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ON THE MECHANISM OF THE REACTION OF ALCOHOLS WITH TRIPHENYLPHOSPHINE AND CARBON TETRACHLORIDE REAGENT[1]

R. Aneja*, A.P. Davies and J.A. Knaggs

Lipid Chemistry Group, Unilever Research Laboratory, Colworth/Welwyn

The Frythe, Welwyn, Herts., U.K.

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The reaction of triphenylphosphine (TPP) and carbon tetrachloride reagent with alcohols normally leads to the corresponding chlorodeoxy derivatives of opposite configuration[2-5]. An alkoxy-chloro-triphenylphosphorane is favoured as an intermediate and fragments into triphenylphosphine oxide and alkyl chloride[3,4]. The stereochemical course may be rationalised [6,7] by treating the fragmentation as a $\sigma 2s + \sigma 2a$ thermal pericyclic reaction (orbital symmetry allowed)[8]. However, in a few cases, the reaction takes an abnormal course, i.e. substitution of OH by Cl proceeds with retention of configuration[2,9] or with concomitant skeletal rearrangement[3,7,10]; these are apparently inconsistent with the proposed concerted fragmentation of the reaction intermediate.

Results using cholesterol and i-cholesterol as the substrates are described in this communication; these provide the first experimental proof for the recent suggestions[3,7] that the phosphorane intermediates may undergo skeletal rearrangements prior to fragmentation by the normal concerted pathway.

The reaction of cholesterol (I) with triphenylphosphine (2 molar equivalents) and carbon tetrachloride (excess, solvent) under reflux for 8 hr, or at room temperature for 10 days gave 3-α-chlorocholest-5-ene (II), 3-β-chlorocholest-5-ene (III), cholesta-3, 5-diene (IV), and 3,5-cyclocholest-6-ene (V) in the proportion shown in the TABLE. The room temperature reaction yielded, in addition, a phosphorus-containing sterol derivative, $C_{45}H_{60}ClOP$, m.p. 133-135°; α_D + 80°; 200 MHz PMR τ 2.1 - 2.4 (15H, complex, aromatic), 5.59 (1H, doublet of multiplets, J_{HP} = 15 Hz, HCOP), 7.6 - 9.0 (29H, complex, HC, H_2C), 9.12, 9.15 (9H, 3 x H_3 C-CH), 9.36 (3H, singlet, H_3 C-C), 9.48 (1H, multiplet, cyclopropane CH_2), 9.60 (3H, singlet, H_3 C-C), no signal for vinylic proton; ^{31}P chemical shift ($CDCl_3$ solution, 35°), -21 ppm (vs. H_3PO_4)[11]. On heating in carbon tetrachloride

solution under reflux for 16 hr, this phosphorus-containing sterol yielded 3-β-chloro-cholest-5-ene (III) and 3,5-cyclocholest-6-ene (V) with only a trace amount of cholesta-3, 5-diene (IV). Available evidence suggests structure VI, with contributions from ion-pair equivalents (e.g. VII), for this phosphorus-containing sterol. The stereochemistry shown (VI) is anticipated from its mode of formation (see later) and can be deduced from its PMR spectrum wherein the high chemical shift (τ 9.60) for 19-$\underline{CH_3}$ suggests spatial proximity of this CH_3 and the substituent at C-6.

The reaction of i-cholesterol[12] (VIII) with the reagent (reflux, 18 hr) gave products shown in the TABLE; at room temperature (4 weeks) the phosphorane VI, identical with the intermediate isolated from cholesterol (see above), and a trace amount of 6-α-chloro-3,5-cyclocholestane (IX) were additional products.

For comparison, the reaction of cholesteryl p-toluenesulphonate with lithium chloride in methyl cyanide (reflux, 16 hr) was examined; somewhat surprisingly, it yielded not only 3-β-chlorocholest-5-ene (III) and cholesta-3,5-diene (IV), but also a minor amount of 3-α-chlorocholest-5-ene (II)[13].

By analogy, the phosphoranes X and VI are anticipated as the initial intermediates in the reaction of cholesterol and i-cholesterol respectively. Because only VI is isolated from both sterols, it must be concluded that the fragmentation of X and VI is accompanied by their mutual isomerisation/equilibration such that the least reactive isomer VI accumulates in the system[14]. This isomerisation could occur via an ion-pair such as VII; the stereochemistry of VI then follows from the known preference for approach to C-6 from the β-face of the homoallylic cation in VII[15].

The main pathways leading to substitution products are outlined in the CHART. 3-α-Chlorocholest-5-ene (II) and 6-α-chloro-3,5-cyclocholestane (IX), albeit in low yield, must arise directly from X and VI respectively. Their formation indicates that a pathway is available which can override the normal strong propensity for homoallylic participation and is consistent with fragmentation of the phosphorane by the concerted symmetry allowed $\sigma^-2s + \sigma 2a$ thermal pericyclic process. The presence of the elimination products suggests concomitant release of HCl which conceivably catalyses the elimination reaction and the transformation of IX and possibly II into III. Finally, VII must be regarded as an intimate ion-pair, but its reaction with Cl^- as an additional pathway to III cannot be ruled out.

TABLE: Composition+ of Reaction Products (Mole %)

No.	Reaction	II	III	IV	V	VI	IX
1	Cholesterol + TPP + CCl_4,under reflux	8	28	13	34	-	-
2	Cholesterol + TPP + CCl_4, at 20°	8	26	5	7	34++	-
3	i-Cholesterol + TPP + CCl_4,under reflux	-	30	trace	48	-	-
4	i-Cholesterol + TPP + CCl_4, at 20°	-	24	-	5	16	1
5	VI + CCl_4, under reflux	-	41	trace	29	-	-
6	Cholesteryl p-toluenesulphonate+LiCl in CH_3CN	8	71	18	-	-	-

+ Analyses by column, thin layer and gas liquid chromatography, and by comparison with the literature, using m.p., UV, IR, α_D and PMR (60 and 220 MH_z); correct elemental analyses were obtained for V and VI.

++ yield variable.

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14 Prior isomerisation of cholesterol to i-cholesterol is unlikely, and in any case, in the overall reaction cholesterol reacts faster than i-cholesterol.

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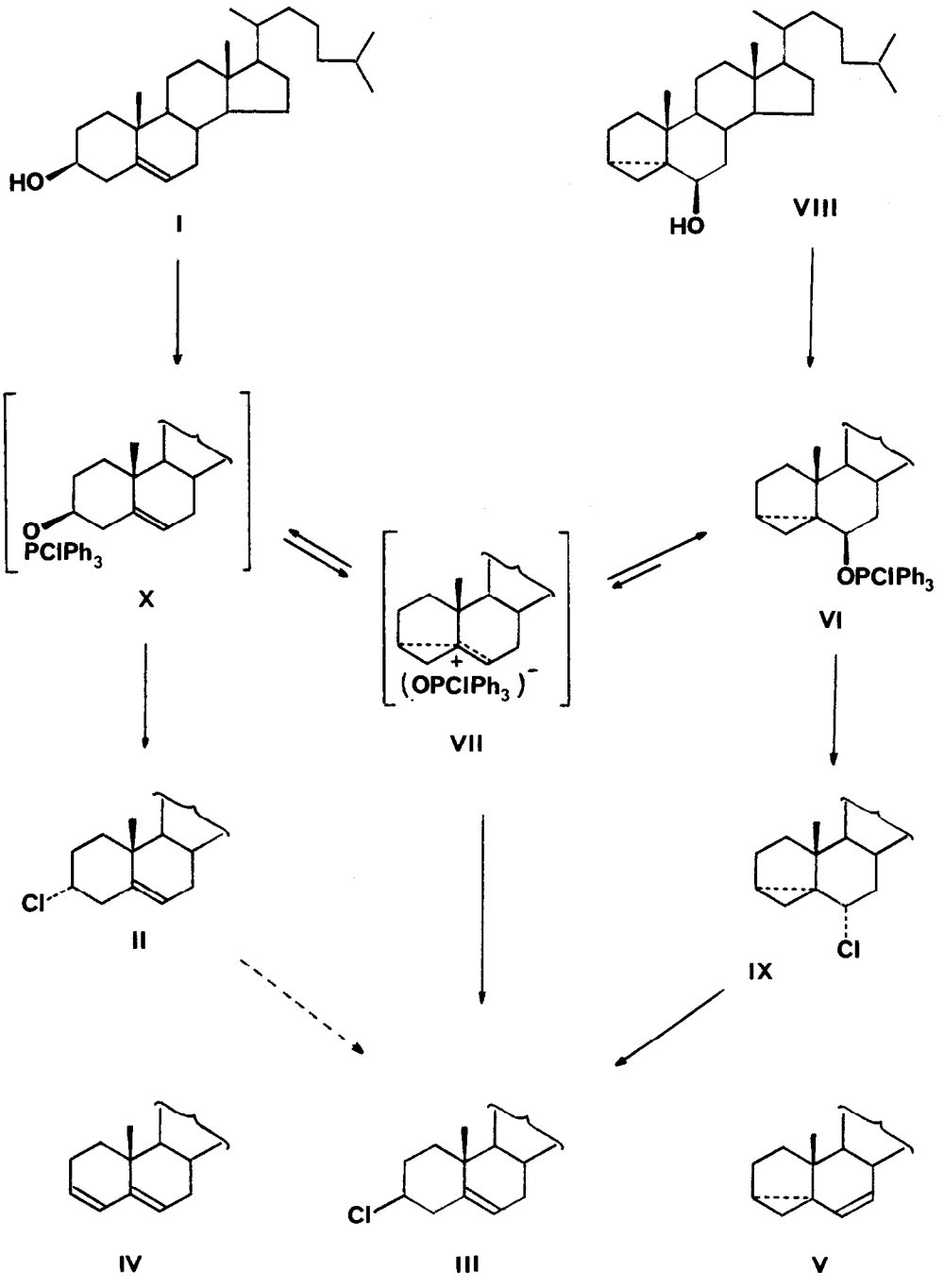
CHART


HO
I
HO
VIII
O
PClPh3
X
(OPClPh3)-
VII
OPClPh3
VI
Cl
II
Cl
IX
IV
Cl
III
V