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EPIMERISATION OF VITAMIN D_3. THE CHOLECALCIFERYL ION

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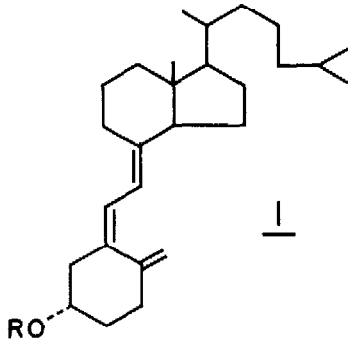
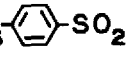
The study of conformational equilibria in vitamin D_3 (cholecalciferol) and related systems necessitated the preparation of their C_3-epimers.[1,2] Although C_3-epivitamin D_3 derivatives had been previously described as intermediates in the partial and total synthesis of vitamin D_3,[3] our objective was their preparation by epimerization of the parent alcohol.

Solvolysis of vitamin D_3 tosylate[4] (1b) in dimethylformamide in the presence of sodium 3,5-dinitrobenzoate gave a mixture which was separated into an unsaturated hydrocarbon (70%), 3,5-dinitrobenzoate (15%), formate (12%) and vitamin D_3 (3%) fractions. The 3,5-dinitrobenzoate fraction ($[\alpha]_D$ + 29° in $CHCl_3$), on basic hydrolysis gave material whose ^{1}H-nmr spectrum was almost superimposable with that of vitamin D_3 (1a).[1,2] The only observable difference in this spectrum was a distortion of the seven line pattern assigned to H at C_3 in vitamin D_3 (1a).[1,2] The fact that this material is a mixture of the C_3-epimeric alcohols 1a and 2a was indicated by the europium induced shifted ^{1}H-nmr spectrum, in which the C_{18}-methyl and H at C_7 showed separate signals for each epimer. The paramagentically less shifted signals were identified as those of 1a and the others were thus assigned to its C_3-epimer 2a.

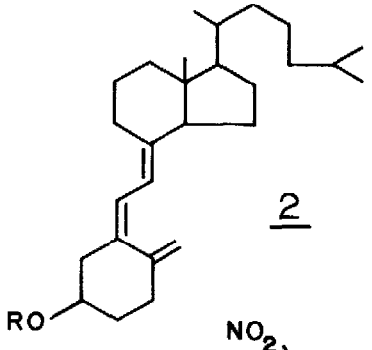


1

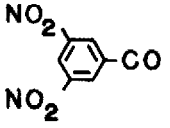
a R = H

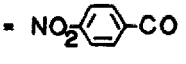
b R = 

c R = HCO



2

d R = 

e R = 

Hydrolysis of the formate fraction gave also a mixture of the C_3-epimeric alcohols 1a and 2a ($[\alpha]_D$ + 40° in C_6H_6), as evidenced from their europium shifted nmr spectrum. A similar mixture of C_3-epimeric formates 1c and 2c (20%) was obtained when the solvolysis of the tosylate 1b was performed in dimethylformamide alone. On the other hand in the presence of sodium p-nitrobenzoate the solvolysis led to the C_3-epimeric mixture of the p-nitroesters 1e and 2e (15%) which according to its $[\alpha]_D$ value (-2.5°, in $CHCl_3$) contained more of the inverted ester 2e. In addition to these, a mixture of C_3-epimeric formates 1c and 2c and an unsaturated hydrocarbon fraction, in similar yield and composition to that obtained before were isolated. Treatment of vitamin D_3 (1a) with triphenylphosphine and diethylazocarboxylate in tetrahydrofuran[5] in the presence of either 3,5-dinitrobenzoic or p-nitrobenzoic acid resulted also in a mixture of the respective esters (ca 25%) 1d and 2d ($[\alpha]_D$ + 1°; $CHCl_3$) or 1e and 2e ($[\alpha]_D$ - 29°, $CHCl_3$). However the more negative rotational values indicated a higher proportion of the C_3-inverted esters than in the respective products from tosylate 1b solvolysis.

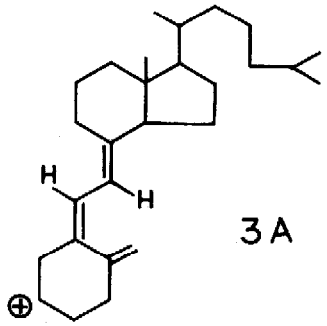
The p-nitrobenzoate ester obtained in the latter reaction was recrystallized from methanol to give the pure C_3-epiester 2e mp 117-118° ($[\alpha]_D$ - 44°, $CHCl_3$, -1°, benzene) the purity of which was established by the europium shifted ^{1}H-nmr spectrum of the hydrolysis product, the C_3-epivitamin, 2a ($[\alpha]_D$ - 45°, $CHCl_3$) lacking the signals of C_{18}-methyl and H at C_7 of vitamin D_3. The ^{1}H-nmr spectrum of 2a was very similar to that of 1a, the H at C_3 appeared also as a seven line pattern, however with a larger coupling constant (J=8.2 Hz instead of J=7.6 Hz).[1,2] This similarity may be explained, considering that the C_3-epimers 1a and 2a exist as a rapidly equilibrating ring A chair conformers having OH - in either axial or equatorial conformation.[1,2] We stipulate[2] that the OH-axial and OH-equatorial conformers of 1a and 2a respectively have identical ^{1}H nmr spectra and the minor differences in the coupling constants of H at C_3 are due to their different population. The larger shifts of C_{18}-methyl and of H- at C_7 in 2a, observed on addition of the shift reagent are consistent with their closer proximity to the europium ion in the OH-axial conformer. Using the $[\alpha]_D$ values for the epivitamin D_3 2a and its esters we have calculated the relative ratios of the C_3-epimeric esters formed in the solvolysis reactions (Table).

The relative high proportion of configurational retention in the solvolysis reactions suggests two independent pathways for the formation of these esters. One - a displacement reaction of a S_N2 character leading mainly to inversion (k_S-type) and the other, an assisted route, leading to a complete retention of configuration (k_D-type).[6] We assume that the latter route involves a homoallylic cation, the cholecalciferyl ion 3. We describe it as having the positive charge unsymmetrically distributed mainly at C_3 and C_6 being thus a resonance hybride of 3A and 3B. The intermediacy of this cation has recently been postulated by us[4,7] to explain the formation of both C_3- and C_6-methylethers[4] on the solvolysis of 1b in methanol.

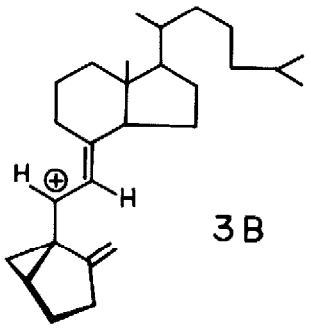
Table. Comparison of percentage of inversion at C_3 in vitamin D_3.

Substance	Nucleophile	Product	$[\alpha]_D$	% Inversion[a]
1b	Na-3,5-dinitrobenzoate + dimethylformamide	1d+2d 1c+2c	$+29^o$ ($CHCl_3$) $+43^o$ (C_6H_6)	41[c] 33[e]
1b	Na-p-nitrobenzoate + dimethylformamide	1e+2e 1c+2c	-2.5^o ($CHCl_3$) $+43^o$ (C_6H_6)	68[d] 33[e]
1b	dimethylformamide	1c+2c	$+45^o$ (C_6H_6)	33[e]
1a[b]	3,5-dinitrobenzoic acid	1d+2d	$+1^o$ ($CHCl_3$)	64[c]
1a[b]	p-nitrobenzoic acid	1e+2e	-29^o ($CHCl_3$)	89[d]

[a]The error in these estimations ca. ±8%. [b]With diethylazocarboxylate and triphenylphosphine in tetrahydrofuran. [c]Calculated using $[\alpha]_D$ + 80° and -44° ($CHCl_3$) for 1d and 2d respectively [d]Calculated using $[\alpha]_D$ + 85° and -44° ($CHCl_3$) for 1e and 2e respectively. [e]Calculated from $[\alpha]_D$ of hydrolyzed product (+40°) using $[\alpha]_D$ + 60° and 0° (C_6H_6) for 1a and 2a respectively.



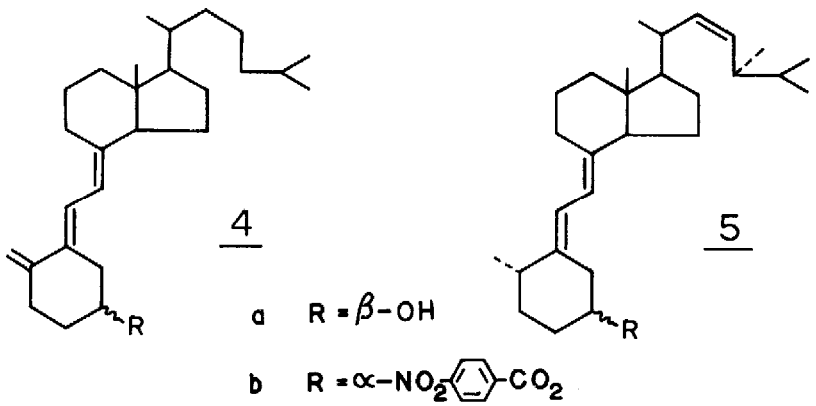
3A



3B

Since the protic solvents favour the formation of a carbonium ion, the solvolysis of 1a in CCl_3CH_2OH - a protic non-nucleophilic solvent, in the presence of either sodium salt of 3,5-dinitrobenzoic or p-nitrobenzoic acids gave a complete retention of configuration at C_3. The purity of the resulting esters 1d, mp 130-131° ($[\alpha]_D$ + 80°, $CHCl_3$) and 1e, mp 124-125° ($[\alpha]_D$ + 85°, $CHCl_3$), was established by the europium induced shifted spectra of their hydrolysis products in which the signals of C_{18}-methyl and H at C_7 of the epivitamin D_3 were absent. Comparison of the solvolysis products of vitamin D_3 triphenylphosphonium p-nitrobenzoate[8] with those of the corresponding cholesteryl derivative reveals a weaker participation of the π-electrons in the former, leading thus to a larger proportion of the C_3 inverted products. The absence of the C_6-esters among the solvolysis products of vitamin D_3 may be explained by the steric inaccessibility of the C_6-position to the comparatively large aryloxy substituents.

Using triphenylphosphine, diethylazocarboxylate and p-nitrobenzoic acid in tetrahydrofuran we have also epimerized transvitamin D_3 (4a) and dihydrotachysterol (5a) to the esters 4b (mp 104-105° $[\alpha]_D$ - 95°, $CHCl_3$) and 5b (mp 100-101°, $[\alpha]_D$ - 141°, $CHCl_3$).



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7. The formula of cyclopropylcarbinyl cation was drawn erronously in Ref. 4. The C_6-H bond should be in antiparallel relationship with C_5-C_{10} and not with C_3-C_5 bond.
8. The reaction of cholesterol with diethylazocarboxylate, triphenyl phosphine and p-nitrobenzoic acid results in a mixture of p-nitrobenzoates, analogous to that reported previously in reaction with benzoic acid (Ref. 5c).