CHEMICAL
&
PHARMACEUTICAL BULLETIN

Vol. 12 No. 1 January 1964

[Chem. Pharm. Bull. 12 (1) 1 ~ 5]

UDC 547.92 : 547.918

1. Hiroshi Mitsuhashi, Kazunori Shibata, Tadashi Sato, and Yuzuru Shimizu : Studies of C-Nor-D-homosteroids. II.[1] The Synthesis of C-Nor-D-homopregnane Derivatives from Steroidal Sapogenins.

(*Faculty of Pharmaceutical Sciences, School of Medicine, Hokkaido University*[*1])

In recent years the preparation and hormonal effects of steroids with altered ring system have been widely investigated. Chemical properties and physiological effects of C-nor-D-homosteroids having the same ring system as jervine have remained unknown. Rearrangement of the usual steroid system into C-nor-D-homosteroids was unexpectedly encountered by Hirschmann[2] and Elks[3] during the investigation on the conversion of hecogenin to the 11, 12-unsaturated sapogenin. We have examined the conversion of several normal steroids to C-nor-D-homosteroids and this paper presents the results of the degradation of C-nor-D-homosapogenin, prepared by the rearrangement of hecogenin, to C-nor-D-homopregnane derivatives.

Hecogenin acetate (I) was reduced with sodium borohydride to a mixture of C_{12}-epimers (II). It is apparent from the comparison of their rotation that the yield of rockogenin (12β-OH) in the mixture was 70%. Separation of the mixture by fractional crystallization failed since a molecular complex was formed by the crystallization conditions used. Separation of the mixture was achieved by conversion of them to the 3,12-diacetates followed by fractional crystallization. Treatment of the epimeric mixture (IIa) with *p*-toluenesulfonyl chloride in pyridine gave the crude 12β-tosylate (III), m.p 127° (decomp.), which contained some of the 12α-epimer. When the tosylate (III), instead of the mesylate used by Elks and Hirschmann, was refluxed with potassium *tert*-butoxide in *tert*-butanol for 4 hours, the products were identical with the C-nor-D-homosapogenins, IV, m.p. 227~228°, and V, m.p. 135~142°, prepared by Hirschmann and Elks. When the tosylate (III) was refluxed in pyridine for 7 hours the same results were obtained as from the treatment with potassium *tert*-butoxide in *tert*-butanol.

The mechanism of this rearrangement was discussed by Hirschmann and Elks. We assume that expulsion of a tosylate anion from tosylate A, as shown in Chart 2, proceeds with formation of the intermediate carbonium ion B and elimination of a proton (some form a, b, and c) gives the olefin C. If the attack of a hydride ion occurs on the intermediate carbonium ion before elimination of a proton, the product is expected to be the saturated material D. Rockogenin 3-acetate 12-tosylate (III) in ether was

*1 Kita-12-jo, Nishi-5-chome, Sapporo, Hokkaido (三橋 博, 柴田和則, 里 忠, 清水 譲).

1) H. Mitsuhashi, Y. Shimizu : Tetrahedron, **19**, 1027 (1963).
2) R. Hirschmann, C.S. Snoddy, Jr., C.F. Hiskey, N.L. Wendler : J. Am. Chem. Soc., **76**, 4013 (1954).
3) J. Elks, G.H. Phillipps, D.A.H. Taylor, L.J. Wyman : J. Chem. Soc., **1954**, 1739.

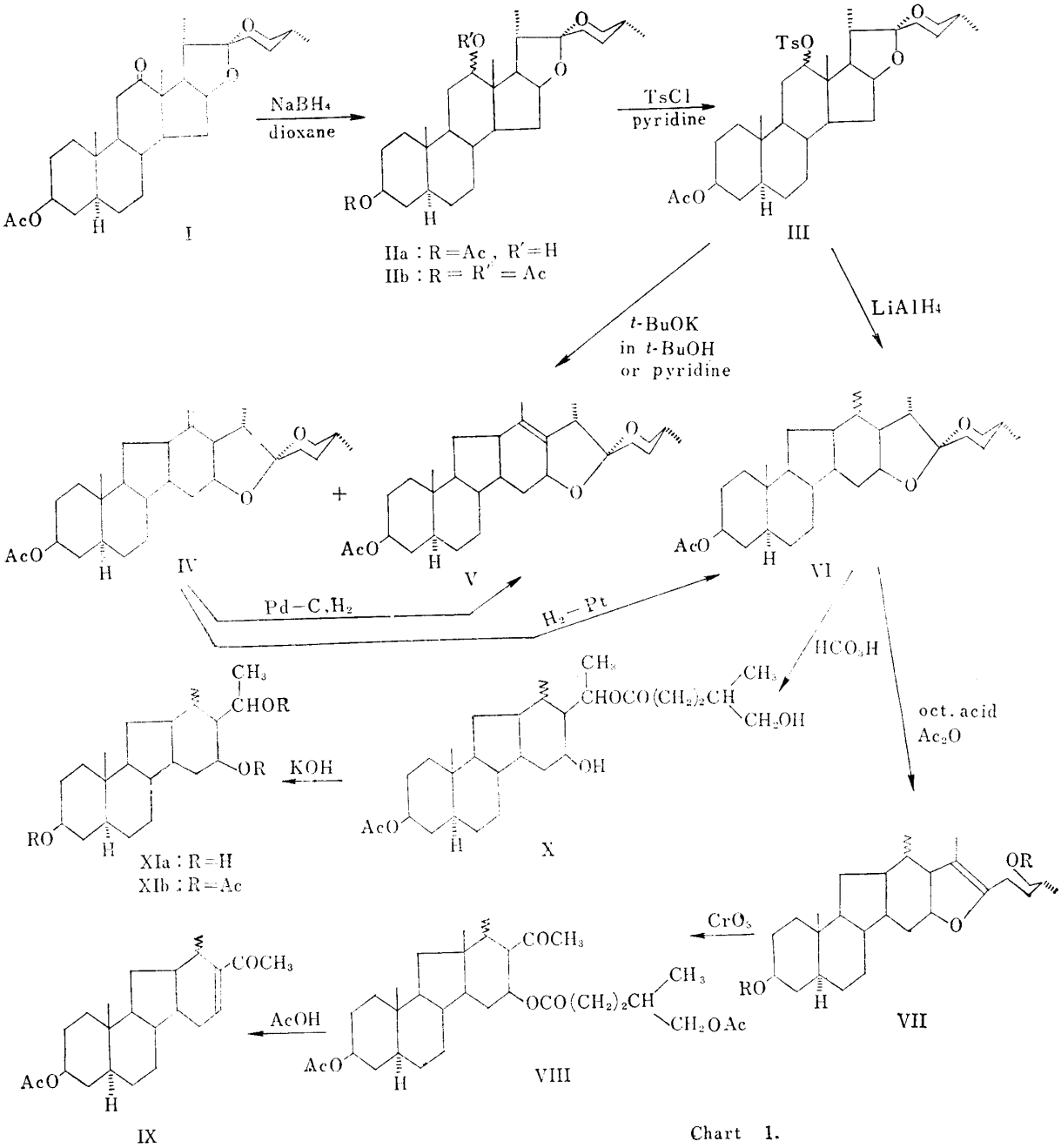

Chart 1.

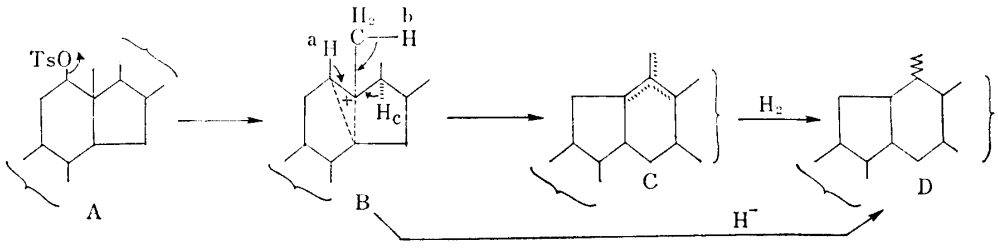

Chart 2.

refluxed with lithium aluminium hydride for 5 hours, gave, besides IV and V, a small amount of the saturated C-nor-D-homosapogenin (VI), confirmed by the mixed melting point and comparison of the infrared spectrum of the acetate with a sample prepared by catalytic hydrogenation of IV. This evidence points to the above-mentioned mechanism for formation of the carbonium ion. Catalytic hydrogenation of a terminal methylene of IV was unexpectedly difficult, but an 80% yield of VI was obtained in tetrahydrofuran and glacial acetic acid with platinum catalyst. When IV is shaken with palladium on charcoal, saturated with hydrogen, it undergoes isomerization to the 17(13)-ene (V).

The first stage of the degradation entailed heating the C-nor-D-homosapogenin in acetic anhydride and octanoic acid at 240°[4] and the product, a yellowish gum, failed to crystallize even after chromatographic separation. This product was oxidized with chromic acid in acetic acid solution followed by hydrolysis with acetic acid to give 3β-acetoxy-C-nor-D-homo-5α-pregn-16-en-20-one (IX) which was separated by chromatography in 30% yield. A pure specimen of C-nor-D-homopseudosapogenin could not be isolated even though formation and separation were attempted in various ways. One attempt which involved refluxing the C-nor-D-homosapogenin (VI) with acetic anhydride under ordinary pressure for 7 hours and subsequent oxidation with chromic acid in acetic acid solution, gave a small amount of C-nor-D-homopregnane derivatives (IX). These results suggest that the C-nor-D-homospiroketal ring system has considerably different properties from the normal ring system.

Another method of degrading a spiroketal ring to C-21 steroids is that of Marker's[5] utilizing the Baeyer-Villiger reaction with permonosulfuric acid (Caro's acid). By applying an improved procedure of Morita's[6], the C-nor-D-homosapogenin (VI) was treated with performic acid in ethylene dichloride and hydrolyzed with alcoholic potassium hydroxide to give C-nor-D-homo-5α-pregnane-3β,16β,20α-triol (XIa, R=H) in 34% yield.

Experimental

Rockogenin 3-Monoacetate (IIa)——A solution of 1 g. of hecogenin acetate (I) in 20 ml. of dioxane was treated with 0.2 g. of $NaBH_4$ in 4 ml. of 50% AcOH. The mixture was adjusted to pH 8 with 5% AcOH, kept at room temperature for 24 hr., acidified, and diluted with H_2O. The solid product was filtered off, washed with H_2O, and dried. This crude product was crystallized from MeOH and methylene chloride, giving 0.84 g. of rockogenin 3-monoacetate as plates, m.p. 217~218°, which was contaminated with the C_{12}-epimer.

Rockogenin 3,12-Diacetate (IIb)——A solution of 990 mg. of IIa (contaminated with C_{12}-epimer) in 10 ml. of pyridine and 5 ml. of Ac_2O was heated 2 hr. The reaction mixture was treated in the usual manner to give IIb (contaminated with 12-epimer). IR ν_{max}^{Nujol} cm^{-1}: 1745, 1240 (acetate), no hydroxyl absorption. $[\alpha]_D^{20}$ −51.5° (c=0.970, $CHCl_3$). Hirschmann, *et al.* reported rockogenin 3,12-diacetate $[\alpha]_D^{20}$ −65° and 12-*epi*-rockogenin-3,12-diacetate $[\alpha]_D^{20}$ −14.9°. When calculated from these values, the foregoing compound (IIa) was contaminated with 27% of the C_{12}-epimer.

Rockogenin 3-Acetate 12-Tosylate (III)——To a solution of 1 g. of rockogenin 3-monoacetate (IIa) in 15 ml. of pyridine was added 1.6 g. of *p*-toluenesulfonyl chloride at 0°. After being left overnight at 25°, the reaction mixture was poured into ice-H_2O and the product extracted with Et_2O. The ethereal solution was evaporated to give the crude tosylate (III), m.p. 127° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1745, 1240 (acetate), 1595, 1170 (tosylate), no hydroxyl absorption.

Conversion of III to IV and V——A solution of 660 mg. of III in 35 ml. of *t*-BuOH containing 0.6 g. of metallic K was refluxed for 4 hr. and then poured into ice H_2O. The mixture was extracted with Et_2O and ethereal solution was washed with HCl solution, $NaHCO_3$, and H_2O, dried, and evaporated. The residue was acetylated with pyridine and Ac_2O. The product was treated in the usual manner

4) A.F.B. Cameron, R.M. Evans, J.C. Hamlet, J.S. Hunt, P.G. Jones, A.G. Long: J. Chem. Soc., **1955**, 2807.
5) R.E. Marker, E. Rohrmann, H.M. Crooks, E.L. Wittle, E.M. Jones, D.L. Turner: J. Am. Chem. Soc., **62**, 525 (1940).
6) K. Morita, S. Noguchi, H. Kono, T. Miki: This Bulletin, **11**, 90 (1963).

and crystallized from methylene chloride-MeOH to 317 mg. of IV, m.p. 221~225°. IR ν_{max}^{Nujol} cm^{-1}: 1745, 1240 (acetate), 1630, 890 (terminal methylene), 90 mg. of V, m.p. 143°. IR ν_{max}^{Nujol} cm^{-1}: 1745, 1240 cm^{-1} (acetate). These products were confirmed by mixed melting point and infrared spectral comparison with an authentic specimen prepared according to the method of Elks.

The mother liquors were chromatographed on alumina, from which 12-*epi*-tosylate was eluted with benzene-Et_2O (9:1), yield 37 mg. m.p. 192°, IR ν_{max}^{Nujol} cm^{-1}: 1745, 1240 (acetate), 1595, 1170 (tosylate), no hydroxyl absorption. In addition a small amount of material, m.p. 109/153°, was separated, but further investigation was given up for lack of material.

To a solution of 1.2 g. of rockogenin 3-acetate 12-tosylate(III) in Et_2O a solution of 1.3 g. of $LiAlH_4$ in 30 ml. of Et_2O was added with stirring. After refluxing for 5 hr., the excess of $LiAlH_4$ was destroyed with Et_2O saturated with H_2O. The ethereal solution was washed with H_2O, dried, and evaporated. The residue was acetylated with pyridine and Ac_2O. The product was crystallized from methylene chloride-MeOH to give 150 mg. (23.7%) of IV, m.p. 222°, and 250 mg. (37%) of V, m.p. 138~140°, which were confirmed by mixed melting point and IR spectral comparison. The mother liquors were chromatographed on alumina, from which 28 mg. of the desired saturated compound, m.p. 160~175°, was eluted with hexane (cf. Chart 2). The mixed melting point of this compound and VI showed no depression and IR spectra of the two compounds were identical.

C-Nor-D-homospirost-13(18)-en-3β-ol Acetate (IV)——To a solution of 1 g. of rockogenin 3-monoacetate (IIa) in 20 ml. of pyridine 1 g. of *p*-toluenesulfonyl chloride was added at 0°. After being left overnight at room temperature, the mixture was refluxed for 7 hr. After cooling, the mixture was poured into ice H_2O, the precipitated crystals were filtered, and recrystallized from methylene chloride-MeOH; yield, 0.34 g. (35%), m.p. 210~220°.

Isomerization of C-Nor-D-homospirost-13(18)-en-3β-ol Acetate (IV) to 13(17)-ene (V)——IV was shaken with 5% Pd-C in EtOH in H_2 stream at atmospheric pressure and room temperature. The product was crystallized from MeOH to give white needles, m.p. 143~145°, undepressed on admixture with an authentic sample.

C-Nor-D-homospirostan-3β-ol Acetate (VI)——A solution of 3.3 g. of IV in 160 ml. each of tetrahydrofuran and AcOH was shaken with 0.8 g. of Adams' catalyst in H_2 stream at atmospheric pressure and room temperature for 4 hr. The catalyst was removed and the filtrate was evaporated under a reduced pressure. The residue was crystallized from Et_2O-MeOH to give 2.7 g. of VI, m.p. 154~154.5°, $[\alpha]_D^{11.5}$ −58.5° (c=1.84, EtOH). Recrystallization from Et_2O-MeOH gave an analytically pure sample of m.p. 155~156°. *Anal.* Calcd. for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found: C, 76.10; H, 10.13.

Pseudo-C-nor-D-homospirostane 3,26-Diacetate (VII)——A solution of 1 g. of C-nor-D-homospirostane 3-acetate (VI) in 1.4 ml. of octanoic acid and 0.5 ml. of Ac_2O was refluxed for 2 hr. The low-boiling fractions were distilled off until the temperature reached 240° and refluxing was continued for 2 hr. thereafter. The reaction mixture was cooled and extracted with Et_2O. The Et_2O extract was washed with 10% NaOH solution and H_2O. Evaporation of the organic phase left a gum that was hydrolysed for 0.5 hr. by refluxing with 10 ml. of MeOH containing 0.5 g. of KOH. Addition of hot H_2O precipitated a white solid which was taken up in Et_2O and ethereal solution was washed with a large amount of H_2O containing a little pyridine, dried, and evaporated. The product in 10 ml. of pyridine was refluxed with 5 ml. of Ac_2O for 0.5 hr., treated in the usual manner, and the oily residue was chromatographed on alumina to give a noncrystalline product.

C-Nor-D-homo-5α-pregn-16-en-20-one 3-Acetate (IX)——The foregoing compound (VII) in 10 ml. of AcOH was treated with 7 ml. of a solution of 1.42*N* chromic acid in 90% AcOH (30% excess) below 30° and after 1.5 hr. the excess of oxidant was destroyed with MeOH. The reaction mixture was extracted with Et_2O and the ethereal solution was washed with 5% $NaHCO_3$ solution and H_2O, dried, and evaporated. The residue was refluxed in 10 ml. of glacial AcOH for 2 hr. The solvent was then removed *in vacuo* and the residue was dissolved in Et_2O. Et_2O extract was washed with $NaHCO_3$ solution and several times with H_2O, and evaporation of the dried solution left a gum that after chromatography on alumina gave 0.24 g. of C-nor-D-homo-5α-pregn-16-en-20-one 3-acetate (IX). One recrystallization from MeOH raised the m.p. to 145°. An analytical sample recrystallized from Et_2O-hexane to long needles, m.p. 145~147.5° (Kofler). UV: λ_{max} 237 mμ, IR ν_{max}^{Nujol} cm^{-1}: 1740, 1240 (acetate), 1655, 1630 (αβ-unsaturated ketone). *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 77.05; H, 9.56. Found: C, 77.08; H, 9.56.

C-Nor-D-homo-5α-pregnane-3β,16β,20α-triol (XIa)——To a solution of 1 g. of C-nor-D-homospirostane 3-acetate (VI) in 5 ml. of ethylene chloride 20 ml. of 99.9% HCOOH and 2 ml. of 30% H_2O_2 were added slowly. The solution was allowed to stand at 50° on a water bath for 1 hr., diluted with H_2O, and the product taken up in methylene chloride. The methylene chloride solution was washed with 5% $FeSO_4$ solution and H_2O, dried, and evaporated. The residue was hydrolyzed with 5% EtOH-KOH. Addition of H_2O precipitated a white solid which was extracted with Et_2O and the ethereal solution was washed with H_2O, dried, and evaporated. The residue was crystallized from MeOH-AcOEt to 0.25 g. of C-nor-D-homo-5α-pregnane-3β,16β,20α-triol (XIb), m.p. 205.5~207°. An analytical sample, needles, m.p. 206.5~207°, from MeOH-isopropyl ether. *Anal.* Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 75.08; H, 10.80.

C-Nor-D-homo-5α-pregnane-3β,16β,20α-triol 3,16,20-Triacetate (XIb)——A solution of 50 mg. of XIa in 4 ml. of pyridine and 2 ml. of Ac_2O was heated on a water bath. After 1 hr., the reaction mixture was treated in the usual manner and the product was crystallized from MeOH to C-nor-D-homo-pregnane-3β,16β,20α-triol 3,16,20-triacetate (XIb), m.p. 207~207.5°. *Anal.* Calcd. for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found: C, 70.19; H, 9.15.

The authors are grateful to Dr. K. Takeda, Director of the Shionogi Research Laboratories, for the supply of the starting material. They are also indebted to Dr. K. Morita for kind suggestion regarding the Baeyer-Villiger reaction. Thanks are also due to Mrs. T. Toma and Miss A. Maeda for the elemental analysis.

Summary

Conversion of hecogenin acetate to C-nor-D-homosapogenin and degradation of its spiroketal ring were achieved according to the scheme shown in Chart 1.

(Received August 17, 1963)

[Chem. Pharm. Bull. 12 (1) 5 ~ 13] *UDC 543.422.4 : 615.778.25*

2. Yo Ueda, Hiroshige Yano, and Tsutomu Momose: Infrared Spectra of Phenylsulfonyl Derivatives. (4). The Infrared Spectra of N-Acylsulfonamide Derivatives. (Organic Analysis. XLVIII*1).

(*Institute of Pharmaceutical Sciences, Faculty of Medicine, Kyushu University**2)

In a previous paper[1] of this series, the infrared spectral effect of SO_2 group on the carbonyl absorption was briefly described in several N-acetylsulfonamide derivatives. In this work, the infrared spectra of 44 kinds of N-acylsulfonamide derivatives, in which 31 kinds were newly synthesized, have been measured and their carbonyl absorptions, SO_2 stretching frequencies, S-N stretching frequencies, C-N stretching frequencies and C-CO-N stretching frequencies are discussed.

Results and Discussion

Carbonyl Absorption

N-Acyl-N-substituted-sulfonamide derivatives had their carbonyl absorptions at longer wave length region than N-acylsulfonamide derivatives either in solution or in solid state as shown in Table I.

The significant fact to be pointed here is that some of the crystalline N-acyl-N-substituted-sulfonamide derivatives had splitted carbonyl absorptions when they were measured in solid state as seen in the table, and lost the phenomenon entirely in solution and liquid states.

The typical diagram is shown in Fig. 1.

---

*1 Part XLVII: This Bulletin, **11**, 1364 (1963).

*2 Katakasu, Fukuoka (上田 陽, 矢野弘重, 百瀬 勉).

1) T. Momose, Y. Ueda, T. Shoji, H. Yano: This Bulletin, **6**, 669 (1958).