They are also indebted to Mr. T. Oba for his co-operation in infrared absorption measurements and to Miss S. Nakamura in elemental analyses. A part of expenses for this work was defrayed by the Grant-in-Aid for Scientific Research from the Ministry of Health and Welfare, which is gratefully acknowledged.

Summary

4,7-Dimethoxy-1*H*-imidazo[4,5-*d*]- and 4,7-dimethoxy-1*H*-*v*-triazolo[4,5-*d*]-pyridazines and some of their derivatives were synthesized from 3,6-dimethoxy-4,5-diaminopyridazine (Ⅳ). Various reactions concerning the cyclization of (Ⅳ) were reported.

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167. Ken'ichi Takeda and Kaname Hamamoto: Studies on the Steroidal Components of Domestic Plants. XXII.[*1] Structure of Metagenin. (2).[1]

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Previously, 5β,25D-spirostane-2β,3β,x-triol (I) was proposed as the structure of metagenin, a steroidal sapogenin isolated from *Metanarthecium luteo-viride* MAXIM.[1] and it was also reported that the position of the unknown hydroxyl group in metagenin was limited to C-6, C-7, or C-11 from infrared absorption spectrum of metagenin triacetate (Va) and by the properties of metagenic acid, an oxidation product of metagenin.

In order to replace the unknown hydroxyl group in metagenin by hydrogen, the Huang-Minlon reduction[2] of the x-keto derivative of metagenin was carried out. Metagenin acetonide (Ⅱa), obtained in the usual manner as described earlier,[1] was converted to x-monoketo derivative (metagenone) (Ⅲb), m.p. 248°, $[\alpha]_D^{25}$ −4.0°, IR λ_{max}^{Nujol} 2.95 (OH) and 5.88 μ (C=O), via ketone acetonide (Ⅲa), m.p. 203~204°, by chromium trioxide oxidation followed by hydrolysis with dilute acetic acid. Metagenone (Ⅲb) formed a diacetate (Ⅲc), m.p. 240~242°, and this acetate again formed the unchanged parent ketone (Ⅲb) by the action of alkali.

Although metagenone (Ⅲb) and its diacetate (Ⅲc) underwent the Huang-Minlon reduction and afforded samogenin diacetate[3,4,*3] (Ⅳb), m.p. 197~198°, in ca. 24% and 30% yield, respectively, when acetylated with acetic anhydride-pyridine, metagenone gave neither a semicarbazone nor hydrazone under the usual conditions. On the other hand, metagenone acetonide (Ⅲa) was not affected by the Huang-Minlon reduction and the unchanged starting material was recovered almost quantitatively.

From these results, it was confirmed that the two vicinal hydroxyl groups are located

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[*1] Part XXI: T. Kubota, K. Takeda: Tetrahedron, **10**, 1 (1960).

[*2] Imafuku, Amagasaki, Hyogo-ken (武田健一, 浜元 要).

[*3] The authentic sample was kindly donated by Dr. C. Djerassi.

1) Part (1): K. Takeda, T. Okanishi, K. Hamamoto, A. Shimaoka, N. Maezono: Yakugaku Zasshi, **77**, 175(1957).

2) Huang-Minlon: J. Am. Chem. Soc., **68**, 2487(1946).

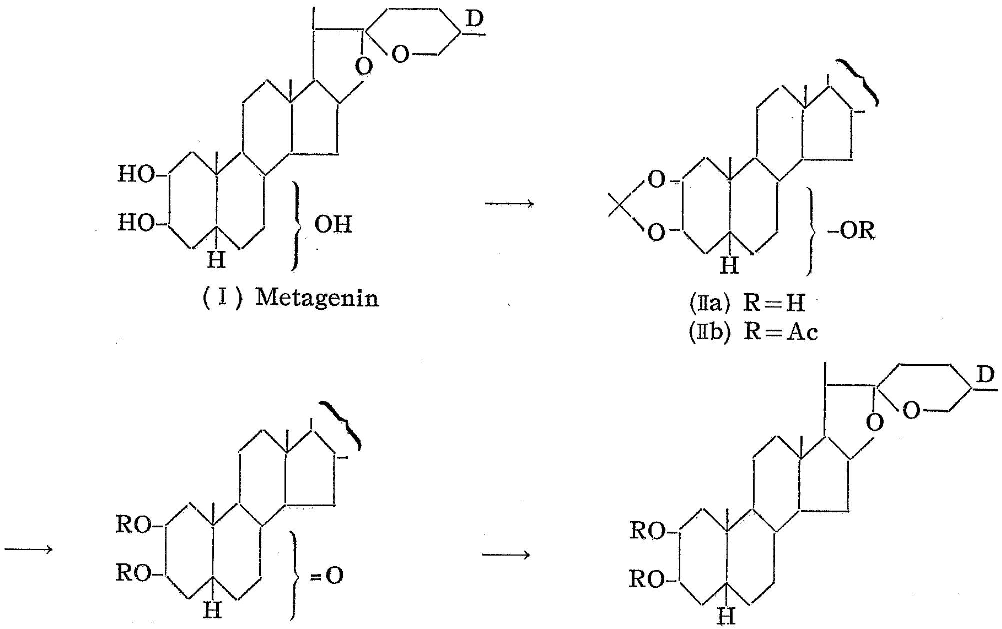
3) R. E. Marker, *et al.*: *Ibid.*, **69**, 2167(1947).

4) (a) C. Djerassi, J. Fishman, J. A. Moore: Chem. & Ind. (London), **1954**, 1320. (b) C. Djerassi, J. Fishman: J. Am. Chem. Soc., **77**, 4291(1955).

at C–2 and C–3, that both are β-oriented, and that the A/B ring juncture is *cis*. Furthermore, position of the keto group in metagenone at C–6 was excluded by the stability of metagenone to alkali.5) The possibility of C–12 ketone in metagenone was also excluded by the mixed melting point determination with mexogenin,*3 m.p. 246°.

Acylation reaction of metagenin (I) was next examined. Metagenin gave only a triacetate1) (Va), m.p. 250~252°, when treated with acetic anhydride and pyridine at room temperature overnight or refluxed with acetic anhydride for one hour. With benzoyl chloride and pyridine, metagenin also gave a tribenzoate (Vb), m.p. 273~275°. When metagenin was acetylated under such mild conditions as with acetic anhydride and pyridine diluted with chloroform,6) it gave a triacetate (Va), a diacetate (Vf), m.p. 226~227°, and a monoacetate (Vd), m.p. 220~221°. This diacetate (Vf) was assumed to be a 2,x-diacetate from the facts to be mentioned below. The monoacetate (Vd) is identical with x-monoacetyl-metagenin, which was obtained via metagenin acetonide acetate (IIb), m.p. 202~204°, by acetylation of metagenin acetonide (IIa), followed by replacement of the acetonide group with dilute acetic acid.

Acetylation of metagenin with acetic acid containing hydrochloric acid, the method reported by Rosenkranz, *et al.*,7) yielded another diacetate (Ve), m.p. 201~202°, as a main

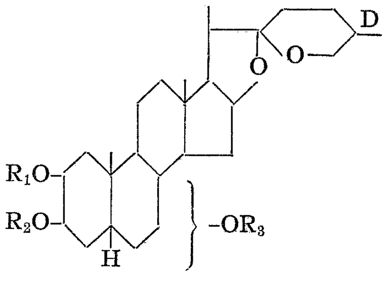


(I) Metagenin

(IIa) R=H
(IIb) R=Ac

(IIIa) $R,R=\genfrac{}{}{0pt}{}{CH_3}{CH_3}{>}C<$
(IIIb) R=H Metagenone
(IIIc) R=Ac

(IVa) R=H Samogenin
(IVb) R=Ac



(Va) $R_1=R_2=R_3=Ac$
(Vb) $R_1=R_2=R_3=Bz$
(Vc) $R_1=Ac,\ R_2=R_3=H$
(Vd) $R_1=R_2=H,\ R_3=Ac$
(Ve) $R_1=R_2=Ac,\ R_3=H$
(Vf) $R_1=R_3=Ac,\ R_2=H$

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5) L. F. Fieser, M. Fieser: "Steroids," 79(**1959**). Reinhold Publishers Corp., New York.
6) K. Takeda, T. Kubota, A. Shimaoka: Tetrahedron, **7**, 62(1959).
7) G. Rosenkranz, O. Mancera, F. Sondheimer: J. Am. Chem. Soc., **76**, 2227(1954).

product, and the diacetate (Vf), m.p. 226~227°, cited above, a new monoacetate (Vc), m.p. 240~241°, and a small amount of the triacetate (Va). The yield of each acetate and the reaction conditions are cited in Table I.

TABLE I. Partial Acetylation of Metagenin

Method	Takeda, *et al.*[6]	Rosenkranz, *et al.*[7]
Metagenin	500 mg.	1 g.
Acetylation reagent	Ac_2O 5 cc.-pyridine 20 cc.-$CHCl_3$ 20 cc.	AcOH 25 cc., containing 0.5 cc. of 35% HCl
Reaction conditions	2~4°, 18 hr.	20°, 22 hr.
Product		
Metagenin triacetate (Va)	83 mg. (13%)	188 mg. (15%)
diacetate (Ve)		464 mg. (39%)
diacetate (Vf)	376 mg. (69%)	223 mg. (20%)
monoacetate (Vc)		254 mg. (23%)
monoacetate (Vd)	94 mg. (17%)	

Since chromium trioxide oxidation of the diacetate (Ve), the main product of this procedure, gave metagenone diacetate (Ⅲc) in a fair yield, the structure of (Ve) was confirmed as 2,3-diacetylmetagenin. The other diacetate (Vf), melting at 226~227°, was therefore assumed to be 2,x-diacetylmetagenin. The monoacetate (Vc) showed no characteristic absorption band at about 8 μ for the 2β,3β-diacetyl group in the 5β-steroids[1] and also it was resistant to acetonide formation. From these findings and conformational considerations, this monoacetate (Vc) was assumed to be 2-monoacetyl-metagenin.

From the above-mentioned results, it is deduced that there is no marked conformational difference among these three hydroxyl groups in metagenin and that the third unknown hydroxyl group may have equatorial conformation. Rigid proof of the above-mentioned two 2-acetyl derivatives (Vc and Vf) is now under investigation in this laboratory.

Experimental

All m.p.s are uncorrected. Rotations were measured in chloroform solution.

Metagenin Acetonide x-Acetate (IIb)—A mixture of 2.5 g. of metagenin acetonide (Ⅱa), 25 cc. of Ac_2O, and 50 cc. of pyridine was left for 18 hr. at room temperature. The crude product, isolated from the reaction mixture in the usual manner, was purified by chromatography on alumina. The eluates with petr. ether and benzene furnished 2.3 g. of a crystalline product, which was recrystallized from MeOH-$CHCl_3$ to fine needles, m.p. 202~204°, $[\alpha]_D^{25}$ −100.1°. *Anal.* Calcd. for $C_{32}H_{50}O_6$: C, 72.41; H, 9.50. Found : C, 72.53; H, 9.47.

Metagenin x-Monoacetate (Vd)—The above-mentioned acetonide (Ⅱb) (2.2 g.) was warmed at 55° for 1.5 hr. with 60 cc. of 50% AcOH. The precipitate formed by evaporation of the solvent was recrystallized from MeOH-$CHCl_3$ to 1.9 g. of needles, m.p. 220~221°, $[\alpha]_D^{20}$ −106.9°. *Anal.* Calcd. for $C_{29}H_{46}O_6 \cdot \frac{1}{2}H_2O$: C, 69.70; H, 9.48. Found : C, 69.67; H, 9.41.

Metagenone Acetonide (IIIa)—To a solution of 0.3 g. of metagenin acetonide (Ⅱa) in 6 cc. of pyridine a solution of 0.23 g. of CrO_3 in 30 cc. of pyridine was added and the mixture was left for 1 hr. at room temperature (25°). The crude precipitate which formed on addition of water was collected, washed with water, and dissolved in AcOEt. AcOEt solution furnished, after evaporation, a crude product (0.3 g.), which was recrystallized from $CHCl_3$-MeOH to 0.25 g. of ketone acetonide (Ⅲa), m.p. 203~204°, $[\alpha]_D^{26}$ −43.1°. *Anal.* Calcd. for $C_{30}H_{46}O_5$: C, 74.03; H, 9.53. Found : C, 74.31; H, 9.49.

Metagenone (IIIb)—a) From Metagenone Acetonide (Ⅲa) : Metagenone acetonide (Ⅲa) (0.3 g.) was warmed for 1.5 hr. at 55° with 8 cc. of 50% AcOH. The reaction mixture was processed as described above for (Vd) and the crude product was recrystallized from $CHCl_3$-MeOH to 0.25 g. of needles, m.p. 247~248°, $[\alpha]_D^{25}$ −4.0°. A mixed m.p. with mexogenin*[3] depressed to 210~214°. *Anal.* Calcd. for $C_{27}H_{42}O_5 \cdot \frac{1}{2}H_2O$: C, 71.12; H, 9.51. Found : C, 71.40; H, 9.44. IR λ_{max}^{Nujol} μ : 5.88 (C=O), 2.59 (OH).

b) From Metagenone Diacetate (Ⅲc) : Metagenone diacetate (Ⅲc) (50 mg.) was refluxed for 1 hr. with 10% EtOH-KOH. The crude product was recrystallized from MeOH to needles, m.p. 246~248°, which were shown by a mixed melting point to be identical with the sample from method (a).

Metagenone Diacetate (IIIc)—a) From Metagenin 2,3-Diacetate (Ve): A solution of 0.4 g. of metagenin 2,3-diacetate (Ve) in 40 cc. of AcOH was oxidized with 1 g. of CrO_3 in 10 cc. of 80% AcOH for 30 min. at room temperature (20°). The crude neutral fraction, isolated by addition of water, extraction with Et_2O, washing with 10% Na_2CO_3 and water, and evaporation of the solvent, was recrystallized from MeOH yielding 250 mg. of prisms, m.p. 240~242°, $[\alpha]_D^{14}$ −60.0°. *Anal.* Calcd. for $C_{31}H_{46}O_7$: C, 70.16; H, 8.74. Found: C, 70.21; H, 8.73. IR $\lambda_{max}^{CS_2}$ μ: 8.21; 8.01 (5β;2β,3β-diacetate); 5.85; 5.74 (C=O).

b) From Metagenone (IIIb): Metagenone (IIIb) (0.8 g.) was heated with 15 cc. of Ac_2O under reflux. The crude product, isolated in the usual manner, was recrystallized from $CHCl_3$-MeOH to 0.9 g., m.p. 240~242°, which proved to be identical with the sample obtained by method (a).

Huang-Minlon Reduction of Metagenone Diacetate (IIIc)—Metagenone diacetate (IIIc) (200 mg.) was refluxed with 4 cc. of triethylene glycol, 0.5 cc. of 80% hydrazine hydrate, and 0.2 g. of KOH for 30 min. at 130~140°. The condenser was removed, the temperature of the solution was permitted to rise to 190°, and refluxing was continued for 1.5 hr. The crude reduction product, precipitated by addition of water, was dissolved in Et_2O and the Et_2O extract was chromatographed on alumina. The MeOH-$CHCl_3$ (1:4) eluates furnished two fractions; A, m.p. 197~201°, and B, m.p. 230~239°. Fraction A was recrystallized from Me_2CO to give samogenin (IVa), m.p. 206~207°, which showed no depression with samogenin prepared from yonogenin.[8] *Anal.* Calcd. for $C_{29}H_{44}O_4 \cdot \frac{1}{2}H_2O$ (IVa): C, 73.43; H, 10.27. Found: C, 73.64; H, 10.34.

The combined crystalline material from fraction A was acetylated with Ac_2O by refluxing for 1 hr. and yielded 59 mg. (30%) of samogenin diacetate (IVb), m.p. 197~198°, which proved to be identical by mixed m.p. and IR comparison with the authentic sample*3 of samogenin diacetate. *Anal.* Calcd. for $C_{31}H_{48}O_6$ (IVb); C, 72.06; H, 9.36. Found: C, 72.44; H, 9.42.

Fraction B, by acetylation and purification on alumina, furnished 124 mg. of metagenone diacetate (IIIc), m.p. 238~240°, which showed no depression with the starting material (IIIc).

Huang-Minlon Reduction of Metagenone (IIIb)—The reduction of metagenone (IIIb) (200 mg.) was carried out exactly as described above for (IIIc) with 4 cc. of triethylene glycol, 0.5 cc. of 80% hydrazine hydrate, and 0.2 g. of KOH. The crude product, isolated as above, was acetylated with Ac_2O and chromatographed on alumina. The benzene eluates furnished 50 mg. (24%) of samogenin diacetate (IVb), m.p. 194~196°, and the Et_2O-benzene (1:9) eluates gave 31 mg. of metagenone diacetate (IIIc) m.p. 234~237°.

Partial Acetylation of Metagenin—a) With Ac_2O-Pyridine-$CHCl_3$: A solution of 500 mg. of metagenin (I) in a mixture of 5 cc. of Ac_2O, 20 cc. of pyridine, and 20 cc. of $CHCl_3$ was left at 2~4° for 18 hr. The reaction mixture was diluted with water, washed with 10% H_2SO_4, 5% NaOH, and water and extracted with Et_2O. The crude product, isolated by solvent evaporation, was chromatographed on alumina. The eluates were separated into the following three fractions.

The first fraction eluted with Et_2O-benzene (1:9) furnished 80 mg. of metagenin triacetate (Va), m.p. 249~252° (from $CHCl_3$-MeOH), which showed no depression with the sample mentioned in Part (1).[1]

The second fraction eluted with Et_2O-benzene (2:8) gave 376 mg. of metagenin 2,x-diacetate (Vf), m.p. 226~227° (from $CHCl_3$-MeOH), $[\alpha]_D^{20}$ −79.8°. *Anal.* Calcd. for $C_{31}H_{48}O_7$ (Vf): C, 69.89; H, 9.08. Found: C, 69.99; H, 9.18. IR λ_{max}^{Nujol} μ: 8.03, 5.81, 5.75 (AcO); 2.78 (OH).

The third fraction eluted with $CHCl_3$ gave 94 mg. of metagenin x-monoacetate (Vd), m.p. 220~221°, identical with the sample mentioned above.

b) With AcOH-HCl Method: A solution of 1 g. of metagenin in 25 cc. of AcOH containing 0.5 cc. of 35% HCl was left for 22 hr. at room temperature (20°). The crude product, processed in the usual manner, was chromatographed on alumina. The first fraction eluted with Et_2O-benzene (1:9) furnished 188 mg. of metagenin triacetate (Va), m.p. 249~252° (from $CHCl_3$-MeOH), identical with the authentic sample.[1]

The second fraction eluted with Et_2O-benzene (2:8) furnished 464 mg. of metagenin 2,3-diacetate (Ve) (from $CHCl_3$-petr. ether), m.p. 201~202°, $[\alpha]_D^{13}$ −67.4°. *Anal.* Calcd. for $C_{31}H_{48}O_7$ (Ve): C, 69.89; H, 9.08. Found: C, 70.12; H, 9.10. IR λ_{max}^{Nujol} μ: 8.21, 8.09, 7.98 (5β;2β,3β-diacetate), 5.75 (AcO); 2.84 (OH).

The third fraction eluted with Et_2O gave 223 mg. of metagenin 2,x-diacetate (Vf), m.p. 225~227°, identical with the sample mentioned above.

The fourth fraction eluted with $CHCl_3$ yielded 254 mg. of metagenin 2-monoacetate (Vc), m.p. 240~241° (from $CHCl_3$-MeOH), $[\alpha]_D^{13}$ −90.2°. *Anal.* Calcd. for $C_{29}H_{46}O_6$ (Vc): C, 70.98; H, 9.45. Found: C, 70.95; H, 9.55. IR λ_{max}^{Nujol} μ: 5.88 (AcO), 2.97, 2.92 (OH).

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[8] K. Takeda, T. Okanishi, A. Shimaoka: This Bulletin, **6**, 532 (1958).

The authors express their deep gratitude to Prof. C. Djerassi for his kind donation of authentic samples of samogenin diacetate and mexogenin. The authors are indebted to Dr. T. Okanishi and Mr. T. Hirata for collecting plant sources, to Mr. N. Maezono for his technical collaboration, to Mr. Y. Matsui for the measurement of infrared absorption spectra, and to the members of analytical section of this laboratory for microanalysis and for measurement of optical rotations.

Summary

Metagenin was derived to samogenin via metagenone or its diacetate by the Huang-Minlon reduction. The possibility of C-6 and C-12 ketone groups in metagenone was excluded from experimental result and thus 5β,25D-spirostane-2β,3β,x-triol (x=7 or 11) was assigned to metagenin.

Partial acetylation of metagenin was carried out by two methods and afforded two diacetates (2,3- and 2,x-) and two monoacetates (2- and x-). The structure of these acetates is discussed.

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UDC 547.569-386 : 546.56

168. Hisashi Tanaka and Akira Yokoyama: Studies on the Sulfur-containing Chelating Agents. III.[*1] Syntheses of β-Mercaptoketones and their Copper Chelates. (3).

(*Faculty of Pharmacy, Kyoto University*[*2])

In the previous papers,[*1,1] it was reported that various kinds of β-mercaptoketones formed chelate compounds with copper. This paper deals with the preparation of β-mercaptoketones with a heterocyclic ring, in an attempt to investigate the influence of the heterocyclic ring to chelate formation. The method of preparation is similar to that described in the previous papers,[*1,1] as shown in Chart 1, by the addition of hydrogen sulfide to corresponding α,β-unsaturated ketones. It was found that in most of the cases, mono- and disulfides were also produced besides the expected mercaptoketones as shown in Table I.

The separation of mercaptoketone from mono- and disulfides was carried out by fractional recrystallization, because mercaptoketone of this series is very unstable towards alkali, so that any kind of alkali could not be used for the separation. In the case of 1,3-di-2-thienyl-2-propen-1-one, bis(1,3-di-2-thienyl-3-oxopropyl) sulfide (VI) was obtained as colorless needles, and only traces of 1,3-di-2-thienyl-3-mercapto-1-propanone (V) were isolated. The yield of (V) was so poor that it could not be purified and analyzed. However, the formation of (V) was confirmed from the results of Rheinboldt test[2] (red) and copper chelate formation. In the case of 1-(2-furyl)-3-phenyl-2-propen-1-one, besides 1-(2-furyl)-3-mercapto-3-phenyl-1-propanone, traces of needles (m.p. 152°), considered to be a disulfide, were isolated, although it could not be confirmed. In the case of 1,3-di-2-furyl-2-propen-1-one, when the reaction was carried out in ethanol, considerable amount

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[*1] Part II. This Bulletin, 8, 280(1960).

[*2] Yoshida, Sakyo-ku, Kyoto (田中 久, 横山 陽).

1) Part I. This Bulletin, 8, 275(1960).

2) H. Rheinboldt: Chem. Ber., **59**, 1311(1926).