A-NOR STEROIDS. 1. THE STEREOCHEMISTRY OF A 2-CARBOMETHOXY-A-NOR-CHOLESTAN-3-ONE OBTAINED VIA THE DIECKMANN CONDENSATION*

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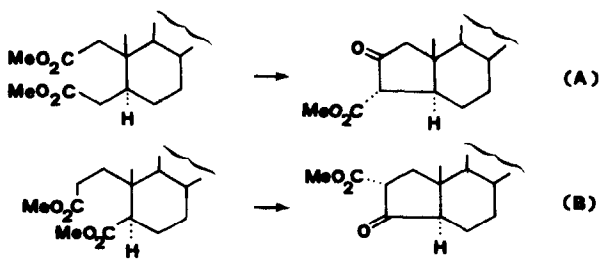
A B S T R A C T

The Dieckmann condensation of dimethyl 3,4-seco-5α-cholestan-3,4-dioate (1), using sodium methoxide in benzene under reflux for two hours, is shown to give 2α-carbomethoxy-A-nor-5α-cholestan-3-one (2). Confirmation of the stereochemistry of the β-keto ester 2 was obtained through its sodium borohydride reduction product, 2α-carbomethoxy-A-nor-5α-cholestan-3β-ol (4).

I N T R O D U C T I O N

It was first reported by Fuchs and Loewenthal (1) that the Dieckmann condensation of dimethyl 2,3-seco-5α-cholestan-2,3-dioate yields a single A-nor β-keto ester, which was assigned the structure of 3β-carbomethoxy-A-nor-5α-cholestan-2-one. A reexamination of the stereochemistry of this ester (2,3) indicated that the carbomethoxyl group has instead the 3α configuration. The Dieckmann condensation was since extended to 2,3-seco diesters of the androstane (4) and the pregnane (3) series, and was shown to yield again the corresponding 3α-carbomethoxy-A-nor-2-ones (Scheme 1,A). We now report the application of the Dieckmann condensation to a 3,4-seco diester of the 5α-cholestane series, which is shown to yield a 2α-carbomethoxy-A-nor-3-one with retention of the 5α configuration (Scheme 1,B).

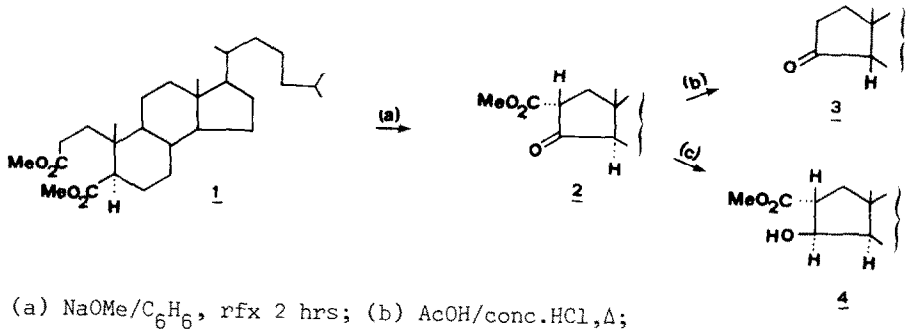
Scheme 1



RESULTS AND DISCUSSION

The dimethyl ester of 3,4-seco-5α-cholestan-3,4-dioic acid (dihydro-Diels' acid) (1), required for the cyclization reaction, was obtained by catalytic hydrogenation of dimethyl 3,4-seco-cholest-5-en-3,4-dioate (Diels' acid dimethyl ester) (5). The Dieckmann condensation was carried out using sodium methoxide in refluxing benzene for two hours. A single β-keto ester was isolated from the reaction in 64% yield and its structure 2 was derived from spectroscopic and chemical data.

The 3-ketone structure of the new β-keto ester was established by hydrolysis and decarboxylation to the known A-nor-5β-cholestan-3-one (3) (1,6). Irrespective of the 5α or 5β configuration of this β-keto ester, the 5β configuration of ketone 3 corresponds to the more stable A/B cis junction (7). Ketone 3 was in fact obtained from both 3,4-seco-5α- and -5β-cholestane-dioic acids on distillation with acetic anhydride (6). It is however known (8,9) that the 5β configuration of ketone 3 should have a considerable deshielding effect on the 19-methyl protons: actually, the 19-methyl singlet of ketone 3 appears at δ 1.10 ppm (10) (1.14 ppm, see experimental) as compared to δ 0.76 ppm for its A/B trans epimer of 5α configuration (11). Since the β-keto ester 2 exhibits likewise a 19-methyl absorption at δ 0.76 ppm and since no difference is observed in the chemical shifts of the 19-methyl protons in the spectra of the methyl esters of both A-nor-5α-cholestan-2α- and -2β-carboxylic acids, δ 0.70 and 0.71 ppm respectively (12), it seems reasonable to conclude that the 5α configuration of the dihydro-Diels' acid was preserved under the stated reaction conditions of the Dieckmann condensation.



(a) $NaOMe/C_6H_6$, rfx 2 hrs; (b) AcOH/conc.HCl,Δ;
(c) $NaBH_4$/MeOH, 48 hrs at r.t.

In agreement with a carbomethoxyl group in position 2 of the cyclopentan-3-one ring of 2, the PMR spectrum of the β-keto ester exhibits a highly deshielded one-proton quartet for the C-2 hydrogen at δ 3.21 ppm. Assuming that a first order analysis for this quartet is valid, the 2-carbomethoxyl configuration should be deduced from a comparison of the observed (apparent) coupling constants with calculated values. Table 1 lists the measured dihedral angles H_2-C-C-H_1 for both the 2α- and 2β-CO_2Me configurations and for a half-chair or an envelope conformation of the cyclopentanone ring A. The corresponding coupling constants were calculated using the modified Karplus equation (13). It is obvious from Table 1 that the observed coupling constants, J = 7.5 and 10 cps, are only consistent with a 2α-CO_2Me configuration and an envelope conformation of ring A.

TABLE 1

Coupling constants calculated for the C-2H of 2

C-2 configuration	Dihedral angle H_2-C-C-H_1	Half-chair conformation angle	J,cps	Envelope conformation angle	J,cps
2β-CO_2Me (2α-H)	2α-H, 1α-H	0°	10	30°	7.5
	2α-H, 1β-H	120°	4	90°	0
2α-CO_2Me(2β-H)	2β-H, 1α-H	120°	4	150°	12
	2β-H, 1β-H	0°	10	30°	7.5

Conclusive evidence supporting the stereochemistry of the β-keto ester 2 was obtained from its sodium borohydride reduction product, the hydroxy ester 4. An intense sharp hydroxyl band at 3630 cm^{-1} and a single carbonyl band at 1738 cm^{-1} in the IR spectrum of this compound in carbon tetrachloride solution strongly suggest (14) a trans relationship between the C-3 hydroxyl and the C-2 ester groups. Moreover, the 19-methyl chemical shift of the hydroxy ester 4 in deuteriochloroform solution, δ 0.97 ppm, is found to be deshielded by 0.21 ppm as compared to the keto ester 2, δ 0.76 ppm; such a deshielding, characteristic of a 1,3-cis relationship between the -OH and the 19-methyl groups (15), is consistent with a 3β configuration of the hydroxyl group. Conse-

quently, the configuration of the carbomethoxyl group should be 2α in both the hydroxy ester 4 and the keto ester 2.

TABLE 2

PMR chemical shifts (in ppm) of compound 4

Signal	$CDCl_3$	C_5D_5N	$\Delta = \delta_{CDCl_3} - \delta_{C_5D_5N}$
19-Me, singlet	0.97	1.23	-0.26
C-2H, multiplet	2.97	3.27	-0.30

The pyridine-induced solvent shifts for the 19-methyl and the C-2 hydrogen of compound 4 (Table 2) confirm their cis stereochemistry relative to the C-3 hydroxyl and hence the configuration of both the carbomethoxyl and hydroxyl groups. Wenkert et al (16) have observed that methyl groups occupying positions 1,3-diaxial to a hydroxyl function experience deshielding effects of the order of 0.20-0.40 ppm in pyridine relative to chloroform. Even in a five-membered ring, as is the case of 5α-androstan-15β-ol, a deshielding of 0.27 ppm was reported (16) for the 18-methyl protons. A similar Δ value (0.26 ppm, Table 2) observed for the 19-methyl group of the analogous cyclopentanol compound 4 supports the 3β configuration of the hydroxyl group. Wenkert et al (16) have also noted that the deshielding of a proton vicinal to a hydroxyl function depends upon the magnitude of the dihedral angle θ between them (as θ decreases in magnitude the Δ value is increased) and that when this angle is approximately 60° a shift of 0.20 - 0.27 ppm to lower field is to be expected. The Δ value of 0.30 ppm (Table 2) observed for the C-2 proton of compound 4 places this proton in a cis relationship to the 3β hydroxyl. The trans relationship between the C-3 hydroxyl and the C-2 ester group is thus confirmed and, consequently, the 2α-CO_2Me configuration of the β-keto ester 2 can now be safely deduced.

Finally, the 3β configuration of the hydroxyl group in compound 4 was indirectly confirmed from a double resonance experiment on the 3α proton signal, a broad multiplet at δ 4.40 ppm. After decoupling the 2β proton at δ 2·97 ppm, the 3α-H signal appeared as a doublet, J=5.5 cps.

Molecular models indicate that this value can only correspond to a cis relationship between the C-3 and C-5 protons (estimated dihedral angle between the 3α and 5α hydrogens is about 35°, calculated coupling constant J = 6.7 cps), since a trans relationship would require a significantly greater coupling constant (estimated dihedral angle between the 3β and 5α hydrogens is about 155°, calculated coupling constant J = 13 cps). It should also be noted that, after decoupling the 3α proton at δ 4.40 ppm, the 2β-H signal of compound 4 at δ 2.97 ppm appeared as a quartet, J = 8 and 10 cps, similar to the quartet of the 2β proton in the keto ester 2.

CONCLUSION

The results concerning the stereochemistry of the β-keto ester 2 indicate that the Dieckmann condensation 1 → 2 proceeds to the more stable α-carbomethoxy configuration, in which 1,3 interaction with the 19-methyl group is avoided. This seems to be a common feature of both the 3-carbomethoxy-A-nor-2-one and 2-carbomethoxy-A-nor-3-one systems in the 5α series (Scheme 1, A and B respectively). Likewise, since borohydride reduction of 3α-carbomethoxy-A-nor-5α-cholestan-2-one (Scheme 1,A) has been shown (2) to give the corresponding 2β-hydroxy compound, a result comparable to the reduction 2 → 4, it seems that in both systems the α side of ring A is the less hindered, allowing easier approach of the hydride to the carbonyl group.

It should finally be emphasized that retention of the 5α configuration during the Dieckmann condensation 1 → 2 was observed only under the defined reaction conditions. The possibility of epimerization at C-5 under more drastic conditions, to give the more stable A/B cis junction, is at present being studied in our laboratory.

EXPERIMENTAL

M.ps were determined in capillary tubes and are uncorrected. IR spectra were obtained with a Perkin Elmer 267 spectrometer as nujol mulls or as 1% solutions in CCl_4. Proton NMR spectra were recorded on a Varian EM-360 spectrometer using solutions of ∿ 50 mg of substance in 0.5 ml of solvent; chemical shifts are given in ppm (δ) downfield from TMS as internal standard and are accurate to ± 0.02 ppm. TLC was performed on silica gel G plates; the eluent was in general chloroform and the spots were observed by exposure to iodine vapors. Elemental analy-

ses were obtained from the microanalytical laboratory of CNRS (France).

Dimethyl 3,4-seco-5α-cholestan-3,4-dioate (1). Two-phase hypobromite oxidation of cholesterol (17) afforded 3,4-seco-cholest-5-en-3,4-dioic acid (Diels' acid). Diels' acid dimethyl ester was obtained from the reaction of its disilver salt with methyl iodide (5). Hydrogenation of Diels' acid dimethyl ester using platinum oxide catalyst in glacial acetic acid (5) afforded the diester 1, mp 124-126° (MeOH); lit. (5), mp 125-126°. $|\alpha|_D^{21°}$ - 11° (c 2.03, Chf); lit. (18), $|\alpha|_D^{21°}$ - 10° (Chf). IR (nujol) 1747, 1740 and 1732 cm^{-1} (ester carbonyls). NMR ($CDCl_3$) 0.65, s, 18-Me; 0.80, s, 19-Me; 0.89 and 0.95, side chain methyls; 3.62 and 3.64, two s, ester methyls.

2α-Carbomethoxy-A-nor-5α-cholestan-3-one (2). Sodium (0.75 g) was added to a mixture of 7 ml of anhydrous methanol and 7 ml of anhydrous benzene under nitrogen. After all of the sodium had reacted, 100 ml of benzene was added and 65 ml of the solvent was distilled using a Dean-Stark apparatus. 1 g of diester 1 was then added and the mixture was stirred and refluxed under nitrogen for 2 hrs. The reaction mixture was cooled and extracted with ether after addition of 5 ml of acetic acid. The ether extracts were washed with water, dried over anhydrous $MgSO_4$ and concentrated under vacuum. The solid residue, 0.98 g, was recrystallized from methanol to give 0.6 g (64%) of a colorless solid, mp 106-108°, which was shown to be homogeneous according to TLC-analysis. Two further recrystallizations from methanol gave an analytically pure sample of compound 2, mp 109-111°, $|\alpha|_D^{20°}$ - 58° (c 2.04, Chf). IR (nujol) 1765 (ketone CO) and 1720 cm^{-1} (ester CO); (CCl_4) 1765 and 1735 cm^{-1}. NMR ($CDCl_3$) 0.67, s, 18-Me; 0.76, s, 19-Me; 0.82 and 0.92, side chain methyls; 3.21, q J=7.5 and 10 cps, 1H, C-2H; 3.72, s, 3H, -COOMe. (Found: C, 77.76; H, 10.77; $C_{28}H_{46}O_3$ requires: C, 78.09; H, 10.77%).

A-Nor-5β-cholestan-3-one (3). The keto ester 2 (0.2 g) was refluxed for 1 hr in 10 ml of acetic acid and 4 ml of conc. HCl. The resulting solution was concentrated under vacuum, water was added to the residue and the mixture was extracted with ether. The ether extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under vacuum. The solid residue, 0.17 g, was recrystallized from methanol to give 0.08 g (46%) of compound 3, mp 74-76°; lit., mp 79-80° (1) and 73-74° (6). $|\alpha|_D^{21°}$ +134° (c 1.94, Chf); lit. (1), $|\alpha|_D$ + 131° (c 1.1, Chf). IR (nujol) 1748 cm^{-1} (ketone CO). NMR ($CDCl_3$) 0.66, s, 18-Me; 1.14, s, 19-Me; 0.80 and 0.90, side chain methyls.

2α-Carbomethoxy-A-nor-5α-cholestan-3β-ol (4). $NaBH_4$ (0.15 g) was added to a solution of 0.25 g of keto ester 2 in 20 ml of methanol and the mixture was stirred at r.t. for 48 hrs. Water (50 ml) was then added, the mixture was extracted with chloroform and the extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under vacuum. The solid residue was submitted to column chromatography over 10 g of neutral alumina (ativity I); elution with hexane-CH_2Cl_2 1:2 afforded 0.20 g of a colorless solid, which was shown to be homogeneous according to TLC-analysis. This was recrystallized from methanol to give 0.11 g (44%) of compound 4, mp 151-152°, $|\alpha|_D^{20°}$ + 15° (c 2.02, Chf). IR (nujol) 3490 (strong sharp band of -OH) and 1722 cm^{-1} (ester CO); (CCl_4) 3630 (strong

sharp band) and 1738 cm^{-1}. NMR ($CDCl_3$) 0.66, s, 18-Me; 0.97, s, 19-Me, 0.80 and 0.90, side chain methyls; 2.97, m, 1H, C-2H; 3.69, s, 3H, -COO-Me; 4.40, br, 1H, C-3H. After decoupling the C-2H at 2.97 ppm, the C-3H signal appears as a doublet, J = 5.5 cps; after decoupling the C-3H at 4.40 ppm, the C-2H signal appears as a quartet, J = 8 and 10 cps. NMR (C_5D_5N) 0.70, s, 18-Me; 1.23, s, 19-Me; 0.86 and 0.95, side chain Mes; 3.27, m, C-2H; 3.64, s, -COOMe. (Found: C, 77.51; H, 11.41; $C_{28}H_{48}O_3$ requires: C, 77.72; H, 11.18%).

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