An Abnormal Reaction of Hypohalous Acids with Hindered Double Bonds

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The isolation of stigmast-5-ene-3α, 7α, 22α-triol from the leaves of the horse chestnut[1] and of Tochinoki *(Aesculum turbinata)*[2] prompted us to investigate methods for the introduction of the oxygen atom into the side chains of stigmastane derivatives.[3] During the course of our investigation, we observed that the double bond of stigmast-22-ene derivatives gave dihalides instead of halohydrins upon conventional treatment with positive halogen compounds such as *N*-bromoacetamide, *N*-bromosuccinimide, isocyanuric bromide or isocyanuric chloride in aqueous dioxane in the presence of perchloric acid. This paper deals with the mechanism of this abnormal reaction.

The treatment of 3β-acetoxy-5α-chlorostigmast-22-ene (II) with *N*-bromoacetamide (NBA), *N*-bromosuccinimide (NBS) or isocyanuric bromide (ICB)[4] in aqueous dioxane in

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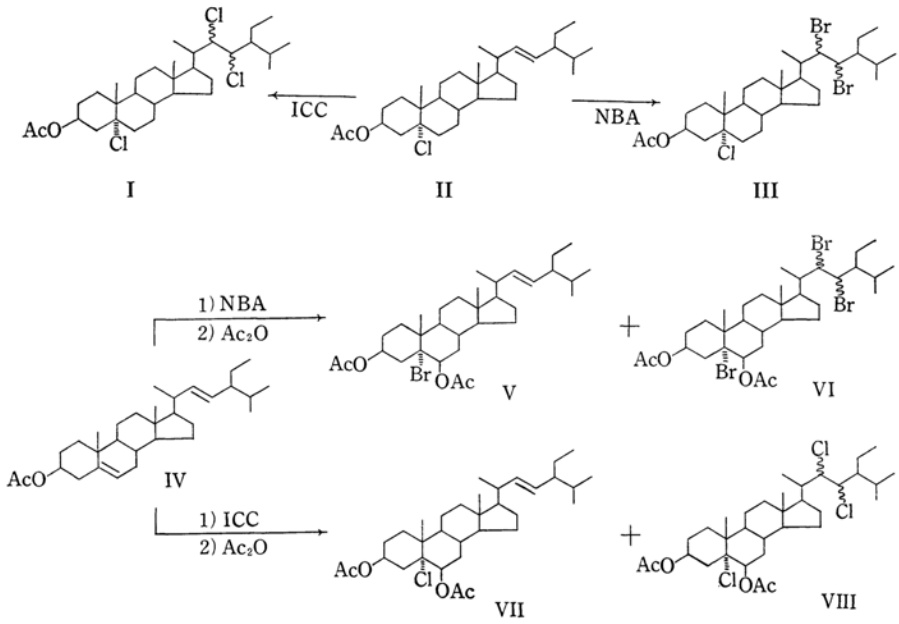
1) F. G. Fischer and H. Mägerlein, *Ann.*, **636**, 88 (1960). There is some doubt on the configuration of an hydroxyl group at C_3.

2) K. Morita, T. Iwama and S. Yoshikawa, unpublished result.

3) K. Morita, T. Iwama and Y. Kamano, This Bulletin, **36**, 1332 (1963).

4) K. Morita, ibid., **31**, 347 (1958).

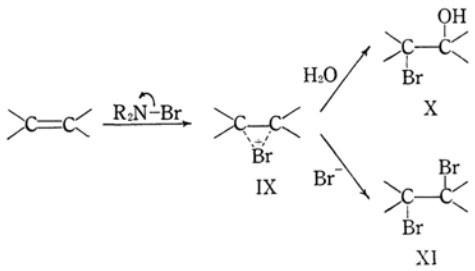


I II III IV V VI VII VIII

the presence of perchloric acid gave 3β-acetoxy-5α-chloro-22ξ, 23ξ-dibromostigmastane (III), while treatment with isocyanuric chloride (ICC) gave 3β-acetoxy-5α, 22ξ, 23ξ-trichlorostigmastane.[5,9]

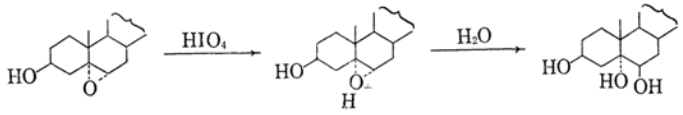
The treatment of stigmasteryl acetate (IV) with 1.4 molar equivalents of *N*-bromoacetamide in aqueous dioxane in the presence of perchloric acid, followed by acetylation and careful chromatography, gave the starting material (IV), 5α-bromo-3β, 6β-diacetoxystigmast-22-ene (V) and 3β, 6β-diacetoxy-5α, 22ξ, 23ξ-tribromostigmastane (VI). The treatment of stigmasteryl acetate (IV) with 1.4 molar equivalents of isocyanuric chloride, followed by acetylation and chromatography, gave the starting material IV 5α-chloro-3β, 6β-diacetoxystigmast-22-ene (VII) and 3β, 6β-diacetoxy-5α, 22ξ, 23ξ-trichlorostigmastane (VIII). These results clearly show that the Δ^{22}-double bond gives dihalides under reaction conditions where the Δ^{5}-double bond gives halohydrins.

The mechanism[6] of the addition of hypohalous acids to olefins is probably the formation of halogenium ring intermediates, IX, followed by an attack of the water molecule on halogenium ions, IX, to furnish halohydrins, X.



IX X XI

Fieser and Rajagopalan[7] reported that the brief refluxing of 5α, 6α-epoxycholestan-3β-ol (XII) with periodic acid in aqueous acetone afforded pure triol, XIV, in a 94% yield. It may most probably be assumed that the reaction proceeds through an oxonium ion intermediate, XIII, that is then attacked by water

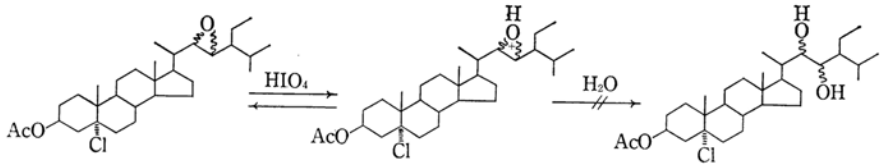


XII XIII XIV

5) When stigmasta-4, 22-dien-3-one was treated with *N*-bromoacetamide or isocyanuric chloride, a small amount of a bromohydrin or a chlorohydrin was obtained, respectively (see experimental part). Therefore, some halohydrins may be present in the mother liquor of the crystallization.

6) Cf. E. S. Gould, "Mechanism and Structure in Organic Chmistry," Henry Holt and Co., New York (1959), pp. 514-527. See also D. J. Cram and G. Hammond, "Organic Chemistry," McGraw-Hill, New York (1959), p. 341.

7) L. F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, **71**, 3938 (1949).



XV XVI

molecule to afford triol, XIV, since the treatment of XII with most acids other than periodic acid either produces esters (CH_3COOH, H_2SO_4) or effects a displacement (HCl).[8]

Similar hydrolytic fission was attempted with 3β-acetoxy-5α-chloro-22ξ, 23ξ-epoxystigmastane[13] (XV) under more drastic conditions without observing any fission of the oxide ring. This fact supports the assumption that the rear side of the 22ξ, 23ξ-oxonium ring XVI is so sterically hindered[14] as to prevent the attack of the water molecule.

We now come to the assumption that the 22ξ, 23ξ-halogenium ions are also inert against the attack of the water molecule, since the configuration of the epoxide ring[16] in XV and that of the halogenium ion ring in the intermediate should be the same. Accordingly, the Br^- or Cl^- that may be present in a small concentration determines whether the reaction will give dibromide X, or dichloride. The reactivity of the Br^- or Cl^- against the halogenium ion, IX, should be greater than that of the water molecule because of their greater polarizability, although the bulkiness of the Br^- and Cl^- are comparable to it.

The evidence presented in this article supports the theory that the water molecule and not the OH^- species attack the halogenium ion intermediate to form halohydrins.

Experimental[17]

3β-Acetoxy-5α, 22ξ, 23ξ-trichlorostigmastane (I).—To a solution of 1.0 g. of 3β-acetoxy-5α-chlorostigmast-22-ene (II)[13] (m. p. 183~185°C) in 60 ml. of dioxane containing 0.3 ml. of 60% perchloric acid and 6 ml. of distilled water, 0.7 g. of isocyanuric chloride (purity 82%) was added; the mixture was then allowed to stand for 50 hr. at room temperature. The mixture was poured into water and extracted with ether. The ethereal extract was washed with 10% aqueous sodium bisulfite, 10% aqueous sodium carbonate and water, dried over anhydrous sodium sulfate, and concentrated. The recrystallization of the residue from ethyl acetate gave 0.3 g. of crystals; m. p. 208~209°C, $[\alpha]_D^{15}$ +20° (*c* 0.67).

IR (KBr) 1736, 1241 cm^{-1}; (no hydroxyl and no Δ^{22}-double bond absorption).

Found: Cl, 18.31. Calcd. for $C_{31}H_{50}O_2Cl_3$: Cl, 18.9%.

3β-Acetoxy-5α-chloro-22ξ, 23ξ-dibromostigmastane (III).—*With N-Bromoacetamide.*—Into a suspension of 5 g. of 3β-acetoxy-5α-chlorostigmast-22-ene (II) in 200 ml. of dioxane, 15 ml. of water, 1.5 ml. of 60% perchloric acid and 1.3 g. of *N*-bromoacetamide was added. The mixture was then warmed at 50°C for 30 min. and allowed to stand at room temperature overnight. Recrystallization of the product from benzene-methanol gave 0.9 g. of crystals; m. p. 205~206°C, $[\alpha]_D^{17}$ +9° (*c* 1.01).

IR (KBr) 1730, 1239 cm^{-1}; (no hydroxyl and no Δ^{22}-double bond).

Found: BrCl, 29.91. Calcd. for $C_{31}H_{51}O_2ClBr_2$: BrCl, 29.94%.

With N-Bromosuccinimide or Isocyanuric Bromide.[4]—When a similar reaction was carried out using *N*-bromosuccinimide or isocyanuric bromide instead of *N*-bromoacetamide, compound III was obtained in 35 and 60% yields respectively. The identity was established by the mixed melting point and infrared spectra. The better yield observed with isocyanuric bromide is probably due to the ease in liberating bromine.

With Bromine.—To a stirred solution of 1 g. of 3β-acetoxy-5α-chlorostigmast-22-ene (II) in 20 ml. of carbon tetrachloride, a solution of 0.33 g. of

8) L. F. Fieser, "Steroids," Reinhold Publishing Co., New York (1959), p. 196.

9) Mori reported that cholest-5-ene gave 5α, 6α-dichlorocholestane[10] instead of a chlorohydrin when treated with bleaching powder in ether in the presence of acetic acid, whereas cholestery esters,[11] cholesteryl halides[12] and cholest-5-en-3-one[13] gave the corresponding chlorohydrins under the same condition. The reason for this is not clear, but it is conceivable that C_3-substituents may have something to do with it and also the concentration of Cl^- may be greater in the system of bleaching-powder-acetic acid. Dihalides are usually formed as by-products when one uses dilute solutions of halogens in water to generate hypohalous acids, since halogens are present in the system as a result of equilibration. We know no examples of positive halogen compounds to attack olefins with the formation of dihalides.

10) S. Mori, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zassi*), **74**, 89 (1953).

11) S. Mori, ibid., **64**, 981 (1943); **74**, 39 (1953).

12) S. Mori, ibid., **74**, 42, 89 (1953).

13) S. Mori, K. Morita and F. Mukawa, *Proc. Japan Acad.*, **32**, 585 (1956).

14) In this connection, it may be noted that C_{22}-keto[16] and C_{23}-kete group in stigmastane series are sterically highly hindered.[13] Attempted fission of the epoxide ring of XV with $LiAlH_4$ in refluxing ether (24 hr.) failed.

15) Fischer and Mägerlein (Ref. 1) reported that C_{22}-carbonyl group in stigmastane derivatives did not form semicarbazones.

16) The configuration of the ring is probably α, since an examination of the Dreiding model seems to indicate that the α-side of Δ^{22}-double bonds of stigmastene derivatives are less hindered (cf. Ref. 13).

17) All melting points were uncorrected. Rotations were measured in chloroform solution. Infrared spectra were determined with a Perkin-Elmer Model 21. We are indebted to miss Sachiko Yoshikawa for some technical assistance and to Sankyo Pharmaceutical Co. for analyses.

bromine in 50 ml. of the same solvent was added over a period of 30 min. at 0°C; the mixture was then allowed to stand at the same temperature overnight. The product was isolated in the way described above. There was obtained 0.6 g. of needles (m. p. 205~206°C) (Found: BrCl, 29.71%). The identity was established by the mixed melting point and by the infrared spectra.

The Reaction of 3β-Acetoxy-5α-chloro-22ξ, 23ξ-dibromostigmastane (III) with Poiling Pyridine. —A solution of 0.7 g. of III in 6 ml. of pyridine was heated under reflux for 11 hr. After it had cooled, the mixture was poured into water and the precipitated solid was collected by filtration. The solid was chromatographed on 30 g. of alumina (300 mesh, Wako Junyaku Co.). Elution with benzene-ether (9:1) and recrystallization from ethanol gave 250 mg. of crystals (m. p. 130~135°C). Although the material showed a weak ultraviolet absorption around 236 mμ, its infrared spectrum was identical with that of stigmasteryl acetate. Three more recrystallizations from ethanol gave pure stigmasteryl acetate (m. p. 138~139°C) (Found: C, 82.35; H, 10.75%).

The Reaction of *N*-Bromoacetamide with Stigmasteryl Acetate (IV). — To a mechanically-stirred solution of 13.6 g. (3 mmol.) of stigmasteryl acetate (IV) in 300 ml. of dioxane containing 3 ml. of 60% perchloric acid and 3 ml. of water, was added 5.8 g. (1.4 mol. eq.) of *N*-bromoacetamide over a period of 5 hr. at room temperature. The reaction mixture was allowed to stand overnight. Then 3% aqueous sodium bisulfite, and a large amount of water were successively added to the stirred solution. The product was extracted with ether four times. The combined ethereal solution was washed with water, dried over anhydrous magnesium sulfate, and evaporated to give 18.6 g. of an oil. The oil was acetylated by treatment with 50 ml. of acetic anhydride and 100 ml. of pyridine overnight at room temperature. The usual manipulation gave 18.6 g. of an oil containing crystals and an oil which was chromatographed on 410 g. of alumina (100 mesh, Sumitomo Kagaku Co.). Elution with 2% ethyl acetate in petroleum ether (b. p. 35~70°C) (fraction, Nos. 7—9) gave 2.58 g. of stigmasteryl acetate (IV). Further elution with the same solvent (Nos. 11—15) gave 4.8 g. of crude 5α-bromo-3β,6β-diacetoxystigmast-22-ene (V) which, on recrystallization from methylene chloride-ethanol, gave 3.5 g. of crystals with a m. p. of 152~155.5°C. The analytical sample was prepared by further recrystallization from ethyl acetate to needles; m. p. 156~158°C; $[\alpha]_D^{18}$ −68° (*c* 0.67, $CHCl_3$).

IR (KBr) 1736, 1244, 1236 (acetate); 973 cm^{-1} (Δ^{22}-double bond).

Found: C, 67.05; H, 9.06; Br, 12.78. Calcd. for $C_{33}H_{53}O_4Br$: C, 66.76; H, 9.00; Br, 13.46%.

Elution with 3 and 4 per cent of ethyl acetate in petroleum ether (Nos. 22—26) gave 462 mg. of crude 5α,22ξ,23ξ-tribromo-3β,6β-diacetoxystigmastane (VI). Recrystallization from methanol gave crystals; m. p. 211.5~212°C, $[\alpha]_D^{18}$ −73° (*c* 0.67, $CHCl_3$).

IR (Nujol) 1745 (shoulder), 1733, 1250, 1230 cm^{-1} (acetate).

Found: C, 52.99; H, 7.09; Br, 32.43. Calcd. for $C_{33}H_{53}O_4Br_3$: C, 52.60; H, 7.09; Br, 31.82%.

Elution with 10% ethyl acetate in petroleum ether (Nos. 32—39) gave 777 mg. of unidentified crystals, IR (Nujol) 3236, 1067, 970, 880, 800 and 765 cm^{-1} (Found: C, 81.80; H, 11.35; Br, 0%), while elution with 20% and 50% ethyl acetate in petroleum ether (Nos. 40—43) (2.276 g.) and recrystallization from ethyl acetate gave other unidentified crystals (m. p. 217.5~218°C). IR (Nujol) 3521, 1712, 1282, 1256, 1038, 970, 878 and 866 cm^{-1}. (Found: C, 74.15; H, 10.67; Br, 3.08%.)

All fractions not described here were uncrystallizable oils.

3β, 6β-Diacetoxy-5α, 22ξ, 23ξ-tribromostigmastane (VI) from V. — To a solution of 2.0 g. of 5α-bromo-3β,6β-diacetoxystigmast-22-ene (V) in 50 ml. of dioxane containing 0.5 ml. of 60% perchloric acid and 0.5 ml. of water, 0.7 g. of *N*-bromoacetamide was added; the mixture allowed to stand overnight at room temperature. The mixture was then poured into water containing some sodium bisulfite, and the product was well extracted with ether. The ethereal solution was washed with aqueous sodium carbonate and with water, dried over anhydrous sodium sulfate, and evaporated. The product was crystallized from methylene chloride-ethanol to give 1.6 g. of VI (m. p. 209~211°C). Its identity was established by the mixed melting point and the infrared spectra.

The Reaction of Isocyanuric Chloride with Stigmasteryl Acetate (IV).—Into a solution of 8 g. (1.7 mmol.) of stigmasteryl acetate (IV) in 150 ml. of dioxane containing 2 ml. of 60% perchloric acid and 2 ml. of water, 2.3 g. of isocyanuric chloride (83% purity) was added with swirling and the mixture was stored in the dark at room temperature (26°C) overnight. When the product was isolated as above, 9.666 g. of the yellow oil were acetylated by treatment with 5 ml. of acetic anhydride and 15 ml. of pyridine overnight at room temperature to give 9.8 g. of an oil, which was chromatographed on 300 g. of alumina (100 mesh, Sumitomo Kagaku Co.). Elution with 2% ethyl acetate in petroleum ether (b. p. 35~70°C) (fraction Nos. 8 and 9) gave 1.586 g. of stigmasteryl acetate (IV) (m. p. 138~138.5°C). Further elution with the same solvent (Nos. 15—21) gave 1.68 g. of 5α-chloro-3β,6β-diacetoxystigmast-22-ene (VII) with a m. p. of 147~151°C. The analytical sample was recrystallized from acetone; m. p. 153~153.5°C, $[\alpha]_D^{18}$ −51° (*c* 0.68).

Found: C, 72.35; H, 9.68; Cl, 6.25. Calcd. for $C_{33}H_{53}O_4Cl$: C, 72.16; H, 9.73; Cl, 6.46%.

Further elution with 2% ethyl acetate in petroleum ether (Nos. 22—24) and recrystallization from methanol gave 361 mg. of 3β,6β-diacetoxy-5α,22ξ,23ξ-trichlorostigmastane (VIII), m. p. 215~217°C, $[\alpha]_D^{18}$ −37° (*c* 0.60).

Found: C, 63.65; H, 8.48; Cl, 17.30. Calcd. for $C_{33}H_{53}O_4Cl_3$: C, 63.91; H, 8.61; Cl, 17.15%.

Bromohydrin of Stigmasta-4,22-dien-3-one.—To a stirred solution of 5 g. of stigmasta-4,22-dien-3-one (m. p. 121~123°C) in a mixture of 100 ml. of ether, 300 ml. of acetone and 30 ml. of water, 1.5 ml. of 60% perchloric acid and 2.0 g. (1.2 mol.) of *N*-bromoacetamide were added; the mixture was

then allowed to stand at room temperature for 24 hr. The product was extracted with ether, washed with 10% aqueous sodium bisulfite and 10% aqueous sodium carbonate and water, dried, and concentrated. The residue was repeatedly recrystallized from acetone to give a small amount of crystals; m. p. 210~212°C $[\alpha]_D^{18}$ +51° (*c* 0.69).

IR (KBr) 3466, 1661 and 1618 cm^{-1} (no Δ^{22}-double bond absorption).

Found: Br, 16.17. Calcd. for $C_{29}H_{47}O_2Br$: Br, 15.85%.

A similar result was obtained when dioxane was used as the solvent instead of a mixture of ether and acetone.

No attempt was made to isolate the dibromide that should be present in the reaction mixture.

The structure of the bromohydrin is pobably 23ξ-bromo-22ξ-hydroxystigmast-4-en-3-one, since the opening of the oxide of the Δ^{22}-double bond of 3β-acetoxy-5α-chlorostigmast-22-ene with hydrogen chloride gave a 22ξ-chloro-23ξ-hydroxy compound.[13] The course of the entering groups to the oxide ring (for Cl^-) and the course to the bromonium ring (for H_2O) are probably the same.

Chlorohydrin of Stigmasta-4, 22-dien-3-one.—To a stirred solution of 0.9 g. of stigmasta-4,22-dien-3-one in a mixture of 60 ml. of dioxane and 6 ml. of water, 0.3 ml. of 60% perchloric acid and 0.7 g. of isocyanuric chloride (purity 63.3%) were added; the mixture was then allowed to stand for 48 hr. The product was extracted as described above, and the residue was repeatedly recrystallized from benzene-methanol to give a small amount of crystals (m. p. 216~218°C). The mixed melting point with the bromohydrin of stigmasta-4,22-dien-3-one described above showed no depression, and the infrared spectrum showed the presence of hydroxyl and α,β-unsaturated ketone groups.

Found: C, 75.51; H, 10.27; Cl, 7.86. Calcd. for $C_{29}H_{47}O_2Cl$: C, 75.20; H, 10.23; Cl, 7.65%.

A similar result was obtained when we used a mixture of ether and acetone instead of dioxane as the solvent.

The Reaction of 3β-Acetoxy-5α-chloro-22ξ, 23ξ-epoxystigmastane (XV) with Hydroiodic Acid.—To a solution of 200 mg. of 3β-acetoxy-5α-chloro-22ξ,23ξ-epoxystigmastane (XV) in 8 ml. of glacial acetic acid, 5 ml. of hydroiodic acid in 10 ml. of acetic acid were added; the mixture was then allowed to stand at room temperature for 20 hr. in the dark. The mixture was poured into water and extracted with ether. The usual manipulation gave 145 mg. of 3β-acetoxy-5α-chlorostigmast-22-ene (II) (m. p. 183~184°C).

Its identity was established by the mixed melting point determination and by a comparison of the infrared spectra.

An Attempted Reaction of 3β-Acetoxy-5α-chloro-22ξ, 23ξ-epoxystigmastane (XV) with Periodic Acid.—To a solution of 0.5 g. of XV[13] (m. p. 137~138°C) in 20 ml. of acetone, 0.4 g. of periodic acid in 6.5 ml. of distilled water was added; the mixture was then heated under reflux for 2 hr. and allowed to stand overnight. The reaction mixture was extracted with ether, and the ethereal extract was washed with water, dried and concentrated. Recrystallization of the residue gave 0.4 g. of the starting material; m. p. and mixed m. p. 137~138°C.

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