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A CONVENIENT NEW PROCEDURE FOR THE OXIDATIVE CLEAVAGE OF THE BILE ACID AND LANOSTEROL SIDE CHAINS

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Abstract—A new method for the degradation of the side chain of lanosterol and bile acids is described. The cleavage was brought about by the action of molecular oxygen on basic solutions of the phenyl ketones (**1**, **7**, and **15**). Thus, the side chains were reduced by two C atoms, leading to the 23,24-bisnor series in appreciable yields. A method for converting the bisnor compounds to 20-ketosteroids is also described. The results obtained indicated that the nature of the degradation products was dependent upon the acidity of the α-hydrogen, the basic strength of the reaction medium and the nature of the solvent. A brief discussion of the mechanism is included.

THE base catalysed oxidation of simple enolisable ketones by molecular oxygen has already been described.[3] The principal products obtained from this reaction are carbonyl compounds and acids resulting from the cleavage of the chain at the junction of the carbonyl group of the parent ketone and the α-carbon. In the presence of an excess of oxygen the primary cleavage products could undergo further oxidation.

In view of the above, we have decided to carry out a new degradative sequence which utilizes this reaction, as part of our continuing program of investigation[4-6] of new methods for the degradation of the side chain of fatty acids, bile acids and lanosterol.

The principal substrates used in this study were the phenyl ketone derivatives of lanosterol (**15**) and bile acids (**1**, **7**) which, as we have previously described,[5-6] are easily obtainable in quantitative yields by an established rearrangement procedure.[7]

RESULTS

I. Oxidative degradations. Pure samples of the ketones **1** and **7** (Scheme I) and **15** (Scheme II), obtained from bile acid and lanosterol precursors,[5-6] were treated with molecular oxygen at ambient temperature. It was established by means of numerous trials that the nature of the oxidation products was dependent upon the type of solvent system used and the basic strength of the medium. Thus, potassium tertiary butoxide in dimethyl formamide-tertiary butyl alcohol (8:2) led to compounds **2** and **8** (Scheme I), compound **16** (Scheme II), and benzoic acid. The experimentally determined stoichiometry indicated that for each mole of product, three moles of molecular oxygen were consumed and two moles of crystalline benzoic acid were formed, starting with one mole of ketone.

To facilitate the removal of benzoic acid and the purification of the oxidation products, after each experiment, the crude mixture was esterified with methanolic hydrochloric acid leading to methyl benzoate and the corresponding esters **3** and **9** (Scheme I) and **17** (Scheme II). After removing most of the methyl benzoate by evaporation under vacuum the mixtures were chromatographed on thin layer plates thus affording pure samples of the respective esters. Thus, ketone **1** was converted to ester **3** with an average yield of 70%, ketone **7** to ester **9** with 60%, and ketone **15** to ester **17** with 55%.

Identification of the products was obtained by IR and NMR spectroscopy and by elemental analysis. For the lanosterol and lithocholic acid derivatives further confirmation was obtained by preparing the corresponding acetates **10** (Scheme I) and **18** (Scheme II), and comparing their physical constants with those previously reported in the literature.[8-9]

When the oxidation of **1** was carried out with an excess of potassium tertiary butoxide in tertiary butyl alcohol, the corresponding phenyl ketone **24a** (Scheme III) was obtained as the only product. Structural identification of the products was achieved by IR and NMR spectroscopy. In the case of compound **24a** further confirmation was obtained by converting it to methyl cholanate **27** (Scheme IV) by the method of Emmons and Lucas.[10] The mixture m.p. of this ester **27** with an authentic sample* of methyl cholanate showed no depression.

*To synthesise this reference sample the olefin **28** (Scheme IV) which was on hand from a previous study[5] was subjected to standard ozonolysis and the resulting acid was esterified with methalolic HCl.

II. Synthesis of 20-ketosteroids

From bisnor precursors. Existing methods for the conversion of compounds in the bisnor cholanic series to 20-ketosteroids are reported to give 40–45% yields.[11,12] We have carried out the same conversion as follows:

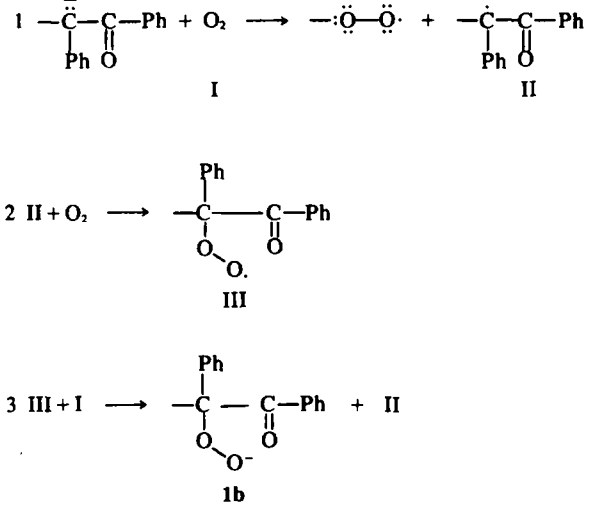
The esters **3**, **9**, and **17** were first hydrolysed back to the corresponding acids **2**, **8**, and **16** with ethanolic potassium hydroxide. The acids were then treated, without further purification, with lead tetraacetate in benzene containing a few drops of pyridine, as per the method of Rosen and Oliva.[13] To avoid side reactions,[14] molecules with OH groups on C_3 were acetylated before the reaction with lead tetraacetate. Thus, the C_{20} acetates **4** and **12** (Scheme I), and **20** (Scheme II) were obtained from the respective acids **2**, **11** and **19**. The compounds **4**, **12**, and **20**, were found by their NMR spectra to be mixtures of diastereomers epimeric around the C_{20} asymmetric carbon.

The total yield for the conversion of **3** to **4** was 63%; of **9** to **12**, 59%; and of **17** to **20**, 43%. LAH reduction of the acetates **4** and **12** (Scheme I) and **20** (Scheme II) gave quantitative yields of the alcohol **5** (Scheme I) and the diols **13** (Scheme I) and **21** (Scheme II). The alcohols were subsequently oxidized with Jones reagent leading to ketones **6** (Scheme I) and diketones **14** (Scheme I) and **22** (Scheme II). Purification of the ketones was achieved by recrystallization and TLC. Identification was made by comparison with authentic samples made in our laboratory.[5-9]

DISCUSSION

A. Mechanism and product composition

The mechanism of the autooxidation of carbanions has been the subject of numerous investigations.[15-20] Our data are consistent with the generally accepted mechanism[17] for the autooxidation of enolisable ketones by molecular oxygen. This mechanism was essentially proposed by Russell *et al*,[18] who have also studied the dependence of the reaction on the relative stability of the particular intermediates and the nature of the solvent system. The oxidative cleavage of our ketones **1**, **7**, and **15** most likely proceeds through the same kind of intermediates as those proposed by Russell. This is supported by the experimentally observed stoichiometry of our oxidations. A probable sequence is shown in Scheme III. The reaction of the phenyl ketone **1** with potassium tertiary butoxide generates the enolate anion **1a**. This anion then reacts with molecular oxygen to form the α-ketohydroperoxide anion **1b** probably by the following sequence:



Decomposition via a 4-centered intermediate (**1c**) similar to that proposed by Doering[15] would lead to the phenyl ketone **24a** (Scheme III). The dependence of the nature of the degradation products we have obtained on the decomposition medium can also be explained on the basis of earlier postulates.[3,18-20] The greater the acidity of the proton α to the carbonyl, the faster the reaction. Thus, compounds **1** (Scheme III), in which the acidity of the proton α to the carbonyl is further enhanced by the presence of the phenyl group, was readily oxidized to the ketone **24a**, even when polar protic solvents were used. But, in polar protic solvents the degradation stopped at the phenyl ketone stage with the loss of only one C atom from the chain. Apparently under the milder conditions* which exist when these solvents are used, the enolate ion

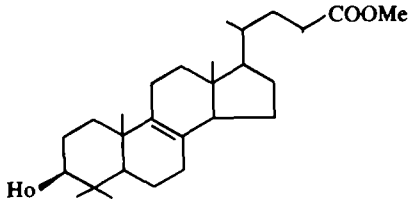
*In the presence of polar protic solvents such as t-BuOH intermediate carbanions of the **1a** type (Scheme III) are highly solvated and thus less reactive. In contrast, in polar aprotic solvents such as DMF the solvation of the carbanion intermediates is very small which results in their reacting with O_2 much more rapidly.

24a' is not sufficiently reactive to undergo further degradation. In contrast, when we have used a polar aprotic solvent or a mixture containing predominantly such a solvent (e.g. DMF-t-BuOH, 8:2) these ions being less solvated were more reactive and therefore the degradation continued to the aldehyde (**29a**) stage. The results of our experiments indicate that under these conditions the rate of oxidation of the aldehyde (**29a**) to the corresponding acid (**2**) is faster than the oxidation of the enolate ion (**29a'**). Thus, the 20-ketosteroid (**30a**) which would have resulted from the further oxidation of these enolate ions was not obtained.

B. Yields

The degradation sequence summarized in Scheme I proceeds with a total yield of 42% for the cholanic series (i.e. from **1** to **6**) and 31% for the lithocholic series (i.e. from **7** to **14**). Taking into account that the ketones **1** and **7** have been prepared[5] from the methyl esters of cholanic and lithocholic acids respectively with an overall yield of 76%, the total yield of the side chain degradations by the present oxidative method is of the order of 32% for methyl cholanate and 23·5% for methyl lithocholate.

The degradation sequence (from **15** to **22**) depicted in Scheme II proceeds with an overall yield of 23%. Considering that the phenyl ketone **15** has been prepared from 3β - hydroxy - 4,4,14α - trimethyl - 5α - cholane - 8 - en - 24 - methanoate



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(**31**) in 78·5% overall yield, the total yield for the degradation of this lanosterol derivative (**31**) is of the order of 18%. These yields compare favorabaly with those reported by other investigators for similar degradations[9,21-26].

EXPERIMENTAL

General. M.ps were taken on a Kofler apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 357 spectrophotometer. NMR spectra were determined on a Jeol Model C60H spectrometer using TMS as internal standard and are reported in ppm. Mass spectra were recorded on a Varian Model CH5 mass spectrometer. For column chromatography Merck silica (0·063–0·2 mm) was always used. Micro-analysis were performed by the microanalysis service of C.N.R.S. at the Gif sur Yvette Laboratories in France. The oxygenations were performed at ambient temperature in the following manner:

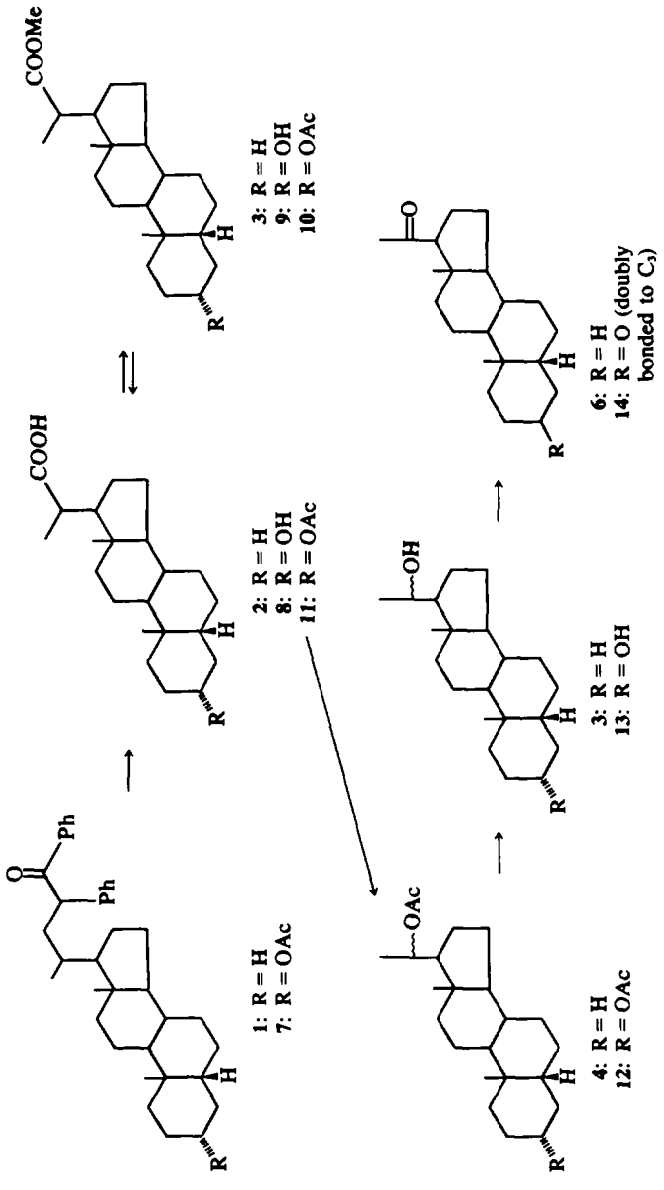
A. *Apparatus used.* To measure the amount of O_2 consumed in each reaction, a standard graduated gas buret of the type commonly used for hydrogenations was utilized. Since the O_2 was stored under water, it was necessary to dry it by passage through a trap containing $CaCl_2$ prior to its introduction into the mixtures.

B. *Base and solvents.* Commercial[27] t-BuOK powder 99% pure, was used in all of our reactions. The solvents consisted of t-BuOH distilled over Na and purified[28] dimethyl formamide. The most complete oxidations were obtained with mixtures of dimethyl formamide (DMF) and t-BuOH (8:2).

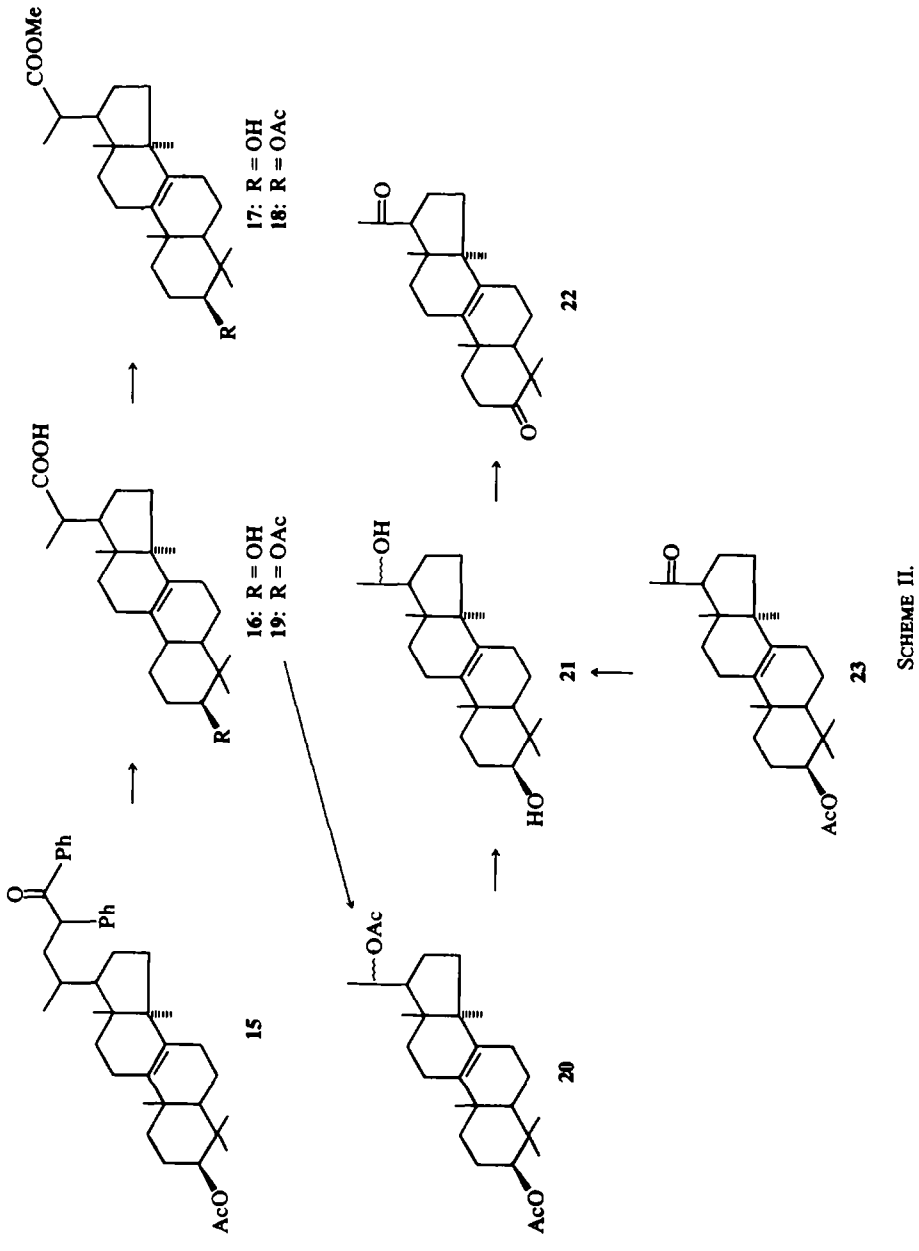
C. *General method of oxygenation.* The reactions were carried out at ambient temp as follows: A soln of ketone in DMF was treated with t-BuOH. The resulting mixture was then placed in an atmosphere of O_2 and stirred magnetically. The stirred mixture was at this point treated with t-BuOK through a side arm attached to the reaction vessel. The absorption of O_2 is initially very rapid but levels off at the end. The mixture was continually stirred until the O_2 absorption stopped completely. The mixture was subsequently acidified with an 6% HCl aq to destroy the excess base. The acidified mixture (pH 1–2) was then extracted with either ether or methylene chloride depending on the solubility of the organic components. The mixture of acids was then directly esterified with methanolic HCl. After the usual workup and evaporation of the solvents, the mixture of esters was heated at 100° under vacuum (3 mm) to remove most of the methyl benzoate. Final purification was achieved by TLC over silica (Merck).

Methyl, 23,24-bisnor-5β-cholanate (**3**). A sample of **1** (250 mg, 0·5 mmol) was dissolved in a mixture of DMF (12 ml) and t-BuOH (3 ml), placed in the oxygenation apparatus and treated with t-BuOK (500 mg). The total O_2 uptake was 31 cc (*ca* 1·5 mmol). On workup a mixture of acids (**2** and benzoic, 280 mg) was obtained which was directly esterified with MeOH (50 ml) and 12N HCl (3 ml). Isolation and purification of **3** was carried out as per the general procedure outlined above. Thus the crude product (180 mg) after TLC involving two successive elutions with pentane-ether (20:1) afforded a pure sample (120 mg, 70%) of **3**. After two recrystallizations from EtOH an analytical sample (m.p. 124–126·5°, lit.[31] 125–126·5°) was obtained: IR (CS_2), 1160, 1740 cm^{-1}; NMR ($CDCl_3$) δ 0·6, 0·85 (6H, s, C_{18} and C_{19} protons), 1·1 (d, C_{21} protons, J = 7 Hz), 2·25 (1H, m, C_{20} proton), 3·55 (3H, s, –COOMe protons). (Found: C, 79·95; H, 10·85; O, 9·24. Calcd. for $C_{23}H_{38}O_2$: C, 79·71; H, 11·05; O, 9·23).

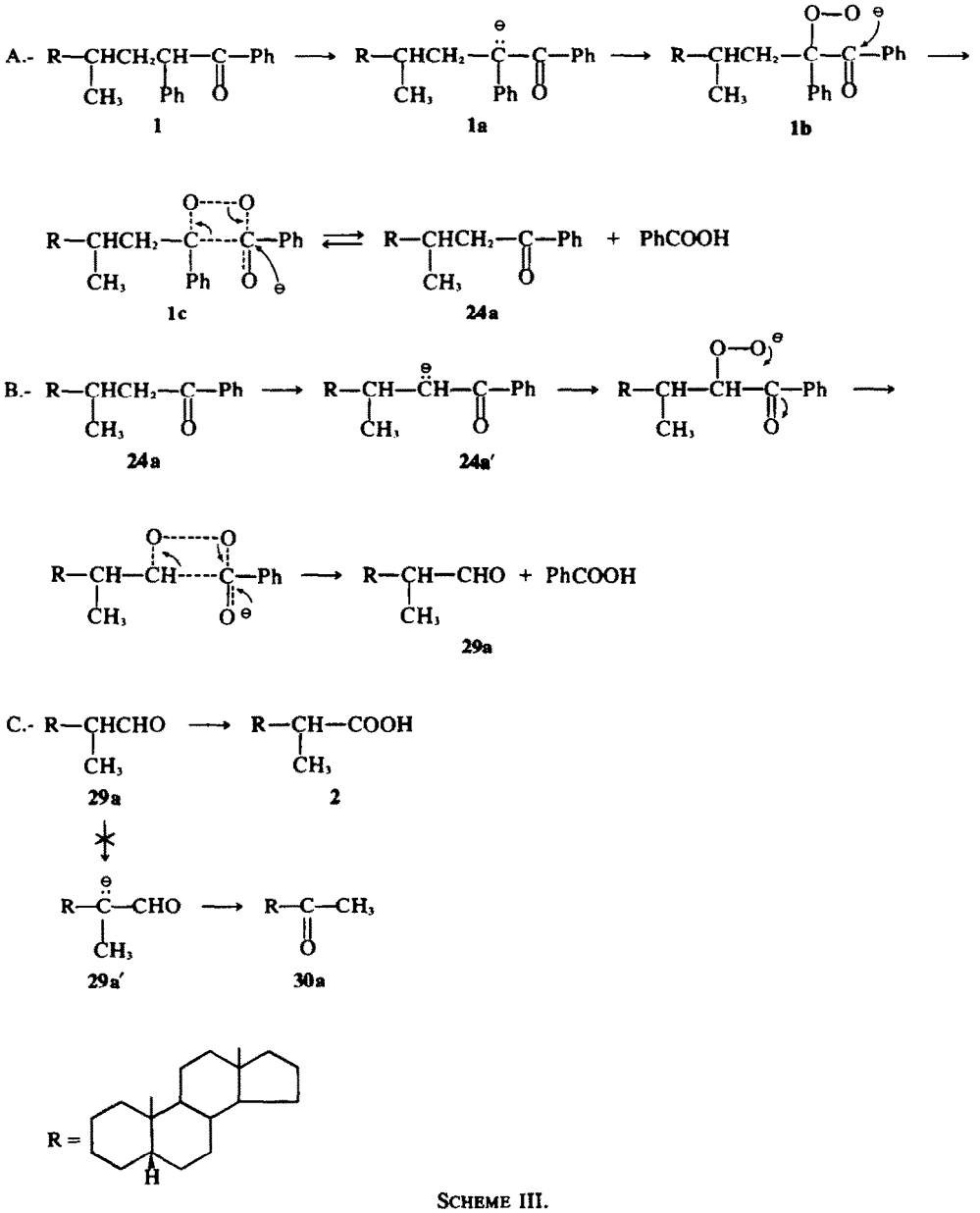
20-Acetoxy-5β-pregnane (**4**). A sample of **3** (350 mg) was hydrolysed back to the acid **2** with 10N NaOH (5 ml) in EtOH (10 ml). The saponification was complete. Acidification of the mixture, followed by ether extraction afforded on solvent evaporation a pure (by TLC) sample (370 mg) of the acid **2**. This product without any further purification was dissolved in dry benzene (10 ml) containing 6 drops of pyridine, treated with lead tetraacetate (1·9 g) and refluxed overnight. At the end of the reaction the inorganic salts were filtered off and washed with ether, combining the washings with the filtrate. The organic phase was then washed successively with a sat $NaHCO_3$ aq and water. After drying and evaporation of the solvent a crude sample (380 mg) of **4** was obtained. Purification was achieved by TLC involving four successive elutions with pentane-ether (25:1). Thus a mixture (220 mg, 63%) of acetates epimeric around the C_{20} asymmetric carbon


COOMe
COOH
Ph
Ph
O
OAc
OH
R
H
1: R = H
7: R = OAc
2: R = H
8: R = OH
11: R = OAc
3: R = H
9: R = OH
10: R = OAc
4: R = H
12: R = OAc
3: R = H
13: R = OH
6: R = H
14: R = O (doubly bonded to C3)

SCHEME I.


COOMe
17: R = OH
18: R = OAc
R
COOH
16: R = OH
19: R = OAc
R
Ph
Ph
O
AcO
15
OAc
AcO
20
OH
HO
21
O
22
O
O
AcO
23

SCHEME II.

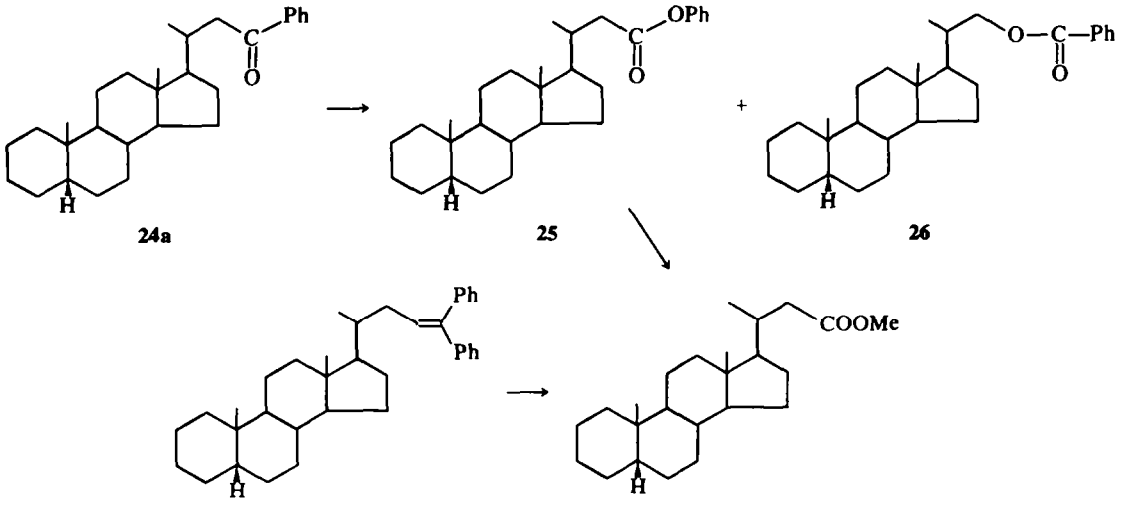


SCHEME III.

was obtained. The mixture was then recrystallized from MeOH: IR (CS_2) 1245, 1735 cm^{-1}; NMR ($CDCl_3$) δ 0·55, 0·6 (3H, two s, C_{18} protons), 0·87 (3H, s, C_{19} protons), 1·95 (3H, s, acetoxy protons), 4·8 (1H, m, C_{20} protons).

5β-Pregnane-20-one (**6**). A sample (200 mg, 0·57 mmol) of **4** was reduced in the usual way with LAH in anhyd ether. On workup a mixture of alcohols (**5**) epimeric around the C_{20} asymmetric carbon was obtained: IR (CS_2) 3600 cm^{-1}. This mixture, without further purification, was dissolved in reagent grade acetone and treated with a few drops of Jones reagent until a permanent orange color developed. After stirring for a few min MeOH was added until the soln became green. The inorganic salts were then filtered off and washed with ether combining the washings with the filtrate. The organic phases were then washed successively with $NaHCO_3$ aq and water. After drying and evaporating the solvents a product (165 mg) was obtained which crystallized spontaneously. TLC of this product on silica under the same conditions as those used in a previous experiment[5] showed that it had the same R_f as the 5β-pregnane-20-one previously synthesized. Recrystallization from EtOH afforded an analytical sample. The m.p. of the product obtained by the present method was 114–116° in agreement with the previously reported[5] value. The mixture m.p. (113–115°) with an authentic sample[5] was undepressed.

Methyl, 23,24-bisnor-3α-hydroxy-5β-cholanate (**9**). A



SCHEME IV.

sample of **7** (930 mg, 1·68 mmol) was dissolved in a mixture of DMF (32 ml) and t-BuOH (8 ml), treated with t-BuOK (1·4 g) and oxidized as per the general procedure. The total amount of O_2 consumed in the oxidation was 106 ml (*ca* 4·8 mmol). The crude product (850 mg) isolated by methylene chloride extraction of the oxidation mixture was esterified without any further purification with MeOH (80 ml) and 12N HCl (5 ml). After the usual extraction, elimination of the methyl benzoate under vacuum, and TLC with pentane-ether (1:3) pure **9** (400 mg, 66%) was obtained. The product obtained from the chromatography was then recrystallized from hexane (m.p. 165–167°). This reaction was repeated several times with various amounts of starting material and the average yield was found to be of the order of 60%: IR (CCl_4) 1165, 1740, and 3620 cm^{-1}; NMR ($CDCl_3$) δ 0·6, 0·87 (6H, two s, C_{18} and C_{19} protons), 1·1 (d, C_{21} protons, J = 7 Hz), 2·35 (1H, m, C_{20} proton), 3·57 (3H, s, –COOMe protons). (Found: C, 75·97; H, 10·37; O, 13·04. Calcd. for $C_{23}H_{36}O_3$: C, 76·19; H, 10·57; O, 13·24).

Methyl, 23,24-bisnor-3α-acetoxy-5β-cholanate (**10**). *This* compound was obtained (90%) from the acetylation of **9** with Ac_2O. After 3 recrystallizations from MeOH an analytical sample was obtained (m.p. 107–109°, lit.[8] 108–109°): IR (CS_2) 1160, 1240, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 0·6, 0·87 (6H, two s, C_{18} and C_{19} protons), 1·1 (3H, d, C_{21} protons, J = 7 Hz), 1·97 (3H, s, acetoxy protons), 2·35 (1H, m, C_{20} proton), 3·57 (3H, s, –COOMe protons), 4·7 (1H, m, 3β proton).

3α-Acetoxy-23,24-bisnor-5β-cholanoic acid (**11**). Hydrolysis of **9** (290 mg) with 10N NaOH (5 ml) in EtOH (10 ml) led back to **8** (280 mg). This acid, which is not very soluble in organic solvents was acetylated without any further purification by means of Ac_2O in pyridine: IR (CS_2) 1240, 1705, and 1735 cm^{-1}.

3,20-Diacetoxy-5β-pregnane (**12**). The above product **11** (280 mg) was dissolved in dry benzene (10 ml) containing 6 drops of pyridine and treated with lead tetraacetate (1·9 g). The mixture was refluxed overnight and allowed to stand for 24 h. The inorganic salts were then removed by filtration and washed with ether combining the washings with the filtrate. Evaporation of the solvents afforded the crude product (300 mg). After purification by TLC with pentane-ether (2:1) a pure sample of **12** (190 mg) was obtained. The total yield for the passage from **10** to **12** was 59%: IR (CS_2) 1240, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 0·62 (3H, s, C_{18} protons, 20 β isomer), 0·68 (3H, s, C_{18} protons, 20 α isomer), 0·95 (3H, s, C_{19} protons, both isomers), 1·22 (d, C_{21} protons, J = 6 Hz), 2·00 and 2·02 (6H, two s, acetoxy protons), 4·7 (2H, m, C_3 and C_{20} protons). The mixture of the two epimers was used in obtaining the NMR spectra. The above constants are in agreement with previously reported[32] values.

5β-Pregnane-3,20-dione (**14**). A sample of **12** (175 mg) was reduced, in the usual way, with LAH (50 mg) in anhy ether (15 ml). Thus, 130 mg of the diol **13** were obtained: IR ($CHCl_3$) 3600 cm^{-1}. The crude diol (110 mg) was then, without any further purification, oxidized with Jones reagent. After purification of the crude product by TLC with pentane-ether (1:3) a pure sample of **14** (100 mg) was obtained. The m.p. of the product after recrystallization from a mixture of ether-hexane was 121–123° (lit.[31] 119–122°). The mixture m.p. of this product with an authentic sample previously prepared[5] in our laboratory was 121–123°.

Methyl, 23,24-bisnor-3β-hydroxy-4,4,14α-trimethyl-8-ene-cholanate (**17**). A sample (850 mg, 1·43 mmol) of **15** was dissolved in DMF (32 ml) and t-BuOH (8 ml), treated with t-BuOK (1·1 g) and submitted to the standard oxidative conditions. The total uptake of O_2 was 95 ml (*ca* 4·3 mmol). The mixture was then extracted with $CHCl_3$ and the crude product obtained (900 mg) was esterified with MeOH (80 ml) and 12N HCl (6 ml). Workup of the mixture as per the general procedure and TLC of the crude product requiring two successive elutions with pentane-ether (1:1) afforded a pure sample (315 mg, 55%) of **17**. After recrystallization from EtOH the product melted at 186–188°. This reaction was repeated many times and the yields obtained were of the order of 50–60%: IR (CCl_4) 1165, 1740, and 3620 cm^{-1}; NMR ($CDCl_3$) δ 0·65, 0·77, 0·87, 0·95 (3H, 3H, 3H, 6H, s, 4α, 4β, 14α, 18, and 19 Me protons), 1·1 (d, C_{21} protons, J = 7 Hz), 3·1 (1H, m_r-$C_{3\alpha}$ proton), 3·57 (3H, s, –COOMe protons). (Found: C, 77·40; H, 10·35; O, 12·04. Calcd. for $C_{26}H_{42}O_3$: C, 77·56; H, 10·52; O, 11·92).

Methyl, 23,24-bisnor-3β-acetoxy-4,4,14α-trimethyl-8-

ene-cholanate (**18**). Acetylation in the 3β position of **17** with Ac_2O in pyridine led smoothly (90%) to **18**. Recrystallization of this product from MeOH-CH_2Cl_2 (5:1) afforded a pure sample (m.p. 182–184°, lit.[9] 185–187°): IR (CS_2) 1165, 1240, and 1740 cm^{-1}; NMR ($CDCl_3$) δ 0·62, 0·85, 0·95, (3H, 9H, 3H, s, 4α, 4β, 14α, 18 and 19 Me protons), 1·08 (d, C_{21} protons J = 7 Hz), 1·98 (3H, s, acetoxy protons), 3·55 (3H, s, –COOMe protons), 4·35 (1H, m, 3α proton).

3β - Acetoxy - 4,4,14α - trimethyl - 8 - ene - 23,24 - bisnor - cholanoic acid (**19**). A sample of **17** (160 mg) was hydrolysed with 10N NaOH (5 ml) in EtOH (10 ml) to the acid **16** (160 mg) and then reacetylated with Ac_2O in pyridine. Thus, after the usual work-up 160 mg of **19** were obtained: IR (CS_2) 1240, 1705 and 1735 cm^{-1}.

3,20-Diacetoxy-4,4,14α-trimethyl-5β-pregn-8-ene (**20**). The product **19** (160 mg) obtained from the previous synthesis was treated with lead tetraacetate (1 g) in dry benzene (10 ml) containing 6 drops of pyridine. The mixture was refluxed for 6 h, after which the organic salts were removed by filtration. The ppt was washed with ether combining the washings with the filtrate. Solvent evaporation afforded the crude product (160 mg). After purification by TLC with pentane-ether (2·5:1) a pure sample (75 mg) of **20** was obtained: IR (CS_2) 1240, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 0·65, 0·7, 0·9, 1·02 (3H, two s, 9H, s, 3H, s, 4α, 4β, 14α, C_{18} and C_{19} Me protons), 1·22 (d, C_{21} protons, J = 6 Hz), 2·00 and 2·05 (two s, acetoxy protons), 4·4 and 4·9 (1H, m, 1H, m, C_3 and C_{20} protons).

4,4,14α-Trimethyl-5β-pregn-8-ene-3,20-dione (**22**)

A. *From* **20**. A sample of **20** (60 mg) was reduced with LAH (35 mg) in anhy ether. Thus, the diol **21** (45 mg) was obtained. TLC with pentane-ether (2:1) showed that this product was pure: IR ($CHCl_3$) 3605 cm^{-1}. Consequently a sample (40 mg) of the diol, without any further treatment, was oxidized with Jones reagent. TLC of the crude oxidation product with pentane-ether (2:1) afforded a pure sample of **22**. The m.p. of this sample (211–214°) was several degrees higher than the previously reported[32,33] values (203–204°; 201–202°): IR (CS_2) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0·65 (3H, s), 0·98 (3H, s) 1·08 and 1·12 (9H, two s), 4α, 4β, 14α, C_{18} and C_{19} Me protons, 2·12 (s, C_{21} protons).

B. *From* **23**. A reference sample of **22** was also prepared starting from **23** which was on hand from a previous study.[6] The synthesis involved simple LAH reduction of the C_3 acetate group and the C_{20} ketone followed by oxidation of the intermediate diol **21** with Jones reagent. After recrystallization from acetone a pure (m.p. 211–215°) sample of the diketone **22** was obtained. The mixture m.p. of the two diketone samples prepared was 210–214°.

23-Phenyl-5β-cholane-23-one (**24a**). When a sample of **1** (250 mg, 0·5 mmol) was dissolved in t-BuOH (10 ml) treated with t-BuOK and oxidized as per the general procedure a quantitative yield (by TLC) of **24a** (Scheme IV) was isolated as the only product. The total O_2 absorption was 10 ml (*ca* 0·5 mmol). After recrystallization from MeOH a pure (m.p. 127–129°) sample of **24a** was obtained: IR (CS_2) 690, 750, 1685, 3020, 3060, and 3080 cm^{-1}; NMR ($CDCl_3$) δ 0·65 and 0·87 (6H, two s, C_{18} and C_{19} protons), 0·92 (3H, d, C_{21} protons, J = 6 Hz), 2·75 (2H, m, C_{22} protons), 7·15–8·17 (5H, m, aromatic protons); mass spec. *m/e* 406 (M^+), 105 (Ph-CO^+), 286 (M–PhCOHCH$_2^+$), 77 (Ph^+).

Phenyl, 23-nor-5β-cholanate (**25**). The trifluoroperacetic acid which is required for the synthesis of **25** was prepared as follows: CH_2Cl_2 (12 ml) was placed in a flask (25 ml) and cooled in an ice bath. H_2O_2 (1·5 ml, 85%) was then added with a new pipette under constant stirring. The mixture was then treated dropwise with trifluoracetic anhydride from a pressure addition funnel. The mixture was stirred for a few more min after all the anhydride had been added. This reagent was then used in the following synthesis:

A soln of **24a** (200 mg, 0·5 mmol) and disodium hydrogen phosphate (900 mg) in CH_2Cl_2 (10 ml) was treated dropwise under stirring with the above trifluoroacetic acid soln (1 ml). After refluxing for 1 h the mixture was decomposed by pouring it over ice and extracted with CH_2Cl_2. After drying and evaporating the solvents the crude product (235 mg) was isolated and purified by TLC involving 3 elutions with pentane-ether (30:1). Thus, two products were isolated: the benzoate ester **26** (20 mg): IR (CS_2) 1275 and 1725 cm^{-1}, and the phenyl cholanate **25** (110 mg): IR (CS_2) 1200 and 1765 cm^{-1}.

Methyl, 23-nor-5β-cholanate (**27**). This compound was prepared from **25** by transesterification. Thus, a sample of **25** (110 mg) was dissolved in MeOH (25 ml), treated with 5 drops conc HCl and refluxed overnight. After the usual workup, 70 mg of the pure **27** were obtained (mp 72–74° after recrystallization from MeOH), IR (CS_2): 1740 cm^{-1}.

The same product **27** was independently synthesised by the ozonolysis of the olefin[5] **28** followed by esterification with MeOH of the acid obtained. The mixture mp of this compound with the product obtained from the above transesterification was undepressed.

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