

SYNTHESIS OF TACHYSTEROL₃

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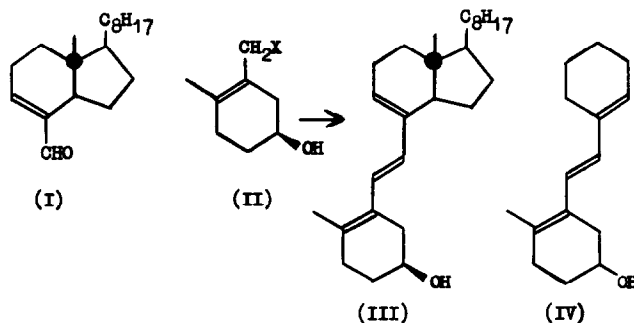
(Received 28 June 1963)

THE tachysterols are 9,10-seco-steroidal trienes which have hitherto been obtained by the geometrical isomerisation of their 6,7-cis-isomers, the precalciferols, either by ultraviolet light,¹ or by iodine and visible light.² In continuation of earlier studies^{3, 4} on the synthesis of conjugated trienes related to the vitamins D we have now effected the first synthesis of tachysterol₃ (III).

We proposed to construct the 6,7-trans-double bond by a Wittig reaction in which the carbonyl component was the bicyclic aldehyde (I). Since this implied the use⁵ of the hydroxyl-containing phosphonium bromide (II; X = PPh₃⁺Br⁻), a preliminary test was made. The racemic diol (II; X = OH) (di-p-nitrobenzoate, m.p. 131-133°) reacted with triphenyl phosphite benzylbromide⁶ and triphenylphosphine giving the

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- 1 Rappoldt, Westerhof, Hanewald and Keverling-Buisman, Rec. Trav. chim. Pays-Bas, 77, 241 (1958).
 - 2 Koevoet, Verloop and Havinga, ibid., 74, 788, 1125 (1955);
Inhoffen and Schaefer, Chem. Ber., 92, 1126 (1959).
 - 3 Harrison and Lythgoe, J. chem. Soc., 837 (1958), and earlier papers in the same series.
 - 4 Harrison and Lythgoe, J. chem. Soc., 843 (1958).
 - 5 For a previous use of a hydroxyl-containing phosphonium bromide in a Wittig reaction, see ref. 4.
 - 6 Laudauer and Rydon, J. chem. Soc., 2224 (1953).

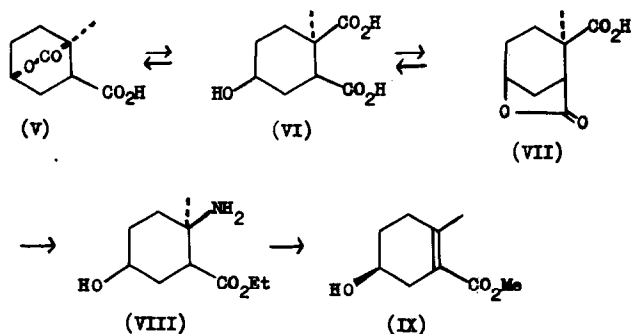
racemic phosphonium bromide (II; $X = PPh_3^+ Br^-$) as a tetrahydrofuran solvate. The corresponding phosphorane and cyclohexene-1-aldehyde gave the crystalline trienol (IV), λ_{max}^{EtOH} 267.5, 277 and 288 m μ ($10^{-3} \epsilon$ 33.3, 44.0 and 32.6) which formed a *p*-nitrobenzoate m.p. 116-118°. These are the first crystalline synthetic compounds with a tachysterol-like chromophore.



For the synthesis of tachysterol₃ itself it proved necessary to use an optically active ring A component. After unsuccessful attempts to resolve the racemate (II; $X = OH$), an indirect method was adopted. Citraconic anhydride and butadiene form an adduct which, after hydrolysis, gives a keto-acid⁷ of hitherto uncertain structure; we degraded it to 4-methylcyclohexanone, so establishing that it is 4-methylcyclohexanone-3,4-dicarboxylic acid. The hydroxy-acid (VI) obtained from it by catalytic reduction gave, depending on the conditions, either a γ -lactonic acid (VII) or a more stable δ -lactonic acid (V). The racemate (V), m.p. 144-146° was resolved (quinine) into the antipodes m.p. 158-160°, $[\alpha]_D - 78.5^\circ$ (CHCl₃) and (not quite optically pure) m.p. 157-159°.

⁷ Newman and Lloyd, *J. org. Chem.*, 17, 577 (1952);
Nazarov and Kucherov, *Izvest. Akad. Nauk S.S.S.R. Otdel. khim. Nauk*, 1462 (1956).

$[\alpha]_D + 77^\circ$ (CHCl_3); the latter, which has the absolute configuration (V) was used for the synthesis of tachysterol₃. It was hydrolysed to the hydroxy-acid (VI), m.p. 158° , $[\alpha]_D - 16.5^\circ$ (EtOH), which was converted into the γ -lactone (VII). Degradation of the carboxyl group via the azide and ethanolysis of the lactone ring gave the amino-ester (VIII), m.p. $86-87.5^\circ$, $[\alpha]_D + 13.5^\circ$ (EtOH). Methylation and Hofmann elimination gave the crude optically active unsaturated ester (IX) which was converted into the di-*p*-nitrobenzoate, m.p. $141-142.5^\circ$, $[\alpha]_D + 33^\circ$ (Me_2CO) of the diol (II; X = OH). This was converted into the phosphonium bromide of absolute configuration (II; X = $\text{PFh}_3^+\text{Br}^-$).



In compounds related to the aldehyde⁸ (I) an 8,9-double bond is less stable than an 8,14-double bond (c.f. tachysterol and isotachysterol⁹) and also, as it proved, less stable than a 9,11-double bond; thus sodium methoxide changed the conjugated ester (XV; R = CO_2Me) into the unconjugated ($\Delta^{9,11}$) isomer. We expected that these

⁸ This aldehyde is described as 8-formyl-des-AB-cholest-8-ene, and numbered on the cholestane system.

⁹ Inhoffen, Brückner, Gründel and Quinkert, *Chem. Ber.*, **87**, 1407 (1954).

circumstances might cause difficulty in preparing material of unambiguous structure (I), and we therefore chose to prepare this aldehyde in the first instance by degradation of cholesterol. An important intermediate in this process appeared to be the hydroxy-acid (AIII; R = OH). We have obtained it by two different routes, one¹⁰ starting from the 3-methyl ether¹¹ of Westphalen's diol, the other from the seco-acid¹² (X). Enol-lactonisation converted the latter into the homoannular diene (XI), m.p. 112-114°, $[\alpha]_D + 72^\circ$ (CHCl₃), $\lambda_{\text{max.}}^{\text{EtOH}}$ 274 m μ (10⁻³ E 7.7), which reacted¹³ with methyl acetylenedicarboxylate giving the adduct (XII), m.p. 155°. Thermal isomerisation¹³ followed by hydrolysis then provided the acid (XIII; R = CH₂:CMe), m.p. 91.5°, $[\alpha]_D + 35.5^\circ$ (CHCl₃). Ozonolysis gave the acid¹⁴ (XIII; R = ac), and by applying the Baeyer-Villiger method the acid (XIII; R = OH), m.p. 133-135°, $[\alpha]_D + 32.5^\circ$ (CHCl₃) was obtained. Its epimer (XIV), m.p. 107-108°, $[\alpha]_D + 12.7^\circ$ (CHCl₃) was converted into the methyl ester benzenesulphonate, which on treatment with alkali gave the unsaturated acid (XV; R = CO₂H), m.p. 120.5-121.5°, $[\alpha]_D - 17.5^\circ$ (CHCl₃), $\lambda_{\text{max.}}^{\text{EtOH}}$ 224 m μ (10⁻³ E 9.1). The corresponding primary alcohol (XV; R = CH₂OH) was oxidised by manganese dioxide giving the aldehyde (I), $\lambda_{\text{max.}}^{\text{EtOH}}$ 235 m μ . It was characterised as the semi-carbazone m.p. 193-194°, $[\alpha]_D - 35.5^\circ$ (AcOH).

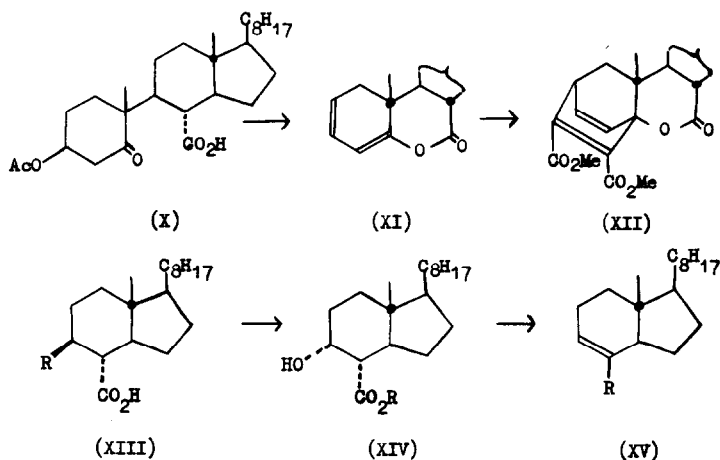
¹⁰ Gell, Littlewood, Lythgoe and Marples, to be published.

¹¹ Davis and Petrow, *J. chem. Soc.*, 2211 (1951).

¹² Günther, Ph.D. Thesis, Leeds, 1958;
Jacobs and Brownfield, *J. Amer. chem. Soc.*, 82, 4033 (1960).

¹³ c.f. Alder and Rickert, *Liebigs Ann.*, 524, 130 (1936);
Pines and Kozlowski, *J. Amer. chem. Soc.*, 78, 3776 (1956).

¹⁴ Fieser, Huang and Goto, *ibid.*, 82, 1600 (1960) have isolated this acid in low yield by direct oxidation of cholesterol.

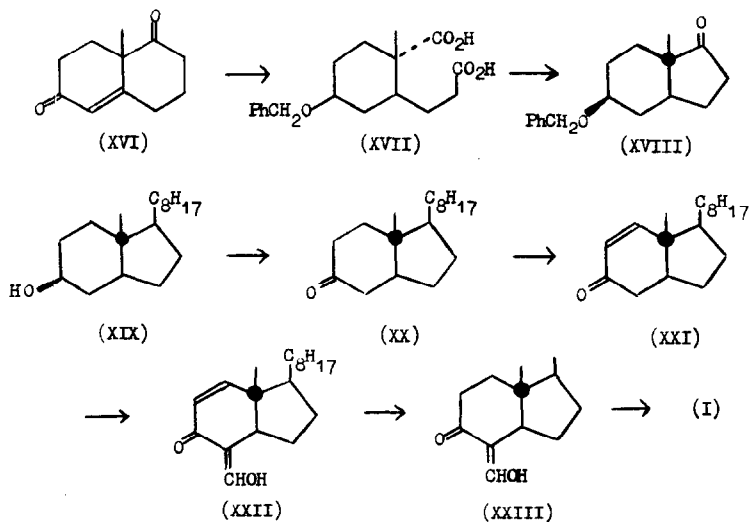


Reaction of the aldehyde (I) with the phosphorane derived from the bromide of absolute configuration (II; $X = PPh_3^+ Br^-$) gave tachysterol₃, isolated as the 3,5-dinitro-4-methylbenzoate, m.p. 136-136.5°, $[\alpha]_D + 32^\circ$ (C_6H_6), λ_{max}^{EtOH} 270 (infl.), 280 and 290 (infl.) $m\mu$ ($10^{-3} \epsilon$ 25.2, 30.1 and 24.9). An authentic sample, prepared by iodine-catalysed isomerisation of precalciferol₃, had m.p. 136-136.5° (lit.¹⁵ 137-138°), $[\alpha]_D + 32.5^\circ$, λ_{max}^{EtOH} 270 (infl.), 280 and 290 (infl.) $m\mu$ ($10^{-3} \epsilon$ 24.3, 29.3 and 24.3).

In a similar manner the enantiomorph of the bromide (II; $R = PPh_3^+ Br^-$) was prepared and brought into reaction with the aldehyde (I), giving epitachysterol₃ 3,5-dinitro-4-methylbenzoate which, after chromatographic purification, had $[\alpha]_D - 36^\circ$ (C_6H_6) and λ_{max} identical with those of the tachysterol₃ ester; the intensity data suggested it was ca. 94%

15 Van de Vliervoet, Westerhof, Keverling-Buisman and Havings, Rec. Trav. chim. Pays-Bas, 75, 1179 (1956).

pure. It did not crystallise per se, but addition of an equal amount of the tachysterol₃ ester caused the separation in over 90% yield of crystals m.p. 90-91.5°. Similar material had previously been obtained from the aldehyde (I) and the racemate of the bromide (II; X = PPh₃⁺ Br⁻). It was not a true complex, since its $[\alpha]_D$ ca. -3° (C₆H₆) was slowly altered by repeated recrystallisation.



The above experiments constitute formal total syntheses of tachysterol₃ and epitachysterol₃, but we naturally wished to synthesise the aldehyde (I) ab initio. This work falls into two parts; first, the synthesis of the ketone (XX); secondly, its transformation into the aldehyde (I). Much previous work was available as precedent for the first part; we chose to start with the readily available¹⁶ diketone (XVI), and have

¹⁶ Newman and Mekler, J. Amer. chem. Soc., **82**, 4039 (1960).

converted it into the acid (XVII), m.p. 165-166°, and thence into the ketone (XVIII) (oxime, m.p. 125.5°). We have still to prepare the optically active forms of the last two compounds, to add the C(17) side-chain, and remove the protecting benzyl group to obtain the alcohol (XIX). This alcohol has 3,5-dinitrobenzoate m.p. 105-106°, $[\alpha]_D + 16.7^\circ$ (CHCl₃); the corresponding ketone (XX), which forms a semicarbazone m.p. 195-197°, $[\alpha]_D + 57.5^\circ$ (CHCl₃) was obtained by oxidation of the acid (XIII; R = OH), the intermediate β-keto-acid losing carbon dioxide.

This allowed the second part of the synthesis to be studied and completed earlier. The ketone (XX) was converted into its dehydro-compound (XXI); the 2,4-dinitrophenylhydrazone had m.p. 176-177°, $[\alpha]_D + 21.9^\circ$ (CHCl₃). The ketone (XXI) readily formed a hydroxymethylene compound (XXII) which on selective catalytic reduction gave the hydroxymethylene ketone (XXIII). When its isopropyl ether was subjected to Dreiding¹⁷ reduction with lithium aluminium hydride it gave the aldehyde (I) in good yield.

Satisfactory analytical figures were obtained for all compounds for which m.p. or $[\alpha]_D$ values are cited above.

¹⁷ Dreiding and Nickel, *ibid.*, 76, 3965 (1954).