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ABSTRACT

Some intramolecular cyclisation reactions of bile acid derivatives have been studied. Photolysis of the N-iodo derivative of 5 β -cholan-24-amide leads to the formation of the epimeric 5 β -cholano-24,20 ϵ -lactones. The N-iodo derivative of 3 α -acetoxy-5 β -cholan-24amide reacts similarly. Reaction of 3 α -acetoxy-5 β -cholan-24-ol with lead tetra-acetate and iodine gives the two 3 α -acetoxy-20 ϵ ,24-oxido-5 β -cholanes, two 3 α -acetoxy-22 ϵ -iodo-20 ϵ ,24-oxido-5 β -cholanes, and the two 3 α -acetoxy-21-iodo-20 ϵ ,24-oxido-5 β -cholanes. The two 3 α -acetoxy-20 ϵ ,24-oxido-5 β -cholanes are also obtained when 3 α -acetoxy-5 β -cholan-24-ol reacts with silver oxide and bromine.

Several intramolecular cyclisation reactions have been developed which result in the functionalisation of non-activated carbon atoms (1). Although these reactions have been extensively applied in steroid chemistry (2,3,4) at the time we began our work they had not been applied to bile acid derivatives in which the reactive functional group was at C_{24} . Such reactions would be expected to functionalise

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 C_{20} and we considered it of interest to see if they would provide a useful route to such compounds. Since we began our study Sarel (5,6) has described his work on the intramolecular cyclisation of 5 β -cholan-24-ol (I, R=H). In this paper we describe intramolecular cyclisation reactions of 5 β -cholan-24-amide (II, R=H), 3 α -acetoxy-5 β -cholan-24amide (II, R=AcO), and 3 α -acetoxy-5 β -cholan-24-ol (I, R=AcO).



(I)

(II)

Barton (7) has shown that photolysis of N-iodoamides, prepared <u>in situ</u> by reaction of the amide with lead tetra-acetate and iodine or t-butyl hypochlorite and iodine, provides a general route to γ -lactones. We have investigated the photolysis of a mixture of 5 β -cholan-24-amide (II, R=H), lead tetra-acetate, and iodine in chloroform. This gives a 1:1 mixture of the epimeric 5 β -cholano-24,20 ϵ -lactones (III, R=H) in 25% yield. Attempts to separate the epimers by p.l.c. were unsuccessful. The main evidence for structure (III, R=H) is a band at 1780 cm⁻¹ in the i.r. spectrum, the appearance of the C₂₁ protons as singlets at 1.44 p.p.m.



(III)

and 1.45 p.p.m. in the 'H n.m.r. spectrum, and the presence of a major peak at $^{\rm m}/e$ 99 in the mass spectrum which can be attributed to fragmentation as shown in Scheme I (X=O).



Scheme 1

Both γ -lactones have previously been separately prepared by oxidation of the oxides (IV, R=H) and (V, R=H) and the optical rotation and spectroscopic data we obtained agrees well with those previously reported (5).

A similar cyclisation reaction carried out on 3α -acetoxy-5 β cholan-24-amide (II, R=AcO) gave a 1:1 mixture of the epimeric γ -lactones (III, R=AcO) in 27% yield. Lower yields were obtained when photolyses were carried out using lead tetra-acetate and iodine in benzene (18%) or t-butyl hypochlorite and iodine in benzene (19%).

Sarel has reported (5,6) that reaction of 5 β -cholan-24-ol (I, R=H) with lead tetra-acetate and iodine in carbon disulphide gives the 20 α ,24-oxide (IV, R=H), 20 β ,24-oxide (V, R=H), 22 α -iodo-20 α ,24-oxide (VI, R=H), and 22 β -iodo-20 β ,24-oxide (VII, R=H) each in 20 α yield. We have investigated the cyclisation of 3 α -acetoxy-5 β -





(V)



cholan-24-ol (I, R=AcO). This compound was obtained by selectively reducing the carboxyl group of 3α -acetoxy-5 β -cholan-24-oic acid either by treating the acid with excess diborane in the presence of ethyl acetate (71% yield) or by converting the acid to the acid chloride and treating this with sodium borohydride in diglyme (47%). The alcohol (I, R=AcO) was treated with lead tetra-acetate and iodine under conditions similar to those used by Sarel (5) for alcohol (I, R=H) but our results differ from theirs in that our yields are much lower and that we obtained further products.

The major products were the 20,24-oxides (IV, R=AcO) and (V, R=AcO). The main evidence for these structures is the appearance of the C_{21} protons as singlets at 1.19 and 1.20 p.p.m. in the 'H n.m.r. spectra, and the base peaks at ^m/e 85 in the mass spectra which can be attributed to fragmentation as shown in Scheme 1 (X=H₂). Comparison of the t.l.c. behaviour and optical rotations of our products with those reported

(5) for oxides (IV, R=H) and (V, R=H) suggests that our product m.p. $127-129^{\circ}$ is the 20 α -oxide (IV, R=AcO) (9% yield) and that our product m.p. $116-118^{\circ}$ is the 20 β -oxide (V, R=AcO) (9% yield).

In addition to these products we obtained low yields of four iodo-oxides. Two of these were obtained pure and were fully characterised but the other two were only obtained as a mixture and the assignment of their structures is based entirely on spectroscopic data. One of the pure products was identified as a 22-iodo-20,24oxide (4.5% yield). The structure follows from the mass spectrum in which the base peak was at ^m/e 211, corresponding to fragmentation as shown in Scheme 1, and the 'H n.m.r. spectrum which had the C21 proton signal as a singlet at 1.40 p.p.m. and the C₂₂ proton signal as a multiplet at 3.96 p.p.m. The C₂₄ proton signal occurred at almost the same position as those due to the C_{24} protons in oxides (IV, R=AcO) and (V, R=AcO) indicating that the iodo substituent was not at C22. The minor component of the iodo-oxide mixture was, from the 'H n.m.r. data, probably another 22-iodo-20,24-oxide (0.5% yield). Assuming that these two isomers are the analogues of those obtained by Sarel (6) comparison of the 'H n.m.r., t.l.c., and optical rotation data with theirs suggests that our pure product, m.p. 76-79 $^{\circ}$, was the 22α -iodo- 20α , 24-oxide (VI, R=AcO) and that the product present in the mixture was the 22β -iodo- 20β , 24-oxide (VII, R=AcO).

The other two iodo-oxides we obtained were the epimers of structure (VIII) (3.5 and 1.5% yield). The structure of the pure product follows from the mass spectrum which had the base peak at $^{m}/e$ 211



(IIIV,

and a major peak (65%) at ^m/e 387 corresponding to the fragmentations shown in Scheme 2, and the 'H n.m.r. spectrum in which the C_{21} protons occurred as a two proton singlet at 3.36 p.p.m. The epimer present in the mixture of iodo-oxides had a similar 'H n.m.r. spectrum. With the data available it is not possible to say which is the 20 α - and which the 20 β - isomer.

In an attempt to improve the yields of cyclised products we photolysed a mixture of 3α -acetoxy-5 β -cholan-24-ol (I, R=AcO) and lead tetra-acetate in benzene containing a small amount of pyridine. In some instances these conditions give better yields of cyclised products than those used above (8), but this was not so in the present case: neither oxide (IV, R=AcO) nor (V, R=AcO) were found amongst the products. In some cases high yields of cyclised products have been obtained by treating alcohols with silver oxide and bromine (9). Treatment of 3α -acetoxy-5 β -cholan-24-ol (I, R=AcO) with this reagent gave



^m/e 387

Scheme 2

oxides (IV, R=AcO) and (V, R=AcO), but the yields 10% and 7% respectively, were much the same as those obtained using lead tetra-acetate and iodine.

The mechanisms for the formation of the γ -lactones and unsubstituted oxides are almost certainly analogous to those occurring in similar cyclisation reactions (1,2,4,7). In each case the formation of both C_{20}^- epimers in comparable yields is consistent with a C_{20}^- radical intermediate. Possible mechanisms for the formation of the 22-iodo compounds have been discussed by Kalvoda and Heusler (4). They suggest they are formed by the reaction sequence outlined in Scheme 3. The epimeric 21-iodo-20£,24-oxides (VIII) probably arise similarly via the olefin (IX). The formation of these iodo-oxides in



Scheme 3



comparable yields to iodo-oxides (VI, R=AcO) and (VII, R=AcO) is surprising since $\Delta^{2O(21)}$ olefins are thermodynamically less stable than $\Delta^{2O(22)}$ olefins.

EXPERIMENTAL

M.p.s. were determined with a Kofler hot-stage apparatus. Optical rotations were measured for solutions in chloroform. 'H N.m.r. spectra were recorded at 100 MHz. for <u>ca</u> 10% solutions in deuteriochloroform containing tetramethylsilane as internal reference. Mass spectra were obtained with a Varian-MAT CH7 single-focusing instrument. Only the principal peaks are reported. Irradiations were carried out with the reactants under dry, oxygen-free nitrogen in a Pyrex flask. The flask was partially immersed in a Pyrex dish containing circulating cold water and the lamp, a 125 w Hanovia mediumpressure mercury-arc lamp, was placed beneath the dish. P.l.c. was carried out using plates coated with silica gel (Merck Kieselgel, H_{254}) and ether-petroleum ether mixtures as eluants. Diglyme was distilled from calcium hydride and stored over molecular sieves. Organic solutions were dried with magnesium sulphate.

<u>5β-cholan-24-amide</u> (II, R=H) - Desoxycholic acid was oxidised (88%) using Jones' reagent and the diketo acid obtained reduced (68%) using the procedure of Huang and Minlon (10) (diethylene glycol as solvent) to give 5β-cholan-24-oic acid, m.p. 165-167[°] (lit. (11), 165[°]), $(\alpha)_D^{22} + 23^{\circ}(\underline{c}\ 1.1)$ (lit. (11), $+ 22^{\circ}$). Reaction of the acid with thionyl chloride in refluxing benzene gave the acid chloride and passage of ammonia gas through a solution of the chloride in benzene gave the amide (62% from the acid), m.p. 186-189[°] (acetone) (lit. (12), 189[°]), $(\alpha)_D^{22} + 25^{\circ}(\underline{c}\ 1.3)$ (lit. (12), $+ 28^{\circ}$), ν_{max} (CHCl₃) 3525, 3410, 1679, and 1592 cm⁻¹.

<u>Lactonisation of 5 β -Cholan-24-amide</u> (II, R=H) - A mixture of the amide (2.2g), lead tetra-acetate (9.4g), and iodine (5.0g) in chloro-form (50ml.) was irradiated at 25° for five hours. The reaction was

worked up using the procedure of Barton, Beckwith, and Goosen (7) except that the lactone fraction was not acetylated but was chromatographed over alumina. The eluate was monitored by i.r. spectroscopy and those fractions with v_{max} <u>ca</u>. 1780 cm⁻¹. (γ -lactone) were combined. P.l.c. of these gave a mixture of the 5 β -cholano-24,20 α - and 20 β - lactones (III, R=H) (540 mg., 25\$) needles m.p. 145-181^O (hexane-ether); (α)²²_D + 21^O (<u>c</u> 0.5); v_{max} (CCl₄) 1780 cm⁻¹.; ^m/e 358 (M⁺, 100\$), 343(M⁺-CH₃, 21), and 99(C₅H₇O₂, 75) (Found: C, 80.1: H, 10.5. C₂₄H₃₈O₂ requires C, 80.4; H, 10.6\$). The 'H n.m.r. spectrum had singlets at δ 0.75(18-H of 20 β -isomer), 0.81(18-H of 20 α -isomer), 0.92(19-H of both isomers), and 1.44 and 1.45 p.p.m. (21-H of both isomers). The intensities of the 18-H signals indicated that both isomers were present in equal amounts. T.l.c. analysis indicated the presence of two components of very similar R_f but attempts to separate them using p.l.c. were unsuccessful.

<u>3\alpha-acetoxy-5\beta-cholan-24-amide</u> (II, R=AcO). - Acetylation of lithocholic acid using acetic anhydride and p-toluenesulphonic acid gave 3α-acetoxy-5β-cholan-24-oic acid (85%), m.p. 167-169° (lit. (13), 169°), $(\alpha)_D^{24}$ (<u>c</u> 1.0) + 43°. Reaction of the acetate with oxalyl chloride in benzene at reflux temperature gave the acid chloride and passage of ammonia gas through a solution of the chloride in benzene gave the amide (80%), m.p. 192-194° (chloroform-hexane) (lit. (14), 193-196°), v_{max} (Nujol) 3440, 3180, 1740, 1670, and 1620 cm⁻¹.

Lactonisation of 3α -Acetoxy-5 β -cholan-24-amide (II, R=AcO) (a) Using lead tetra-acetate with chloroform as solvent. A mixture of the amide (3.0g.), lead tetra-acetate (9.4g) and iodine (5.0g.) in chloroform (50ml.) was irradiated at 25° for five hours. The reaction was then worked up using the procedure described by Barton, Beckwith, and Goosen (7). Acetylation of the neutral and/or basic fraction and crystallisation of the product from chloroform-pentane gave starting material (0.45g., 15%). The lactonic fraction was acetylated and the crude product was chromatographed on alumina. Elution with ether-ben-

zene (1:9) gave a mixture of 3α -acetoxy-5 β -cholano-24,20 α - and 20 β lactones (III, R=AcO) (0.70g., 23%, 27% allowing for recovered starting material), m.p. 110-114[°] (pentane-ether); v_{max} (CCl₄) 1780 and 1745 cm⁻¹; ^m/e 416(M⁺, 28%), 356(M⁺-AcOH, 100), 341(M⁺-AcOH and CH₃, 18), and 99(C₅H₇O₂, 96) (Found: C, 74.7; H, 9.6. C₂₆H₄₀O₄ requires C, 75.0; H, 9.7%) The 'H n.m.r. spectrum had singlets at δ 0.74 (18-H of 20 β -isomer), 0.80 (18-H of 20 α -isomer), 0.94 (19-H of both isomers), 1.45 (21-H of both isomers), and 2.03 p.p.m. (acetate methyl). The intensities of the 18-H signals indicated that both isomers were present in equal amounts. Attempts to separate the components by p.1.c. were unsuccessful.

(b) Using lead tetra-acetate with benzene as solvent. - A similar experiment to the above was carried out using benzene as the solvent. The yields of the γ -lactone mixture was 18%.

(c) Using t-butyl hypochlorite. A similar experiment to that in (b) was carried out using t-butyl hypochlorite (15) (1.0g.) in place of lead tetra-acetate. The yield of the γ -lactone mixture was 19%.

 3α -Acetoxy-5 β -cholan-24-ol (I, R=AcO)

(a) <u>Using diborane</u>. - Sodium borohydride (2.4g.) was cautiously added to 3α -acetoxy-5 β -cholan-24-oic acid (8.4g.) in diglyme (40ml.) under nitrogen. Ethyl acetate (40ml.) was added and then boron trifluoride etherate (4.5ml.) in diglyme (5.0ml.) was added drop-wise over 20 mins. Twenty minutes after the addition was complete the mixture was poured onto crushed ice (200g.). The product was extracted with ether and the extracts were repeatedly washed with water to remove diglyme. Evaporation of the dried extracts gave the crude product as an oil. This was dissolved in ether and absorbed onto an alumina column. Elution with ether gave 3α -acetoxy-5 β -cholan-24-ol (I, R=AcO) (5.8g., 71%), m.p. 66-69° (methanol), $\{\alpha\}_D^{2O}$ (<u>c</u> 1.5) + 43°; ν_{max} (CCl₄) 3620 and 1740 cm⁻¹.; δ 0.66 (s, 18-H), 0.93 (m, 19- and 21-H), 2.01 (s, acetate methyl), 3.60 (m, 24-H), and 4.72 p.p.m. (m, 3β -H); ^m/e 404 (M⁺, 3%), 344 (M⁺-60, 100), and 215 (23). (Found C, 77.2; H, 10.95. Calc. for C₂6H₄₄O₃ C, 77.2; H, 10.9%). Elution

with a mixture of methylene chloride and methanol (99:1) gave $3\alpha,24$ -dihydroxy-5 β -cholane (130mg., 2\$), m.p. 180-182°, identified by comparison (mixed m.p., i.r., t.l.c.) with an authentic sample. (b) <u>Using sodium borohydride</u>. - 3α -Acetoxy-5 β -cholan-24-oic acid (6.0g.) was converted into the acid chloride as before and the chloride was dissolved in diglyme (50ml.). Sodium borohydride (4.0g.) in diglyme (50ml.) was added dropwise with stirring at 20° over 0.5h. Two hours later the reaction mixture was added to excess water. Work up as above gave 3α -acetoxy-5 β -cholan-24-ol (I, R=AcO) (2.7g., 47\$) identical with the above product.

Cyclisation of 3α -Acetoxy-5 β -cholan-24-ol (I, R=AcO) using Lead Tetra-acetate.

(a) <u>Under thermal conditions</u>. - The substrate (4.04g.), lead tetraacetate (18g.) and iodine (2.5g.) were dissolved in carbon disulphide (250ml.) and the solution was stirred in the dark under nitrogen for 50 hours at 20° . The solvent was then evaporated and the residue extracted with ether. The extracts were treated with saturated aqueous potassium iodide and the mixture filtered. The ether layer of the filtrate was separated and washed with saturated aqueous potassium iodide, aqueous sodium thiosulphate, and water. The dried ethereal solution was evaporated and the residue subjected to p.l.c. Five main fractions were obtained.

<u>Fraction 1</u>, R_f 0.38, was an epimer of 3α-acetoxy-20ε,24-oxido-5β -cholane (probably V, R=AcO) (370mg., 9%), m.p. 116-118° (hexane), $(\alpha)_D^{2O}$ (<u>c</u> 1.3) + 35°; ν_{max} (CS₂) 1740 and 1048 cm⁻¹; δ 0.70 (s, 18-H), 0.93 (s, 19-H), 1.19 (s, 21-H), 2.02 (s, acetate methyl), 3.72 (m, 24-H), and 4.71 p.p.m. (m, 3β-H); ^m/e 402 (M⁺, 0.4%), 387 (M⁺-15, 11), and 85 (C₅H₉O, 100) (Found C, 77.85; H, 10.5 Calc. for C₂₆H₄₂O₃ C, 77.6; H, 10.5%).

<u>Fraction 2</u>, R_f 0.46, was the second epimer of 3α-acetoxy-20ε,24 -oxido-5β-cholane (probably IV, R=AcO) (36lmg., 9%), m.p. 127-129[°] (hexane), $(\alpha)_D^{2O}$ (<u>c</u> 1.0) + 38[°]; ν_{max} (CS₂) 1740 and 1046 cm⁻¹; δ 0.78 (s, 18-H), 0.93 (s, 19-H), 1.20 (s, 21-H), 2.02 (s, acetate methyl),

3.80 (m, 24-H), and 4.72 p.p.m. (m, 3β-H); $^{m}/e$ 402 (M⁺, 1%), 387 (M⁺-15, 33), and 85 (C₅H₉O, 100) (Found C, 77.8; H, 10.7%).

<u>Fraction 3</u>, R_f 0.72, was an epimer of 3α-acetoxy-21-iodo-20ε, 24-oxido-5β-cholane (VIII) (192mg., 3.5%), m.p. 147-150[°] decomp. (hexane), $(\alpha)_{D}^{20}$ (<u>c</u> 0.8) + 36.5[°]; ν_{max} (CS₂) 1740 cm⁻¹.; δ 0.77 (s, 18-H), 0.93 (s, 19-H), 2.02 (s, acetate methyl), 3.36 (s, 21-H), 3.91 (m, 24-H), and 4.70 p.p.m. (m, 3β-H); ^m/e 528 (M⁺, 0.1%), 387 (M⁺-CH₂I, 65), 211 (C₁H₈IO, 100), 85(80%) and 84 (80%) (Found C, 59.4; H, 7.6. Calc. for C₂₆H₄₁IO₃ C, 59.1; H, 7.8%).

<u>Fraction 4</u>, R_f 0.80, was a stereoisomer of 3α-acetoxy-22ε-iodo -20ε,24-oxido-5β-cholane (probably VI, R=AcO) (237mg., 4.5%), m.p. 76-79° (hexane), $(\alpha)_D^{20}$ (<u>c</u> 0.5) + 32°; ν_{max} (CS₂) 1740 cm⁻¹; δ 0.79 (s, 18-H), 0.93 (s, 19-H), 1.40 (s, 21-H), 2.02 (s, acetate methyl), 2.37 (m, 23-H), 3.74 (m, 24-H), 3.96 (m, 22-H), and <u>ca.</u> 4.7 p.p.m. (m, 3β-H); ^m/e 528 (M⁺, 1.6%), 257 (M⁺-60-C₅H₈IO, 57), 211 (C₅H₈IO, 100), 85 (60%), and 84 (80%) (Found C, 59.45; H, 7.8%).

<u>Fraction 5</u>, R_f 0.58, was an oil (102mg.) which contained two iodo-oxides. It had v_{max} (CS₂) 1740 cm⁻¹.; ^m/e 528 (M⁺, 0.3%), 387 (100), 257 (50), 211 (80), 85 (50), and 84 (51) (Found C, 59.0; H, 7.7%). The major component (75%) was the 21-iodo-20£,24-oxide (1.5%) epimeric with that present in fraction 3. It had δ 0.70 (s, 18-H), 0.92 (s, 19-H), and 3.25 p.p.m. (s, 21-H). The minor component (25%) was probably a 22£-iodo-20£,24-oxide (0.5%) stereoisomeric with that present in fraction 4. It had δ 0.72 (s, 18-H), 0.92 (s, 19-H), and 1.27 (s, 21-H).

(b) <u>Under photolytic conditions</u>. - A mixture of the substrate (1.3g.) and lead tetra-acetate (7.5g.) in benzene (200ml.) containing pyridine (2ml.) was irradiated under nitrogen at 20° . After 2½ hours much starting material remained (t.l.c.). Five and a half hours later the reaction was worked up. The crude product (1.3g.) contained at least six components but, by t.l.c. and 'H n.m.r. spectroscopic analysis, very little (<2%), if any, of the characterised products obtained from the thermal reaction were present.

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Cyclisation of 3α -Acetoxy-5 β -cholan-24-ol (I, R=AcO) using Silver Oxide

This reaction procedure is based on that reported by Mihailovic, Cekovik and Stankovic (9). A mixture of the substrate (600mg.), silver oxide (3.3g., freshly prepared), bromine (0.75ml.), hexane (15ml.), and chloroform (3ml.) was vigorously stirred under nitrogen at 23[°]. After 14 hours t.l.c. analysis indicated that much starting material remained. Sixteen hours later the reaction was worked up in the usual way (9). The crude product, an oil (540mg.), contained at least six components by t.l.c. analysis. P.l.c. gave an oxide (probably V, R=AcO) (40mg., 7%) m.p. 116-118[°], identical by spectral comparison with the product from the lead tetra-acetate cyclisation and an oxide (probably IV, R=AcO) (60mg., 10%), m.p. 127-129[°], identical by spectral comparison with the product obtained from the lead tetra-acetate cyclisation.

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