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FORMATION OF A 3,5-CYCLOCHOLESTAN-6α-yl DERIVATIVE IN A NUCLEOPHILIC SUBSTITUTION REACTION OF CHOLESTEROL[1]

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In extensive earlier studies[2,3,4], the reactions of nucleophilic reagents with cholesterol derivatives, particularly cholesteryl toluene-p-sulphonate, have yielded three types of substitution products, based respectively on (i) cholest-5-en-3β-yl, (ii) cholest-5-en-3α-yl and (iii) 3,5-cyclo-cholest-6β-yl structures. No product based on 3,5-cyclo-cholest-6α-yl has been obtained from such reactions and this has been attributed to the non-availability of an appropriate reaction pathway for its formation[5]. We now report that substitution products based on each of these four structures are formed in the reaction of cholesterol with a mixture of triphenylphosphine (TPP), diethylazodicarboxylate (DEADC) and benzoic acid (PhCOOH), a reagent mixture which on reaction with a variety of other alcohols simply effects substitution of the hydroxyl group by benzoyloxy group with inversion of configuration[6,7,8].

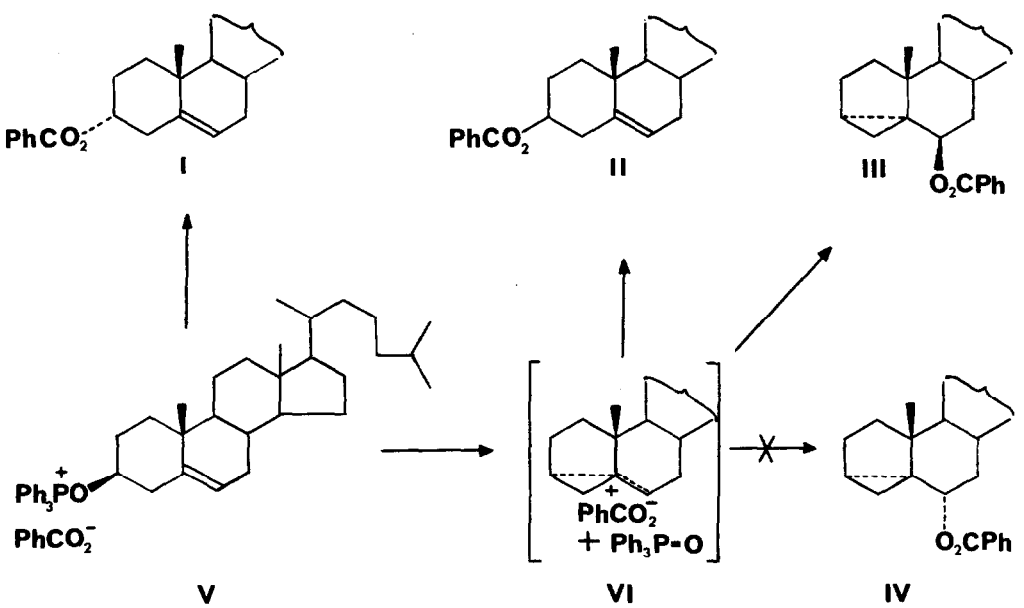
In a typical experiment at 0°, a solution of DEADC (5.3 g) in anhydrous ether (75 ml) was added dropwise to a stirred solution of cholesterol (11.6 g), PhCOOH (3.7 g) and TPP (7.9 g) in anhydrous ether (150 ml). After 3 hr. thin layer chromatography (Kieselgel GF254; hexane-ether, 4:1) revealed the presence of four steroidal benzoates and a hydrocarbon fraction; pure products were isolated by chromatography on Kieselgel (E. Merck) columns and crystallization, and were identified respectively as cholest-5-en-3α-yl benzoate (I) m.p. 101.1° $[\alpha]_D^{22}$ - 38.4°; cholest-5-en-3β-yl benzoate (II) m.p. 146.1° $[\alpha]_D^{22}$ - 13.4°; 3,5-cyclo-cholest-6β-yl benzoate (III)[9], colourless viscous oil, $[\alpha]_D^{22}$ + 53.8° and 3,5-cyclocholest-6α-yl benzoate (IV) m.p. 131.6°, $[\alpha]_D^{22}$ + 83.2°. The relative yields (mole %)

were: I, 11%; II, 20%; III, 23%; IV, 14%; total benzoates 68%. The hydrocarbon fraction was a mixture (1:1) of cholest-3,5-diene and 3,5-cyclocholest-6-ene[10], total yield 19%.

Comparable results were obtained in other solvents (THF, benzene, CH_2Cl_2) or with a different order of addition of reagents. The highest proportional yield (40%) of the 3α-benzoate (I) was obtained in tetrhydrofuran at -60°, but I was not the exclusive product in any experiment[10].

Studies by Brunn and Huisgen[11] and by Mitsunobu and Eguchi[6,7] on the mechanism of the reaction between TPP, DEADC, carboxylic acid and alcohol have shown that an alkoxy triphenylphosphonium salt of the carboxylic acid is an intermediate and that nucleophilic attack by carboxylate ion on this intermediate displaces TPPO with formation of the carboxylic ester of the enantiomeric alcohol. Accordingly, the reaction of cholesterol with this reagent should involve cholesteryl triphenylphosphonium benzoate (V) as an intermediate. Plausible pathways for the formation of some of the products from (V) are given in CHART 1. This shows that concerted displacement of TPPO during nucleophilic attack at C-3 by benzoate ion yields the 3α-benzoate I, whereas reaction with C = C participation leading initially to the Winstein type homoallylic carbocation VI yields the 3β-benzoate II as well as the 3,5-cyclo-

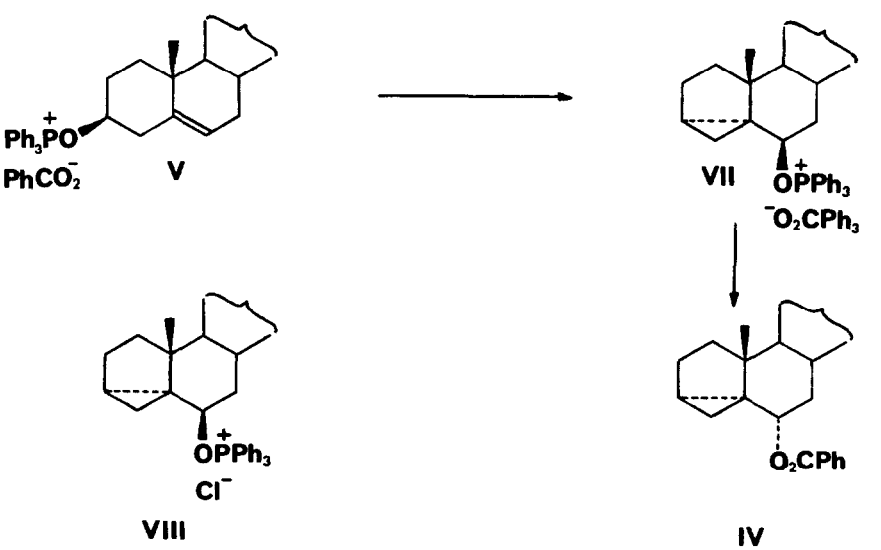
CHART 1



cholestan-6β-yl benzoate III. Since successful attack by nucleophiles at the 6α-position in the carbocation VI is considered to be precluded on stereo-electronic grounds[5], the origin of the fourth product, 3,5-cyclocholestan-6α-yl benzoate IV is a matter for speculation.

We suggest that for the formation of 3,5-cyclocholestan-6α-yl benzoate (IV), the main reaction intermediate, cholesteryl triphenylphosphonium benzoate (V) initially isomerises into i-cholesteryl triphenylphosphonium benzoate (VII), Chart 2. Isomerisation, presumably via the homoallylic carbocation (VI), is followed by nucleophilic attack (S_N2 type) by benzoate ion at the 6α-position in (VII) leading to TPPO and the unusual product IV. This suggestion is based, inter alia, on our experience with the reaction of alcohols with the reagent TPP-CCl_4 which normally effects substitution of OH by Cl with inversion of configuration[12-17]. This reaction is closely related to the alcohol-TPP-DEADC-carboxylic acid reaction in that the putative intermediates and mechanistic course are similar. In an earlier publication[18] we have described the reaction of cholesterol with TPP - CCl_4 reagent. More recently our data suggests that one of the products isolated from this reaction, which is an intermediate for chlorodeoxy derivatives, should be formulated as i-cholesteryl triphenylphosphonium chloride (VIII).

CHART 2



FOOTNOTES AND REFERENCES

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9. Identical (IR, 220 MHz ^{1}H NMR, $[\alpha]_D$) with the product obtained by the reaction of benzoyl chloride (pyridine) with i-cholesterol.

10. In a communication on the reactions of saturated steroidal alcohols, the reaction of cholesterol with benzoic acid, TPP and DEADC has been mentioned briefly and the 3α-benzoate (I) reported as the only product (A.K. Bose, B. Lal, W.A. Hoffman III and M.S. Manhas, Tetrahedron Letters, 1619 (1973). However, Prof. Bose has kindly informed us that the composition of the products depends on the reaction conditions.

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