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109. **Toshio Nambara**: Analytical Chemical Studies on Steroids. V.[*1] The Synthesis and Rotatory Dispersion of 12-Dehydrodigoxigenin and Some Related Compounds.

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In extention of the previous studies on the stereochemistry of C/D-*cis* steroids,[1~5] an interest in conformation of ring C prompted the author to examine the optical properties of 12-oxo-14β-steroids. Inspection of Dreiding model shows that ring C of C/D-*trans* steroid exists in frozen chair-conformation, whereas that of C/D-*cis* steroid is flexible between chair- and boat-form. The present paper describes the synthesis of some 12-oxosteroids related to 12-dehydrodigoxigenin and their optical rotatory dispersion.

The initial project for this work was directed to the preparation of 12-oxo-3β,14β-dihydroxy-5β-etianic acid 3-acetate and its methyl ester. A key intermediate for these compounds, 3β,12β,14β-trihydroxy-5β-etianic acid 3-acetate, has already been reported by Schindler[6] as one of the ozonization products of digoxigenin diacetate, but the yield was not satisfactory. Therefore, the author attempted to synthesize the desired compounds by means of degradation of digoxin through the different route as shown in Chart 1. First, 12-dehydrodigoxigenin acetate (Ⅱb) was prepared from digoxin (Id) by chromium trioxide oxidation, and subsequent acid hydrolysis and acetylation according to the method of Yamada.[7] An alternative method for the synthesis of Ⅱb was effected by oxidation of digoxigenin 3-acetate (Ib) with chromium trioxide in acetic acid. Ⅱb thus obtained was submitted to oxidation with potassium permanganate in acetone to furnish 12-oxo-3β,14β-dihydroxy-5β-etianic acid 3-acetate (Ⅲ), m.p. 235~237° (decomp.), as an acid product. On treatment with diazomethane in the usual way Ⅲ was converted to methyl 12-oxo-3β,14β-dihydroxy-5β-etianate 3-acetate (Ⅳ), m.p. 172~174°, in quantitative yield. Alternatively, a starting material, 3β,12β,14β-trihydroxy-5β-etianic acid 3,12-diacetate (Ⅴb), prepared from digoxigenin (Ia) following the procedure of Reichstein and his co-worker,[8] was subjected to partial hydrolysis. Treatment of Ⅴb with potassium bicarbonate in hydrous methanol at room temperature for a week resulted in recovery of the starting material, while with potassium carbonate Ⅴb was completely hydrolyzed to provide 3β,12β,14β-trihydroxy-5β-etianic acid (Ⅴa). However, when transformed to its methyl ester (Ⅵ), and then treated with potassium bicarbonate in hydrous methanol at room temperature for several days followed by chromatography on alumina, methyl 3β,12β,14β-trihydroxy-5β-etianate 3-acetate (Ⅶ), m.p. 219~221°, was obtained in *ca.* 90% yield. Oxidation of Ⅶ with chromium trioxide in acetic acid gave the corresponding 12-dehydro derivative, which proved to be identical with the sample obtained through another sequence described above. Then, hydrogenation of butenolide group of Ⅱb was carried out. On catalytic reduction over

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[*1] Part Ⅳ: This Bulletin, **13**, 78 (1965).

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1) T. Nambara, J. Fishman: J. Org. Chem., **26**, 4569 (1961).

2) *Idem*: *Ibid.*, **27**, 2131 (1962).

3) C. Djerassi, J. Fishman, T. Nambara: Experientia, **17**, 565 (1961).

4) T. Nambara, K. Hirai: This Bulletin, **12**, 836 (1964).

5) T. Nambara: *Ibid.*, **12**, 1253 (1964).

6) O. Schindler: Helv. Chim. Acta, **39**, 1698 (1956).

7) A. Yamada: This Bulletin, **8**, 19 (1960).

8) M. Steiger, T. Reichstein: Helv. Chim. Acta, **21**, 828 (1938).

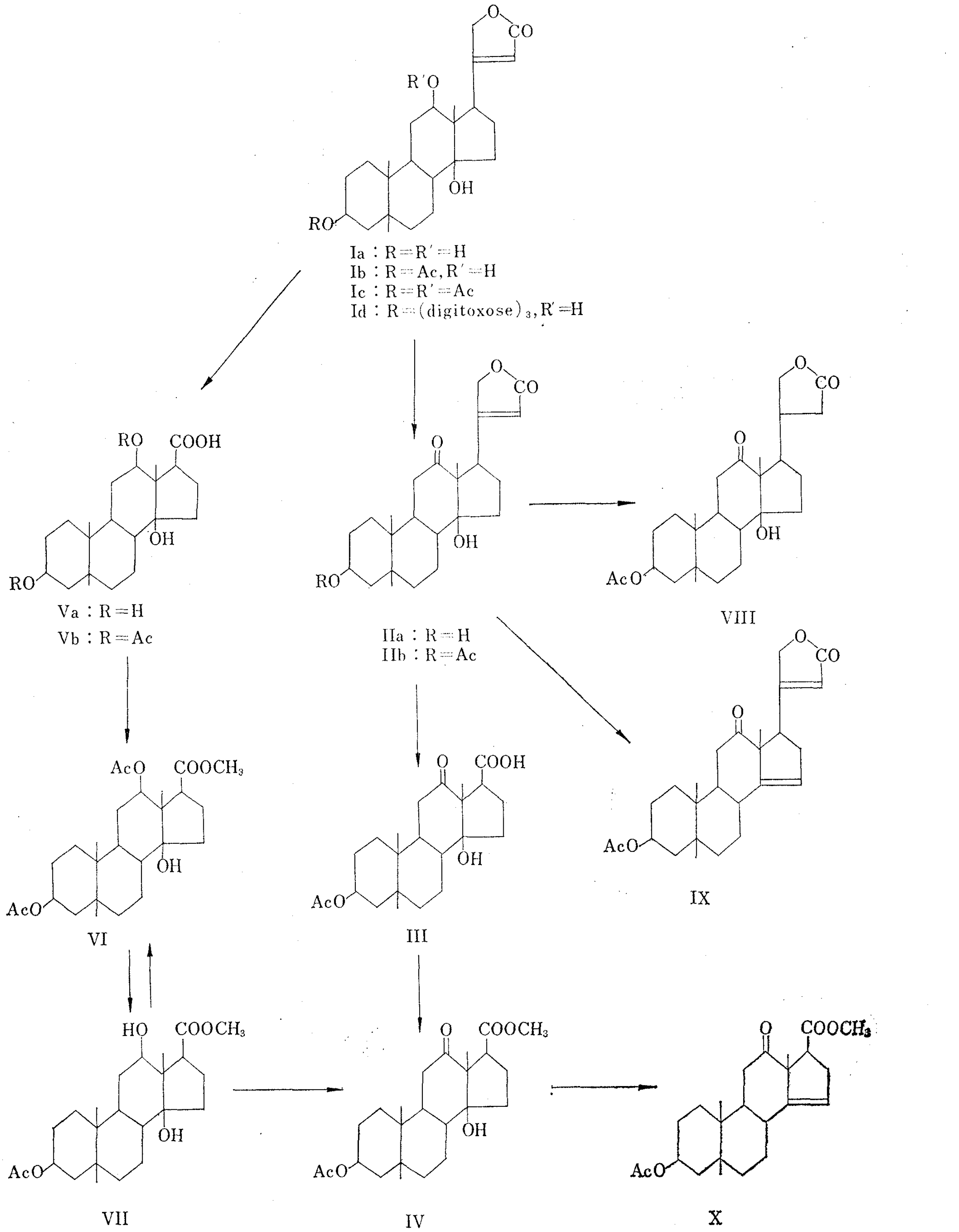

Chart 1.

palladium-on-charcoal, approximately one molar equivalent of hydrogen was taken up and the saturated compound (Ⅷ), m.p. 185~187°, was afforded almost quantitatively.

In addition, for comparison with the optical properties of the above-mentioned C/D-*cis* steroids, the preparation of some 14-anhydro compounds was also attempted. When Ⅱb was treated with thionyl chloride in pyridine in the usual manner, 3β-hydroxy-12-oxo-5β-card-14,20(22)-dienolide acetate (Ⅸ), m.p. 203~205°, was furnished as

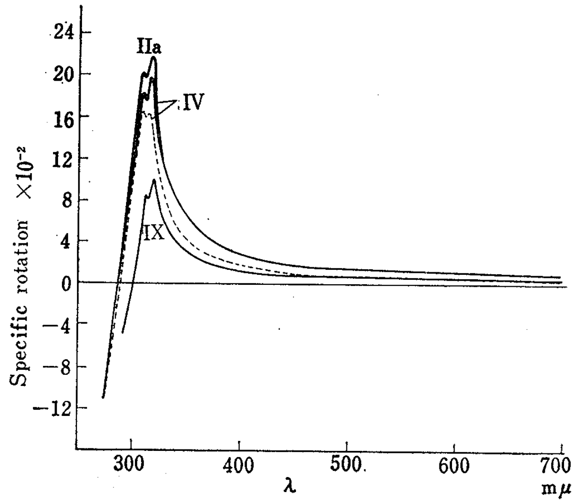

Fig. 1. Optical Rotatory Dispersion Curves in Methanol (------) and Dioxane (——)

IIa : 12-Dehydrodigoxigenin
IV : Methyl 12-oxo-$3\beta,14\beta$-dihydroxy-5β-etianate 3-acetate
IX : 3β-Hydroxy-12-oxo-5β-card-14,20(22)-dienolide acetate

a sole product in fairly good yield. The newly introduced double bond was tentatively assigned between C-14 and C-15 on the basis of the analogous reactions. Dehydration of 14β-hydroxyl group of IIb was also accomplished by refluxing the ethanolic solution with sulfuric acid and subsequent reacetylation in the usual way. Likewise, IV was readily converted to methyl 3β-hydroxy-12-oxo-5β-eti-14-enate acetate (X) with thionyl chloride and pyridine.

The rotatory dispersion curves of these 12-oxosteroids were measured in methanol and dioxane. The results observed are summarized in Table I, and the typical curves are illustrated in Fig. 1. Djerassi, *et al.* reported that optical rotatory dispersion of some 12-oxo-14β-steroids including IV as an only example of C-11-unsubstituted one exhibited the strongly positive Cotton effect.[9] In fact, all the compounds of C/D-*cis* fusion hereby examined by the author also showed the

Table I. Optical Rotatory Dispersion Data

Compound	Solvent	Conc. (c)	Temp. (°C)	Specific rotation					
IIa	dioxane	0.128	13	700 :	+70°;	589 :	+89°;	314 :	+2170° (p);
				308 :	+1940° (tr);	305 :	+1980° (p);	275 :	−1240°.
IIb	MeOH	0.205	31	700 :	+49°;	589 :	+73°;	313 :	+1930° (p);
				308 :	+1840° (tr);	306 :	+1950° (p);	277 :	−976°.
IIb	dioxane	0.098	23	700 :	+61°;	589 :	+82°;	314 :	+1950° (p);
				308 :	+1750° (tr);	305 :	+1840° (p);	281 :	−939°.
III	MeOH	0.275	32	700 :	+73°;	589 :	+91°;	313 :	+1940° (p);
				310 :	+1920° (tr);	306 :	+1960° (p);	271 :	−1670°.
IV	MeOH	0.184	23	700 :	+44°;	589 :	+87°;	314 :	+1610° (p);
				310 :	+1590° (tr);	306 :	+1630° (p);	283 :	−761°.
IV	dioxane	0.284	19.5	700 :	+88°;	589 :	+111°;	315 :	+1980° (p);
				309 :	+1730° (tr);	306 :	+1780° (p);	282 :	−1250°.
VIII	MeOH	0.129	10	700 :	+62°;	589 :	+106°;	314 :	+1550° (pl);
				309 :	+1550° (pl);	306 :	+1570° (p);	270 :	−1290°.
VIII	dioxane	0.126	8	700 :	+40°;	589 :	+60°;	315 :	+1670° (p);
				309 :	+1460° (tr);	306 :	+1470° (p);	280 :	−1470°.
IX	MeOH	0.230	13	700 :	+35°;	589 :	+52°;	314 :	+970° (p);
				308 :	+880° (tr);	305 :	+910° (p);	289 :	−209°.
IX	dioxane	0.149	12.5	700 :	+50°;	589 :	+64°;	315 :	+1060° (p);
				309 :	+860° (tr);	306 :	+880° (p);	290 :	−500°.
X	MeOH	0.337	10.5	700 :	+30°;	589 :	+59°;	310 :	+1320° (inf);
				306 :	+1380° (p);	275 :	+252°.		
X	dioxane	0.303	14	700 :	+96°;	589 :	+134°;	315 :	+1305° (p);
				310 :	+1270° (tr);	306 :	+1320° (p);	277 :	+238°.

MeOH : methanol p : peak tr : trough inf : inflection pl : plain peak

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9) C. Djerassi, O. Halpern, V. Halpern, O. Schindler, Ch. Tamm : Helv. Chim. Acta, **41**, 250 (1958).

strongly positive Cotton effect. In the present case, however, marked resolution of extremum was observed in dioxane as already mentioned on several examples,[10] and a characteristic feature of the rotatory dispersion curve, rotation of the first peak being somewhat larger than that of the second one, was distinctly noted. When measured in methanol, magnitude of rotation of the first peak changed to be rather smaller compared with that of the second one or only single peak appeared accompanied with shoulder. Δ^{14}-12-Oxosteroids also exhibited the positive Cotton effect curve having extremum of reduced rotation at the same wave length as those of 14β-series, resolution of the peak being again quite noticeable in dioxane.

On the basis of the octant rule the positive Cotton effect would be predicted for 12-oxosteroids having C-ring in chair-form, where ring B and A situated in far-upper-left octant would be dominant contributors even though ring D in upper-right would make a negative contribution to a certain extent. On the other hand, ring C being in boat-conformation, the situation around 12-oxo group would be changed in such a manner that the main substituents are located in far-upper-right octant to exhibit the negative Cotton effect. It has already been substantiated that the presence of carboxylic acid function and butenolide group at C-17 do not play any important role in influencing the distinguishing feature of the Cotton effect curve of oxosteroids.[9] Accordingly, it is now supposed that ring C of these 12-oxo-14β-steroids may be exclusively in chair-conformation.*3

Further studies on the stereochemistry of C/D-*cis* steroid are being conducted in this laboratory.

Experimental*4

12-Oxo-3β,14β-dihydroxy-5β-card-20(22)-enolide (12-Dehydrodigoxigenin) (IIa)——Prepared from digoxin (Id) using the procedure of Yamada.[7] m.p. 269～272°.

12-Oxo-3β,14β-dihydroxy-5β-card-20(22)-enolide 3-acetate (12-Dehydrodigoxigenin 3-acetate) (IIb)——i) To a solution of digoxigenin 3-acetate (Ib)[7] (110 mg.) dissolved in AcOH (1.5 ml.) was added 2% CrO_3-AcOH (1.5 ml.) and the reaction mixture was allowed to stand at room temperature for 5 hr. After addition of MeOH (3 ml.) to decompose the excess CrO_3 and allowing to stand at room temperature overnight, the solution was concentrated under a reduced pressure and the residue obtained was extracted with AcOEt. The extract was washed with 5% $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and the solvent was evaporated to give a crystalline product. Recrystallization from acetone-hexane gave IIb (98 mg.) as colorless needles. m.p. 224～225°.

ii) Usual acetylation of IIa with Ac_2O in pyridine afforded IIb in quantitative yield. m.p. 224～225° (reported m.p. 228～229°).[7] Mixed melting point on admixture with the sample obtained in i) showed no depression.

3β,12β,14β-Trihydroxy-5β-etianic Acid 3,12-Diacetate (Vb)——Prepared from digoxigenin 3,12-diacetate (Ic) using the procedure of Steiger, *et al.*, m.p. 227～229° (reported m.p. 229～230°).[8]

Methyl 3β,12β,14β-Trihydroxy-5β-etianate 3,12-Diacetate (VI)——Vb (250 mg.) was treated with CH_2N_2 in ether in the usual manner. Recrystallization from acetone-hexane gave VI (182 mg.) as colorless prisms. m.p. 183～184°, $[\alpha]_D^{26.8}$ +46.0° (c=1.11). *Anal.* Calcd. for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50. Found : C, 66.90; H, 8.69. Pataki, *et al.* prepared this compound through the different route and reported it m.p. 185～186°.[11]

12-Oxo-3β,14β-dihydroxy-5β-etianic Acid 3-Acetate (III)——To a solution of IIb (100 mg.) dissolved in acetone (10 ml.) was added pulverized $KMnO_4$ (150 mg.) and the reaction mixture was shaken at room temperature for 2 hr. After evaporation of solvent the reaction product obtained was extracted with ether

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*3 Added in proof : During the preparation of this manuscript, the author received a paper reported that 3β-hydroxy-13α-androst-5-en-16,17-dione exists in Δ^{15}-enol form, where C-ring would probably be in either boat or twist conformation (L. J. Chinn : J. Org. Chem., **29**, 3304 (1964)).

*4 All melting points were determined on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ unless otherwise stated.

10) C. Djerassi : "Optical Rotatory Dispersion," p. 30, McGraw-Hill Book Co., New York (1960).

11) S. Pataki, K. Meyer, T. Reichstein : Helv. Chim. Acta, **36**, 1295 (1953).

for removal of neutral substances. The residue was acidified with N H_2SO_4 and extracted again with ether. The organic layer was washed with H_2O, dried over anhyd. Na_2SO_4 and concentrated to give a crystalline product (64 mg.). Recrystallization from aq. MeOH afforded III as colorless needles. m.p. 235～237°(decomp.), $[\alpha]_D^{26.8}$ +100.9°(c=0.84). *Anal.* Calcd. for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found : C, 67.07; H, 8.14.

3β,12β,14β-Trihydroxy-5β-etianic Acid (Va)——To a solution of Vb (100 mg.) dissolved in MeOH (20 ml.) was added 4% K_2CO_3 (5 ml.) and the mixed solution was allowed to stand at room temperature for 48 hr. The reaction mixture was neutralized and concentrated at a reduced pressure. The crude product thus obtained was recrystallized from MeOH-ether to give Va as colorless prisms. m.p. 240～244°(decomp.), $[\alpha]_D^{19.1}$ +31.1°(c=0.33, MeOH). *Anal.* Calcd. for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found : C, 67.91; H, 8.96. (Reported m.p. 248～249°(decomp.)).[8)]

Methyl 3β,12β,14β-Trihydroxy-5β-etianate 3-Acetate (VII)——To a solution of VI (100 mg.) in MeOH (25ml.) was added 4% $KHCO_3$ solution (5 ml.) and the reaction mixture was allowed to stand at room temperature for 10 days. After neutralization with a few drops of AcOH the solution was concentrated and extracted with AcOEt. The extract was washed with H_2O and dried over anhyd. Na_2SO_4. After evaporation of solvent the crude product was dissolved in benzene and chromatographed on Al_2O_3 (4 g.). Elution with benzene-ether (8:2) gave a crystalline product (81 mg.). Recrystallization from acetone-hexane yielded VII as colorless prisms. m.p. 219～221°, $[\alpha]_D^{23.6}$ +6.7°(c=0.45). *Anal.* Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found : C, 67.18; H, 8.81. Schindler prepared this compound by the different method and reported it m.p. 223～225°.[6)] Reacetylation of VII gave VI quantitatively.

Methyl 12-Oxo-3β,14β-dihydroxy-5β-etianate 3-Acetate (IV)——i) To a solution of VII (15 mg.) dissolved in AcOH (0.2 ml.) was added 2% CrO_3-AcOH solution (0.2 ml.) and the reaction mixture was allowed to stand at room temperature for 3 hr. After addition of MeOH (0.4 ml.) to decompose the excess CrO_3 and standing at room temperature overnight, the solution was concentrated under a reduced pressure and the residue obtained was extracted with AcOEt. The extract was washed with 5% Na_2CO_3 and H_2O, dried over anhyd. Na_2SO_4 and the solvent was evaporated to give a crystalline product. Recrystallization from acetone-hexane gave IV (13 mg.) as colorless needles. m.p. 172～174°, $[\alpha]_D^{17.0}$ +109.6°. (c=0.50). *Anal.* Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found : C, 67.75; H, 8.35. Schindler prepared this compound by the different method and reported it m.p. 180～182°.[6)]

ii) III was treated with CH_2N_2-ether solution in the usual manner. After decomposition of excess CH_2N_2 with AcOH, the solution was washed with N NaOH, N HCl and H_2O successively, dried over anhyd. Na_2SO_4. Upon evaporation of solvent and recrystallization from acetone-hexane IV was provided as colorless prisms almost quantitatively. m.p. 172～174°. Mixed melting point on admixture with the sample obtained in i) showed no depression.

12-Oxo-3β,14β-dihydroxy-5β,20ξ-cardanolide 3-Acetate (VIII)——A solution of IIb (50 mg.) dissolved in EtOH (25 ml.) was shaken with 5% Pd/C (25 mg.) for 24 hr. in the stream of H_2 at room temperature under atmospheric pressure. After removal of catalyst by filtration, the filtrate was concentrated to give crystalline product. Recrystallization from acetone-hexane afforded VIII (46 mg.) as colorless needles, m.p. 185～187°, $[\alpha]_D^{18.0}$ +67.6°(c=0.50). *Anal.* Calcd. for $C_{25}H_{36}O_6 \cdot \frac{1}{2}H_2O$: C, 68.00; H, 8.45. Found : C, 68.06; H, 8.48. An ethanolic solution of VIII showed no UV absorption in the region characteristic for α,β-unsaturated-lactone system.

3β-Hydroxy-12-oxo-5β-card-14,20(22)-dienolide Acetate (IX)——i) A solution of IIb (80 mg.) dissolved in EtOH (5 ml.) containing conc. H_2SO_4 (0.5 g.) was refluxed for 6 hr. After addition of H_2O (10 ml.), EtOH was evaporated *in vacuo* and the reaction mixture was extracted with AcOEt. The organic layer was washed with 5% $NaHCO_3$, H_2O and dried over anhyd. Na_2SO_4. After evaporation of solvent, the residue thus obtained was treated with pyridine (1 ml.) and Ac_2O (0.4 ml.) at room temperature for 12 hr. On usual work-up, a semi-solid product obtained was chromatographed on alumina (3 g.). Elution with benzene and benzene-ether (8:2) afforded crystalline product (25 mg.). Recrystallization from MeOH gave IX as colorless needles. m.p. 203～205°. $[\alpha]_D^{19.1}$ +56.0°(c=0.38). *Anal.* Calcd. for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found : C, 73.05; H, 7.95.

ii) To a solution of IIb (95 mg.) dissolved in pyridine (1 ml.) was added $SOCl_2$ (0.1 ml.) under cooling in ice-water and the solution was allowed to stand at 0° for 24 hr. The reaction mixture was diluted with ether and washed with 5% $NaHCO_3$, H_2O and dried over anhyd. Na_2SO_4. Upon evaporation of solvent a crystalline residue was obtained. Recrystallization from MeOH gave IX (90 mg.) as colorless needles. m.p. 202～203°. Mixed melting point on admixture with the sample obtained in i) showed no depression.

Methyl 3β-Hydroxy-12-oxo-5β-eti-14-enate Acetate (X)——Prepared from IV by treatment with $SOCl_2$ in pyridine using the procedure of Schindler. m.p. 105°(reported m.p. 105°).[6)]

Measurement of Optical Rotatory Dispersion——Measurement of optical rotatory dispersion curves was carried out employing Nihon-Bunko optical rotatory dispersion recorder Model ORD/UV-5.

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Summary

Some 12-oxosteroids related to 12-dehydrodigoxigenin were synthesized and their optical rotatory dispersion was examined. On the basis of the optical data obtained conformation of ring C of these 12-oxo-14β-steroids was discussed.

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110. **Ryoichi Miyake, Yoshizo Shimamura, and Hisa Yajima :** Kinetics of Fat Hydrogenation.[*1]

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Preliminary remarks: In the previous paper[1] it is concluded that the reaction is of zero order with respect to the concentration of substrate in the hydrogenation of whale oil on copper catalyst, whereas its rate is retarded by self-poisoning. An effort was made to formulate the poisoning effect, however, it was noticed that this condition was not restricted to any special material. This article follows the previous paper wherein examples are presented with the most familiar materials, oleic acid ester and nickel catalyst.

Discussion, however, is centered on the independency of concentration of substrate in greater detail with the advancing of the hypothesis of local mobility of reactants on catalyst surface, and in connection with this the conditions are criticized, under which the most acceptable Langumuir-Hinshelwood theory is applicable.

Under these considerations, it is hoped that liquid hydrogenation may be proved to be providing a potent basis to the development of the theory heterogeneous catalytic reaction keeping pace with ethylene hydrogenation.

Fat hydrogenation, having a tremendous literature, is most pertinent for advancing a general theory of liquid hydrogenation. Nevertheless, it has not played a significant roll in the relevant field of kinetic or the chemical engineering as its studies had been confined chiefly for practical purposes. In other words, it has not established its own theory, from which imaginative endeavors can be evolved.

The principal reason for this retrogression lies without a doubt in the complexities in determining the reaction order with respect to the concentration of substrate, which is at least one of the important starting points to reach a overall self-consistent comprehension.

There have appeared many references concerning the reaction order, reporting zero, first, and a combination of both, since the establishment of fat hydrogenation industry. If reviewing the recent literatures appearing in J. Am. Oil Chemists' Soc.,

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[*1] Presented at the Annual Meeting of Chem. Soc. Japan, April 6, 1951.

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[1] R. Miyake, Y. Shimamura : Bull. Chem. Soc. Japan, **29**, 611 (1956).