A Synthesis of D-*ribo*-2-Benzamido-1,3,4-trihydroxyoctadec-8-yne

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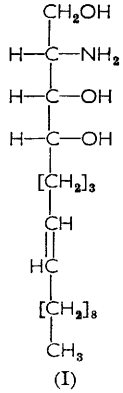
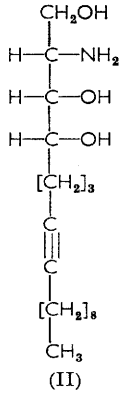
D-*ribo*-2-Benzamido-1,3,4-trihydroxyoctadec-8-yne, the acetylenic analogue of *N*-benzoyl dehydrophytosphingosine, has been synthesised from D-glucosamine. A convenient method for the preparation of long-chain alk-1-ynes is also described.

In preceding Papers we have described syntheses of C18- and C20-phytosphingosines from both 2-amino-2-deoxy-D-glucose [1a] and D-galactose.[1b] An unsaturated analogue of C18-phytosphingosine ("dehydrophytosphingosine") was detected in plant seed phytoglycolipids by Carter and his co-workers [2] and the relative proportions of phytosphingosine and dehydrophytosphingosine in the phytoglycolipids of various seeds were determined.[3] It has been shown that the dehydrophytosphingosine from flax and soybean lipids [3] and from peanut lipids [4] can be reduced catalytically to give C18-phytosphingosine and that the structure [3] of dehydrophytosphingosine is D-*ribo*-2-amino-1,3,4-trihydroxyoctadec-*trans*-8-ene (I). The recent discovery of phytosphingosine in human brain and kidney lipids and the close association of phytosphingosine and dehydrophytosphingosine in plant lipids suggests that dehydrophytosphingosine may also be present in animal lipids.



(I)



(II)

In the present Paper we describe a synthesis of the *N*-benzoyl derivative of the acetylenic analogue (II) of dehydrophytosphingosine *via* the aldehyde (III) which was used in the synthesis of phytosphingosine described previously.[1a]

A Wittig reaction between the aldehyde (III) and the stable phosphorane $Ph_3P{=}CH{\cdot}CO_2Et$,[5] gave the unsaturated ester (IV), which was reduced catalytically to give the saturated ester (V). Reduction of compound (V) with lithium aluminium hydride under conditions which did not affect the oxazoline ring [6] gave the alcohol (VI) which was converted into the methanesulphonate (VII). Compound (VII) was converted into the iodide (VIII) by the action of sodium iodide in boiling acetone.

Undec-1-yne was required to extend the carbon chain and a new method for the preparation of this compound and related long-chain alk-1-ynes was investigated. The standard reaction for the preparation of alk-1-ynes involving the condensation of alkyl halides with sodium acetylide in liquid ammonia at the boiling point is not applicable to the preparation of long-chain alk-1-ynes because of the insolubility of the long-chain alkyl halides in liquid ammonia at this temperature. However, by using an autoclave and carrying out the reaction at room temperature the condensation does occur.[7] To avoid using this technique Jenny and Meier [8] have used *NN*-dimethylformamide and Normant [9] has used hexamethylphosphoramidate

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[7] (*a*) T. H. Vaughn, G. F. Hennion, R. R. Vogt, and J. A. Nieuwland, *J. Org. Chem.*, 1937, **2**, 1; (*b*) B. B. Elsner and P. F. M. Paul, *J. Chem. Soc.*, 1951, 893.

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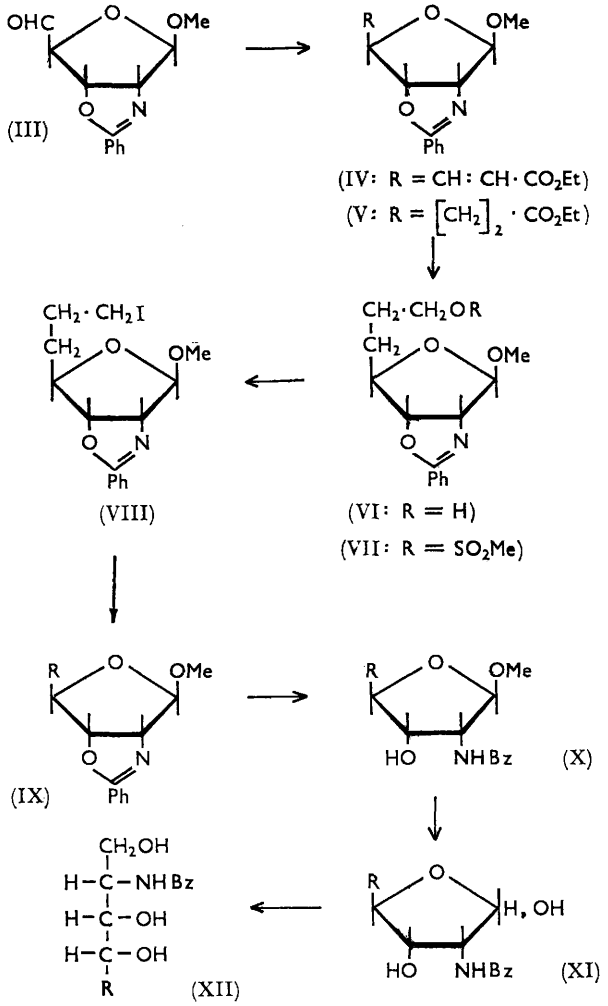
as solvents. Recently [10] solutions of a complex of acetylene and sodium acetylide prepared in dimethyl sulphoxide have been used in alkynylation reactions. We have found that these solutions react exothermically



R = $[CH_2]_3{\cdot}C{\equiv}C{\cdot}[CH_2]_8{\cdot}CH_3$ in compounds (IX—XII)

with long-chain alkyl bromides at room temperature to give the long-chain alk-1-ynes in high yield. Undec-1-yne, pentadec-1-yne, and eicos-1-yne were conveniently prepared in approximately 90% yields using this method.

Undec-1-yne was converted into the lithium derivative by the action of phenyl-lithium in tetrahydrofuran and the lithium acetylide was condensed with the iodide (VIII) to give the acetylene (IX). Compound (IX) was converted into D-*ribo*-2-benzamido-1,3,4-trihydroxyoctadec-8-yne (XII) *via* the intermediates (X) and (XI) in the same way as described for the saturated compounds in a previous Paper.[1a] Catalytic reduction of the acetylenic bonds in compounds (IX and XII) gave the corresponding saturated derivatives which were identical to those described previously.[1a]

[10] J. Kříž, M. J. Beneš, and J. Peška, *Tetrahedron Letters*, 1965, 2881.

The partial reduction of the acetylenic bond in compounds (IX, X, or XII) to give a *trans*-ethylenic bond is under investigation.

EXPERIMENTAL

For general details see previous Paper.[1a]

Ester (V).—A solution of ethoxycarbonylmethylenetriphenylphosphorane [5] ($Ph_3P{=}CH{\cdot}CO_2Et$) (30 g., 0·086 mole) in benzene (500 ml.) was added to a solution of the aldehyde (III) [1a] (21 g., 0·085 mole) in benzene (100 ml.). After 1 hr. at room temperature, thin-layer chromatography (t.l.c.) (ether as mobile phase) showed complete conversion of the aldehyde (R_f 0·6) into an unsaturated product (R_f 0·9). The solvent was evaporated and the residue was taken up in ether (600 ml.) and set aside overnight at room temperature; the triphenylphosphine oxide which separated was removed by filtration. The solution was concentrated (to 100 ml.) and cooled to give more triphenylphosphine oxide, which was separated. Evaporation of the solvent gave the ester (IV) as a syrup [$\nu_{max.}$ 1645 (C=N) and 1720 $cm.^{-1}$ (CH=CH–CO_2Et)]. The syrup was dissolved in glacial acetic acid (200 ml.) and hydrogenated in the presence of 10% palladium on charcoal until no more hydrogen was taken up. After filtration and evaporation of the solvent the product was obtained as a syrup, which solidified on standing and was recrystallised from aqueous ethanol to give the *ester* (V) as needles (14 g.), m. p. 64—66°, $[\alpha]_D$ −19° (*c* 0·7 in chloroform) (Found: C, 63·8; H, 6·7; N, 4·3. $C_{17}H_{21}NO_5$ requires C, 63·9; H, 6·6; N, 4·4%).

Alcohol (VI).—A solution of the ester (V) (13·4 g., 0·042 mole) in dry ether (500 ml.) was added to a solution of lithium aluminium hydride (1·2 g., 0·031 mole) in dry ether (200 ml.) at 0°, during 10 min. After a further 15 min. at 0° t.l.c. (ether as mobile phase) showed conversion of the ester (V) (R_f 0·8) into the product (R_f 0·3). Ethyl acetate (1 ml.) and then water were added until the inorganic material was in the form of a fine white powder, which was removed by filtration. The solution was dried (K_2CO_3) and evaporated to give the product as a syrup which solidified on standing. Recrystallisation from ethyl acetate light petroleum (1 : 3) gave the *alcohol* (VI) (9 g.) as feathery needles, m. p. 83—84°, $[\alpha]_D$ −41° (*c* 1 in chloroform) (Found: C, 65·0; H, 7·1; N, 4·9. $C_{15}H_{19}NO_4$ requires C, 65·0; H, 6·9; N, 5·05%).

Methanesulphonate (VII).—Methanesulphonyl chloride (4 g., 0·035 mole) was added to a solution of the alcohol (VI) (9 g., 0·032 mole) in dry pyridine (50 ml.) at 0°. After 1 hr. at 0°, water (2 ml.) was added and the solution was poured into ice–water with stirring. The solid product (9·5 g.) was collected, dried, and recrystallised from cyclohexane to give the *methanesulphonate* (VII) as needles, m. p. 95—96°, $[\alpha]_D$ −22° (*c* 0·4 in chloroform) (Found: C, 54·2; H, 5·8; N, 3·8; S, 8·7. $C_{16}H_{21}NO_6S$ requires C, 54·1; H, 6·0; N, 3·9; S, 9·0%).

Iodide (VIII).—A solution of the methanesulphonate (VII) (9 g.) and dry sodium iodide (30 g.) in dry acetone (300 ml.) was heated under reflux for 30 min. when t.l.c. (ether as mobile phase) showed complete conversion of the methanesulphonate (R_f 0·3) to the product (R_f 0·9). Most of the acetone was evaporated and the residue was diluted with water and extracted with chloroform. The solution was dried ($MgSO_4$) and evaporated, and the solid product was recrystallised from light petroleum (b. p. 60—80°) to give

the *iodide* (VIII) (9 g.) as needles, m. p. 86—87°, $[\alpha]_D$ +1·5° (*c* 1 in chloroform) (Found: C, 46·7; H, 4·6; N, 3·6; I, 32·9. $C_{15}H_{18}INO_3$ requires C, 46·5; H, 4·7; N, 3·6; I, 32·8%).

Undec-1-yne.—"Sodium hydride 50% in oil" (Koch-Light) (10 g.) was added to dry dimethyl sulphoxide [11] (200 ml.) and the mixture was stirred in a dry nitrogen atmosphere at 65—70° until no more hydrogen was evolved. The solution was cooled to room temperature, triphenylmethane (10 mg.) was added as an indicator, and dry acetylene was passed through the stirred solution. When the pink colour had disappeared, a white precipitate was present, but after continued passage of acetylene, a blue-black solution of the sodium acetylide–acetylene complex resulted.[10] The solution was then cooled in ice and nonyl bromide [37 g., prepared by the Hunsdiecker reaction [12] from decanoic acid (B.D.H., "99% by g.l.c."), b. p. 107°/15 mm., n_D^{19} 1·4548, lit.,[13] b. p. 94—95°/10 mm., n_D^{25} 1·4523] was added dropwise with stirring during 15 min. under a dry nitrogen atmosphere. After the addition was complete the solution was stirred at room temperature for 30 min. and then water was added slowly with stirring to decompose the excess of sodium acetylide. Water (200 ml.) was added and the mixture was extracted with light petroleum (2 × 100 ml.), the extract dried (K_2CO_3), and the solvent evaporated. Distillation of the residue gave undec-1-yne (24 g., 88%), b. p. 86°/18 mm., n_D^{19} 1·4313 (Found: C, 86·5; H, 13·1. Calc. for $C_{11}H_{20}$C: 86·8; H, 13·2%), lit.,[14] b. p. 94·5°/25 mm., n_D^{20} 1·4309. The mercury derivative prepared from an alkaline mercuric iodide solution [15] had m. p. 82—84° (lit.,[16] m. p. 79—79·3°).

In the same way, pentadec-1-yne was prepared from tridecyl bromide.[1a] Yield 88%, b. p. 140°/15 mm., n_D^{20} 1·4425 (Found: C, 86·2; H, 13·3. Calc. for $C_{15}H_{28}$: C, 86·5; H, 13·5%), lit.,[17] b. p. 112—113°/5 mm., n_D^{20} 1·4410. The mercury derivative of pentadec-1-yne had m. p. 94—95° (lit.,[17] m. p. 93°). Eicos-1-yne was prepared in the same way from octadecyl bromide. Yield 92%, b. p. 145°/0·4 mm., m. p. 34—37° (Found: C, 86·2; H, 13·7. Calc. for $C_{20}H_{38}$: C, 86·3; H, 13·75%) lit.,[18] b. p. 153°/1·1 mm., m. p. 33—34°. The mercury derivative of eicos-1-yne had m. p. 102—105°.

Acetylene (IX).—A solution of phenyl-lithium in ether (40 ml., 0·77N; 0·03 mole) was added to a solution of undec-1-yne (6 g., 0·04 mole) in dry tetrahydrofuran (100 ml.) under a dry nitrogen atmosphere. The iodide (VIII) (7 g., 0·018 mole) was added and the solution was heated under reflux for 12 hr. After this time, t.l.c. [ether–light petroleum (1 : 1) as mobile phase] showed almost complete conversion of the iodide (R_f 0·5) to the product (R_f 0·7). Water was added to decompose the excess of acetylide and most of the solvent was removed by evaporation. The residue was diluted with water and extracted with ether, the extract dried, and the solvent evaporated to give an oil which was chromatographed on alumina. Elution with light petroleum removed undec-1-yne and elution with benzene gave the *acetylene* (IX) (6 g.) as a syrup which solidified on cooling, m. p. 36—38°, $[\alpha]_D$ −12·2° (*c* 0·9 in chloroform) (Found: C, 76·0; H, 8·8; N, 3·4. $C_{26}H_{37}NO_3$ requires C, 75·9; H, 9·1; N, 3·4%).

The acetylene (IX) was reduced with hydrogen in the presence of 10% palladium on charcoal to give the corresponding saturated derivative, m. p. and mixed m. p. with material prepared previously [1a] 52—54°, $[\alpha]_D$ −19° (*c* 0·5 in chloroform) (Found: C, 74·9; H, 10·0; N, 3·3. Calc. for $C_{26}H_{41}NO_3$: C, 75·2; H, 9·95; N, 3·4%).

Amide (X).—A solution of the acetylene (IX) (5·8 g., 0·014 mole) in methanol (125 ml.) and N-hydrochloric acid (15 ml.) was heated under reflux for 30 min. The solution was cooled and potassium carbonate (2 g.) was added and the methanol evaporated. The residue was extracted with ether, the extract dried (K_2CO_3), and the solvent evaporated to give a syrup which solidified on standing. Recrystallisation from light petroleum gave the *amide* (X) (4·5 g.) as needles, m. p. 66—68°, $[\alpha]_D$ +15° (*c* 0·5 in chloroform) (Found: C, 72·5; H, 8·9; N, 3·2. $C_{26}H_{39}NO_4$ requires C, 72·7; H, 9·15; N, 3·3%).

Amide (XI).—The amide (X) (3·5 g.) was added to a solution of dioxan (70 ml.) and N-hydrochloric acid (17 ml., 0·25N) at 100°. After 10 min., the solution was cooled and water (200 ml.) was added. After cooling to 0° the white solid was removed by filtration, dried, and recrystallised from light petroleum to give the *amide* (XI) (2 g.) as needles, m. p. 86—88°, $[\alpha]_D$ +26° (*c* 1·2 in chloroform) (Found: C, 72·3; H, 9·1; N, 3·3. $C_{25}H_{37}NO_4$ requires C, 72·3; H, 9·0; N, 3·4%).

D-ribo-2-*Benzamido*-1,3,4-*trihydroxyoctadec*-8-*yne* (XII).—Sodium borohydride (0·75 g.) was added to a solution of the amide (XI) (1·8 g.) in methanol (20 ml.) at 0°. After 1·5 hr., glacial acetic acid (5 ml.) was added and the solvents were removed by evaporation. Several portions of methanol were evaporated from the residue to remove boric acid and the solid product was recrystallised from ethyl acetate to give the *product* (XII) (0·8 g.) as needles, m. p. 84—86°, $[\alpha]_D$ −1·8° (*c* 1·2 in pyridine) (Found: C, 71·7; H, 9·3; N, 3·4. $C_{25}H_{39}NO_4$ requires C, 71·9; H, 9·4; N, 3·4%).

The acetylene (XII) was reduced with hydrogen in the presence of 10% palladium on charcoal. Recrystallisation of the product from ethyl acetate gave D-*ribo*-2-benzamido-1,3,4-trihydroxyoctadecane, m. p. and mixed m. p. with material prepared previously,[1a] 135—136°.

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