Dehydrobromination of 16-Bromodihydroenmein-type Compounds

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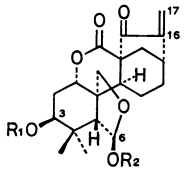
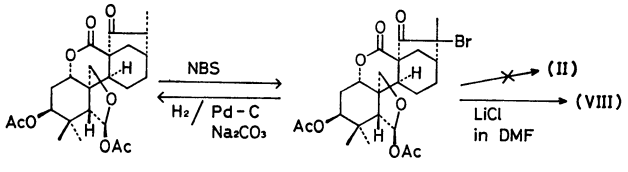
16-Bromodihydroenmein diacetate (IV) obtained from dihydroenmein diacetate (III) by bromination with *N*-bromosuccinimide was dehydrobrominated with lithium chloride in dimethylformamide to give a product, the structure of which was elucidated as the intermolecular ether (VIII). The dimeric ether compound was also formed by similar reactions from the derivative of isodocarpin.

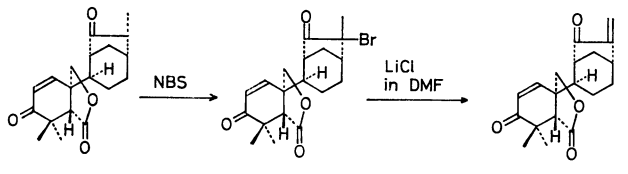
About 10 years ago, during experiments for structual elucidation of enmein (I),[1] an attempt was made to revert 16-bromodihydroenmein diacetate (IV), obtained by bromination of dihydroenmein diacetate (III),[1,2,3] to enmein diacetate (II) by dehydrobromination. Unexpectedly, however, a structually unknown compound (VIII) of mp 282—283 °C (decompn.) was obtained instead of enmein diacetate (II). On the other hand, the dehydrobromination of VI gave an expected unsaturated compound (VII).[1] In order to elucidate the structure of VIII and to find what kind of reaction had occurred in the case of IV, the following experiments were carried out.



(I) $R_1 = R_2 = H$
(II) $R_1 = R_2 = Ac$
(XIII) $R_1 = Ac$, $R_2 = Et$
(XIV) $R_1 = Ac$, $R_2 = Me$
(XVII) $R_1 = Ac$, $R_2 = H$



(III) (IV)

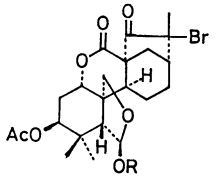


(V) (VI) (VII)

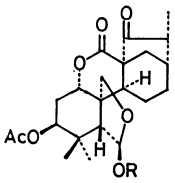
Bromination of dihydroenmein diacetate (III) was carried out repeatedly. But the results were not the same, although the experimental conditions were similar, *i.e.*, the material was treated with *N*-bromosuccinimide in chloroform in the presence of benzoyl peroxide, giving one of the three products (never a mixture of these in one experiment), $C_{24}H_{31}O_8Br$ (IV), mp 235 °C, $C_{24}H_{33}O_7Br$ (IX), mp 223 °C (decompn.), or $C_{23}H_{31}O_7Br$ (X), mp 220—222 °C (decompn.).

In the NMR spectra of IV, IX, and X, the signal for C_{17} secondary methyl present in III was no longer observed, and a signal for tertiary methyl group having a bromine in α-position appeared at δ 1.93, 1.85, and 1.82, respectively. The signal for C_6–H in III was shifted to higher magnetic field in the spectra of IX and X, suggesting an ether linkage in these compounds.[5]

Catalytic reductions of IV, IX, and X over palladium-charcoal–sodium carbonate catalyst afforded dihydroenmein diacetate (III), dihydroenmein 3-acetate 6-ethyl acetal (XI), and dihydroenmein 3-acetate 6-methyl acetal (XII), respectively, which confirmed that bromination had occurred at C_{16} position in these cases. In addition, the acetoxyl group at C_6 position had been converted to ethoxyl or methoxyl group by ethanol or methanol contaminated in chloroform to form IX or X, respectively.



(IX) R=Et
(X) R=Me
(XXII) R=H



(XI) R=Et
(XII) R=Me

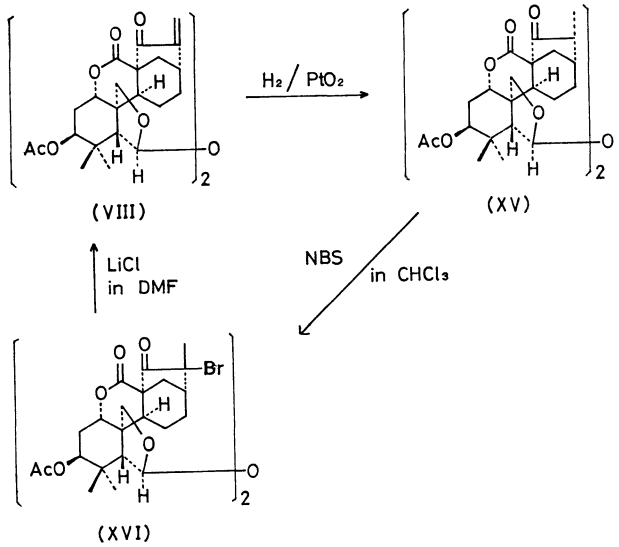
Dehydrobromination of the ethyl- and methyl-acetal type monobromo compound (IX and X) normally gave enmein 3-acetate 6-ethyl acetal (XIII)[5] and enmein 3-acetate 6-methyl acetal (XIV), respectively.

The dehydrobromination of IV with lithium chloride in dimethylformamide was not successful for preparing the expected enmein diacetate (II), but instead gave a high melting substance (VIII). Experiments were also carried out under the following conditions: with (i) pyridine, (ii) collidine, (iii) lithium chloride–pyridine, (iv) lithium carbonate–dimethylformamide, and (v) lithium bromide–dimethylformamide. Under the reaction conditions (i) to (iv) only the starting material was recovered, while in the case of (v) a small amount of VIII was obtained.

The UV, IR, and NMR spectra of VIII were almost identical with those of enmein diacetate (II), with

exception that the peak due to C_6–H in II appearing at δ 6.07 in its NMR spectrum shifted to δ 5.21 in the spectrum of VIII. The compound VIII was not reduced with palladium-carbon catalyst but was reduced to XV over platinum oxide catalyst. Bromination of XV with *N*-bromosuccinimide and dehydrobromination of the bromo compound (XVI), mp 277—278 °C (decompn.), with lithium chloride-dimethylformamide gave VIII.

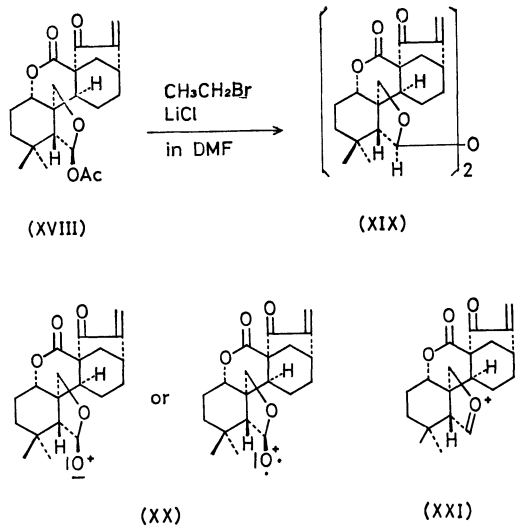
The reaction and spectral data of VIII suggested etherification of C_6-acetate in II, as in XIII and XIV. Hydrolysis of VIII with acetic acid afforded enmein 3-acetate (XVII).[6] The most plausible explanation for the structure of VIII is an intermolecular ether formation between two molecules of enmein 3-acetate. Molecular weight of VIII was therefore measured by the vapor pressure depression method, as the mass spectral method was not effective, and a value of 794 (calcd 791) was obtained. Consequently, VIII must have been formed from two molecules of enmein 3-acetate (XVII) by ether linkage of the hydroxyl group at C_6 position.



(VIII) (XV) (XVI)

This conclusion is supported from the following experiments. Treatment of dihydroenmein diacetate (III) with lithium chloride-dimethylformamide recovered the starting material, but addition of ethyl bromide in this reaction resulted in etherification to give XV. The same was true in the case of enmein 3-acetate (XVII), recovering the starting material with the use of lithium chloride-dimethylformamide but on addition of ethyl bromide affording VIII.

The same reaction on isodocarpin acetate (XVIII)[5,7] also gave an intermolecular ether (XIX). The IR and NMR spectra did not show the presence of any acetyl group in its molecule, and a diamagnetic shift of C_6–H signal was observed when compared with that of XVIII. (See experimental section.) The mass spectrum of XIX showed the molecular ion peak at *m/e* 674 and characteristic fragment ion peaks at *m/e* 345 and 329, respectively assignable to XX and XXI. Thus, it was confirmed that XIX was an intermolecular ether of two isodocarpin molecules.



(XVIII) (XIX) (XX) (XXI)

The formation of the dimeric ethers can be accounted for the catalytic action of hydrogen bromide generated *in situ* from ethyl bromide. Thus, the ether (VIII) was also obtained from enmein 3-acetate (XVII) with dry hydrogen bromide in dimethylformamide.

It is concluded from the results of these experiments that, in the bromination of C_{16}–H and dehydrobromination of C_{16}–bromo derivatives in enmein analogs, bromination and dehydrobromination progresses without any abnormal reaction, but a variety of etherification takes place at the acetal-hydroxyl group in C_6 position. Also, the present series of experiments has finally realized a plan made 10 years ago to convert dihydroenmein (II) to enmein (I) *via* 6-acetate derivative.

Experimental

NMR spectra were determined on a JEOL HL-60 (60 MHz) spectrometer in deuterochloroform solutions. IR spectra were recorded on Nujol mull with a Japan Spectroscopic IR-S spectrophotometer. Melting points were measured on a Yanagimoto micromelting point determination apparatus, and uncorrected. Column chromatography was performed with Mallinckrodt silicic acid.

(i) 16-Bromodihydroenmein Diacetate (IV). A mixture of dihydroenmein diacetate (III)[1,2,3] (550 mg), *N*-bromosuccinimide (230 mg), a few mg of benzoyl peroxide, and chloroform (20 ml) was heated under reflux for 3.5 hr. The reaction mixture was chromatographed on silica gel (10 g). Elution with chloroform yielded a crystalline product, which was recrystallised from ethanol to give 16-bromodihydroenmein diacetate (IV) (350 mg) as colorless prisms, mp 235 °C, ν_{max} 1760, 1730, 1240, and 1045 cm^{-1}, δ 1.04 and 1.06 (each 3H, s, *tert*-CMe), 1.93 (3H, s, >C(Br)–CH_3), 1.98 and 2.12 (each 3H, s, OAc), 4.08 (2H, s, –O–CH_2–C<), 4.68 (1H, dd, J=11 and 7 Hz, $H_{1\beta}$), 4.92 (1H, br.s, $H_{3\alpha}$), 6.18 (1H, s, H_6).

(ii) 16-Bromodihydroenmein 3-Acetate 6-Ethyl Acetal (IX). The procedure was same as (i). 16-Bromodihydroenmein 3-acetate 6-ethyl acetal (IX) obtained was colorless plates, mp 223 °C (decompn.), Found: C, 56.11; H, 6.58%. Calcd for $C_{21}H_{33}O_7Br$: C, 56.16; H, 6.50%, ν_{max} 1760, 1730, 1250, and 1045 cm^{-1}, δ 0.95 and 0.99 (each 3H, s, *tert*-CMe), 1.04 (3H, t, J=7.5 Hz, *sec*-CMe), 1.85 (3H, s, >C(Br)–CH_3), 2.06 (3H, s, OAc), 3.52 (2H, q, J=7.5 Hz, –OCH_2CH_3),

3.78 and 3.99 (each 1H, AB-q, J=10.5 Hz, -O-CH_2-C<), 4.60 (1H, dd, J=11 and 7 Hz, $H_{1\beta}$), 4.72 (1H, m, $H_{3\alpha}$), 4.81 (1H, s, H_6).

(iii) 16-Bromodihydroenmein 3-Acetate 6-Methyl Acetal (X). The procedure was same as (i). 16-Bromodihydroenmein 3-acetate 6-methyl acetal (X) obtained was colorless prisms, mp 220—222 °C (decompn.), Found: C, 55.29; H, 6.28%. Calcd for $C_{23}H_{31}O_7Br$: C, 55.52; H, 6.26%, ν_{max} 1760, 1730, 1240, and 1045 cm^{-1}, δ 1.00 and 1.04 (each 3H, s, *tert*-CMe), 1.82 (3H, s, >C(Br)-CH_3), 2.13 (3H, s, OAc), 3.27 (3H, s, OMe), 3.90 and 4.10 (each 1H, AB-q, J=9.5 Hz, -O-CH_2-C<), 4.70 (1H, dd, J=11.5 and 7.5 Hz, $H_{1\beta}$), 4.82 (1H, s, H_6), 4.91 (1H, t, J=3.5 Hz, $H_{3\alpha}$).

(iv) Hydrolysis of 16-Bromodihydroenmein 3-Acetate 6-Ethyl Acetal (IX). A mixture of 16-bromodihydroenmein 3-acetate 6-ethyl acetal (IX) (2 g), acetic acid (65 ml), and water (25 ml) was heated at 100 °C for 3 hr. The mixture was extracted with chloroform, and the solution was washed with water, 10% sodium carbonate aqueous solution and water, successively, and dried over anhydrous sodium sulfate. The solvents were removed to give 16-bromodihydroenmein 3-acetate (XXII), ν_{max} 3440, 1760, 1720, 1240, and 1040 cm^{-1}.

(v) Acetylation of 16-Bromodihydroenmein 3-Acetate (XXII). It was carried out with pyridine and acetic anhydride in the usual way. The product was recrystallised from ethanol to give 16-bromodihydroenmein diacetate (IV) as colorless plates, which was identical with an authentic sample derived from dihydroenmein diacetate (III) by bromination in IR.

(vi) Attempted Dehydrobromination of 16-Bromodihydroenmein Diacetate (IV). (a) A mixture of 16-bromodihydroenmein diacetate (IV) (150 mg) and pyridine (5 ml) was refluxed under nitrogen gas for 4 hr. The mixture was extracted with diethyl ether. The solution was washed with 2M-hydrochloric acid and water, and dried over anhydrous sodium sulfate. After evaporation of solvents, the residue was recrystallized from ethanol to give crystals (94 mg), which were identical with IV in IR.

(b) A mixture of 16-bromodihydroenmein diacetate (IV) (200 mg) and collidine (3 ml) was refluxed under nitrogen gas for 1 hr. The mixture was extracted with chloroform. The chloroform layer was washed with 2M-hydrochloric acid and water, and dried over anhydrous sodium sulfate. The solvent was removed and the concentrate was chromatographed on silica gel. Elution with chloroform–methanol (99: 1) yielded a crystalline product (91 mg), which was recrystallised from ethanol. This compound was identical with IV in IR.

(c) A mixture of 16-bromodihydroenmein diacetate (IV) (200 mg), lithium chloride (50 mg), and pyridine (1.5 ml) was heated at 100 °C under nitrogen gas for 2 hr. The mixture was diluted with water. The precipitate formed was collected by filtration, dried and chromatographed on silica gel. Elution with chloroform yielded a crystalline product (114 mg), which was recrystallized from ethanol. This compound was identical with IV in IR.

(d) When the reaction time was extended to 5 hr in the case of (vi-c), 16-bromodihydroenmein diacetate (IV) was recovered.

(e) A mixture of 16-bromodihydroenmein diacetate (IV) (200 mg), lithium chloride (140 mg), and pyridine (4 ml) was heated at 100 °C under nitrogen gas for 3 hr. The mixture was treated in a similar manner as (vi-c) to recover IV.

(f) A mixture of 16-bromodihydroenmein diacetate (IV) (200 mg), lithium carbonate (43 mg), and dimethylformamide (1.5 ml) was heated at 100 °C under nitrogen gas for 5 hr. The mixture was treated in a similar manner as (vi-c) to recover IV.

(g) A mixture of 16-bromodihydroenmein diacetate (IV) (500 mg), lithium chloride (120 mg), and dimethylformamide (3 ml) was heated at 110 °C under nitrogen gas for 3.5 hr. The mixture was treated in a similar manner as (vi-c). The crude product was chromatographed on silica gel (10 g), Elution with chloroform–methanol (99: 1) yielded a crystalline product, which was recrystallised from ethanol to give VIII (198 mg) as colorless prisms, mp over 295 °C, Found: C, 65.97; H, 6.94%; mol wt (vapor pressure depression method), 794. Calcd for $C_{44}H_{54}O_{13}\cdot 1/2H_2O$: C, 66.07; H, 6.93%; mol wt, 790.9, λ_{max} (ethanol) 233 nm (ε 14040), ν_{max} 1750, 1710, 1640, 1230, and 1050 cm^{-1}, δ 0.80 and 0.98 (each 6H, s, *tert*-CMe), 2.03 (6H, s, OAc), 3.08 (2H, m, H_{13}), 3.88 and 4.01 (each 2H, AB-q, J=10 Hz, -O-CH_2-C<), 4.57 (2H, dd, J=10.5 and 7 Hz, $H_{1\beta}$), 4.81 (2H, br.s, $H_{3\alpha}$), 5.21 (2H, s, H_6), 5.40 and 5.95 (each 2H, s, >C=CH_2).

(h) A mixture of 16-bromodihydroenmein diacetate (IV) (200 mg), lithium bromide (70 mg), lithium carbonate (30 mg) and dimethylformamide (2 ml) was heated at 100 °C under nitrogen gas for 6 hr. Treating in a similar manner as (vi-g) gave a few amount of VIII.

(vii) Catalytic Hydrogenation of VIII. In dioxane (20 ml), VIII (800 mg) was hydrogenated over platinum oxide (93 mg). The crude product was chromatographed on silica gel. Elution with chloroform yielded a crystalline product (346 mg), which was recrystallised from ethanol to give XV as colorless needles, mp over 300 °C, Found: C, 65.12; H, 7.53%. Calcd for $C_{44}H_{58}O_{13}\cdot H_2O$: C, 65.01; H, 7.44%, ν_{max} 1735, 1240, and 1040 cm^{-1}, δ 0.95 and 1.03 (each 6H, s, *tert*-CMe), 1.11 (6H, d, J=7 Hz, *sec*-CMe), 2.75 (6H, s, OAc), 3.98 (4H, t, J=10.5 Hz, -O-CH_2-C<), 4.58 (2H, dd, J=10.5 and 7 Hz, $H_{1\beta}$), 4.87 (2H, br.s, $H_{3\alpha}$), 5.30 (2H, s, H_6).

(viii) Bromination of XV. A mixture of XV (200 mg), *N*-bromosuccinimide (85 mg), a few mg of benzoyl peroxide, and chloroform (15 ml) was refluxed for 3.5 hr. The mixture was concentrated, and chromatographed on silica gel (5 g). Elution with chloroform yielded a crystalline product (134 mg), which was recrystallised from ethanol to give XVI as colorless needles, mp 277—278 °C (decompn.), ν_{max} 1750, 1725, and 1235 cm^{-1}, δ 0.92 and 1.03 (each 6H, s, *tert*-CMe), 1.87 (6H, s, >C(Br)-CH_3), 2.08 (6H, s, OAc), 4.01 (4H, t, J=11 Hz, -O-CH_2-C<), 4.64 (2H, dd, J=11 and 7.5 Hz, $H_{1\beta}$), 4.88 (2H, br.s, $H_{3\alpha}$), 5.27 (2H, br.s, H_6).

(ix) Dehydrobromination of XVI. A mixture of XVI (60 mg), lithium chloride (15 mg) and dimethylformamide (0.5 ml) was heated at 110 °C under nitrogen gas for 5 hr. The mixture was diluted with ice–water, and the precipitates collected by filtration were chromatographed on silica gel. Elution with chloroform–methanol (99: 1) yielded a crystalline product (27 mg) which was recrystallized from ethanol to give colorless prisms. This compound was identical with VIII derived from 16-bromodihydroenmein diacetate (IV) by dehydrobromination in IR and NMR.

(x) Hydrolysis of VIII. To VIII (200 mg) acetic acid (10 ml) and water (5 ml) were added, and heated at 110 °C for 45 hr. The mixture was extracted with chloroform, and the extract was washed with water, 10% sodium carbonate aqueous solution, and water, successively, and dried over sodium sulfate. After concentration the residue was recrystallised from ethanol to give enmein 3-acetate (XVII) (63 mg) as colorless needles, ν_{max} 3420, 1750, 1710, 1640, and 1270 cm^{-1}. Enmein 3-acetate (XVII) obtained as above was identical with an authentic sample[6] in IR.

(xi) Reaction of Dihydroenmein Diacetate (III) with Lithium Chloride and Dimethylformamide. A mixture of dihydroenmein diacetate (III) (210 mg), lithium chloride (60 mg), and dimethylformamide (1.5 ml) was heated at 110 °C under

nitrogen gas for 3.5 hr. The mixture was treated in a similar manner for VIII shown in (vi-g). The crude product was chromatographed on silica gel. Elution with chloroform yielded a crystalline product (125 mg), which was recrystallised from ethanol. This compound was identical with III in IR.

(xii) Reaction of Dihydroenmein Diacetate (III) with Lithium Chloride, Dimethylformamide, and Ethyl Bromide. A mixture of dihydroenmein diacetate (III) (250 mg), lithium chloride (60 mg), dimethylformamide (1.5 ml) and ethyl bromide (1.5 ml) was heated at 110 °C under nitrogen gas. After 2 hr, ethyl bromide was added to the mixture and the heating was continued for 2 hr. The mixture was treated in a similar manner for VIII shown in (vi-g), to give XV (71 mg), which was identical with an authentic sample (XV) obtained from VIII by hydrogenation in IR.

(xiii) Reaction of Enmein 3-Acetate (XVII) and Dimethylformamide. Enmein 3-acetate (XVII)[6] (200 mg) in dimethylformamide (1.5 ml) was heated at 110 °C for 4 hr. The product was identical with XVII in IR.

(xiv) Reaction of Enmein 3-Acetate (XVII) with Lithium Chloride, Dimethylformamide, and Ethyl Bromide. A mixture of enmein 3-acetate (XVII) (200 mg), lithium chloride (40 mg), dimethylformamide (1.5 ml), and ethyl bromide (1 ml) was heated at 110 °C under nitrogen gas for 4 hr. After 2 hr, ethyl bromide was added to the mixture and the heating was further continued for 2 hr. The mixture was treated as usual and the crude product was chromatographed on silica gel. Elution with chloroform yielded a crystalline product, which was recrystallized from ethanol to be identical with VIII in IR.

(xv) Reaction of Isodocarpin Acetate (XVIII) with Lithium Chloride, Dimethylformamide and Ethyl Bromide. A mixture of isodocarpin acetate (XVIII)[5,7] (150 mg), lithium chloride (40 mg), dimethylformamide (1.5 ml), and ethyl bromide (1 ml) was heated at 110 °C under nitrogen gas for 4 hr. After 2 hr, ethyl bromide was added to the mixture. The reaction mixture was diluted with water, and the precipitates formed were collected by filtration, dried and chromatographed on silica gel. Elution with chloroform yielded a crystalline product, which was recrystallised from ethanol to give XIX (59 mg) as colorless needles, mp over 300 °C, Found: C, 70.65; H, 7.50%. Calcd for $C_{40}H_{50}O_9 \cdot 1/3H_2O$: C, 70.56; H, 7.50%, *m/e* 674 (M^+), ν_{max} 1750, 1710, 1640, and 995 cm^{-1}, δ 0.85 and 0.96 (each 6H, s, *tert*-CMe), 3.11 (2H, dd, $J=9$ and 4 Hz), 3.87 and 4.07 (each 2H, AB-q, $J=9.5$ Hz, $-O-CH_2-C\langle$), 4.34 (2H, t, $J=8.5$ Hz, $H_{1\beta}$), 5.20 (2H, s, H_6), 5.45 and 5.98 (each 2H, s, $>C=CH_2$).

(xvi) Reaction of Enmein 3-Acetate (XVII) in Dimethylformamide under Hydrogen Bromide Gas. Enmein 3-acetate (XVII) (200 mg) in dimethylformamide (4 ml) was heated at 110 °C under dry hydrogen bromide gas for 2.5 hr. The reaction mixture was diluted with water, and the precipitates collected by filtration were treated by the preparative thin-layer chromatography on silica gel. Elution with chloroform–methanol (9: 1) yielded two crystalline products which were recrystallised from ethanol, respectively. The first product as colorless prisms (44 mg) was identical with VIII in IR, and the second compound as colorless prisms (43 mg) was the starting material (XVII).

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