

Transesterification Using Hydrogen Bromide in Diethyl Ether—A Means of Identifying Components of Mixtures of Fatty Esters

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Abstract □ The literature claim that treatment of methyl acrylate with hydrogen bromide in diethyl ether gives methyl 3-bromopropionate exclusively is shown to be erroneous. Transesterification occurs and ethyl 3-bromopropionate is also a product of the reaction. In the same way, methyl and ethyl 3-bromo-2-methylpropionate were obtained from methyl methacrylate. This transesterification reaction is of value in identifying components of mixtures of fatty esters. Thus, a mixture of six butyl esters was converted to one containing the respective ethyl esters in the same relative proportions. The presence of small quantities of impurities in a commercial mixture of cetyl stearate and cetyl palmitate was revealed, and the alcohol component and acid components (as ethyl esters) of the two major constituents were identified by GLC, rapidly and in the presence of each other.

Keyphrases □ Fatty ester mixtures—component identification □ Transesterification, fatty esters—HBr in diethyl ether □ GLC—separation, identity □ IR spectrophotometry—identity □ Mass spectroscopy—identity □ NMR spectroscopy—identity

Relatively large quantities of the esters, methyl 3-bromopropionate (*Ia*) and methyl 3-bromo-2-methylpropionate (*Ib*) were required for the synthesis of new medicinal compounds. When the preparation of these esters was attempted, using a previously reported



I

a, R = H; R' = Me
b, R = Me; R' = Me
c, R = Me; R' = Et



II

a, R = H *b*, R = Me

method (1), an interesting transesterification reaction

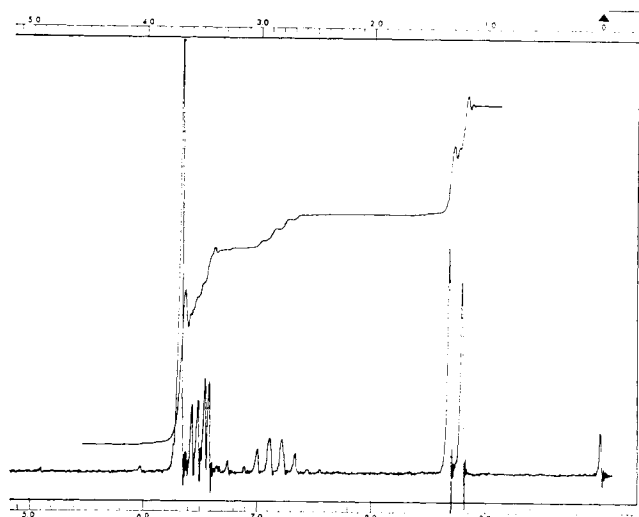


Figure 1—NMR spectrum of methyl 3-bromo-2-methylpropionate.

was observed which has an application in natural product chemistry. This transesterification reaction is the subject matter of this communication.

METHODS

The preparation of methyl 3-bromopropionate (*Ia*) and methyl 3-bromo-2-methylpropionate (*Ib*) from methyl acrylate (*IIa*) and methyl methacrylate (*IIb*), respectively, have been reported (1-3). The acrylates are treated with hydrogen bromide in various solvents. The hydrobromination of methyl acrylate in ether is said to give methyl 3-bromopropionate exclusively, and in good yield (1). When, however, the same conditions were used by the authors to hydrobrominate methyl methacrylate, a single product was not obtained. A gas-chromatogram of the reaction mixture revealed that there were two major components present in approximately equal amounts. The mixture was separated by fractional distillation using a spinning-band fractionating column. An NMR study (Figs. 1 and 2) was successful in identifying the two components as methyl 3-bromo-2-methylpropionate (*Ib*) and the corresponding ethyl ester (*Ic*). The 3-proton singlet at τ 6.32 in Fig. 1 is due to the protons of the OCH_3 group; the 3-proton triplet centered at τ 8.73 (overlapped by a 2-proton doublet of the 2-methyl group) and the 2-proton quartet at τ 5.84 in Fig. 2 are ascribed to the methyl and methylene protons, respectively, of the OCH_2CH_3 group. Elemental analyses, and comparisons of the NMR and IR spectra of both products with authentic samples of *Ib* and *Ic* confirmed that hydrobromination of methyl methacrylate in diethyl ether gives both the methyl and ethyl esters of 3-bromo-2-methylpropionic acid.

The original reaction was then performed for a longer time. The yield of the ethyl ester improved at the expense of the methyl ester although complete transesterification was not observed. When the hydrobromination reaction was repeated using ethyl methacrylate, a very good yield of *Ic* was isolated and was identical (b.p., IR, GLC, NMR) with the ethyl ester obtained from the methyl methacrylate reaction.

These results suggested that the claim (1) that methyl 3-bromopropionate was obtained in 84% yield from methyl acrylate, by

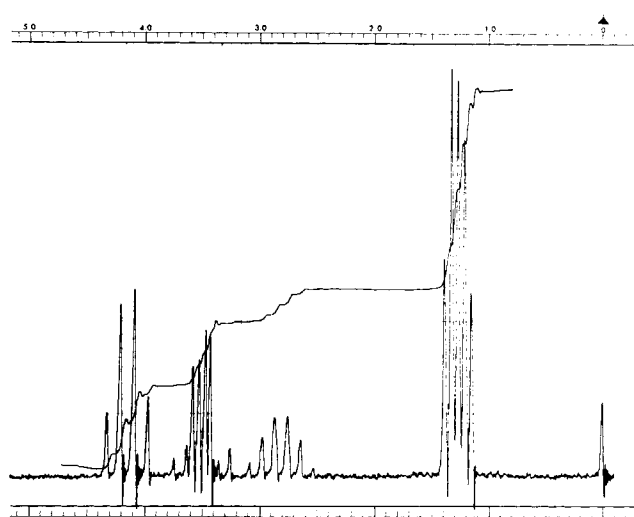


Figure 2—NMR spectrum of ethyl 3-bromo-2-methylpropionate.

Table I—Composition of a Commercial Sample of Butyl Stearate

| Component | Retention Time, min. | Composition, % | Identity |
|--|----------------------|----------------|----------------------|
| Before Treatment with HBr/Et₂O | | | |
| 1 | 26.7 | 2.42 | Butyl tridecanoate |
| 2 | 28.1 | 0.35 | Butyl pentadecanoate |
| 3 | 29.9 | 48.26 | Butyl palmitate |
| 4 | 30.8 | 2.27 | Butyl heptadecanoate |
| 5 | 32.4 | 45.39 | Butyl stearate |
| 6 | 34.1 | 1.31 | Butyl nonadecanoate |
| After Treatment with HBr/Et₂O | | | |
| 1 | 22.6 | 2.62 | Ethyl tridecanoate |
| 2 | 24.3 | 0.38 | Ethyl pentadecanoate |
| 3 | 26.1 | 47.55 | Ethyl palmitate |
| 4 | 27.3 | 2.32 | Ethyl heptadecanoate |
| 5 | 28.8 | 43.59 | Ethyl stearate |
| 6 | 30.4 | 3.71 | Ethyl nonadecanoate |

reacting the latter with hydrogen bromide in ether, was erroneous. This reaction, therefore, was repeated using the reported conditions, and, as expected, a mixture of the ethyl and methyl esters of 3-bromopropionic acid resulted. The ethyl ester, in fact, was the major product.

Higher esters can also be converted with ease to ethyl esters by this method. The transesterification of a pure sample of butyl acetate was studied gas-chromatographically. Within 24 hr., 43% of the butyl ester had been converted to ethyl acetate. After 48 hr., the conversion was 57% complete. Maximum transesterification (63%) occurred after 150 hr. Complete transesterification was possible only if the solvent was removed and replaced with fresh diethyl ether containing hydrogen bromide.

Application of this transesterification reaction to the identification of the components of mixtures of fatty esters was made. A commercial sample of butyl stearate was gas chromatographed and shown to be a mixture containing two major constituents (>90% of the total) and four minor components (Table I). The two major constituents were collected and their mass spectra recorded. Both spectra were typical of long-chain saturated aliphatic esters (4). The more volatile component showed a parent ion, *m/e* 312; the parent ion of the less volatile major constituent had a mass (*m/e*) of 340. These two components are identified as butyl palmitate and butyl stearate, respectively. A plot of log retention time of each ester component in the mixture *versus* number of carbon atoms of the corresponding acid gave a straight line (Fig. 3) and in this way the minor components of the mixture were tentatively identified (Table I) (*cf.* 5, 6).

A solution of the commercial butyl stearate in ether was treated with hydrogen bromide. The reaction mixture was also gas chromatographed and this confirmed that all six butyl esters were converted at approximately the same rate to the corresponding ethyl esters (Table I). The plot of retention time of each component *versus* the number of carbon atoms of the corresponding acid portion

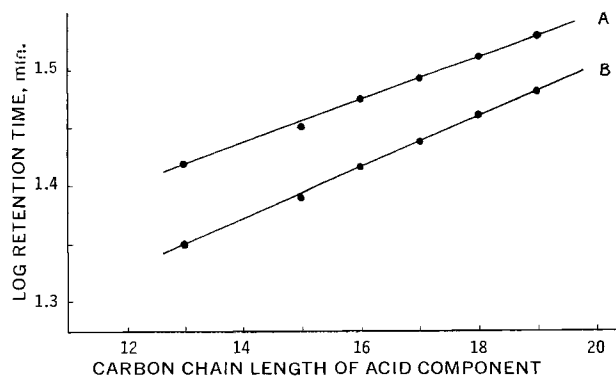
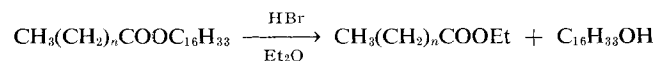


Figure 3—Retention times and carbon chain lengths of A, the butyl esters present in; and B, ethyl esters obtained from a commercial sample of butyl stearate.

again gave a straight line (Fig. 3) which substantiated the tentative identifications of the butyl esters. The mass spectra of the two major ethyl ester components confirmed that they were ethyl palmitate (*m/e* 284) and ethyl stearate (*m/e* 312). The IR spectra of both esters were virtually identical and were typical of long-chain fatty esters.

This transesterification reaction was also used to characterize a mixture of higher naturally occurring fatty esters. The normal method employed to do this is to hydrolyze the mixture of esters, separate the acid and alcohol components, convert the acid components to their methyl or ethyl esters, and then identify the acids (as their methyl or ethyl esters) and the alcohols by gas chromatographing them separately and comparing their retention times with those of reference standards (6). By employing the transesterification reaction, however, the acid and alcohol components of a mixture of two higher fatty esters were rapidly identified. Separation of the acid and alcohol components was not necessary. A commercial mixture of cetyl stearate was gas chromatographed, but due to the low volatility of these esters this was a lengthy procedure. A complete separation of one component from the other was not attained (Fig. 4) and the presence of minor components was not revealed. A solution of the mixture in ether was treated with hydrogen bromide and the reaction mixture was gas chromatographed. The components were readily and rapidly separated and the presence of small quantities of impurities revealed (Fig. 4). Fractions A, B, and C were collected and a mass spectrum and an IR spectrum of each were recorded. The IR spectrum of Fraction A was typical of that of a long-chain alcohol. The parent peak (*m/e* 242) was absent from the mass spectrum, but the presence of a relatively abundant ion of *m/e* 224 (M-18) readily identified (7) the alcohol as cetyl alcohol (C₁₆H₃₃OH). The IR spectra of Fractions B and C showed strong carbonyl absorption bands at 1,740 cm.⁻¹ and C—H stretching bands near 3,000 cm.⁻¹. Fractions B and C, therefore, were long-chain fatty esters. Fraction B was ethyl palmitate and Fraction C was ethyl stearate; the parent peaks in their mass spectra were located at *m/e* 284 and 312, respectively. The action of ethereal hydrogen bromide on these cetyl esters can be depicted as shown:



The utility of this transesterification reaction to the identification of small quantities of natural products was demonstrated. A 50-mg. sample of the cetyl palmitate/cetyl stearate mixture was hydrobrominated for only 10 min., after which time the presence in the reaction mixture of cetyl alcohol, ethyl palmitate, and ethyl stearate could be readily identified by means of GLC.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer¹; all were run as thin films. NMR spectra were determined on an NMR spectrophotometer² using tetramethylsilane (TMS) as internal standard and carbon tetrachloride as solvent. Mass spectra were recorded on an instrument³ equipped with a heated inlet system operating at approximately 150°; the electron beam energy was 70 eV. For GLC determinations, SE-30 (10%) on diatomaceous earth (Diatoport S) contained in a stainless steel column 1.82 m. × 0.62 cm. (6 ft. × 1/4 in.) was employed, and unless stated otherwise, retention times quoted below were determined when (a) the column temperature was 125°; (b) the injection port temperature was 150°; and (c) the helium flow rate was 60 ml./min. A gas chromatograph⁴ was employed and percentages were calculated by measuring the areas under the curve using the triangulation method.

Reaction of Methyl Methacrylate with Hydrogen Bromide—Dry hydrogen bromide gas was passed through a solution of methyl methacrylate (50 g.; 0.5 mole) in diethyl ether (200 ml.) at 0° for 30 min. (weight increase 49 g.). The reaction mixture was kept at room temperature for 48 hr., then flash evaporated to give an oil which was dissolved in ether (100 ml.). The ether solution was washed with 10% sodium carbonate solution (3 × 25 ml.) and water (2 × 25 ml.), then dried (Na₂SO₄). (Acidification of the basic extract

¹ Beckman IR-10.

² Varian 60 mc.

³ A. E. I. MS9.

⁴ F & M model 500.

with hydrochloric acid gave an aliphatic acid, m.p. 210–215°, which was not identified.) The ether was removed and the oil obtained (96.5 g.) was distilled under reduced pressure. The major fraction, b.p. 93–99°/43 mm., was collected. A portion (4 μ l.) was gas chromatographed, using the general method. Two major components were present: Fraction 1 (46.4%), retention time 1.20 min.; Fraction 2 (53.6%), retention time 1.65 min.

Fractional distillation of the mixture using a spinning-band column separated the two components. Fraction 1, b.p. 69–70°/18 mm., was methyl 3-bromo-2-methylpropionate [lit. (2) b.p. 67°/17 mm.].

Anal.—Calcd. for $C_5H_9BrO_2$: C, 33.27; H, 4.97; Br, 44.20. Found: C, 32.81; H, 4.62; Br, 44.50.

Fraction 2, b.p. 78.5–79°/18 mm., was ethyl 3-bromo-2-methylpropionate [lit. (8) b.p. 91–93°/19 mm.].

Anal.—Calcd. for $C_6H_{11}BrO_2$: C, 36.92; H, 5.64. Found: C, 37.15; H, 5.68.

Reaction of Ethyl Methacrylate with Hydrogen Bromide—The method was essentially that described for the methyl ester. The sole product, ethyl 2-bromo-2-methylpropionate, had b.p. 125–135°/30 mm. and had a retention time (GLC) of 1.6 min.

Reaction of Methyl Acrylate with Hydrogen Bromide—The method used was the same as that described above for methyl methacrylate. In this instance, the two neutral products were methyl 3-bromopropionate (38.6%), retention time (GLC) 0.9 min., and ethyl 3-bromopropionate (61.4%), retention time 1.4 min. Their b.p.'s, IR spectra, and GLC behavior were identical to those of authentic samples.

Reaction of a Commercial Sample of Butyl Stearate⁵ with Hydrogen Bromide.—A solution of butyl stearate (12.5 g.; 0.04 mole) in diethyl ether (150 ml.) was cooled to 0°. Dry hydrogen bromide gas was passed through this solution for 30 min. (weight increase 68.5 g.). The reaction mixture was left at room temperature for 24 hr. The mixture separated into two layers. The lower layer was miscible with ether; the upper layer was miscible with water. The latter was diluted with water and extracted with ether, and this ether extract was combined with the ethereal lower layer. The combined extract (300 ml.) was washed with aqueous sodium bicarbonate solution (5 \times 100 ml.), then water, and dried (Na_2SO_4). The ether was removed and a pale yellow oil (13.1 g.) was obtained. Gas chromatography using the general method showed that the oil was a mixture of six components (Table I and Fig. 3).

Reaction of a Cetyl Palmitate/Cetyl Stearate Mixture⁶ with Hydrogen Bromide—A solution of the mixture of esters (25 ml.) in diethyl ether (200 ml.) was treated with hydrogen bromide in a manner which was essentially the same as that described above for the treatment of methyl methacrylate. The final product was a pale yellow oil (21.8 g.) which was gas chromatographed using the general method and the three major components (Fig. 4) were collected. Component A was cetyl alcohol. IR spectrum: 3,330 (m) (O—H); 2,865 (S), 2,955 (S) (C—H) cm^{-1} . Mass spectrum: 224 (84%), $[CH_3(CH_2)_{13}CH=CH_2]^+$, m/e (percent abundance relative to peak at m/e 57 = 100). Component B was ethyl palmitate. IR spectrum: 1,742 (S) (ester C=O); 2,850 (S), 2,920 (S) (C—H) cm^{-1} . Mass spectrum: 284 (14.5%), $[CH_3(CH_2)_{14}COOC_2H_5]^+$; 239 (7.5%),

$[CH_3(CH_2)_{14}CO]^+$, m/e (percent abundance relative to peak at m/e 88 = 100). Component C was ethyl stearate. IR spectrum 1,742 (S) (ester C=O); 2,850 (S), 2,920 (S) (C—H) cm^{-1} . Mass spectrum: 312 (16%), $[CH_3(CH_2)_{16}COOC_2H_5]^+$; 267 (5.5%), $[CH_3(CH_2)_{16}CO]^+$, m/e (percent abundance relative to peak at m/e 88 = 100).

Gas Chromatography of the Commercial Sample of Butyl Stearate—A portion (5 μ l.) of the sample was gas chromatographed using the general method and the results obtained are presented in Table I. The two major components (retention times 29.9 and 32.4 min.) were collected. The former was butyl palmitate. IR spectrum: 1,743 (S) (ester C=O); 2,850 (S), 2,920 (S) (C—H) cm^{-1} . Mass

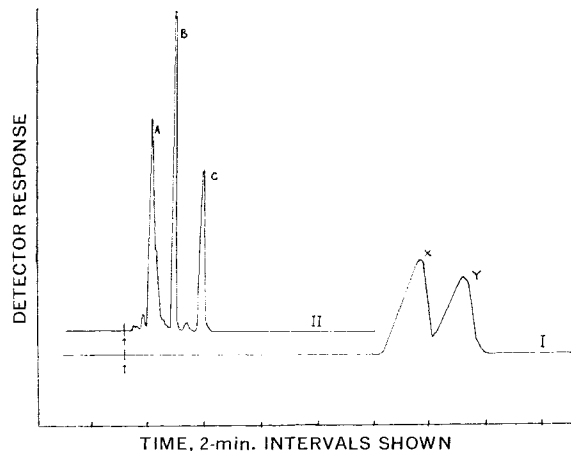


Figure 4—Gas chromatogram of cetyl palmitate/cetyl stearate mixture before (I), and after (II), treatment with hydrogen bromide in diethyl ether. A, cetyl alcohol; B, ethyl palmitate; C, ethyl stearate; X, cetyl palmitate; Y, cetyl stearate.

spectrum: 312 (23%), $[CH_3(CH_2)_{14}COOC_4H_9]^+$, 256 (50%), $[CH_3(CH_2)_{14}COOH]^+$, m/e (percent abundance relative to peak at m/e 57 = 100). The second major component was butyl stearate. IR spectrum: 1,742 (S) (ester C=O); 2,850 (S), 2,920 (S) (C—H) cm^{-1} . Mass spectrum: 340 (11%), $[CH_3(CH_2)_{16}COOC_4H_9]^+$; 284 (16%), $[CH_3(CH_2)_{16}COOH]^+$, m/e (percent abundance relative to peak at m/e 28 = 100).

Gas Chromatography of the Cetyl Palmitate/Cetyl Stearate Mixture—A small portion (5 μ l.) was gas chromatographed using the instrument and column previously described. A programmed temperature operation was employed (initial column temperature 250°; temperature increase 4°/min.; final column temperature 350° and held; detector temperature 375°) and in this way two fractions were obtained (Fig. 4). Fraction X was cetyl palmitate. IR spectrum: 1,742 (S) (ester C=O); 2,850 (S), 2,920 (S), 2,950 (S) (C—H) cm^{-1} . Mass spectrum: 257 (12.5%), 256 (7%), 224 (26.5%) m/e (percent abundance relative to peak at m/e 57 = 100). Fraction Y was cetyl stearate. IR spectrum: 1,742 (S) (ester C=O); 2,850 (S), 2,920 (S), 2,955 (S) (C—H) cm^{-1} . Mass spectrum: 285 (16%); 284 (10.5%); 267 (6.5%), 224 (44.5%), m/e (percent abundance relative to peak at m/e 57 = 100).

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⁵ Practical grade, purchased from Matheson, Coleman & Bell via Canadian Laboratory Supplies Ltd., Edmonton, Canada.

⁶ The mixture was purchased from a commercial source (K & K Laboratories, Plainview, N. Y.) and was reputed to be a sample of cetyl stearate.