authentic 4-methoxypyridazine hydrochloride[13] by mixed melting points and by comparison of IR spectra.

Free base, m.p. 42~44° was obtained by passing the above hydrochloride in MeOH through Amberlite IRA 410 (OH^-). No m.p. depression was observed on admixture with authentic 4-methoxypyridazine.[13]

Picrate : m.p. 143~144°(from MeOH). *Anal.* Calcd. for $C_6H_6ON_2 \cdot C_6H_3O_7N_3$: C, 38.95; H, 2.67; N, 20.65. Found : C, 39.10; H, 2.66; N, 21.10.

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Summary

Pyridazine 1-oxide (I) was nitrated to 4-nitropyridazine 1-oxide (II) with a mixed acid under a vigorous condition. The structure of II was confirmed as follows. i) Hydrogenation of II itself and methoxypyridazine 1-oxide (VI), derived from II, gave the known 4-aminopyridazine and 4-methoxypyridazine, respectively. ii) Pyridazinol 1-oxide obtained by hydrolysis of VI formed N-methoxypyridazinone with methyl *p*-toluenesulfonate and sodium methoxide. iii) VI was identical with the compound obtained by hydrogenation of 4-methoxy-3,6-dicholoropyridazine 1-oxide, whose structure was established by its correlation to the known 3,4,6-trimethoxypyridazine 1-oxide. In addition, some reactions related to II were described.

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18. Katsura Morita, Shunsaku Noguchi, Hiroshi Kono, and Takuichi Miki : Synthesis of Polyhydroxysteroids. I. A Modified Degradation of the Diosgenin Side Chain.*1

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Side chain degradation of steroidal sapogenins has been carried out by Marker's method,[1,2] which involves transformation of sapogenins into pseudosapogenin acetates and subsequent chromic anhydride oxidation followed by hydrolysis to give pregnenolones. Owing to various improvements later performed by other investigators[3~5] the production yields of 3β-hydroxypregna-5,16-dien-20-one from diosgenin, for instance, are reported to be above 60%.

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*1 This paper constitutes Part XXV of Takeda Laboratories' series entitled "Steroids," which is continued from Nishikawa's "Steroids"; Part XXIV : Yakugaku Zasshi, **81**, 385 (1961).

*2 Juso-nishino-cho, Higashiyodogawa-ku, Osaka (森田 桂, 野口俊作, 河野 海, 三木卓一).

1) R.E. Marker, E. Rohrmann : J. Am. Chem. Soc., **61**, 3592 (1939); **62**, 518 (1940).
2) R.E. Marker, R.B. Wagner, P.R. Ulshafer, E.L. Wittbecker, D.P.J. Goldsmith, C.H. Ruof : *Ibid.*, **69**, 2167 (1947).
3) D.H. Gould, H. Staeudle, E.B. Hershberg : *Ibid.*, **74**, 3685 (1952).
4) W.G. Dauben, G.J. Fonken : *Ibid.*, **76**, 4618 (1952).
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.

In another route of degradation, which was also described by Marker *et al.*, sarsasapogenin was treated with peracetic acid and the resulting oxidation product was hydrolyzed with alkali to yield 5β-pregnane-3β,16β,20α-triol.[6]

This latter method, however, had not been applied to diosgenin, until Nawa*[3] found that diosgenin on treatment with performic acid followed by hydrolysis of the oxidation product gave rise to 5α-pregnane-3β,5,6β,16β,20α-pentol (II) in 65% yield.

The pentol II thus obtained was recognized by Nakao and his co-workers[7] to show a biologically interesting sodium excreting activity in the animal test, of which details will be described elsewhere by the same authors.

Then an attempt was made to protect the 5,6-double bond of diosgenin prior to the performic acid oxidation.

Since bromination of diosgenin acetate had been known to affect the carbon at C-23, we decided to investigate the chlorination of the sapogenin actate and this proved to give a satisfactory result.

In benzene containing a small amount of pyridine, diosgenin acetate and an equimolar quantity of chlorine in carbon tetrachloride gave a product melting at 210° (decomp.), to which was assigned the 5α,6β-dichloride configuration (IIIa).

Chlorination with iodobenzene dichloride[8] in dry chloroform gave, on the other hand, another isomeric 5α,6α-dichloride (IIIb) melting at 274~276° (decomp.).

When diosgenin acetate dissolved in dimethylformamide was treated with chlorine in carbon tetrachloride, the reaction took an entirely different course giving a good yield of a new substance which is different from both the 5α,6β-dichloride (IIIa) and 5α,6α-dichloride (IIIb). The structure of this substance was soon established to be

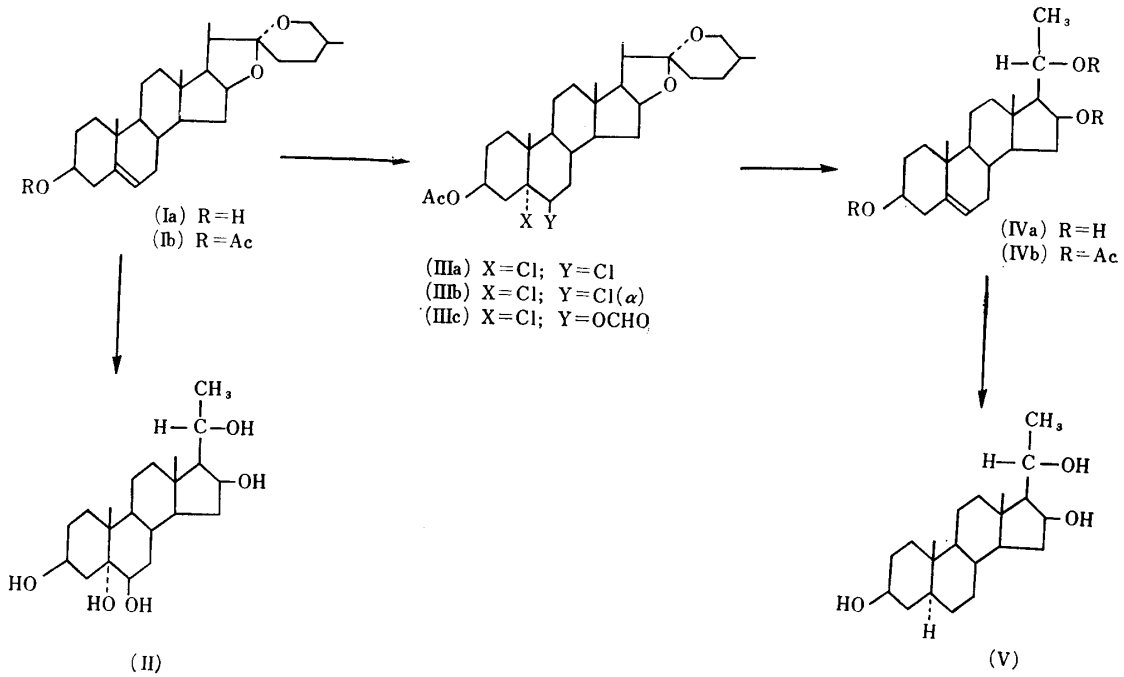


Chart 1.

*[3] Private communication by Dr. H. Nawa to whom the authors are grateful.

6) R.E. Marker, E.M. Jones, J. Krueger : J. Am. Chem. Soc., **62**, 2532 (1940).
7) T. Nakao, K. Hiraga, T. Saito, Y. Murayama : Jikei Medical Journal, **6**, 116 (1959).
8) D.H.R. Barton, E. Miller : J. Am. Chem. Soc., **72**, 370 (1950); D.H.R. Barton, E. Miller, H.T. Young : J. Chem. Soc., **1951**, 2598; L.J. Andrews, R.M. Keefer : J. Am. Chem. Soc., **80**, 1723 (1958).

3β-acetoxy-5-chloro-6β-formyloxy-5α,25D-spirostan (IIIc) by means of parallel experiments in the cholesterol series and the examination of the infrared spectra.

Isomeric dichlorides (IIIa, IIIb) and the formyloxychloride (IIIc) gave, on oxidation with performic acid followed by treatment with zinc and acetic acid, and hydrolysis, a new pregnenetriol : pregn-5-ene-3β,16β,20α-triol (IVa).

The structure of this pregnenetriol was confirmed by the catalytic reduction of the compound into 5α-pregnane-3β,16β,20α-triol (V).

In this way, pregn-5-ene-3β,16β,20α-triol (IVa) was obtained in 60~70% overall yield from diosgenin acetate.

Since, as already described, diosgenin acetate on chlorination in dimethylformamide gave 3β-acetoxy-5α-chloro-6β-formyloxy-25D-spirostan (IIIc), the authors carried out the following experiments in order to secure the general applicability of this novel reaction.

Cholesterol acetate was hence treated in dimethylformamide with a slight excess of chlorine in carbon tetrachloride, and the reaction mixture was diluted with water to separate a crystalline product, which showed the correct analysis for 3β-acetoxy-5α-chloro-6β-formyloxycholestane (VI). This product VI exhibited a characteristic infrared absorption band at 1170 cm^{-1}, which is attributable to the C-O-C of the formyloxy group. VI was hydrolyzed with methanolic hydrochloric acid to 5α-chlorocholestane-3β,6β-diol (VII).

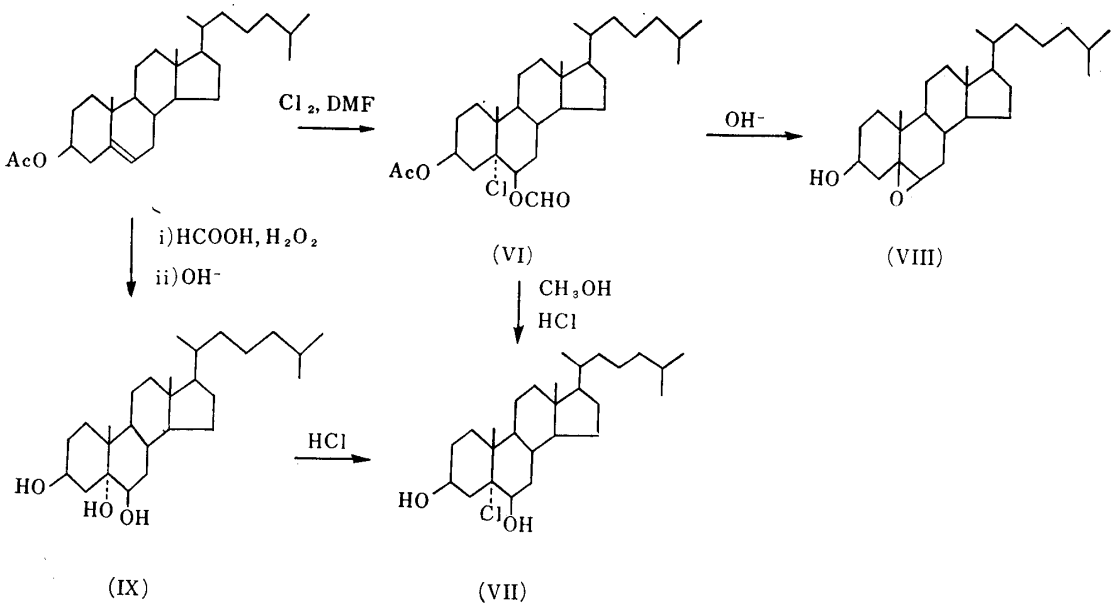
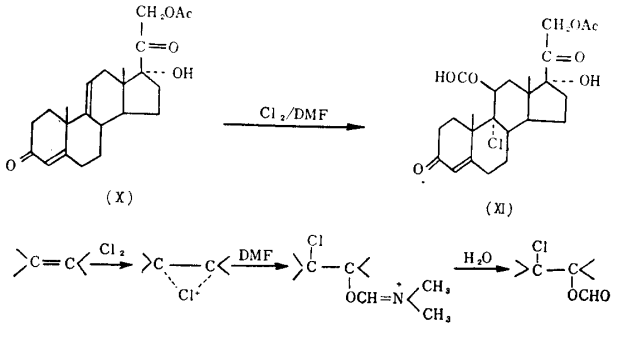


Chart 2.



DMF : dimethylformamide

Chart 3.

Attempted hydrolysis of VI with alkali gave cholesterol β-oxide (VIII) in good yield. These results are fully illustrated by the reasonable assumption of the reaction mechanisms as shown in the following scheme :

In the same manner, 21-acetoxy-17α-hydroxypregna-4,9(11)-diene-3,20-dione (X)[9] on treatment with chlorine in dimethylformamide gave 9α-chloro-11β-formyloxy-21-acetoxy-17α-hydroxypregn-4-ene-3,20-dione (XI).

The only observation which seems to be parallel to our findings is that reported by Reimann *et al.*,[10] who described a reaction of N-chlorosuccinimide with 9(11)-dehydroprogesterone in dimethylformamide in the presence of fluoride and obtained a product, for which they assigned the structure of 9α-chloro-11β-formyloxyprogesterone from the elementary analysis and theoretical consideration of the reaction mechanism.

Experimental*4

Chlorination of Diosgenin Acetate (I)——a) To a stirred solution of 46.5 g. (1 mole) of I and 8 g. (1 mole) of pyridine in 400 cc. of dry benzene was added dropwise a saturated solution of Cl_2 (1.1 mole) in CCl_4. The reaction was run at room temperature and the solvent was removed under reduced pressure. The resulting 5α,6β-dichloride (IIIa) was crystallized by dissolution in 100 cc. of CH_2Cl_2, addition of 350 cc. of MeOH and evaporation of CH_2Cl_2; yield 44 g., m.p. 200~220°. This crude material was shown to be pure enough for subsequent reactions.

The analytical sample was obtained by recrystallization from MeOH and melted at 210° (decomp.). $[\alpha]_D^{21}$ −103° (c=1.0, $CHCl_3$). *Anal.* Calcd. for $C_{29}H_{44}O_4Cl_2$: C, 66.02; H, 8.41; Cl, 13.46. Found : C, 66.03; H, 8.43; Cl, 13.55.

b) To a stirred solution of 4.65 g. of I in 60 cc. of anhyd. $CHCl_3$ was added 2.9 g. of iodo-benzene dichloride and the mixture was refluxed on a steam bath for 30 min., during which the solution turned to pale brown. The solvent was evaporated under reduced pressure and the residue was crytallized from MeOH to give a white crystalline product; yield 4.0 g.; m.p. 256° (sint. at 230°).

This product, which exhibited the correct analysis for a dichloride and was assumed to have the 5α,6α-dichloride configuration IIIb, was recrystallized from AcOH giving 3.5 g. of needles, m.p. 274~276° (decomp.), $[\alpha]_D^{21}$ −90° (c=0.5, $CHCl_3$). *Anal.* Calcd. for $C_{29}H_{44}O_4Cl_2$: C, 66.02; H, 8.41; Cl, 13.46. Found : C, 66.21; H, 8.52; Cl, 13.27.

c) To a solution of 800 mg. of I in 20 cc. of CH_2Cl_2·dimethylformamide (2:1) was added 4 cc. of 10% solution of Cl_2 in CCl_4. After two or three min. a small amount of water was added and the solvent was removed under reduced pressure to give a crystalline product, which was collected, washed with MeOH and dried; yield, 500 mg.

The analytical sample of the formyloxychloride (IIIc) was obtained by recrystallization from MeOH, m.p. 267~270° (decomp.), $[\alpha]_D$ −114° (c=1.0, $CHCl_3$). *Anal.* Calcd. for $C_{30}H_{45}O_6Cl$: C, 67.10; H, 8.38; Cl, 6.62. Found : C, 67.04; H, 8.18; Cl, 6.96.

Pregn-5-ene-3β,16β,20α-triol (IVa)——To a solution of 20 g. of IIIa (m.p. 210~214°) in 100 cc. of ethylene chloride and 400 cc. of 99% HCOOH was added 40 cc. of 35% H_2O_2 and the mixture was warmed on a steam bath to keep the temperature at 50° for 1 hr. Solvent was removed under reduced pressure to a volume of 100 cc. and the solution was poured into 500 cc. of water. The mixture was then extracted with CH_2Cl_2 and the organic layer was washed with water, dried over Na_2SO_4 and evaporated. The residue was redissolved in 300 cc. of AcOH and the solution was stirred at 60~70° for 1~2 hr., during which was added 50 g. of Zn dust in small portions.

The reaction mixture was then filtered and the filtrate was again evaporated to dryness. The residue dissolved in 300 cc. of MeOH was treated with 50 cc. of 40% NaOH and the mixture was allowed to stand overnight. Water was added to the mixture, neutralized with AcOH and the solvent was evaporated *in vacuo* to give a white crystalline product, which was collected, dried and recrystallized from AcOEt; yield, 10 g.; m.p. 238~241°. The analytical sample was obtained by recrystallization from the same solvent giving needles, m.p. 241~242°, $[\alpha]_D^{20}$ +36° (c=1.0, MeOH-$CHCl_3$ (2:1)). *Anal.* Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found : C, 75.32; H, 10.20.

When IIIb or IIIc was used in place of IIIa in the reaction and worked up as described above, the same pregnenetriol IVa was obtained in comparative yields.

*4 All melting points are uncorrected.

9) J. Fried, E. F. Sabo : J. Am. Chem. Soc., **79**, 1130 (1957).
10) H. Reimann, E. P. Oliveto, R. Neir, M. Eisler, P. Perlman : *Ibid.*, **82**, 2308 (1960).

Acetylation of IVa in pyridine-Ac_2O afforded the triacetate IVb, m.p. 196~198°. *Anal.* Calcd. for $C_{27}H_{41}O_6$: C, 70.40; H, 8.75. Found: C, 70.14; H, 8.70.

5α-Pregnane-3β,16β,20α-triol (V)——A solution of 5 g. of IVa in 250 cc. of AcOH was shaken with H_2 over Pd-C catalyst at room temperature. During 12 hr. the solution absorbed 33 cc. of H_2. The catalyst was removed by filtration and the filtrate gave on evaporation a crystalline product.

After recrystallization from MeOH, V melted at 233~234°. Identity with an authentic material was established by direct comparison (IR spectrum and mixed melting point).

5α-Chlorocholestane-3β,6β-diol 3-acetate 6-formate (VI)——To a solution of 2.0 g. of cholesterol acetate in 10 cc. of dimethylformamide was added 10% solution of Cl_2 in CCl_4 until a pale yellow color persists. MeOH was then added to the solution, which caused a rapid precipitation of VI as colorless needles; yield, 1.1 g., m.p. 175~177°.

The analytical sample was obtained by recrystallization from MeOH; m.p. 186~187°; $[\alpha]_D^{22}$ −64° (c=1.0, $CHCl_3$). *Anal.* Calcd. for $C_{30}H_{49}O_4Cl$: C, 70.80; H, 9.70; Cl, 6.96. Found: C, 70.84; H, 9.87; Cl, 6.80.

5α-Chlorocholestane-3β,6β-diol (VII)——a) A mixture of 100 mg. of VI and 2 cc. of MeOH containing 0.02 cc. of chlorosulfonic acid was warmed on a steam bath at 40~50° for 1 hr. to dissolve crystals of VI. After three days a crystalline product which precipitated on the walls was collected and purified by recrystallization from MeOH; m.p. 174~175°(decomp.), $[\alpha]_D^{21}$ −23°(c=1.0, $CHCl_3$). On admixture with an authentic sample prepared according to b), this showed no depression and the IR spectra of both specimens were identical.

b) A solution of 5α-cholestane-3β,5,6β-triol (IX) dissolved in $CHCl_3$ was saturated with dry HCl and the solution was allowed to stand at room temperature overnight. Water was added and the $CHCl_3$ layer separated, washed with water, dried and the solvent evaporated. Recrystallization from MeOH afforded the analytical sample of VII as colorless needles, m.p. 173~174°.

5β,6β-Epoxycholestan-3β-ol (VIII)——To a mixture of 500 mg. of VI and 30 cc. of MeOH was added 3 cc. of 15% aq. NaOH and the mixture was heated on a steam bath for 10 min. A few drops of AcOH was then added to the solution and the solvent was removed under reduced pressure.

The residue dissolved in CH_2Cl_2 was washed with water, dried and evaporated to give VIII; m.p. 125~130°; yield, 410 mg.

Recrystallization from MeOH raised the m.p. to 132~133°; $[\alpha]_D^{21}$ +1.5°(c=1.0, EtOH).

Identity with an authentic sample was confirmed by mixed melting point and comparison of the IR spectra.

9α-Chloro-11β,17α,21-trihydroxypregn-4-ene-3,20-dione 11-fomate 21-acetate (XI)——To a solution of 1.0 g. of 17α,21-dihydroxypregna-4,9(11)-diene-3,20-dione 21-acetate(X)in 30 cc. of dimethylformamide was added 2.6 cc. of 10% Cl_2 in CCl_4.

Water (50 cc.) was added to the solution and the mixture was extracted with CH_2Cl_2.

The extract was washed with water, dried and evaporated and the residue was recrystallized twice from MeOH to give 350 mg. of XI, m.p. 204~207°. *Anal.* Calcd. for $C_{24}H_{31}O_7Cl$: C, 61.73; H, 6.70; Cl, 7.60. Found: C, 61.55; H, 7.00; Cl, 8.16.

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Thanks are also due to Mr. M. Kan for elementary analyses and to Mr. H. Nakamachi for optical measurement.

Summary

Chlorination of diosgenin acetate followed by treatment with performic acid, dechlorination, and hydrolysis has given pregn-5-ene-3β,16β,20α-triol in 60~70% overall yield.

When the chlorination was conducted in a dimethylformamide solution, the main product was 3β-acetoxy-5-chloro-6β-formyloxy-5α,25D-spirostan.

Validity of this novel reaction was confirmed by expriments in the cholesterol series.

Synthesis of 9α-chloro-11β-formyloxysteroids from $\Delta^{9(11)}$-steroids has also been facilitated.

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