Dipicrolonate: Recrystallized from MeOH, m.p. 180～188° (decomp.). *Anal.* Calcd. for $C_{34}H_{48}O_4N_2 \cdot 2C_{10}H_8O_5N_4$: C, 61.22; H, 5.95; N, 13.0. Found: C, 60.75; H, 5.98; N, 13.11.

Dimethiodide (XVI): Recrystallized from a mixture of MeOH, EtOH, and ether, m.p. 145～175° (decomp.). *Anal.* Calcd. for $C_{34}H_{48}O_4N_2 \cdot 2CH_3I \cdot 2H_2O$: C, 49.76; H, 6.68; N, 3.22. Found: C, 49.83; H, 6.85; N, 3.27.

Summary

Seven kinds of 2,2′-polymethylene-bis(3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinolines) were obtained by the condensation of 2,3-methylenedioxy-5-(β-bromopropyl)-6-bromomethylbenzene and polymethylenediamines. The presence of curare-like actions in these compounds were examined with their dimethiodides.

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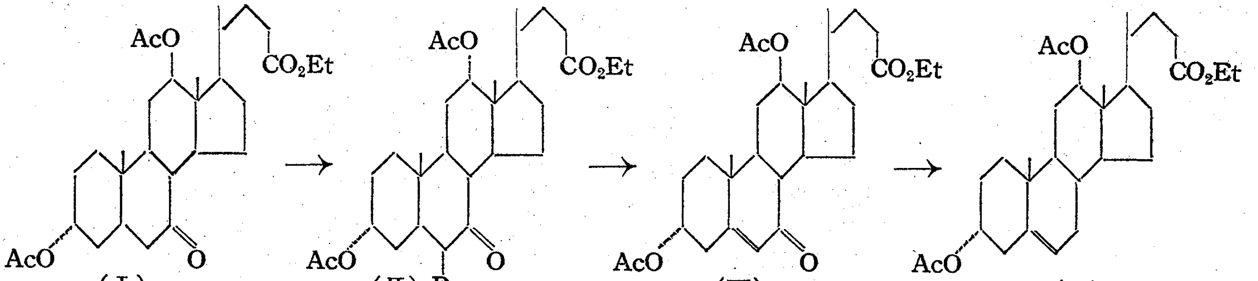
80. **Ken'ichi Takeda, Kikuo Igarashi, and Taichiro Komeno**: Bile Acids and Steroids. V.* Bromination of Methyl 3α-Acetoxy-7-oxocholanate and the Configuration of Bromine in the Related Compounds.

(*Research Laboratory, Shionogi & Co., Ltd.***)

In the third report of this series,[1] two monobromo compounds, (IIa), m.p. 136°, [α]$_D$: +31.9°, and (IIb), m.p. 162°, [α]$_D$: +34.6°, were shown as being obtained by the bromination of 3α,12α-diacetoxy-7-oxocholanic acid ester (I) in glacial acetic acid. Through dehydrobromination of these compounds by refluxing with pyridine-silver nitrate, two isomeric α,β-unsaturated ketones, (IIIa) and (IIIb), were formed. From these facts it was concluded that the two isomers, (IIa) and (IIb), were not epimers arising from the configuration of the bromine atom.



(I) (II) Br (III) (IV)

(a) m.p. 136°, [α]$_D$: +31.9° (a) m.p. 168° m.p. 172°

(b) m.p. 162°, [α]$_D$: +34.6° (b) m.p. 213°

In the present paper, the results of similar investigations on methyl 3α-acetoxy-7-oxocholanate (V) are reported.

By the bromination of (V) in glacial acetic acid as in the previously described manner, two crystals were recognized by their melting points, (VIII), m.p. 176°, [α]$_D$: +66.6°, and (VII), m.p. 167°, [α]$_D$: −20.2°, and (VIII) was always obtained in a large yield than (VII). Analytical values showed that both were monobromo derivatives of (V). These two were synthesized also from the enol acetate of (V) according to the following procedures

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* Part IV: Ann. Rept. Shionogi Lab., 4, 43(1954).

** Imafuku, Amagasaki, Hyogo-ken (武田健一, 五十嵐喜九男, 米野太一郎).

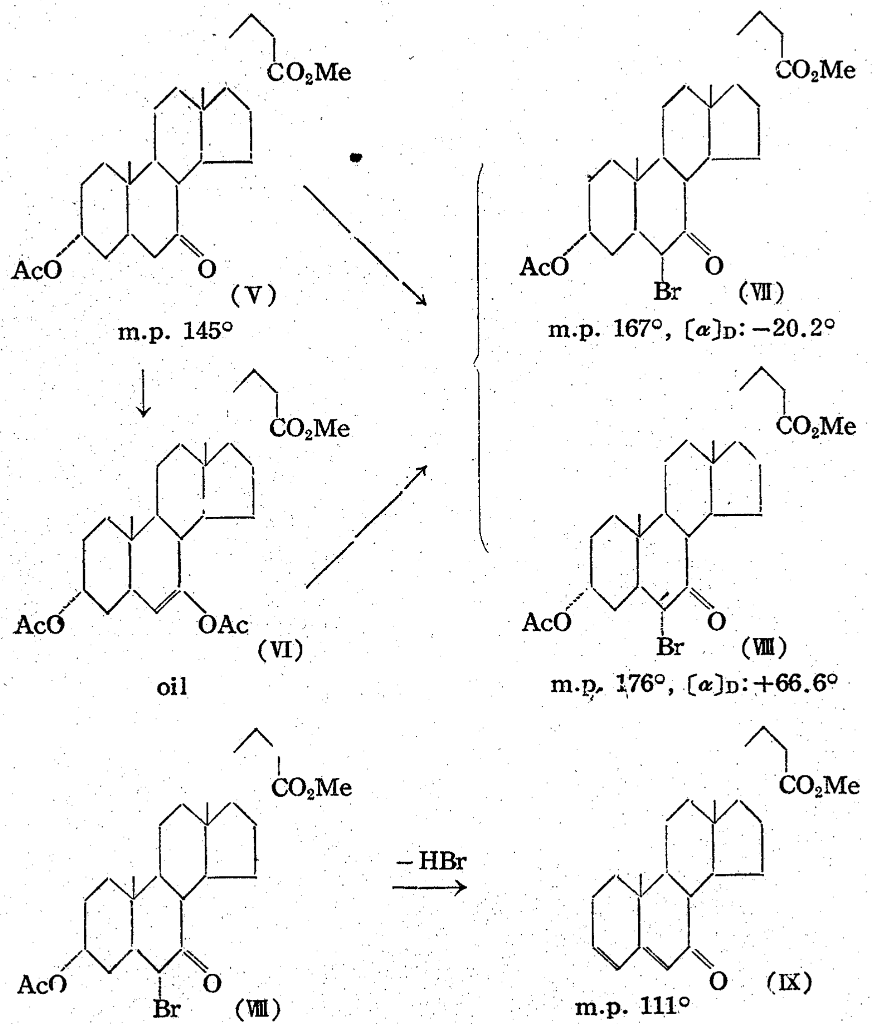
[1] K. Takeda, T. Komeno: J. Biochem. (Japan), **41**, 385(1954).

(the enol acetate (VI) was prepared by treating (V) with acetic anhydride[2] or isopropenyl acetate[3], with *p*-toluenesulfonic acid as a catalyst) :

i) Application of bromine in a strongly chilled (−70°) ether.
ii) By the action of N-bromosuccinimide.
iii) By the action of hypobromous acid in dioxane.

In all these cases, a small amount of oily product was noticed besides crystals. The yield of (VII), m.p. 167°, obtained from the enol acetate was found to be somewhat better than that obtained from (V).

Majority of the compound (VII), m.p. 167°, underwent epimerization into (VIII), m.p. 176°, by treatment with sodium iodide in ethanol or by refluxing with pyridine or collidine.



(V) m.p. 145°

(VII) m.p. 167°, [α]D: −20.2°

(VI) oil

(VIII) m.p. 176°, [α]D: +66.6°

(VIII)

(IX) m.p. 111°

The compound (VIII), unlike (IIa) or (IIb), strenuously resists dehydrobromination through refluxing with pyridine-silver nitrate. After thirty hours of this refluxing, there were obtained crystals of (IX), m.p. 111°, which indicated a peak of ultraviolet absorption spectrum at 279 mμ (log $\varepsilon = 4.38$) ; this peak did not correspond with that of simple α,β-unsaturated ketones, but was in good agreement with that of the dienones. Elemental analysis showed that it has a composition corresponding to (IX). From these facts it is obvious that the dienones are formed by the elimination of one mole of acetic acid from α,β-unsaturated ketone. Similar reactions[2] were observed to occur in the case of saponification of α,β-unsaturated ketones such as 3-acetoxy-Δ^5-7-ketones. The difficulty

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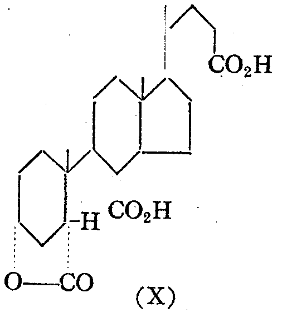
[2] Paul Z. Bedoukian : J. Am. Chem. Soc., **67**, 1430(1945).
[3] Hugh J. Hagemeyer, Jr., David C. Hull : Ind. Eng. Chem., **41**, 2920(1949).

of dehydrobromination (VIII) as compared with (II) cannot be clearly explained. Results of the above-mentioned epimerization, dehydrobromination, and saponification[4] revealed that the position of the bromine atom in these two monobromo compounds is at C_6 and not C_8. The fact that the C_6-bromo compound was obtained by the bromination of the enol acetate (VI) showed that the double bond of the enol acetate exists between C_6 and C_7, predominantly.


(X)

Hirschmann and Wendler[5] isolated a tricarboxylic acid monolactone (X) by oxidation of 7-oxoenolacetate of 3α-acetoxy-7,12-dioxocholanate with ozone and indicated that its enolization occurred between C_6 and C_7. This is the same as the present results.

The absorptions in the ultraviolet and infrared spectra of the ketone of the four bromo compounds, (IIa), (IIb), (VII), and (VIII), described above are compared in Table I.

TABLE I.

Compound	m.p. °C	UV, mμ (log ε)	IR, μ	[α]D	Configuration
(IIa)	136	282 (1.46)	5.76	+31.9	α (e)
(IIb)	162	282 (1.47)	5.76	+34.6	α (e)
(VII)	167	312 (2.14)	5.76, 5.84	+66.6	β (p)
(VIII)	176	282 (1.53)	5.76	−20.2	α (e)

According to Heilbron's concept,[6] the ultraviolet absorption shifts about 30 mμ toward longer wave lengths when the bromine atom is polar against the carbonyl group as compared with that of equatorial. Jones[7] reported that in the infrared absorption, the equatorial bromine atom shifts about 20 cm^{-1}. From these facts it was considered that the bromine atom of (IIa), (IIb), and (VIII) was equatorial (α-configuration) while only that in (VII) was polar (β-configuration), and their rotation values were also explained. According to the results of Corey,[8] polar atom is more stable than the equatorial in the normal 7-oxo-6-bromosteroids. In the present experiments it may be considered that (VII) has been epimerized to a more stable α-configuration, (VIII), by various treatments.

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Experimental

1) **Bromination of Methyl 3α-Acetoxy-7-oxocholanate** (V)—To a solution of 10 g. of (V) dissolved in 80 cc. of glacial AcOH, 3.6 g. of Br_2 dissolved in 10 cc. of AcOH containing 2 drops of 48% of HBr was added. The mixture was allowed to stand at room temperature until Br color disappeared, and poured into water. The solid that appeared was collected by filtration, dried, and crystallized by adding a small amount of ether. Fractional recrystallization from ether, MeOH, or acetone gave 6.5 g. of plates (VIII), m.p. 176°; λ_{max}^{EtOH} 282 mμ (log ε=1.53); λ_{max} 5.76 μ (C=O); $[\alpha]_D^{15}$: −20.2° (c=0.19214, 94% EtOH); and 2 g. of needles (VII), m.p. 167°; λ_{max}^{EtOH} 312 mμ (log ε=2.14), λ_{max}^{Nujol} 5.76, 5.84 μ (C=O); $[\alpha]_D^{15}$: +66.6° (c=0.2175, 94% EtOH). *Anal.* Calcd. for $C_{27}H_{41}O_5Br$: C, 61.71; H, 7.81; Br, 15.24. Found for (VII) : C, 61.85; H, 8.03; Br, 15.40. Found for (VIII) : C, 61.49; H, 7.72; Br, 14.79.

2) **Bromination of Enol Acetate** (VI)—i) In ether : To a solution of 0.5 g. of the enol acetate (VI) dissolved in 50 cc. of dry ether and chilled to −70°, 0.2 g. of Br_2 dissolved in 2 cc. of glacial AcOH was added rapidly. The mixture was allowed to stand for 2 hrs. at 0° and treated in the usual manner. The ether was concentrated, petroleum ether was added, and the precipitate thereby formed was collected by filtration, dried, and crystallized as above. Yield, 0.1 g. of needles, m.p. 167°, 0.15 g. of plates, m.p. 175°, and 0.3 g. of a mixture, m.p. 120~140°.

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4) The detailed results of the saponification will be given in the following report.
5) R. Hirschmann, N. L. Wendler : J. Am. Chem. Soc., **75**, 2361(1953).
6) J. Barr, I. M. Heilbron, E. R. H. Jones, F. S. Spring : J. Chem. Soc., **1938**, 334.
7) R. N. Jones, D. A. Ramsay, F. Herling, K. Dobriner : J. Am. Chem. Soc., **74**, 2828(1952).
8) E. J. Corey : *Ibid.*, **76**, 175(1954).

ii) N-bromosuccinimide in acetone-water: A solution of 1 g. of enol acetate and 0.4 g. of N-bromosuccinimide dissolved in 50 cc. of dry CCl_4 was refluxed for 45 minutes. After filtration, the solvent was evaporated to dryness and the residue was chromatographed. Only an oily product and the starting material (0.6 g.) were obtained.

To a solution of 1 g. of the enol acetate dissolved in 40 cc. of acetone, 1.4 g. of N-bromosuccinimide, 1 g. of NaOAc, 1.1 cc. of glacial AcOH, and 20 cc. of water, some acetone was added to effect complete solution and the mixture was allowed to stand for 2 hrs. at a room temperature. After treatment in the usual manner, 150 mg. of needles, m.p. 167°, was obtained and the residue was chromatographed. A small amount of plates, m.p. 176°, 0.6 g. of impure product, m.p. 120~140°, and an oily product were obtained.

iii) Hypobromous acid in dioxane: To a solution of the enol acetate dissolved in dioxane, freshly prepared HBrO (ca. 3 moles) was added and the mixture was allowed to stand for 3 hrs. After treatment in the usual manner, needles, m.p. 167° (15% yield), plates, m.p. 176° (10% yield), and an oily product were obtained.

3) **Epimerization of (VII)**—A mixture of 200 mg. of (Ⅶ) in 15 cc. of pyridine was refluxed for 22 hrs. and after treatment in the usual manner, 120 mg. of (Ⅷ) was obtained. Similarly, (Ⅷ) was obtained when collidine was used as a solvent instead of pyridine.

To a solution of (Ⅶ) dissolved in benzene, NaI dissolved in warm EtOH was added and allowed to stand overnight. The solvent was removed under a reduced pressure, the residue was extracted with ether, and after treatment in the usual manner, plates, m.p. 175°, was obtained similarly.

4) **Dehydrobromination of (VIII)**—i) A mixture of 1 g. of (Ⅷ), 3 g. of $AgNO_3$, and 30 cc. of pyridine was refluxed for 9 or 20 hrs. Only the starting material (over 50%) was recovered.

ii) A mixture of 1 g. of (Ⅷ), 3 g. of $AgNO_3$, and 30 cc. of pyridine was heated for 30 hrs. on an oil bath and after treatment in the usual manner, the residue was dissolved in benzene and chromatographed. The first eluate (250 mg.) was crystallized from MeOH, m.p. 111°, λ_{max}^{EtOH} 279 mμ (log ε =4.38), λ_{max} 5.77, 6.01, 6.14, and 6.18 μ. *Anal.* Calcd. for $C_{25}H_{36}O_3$: C, 78.08; H, 9.44. Found: C, 78.17; H, 9.19.

5) **Enol Acetylation of (V)**—i) Isopropenyl acetate method: A mixture of 5 g. of the 7-ketone (V), 0.7 g. of *p*-toluenesulfonic acid, 20 cc. of isopropenyl acetate, and 200 cc. of benzene was slowly concentrated to approximately one-half the original volume by distillation over a period of 5 hours. Additional 10 cc. of isopropenyl acetate was added after the 2nd and 3rd hr. The solvent was evaporated to dryness under a reduced pressure, the residue was extracted with ether, the ethereal solution was washed with $NaHCO_3$ solution and water, and the ether was evaporated. The residue was dissolved in petroleum ether and chromatographed. Four grams of oily enol acetate was obtained and the absorption band of a ketone in ultraviolet spectrum was not found.

ii) Acetic anhydride method: A mixture of 10 g. of (V), 4.6 g. of *p*-toluenesulfonic acid, and 200 cc. of Ac_2O was distilled slowly during 6 hrs. in N_2 atmosphere. The solvent was removed to dryness under a reduced pressure and after similar treatment as described above, 7.5 g. of the enol acetate (V) was obtained.

Summary

By the bromination of methyl 3α-acetoxy-7-oxocholanate, two kinds of monobromo compound were obtained. These compounds were also obtained by the bromination of methyl 3α-acetoxy-7-oxocholanate enol acetate and their relative relations were studied. The configurations of the bromine atoms in methyl 3α-acetoxy-6-bromo-7-oxocholanate and methyl 3α,12α-diacetoxy-6-bromo-7-oxocholanate were studied.

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