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Hiroshi Mitsuhashi, Kazunori Shibata, and Namio Uehara : Lead Tetraacetate Cleavage of 20-Hydroxyspirostans.

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Marker, Wagner, and co-workers[1] oxidized hecogenin with chromic acid in acetic acid and isolated a supposed "5α-pregn-16-ene-3,12,20-trione hydrate." Wall and Walens[2] oxidized cyclopseudosapogenins with chromic acid and also isolated a similar product. Subsequently, Callow and James[3] 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 it 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.

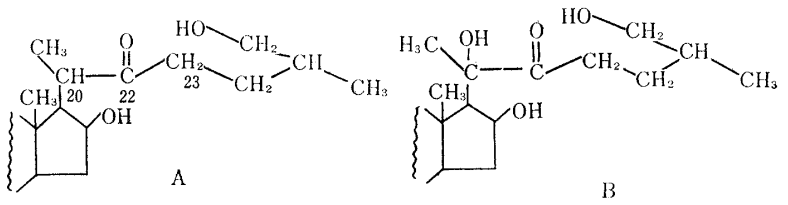

Chart 1.

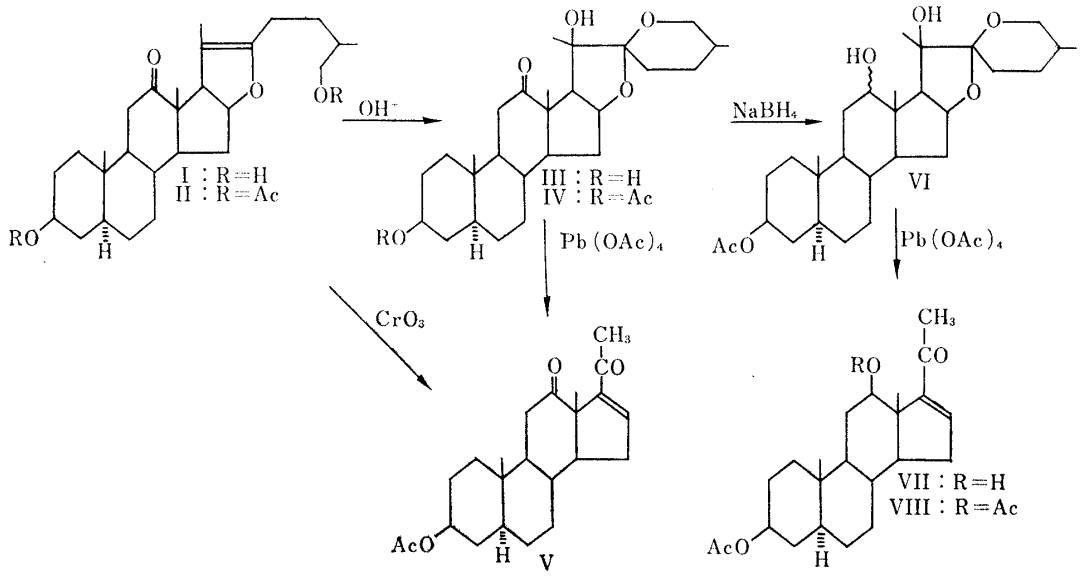

Chart 2.

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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, VI) 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 3β-acetoxy-5α-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-dihydroxyspirostane (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 λ_{max}^{EtOH} mμ (ε): 243 (8,900) and IR ν_{max}^{Nujol} cm^{-1}: 3400 (OH), 1740, 1245 (acetate), 1640 (conjugated C=O), 1585 (conjugated C=C) to be 3β-acetoxy-12β-hydroxy-5α-pregn-16-en-20-one (VII). The diacetate (VIII) of VII was identical with 3β,12β-diacetoxy-5α-pregn-16-en-20-one prepared from pseudorockogenin triacetate.[6]

Experimental

Monoperphthalic Acid Oxidation of Pseudohecogenin (I) to 3β,20-Dihydroxy-5α-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 H_2O, and dried. This product was crystallized from CH_2Cl_2-EtOAc, giving 3.7 g. of a white needles, m.p. 215~220°. An analytical sample was crystallized from CH_2Cl_2-EtOAc, m.p. 238~242°, $[\alpha]_D$ +11.1°(c=1.08; EtOH). *Anal.* Calcd. for $C_{27}H_{42}O_5$: 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 Ac_2O at 100° for 0.5 hr., and crystallized from MeOH, m.p. 254~259°, $[\alpha]_D$ −9.15 (c=1.42; $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3560 (OH), 1745, 1250 (acetate). *Anal.* Calcd. for $C_{29}H_{44}O_6$: C, 71.28; H, 9.08. Found: C, 71.41; H, 9.14.

Lead Tetraacetate Oxidation of Acetate (IV) to 3β-Acetoxy-5α-pregn-16-ene-12,20-dione (V)——20-Hydroxy-5α-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 CH_2Cl_2. The extract was washed with d. $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was crystallized from ether to give white needles (0.3 g.), m.p. 293.5~297.5°, IR ν_{max}^{Nujol} cm^{-1}: 3560 (OH), 1740, 1240 (acetate), 1700 (C=O). Analytical sample, recrystallized from MeOH, had m.p. 292~293.5°, $[\alpha]_D$ −22.5°(c=1.15; $CHCl_3$). *Anal.* Calcd for $C_{31}H_{46}O_8$: 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 Al_2O_3 (15 g.). Benzene-EtOAc (8:2) fraction gave 100 mg. (13%) 3β-acetoxy-5α-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 3β,20-Dihydroxy-5α-spirostan-12-one 3-Acetate (IV) to 12,20-Diol 3-Acetate (VI)——A solution of 3β,20-dihydroxy-5α-spirostan-12-one 3-acetate (8 g.) in dioxane (200 ml.) and CH_3CN (200 ml.) was treated with $NaBH_4$ (3 g.) in 50%-CH_3CN (30 ml.) at room temperature for 72 hr. The excess reagent was destroyed with AcOH and H_2O was added. The precipitated crystals were filtrated, washed with much H_2O, dried, and recrystallized from CH_2Cl_2-MeOH to give a white needles (6.8 g., 85%), m.p. 233~236°, $[\alpha]_D$ −53.8°(c=1.15; EtOH), IR ν_{max}^{Nujol} cm^{-1}: 3400 (broad; OH), 1740, 1240 (acetate), no carbonyl absorption. *Anal.* Calcd. for $C_{29}H_{46}O_6$: C, 70.98; H, 9.45. Found: C, 71.04; H, 9.55.

Lead Tetraacetate Oxidation[*2] **of 12,20-Diol (VI) to 3β,12β-Dihydroxy-5α-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 P_2O_5 *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 5α-spirostane-3β,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 CH_2Cl_2, washed with d. $NaHCO_3$ 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°, $[\alpha]_D$ ±0°(c=0.9, EtOH). *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found : C, 73.59; H, 8.91.

Acetylation to 3β,12β-Diacetate——The 12β-Hydroxyl group of Compound (Ⅶ) is considerably resistant to acylation. A solution of 12β-hydroxy compound (Ⅶ) in equal volumes of pyridine and Ac_2O 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 $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found : C, 72.24; H, 8.93.

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

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In part Ⅱ[1] and Ⅲ*2 of this series, it was shown that the amino groups of 6-aminopyridazine 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-dichloropyridazine[2] (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-aminopyridazine N-oxide (Ⅲc) by catalitic 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-aminopyridazine 1-oxide, and 5-chloropyridazine 1-oxide, respectively.

When 4-amino-3,5-dichloropyridazine[2] (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 Ⅷd) 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-oxide[4] (Ⅸ) with hydrobromic acid.

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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).