1037. *Studies in the Synthesis of Long-chain Hydroxy-acids. Part II*[1]

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Experiments towards the synthesis of long-chain hydroxy-acids related to the mycolic acids by a route involving the use of thiophen as a chain-extender are reported. 3-Hydroxy-2-tetradecyltricosyl acetate has been prepared.

The present work was undertaken in connection with studies[2] of the mycolic acids isolated from human tubercle bacilli (strains D.T., P.N., and C[3]). The mycolic acids are β-hydroxy-acids of high molecular weight with a long alkyl side-chain in the α-position;[4] they may also contain a methoxyl, carbonyl, or an additional hydroxyl group further away. We aimed at the synthesis of analogues having the structural features (I) where R^1, R^2, R^3, and R^4 are long alkyl chains, and X = Me. A possible intermediate for this synthesis is the acid (II), and in the present studies we investigated a route to this acid which involved the use of thiophen as a chain-extender.

In a preliminary experiment methyl 2-heptyl-3-hydroxynonanoate (III; $R^2 = \text{n-}C_7H_{15}$; $Y = \text{n-}C_6H_{13}$), obtained by a Reformatzky reaction between methyl 2-bromononanoate[5] and heptaldehyde, was converted into the acetoxy-acid (IV; $R^2 = \text{n-}C_7H_{15}$; $Y = \text{n-}C_6H_{13}$). A Friedel–Crafts reaction involving the corresponding acid chloride and 2-tetradecylthiophen[6] gave the thienyl ketone (V; $n = 13$; $R^2 = n\text{-}C_7H_{15}$; $Y = \text{n-}C_6H_{13}$).

In further experiments methyl 2-hydroxymethylhexadecanoate (III; $R^2 = \text{n-}C_{14}H_{29}$;

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[1] Part I, E. D. Morgan and N. Polgar, *J.*, 1958, 4077.
[2] C. Malani and N. Polgar, *J.*, 1963, 3092.
[3] H. H. Green, *Veterinary J.*, 1946, **102**, 267.
[4] J. Asselineau and E. Lederer, *Biochim. Biophys. Acta*, 1951, **7**, 126.
[5] H. Reinheckel, *Chem. Ber.*, 1960, **93**, 2222.
[6] Ng. Ph. Buu-Hoï, Ng. D. Xuong, R. Royer, and D. Lavit, *J.*, 1953, 547.

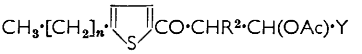
$Y = H$) was prepared by a Reformatzky reaction between methyl 2-bromohexadecanoate and formaldehyde. Hydrolysis of this ester, followed by acetylation, gave the acetoxy-acid (IV; $R^2 = n\text{-}C_{14}H_{29}$; $Y = H$). Reaction of the corresponding acid chloride with 2-hexadecylthiophen[7] in the presence of stannic chloride gave the thienyl ketone (V; $n = 15$; $R^2 = n\text{-}C_{14}H_{29}$; $Y = H$). Desulphurisation of the latter with Raney nickel yielded 3-hydroxy-2-tetradecyltricosyl acetate (VI; $n = 15$; $R^2 = n\text{-}C_{14}H_{29}$), which would be convertible by known procedures into the acid of structure (II).

$R^1CH(OX)\cdot CHR^2\cdot CH_2\cdot CHR^3\cdot CH(OH)\cdot CHR^4\cdot CO_2H$ (I)

$R^1CH(OX)\cdot CHR^2\cdot CH_2\cdot CHR^3\cdot CO_2H$ (II)

$MeO_2C\cdot CHR^2\cdot CH(OH)\cdot Y$ (III)

$HO_2C\cdot CHR^2\cdot CH(OAc)\cdot Y$ (IV)



(V)

$CH_3\cdot[CH_2]_{n+4}\cdot CH(OH)\cdot CHR^2\cdot CH_2\cdot OAc$ (VI)

EXPERIMENTAL

Petrol refers to light petroleum of b. p. 40—60°. The alumina used for chromatography (Spence, type H) was treated with acetic acid according to Farrar *et al.*[8] and the activity determined by the method of Heřmánek *et al.*[9]

2-*Alkylthiophens*.—These were prepared by a Friedel–Crafts reaction involving the appropriate acid chloride and thiophen, followed by reduction of the resulting thienyl ketone, as described by Miller *et al.*[7] 2-Tetradecylthiophen had b. p. 150—152°/0·5 mm. (Buu-Hoï *et al.*[6] record b. p. 212—214°/15 mm.) (Found: C, 77·1; H, 11·4; S, 11·4. Calc. for $C_{18}H_{32}S$: C, 77·1; H, 11·4; S, 11·2%). 2-Hexadecylthiophen had b. p. 161—163°/29 mm. (Miller *et al.*[7] give b. p. 147—147·5°/0·2 mm.) (Found: C, 77·8; H, 11·8; S, 10·4. Calc. for $C_{20}H_{36}S$: C, 77·8; H, 11·8; S, 10·4%).

2-*Bromo-esters*.—The procedure described by Mendel *et al.*[10] was followed. Methyl 2-bromononanoate distilled at 76—78°/0·1 mm. (Reinheckel[5] gives b. p. 128°/13 mm.) (Found: C, 47·7; H, 7·8; Br, 31·6. Calc. for $C_{10}H_{19}BrO_2$: C, 47·8; H, 7·6; Br, 31·9%). Methyl 2-bromohexadecanoate had b. p. 158—162°/0·35 mm., n_D^{22} 1·4624. Reinheckel[5] records b. p. 134°/0·06 mm., n_D^{20} 1·4630) (Found: C, 58·3; H, 9·4; Br, 22·9. Calc. for $C_{17}H_{33}BrO_2$: C, 58·5; H, 9·5; Br, 22·9%).

Methyl 2-*Heptyl*-3-*hydroxynonanoate* (III; $R^2 = n\text{-}C_7H_{15}$; $Y = n\text{-}C_6H_{13}$).—A 20 c.c. portion of a solution of methyl 2-bromononanoate (84 g.) and heptaldehyde (45 c.c.) in benzene (100 c.c.) was added to zinc dust (22 g.) in benzene (150 c.c.), and the mixture heated until the reaction started. The remainder of the solution was then added with stirring at such a rate that the mixture boiled gently, and refluxing continued for a further 2 hr. The product was poured into dilute hydrochloric acid, extracted with ether, and the benzene–ether layer washed with water. Distillation of the dried ($MgSO_4$) extract gave the *hydroxy-ester* (57 g.) as an oil, b. p. 146°/0·5 mm. (Found: C, 71·3; H, 12·0. $C_{17}H_{34}O_3$ requires C, 71·3; H, 11·9%).

Methyl 2-*Hydroxymethylhexadecanoate* (III; $R^2 = n\text{-}C_{14}H_{29}$; $Y = H$).—Methyl 2-bromohexadecanoate (2·5 g.), granulated zinc (3·5 g.), paraformaldehyde (5 g.), and 1 : 1 benzene–toluene (30 c.c.) were refluxed with stirring; a few granules of zinc, previously heated with a little bromo-ester, were added to initiate the reaction. After heating under reflux for 1 hr. more bromo-ester (12·5 g.) and paraformaldehyde (2·5 g.) in 1 : 1 benzene–toluene (20 c.c.) were introduced during 1 hr. and refluxing continued for another 6 hr. The mixture was poured into dilute sulphuric acid (50 c.c.) and extracted with benzene. The product was chromatographed in petrol on alumina (activity III; 200 g.). Elution with petrol, followed by 1 : 1 petrol–benzene gave mainly material containing no hydroxyl. Further elution with ether afforded *methyl 2-hydroxymethylhexadecanoate* (1·8 g.) as crystals, m. p. 36—37° (Found: C, 71·6; H, 11·9. $C_{18}H_{36}O_3$ requires C, 71·9; H, 12·1%).

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[7] K. E. Miller, C. Haymaker, and H. Gilman, *J. Org. Chem.*, 1959, **24**, 622.

[8] K. R. Farrar, J. C. Hamlet, H. B. Henbest, and E. R. H. Jones, *J.*, 1952, 2657.

[9] S. Heřmánek, V. Schwarz, and Z. Čekan, *Coll. Czech. Chem. Comm.*, 1961, **26**, 3170.

[10] H. Mendel and J. Coops, *Rec. Trav. chim.*, 1939, **58**, 1133.

1-*Hexyl*-2-(5-*tetradecyl*-2-*thenoyl*)*nonyl Acetate* (V; $n = 13$; $R^2 = n\text{-}C_7H_{15}$; $Y = n\text{-}C_6H_{13}$).—Methyl 2-heptyl-3-hydroxynonanoate (10 g.) was hydrolysed by refluxing methanolic potassium hydroxide (20 g. in 100 c.c.), and the liberated acid, isolated by ether-extraction, was acetylated by heating it under reflux in benzene (20 c.c.) with acetic anhydride (150 c.c.) for 2 hr. The product, isolated in the usual manner, showed in its infrared spectrum the presence of anhydride; it was refluxed with glacial acetic acid (50 c.c.) for 1 hr. Removal of the acetic acid by distillation gave the acetoxy-acid, a portion (3·9 g.) of which was converted into its acid chloride by means of thionyl chloride.

Stannic chloride (1 c.c.) in benzene (9 c.c.) was added dropwise with stirring to a solution of the above acid chloride and 2-tetradecylthiophen (2·3 g.) in benzene (20 c.c.) at 0° during 20 min. After being stirred for a further 1·25 hr. at room temperature, the mixture was acidified with dilute hydrochloric acid and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated. The product was chromatographed in petrol on alumina (activity III—IV; 120 g.). After elution with petrol, further elution with ether gave the *thienyl ketone* as an oil (1·6 g.), n_D^{18} 1·4930 (Found: C, 74·6; H, 11·0; S, 5·5. $C_{36}H_{64}O_3S$ requires C, 75·0; H, 11·0; S, 5·5%).

3-*Hydroxy*-2-*tetradecyltricosyl Acetate* (VI; $n = 15$; $R^2 = n\text{-}C_{14}H_{29}$).—Methyl 3-hydroxy-2-tetradecylpropionate (3·8 g.) was hydrolysed by means of aqueous-ethanolic potassium hydroxide. Acidification with dilute sulphuric acid, followed by ether-extraction gave the corresponding acid as a solid, m. p. 76—77° (3·5 g.). A portion (2 g.) of this acid was acetylated by means of acetyl chloride (4 c.c.) in pyridine (20 c.c.). The product, isolated in the usual manner, showed in its infrared spectrum an anhydride band (1802 cm.$^{-1}$); it was heated under reflux with glacial acetic acid (40 c.c.) for 2 hr. The excess of acetic acid was then distilled off under reduced pressure, and the residue poured into water. Ether-extraction gave the acetoxy-acid (1·89 g.), m. p. 51°, which was converted into its acid chloride by means of thionyl chloride. Stannic chloride (2·6 g.) in benzene (10 c.c.) was added during 0·5 hr. at 0° with stirring to the above acid chloride and 2-hexadecylthiophen (1·76 g.) in benzene (10 c.c.). The solution was stirred at room temperature for 3 hr.; 10% hydrochloric acid was then added and the mixture stirred for 0·5 hr. The benzene layer was separated, washed with dilute hydrochloric acid, then with water, dried ($MgSO_4$), and evaporated. The residue was chromatographed in benzene on alumina (activity III—IV; 80 g.). Benzene (400 c.c.) eluted the thienyl ketone (2·4 g.) which was refluxed with Raney nickel (from 43 g. of nickel–aluminium alloy, prepared as described previously [11]) in ethanol (150 c.c.) with stirring for 60 hr. The nickel was filtered off, and the filtrate evaporated. The product was chromatographed in petrol on alumina (activity III—IV; 70 g.). The following fractions were taken: (1) petrol (360 c.c.) (0·36 g.); (2) petrol–benzene (9 : 1, 500 c.c.) (0·16 g.); (3) ether (300 c.c.) (0·42 g.). Fraction (3), m. p. 37—38°, consisted of 3-*hydroxy*-2-*tetradecyltricosyl acetate* (Found: C, 78·7; H, 13·1. $C_{39}H_{78}O_3$ requires C, 78·7; H, 13·2%); its infrared spectrum in Nujol showed a hydroxyl band at 3333 cm.$^{-1}$, and carbonyl bands at 1709 and 1681 cm.$^{-1}$; in carbon tetrachloride solution the spectrum showed only one carbonyl band at 1724 cm.$^{-1}$.

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[11] N. Polgar and W. Smith, *J.*, 1963, 3085.