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A SHORT AND EFFICIENT DEGRADATION OF THE BILE ACID SIDE CHAIN. SOME NOVEL REACTIONS OF SULPHINES AND α-KETOESTERS

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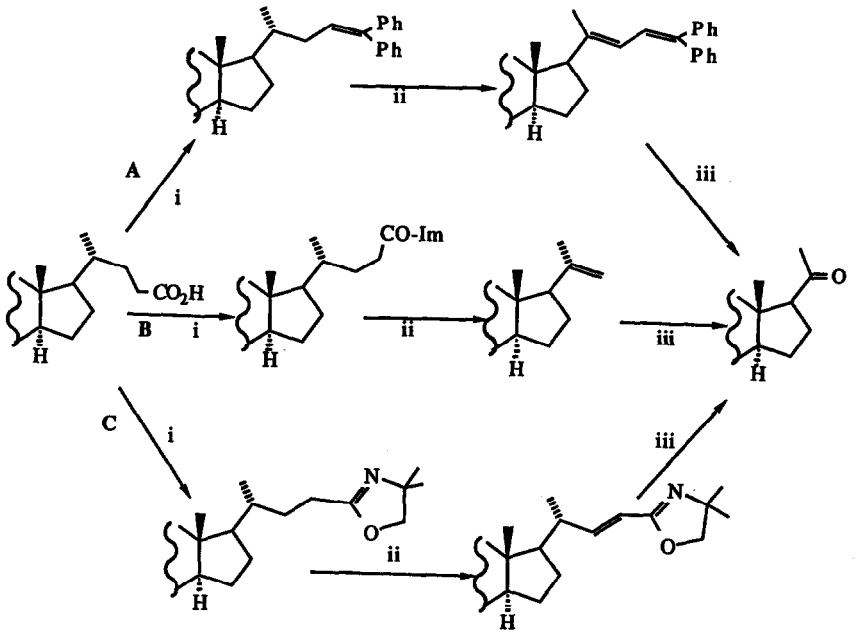
Abstract : 11-Oxo-lithocholic acid acetate 5 is easily converted into the 23-sulphinyl derivative 6 by treatment with thionyl chloride and pyridine followed by addition of methanol. The sulphine group can be cleaved to the 23-ketone 9 in high yield using a variety of oxidising agents such as ozone, sodium hypochlorite, hydrogen peroxide or dinitrogen tetroxide or alternatively by exposure to acetic anhydride-sulphuric acid. With dinitrogen tetroxide, the reaction can be stopped at the oxime 10 stage. Finally aerial oxidation in the presence of an organic base and catalytic amounts of copper (II) salts degraded efficiently the keto-ester 9 into the 20-ketone 19. By operating under mild conditions, the intermediate 22-aldehyde 18 can be isolated in good yield.

Cholic and desoxycholic acids 1 and 2 from ox bile are major raw materials for the commercial production of corticosteroids. They are readily available in large quantities, and the 12-hydroxy group can be used as a handle to introduce the correct functionality in the C-ring of cortisone and its important derivatives.[1] The transformation process is perhaps one of the most complex of the pharmaceutical industry in that some of the more elaborate derivatives require up to forty synthetic steps, each painstakingly developed and optimised.

A key operation in the synthetic sequence concerns the removal of the three extra carbons of the bile acid side-chain in order to arrive at the pregnane skeleton as shown in Scheme 1. The early Barbier-Wieland[2] procedure which cuts away one carbon at a time by an alternation of Grignard additions followed by oxidation steps was soon superseded by the vastly more efficient degradation method of Meystre and Miescher[3] (path A) on which the actual industrial process is based. A number of alternative procedures have since been described in the literature,[4] most being inferior variants of the original sequence. Worthy of note however is a concise and elegant approach using a Norrish type II fragmentation of the imidazolide derivative[4i] (path B). Unfortunately the photochemical step is not easily amenable to scale up.



A: i) MeOH, H^+ ; PhMgCl ; H^+ ; ii) NBS ; Base ; iii) CrO_3

B: i) Carbonyl diimidazole ; ii) hv (u.v.) ; iii) O_3

C: i) $Me_2CNH_2CH_2OH$, boric acid, xylene ; ii) $PhSeO_2H$. iii) $COCl_2$, pyridine ; O_3

Scheme 1

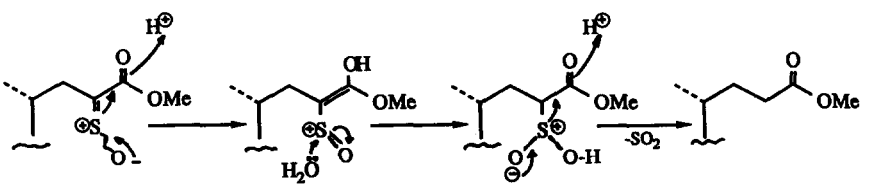
The main drawback of the Meystre-Miescher degradation is the use of relatively expensive (PhMgCl and NBS) or environmentally objectionable (CrO_3) reagents. In the hope of palliating these shortcomings, we produced a first solution to this problem based on the versatile chemistry of 4,5-dihydro-oxazolines[5] (path C). The overall yield is excellent (90%) and the benzeneseleninic acid employed is easily recycled; however, the cost of selenium compelled us to look for a cheaper alternative. We therefore developed an entirely different scheme which seems to comply with the usual industrial requirements of efficiency, cheapness and environmental safety. This work, which was reported as a short communication,[6] is now described in detail.

Our second approach to the degradation of the bile acid side chain has its origin in a somewhat unusual reaction of thionyl chloride. This reagent is well known for its ability to convert acids into acid chlorides.[7] If the starting acid contains enolisable hydrogens and in the presence of pyridine, the reaction goes further than the acid chloride leading to sulphines, chlorosulphenyl chlorides and to compounds derived therefrom. A similar pattern of reactivity is sometimes observed with other easily enolisable carbonyl derivatives.[7] This reaction is generally quite complex with simple substrates and has more or less been neglected as a potentially useful synthetic method.

Researchers at Roussel-Uclaf[8] however noted that in the case of 11-oxo-lithocholic acid formate 3, treatment with thionyl chloride and pyridine resulted, after hydrolysis, in the clean formation of sulphine 4. It appeared to us that if such a sulphine could be easily converted into a keto-ester (e.g. 9), the degradation problem would be much simplified.

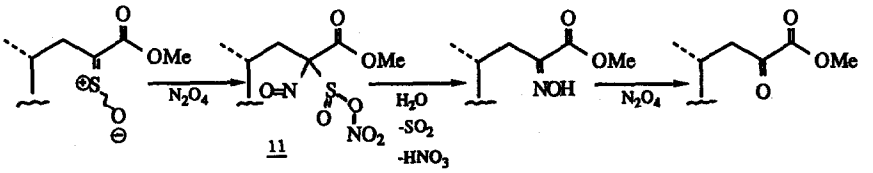
Starting with the corresponding acetate 5, we repeated the thionyl chloride reaction but used a methanolic quench instead of aqueous hydrolysis. The reaction is performed in dichloromethane using 2-3 eq. of thionyl chloride and excess pyridine. Addition of methanol furnished directly the sulphine methyl ester 6 in good yield (78%) along with a small amount of sulphinate 7 (ca. 10%) isolated as a mixture of isomers. Sulphine 6 in contrast was a nice crystalline solid that appeared from its spectroscopic data to consist of only one geometrical isomer; however, no attempt was made to determine its stereochemistry as this was of no consequence to the subsequent steps. Sulphinate 7 could arise from the further but relatively slow reaction of 6 with methanol. Indeed heating the sulphine with methanol and pyridine gave the sulphinate in good yield. After some experimentation we found that neutralising the excess pyridine with anhydrous camphorsulphonic acid prior to the addition of methanol supressed the formation of the undesirable sulphinate and raised the yield of sulphine 6 to 86%.

We next examined the conversion of the sulphine group into a ketone.[9] Photodesulphurisation,[9a] acid hydrolysis[9b] and a number of oxidising agents such as peracids,[9b] singlet oxygen[9c] or ozone[9d] were known to effect this transformation on simpler substrates. In our case, acid hydrolysis simply removed the sulphine group to give ester 8 in excellent yield (97%). Unlike isolated sulphine groups, the presence of the ester function modifies the course of the reaction leading to overall desulphinylation as shown by the putative mechanism displayed in Scheme 2. In contrast, no reaction was observed with common peracids or with hydrogen peroxide under neutral or acidic conditions in a biphasic medium. In a homogeneous tetrahydrofuran solution cleavage of the sulphine group by hydrogen peroxide did take place and afforded keto-ester 9 in 48% yield. The moderate yield is presumably due to further degradation of the keto-ester by the oxidant. Better yields of 9 could be secured by using an alkaline biphasic medium (dichloromethane/5% aq. K_2CO_3/30% H_2O_2; 75% yield) or by employing sodium molybdate and hydrogen peroxide in methanol at 0°C as the oxidising system (85% yield). Other oxidants were tried with mixed sucess. Thus sodium hypochlorite and potassium permanganate gave good yields of ketone (80 and 84% respectively) whereas the yield with sodium chlorite or chromium trioxide was rather poor (47 and 21%).



Scheme 2

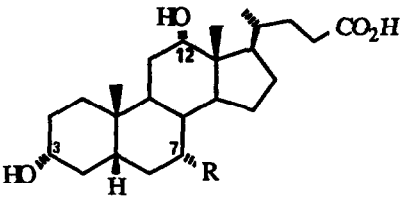
In contrast, ozone turned out to be an excellent reagent for effecting the oxidative cleavage of the sulphine group. The ozonolysis could be performed at 0°C and, following the usual reductive work up, produced keto-ester 9 in 95% yield. Another reagent which gave interesting and usuful reactions is nitrogen tetroxide. Used in excess in carbon tetrachloride, this oxidant smoothly converted the sulphine into a keto group in very high yield (96%). Oxime 10 seems to be an intermediate in this reaction since it could be isolated in 78% yield by exposing the sulphine to only a slight excess of nitrogen tetroxide at the lower temperature of 0°C. These novel transformations may proceed through the mechansim shown in Scheme 3. Thus, nitrosation of the sulphine group leads to an intermediate 11 which can undergo hydrolysis to give the oxime, nitric acid and sulphur dioxide; the latter may be further oxidised to sulfur trioxide under the reaction conditions. Finally, the well known cleavage of oximes[10] through nitrosation furnished the desired keto-ester 9.



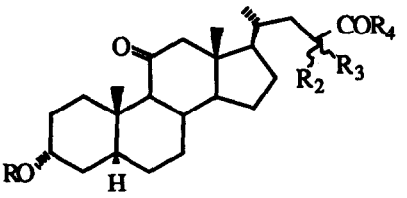
Scheme 3

Other interesting and apparently unprecedented reactions were observed with nitrogen tetroxide and the related nitrosyl chloride. Thus, treatment of the α-sulphinyl acid chloride 12, which is the product of the above thionyl chloride reaction before aqueous or methanolic quench, with excess N_2O_4 gave a mixture of the 24-nor acid 13 (55%) and its corresponding nitrile 14 (42%). The formation of the latter is probably the result of an abnormal Beckman rearrangement. With nitrosyl chloride, the nitrile becomes essentially the exclusive product, isolated in 86% yield. A similar pattern of reactivity obtains (see Table) when starting with the simple acid chloride 15 itself and in the presence of pyridine. In this case, the same intermediates are formed by the electrophilic addition of the nitrosating agent onto the ketene produced by the action of pyridine on the acid chloride. Incidentally, these reactions constitute a simple method for converting a carboxylic acid into the corresponding nor-acid or nitrile.

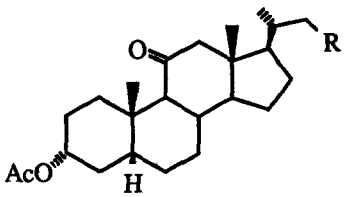
From an industrial standpoint, perhaps the best reagent for cleaving the sulphine group turned out to be acetic anhydride and a small amount of a strong mineral acid. The mechanistic rational behind the use of this system is outlined in Scheme 4. Strong acids are known to enhance considerably the acetylating power of acetic anhydride.[11] In this case, acetylation of the sulphine would lead to intermediate 16 which can undergo a fragmentation reaction to produce the desired ketone 9, sulphur and give back a molecule of acetic anhydride. After some experimentation, we found that acetic anhydride-sulphuric acid in dichloromethane to be quite efficient allowing the obtention of keto-ester 9 in 90% yield after a reaction time of 15 minutes at room temperature.



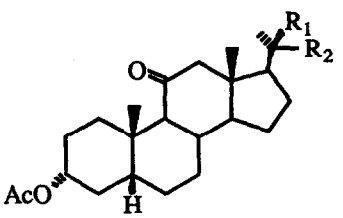
1, R= OH
2, R= H



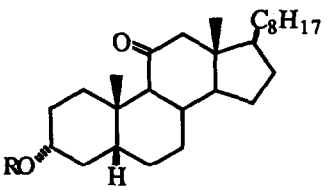
3, R= HCO-; R_2=R_3= H ; R_4= OH
4, R= HCO-; R_2=R_3= S=O ; R_4= OH
5, R= Ac ; R_2=R_3= H ; R_4= OH
6, R= Ac ; R_2=R_3= S=O ; R_4= OMe
7, R= Ac ; R_2= SO_2Me ; R_3= H ; R_4= OMe
8, R= Ac ; R_2=R_3= H ; R_4= OMe
9, R= Ac ; R_2=R_3= O ; R_4= OMe
10, R= Ac ; R_2=R_3= NOH ; R_4= OMe
12, R= Ac ; R_2=R_3= S=O ; R_4= Cl
15, R= Ac ; R_2=R_3= H ; R_4= Cl
20, R= Ac ; R_2=R_3= O ; R_4= β-Cholestanyloxy
24, R= Ac ; R_2=R_3= O ; R_4= Ph_2C=$CHCH_2CH_2O$-



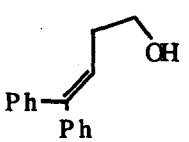
13, R= CO_2H
14, R= CN



18, R_1= H ; R_2= -CHO
19, R_1, R_2= O



21, R= H
22, R= HCO-
23, R= HO_2CCO-



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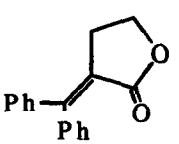

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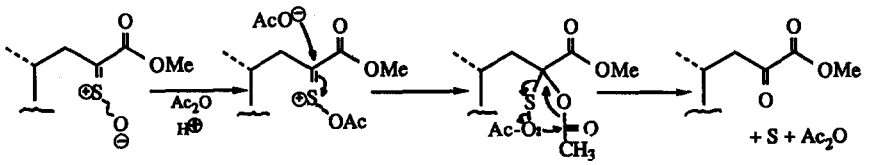
Table

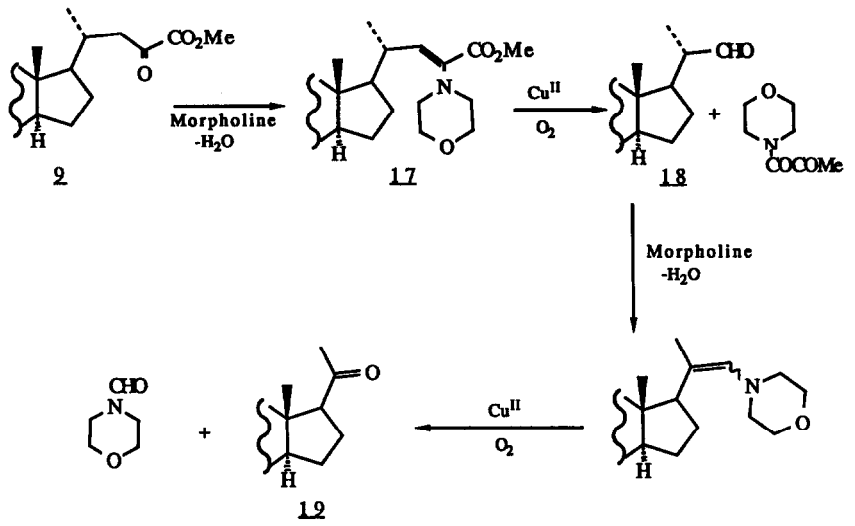
Entry	Starting Material	Reagent (eq.)	Solvent	Reaction Temp. (time)	Products (Yield %)
1	6	N_2O_4 (1.5)	CCl_4	0°C (30 min.)	10 (78)
2	6	N_2O_4 (excess)	CCl_4	20°C (16 h)	9 (96)
3	12	N_2O_4 (10)	CCl_4	20°C (18 h)	13 (55); 14 (42)
4	12	NOCl (10)	CH_2Cl_2	0°C (1.5 h)	14 (86)
5	15	N_2O_4/pyr (8/10)	CH_2Cl_2	0°C (1.5 h)	13 (57); 14 (43)
6	15	NOCl/pyr (8/10)	CH_2Cl_2	20°C (1.7 h)	13 (33); 14 (51)

Although, according to the proposed mechanism, the role of the acetic anhydride should be catalytic, no attempt was made to exploit this in practice. The presence of the sulphuric acid is necessary; acetic anhydride on its own does not induce the reaction even at high temperature.



Scheme 4

Having established several good procedures for the obtention of the key intermediate 9 from sulphine 6, we turned next to the actual degradation process. Some twenty years ago, Van Rheenen[12] reported that the double bond in enamines is easily cleaved by triplet oxygen in the presence of copper salts to give an amide and a carbonyl derivative. In particular, enamines derived from 22-aldehydes yield 20-ketosteroids. It appeared to us therefore that if an enamine of the keto-ester 9 such as 17 was subjected to a similar treatment it should produce the corresponding 22-aldehyde 18 which in turn would lead to the desired 20-ketone 19 as outlined in Scheme 5.



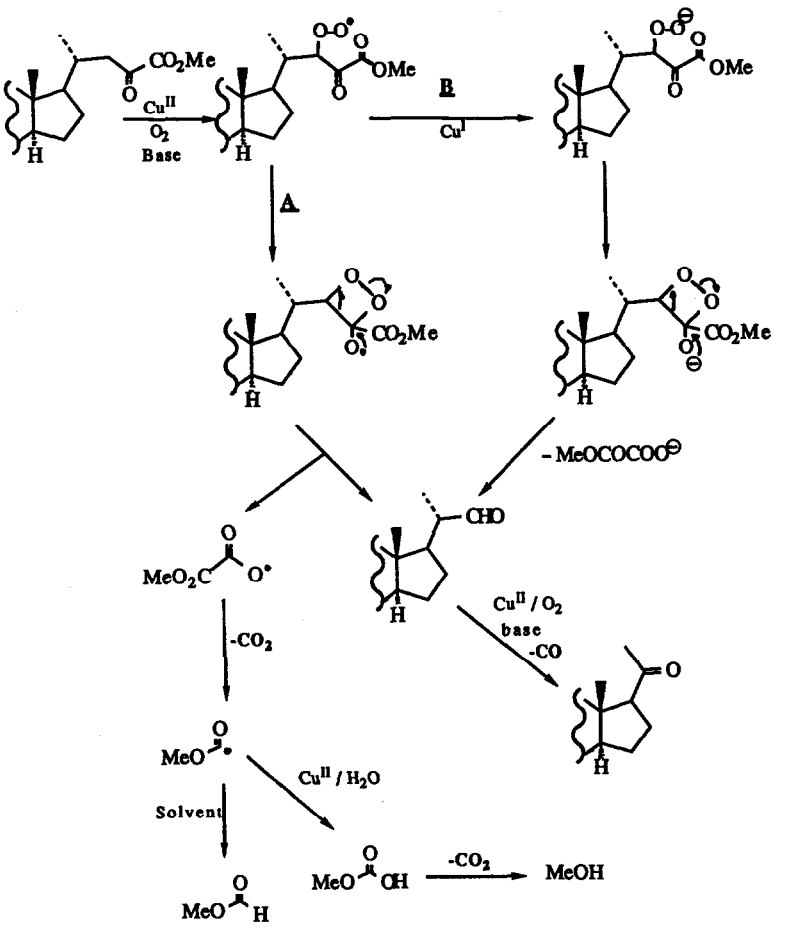
2 17 18 19

Scheme 5

In the event, stirring a solution of 9 in chloroform containing morpholine and cupric chloride under air indeed gave a high yield (85%) of aldehyde 18. However, the degradation did not proceed further even after a prolonged reaction time. This observation casts doubt on the actual intermediacy of the morpholine enamine 17 in this process. The morpholine seems to be acting simply as base since replacing it with N-methyl morpholine or triethylamine did not alter the course of the reaction. The fact that the degradation could be cleanly stopped at the 22-aldehyde stage is extremely useful in view of the importance of such aldehydes for the construction of unusual side-chains present in many naturally occuring steroids.[13]

Clearly, the keto-ester is much more susceptible to reaction with oxygen in the presence of base and copper salts than the ensuing aldehyde, and more vigorous conditions which normally cleave the latter should be sufficient to effect the complete degradation of the side chain all the way to the 20--ketosteroid. Such conditions have again been described by Van Rheenen[14] following some earlier observations made by Brackman[15] and co-workers. Indeed, stirring under air or oxygen, a warm (40°C) solution of keto-ester 9, 1,4-diazabicyclo[2,2,2]octane (DABCO), and a catalytic quantity of cupric acetate-2,2'-bipyridine complex in dimethylformamide for several hours gave the desired ketone 19 in excellent yield (92%). The intermediate aldehyde 18 is rapidly formed and then slowly converted into 20-ketone 19, as monitored by thin layer chromatography or by actual isolation. The degradation is thus achieved in three unoptimised steps from the starting acid 5 in an overall yield of 75-80% using cheap, readily accessible reagents. Furthermore, the sequence can be geared into producing 22-aldehydes, useful as starting materials for the partial synthesis of other more complex steroids.

A number of plausible mechanisms, patterned after those proposed for the degradation of α-hydroperoxy ketones,[16] may be postulated for the reaction of the keto-ester 9 with oxygen in the presence of base and copper (II) salts. For example, as shown in Scheme 6, path A, the hydroperoxy radical obtained by oxidation of the enolate and reaction with triplet oxygen can cyclise to a dioxetane intermediate which can then collapse to the aldehyde and an oxalate radical; decarboxylation followed by either hydrogen abstraction from the solvent or oxidation by copper II would finally give methyl formate or methanol. Overall, one or two molecules of carbon dioxide should be generated depending on the fate of the putative methoxycarbonyl radical.



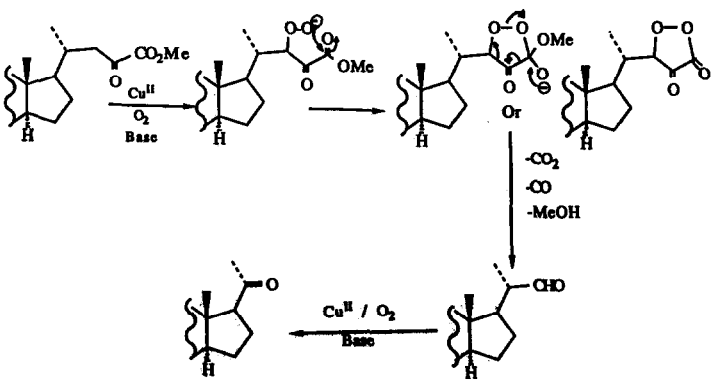
Scheme 6

The ionic version arises (path B) if the hydroperoxy radical is first reduced by copper (I) to the hydroperoxide anion before cyclisation. In this case, besides the aldehyde, one molecule of hemioxalate is also produced.

In order to trace the fate of the ketone and ester groups, the small methyl ester was replaced by the heavier cholestanyl derivative 20. Following the usual oxidative degradation, cholestanol 21 was isolated in quantitative yield. Moreover, cholestanyl formate 22 and hemioxalate 23 were prepared and found to be totally unaffected by the reaction conditions. These observations are neither compatible with pathway B which predicts the formation of a hemioxalate nor with a hydrogen abstraction leading to formate. To check for the presence of an alkoxy carbonyl intermediate, we next prepared ester 24 derived from 4,4-diphenyl-3-butenol 25 and degraded it as before. Again, only alcohol 25 was recovered; no cyclised products such as 26 expected from the addition of the alkoxy carbonyl radical[17] to the olefinic bond followed by oxidation of the intermediate carbon radical by Cu^{II}[18] were observed. These results seem to rule out paths A and B of Scheme 6.

A final proof against either of these mechanistic routes was obtained by quantitatively analysing the amount of carbon dioxide and monoxide, if any, generated in the process. The latter was first oxidised to the dioxide by passing it over hot iodine pentoxide before converting it into the insoluble barium carbonate.[19] In the event, degradation of keto-ester 9 to ketone 19 produced one mole of CO_2 and two moles of CO. Earlier work by Van Rheenen[14] demonstrated the formation of one mole of carbon monoxide on cleavage of 22-aldehydes under these conditions. The conversion of 9 into 18 must therefore involve the formation of one mole each of CO_2 and CO, thus ruling out completely both pathways in Scheme 5 since neither invokes the co-production of carbon monoxide.

One possible mechanism that is in accord with all our experimental observations is expressed in Scheme 7. Cyclisation of the hydroperoxide group takes place on the ester carbonyl to give intermediate 27 which can either fragment directly to the aldehyde, alcohol and one mole each of carbon dioxide and monoxide or, alternatively, proceed to the α-keto-γ-perlactone before finally collapsing. Such α-ketoperlactones have been implicated by Kagan and Mayers[20] in the thermal autoxidation of ethyl 3-phenyl-2-oxobutanoate who proposed a similar mode of fragmentation.



Scheme 7

Experimental

Melting points are uncorrected. Unless otherwise stated, NMR data (60 MHz) are for deuterochloroform solutions with tetramethylsilane as internal standard. I.R. spectra are of dichloromethane solutions unless stated to the contrary. Specific rotations were measured using chloroform solutions (C=1). Usual workup consisted in washing the organic phase with water until neutrality then with saturated brine followed by drying over sodium sulphate and evaporation under reduced pressure. 3_{α}-Hydroxy-11-oxo-cholanic acid was generously supplied by Roussel-Uclaf.

Methyl 3_{α}-acetoxy-11-oxo-23-sulphinyl cholanate 6

Freshly distilled thionyl chloride (0.074 ml, 1.02 mmole) was added dropwise to a solution of 3_{α}-acetoxy-11-oxo-cholanic acid 5 (200 mg, 0.463 mmole) and pyridine (0.37 ml, 4.63 mmoles) in dry dichloromethane (2 ml) cooled to 10-12°C. The resulting solution was then stirred at room temperature for 30 min., cooled to 0°C and treated with excess methanol (1 ml). After stirring for 10 min., the mixture was poured into dilute HCl (0.5N) and extracted with dichloromethane. Following the usual workup, the residue was purified by chromatography on silica using ethylacetate-hexane (1:4) to give sulphine 6 (164 mg, 72%); m.p. 190-191°C (ethyl acetate-hexane); $[\alpha]_D$ + 8°; λ_{max} (methanol): 288 nm (log ϵ: 3.07); ν_{max}: 1730, 1700, 1100, 1020 cm^{-1}; δ_H: 4.70 (1H, broad), 3.86 (3H, s), 2.04 (3H, s), 1.07 (3H, s), 0.63 (3H, s); m/z: 492 (M^+). (Found: C, 66.04; H, 8.29; S, 6.31; Calc. for $C_{27}H_{40}O_6S$: C, 65.82; H, 8.18; S, 6.51%).

A small amount of methyl sulphinate 7 (44 mg, 18%) was also isolated. This compound was recrystallised from methanol; m.p. 115-117°C; $[\alpha]_D$ + 73°; ν_{max}: 1720, 1700, 1120 cm^{-1}; δ_H (200 MHz): 4.75 (1H, broad), 3.82 and 3.78 (6H, 2s), 2.03 (3H, s), 1.15 (3H, s), 0.62 (3H, s); m/z: 524 (M^+), 493, 464. (Found: C, 64.26; H, 8.75; S, 5.84; Calc. for $C_{28}H_{44}O_7S$: C, 64.09; H, 8.45; S, 6.11%). This compound could also be obtained by heating sulphine 6 (200 mg) in dry methanol (5 ml) containing a little pyridine (0.3 ml) for 3 hours under argon. Acidification with dilute HCl and extraction with dichloromethane followed by the usual workup gave methylsulphinate 7 (136 mg, 64%).

Improved Procedure for Preparing Sulphine 6

To a solution of acid 5 (1.12 g) in dichloromethane (11 ml) and pyridine (2.1 ml) cooled to 10-12°C was added dropwise freshly distilled thionyl chloride (0.42 ml). After stirring at room temperature for 0.5 hours, the solution was cooled to 0°C, treated portionwise with anhydrous camphorsulphonic acid (3.62 g), then allowed to warm to room temperature before addition of anhydrous methanol (4 ml). Concentration of the mixture under vacuum and chromatography of the residue gave pure sulphine 6 (1.1 g, 86%).

Methyl 3_{α}-Acetoxy-11-oxo-cholanate 8

A solution of sulphine 6 (200 mg) in 90% alcohol (15 ml) containing HCl (0.6 g) was kept at room temperature for 8 hours. After partial concentration, the residue was extracted with dichloromethane followed by the usual workup to give the known ester 8 (176 mg, 97%); m.p. 129-130°C (lit.[21] 132-134°C).

Methyl 3_{α}-acetoxy-11,23-dioxocholanate 9

A) Via ozonolysis. Excess ozone was passed through an ice-cold solution of sulphine 6 (250 mg) in dichloromethane (4 ml) and methanol (1 ml). Dimethyl sulphide (0.1 ml) was added and the solvents evaporated under reduced pressure. Chromatography of the residue (ethyl acetate-hexane 1:1) gave the pure keto-ester 9 (222 mg, 95%); m.p. 117-118°C; $[\alpha]_D$ + 72°; ν_{max}: 1720, 1700, 1690 cm^{-1}; δ_H: 4.67 (1H, broad), 3.81 (3H, s), 1.98 (3H, s), 1.15 (3Hs, s),

0.64 (3H, s); m/z: 460 (M^+), 400, 385, 373. (Found: C, 70.69; H, 8.85; Calc. for $C_{27}H_{40}O_6$: C, 70.40; H, 8.85%).

B) Via oxidation with hydrogen peroxide/K_2CO_3. A solution of sulphine 6 (113 mg) in dichloromethane (5 ml) was treated successively with 30% H_2O_2 (1 ml) and 5% aqueous K_2CO_3 (1 ml). The resulting mixture was stirred at room temperature for 24 hours and subjected to the usual workup procedure. Purification of the residue as above afforded keto-ester 9 (79 mg, 75%).

C) Via oxidation with hydrogen peroxide/sodium molybdate. To an ice-cold solution of sulphine 6 (203 mg) in methanol (2 ml) and dichloromethane (0.5 ml) was added sodium molybdate (106 mg), 30% H_2O_2 (0.8 ml) and water (1.6 ml). The resulting mixture was stirred at 0°C for 36 hours, diluted with water and extracted with dichloromethane. Usual workup and purification gave keto-ester 9 (160 mg, 85%).

D) Via oxidation with sodium hypochlorite. A mixture of sulphine 6 (100 mg) in dichloromethane (2 ml) and 4N sodium hypochlorite (0.2 ml) was stirred at room temperature for 2.5 hours then cooled in ice and treated with excess sodium metabisulphite. Dilution with water (10 ml) followed by the usual workup and chromatography furnished keto-ester 9 (75 mg, 80%).

E) Via oxidation with potassium permanganate. A mixture of sulphine 6 (246 mg) in dichloromethane (5 ml) and potassium permanganate (160 mg) in water (5 ml) was stirred at room temperature for 3 hours then diluted with water and extracted with dichloromethane. Normal workup and chromatography gave keto-ester 9 (193 mg, 84%).

F) Via oxidation with dinitrogen tetroxide. Nitrogen tetroxide gas was passed through a solution of sulphine 6 (70 mg) in carbon tetrachloride (3 ml) for 1 min. The dark green solution was kept for 16 hours at room temperature then poured into an aqueous urea solution and extracted with dichloromethane. Normal workup and chromatography gave keto-ester 9 (63 mg, 96%).

G) Via treatment with acetic anhydride-sulphuric acid. Acetic anhydride (1.15 ml) and 95% sulphuric acid (0.035 ml) were dissolved in dichloromethane (8.8 ml) and the sulphine (300 mg) was treated with 1 ml of this solution. After stirring for 15 min. at room temperature, the mixture was diluted with dichloromethane (10 ml) and 5% aqueous potassium carbonate (5%). Further stirring overnight followed by the usual workup and chromatography afforded keto-ester 9 (253 mg, 90%).

Methyl 3α-acetoxy-11-oxo-23-oximinocholanate 10

A solution of nitrogen tetroxide (350 mg) in carbon tetrachloride (22 ml) was prepared and cooled to 0°C. A measured volume (1.2 ml) of this solution was then added dropwise to an ice-cold solution of sulphine 6 (68 mg) in carbon tetrachloride (3 ml). After 30 min. at 0°C, the mixture was poured into an aqueous urea solution and extracted with dichloromethane. Normal workup and chromatography on silica of the residue using a mixture of ethyl acetate-hexane (1:1) gave oxime 10 (55 mg, 78%); m.p. 240-245°C (ethyl acetate-dichloromethane); $[\alpha]_D$ + 5°; ν_{max}: 1720, 1695 cm^{-1}; δ_H: 8.75 (1H, broad), 4.65 (1H, broad), 3.80 (3H, s), 2.00 (3H, s), 1.4 (3H, s), 0.62 (3H, s); m/z: 475 (M^+), 457, 415.

3α-Acetoxy-11-oxo-23 nor-cholanenitrile 14

To a solution of 3α-acetoxy-11-oxo-cholanic acid (270 mg) and pyridine (0.5 ml) in dichloromethane (2.5 ml) cooled to 10°C was added slowly thionyl chloride (0.1 ml). The mixture was allowed to warm to ca. 20°C and kept at this temperature for 30 min. The resulting mixture was then cooled to 0°C and treated dropwise with a solution of nitrosyl chloride (0.4 g) in dichloromethane (2.5 ml). After stirring at 0°C for 1.5 hours, the

solvents were evaporated in vacuo and the residue purified by chromatography on silica using ethyl acetate-hexane (1:1) to give nitrile 14 (214 mg, 86%); m.p. 196-198°C (methanol); $[\alpha]_D$ + 73°; ν_{max} (nujol): 2040, 1730, 1710 cm^{-1}; δ_H: 4.7 (1H, broad), 2.02 (3H, s), 1.17 (3H, s), 0.63 (3H, s); m/z: 399 (M^+), 339. (Found: C, 74.95; H, 9.17; N, 3.59; Calc. for $C_{25}H_{37}NO_3$: C, 75.15; H, 9.33; N, 3.51%).

3α-Acetoxy-11-oxo-5β-pregnane-20-carbaldehyde 18

A mixture of keto-ester 9 (211 mg), cuprous chloride (30 mg) and morpholine (0.16 ml) in chloroform (5 ml) was stirred under air for 15 hours. Evaporation and chromatography of the residue on silica using ethyl acetate:hexane (1:1) gave the known aldehyde 18 as a white solid (151 mg, 85%) which was recrystallised from dichloromethane; m.p. 197-200°C (lit.[22] 194°C).

3α-Acetoxy-5β-pregnane-11,20-dione 19

A mixture of keto-ester 9 (72 mg), DABCO (8.5 mg), cupric acetate (3 mg) and 2,2'-dipyridyl (3 mg) in dimethylformamide (5 ml) was stirred for 12 hours at 40°C under air. The solvent was removed in vacuo and the residue purified by chromatography on silica using ethyl acetate-hexane (1:1) to give ketone 19 (54 mg, 92%); m.p. 130°C (ether-pentane); $[\alpha]_D$ + 125° (lit.[23] m.p. 129-130°C; $[\alpha]_D$ = 130±2°).

(3β-Cholestanyl) 3α-acetoxy-11,23-dioxocholanate 20

A solution of 3α-acetoxy-11-oxocholanic acid 5 (600 mg) and pyridine (1.1 ml) in dichloromethane (6 ml) was treated with thionyl chloride (0.22 ml) as above. The solution was then cooled to 0°C, treated portionwise with anhydrous camphorsulphonic acid (1.9 g) and allowed to warm to room temperature. Cholestanol (1.1 g) was added and, after 20 min. at room temperature, the mixture was heated to reflux for 2.5 hours, cooled, poured into ice-water (50 ml), and extracted with dichloromethane. After the usual workup, the residue was dissolved in dichloromethane (10 ml) and ozone was passed through the cooled (-78°C) solution for a few minutes. The resulting ozonides were reduced with dimethyl sulphide (0.3 ml) and the solvent evaporated under reduced pressure. Purification of the residue by chromatography on silica afforded the pure keto-ester 20 (636 mg, 56%) as a white crystalline solid; m.p.: 196-198°C (ethanol); $[\alpha]_D$ + 43°; ν_{max} (nujol): 1745, 1725, 1705 cm^{-1}; δ_H: 4.7 (2H, broad), 2.0 (3H, s), 1.2 (6H, s), 0.68 (6H, s); m/z: 816 (M^+), 802, 773, 756. (Found: C, 77.52; H, 10.41; Calc. for $C_{53}H_{84}O_6$: C, 77.89; H, 10.36%).

Oxidative Degradation of keto-ester 20

A solution of keto-ester 20 (335 mg), DABCO (23 mg), and a mixture of cupric acetate and 2,2'-dipyridyl (1:1 W/W; 15 mg) in dimethyl formamide (5 ml) was stirred for 3 days at 40°C under air. Evaporation of the solvent and purification of the residue by chromatography on silica using ethyl acetate-hexane (1:1) gave ketone 19 (109 mg, 72%) and cholestanol 21 (160 mg, 100%) identical with authentic material.

(4,4-Diphenyl-3-butenyl-)3α-acetoxy-11,23-dioxocholanate 24

A solution of 3α-acetoxy-11-oxocholanic acid 5 (2.4 g) and pyridine (4.5 ml) in dichloromethane (25 ml) was treated with thionyl chloride (0.9 ml) as before. 1,1-Diphenyl-1,4-butanediol[24] (3.36 g) was added and the resulting mixture heated to reflux for one hour. After cooling, it was poured into excess dilute (0.5N) HCl and extracted with dichloromethane. Normal workup afforded the crude intermediate sulphine which was dissolved in a solution of acetic anhydride and sulphuric acid in dichloromethane (8.3 ml of the same mixture used for cleaving sulphine 9 above). Stirring was continued at room temperature for 45 min. Workup gave a residue which was taken up in dichloromethane (15

ml) and treated with 5% aqueous potassium carbonate (15 ml) and 30% hydrogen peroxide (15 ml). The resulting mixture was vigorously stirred at room temperature for 2-5 hours, the organic phase separated, dried over sodium sulphate and concentrated in vacuo. Chromatography of the residue on silica using ethyl acetate-hexane (1:1) gave keto-ester 24 (1.31 g, 36%); m.p. 79°C (dichloromethane-pentane); $[\alpha]_D$ + 28° (c = 1.8); ν_{max}: 1730, 1700 cm^{-1}; δ_H: 7.05 (10H, bs), 5.9 (1H, t, J=3 Hz), 4.6 (1H, broad), 1.15 (3H, s), 0.63 (3H, s); m/z: 652 (M^+), 592, 517. (Found: C, 77.27; H, 8.03; Calc. for $C_{42}H_{52}O_6$: C, 77.34; H, 7.89%).

Oxidative degradation of keto-ester 24

A solution of keto-ester 24 (200 mg), DABCO (17 mg), cupric acetate (6 mg), and 2,2'-dipyridyl (6 mg) in dimethylformamide was stirred at 40°C under an atmosphere of oxygen for 3 days. Evaporation of the solvent under reduced pressure and chromatography of the residue on silica using ethyl acetate-hexane (1:4) gave 20-keto steroid 19 (86 mg, 74%) and a liquid identified as the known[24] 4,4-diphenyl-3-buten-1-ol 25 (53 mg, 76%); ν_{max} (neat): 3350, 1600, 1500 cm^{-1}; m/z: 224 (M^+), 193; δ_H: 7.12 (10H, bs), 6.0 (1H, t, J=3.5 Hz), 3.66 (2H, t, J=3 Hz), 2.36 (2H, q, J=3.5 Hz).

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