melting points have been observed.³⁾ The acetate (IV) of III was heated with a small excess of lead tetraacetate in 90% AcOH at 60° for 2 hr., and the product 3 β -acetoxy-5 α -pregn-16-ene-12,20-dione (V), was separated by chromatography, and was identical with an authentic sample prepared from pseudohecogenin diacetate (II) by chromic acid oxidation.⁵⁾ Reduction of IV with sodium borohydride gave the 12,20-dihydroxyspirostan (VI) in 80~90% yields, which was oxidized with lead tetraacetate in the same manner as described above, and the product (40~50% yields) m.p. 220~224.5° (Kofler), crystallized from ether, was shown by UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (ϵ): 243 (8,900) and IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3400 (OH), 1740, 1245 (acetate), 1640 (conjugated C=O), 1585 (conjugated C=C) to be 3 β -acetoxy-12 β -hydroxy-5 α -pregn-16-en-20-one (VII). The diacetate (VIII) of VII was identical with 3 β ,12 β -diacetoxy-5 α -pregn-16-en-20-one prepared from pseudo-rockogenin triacetate.⁶⁾

Experimental

Monoperphthalic Acid Oxidation of Pseudohecogenin (I) to 3 β ,20-Dihydroxy-5 α -spirostan-12-one (III)

Pseudohecogenin (5 g.) in dioxane (150 ml.) was treated with ethereal monoperphthalic acid (ca. 1.2 moles) at room temperature for a week. Water was added and the precipitated crystalline product was filtered off, washed with H₂O, and dried. This product was crystallized from CH₂Cl₂-EtOAc, giving 3.7 g. of a white needles, m.p. 215~220°. An analytical sample was crystallized from CH₂Cl₂-EtOAc, m.p. 238~242°, $[\alpha]_D^{25} +11.1^\circ$ (c=1.08; EtOH). *Anal.* Calcd. for C₂₇H₄₂O₅: C, 72.61; H, 9.48. Found: C, 72.85; H, 9.25. The 3-acetate (IV) was obtained by treating III with equal volumes of pyridine and Ac₂O at 100° for 0.5 hr., and crystallized from MeOH, m.p. 254~259°, $[\alpha]_D^{25} -9.15^\circ$ (c=1.42; CHCl₃). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3560 (OH), 1745, 1250 (acetate). *Anal.* Calcd. for C₂₉H₄₄O₆: C, 71.28; H, 9.08. Found: C, 71.41; H, 9.14.

Lead Tetraacetate Oxidation of Acetate (IV) to 3 β -Acetoxy-5 α -pregn-16-ene-12,20-dione (V)—20-Hydroxy-5 α -spirostan-12-one 3-acetate (1 g.) was dissolved in a solution containing Pb(OAc)₄ (1.18 g.; 30% excess) in 90% AcOH (20 ml.). The solution was heated at 60° for 2 hr. and then treated with ethylene glycol to destroy the excess Pb(OAc)₄. The organic phase was distilled off and the residue was extracted with CH₂Cl₂. The extract was washed with d. NaHCO₃ and H₂O, dried over anhyd. Na₂SO₄ and evaporated. The residue was crystallized from ether to give white needles (0.3 g.), m.p. 293.5~297.5°, IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3560 (OH), 1740, 1240 (acetate), 1700 (C=O). Analytical sample, recrystallized from MeOH, had m.p. 292~293.5°, $[\alpha]_D^{25} -22.5^\circ$ (c=1.15; CHCl₃). *Anal.* Calcd. for C₃₁H₄₆O₈: C, 68.10; H, 8.48. Found: C, 68.28; H, 8.15. This substance appears to be an 11-acetoxylated spirostan. The residue from the mother liquors (0.47 g.) was chromatographed on Al₂O₃ (15 g.). Benzene-EtOAc (8:2) fraction gave 100 mg. (13%) 3 β -acetoxy-5 α -pregn-16-ene-12,20-dione (V), m.p. 170~175°; after crystallization from ether m.p. 177~178°; identical with a sample prepared by direct oxidation of pseudohecogenin diacetate (II) by thin-layer chromatography and mixed melting point.

Borohydride Reduction of 3 β ,20-Dihydroxy-5 α -spirostan-12-one 3-Acetate (IV) to 12,20-Diol 3-Acetate (VI)—A solution of 3 β ,20-dihydroxy-5 α -spirostan-12-one 3-acetate (8 g.) in dioxane (200 ml.) and CH₃CN (200 ml.) was treated with NaBH₄ (3 g.) in 50%-CH₃CN (30 ml.) at room temperature for 72 hr. The excess reagent was destroyed with AcOH and H₂O was added. The precipitated crystals were filtrated, washed with much H₂O, dried, and recrystallized from CH₂Cl₂-MeOH to give a white needles (6.8 g., 85%), m.p. 233~236°, $[\alpha]_D^{25} -53.8^\circ$ (c=1.15; EtOH), IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3400 (broad; OH), 1740, 1240 (acetate), no carbonyl absorption. *Anal.* Calcd. for C₂₉H₄₆O₆: C, 70.98; H, 9.45. Found: C, 71.04; H, 9.55.

Lead Tetraacetate Oxidation^{*2} of 12,20-Diol (VI) to 3 β ,12 β -Dihydroxy-5 α -pregn-16-en-20-one 3-acetate (VII)—Lead tetraacetate (1.01 g., 98% purity, 10% excess) was added under stirring to a solution

^{*2} Lead tetraacetate was dried over KOH and P₂O₅ *in vacuo*, and titrated by idometry.

5) A. F. B. Cameron, R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, A. G. Long: *J. Chem. Soc.*, 1955, 2807.

6) R. Tschesche, G. Brugmann, H. W. Marquardt, H. Machleidt: *Ann.*, 648, 185 (1961).

of 5 α -spirostane-3 β ,12,20-triol 3-acetate. The reaction mixture was maintained at 60~65° for 2 hr., and solvent then removed under reduced pressure. The residue was extracted with CH₂Cl₂, washed with d. NaHCO₃ and dried. The organic phase was distilled and the residue crystallized from ether to give white needles (0.34 g., 43%), m.p. 217~219°. An analytical sample, recrystallized from MeOH, had m.p. 220~224.5°, $[\alpha]_D^{20} \pm 0^\circ$ (c=0.9, EtOH). *Anal.* Calcd. for C₂₃H₃₄O₄: C, 73.76; H, 9.15. Found: C, 73.59; H, 8.91.

Acetylation to 3 β ,12 β -Diacetate—The 12 β -Hydroxyl group of Compound (VI) is considerably resistant to acylation. A solution of 12 β -hydroxy compound (VI) in equal volumes of pyridine and Ac₂O was heated on boiling water bath for 16 hr., but the yield of diacetate were ca. 50% and less. White needles from MeOH, m.p. 134~137°, identical with an authentic sample prepared from pseudorockogenin diacetate. *Anal.* Calcd. for C₂₅H₃₆O₅: C, 72.08; H, 8.71. Found: C, 72.24; H, 8.93.

(Received August 2, 1965)

[Chem. Pharm. Bull.
14(3) 303~306 (1966)]

UDC 547.852.2.07

Shigeru Sako^{*1}: Syntheses of Pyridazine Derivatives. IV.^{*2} Halogenopyridazine 1-Oxides.

(National Institute of Hygienic Sciences^{*3})

In part II¹⁾ and III^{*2} of this series, it was shown that the amino groups of 6-amino-pyridazine 1-oxide and 4-amino-3,6-dimethylpyridazine 1-oxide were changed to chlorine by Gattermann reaction. The present paper describes the displacement of the amino groups on 3-, 4-, 5-, and 6-positions of pyridazine 1-oxide by diazotization and the preparation of several halogenopyridazine 1-oxides.

Oxidation of 5-amino-3,4-dichloropyridazine²⁾ (m.p. 178°) (I) with an ethereal solution of monoperphthalic acid gave 77% of its N-oxide (II). II was also obtained by hydrogen peroxide-glacial acetic acid oxidation in a poor yield. II was dehalogenated to 5-amino-pyridazine N-oxide (IIIc) by catalytic hydrogenation over palladium-charcoal. Diazotization of IIIc in hydrochloric acid gave 5-chloropyridazine N-oxide (IV). The chlorine of IV was displaced to a methoxy group by sodium methoxide and this methoxy derivative was identical with 5-methoxypyridazine 1-oxide prepared by Natsume.³⁾ Thus, it became clear that II, IIIc, and IV were 5-amino-3,4-dichloropyridazine 1-oxide, 5-amino-pyridazine 1-oxide, and 5-chloropyridazine 1-oxide, respectively.

When 4-amino-3,5-dichloropyridazine²⁾ (m.p. 151°) (V) was oxidized in ether with monoperphthalic acid, its N-oxide (VI) was obtained, in 43% yield. Treatment of VI in hydrochloric acid with sodium nitrite gave trichloropyridazine 1-oxide, which was identical with 3,4,5-trichloropyridazine 1-oxide (VII) prepared from II by the same method. Accordingly, VI was 4-amino-3,5-dichloropyridazine 1-oxide.

3-, 4-, 5-, and 6-bromopyridazine 1-oxides (VIIIa, VIIIb, VIIIc, and VIId) were prepared by diazotization of corresponding aminopyridazine 1-oxides (III) in hydrobromic acid, in 8%, 63% (Gattermann reaction), 40%, and 22% yield, respectively. 4-Bromopyridazine 1-oxide (VIIIb) was easily prepared by heating 4-nitropyridazine 1-oxide⁴⁾ (K) with hydrobromic acid.

^{*1} Present address: Ukima Plant, Chūgai Pharmaceutical Co., Ltd., Ukima, Kita-ku, Tokyo.

^{*2} Part III. S. Sako: This Bulletin, 11, 337 (1963).

^{*3} Tamagawa-yoga-machi, Setagaya-ku, Tokyo (佐子 茂).

1) S. Sako: This Bulletin, 11, 261 (1963).

2) T. Kuraishi: *Ibid.*, 4, 497 (1956); *Idem*: *Ibid.*, 6, 641 (1958).

3) T. Itai, S. Natsume: This Bulletin, 10, 643 (1962).

4) *Idem*: *Ibid.*, 11, 83 (1963).