## 820. *Studies in the Synthesis of Mycolic Acid.*

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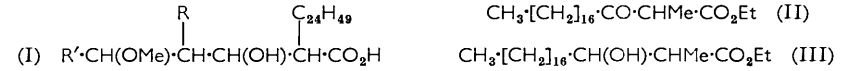
A synthetic route to mycolic acid involving conversion of an α-halogenoalkyl methyl ether, by malonic ester condensation, into an α-alkyl-substituted β-methoxy-acid has been examined. In a model experiment, 3-methoxy-2-propylpentanoic acid (VII; R = H) was prepared, and by further processes transformed into ethyl 2-(1-hydroxy-3-methoxy-2-propylpentyl)eicosanoate (X). In another series of experiments ethyl 5-chloro-2-ethoxycarbonyl-3-methoxy-2-propylpentanoate (V) was synthesised from 1 : 3-dichloropropyl methyl ether (IV) and ethyl propylmalonate, with a view to utilising the terminal chlorine for attachment of a long carbon chain.

The preparation of ethyl 3-hydroxy-2-methyleicosanoate (III) through ethyl 2-methyl-3-oxoeicosanoate (II) is also described.

The present work was undertaken concurrently with the degradative studies of mycolic acid already described.[1] In the initial stages of this work it appeared of interest to synthesise, as models, branched-chain β-hydroxy-acids with a methoxyl group in the δ-position, and alkyl branches in the α- and γ-positions to the carboxyl group, thus having a structure corresponding to formula (I) (where R and R′ are alkyl chains) which has been proposed by Aebi, Vilkas, and Lederer [2] for an acid isolated from the strain " Brèvannes " of tubercle bacilli. Although in our earlier communication [1] we concluded that in our sample of mycolic acid the methoxyl group is farther away from the carboxyl group, the present synthetic studies were continued; the synthetic route described below could be readily modified to introduce the requisite alkyl residue between the carbon atoms bearing the hydroxyl and the methoxyl group.

In our first attempt, we prepared ethyl 2-methyl-3-oxoeicosanoate (II) by reaction of stearoyl chloride with ethyl tetrahydro-2-pyranyl methylmalonate according to Bowman and Fordham's procedure,[3] catalytic hydrogenation in the presence of Raney nickel (cf. Skogh [4]) then giving the hydroxy-ester (III). We then tried to *O*-methylate this




ester, with the intention of using the methoxy-acid chloride as starting point for processes analogous to those given above for stearoyl chloride; however, various attempts to methylate the hydroxy-ester (III) were unsuccessful.

[1] Morgan and Polgar, *J.*, 1957, 3779.
[2] Aebi, Vilkas, and Lederer, *Bull. Soc. chim. France*, 1954, 79.
[3] Bowman and Fordham, *J.*, 1952, 3945.
[4] Skogh, *Acta Chem. Scand.*, 1952, **6**, 809.

In further experiments, we studied the condensation of α-halogenoalkyl ethers with a sodiomalonic ester (cf. ref. 5), to give, after hydrolysis and decarboxylation, a β-alkoxy-acid. First, 1 : 3-dichloropropyl methyl ether (IV), readily available from acraldehyde by addition of hydrogen chloride and methanol,[6] was converted by reaction with ethyl sodiopropylmalonate into ethyl 5-chloro-2-ethoxycarbonyl-3-methoxy-2-propylpentanoate (V), and we intended to utilise the terminal chlorine for attaching a long carbon chain. Since this chain-lengthening involves known procedures, we decided to test the remaining stages of the proposed synthesis by using, meanwhile, as a model ethyl 2-ethoxycarbonyl-3-methoxy-2-propylpentanoate (VI); this was obtained by condensation of 1-chloropropyl methyl ether (cf. ref. 7) with ethyl sodiopropylmalonate. The same product (VI) resulted on reduction of the chloro-ester (V) by means of zinc amalgam and acetic acid; this confirmed the structure (V) assigned to the chloro-ester.

Difficulties were experienced with the conversion of the malonic ester (VI) by the usual successive stages (hydrolysis, decarboxylation) into the β-methoxy-acid (VII; R = H) owing to partial loss of the methoxyl group during decarboxylation. The best yields were obtained by partial hydrolysis of the ester (VI) to the corresponding half-ester, followed by decarboxylation under reduced pressure; from the resulting mixture of ethyl 3-methoxy-2-propylpentanoate (VII; R = Et) with the unsaturated ester arising by elimination of the methoxyl group the unsaturated ester was removed by oxidation with potassium permanganate in acetone. Alkaline hydrolysis of the methoxy-ester (VII; R = Et) readily gave the corresponding acid (VII; R = H).

The conversion of this acid into its chloride was then investigated. Reaction of the acid with thionyl chloride in benzene solution resulted in removal of the methoxyl group, which also occurred when nitrogen was passed through the solution (in order to remove hydrogen chloride) during the preparation of the acid chloride. The methoxy-acid chloride was, however, readily obtained by treatment of the acid with thionyl chloride in the presence of pyridine.

(IV) $Cl\cdot[CH_2]_2\cdot CHCl\cdot OMe$

(V) $Cl\cdot[CH_2]_2\cdot CH(OMe)\cdot C(CO_2Et)_2$, $[CH_2]_2\cdot CH_3$

$CH_3\cdot CH_2\cdot CH(OMe)\cdot C(CO_2Et)_2$ (VI), $[CH_2]_2\cdot CH_3$

$CH_3\cdot CH_2\cdot CH(OMe)\cdot CH\cdot CO_2R$ (VII), $[CH_2]_2\cdot CH_3$

The next step was the reaction of the acid chloride with an alkyl-substituted malonic ester by Bowman and Fordham's procedure;[3] octadecylmalonic ester was chosen as a model. Accordingly, the latter was converted by partial hydrolysis into ethyl hydrogen octadecylmalonate, and thence, by reaction with 2 : 3-dihydropyran in the presence of toluene-*p*-sulphonic acid, into ethyl tetrahydro-2-pyranyl octadecylmalonate (VIII; Py = tetrahydro-2-pyranyl). The sodio-derivative of this malonic ester on condensation with the chloride derived from the acid (VII; R = H) afforded the keto-ester (IX) which,

(VIII) $PyO_2C\cdot CH\cdot CO_2Et$, $[CH_2]_{17}\cdot CH_3$

$CH_3\cdot CH_2\cdot CH(OMe)\cdot CH\cdot CH(OH)\cdot CH\cdot CO_2Et$ (X), $CH_3\cdot[CH_2]_2$, $[CH_2]_{17}\cdot CH_3$

(IX) $CH_3\cdot CH_2\cdot CH(OMe)\cdot CH{-}CO{-}CH\cdot CO_2Et$, $CH_3\cdot[CH_2]_2$, $[CH_2]_{17}\cdot CH_3$

without purification, was reduced directly with sodium borohydride. Chromatography of the product over alumina afforded ethyl 2-(1-hydroxy-3-methoxy-2-propylpentyl)-eicosanoate (X).

It is of interest to note that the infrared spectrum (Nujol) of the ester (X), possessing

[5] Hill and Keach, *J. Amer. Chem. Soc.*, 1926, **48**, 257.
[6] Duliere, *Bull. Soc. chim. France*, 1923, **33**, 1647.
[7] Henze, Benz, and Sutherland, *J. Amer. Chem. Soc.*, 1949, **71**, 2122.

a secondary methoxyl group, shows the methoxyl band at 1093 cm.$^{-1}$ in agreement with that of methyl mycolate. As already pointed out,[8] there appears to be a difference in the position of this band between aliphatic compounds with a secondary and those with a tertiary methoxyl group.

## Experimental

*Ethyl 2-Methyl-3-oxoeicosanoate* (II).—The procedure of Bowman and Fordham [3] was followed. Concentrated sulphuric acid (10 drops) was added to a solution of 2 : 3-dihydropyran (63 g.; purified by refluxing over sodium, and distillation) in dry benzene (500 c.c.), and then ethyl hydrogen methylmalonate [9] (73 g.) in benzene (500 c.c.) was introduced at $<30°$. After a further hr., traces of acid were removed by stirring the mixture with potassium hydroxide (30 g.) for 0·5 hr. The benzene solution was then decanted, and benzene and excess of dihydropyran were removed under reduced pressure (bath temperature $<30°$), to give ethyl tetrahydro-2-pyranyl methylmalonate. This ester (46 g.) was converted into its sodio-derivative by adding it in benzene (150 c.c.) with cooling ($<35°$) to powdered sodium (4·8 g.) and benzene (300 c.c.). When all the sodium had dissolved, a solution of stearoyl chloride (60·5 g.; obtained from stearic acid, m. p. 69—69·5°, by means of thionyl chloride) in benzene (200 c.c.) was added with stirring. After a further 0·5 hour's stirring, acetic acid (20 c.c.) was added and the mixture refluxed for several hr. (to complete the decarboxylation), then poured into water. The benzene layer, after being concentrated, deposited on cooling stearic acid which was filtered off. The remaining solution was diluted with light petroleum (b. p. 80—100°) and shaken with 1% aqueous-methanolic (1 : 1) sodium hydroxide in order to remove the remaining stearic acid. Evaporation of the benzene–petroleum solution gave *ethyl 2-methyl-3-oxoeicosanoate* (16·8 g.), m. p. 40—41° (from ethanol) (Found: C, 75·1; H, 11·9. $C_{23}H_{44}O_3$ requires C, 75·0; H, 12·0%).

*Ethyl 3-Hydroxy-2-methyleicosanoate* (III).—The above oxo-ester (11 g.) was hydrogenated in ethanol (150 c.c.) in the presence of triethylamine [10] (1 c.c.) with Raney nickel (W-2) at 125 atm./100° in 5 hr. (cf. ref. 4). Evaporation of the filtered solution gave *ethyl 3-hydroxy-2-methyleicosanoate*, m. p. 43—44·5° (from ethanol) (Found: C, 74·4; H, 12·5. $C_{23}H_{46}O_3$ requires C, 74·5; H, 12·5%).

*Attempted O-Methylation of Ethyl 3-Hydroxy-2-methyleicosanoate.*—(i) The hydroxy-ester (10·6 g.) was refluxed with methyl iodide (80 g.) and silver oxide (13 g.; added in small portions) for 8 hr. On isolation of the product unchanged hydroxy-ester was obtained.

(ii) The hydroxy-ester (0·5 g.) in benzene (20 c.c.) was added to powdered potassium (0·4 g.) under benzene (25 c.c.), and the mixture refluxed for 1 hr.; methyl iodide (20 c.c.) was then added and the refluxing continued for another 3 hr. The product was an oil which showed $\lambda_{max.}$ 2120 Å ($\varepsilon$ 3625 in *cyclo*hexane). The procedure was repeated in a similar way, except that the mixture was refluxed with potassium for only 15 min., then refluxed with methyl iodide for 15 min.; the product (Found: C, 81·5; H, 13·3%) contained, according to its infrared spectrum, no hydroxyl and little methoxyl.

(iii) The hydroxy-ester (0·5 g.) was heated on a steam-bath with sodium hydride (1 g.) in ethylene glycol diethyl ether (10 c.c.) for 5 min., methyl iodide (15 c.c.) was then added, and the whole refluxed for 10 min. The product obtained on acidification was a complex mixture containing unsaturated material; its infrared spectrum showed no strong methoxyl band.

(iv) The hydroxy-ester was recovered unchanged after being treated in ethereal solution with sodamide and dimethyl sulphate.

(v) The hydroxy-ester (0·4 g.) was heated on a steam-bath with red phosphorus (24 mg.) and iodine (0·25 g.) for 3 hr. The product was extracted with ether, and to the ethereal extract a solution of sodium (46 mg.) in methanol (1 c.c.) was added; a precipitate of sodium iodide resulted. The mixture was shaken with water, and the ethereal layer dried ($MgSO_4$) and evaporated. The residue was according to its infrared spectrum a mixture of $\alpha\beta$-unsaturated acid and ester; there was no evidence of the presence of methoxyl.

*Ethyl 2-Ethoxycarbonyl-3-methoxy-2-propylpentanoate* (VI).—Ethyl propylmalonate (40·4 g.) was introduced slowly, with stirring, on to sodium (4·6 g.; small pieces) under ether (100 c.c.). When all the sodium had dissolved, freshly prepared 1-chloropropyl methyl ether [7] (27·5 g.;

[8] Lewis and Polgar, *J.*, 1958, 102.
[9] Breslow, Baumgarten, and Hauser, *J. Amer. Chem. Soc.*, 1944, **66**, 1287.
[10] Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 695.

b. p. 44°/100 mm.) in benzene–ether (1 : 1) was added quickly (vigorous reaction). The mixture was refluxed with stirring for 0·5 hr., then acidified (glacial acetic acid), diluted with water, and extracted with ether. Distillation gave *ethyl 2-ethoxycarbonyl-3-methoxy-2-propylpentanoate* (35·9 g.), b. p. 136—140°/11 mm., $n_D^{18}$ 1·4360 (Found: C, 61·3; H, 9·45. $C_{14}H_{26}O_5$ requires C, 61·3; H, 9·55%).

*Ethyl 5-Chloro-2-ethoxycarbonyl-3-methoxy-2-propylpentanoate* (V).—1 : 3-Dichloropropyl methyl ether [6] (36·9 g.; b. p. 50—52°/19 mm.) was condensed with ethyl sodiopropylmalonate (from 44·5 g. of ethyl propylmalonate and 5·05 g. of sodium in 50 c.c. of ether) in the manner described in the preceding section. Isolation of the product as above gave *ethyl 5-chloro-2-ethoxycarbonyl-3-methoxy-2-propylpentanoate* (37·3 g.), b. p. 140—145°/1 mm., $n_D^{20}$ 1·4460 (Found: C, 55·7; H, 8·1. $C_{14}H_{25}O_5Cl$ requires C, 55·4; H, 8·15%). Reduction of this chloro-ester by refluxing it with zinc amalgam (150 g.) and glacial acetic acid (500 c.c.) for 24 hr. gave ethyl 2-ethoxycarbonyl-3-methoxy-2-propylpentanoate (VI), b. p. 150—160°/19 mm., $n_D^{16}$ 1·4355 (Found: C, 61·0; H, 9·3%), together with *ethyl 3-acetoxy-2-ethoxycarbonyl-2-propylpentanoate*, b. p. 190—194°/19 mm., $n_D^{18}$ 1·4510 (Found: C, 59·6; H, 9·0. $C_{15}H_{26}O_6$ requires C, 59·6; H, 8·7%); the latter arose by replacement of the methoxyl group by acetoxyl.

*3-Methoxy-2-propylpentanoic Acid* (VII; R = H).—Ethyl 2-ethoxycarbonyl-3-methoxy-2-propylpentanoate (33·5 g.) was refluxed with potassium hydroxide (7·9 g.) in ethanol (150 c.c.) for 4 hr. After acidification with dilute hydrochloric acid, the mixture was extracted with ether, and the ethereal solution re-extracted with 5% aqueous sodium hydroxide. Acidification of the aqueous phase gave the acidic fraction (half-ester, together with some di-acid) which was collected with ether, then decarboxylated by distillation under reduced pressure. The product was taken up in ether, washed with 5% aqueous sodium hydroxide (to remove acidic material arising by decarboxylation of the di-acid), then distilled, to give the crude ethyl ester (19·7 g.), b. p. 100—110°/12 mm., $n_D^{19}$ 1·4295 (the infrared and ultraviolet spectra showed the presence of some αβ-unsaturated material). Powdered potassium permanganate was added to a refluxing solution of this ester (18 g.) in acetone (100 c.c.) in portions until the rate of oxidation became very slow; the mixture was then set aside with a slight excess of potassium permanganate for 2 hr. After addition of sodium hydrogen sulphite and dilute hydrochloric acid, the mixture was extracted with ether. Distillation of the dried ($MgSO_4$) extract gave *ethyl 3-methoxy-2-propylpentanoate* (12·7 g.), b. p. 100—110°/12 mm., $n_D^{19}$ 1·4222 (Found: C, 64·9; H, 10·8. $C_{11}H_{22}O_3$ requires C, 65·2; H, 11·0%). This ester was hydrolysed by refluxing 5% aqueous-ethanolic (1 : 1) potassium hydroxide for 4 hr. Unhydrolysed ester was removed by ether-extraction, and the aqueous phase acidified with dilute hydrochloric acid, then extracted with ether. After being washed with water until the washings were neutral to litmus, the ethereal solution was distilled, to give *3-methoxy-2-propylpentanoic acid*, b. p. 142—145°/16 mm., $n_D^{19}$ 1·4352 (Found: C, 61·7; H, 10·2. $C_9H_{18}O_3$ requires C, 62·0; H, 10·4%). The *amide*, prepared *via* the acid chloride, itself obtained by means of thionyl chloride in the presence of pyridine (see following section), crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 72—73° (Found: C, 62·7; H, 10·9. $C_9H_{19}O_2N$ requires C, 62·5; H, 11·0%). When a benzene solution of the acid was refluxed with thionyl chloride, the resulting acid chloride gave with ammonia an amide, m. p. 113—113·5° (from ethanol) (Found: C, 68·2; H, 10·5; N, 9·7. Calc. for $C_8H_{15}ON$: C, 68·0; H, 10·7; N, 9·9%), loss of the elements of methanol having taken place; Macq [11] gives m. p. 115·5° for the higher-melting isomer of 2-propylpent-2-enamide.

*Ethyl 2-(1-Hydroxy-3-methoxy-2-propylpentyl)eicosanoate* (X).—Ethyl octadecylmalonate (b. p. 198—200°/0·3 mm.; prepared from octadecyl iodide and ethyl sodiomalonate in the usual manner) was converted, by the procedure given by Breslow *et al.*[9] for the preparation of ethyl hydrogen methylmalonate, into ethyl hydrogen octadecylmalonate, m. p. 61—62° (Found: C, 71·6; H, 11·4. Calc. for $C_{23}H_{44}O_4$: C, 71·8; H, 11·5%). This reacted with 2 : 3-dihydropyran in the presence of toluene-*p*-sulphonic acid (cf. Bowman and Fordham [3]), affording ethyl tetrahydro-2-pyranyl octadecylmalonate, m. p. 59—60° (decomp.) (crude product).

Thionyl chloride (2·15 c.c.) in benzene (5 c.c.) was added with stirring to a solution of 3-methoxy-2-propylpentanoic acid (3·9 g.) and pyridine (2·5 g.) in benzene (10 c.c.), cooled in an ice-bath; the mixture was left at 0° for 30 min., and at room temperature for another 30 min. The benzene was then removed under reduced pressure at room temperature. The resulting crude acid chloride was condensed with ethyl tetrahydro-2-pyranyl octadecylsodiomalonate

[11] Macq, *Bull. Acad. roy. Belg., Cl. Sci., Ser* 5, 1926, **12**, 753; *Chem. Zentr.*, 1927, I, 880.

(from 9·9 g. of the malonic ester and 0·54 g. of sodium in 100 c.c. of benzene) according to the general procedure.[3] The mixture was worked up as described,[3] except that the resulting material was heated at 130°/0·4 mm. to remove volatile substances. The crude oxo-ester (4·5 g.) so obtained was dissolved in ethanol, and a suspension of sodium borohydride (0·5 g.) in ethanol–water (9 : 1, 20 c.c.) was added carefully. The mixture was set aside for 1 hr., then 5% aqueous sodium hydroxide was added to decompose the borate complex. The organic material was extracted with ether, and the extract washed with dilute hydrochloric acid and water, then dried ($MgSO_4$) and evaporated. The residue was chromatographed in light petroleum (b. p. 40—60°) on alumina (Spence, type H; activity III on the scale of Brockmann and Schodder [12]). Elution with light petroleum gave fractions containing some ethyl eicosanoate and unsaturated material. Further elution with benzene and benzene–ether gave *ethyl 2-(1-hydroxy-3-methoxy-2-propylpentyl)eicosanoate*, m. p. 63—65° after crystallisation from light petroleum (b. p. 40—60°) (Found: C, 74·6; H, 12·3. $C_{31}H_{62}O_4$ requires C, 74·7; H, 12·5%).

This work was carried out during the tenure of an Imperial Oil Graduate Research Fellowship (by E. D. M.).

Dyson Perrins Laboratory, Oxford University. [*Received, July 11th*, 1958.]

[12] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.