Reaction of Long Chain Triol Acids with Hydrogen Bromide

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The reaction of hydrogen bromide (HBr) with long chain triol acids has been investigated in some detail. The 9, 10, 12-trihydroxy stearic acid (I) on treatment with HBr yielded three products, namely 9(10)-bromo-10(9)-hydroxy-12-bromo (III), 9(10)-bromo-10(9)acetoxy-12-bromo (IV) and 9,10-dibromo-12-hydroxy (V) stearic acids. When 9,12,13-trihydroxy stearic acid (II) was subjected to the same reaction under similar conditions, 12,13-dibromo-9-hydroxy (VI), 12(13)-bromo-13(12) acetoxy-9-bromo (VII) stearic acids were obtained. The structure of these products were established on the basis of their elemental values, spectral data and chemical evidence.

KEY WORDS: β- and γ-hydroxy olefinic acids, hydrogen bromide, 9,10,12-trihydroxystearic acid, and 9,12,13-trihydroxystearic acid.

The substitution of hydroxy function by halogen has been used frequently in studies of the chemistry of fatty acids. A series of studies on hydrogen bromide (HBr) reaction of vicinal diols have previously been carried out by our research group (1-3). Literature reports (4) about the reaction of mid-chain triol fatty acids have shown the neighboring group participation and the effect on the overall chemistry of unusual fatty acids. On the basis of these observations, it was desirable to investigate the action of HBr on triol fatty acids.

MATERIALS AND METHODS

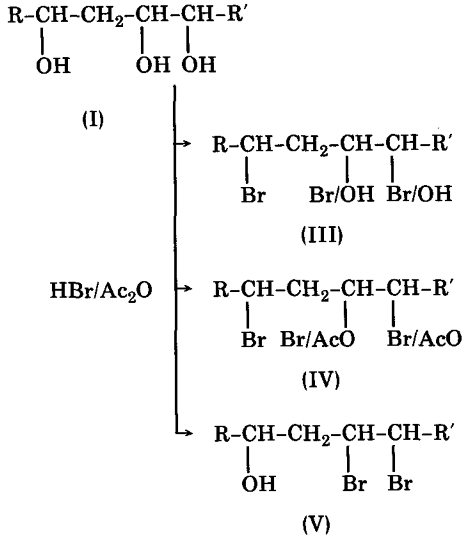
Similar methods were used as given in our earlier reports (5,6). Preparation of compounds (I) and (II) was achieved by the hydroxylation of naturally occurring β and γ-hydroxy olefinic acids (4).

EXPERIMENTAL PROCEDURES

Reaction of 9,10,12-trihydroxy (I) and 9,12,13-trihydroxy (II) stearic acids with hydrogen bromide. The 9,10,12-trihydroxy stearic acid (I; 1.5 g) was heated with a solution of 48% HBr (8 mL) in acetic anhydride (24 mL) for 6 hr at 90°C (7). The cooled reaction mixture was extracted with ether, and washed and dried over anhydrous sodium sulfate. This yielded a brown syrup liquid which, on column chromatographic separation on silica gel, resolved in the following three products:

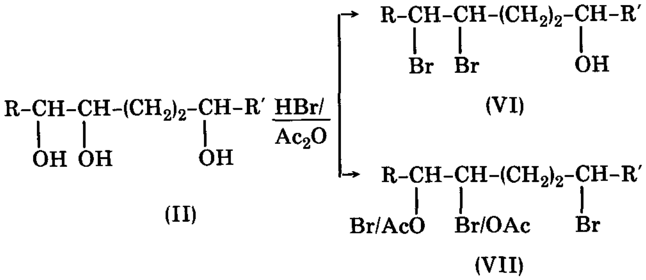
Compound (III). Elution with petroleum ether:ether (92:8; v/v) gave a light brown liquid (yield, 18%). It gave a positive Beilstein test for halogen, i.e., bromine. Analysis: Found. C, 47.31; H, 7.32 for $C_{18}H_{35}O_3Br_2$; Calcd. C, 47.05; H, 7.65%; IR(CCl_4; cm^{-1}) : 3530(-OH), 1720(C̲O̲OH), 610(-C-Br). NMR(CCl_4, δ): 4.30 br signal (3H, 2 × -CH̲-Br, -CH̲-OH), 3.9 br singlet (1H, -C-OH̲, Deuterium exchangeable), 9.45 broad singlet (1H, COOH̲, D_2O exchangeable) and other usual fatty acid signals.

Compound (IV). Elution with petroleum ether:ether (88:12, v/v) gave another brown, oily component (yield, 62%). It responded to a Beilstein test for bromine. Analysis: Found. C, 48.38; H, 7.58 for $C_{20}H_{36}O_4Br_2$; Calcd. C, 48.0; H, 7.2%; IR($CHCl_3$; cm^{-1}): 1740 (acetate carbonyl), 1710 (-C̲O̲OH), 1225 (-C-O-), 600 (-C-Br). NMR (CCl_4; δ) : 4.1 m(1H, CH̲-OAc), 4.04 m(2H, 2 × CH̲-Br), 2.09 s(3H, O-CO-CH̲₃) and normal fatty acid signals.



R = $(CH_2)_5$-CH_3; R′ = $(CH_2)_7$-COOH

SCHEME 1



R = $(CH_2)_4$-CH_3; R′ = $(CH_2)_7$-COOH

SCHEME 2

Compound (V). Final elution with petroleum ether:ether (86:14, v/v) gave the compound as a light brown oil (yield, 12%) which responded to Beilstein tests. Analysis: Found. C, 46.98; H, 6.96 for $C_{18}H_{35}O_3Br_2$; Calcd. C, 47.05; H, 7.65%). IR(CCl_4, cm^{-1}): 3570-3520(-OH), 1720(-C̲O̲OH), 670(-C-Br). NMR(CCl_4, δ) : 4.08 br, m(3H, CH̲-OH, 2 × CH̲-Br), 3.88 br signal (1H, -CH-OH̲, D_2O exchangeable) and normal fatty acid signals. MS: 459 ($M^{+\cdot}$, absent), *m/z* 211.

A similar treatment of trihydroxy acid (II) with HBr produced a brown syrup, and its column chromatographic separation gave following two products (VI, VII).

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Compound (VI). First elution with petroleum ether: ether (90:10, v/v) gave a light brown oil (yield, 52%), which gave a positive Beilstein test. Analysis: Found. C, 47.40; H, 7.18 for $C_{18}H_{34}O_3Br_2$; Calcd., C, 47.16; H, 7.42%; IR ($CHCl_3$, cm^{-1}): 3630 (-OH), 1710 (-C$\underline{\text{O}}$OH), 615 (-C-Br). NMR(CCl_4, δ) : 4.06 br, m(3H, 2 × C$\underline{\text{H}}$-Br, C$\underline{\text{H}}$-OH), 3.9 br signal (1H, CH-O$\underline{\text{H}}$, D_2O exchangeable) with other usual fatty acid signals. MS: 459 ($M^{+\cdot}$ absent), *m/z* 280.

Compound (VII). Second elution with petroleum ether: ether (88:12, v/v) gave another brown oily product (yield, 45%) which responded to a Beilstein test. Analysis: Found, C, 48.38; H, 7.58 for $C_{20}H_{36}O_4Br_2$; Calcd. C, 48.0; H, 7.2%; IR($CHCl_3$, cm^{-1}) : 1740 (acetate carbonyl), 1710 (-C$\underline{\text{O}}$OH), 1220 (-C-O), 600 (-C-Br). NMR (CCl_4, δ) : 2.08 s(3H, -O-CO-CH_3), 3.94 m(2H, 2 × CH-Br), 4.9 m (1H, -C$\underline{\text{H}}$-OAc).

DISCUSSION

9,10,12-Trihydroxy stearic acid (I), when treated with 48% HBr in acetic anhydride under similar conditions to those of Myers (7), yielded a reaction mixture which is separable into three products: 9(10)-bromo-10(9) hydroxy-12-bromo (III), 9(10)-bromo-10(9)-acetoxy, 12-hydroxy (IV) and 9,12-dibromo, 12-hydroxy (V) stearic acids. Compounds (III, IV, V) gave a positive Beilstein test, indicating the presence of halogen (bromine). Compound (III) has structures revealing IR bands at 3530 (OH), 1720 (COOH) and 610 cm^{-1} (Br). NMR has illustrated a structure supporting a broad signal at δ 4.3 for three protons ascribable to the protons attached to hydroxy and bromine bearing carbons. A D_2O shake has reduced the integration of the signal by one proton.

Compound (IV) has shown two characteristic IR bands in the carbonyl region at 1740 (O-C$\underline{\text{O}}$-CH_3) and 1710 cm^{-1} ($\underline{\text{CO}}$OH). NMR spectrum has revealed three significant peaks, one at higher field at δ 2.09 s(3H, O-CO-CH_3), and two at down field at δ 4.1 m(1H, CH-OAc) and 4.04 m(2H, 2 × CH-Br).

Diagnostic IR bands for Compound (V) were observed at 3570–3520 (OH), 1720 (COOH) and 670 cm^{-1} (C-Br). Besides usual fatty acid signals, NMR spectrum gave an additional broad signal centered at δ 4.08, which integrated three protons attached to carbon bearing bromine and hydroxy group. The MS of V did not show molecular ion at *m/z* 459. but the highest peak, observed at *m/z* 211, corresponds first to the loss of two HBr molecules and then α-cleavage at C_{12}–C_{13}, thus establishing the position of the hydroxyl group at C_{12}.

The work was further extended to another substrate, 9,12,13-trihydroxy stearic acid (II) which, under similar reaction conditions, provided only two products—9-hydroxy-12,13-dibromo (VI) and 9-bromo-12(13)bromo-13(12)-acetoxy (VII) stearic acids. Both Compounds have positive Beilstein tests.

Both Compounds (VI, VII) have displayed IR bands in the region of 600 cm^{-1} (C-Br). These compounds are different in their carbonyl region. The compound (VI) has a band at 1710 cm^{-1} (COOH), while (VII) has two absorptions in this region, one at 1710 (COOH) and another at 1740 cm^{-1} ($OCOCH_3$). IR spectrum of VI also has shown a significant absorption at 3630 (CO$\underline{\text{OH}}$). The NMR spectrum for VI illustrated a structurally important multiplet centered at δ 4.06 (3H, -C$\underline{\text{H}}$BrC$\underline{\text{H}}$Br(CH_2)$_2$-C$\underline{\text{H}}$-OH). The Compound (VII) has three structures establishing NMR peaks, one at high field at δ 2.08 s(3H, O-COC$\underline{\text{H}}_3$) and two in the down field region at δ 3.95 m(2H, 2 × CH-Br) and 4.94 m(1H, -C$\underline{\text{H}}$-O-$COCH_3$). MS of VI is more informative. Molecular ion at *m/z* 459 was absent, but instead the prominent peaks were observed at *m/z* 280 and 279. The ion peak at *m/z* 280 may result by the 1,2-loss of bromine radicals and elimination of water molecule. The peak which established the location of OH group at C_9 was observed at *m/z* 155.

The chemical evidence supporting the idea that III is a vicinal bromohydroxy and not a vicinal dibromo compound was obtained by treating it with Zn dust which did not yield the expected alkene, as is generally the case with vicinal dibromides (V, VII). The debromination of V and VII yielded corresponding alkenoic acids. These alkenoic acids did not respond to the Beilstein test (Halogen), but responded to the tetranitromethane test (olefin). The IR and NMR spectra are superimposable, with that of authentic samples of 12-hydroxy-octadec-9-enoic and 9-hydroxy-octadec-12-enoic acids.

Furthermore, chemical support to confirm that the Compounds (IV) and (VII) are bromoacetoxy derivatives of I and II, these compounds were refluxed for 2 hr with Zn-AcOH to yield the corresponding bromo alkenoic acids. New compounds responded to Beilstein and tetranitromethane tests. The IR spectra showed two structure confirming bands in the region of 670 (C–Br) and 970 cm^{-1} (olefine).

The results of the reaction of HBr with the triol acids (I) and (II) gave products (III), (IV), (V) and (VI), (VII). It is presumed that the hydroxy group at C_9 and C_{12} of the two olefinic acids may play a role in governing the course of HBr reaction.

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