Chem. Pharm. Bull. 14(3) 247~255 (1966)

UDC 547.92.07 : 581.19

37. Ken'ichi Takeda, Kaname Hamamoto, Kusuo Horiki, and Etsuko Honda : On Steroidal Sapogenins. IX.*1 Some Derivatives of Metagenin Related to Steroidal Hormones (Part 1).

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Recently, the structures of metagenin and nogiragenin, isolated from *Metanarthecium luteo-viride* MAXIM., were established as Ia[1] and II.[2] As both of them involved

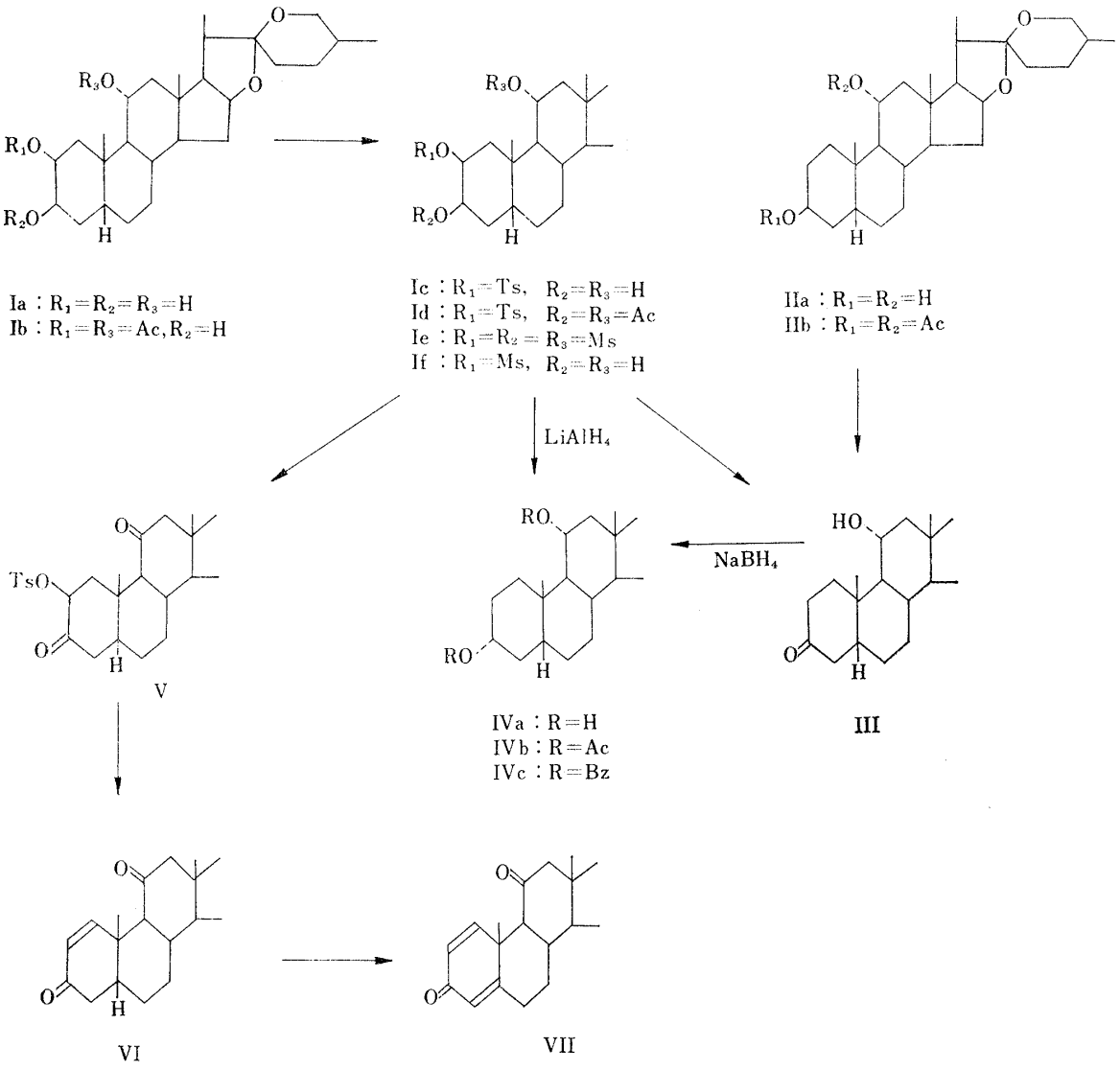

Chart 1.

*1 Part Ⅷ. K. Takeda, K. Hamamoto, K. Sasaki, N. Maezono, A. Murabayashi : Steroids, 27 (1963).

*2 Fukushima-ku, Osaka (武田健一, 浜元 要, 堀木樟夫, 本田悦子).

1) *a*) K. Takeda, T. Okanishi, K. Hamamoto, A. Shimaoka, N. Maezono : J. Pharm. Soc., **77**, 175 (1957). *b*) K. Takeda, K. Hamamoto : This Bulletin, 8, 1004 (1960). *c*) K. Hamamoto : *Ibid.*, 8, 1099 (1960). *d*) *Idem* : *Ibid.*, **9**, 32 (1961).

2) K. Takeda, T. Okanishi, H. Osaka, A. Shimaoka, N. Maezono : *Ibid.*, **9**, 388 (1961).

11α-hydroxyl group, these sapogenins seemed to be very useful starting materials for the synthesis of the 11-oxygenated steroidal hormones.

The present work is concerned with some interesting reactions of the metagenin derivatives as intermediates of steroidal hormones.

It was previously reported[1b] that metagenin (Ia) was partially acetylated with acetic anhydride-pyridine-chloroform at low temperature to yield metagenin 2,11-diacetate (Ib). Now we examined the possibilities of preparing 2,11-ditosylate and 2,11-dimesylate from metagenin (Ia).

In the case of tosylation, treatment of Ia with tosyl chloride in pyridine gave only monotosylate, m.p. 139°, and neither ditosylate nor tritosylate was obtained, even by prolonging the reaction time. From the fact that this monotosylate gave nogiragenone (III),[2] when treated with collidine, it was confirmed that the tosyloxy group was located at position 2. The 2-monotosylate (Ic) was resistant to further tosylation but when submitted to acetylation it afforded amorphous 2-tosyloxy-3,11-diacetoxymetagenin (Id).

Reduction of the latter compound with lithium aluminum hydride gave 3α,11α-diol (IVa), m.p. 105°, accompanying the epimeric 3β-hydroxyl derivative, and was identical in all respects with the 3α,11α-diol and its diacetate obtained by sodium borohydride reduction of nogiragenone (III). Lithium aluminum hydride reduction of metagenin 2-monotosylate (Ic), also gave the same result.

2-Monotosylate (Ic) was oxidized to the 3,11-dione (V), m.p. 135°(decomp.), with chromium trioxide in acetone and this diketone was converted to 5β-spirost-1-ene-3,11-dione (VI), m.p. 212°, with collidine or lithium bromide-lithium carbonate-dimethyl formamide mixture.[3] Dehydrogenation of VI with dichlorodicyanobenzoquinone in dioxane afforded the known 25D-spirosta-1,4-diene-3,11-dione (VII), m.p. 247°.[4]

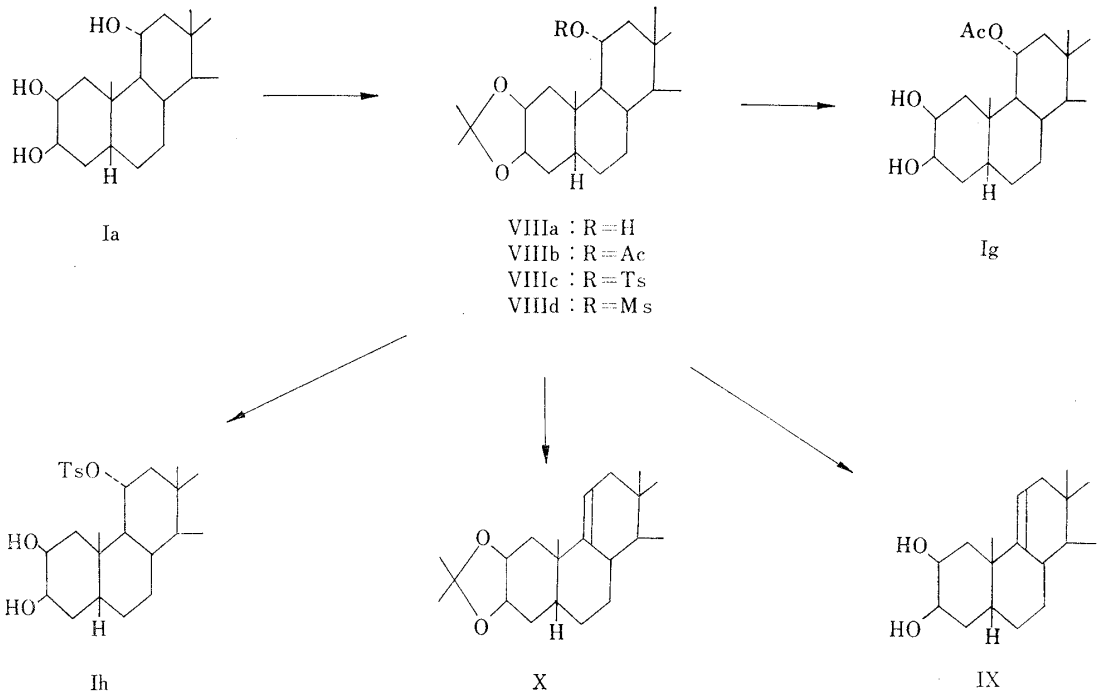

Chart 2.

3) *a*) R. P. Holysz : J. Am. Chem. Soc., **75**, 4432 (1953). *b*) R. Joly, J. Warrant, G. Nominé, D. Bertin: Bull. soc. chim. France, **1958**, 366. *c*) L. Ehrmann, K. Hersler, Ch. Mystre, P. Wieland, G. Anner, A. Wettstein : Helv. Chim. Acta, **42**, 2548 (1959).

4) D. N. Kirk, D. K. Patel, V. Petrow : J. Chem. Soc., **1957**, 1046.

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On the other hand, in the case of mesylation in pyridine only trimesylate (Ie) was obtained, and under rather mild conditions (pyridine-chloroform (1:2)) mainly amorphous monomesylate (If) was obtained together with the trimesylate (Ie) as a by-product. The required 2,11-dimesylate was not yielded. Since the monomesylate (If) also gave nogiragenone (Ⅲ) when treated with collidine, mesylation occurred at position 2 as in the case of tosylation.

As partial tosylation or mesylation at both positions 2 and 11 of metagenin (Ia) was unsuccessful we next turned to synthesize 11-monotosylate or 11-monomesylate, after protecting the 2 and 3 hydroxyl groups. As was reported in the previous paper, metagenin 11-monoacetate was obtained by acetylation of metagenin acetonide (Ⅷa) followed by the action of 70% aqueous acetic acid.

11α-Tosyloxy-metagenin acetonide (Ⅷc), m.p. 143°(decomp.), was obtained by tosylation of the acetonide (Ⅷa) in pyridine in the usual manner. However, the product obtained by treatment of Ⅷc with 70% aqueous acetic acid was not the desired metagenin 11-monotosylate, but the unexpected 5β-spirost-9(11)-ene-2β,3β-diol (Ⅸ), which was identical with the specimen prepared from 11-epimetagenin by the action of methanolic hydrochloride.[1c] 11α-Tosyloxy-metagenin (Ih) was obtained by the action of perchloric acid at room temperature in quantitative yield.

It might be expected that the 11α-tosyl group would undergo elimination easily and so treatment of Ⅷc with aluminum oxide was examined and the expected 5β-spirost-9(11)-ene-2,3-diol acetonide (Ⅹ), m.p. 149°, was obtained. This was identified by its conversion to 2,3-diol (Ⅸ).

Treatment of 11α-mesyloxy-metagenin acetonide (Ⅷd), m.p. 160°(decomp.), obtained as in the case of Ⅷc, with aqueous acetic acid also gave 5β-spiost-9(11)-ene-2,3-diol (Ⅸ). However, its reactivity of aluminum oxide seemed less sensitive and the starting material was recovered.

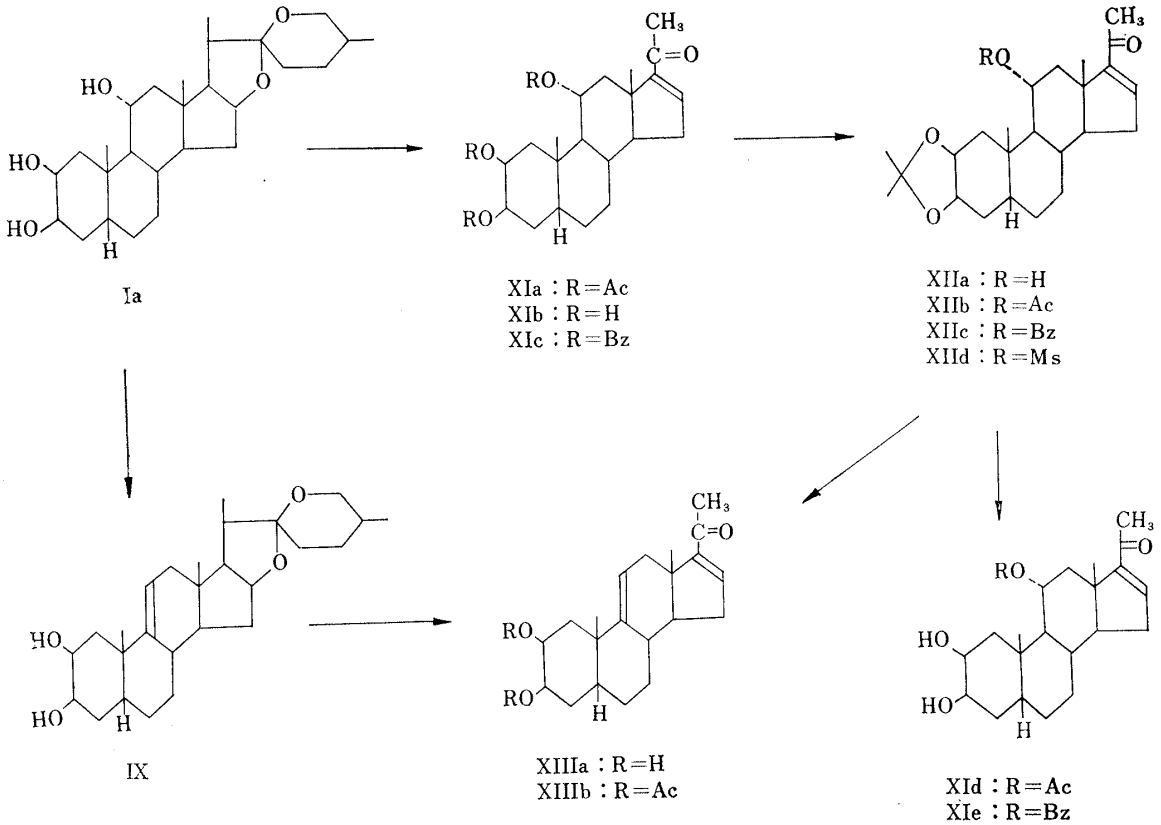

Chart 3.

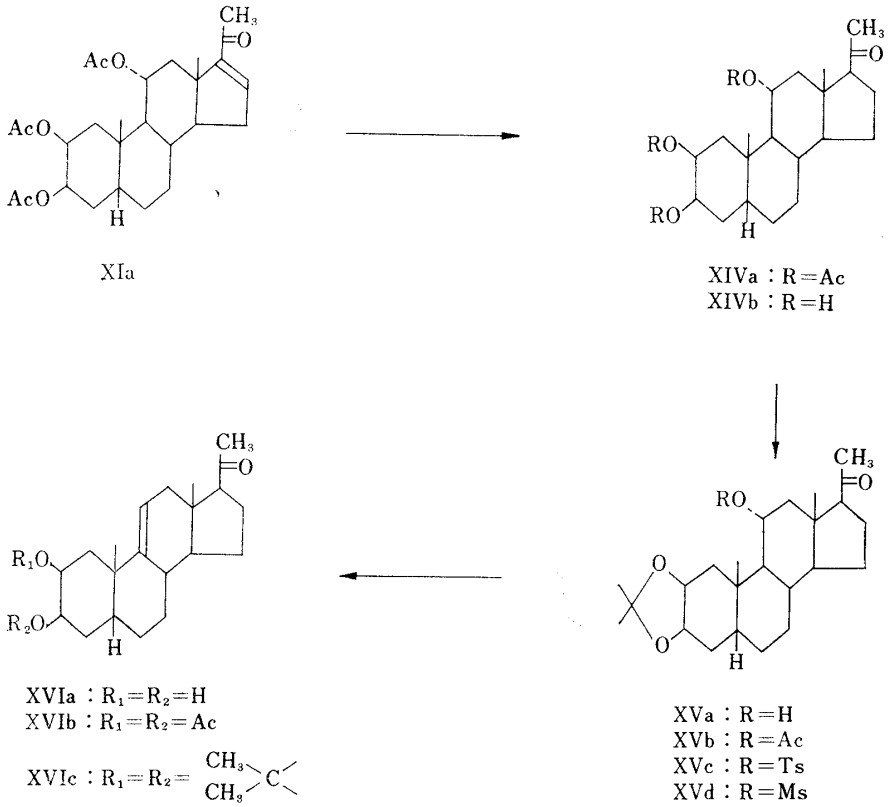

Chart 4.

Since these easy eliminations of the tosyl or mesyl group under such mild conditions was of interest, the same reaction was applied to the 20-ketopregnane series without the spiro ketal side-chain in order to confirm this phenomenon.

Metagenin (Ia) was degraded to 5β-pregn-16-ene-2β,3β,11α-triol-20-one triacetate (XIa), m.p. 210°, in 65% yield according to the method developed by Mueller.[5] Saponification of XIa with alkali gave the triol (XIb), which was converted to its tribenzoate (XIc), m.p. 239°, or acetonide (XIIa), m.p. 177°. Acetylation or benzoylation of the 2,3-acetonide (XIIa) afforded its 11α-acetoxy-acetonide, m.p. 200°, or 11α-benzoyloxy-acetonide (XIIc), m.p. 187°, respectively. Each derivative gave the expected 2,3,11-triol 11-monoacetate, m.p. 228°, or 11-monobenzoate, m.p. 181°, by the treatment with aq. acetic acid.

Although the above-obtained 11α-hydroxy-actonide (XIIa) resisted tosylation with tosyl chloride in pyridine at room temperature, the mesylate (XIId) was obtained as an amorphous substance under the same conditions. This mesylate, by the elimination reaction of aqueous acetic acid, gave 2β,3β-dihydroxy-5β-pregna-9(11), 16-dien-20-one (XIIIa), m.p. 179°. This was identical with the authentic sample obtained by the saponification of 2β,3β-dihydroxypregna-9(11),16-dien-20-one diacetate (XIIIb), derived from spirost-9(11)-ene-2β,3β-diol (IX) by the usual spiro-ketal side-chain degradation method.

2β,3β,11α-Trihydroxy-5β-pregnan-20-one (XIVb) showed an almost similar behavior with 2β,3β,11α-trihydroxy-5β-pregn-16-en-20-one (XIIa). 5β-Pregnatriolone triacetate (XIVa), m.p. 223°, was synthesized by catalytic hydrogenation of XIa with palladium-on-charcoal in methanol or ethyl acetate and its alkaline hydrolysis afforded triol (XIVb), m.p. 141°. A syrupy 11α-hydroxy-acetonide (XVa), which was obtained from XIVa in the usual manner, was able to purify as an crystalline acetate (XVb), m.p. 152°.

5) G. P. Mueller : Nature, **181**, 177 (1958).

11α-Tosyloxy-acetonide (XVc) was transformed to $\Delta^{9(11)}$-acetonide (XVIc), as an amorphous powder, by the action of alumina but the 11α-mesyloxy derivative (XVd) was not affected by alumina but it afforded the $\Delta^{9(11)}$-derivative (XVIa), m.p. 137°, with 70% aqueous acetic acid as in the case of the spirostane derivatives.

These results showed that in the course of partial acylation of metagenin (Ia), the 2β-tosyloxy group inhibited further tosylation of 11α- and 3β-hydroxyl groups and that the 11α-tosyl or 11α-mesyl group was easily eliminated with aqueous acetic acid. The failure to further tosylation of (Ic) may be due to the bulkiness of the group as compared with the acetyl, benzoyl or mesyl group, because in these cases acylation proceeded normally to give the corresponding triacyl derivatives of metagenin (I).

The elimination reaction of a $C_{11\alpha}$-hydroxyl group may be conveniently explained by an EI mechanism, which is to be reported later.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Ultraviolet spectra were recorded on a Hitachi Recording Spectrophotometer Model DS 301 : infrared spectra were determined with a Nippon Bunko DS-201B spectrometer. Specific rotations were recorded in chloroform containing 1% ethanol with a Rudolf polarimeter.

Metagenin 2-Monotosylate (Ic)——To a solution of 1.0 g. of metagenin (Ia) dissolved in 30 ml. of pyridine was added 2.6 g. (ca. 4 eq.) of tosyl chloride with ice-cooling and the mixture was allowed to stand for 15 hr. at room temperature. After the mixture was diluted with 500 ml. of water and allowed to stand for 1.5 hr., the precipitate was extracted with the mixture of ether-$CHCl_3$ (1:1). The extract was washed, dried and the solvent was evaporated, leaving 1.44 g. of yellow syrup. Treatment with petr. ether-ether mixture afforded (Ic), m.p. 138~139° (decomp.), $[\alpha]_D^{23.5}$ −77.1° (c=1.006). *Anal.* Calcd. for $C_{34}H_{50}O_7S$: C, 67.62; H, 8.35; S, 5.32. Found : C, 67.73; H, 8.43; S, 5.06. IR ν_{max}^{Nujol} cm^{-1} : 3580. The same result was obtained in the case of treatment for 70 hr.

Nogiragenone (III) from 2-Monotosylate (Ic)——The solution of 170 mg. of Ic dissolved in 6 ml. of collidine was refluxed and treated as usual. Recrystallization from *n*-hexane-$CHCl_3$ gave needles, m.p. 251~253°, of which the mixed m.p. and IR with nogiragenone (III) were identical.

25D,5β-Spirostane-3α,11α-diol (IVa), Diacetate (IVb) and Dibenzoate (IVc)——a) $NaBH_4$ reduction of nogiragenone (III) : To a solution of 73 mg. of nogiragenone (III) dissolved in 25 ml. of MeOH was added the solution of 50 mg. of $NaBH_4$ suspended in 5 ml. of MeOH and the mixture allowed to stand for 3 hr. at room temperature. To the reaction mixture 30 ml. of H_2O and AcOH was added, MeOH was distilled off *in vacuo* and the residue was extracted with ether. The extract was washed and dried over Na_2SO_4. The residue (72 mg.) was purified through Al_2O_3 column. The syrupy substance (66 mg.) eluted from benzene-ether (1:1) mixture and ether was acetylated with 1.5 ml. of pyridine and 1.5 ml. of acetic anhydride, standing overnight at room temperature. Usual work-up gave 69 mg. of syrup which was purified by Al_2O_3 chromatography. From the benzene fraction 62 mg. of IVb m.p. 215~223°, was obtained and recrystallization from $CHCl_3$-MeOH mixture gave white needles, m.p. 225~227°, $[\alpha]_D^{22}$ −59.2°. *Anal.* Calcd. for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found : C, 71.86; H, 9.40. IR ν_{max}^{Nujol} cm^{-1} : 1723, 1735 (1240, 1250). This material showed no depression of melting point on admixture with 3α,11α-diacetate (IVb).

The above-mentioned crystal of diacetate (IVb), was hydrolyzed with 10% methanolic potassium hydroxide solution. A crystal, m.p. 102~105°, was obtained and recrystallization from dil. MeOH gave a white crystal, m.p. 115~116°. $[\alpha]_D^{23.5}$ −77.3° (c=1.015). *Anal.* Calcd. for $C_{20}H_{44}O_4 \cdot H_2O$: C, 71.96; H, 10.29. Found : C, 72.40; H, 10.41.

b) From metagenin 2-monotosylate (Ic) : 1.14 g. of metagenin 2-tosylate dissolved in 10 ml. of each pyridine and Ac_2O was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water and the resulting precipitate was filtered off. The usual work-up gave a powder and melted at 123~128°. A solution of 0.6 g. of acetoxy-tosylate (Id) dissolved in tetrahydrofurane (THF) was added to a solution of 1 g. of $LiAlH_4$ suspended in 20 ml. of THF and the mixture was refluxed for 6 hr. on a water bath. When cooled, excess $LiAlH_4$ was decomposed by addition of 150 ml. of H_2O, the hydroxide that precipitated out was dissolved by addition of dil. HCl, and the solution was extracted with $CHCl_3$. Syrupy residue (0.44 g.) was purified by Al_2O_3 chromatography and the fraction eluted with ether-$CHCl_3$ (1:1) mixture and $CHCl_3$ afforded 0.25 g. of syrup. A mixture of this syrup and Ac_2O was heated for 1 hr. on a water bath and treated as usual. Recrystallization from MeOH gave a crystal, m.p. 215~220°, which was identical with the 3α,11α-diacetate (IVb), mentioned in (a), in all respects.

c) $LiAlH_4$ reduction of metagenin 2-monotosylate (Ic) : To a solution of 1.41 g. of metagenin 2-tosylate (Ic) dissolved in 50 ml. of anhyd. ether was added a solution of 2 g. of $LiAlH_4$ suspended in 20

ml. of anhyd. ether and the mixture was heated for 5 hr. under reflux. The same after-treatment mentioned in (a) gave 0.94 g. of syrup. Of this product 0.74 g. dissolved in 10 ml. of pyridine and 1 ml. of benzoyl chloride was allowed to stand overnight at room temperature. The reaction mixture was poured into water, extracted with ether and washed with H_2O, dil. HCl, 5% Na_2CO_3, H_2O, dried over Na_2SO_4, and was evaporated to dryness. The residue was purified by Al_2O_3 chromatography, from which 0.77 g. of 3α,11α-diol dibenzoate (IVc) eluted with petr. ether-benzene (1:1) fraction was obtained. IVc, m.p. 177~178°. $[\alpha]_D^{23}$ −83.3°(c=1.081). *Anal.* Calcd. for $C_{41}H_{52}O_6$: C, 76.84; H, 8.18. Found: C, 77.01; H, 8.20.

Dibenzoate, obtained above, was hydrolysed to IVa, m.p. 102~105°, identified with the sample of 3α,11α-diol on admixture.

2-Tosyloxy-25D,5β-spirostane-3,11-dione (V)——A mixture of CrO_3-H_2SO_4 (1.2 eq.) was added to a solution of 2.0 g. of metagenin 2-monotosylate (Ic) in 10 ml. of acetone during 3 min. and immediately poured into a large volume of ice-water. The precipitate was extracted with ether, washed, dried and the solvent was removed. Recrystallization from petr. ether-ether afforded V, m.p. 133~135°(decomp.). $[\alpha]_D^{24}$ −58.0°(c=0.983). *Anal.* Calcd. for $C_{34}H_{46}O_7S\cdot H_2O$: C, 65.99; H, 7.58. Found: C, 66.20; H, 7.52. IR ν_{max}^{Nujol} cm^{-1}: 1739, 1706 (>C=O), 1602, 1175 (-OTs).

25D,5β-Spirost-1-ene-3,11-dione (VI)——To a solution of 1.0 g. of 2-tosyloxy-3,11-dione (V) in 32 ml. of dimethylformamide was added each 2.5 g. of LiBr and Li_2CO_3, and heated with stirring under N_2 atmosphere for 15 hr. avoiding moisture, at 90~95°. Pouring the reaction mixture into ice-water, the precipitate was extracted with ether, the extract washed with dil. HCl, H_2O and dried. The solvent was distilled off to give 630 mg. of oily substance. Purification by Al_2O_3 chromatography gave 547 mg. of VI, m.p. 187~211°, eluted by benzene-petr. ether and benzene. Pure VI, (petr. ether-ether mixture) needles, m.p. 209~212°. $[\alpha]_D^{24}$ +18.5 (c=0.985). *Anal.* Calcd. for $C_{27}H_{38}O_4$: C, 76.02; H, 8.96. Found: C, 75.93; H, 8.98. IR ν_{max}^{Nujol} cm^{-1}: 1701 (>C=O), 1683 (conjugated C=O); 1615 (>C=C<). Treatment of V with collidine gave the same product.

25D-Spirosta-1,4-diene-3,11-dione (VII)——To a solution of 120 mg. of 1-ene-3,11-dione (VI) dissolved in 10 ml. of anhydrous dioxane, was added 160 mg. of DDQ (1.2 eq.) and refluxed for 15 hr. in an oil bath. After cooling, precipitated DDH was filtered off and the filtrate was evaporated under reduced pressure. Purification of the residue by Al_2O_3 chromatography gave 89 mg. of crystals, m.p. 220~235°, which were recrystallized from *n*-hexane-$CHCl_3$ mixture to give prisms, m.p. 244~247°. $[\alpha]_D^{24.5}$ +38.0 (c=1.004). *Anal.* Calcd. for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.48; H, 8.49. IR ν_{max}^{Nujol} cm^{-1}: 1702 (>C=O), 1666 (conjugated >C=O), 1631, 1607 (>C=C<).

Mesylation of Metagenin (Ia)——Under chilling, 0.5 g. of MsCl (3 mole × 1.3) was added dropwise to a solution of 0.5 g. of metagenin (Ia) dissolved in the mixture of 7.5 ml. of pyridine and 15 ml. of $CHCl_3$ and allowed to stand for 3 hr. at 0°. The reaction mixture was worked up as usual and an oily substance was obtained. Separation by silica gel chromatography gave 0.16 g. of crude Ie, m.p. 140~144° (decomp.) from petr. ether-benzene (1:1) fraction and 0.43 g. of If as an amorphous powder, m.p. 147~150°.

After 113 mg. of this ether eluate was refluxed with 3 ml. of collidine for 6 hr., 75 mg. of an oily product was obtained which was purified by Al_2O_3 chromatography. From benzene-ether (9:1) elution, 44 mg. of nogiragenone (III), m.p. 243~245°, was obtained. From MeOH fraction, 0.1 g. of the starting material was recovered.

11α-Tosyloxy-25D,5β-spirostane-2β,3β-diol Acetonide (VIIIc)——To a solution of metagenin acetonide (VIIIa) in 36 ml. of pyridine was added 4.5 g. of TsCl and the mixture allowed to stand overnight at room temperature. Work-up in the usual manner afforded 3.2 g. of VIIIc as needles (from *n*-hexane-$CHCl_3$), m.p. 142~143°. $[\alpha]_D^{24}$ −62.1°(c=1.055). *Anal.* Calcd. for $C_{37}H_{54}O_7S$: C, 69.14; H, 8.47. Found: C, 69.19; H, 8.70. IR ν_{max}^{Nujol} cm^{-1}: 1600, 1170 (-OTs), 1360 (acetonide).

11α-Mesyloxy-25D,5β-spirostane-2β,3β-diol Acetonide (VIIId)——To a solution of 0.440 g. of metagenin acetonide (VIIIa) dissolved in 7 ml. of pyridine was added 0.44 g. of MsCl and the mixture allowed to stand overnight at room temperature. The reaction mixture was treated as usual and 0.598 g. of yellow needle was obtained. Recrystallization from petr. ether afforded VIIId, needles, m.p. 159~160°(decomp.). $[\alpha]_D^{24}$ −86.5°(c=0.994). *Anal.* Calcd. for $C_{31}H_{50}O_7S\cdot\frac{1}{2}H_2O$: C, 64.64; H, 8.93. Found: C, 64.70; H, 8.97.

25D,5β-Spirost-9(11)-ene-2β,3β-diol (IX)——a) From 11α-tosyloxy-acetonide (VIIIc): A solution of 1.5 g. of tosyloxy-acetonide (VIIIc) dissolved in 70 ml. of 70% acetic acid was heated for 3 hr. at 60~65° in a water bath. The reaction mixture was concentrated to ca. ⅔ volume, extracted with ether, washed with 5% Na_2CO_3, H_2O, dried and the extract was evaporated to leave 1.7 g. of white crystals. Recrystallization of above crystals from *n*-hexane-$CHCl_3$ mixture afforded 0.865 g. of IX, needle, m.p. 174~176° which was identified with the authentic sample.

b) From 11α-mesyloxy-acetonide (VIIId): 100 mg. of mesyloxy-acetonide (VIIId) was treated with 50% acetic acid for 1 hr. as described above. The obtained 123 mg. of amorphous substance was purified by silica gel chromatography. From ether fraction, 93 mg. of IX was obtained. Crystallization from petr. ether afforded pure IX, m.p. 174~176°.

25D,5β-Spirost-9(11)-ene-2β,3β-diol Acetonide (X)——In a solution of 500 mg. of tosyloxy-acetonide (Ⅷc) dissolved in 30 ml. of benzene 15 g. of Al_2O_3 (E. Merck standardized) was suspended and stirred for 20 hr. at room temperature. Al_2O_3 was separated by filtration and washed with $CHCl_3$ for several times. Filtrates and washings were combined and evaporated to leave 320 mg. of crystals, m.p. 144~149°, which was recrystallized from MeOH-ether gave X, needles, m.p. 148~149°. $[\alpha]_D^{24}$ −78.1° (c=1.039). *Anal.* Calcd. for $C_{30}H_{46}O_4$: C, 76.55; H, 9.85. Found: C, 76.64; H, 9.87. IR ν_{max}^{Nujol} cm^{-1}: 3036 (>C=C<), 1370 (acetonide).

A solution of 580 mg. of X in 70% acetic acid was warmed at 60~65° for 1.5 hr. in a water bath, and the reaction mixture was evaporated to ⅔ volume and poured into a large volume of ice-water. The precipitate was extracted with $CHCl_3$-ether (1:1), washed, dried and evaporated to give 530 mg. of Ⅸ, m.p. 174~176°.

11α-Tosyloxy-25D,5β-spirostane-2β,3β-diol (Ih)——To a solution of 1.05 g. of the tosyloxy-acetonide (Ⅷc), in 20 ml. of dioxane was added 2 ml. of 70% perchloric acid and 5 ml. of water with ice cooling and the reaction mixture was allowed to stand for 1 hr. at room temperature. Then 5% aqueous sodium carbonate solution was added to the solution, and the product was isolated with ether. Recrystallization from *n*-hexane-chloroform yielded 890 mg. of tosyloxy-diol (Ih), m.p. 156~157° (decomp.), $[\alpha]_D^{24.5}$ −54.6 (c=0.786). IR ν_{max}^{Nujol} cm^{-1}: 3600, 3553 (OH). *Anal.* Calcd. for $C_{34}H_{50}O_7S$: C, 67.74; H, 8.36. Found: C, 67.85; H, 8.49.

2β,3β,11α-Triacetoxy-5β-pregn-16-en-20-one (XIa)——Five grams of metagenin (Ia) was heated 30 min. with 23.5 ml. of acetic anhydride, 1.6 g. of pyridine hydrochloride was added and heating continued for 3 hr. The mixture was cooled, diluted with 2.6 ml. of acetic acid and 4.6 ml. of water and added 2.9 g. of chromic anhydride in 28 ml. of 90% acetic acid while stirring. The temperature was maintained at 15~20°. After standing at 25° for 3 hr. the solution was treated first with 1.7 ml. of 37% formaldehyde and then with 4.25 g. of sodium acetate. The stirred suspension was heated on a water bath for 1 hr., cooled and diluted gradually with 300 ml. of cold water. A white precipitate was collected, washed and dried (5.29 g.). It was absorbed on Al_2O_3 and 3.728 g., m.p. 196~210° of crystal was eluted from benzene-petr. ether (1:1), benzene and ether-benzene (1:9). Recrystallization from $CHCl_3$-MeOH afforded 3.435 g. of prisms, m.p. 204~207°. Pure Ⅺa, m.p. 209~210°. $[\alpha]_D^{23.5}$ +2.7° (c=1.073). *Anal.* Calcd. for $C_{27}H_{38}O_7$: C, 68.32; H, 8.07. Found: C, 68.31; H, 8.12. IR ν_{max}^{Nujol} cm^{-1}: 1743, 1255, 1216 (AcO-), 1729 (C=O), 1661, 1593 (α,β-unsat. ketone).

2β,3β,11α-Trihydroxy-5β-pregn-16-en-20-one (XIb)——Five hundred milligrams of acetate (Ⅺa) was saponified with 5% methanolic potassium hydroxide to give 385 mg. of Ⅺb. Pure Ⅺb (from acetone), needles, m.p. 229~231°. $[\alpha]_D^{23.5}$ +13.1° (c=1.073). *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.24; H, 9.31. IR ν_{max}^{Nujol} cm^{-1}: 3380 (OH), 1660 (20-ketone), 1590 (Δ^{16}). Its tribenzoate (Ⅺc), m.p. 237~239°. $[\alpha]_D^{24}$ −94.7° (c=1.000). *Anal.* Calcd. for $C_{42}H_{44}O_7$: C, 76.34; H, 6.71. Found: C, 76.21; H, 6.77. IR ν_{max}^{Nujol} cm^{-1}: 1710, 1720 (1272, 1280) (φCOO-), 1660 (conjugated >C=O).

2β,3β,11α-Trihydroxy-5β-pregn-16-en-20-one Acetonide (XIIa)——To a solution of 200 mg. of triol (Ⅺb) dissolved on 26 ml. of acetone was added 26 mg. of *p*-toluene sulfonic acid and the mixture refluxed for 13 hr. on a water bath avoiding moisture. Work-up as usual followed by Al_2O_3 chromatography gave 203 mg. of Ⅻa, fine needles, m.p. 171~177° from benzene-ether (1:1) fraction. *Anal.* Calcd. for $C_{24}H_{36}O_4$: C, 74.18; H, 9.34. Found: C, 74.53; H, 9.47. IR ν_{max}^{Nujol} cm^{-1}: 3473 (OH), 1670 (20-ketone), 1591 (Δ^{16}). Its acetate (Ⅻb), colorless needles (from petr. ether-ether), m.p. 199~200°. $[\alpha]_D^{24.5}$ −26.0° (c=1.014). *Anal.* Calcd. for $C_{26}H_{38}O_5$: C, 72.52; H, 8.89. Found: C, 72.73; H, 8.90. IR ν_{max}^{Nujol} cm^{-1}: 1725 (1250) (-OAc), 1680 (conjugated >C=O), 1600 (C=C). Its benzoate (Ⅻc), needles, m.p. 185~187°. $[\alpha]_D^{22.5}$ −62.1° (c=1.077). *Anal.* Calcd. for $C_{31}H_{40}O_5$: C, 75.57; H, 8.18. Found: C, 75.73; H, 8.51. IR ν_{max}^{Nujol} cm^{-1}: 1705 (1280) (φCOO-), 1660 (conjugated >C=O), 1590 (φ-).

2β,3β,11α-Hydroxy-5β-pregn-16-en-20-one 11-Acetate (XId)——The acetoxy-acetonide (Ⅻb) (37 mg.) obtained above, was treated with 70% acetic acid by heating for 3 hr. at 60~65° on a water bath and extracted with ether-$CHCl_3$ (3:1) mixture.

The organic layer was washed, dried over Na_2SO_4 and evaporated under reduced pressure to leave 35 mg. of an oily product. Recrystallization from ether afforded Ⅺd, needles, m.p. 227~228°. $[\alpha]_D^{24.5}$ −33.2° (c=1.013). *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.72; H, 8.79. IR ν_{max}^{Nujol} cm^{-1}: 3580 (OH), 1710 (1260) (-OAc), 1650 (conjugated >C=O).

2β,3β,11α-Trihydroxy-5β-pregn-16-en-20-one 11-Benzoate (XIe)——Benzoyloxy-acetonide (Ⅻc) (34 mg.) was treated as above to give 26 mg. of crystalline substance which was recrystallized from petr. ether-ether to afford 20 mg. of Ⅺe, needles, m.p. 179~181°. $[\alpha]_D^{24}$ −92.4° (c=0.951). *Anal.* Calcd. for $C_{28}H_{36}O_5$: C, 74.30; H, 7.96. Found: C, 74.11; H, 8.00. IR ν_{max}^{Nujol} cm^{-1}: 3400 (-OH), 1710 (1280) (φCOO-), 1590 (φ-), 1660 (conjugated >C=O).

2β,3β-Dihydroxy-5β-pregna-9(11),16-dien-20-one (XIIIa)——a) From 11α-mesyloxyacetonide: To a mixture of 168 mg. of Ⅻa in 3.5 ml. of pyridine was added dropwise 168 mg. of mesyl chloride and

allowed to stand overnight at room temperature. After dilution of the reaction mixture, the precipitate was extracted with $CHCl_3$, the extract was washed with 10% H_2SO_4, H_2O, dried and evaporated to leave 214 mg. of an oily residue. This product did not crystallize and was treated with 10 ml. of 70% acetic acid at 60～65° for 3 hr. in a water bath. By the usual treatment, 176 mg. of yellow oil was obtained and recrystallized from ether to give 49 mg. of XIIIa, needle, m.p. 166～168°. *Anal.* Calcd. for $C_{21}H_{30}O_3 \cdot \frac{1}{2} H_2O$: C, 74.29; H, 9.20.Found: C, 74.48; H 9.23. IR ν_{max}^{Nujol} cm^{-1}: 3425, 3325 (OH), 1661 (20-ketone), 1594 (Δ^{16}).

b) From 25D,5β-spirost-9(11)-ene-2β,3β-diol (IX): 9(11)-ene-2,3-diol (IX) (405 mg.) was heated 30 min. with 2 ml. of acetic anhydride; 0.16 g. of pyridine hydrochloride was added and heated for further 3 hr. The reaction mixture was then oxidized with 0.24 g. of chromium trioxide as in the case of XIa. An oily product (527 mg.) was obtained which was purified by Al_2O_3 chromatography to afford 140 mg. of crude XIIIb from benzene elutions. Recrystallization from *n*-hexane gave 111 mg. of pure XIIIb, m.p. 140～145°. $[\alpha]_D$ +73.2°(c=1.264). *Anal.* Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 71.91; H, 8.51. Diacetate (XIIIb) (111 mg.), obtained above, was saponified by refluxing with 2 ml. of methanolic potassium hydroxide and the mixture was treated as usual to afford 61 mg. of XIIIa which was identical with the sample of 2β,3β-diol obtained in (a).

2β,3β,11α-Triacetoxy-5β-pregnan-20-one (XIVa)——A solution of 2.0 g. of 16-en-20-one (XIa) dissolved in 30 ml. of EtOAc was shaken with 10% palladium charcoal catalyst under hydrogen atmosphere. After removal of the catalyst and evaporation of the solvent under reduced pressure, a crystalline residue was obtained and recrystallized from MeOH-$CHCl_3$ to afford 1.5 g. of XIVa, plates, m.p. 216～219°. $[\alpha]_D^{22.5}$ +44.4°(c=1.018). *Anal.* Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 67.94; H, 8.41. IR ν_{max}^{Nujol} cm^{-1}: 1703 (ketone). Treatment of XIVa with 5% methanolic potassium hydroxide gave free triol (XIVb), prism (from acetone), m.p. 137～141°. $[\alpha]_D^{23.5}$ +48.8°(c=0.551). *Anal.* Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.49; H, 9.81. IR ν_{max}^{Nujol} cm^{-1}: 3330～3470 (OH), 1715 (>C=O).

11α-Acetoxy-2β,3β-isopropylidenedioxy-5β-pregnan-20-one (XVb)——A solution of 1.0 g. of triol (XIVb) dissolved in 100 ml. of anhydrous acetone containing 0.5 ml. of 72% perchloric acid was stirred for 2 hr. at room temperature, neutralized with 5% Na_2CO_3 and the excess acetone was evaporated under reduced pressure and the reaction mixture was extracted with ether. The residue, after evaporation of ether, was 1 g. of an oily substance and purified as its acetate (XVb). Acetylation of 930 mg. of the crude 11α-hydroxy acetonide (XVa), with 5 ml. of Ac_2O and 9 ml. of pyridine at room temperature followed by recrystallization from petr. ether-ether gave 500 mg. of XVb, long needles, m.p. 150～152°. $[\alpha]_D^{25}$ +21°(c=1.109). *Anal.* Calcd. for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 71.88; H, 9.29. IR ν_{max}^{Nujol} cm^{-1}: 1727 (1246) (-OAc), 1702 (>C=O). The acetate (XVb) (500 mg.) was refluxed with 40 ml. of 5% methanolic potassium hydroxide and the usual after-treatment gave 490 mg. of oily product. Crystallization was also unsuccessful.

2β,3β-Dihydroxy-5β-pregn-9(11)-en-20-one (XVIa)——a) A solution of 2.4 g. of 11α-hydroxy-acetonide (XVa) was tosylated with 2.4 g. of tosyl chloride in pyridine and worked up as usual to give an amorphous XVc, 3.12 g. (IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1710 (C=O), 1170 (-OTs), 1600 (CH_3-C_6H_4-). A solution of 2.7 g. the crude tosyloxy-acetonide (XVc) dissolved in 135 ml. of 60% acetic acid was warmed for 2 hr. at 60～65° in a water bath and adding water the reaction mixture was distilled to ⅔ volumes. There was obtained 1.2 g. of crystalline substance m.p. 98～102°. Recrystallization from acetone-*n*-hexane afford 1.12 g. (XVIa), needles, m.p. 135～136°. $[\alpha]_D^{24.5}$ +66.3°(c=0.475). *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.08; H, 9.81. IR ν_{max}^{Nujol} cm^{-1}: 3290 (OH), 3020 (-C(H)=C), 1713 (>C=O).

2β,3β-Diacetoxy-5β-pregn-9(11)-en-20-one (XVIb)——a) 9(11)-ene-2β,3β-diol (XVIa) (986 mg.) was acetylated by the usual manner to give 620 mg. of XVIb, needles from *n*-hexane-ether, m.p. 122～125°. $[\alpha]_D^{28}$ +68.0°(c=1.038). *Anal.* Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.13; H, 8.82. IR ν_{max}^{Nujol} cm^{-1}: 1735 (1245) (OAc), 1708 (>C=O).

b) A solution of 700 mg. of 11α-tosyloxy-2,3-acetonide (XVc) in 15 ml. of benzene was absorbed on 21 g. of Al_2O_3 for 18 hr. at room temperature. Elution from benzene afforded 615 mg. of an amorphous XVIc which showed no tosyloxy band in infrared spectra and positive tetranitromethane color test. XVIc was dissolved in 26.3 ml. of 70% acetic acid and treated as above to afford 450 mg. of an oily material which was acetylated with 5 ml. each of pyridine and acetic anhydride. XVIb (370 mg.) m.p. 119～121°, was obtained and identical with an authentic sample.

c) To a solution of 250 mg. of 11α-hydroxy-acetonide (XVa) dissolved in 2 ml. of pyridine was added 1.5 ml. of mesyl chloride under cooling and the reaction mixture was let to stand overnight at room temperature. A usual treatment gave 254 mg. of an oily XVd which could not be crystallized. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (C=O), 1170 (-OMs). The crude mesyloxy-acetonide (XVd) (217 mg.) was treated with 70% acetic acid and oily product (190 mg.) was obtained. This was immediately acetylated as usual and 180 mg. of an oily product was obtained. This was purified by Al_2O_3 chromatography. Recrystallization from MeOH-ether gave XVIb, needles, m.p. 122～125°.

Summary

Since metagenin (Ia) and nogiragenin (IIa) have inherently 11α-hydroxyl group, both of them seemed to be the most convenient starting materials for the synthesis of cortical hormone intermediates. Several kinds of intermediates were prepared and during the course of the syntheses of them, an easy dehydration of the 11α-hydroxyl group was found.

(Received August 9, 1965)

[Chem. Pharm. Bull. 14(3) 255~262 (1966)]

UDC 615.778.25-011 : 615.41-014 : 54-386

38. Keiji Ito and Keiji Sekiguchi: Studies on the Molecular Compounds of Organic Medicinals. II.*1 Application of the Solubility Product Principle and Consideration by the Phase Rule to the Solubility Phenomena of the Molecular Compound of Sulfanilamide and Sulfathiazole.*2

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Previously, the dissolution behavior of the molecular compound of sulfanilamide and sulfathiazole was investigated and it was observed that the compound dissociates to an appreciable extent into its components. Also, the stability constants were determined both at the stable and the metastable solubility equilibria. Validity of the assumption made for the determination was supported by the satisfactory agreement of the two constants.

In the present paper, solubility determination of the molecular compound is carried out in a series of aqueous solutions containing varying amounts of sulfanilamide in order to examine whether the solubility product principle can be applied to such a slightly soluble organic molecular compound. Based on this principle, a new method of calculating the value of the saturated concentration of the compound itself is proposed. Moreover, the influence of each one of the sulfonamides to the solubility of the other is investigated and the whole results are discussed by the phase rule.

Results and Discussion

Influence of Sulfanilamide on the Solubility of the Molecular Compound; Application of the Solubility Product Principle

So far as the solubility product principle is to hold in any saturated solution of the molecular compound, it can be shown that

$$L=[ST]_{sat}\cdot K'=[S][T] \qquad (1)$$

*1 Part I: This Bulletin, **13**, 405 (1965).

*2 This work was presented at the Hokkaido Branch Meeting of Pharmaceutical Society of Japan, Dec. 15, 1962.

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