Total Synthesis of Precalciferol$_3$

By J. DIXON, P. S. LITTLEWOOD, B. LYTHGOE,* and A. K. SAKSENA
(*Department of Organic Chemistry, The University, Leeds* LS2 9JT)

Summary Precalciferol$_3$ (5) has been obtained by synthesis for the first time, using the route (1) + (2) → (5).

THE precalciferols,[1,2] discovered by Velluz and his colleagues, are among the most interesting of the 9,10-seco-steroids. Thus, precalciferol$_3$ (5), the immediate product of irradiation of 7-dehydrocholesterol, enters into a photochemical equilibrium with tachysterol$_3$ and into a thermal equilibrium with vitamin D$_3$. Its provenance from each of these three sources has a photochemical basis, and hitherto no synthesis of a precalciferol has been realised. We now report a direct chemical synthesis of precalciferol$_3$ by the route (1) + (2) → (5).

We selected this route in the belief that the simplest source of the central *cis*-double bond of precalciferol$_3$ would be the acetylene link of an en-yn-ene (4). Acetylenic routes to model compounds related to the precalciferols have been studied previously.[3] It seems, however, that in the past, en-yn-enes related to (4) have been obtained in a near-homogeneous state only where their structures were so simple that the terminal double bonds, generally introduced by dehydration methods, were unable to find alternative positions to occupy. In the present work, double-bond position was given special attention. The homogeneous en-yne[4] (2) was used as the source of ring A and the acetylene link, so that the position of the ring-A double bond would be unambiguous. It was also clear that generation of the ring-c double bond by dehydration of a tertiary alcohol such as (3; X = H) would probably give mixtures of double-bond isomers in which the $\Delta^{8(14)}$- would predominate over the $\Delta^{8(9)}$-isomer. We therefore took steps to secure the latter by the use of non-dehydrative methods, explored in model experiments.

The bromohydrin (6; X = Br; R = C_8H_{17}), obtained from the bromo-ketone (1; X = Br) and the lithium derivative of 1-ethynyl-2-methylcyclohex-1-ene,[4] gave with zinc and acetic acid the (*ca.* 70% pure) en-yn-ene (7; R = C_8H_{17}). The yield of the bromohydrin was poor, and as this was attributed partly to steric hindrance from the axial bromine atom in (1; X = Br), we studied the effect of an equatorial group in its place. The trimethylsilyl ether of 3β-hydroxycholestan-4-one and the lithium derivative of 1-ethynyl-2-methylcyclohex-1-ene gave the *cis*-diol (8), m.p. 131—133°, in satisfactory yield. Desulphurisation[5] of its thionocarbonate gave the essentially pure en-yn-ene (9), λ_{max} 272 nm (ϵ 21,100), λ_{infl} 257 and 284 nm (ether–ethanol). In applying similar methods to analogues of (8) containing a hydroxy-group in the monocyclic part, this group had to be selectively protected prior to formation of the thionocarbonate; this was accomplished successfully, but unacceptable losses were thereby incurred. A preferable procedure arose from the observation that chloroketones such as (1; X = Cl) gave satisfactory yields in acetylenic condensations (smaller halogen atom?). Thus the analogue of (1; X = Cl) with a 22,23-dihydroergosteryl side-chain gave the chlorohydrin (6; X = Cl; R = C_9H_{19}) in over 65% yield. Reaction[6] with bis(ethylenediamine)-chromium(II) in dimethylformamide gave, in over 65% yield, essentially pure en-yn-ene (7; R = C_9H_{19}), λ_{max} 273·5 and 288·5 nm (ϵ 19,300 and 14,000), λ_{infl} 263 nm (cyclohexane); it showed one vinyl H (τ 4·22 in carbon tetrachloride).

For the synthesis of precalciferol$_3$, the trimethylsilyl ether of the en-yne (2), as the lithium derivative, reacted with the chloro-ketone (1; X = Cl) to give the chlorohydrin (3; X = Cl), m.p. 110·5°. Reaction with bis(ethylenediamine)chromium(II) gave the essentially pure en-yn-ene (4), λ_{max} 271 and 286 nm (ϵ 20,100 and 15,900), λ_{infl} 262 nm (ether). Semihydrogenation with Lindlar's catalyst in light petroleum, followed by chromatographic removal of unchanged en-yn-ene, gave precalciferol$_3$, isolated as the 3,5-dinitrobenzoate, m.p. 97·5—98·5°, $[\alpha]_D^{20}$ + 51·6° (chloroform), identified by comparison with authentic[7] material, m.p. 97·5—98·5°, $[\alpha]_D^{20}$ + 52·5° (chloroform). Its thermal isomerisation[1] in benzene gave vitamin D$_3$ 3,5-dinitrobenzoate, m.p. 129—130°, $[\alpha]_D^{20}$ + 95° (chloroform).

The chloro-ketone (1; X = Cl) used in this work was obtained from 9α-chloro-des-AB-cholestan-8β-ol, m.p. 44—46°, and the overall yield from this chlorohydrin to crystalline precalciferol$_3$ 3,5-dinitrobenzoate was over 25%. In turn, the chlorohydrin was obtained from des-AB-cholestan-8β-ol[8] (10) *via* des-AB-cholest-8-ene (11). The 8β-ol (10) has been obtained[9] by formal total synthesis; experiments on an independent total synthesis of the chloro-ketone (1) will be reported later. The present work constitutes the first total synthesis of precalciferol$_3$, and also the first synthetic route to vitamin D$_3$ by non-photochemical[10] methods.

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[9] H. H. Inhoffen, G. Friedrich, D. Kampe, and O. Berges, *Chem. Ber.*, 1959, **92**, 1772; and earlier papers.
[10] A photochemical route in which the 8β-ol (10) was transformed *via* relay compounds into vitamin D$_3$ (0·1% yield) has been reported by H. H. Inhoffen and his co-workers; see *Chem. Ber.*, 1958, **91**, 2309 and refs.