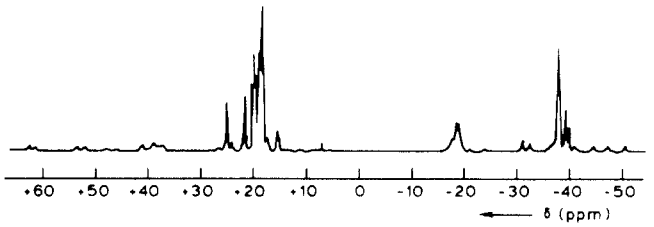

Figure 2. 300-MHz ^1H NMR spectrum of a 0.1 M solution of $Yb(fod)_3$ in $CDCl_3$ at -38 °C.

The existence of an entity in which the Yb^{3+} ion is coordinated by four fod ligands can be deduced from 100-MHz ^1H NMR spectra of mixtures of $Yb(fod)_3$ and the neutral ligand Hfod in $CDCl_3$, which showed at 25 °C a single *t*-Bu signal (Figure 1A). Therefore, at this temperature fast exchange between $Yb(fod)_3$ and Hfod exists. This exchange might take place *via* a complex $H[Yb(fod)_4]$ (eq 1). A decrease of the temperature to -27 °C caused

$$Yb(fod)_3 + Hfod \rightleftharpoons H[Yb(fod)_4] \quad (1)$$

a splitting in the spectrum and then both the $Yb(fod)_3$ and the Hfod signals were observed (Figure 1B). Moreover, small signals at δ 3.66 and 17.1 were present, which might be assigned to the *t*-Bu and CH groups in $H[Yb(fod)_4]$, respectively.

It should be noted that at these temperatures the ligands in $Yb(fod)_3$ as well as in $Yb(fod)_3$·Kfod and $H[Yb(fod)_4]$ give rise to only one *t*-Bu and one CH resonance in the 100-MHz ^1H NMR spectrum. Since at the concentrations used (0.01 M) bimolecular exchange reactions are rather slow, it may be concluded that the fod ligands in these complexes are still rapidly rearranging intramolecularly in such a way that these ligands are effectively magnetically equivalent.[12]

At higher concentrations (0.1 M) the ^1H NMR spectrum of $Yb(fod)_3$ is very complex. At 300 MHz and -38 °C at least 40 peaks were observed (Figure 2), which coalesced at about 115 °C to two broad peaks (*t*-Bu and CH). As the complexity of the spectra appeared to be dependent on the concentration, it seems most likely that these phenomena are due to self-association of $Yb(fod)_3$. Several $Ln(dpm)_3$ shift reagents (dpm = 2,2,6,6-tetramethyl-3,5-heptanedionate) are known to crystallize as dimeric units through sharing of two oxygen atoms by the lanthanide ions.[13] A single dimer structure, however, cannot explain the large number of peaks in the concentrated solution of $Yb(fod)_3$, even when it is assumed that the intramolecular reorientation of the fod ligands and the rotation of the *t*-Bu groups are slow with respect to the NMR time scale. Moreover, the concentration dependence appeared to be inconsistent with a monomer/dimer equilibrium. Therefore, it seems more likely that several dimer configurations and/or oligomers of $Yb(fod)_3$ are present. Anyhow, these results show that in concentrated solutions complex exchange phenomena take place. Since for the evaluation of absolute bound shifts of lanthanide–substrate complexes measurements at a large range of shift reagent/substrate ratios are needed,[14] measurements at high $Ln(fod)_3$ concentrations usually cannot be circumvented. Great care should be taken in the interpretation of these data. On the other hand, the use of relative bound shifts, which usually are obtained from data at low shift reagent/substrate ratios, may lead to other complications.[5a] Probably the best way to determine bound shifts is a direct measurement of these shifts in NMR spectra at low temperatures and high magnetic fields, in which both the shift reagent substrate complex and the free substrate are observed.

(12) De Boer, J. W. M.; Sakkers, P. J. D.; Hilbers, C. W.; De Boer, E. *J. Magn. Reson.* **1977**, *26*, 253.
(13) Erasmus, C. S.; Boeyens, J. C. A. *Acta Crystallogr., Sect. B* **1970**, *26*, 1843.
(14) Lenkinski, R. E.; Elgavish, G. A.; Reuben, J. *J. Magn. Reson.* **1978**, *32*, 367.

Experimental Section

The 100-MHz ^1H NMR spectra were obtained on a Varian XL-100-15 spectrometer system in the pulse-FT mode. The 300-MHz ^1H NMR spectra were measured on a spectrometer, built at the Department of Applied Physics.[15] Mass spectra were measured on a Varian-Mat 311A spectrometer with a direct insertion probe at temperatures between 50 and 100 °C. All solvents used were dried on zeolite KA prior to use.

$Yb(fod)_3$·Kfod. A solution of 10.67 g of Hfod (36 mmol) in 10 mL of MeOH was neutralized with 9 mL of 4 N KOH. The solution obtained was added to 2.56 g of $Yb(NO_3)_3·5H_2O$ (5.7 mmol) dissolved in a minimal amount of MeOH. The dispersion obtained was added with stirring to 400 mL of H_2O. The white precipitate was filtered to yield 7.72 g of $Yb(fod)_3$·Kfod (5.6 mmol, 98%). Further purification was achieved by recrystallization from CCl_4 at -20 °C; mp 123-124 °C; ^1H NMR ($CDCl_3$) δ 0.93 (br s, *t*-Bu), -1.78 (br s, CH); mass spectrum (70 eV), important peaks at *m/z* 1393 (M), 1374 (M - F), 1354 (M - K), 1098 (M - fod), 1059 ($Yb(fod)_3$), 1002 ($Yb(fod)_3$ - *t*-Bu), 764 ($Yb(fod)_2$), 295 (fod).

Purification of $Yb(fod)_3$ Contaminated with $Yb(fod)_3$·Kfod. A mixture of $Yb(fod)_3$ and $Yb(fod)_3$·Kfod (400.0 mg, ratio about 1:1) was dissolved in 2 mL of CCl_4. The solution obtained was shaken with an aqueous 0.2 M $YbCl_3$ solution (5 × 1 mL) and after that dried on zeolite KA. After evaporation of the solvent and drying under vacuo over zeolite KA, 385.0 mg of $Yb(fod)_3$ was obtained.

Alternatively, the 1:1 mixture could be purified by shaking the CCl_4 solution with 0.1 N HCl (2 × 1 mL). After that the solution was washed with 1 mL of H_2O. Then the Hfod formed was removed quantitatively by treatment of the solution with zeolite NaX. Evaporation of the solvent gave 150 mg of $Yb(fod)_3$. Further purification was obtained by recrystallization from CH_2Cl_2 at -30 °C.

Registry No. 1, 100-76-5; 2, 107-10-8; $Yb(fod)_3$·Kfod, 76927-67-8; $Yb(fod)_3$, 18323-96-1; Hfod, 17587-22-3; $H[Yb(fod)_4]$, 76927-68-9.

(15) Mehlkopf, A. F. Thesis, Delft University of Technology, 1978.

Potential Bile Acid Metabolites. 3.[1] A New Route to Chenodeoxycholic Acid[2]

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Received October 9, 1980

In continuation of a program of synthesis of potential bile acid metabolites, a need for a moderate supply of chenodeoxycholic acid (1) prompted us to examine literature preparations of the compound, of which there are several.[4] All of these methods, save one,[5] involve reduction

(1) Part 2: F. C. Chang, *J. Org. Chem.*, **44**, 4567 (1979).
(2) 3a,7a-Dihydroxy-5β-cholanic acid. All cholanic acid derivatives mentioned in this work are of the 5β series; the 5β designations are omitted in their names. Chenodeoxycholic acid, one of the "primary" bile acids of higher vertebrates, is used in treatment of gallstones.
(3) On leave, Nihon University, Japan.
(4) (a) L. F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, **72**, 5530 (1950); (b) I. G. Anderson, G. A. D. Haslewood, H. S. Wiggin, and I. D. P. Wotton, *Nature*, **169**, 621 (1952); (c) Y. Sato and N. Ikekawa, *J. Org. Chem.*, **24**, 1367 (1959); (d) E. Hauser, E. Baumgartner and K. Meyer, *Helv. Chim. Acta*, **43**, 1595 (1960); (e) A. F. Hofmann, *Acta Chem. Scand.* **17**, 173 (1963); (f) S. L. Hsia in "The Bile Acids", Vol. I., P. P. Nair and D. Kritchevsky, Eds., Plenum Press, New York, 1971, p 110.

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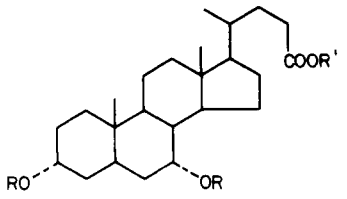
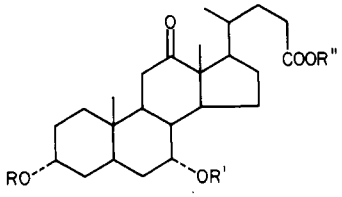
of some form of 3α,7α-dihydroxy-12-oxocholanic acid (2), either as its 7-acetate **2a**, methyl ester 7-acetate **2b**, or methyl ester diacetate **2c**, by the Huang–Minlon modification of the Wolf–Kishner reaction.



1, R = R' = H
1a, R = Ac; R' = Me

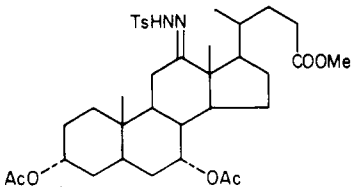


2, R = R' = R'' = H
2a, R = R'' = H; R' = Ac
2b, R = H; R' = Ac; R'' = Me
2c, R = R' = Ac; R'' = Me

On repeating these preparations we encountered the same difficulties and problems described in detail by both Hauser, Baumgartner, and Meyer[4d] and Hofmann,[4e] which led us to investigate alternative syntheses.

We now report a simplified method for preparing **1**, based on the work of Hutchins and Natale,[6] which proceeds through easily prepared, well-defined intermediates and affords a pure product in good yield without requiring a column chromatographic purification step, in contrast to previous procedures.

As with earlier preparations the starting compound is the keto diacetate **2c**. Its tosylhydrazone **3**, obtained



3

crystalline in 72% isolated yield, upon $NaBH_4$ reduction in acetic acid gives the diacetate **1a** (crystalline, 53% isolated yield). Hydrolysis of **1a** to **1** is quantitative. Thus, since **2c** can be obtained from cholic acid in nearly quantitative yield,[4a] the overall yield of good quality **1** from cholic acid (the only practical starting material for preparing bile acids) is at least 38% (based only on first-crop recrystallized **3** and **1a**).[7]

Mild conditions are critical for successful preparation of intermediates **3** and **1a**.[8,9] Exploratory experiments in which reflux temperatures and a strong acid catalyst were used for preparing **3**[6] resulted in unsatisfactory yields and poor product. The $NaBH_4$ reduction requires a controlled temperature throughout.

Among bile acids in general, unreliability of melting points as criteria of purity is well-known; the wide variation of reported melting points for **1** is especially notorious (see Experimental Section). Hofmann in a meticulous study[4e] concluded that a highly purified (by column chromatography) product crystallized from ethyl acetate–heptane has a melting point of 119 °C. However, subsequent reports from several laboratories[10a–c] have shown that the 119 °C crystals contained tenaciously held solvated heptane, the pure acid has a melting point of 172 °C,[10c] and a crystalline product of this melting point can be obtained by crystallization from acetonitrile.[10d]

Acid **1**, prepared by our procedure and crystallized from ethyl acetate–hexane, melted at 121 °C (elemental analysis indicated that the product is a solvate containing 0.2 mol of hexane) but when recrystallized from acetonitrile yielded crystalline acid with correct elemental analysis which melted at 172.5 °C. TLC comparison of our 121 and 172.5 °C crystalline products, as well as precipitated **1** (dried at 100 °C without crystallization), gave single spots which are identical (cospot) with authentic **1**.[11]

Experimental Section

Melting points were determined on an electric micro hotstage and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 137 spectrophotometer. NMR spectra were determined on a Perkin-Elmer R-32 instrument, with deuteriochloroform containing Me_4Si as solvent. Solvents were removed by distillation at 50 °C under reduced pressure.

Methyl 3α,7α-Diacetoxy-12-oxocholanate Tosylhydrazone (3). To methyl 3α,7α-diacetoxy-12-oxocholanate (**2c**),[4a] 10.1 g (0.02 mol), stirred in 200 mL of acetic acid was added gradually 7.5 g (0.04 mol) of *p*-toluenesulfonyl hydrazide. After 12 h of standing at room temperature the mixture was diluted with water and extracted with CH_2Cl_2 (2×). The combined CH_2Cl_2 extract was washed with 5% $NaHCO_3$ solution and then with H_2O to neutrality, dried with Drierite, and evaporated to an oil which, when treated with a small volume of methanol, crystallized. Recrystallization from methanol yielded 9.7 g (72%) of **3** as fine needles: mp 146.0–147.0 °C; IR (KBr) 5.80 (C=O), 3.15, 6.15, 6.30, 7.52, 8.65 (s), 12.31 μm (tosyl hydrazone);[9] NMR δ 0.81 (3 H, s, C-18 Me), 0.96 (3 H, s, C-19 Me), 2.00 and 2.01 (each 3 H, s, OCO**Me**), 2.42 (3 H, s, Ar**Me**), 3.65 (3 H, s, OMe), 4.51 (1 H, br m, C-3 CHOAc), 4.91 (1 H, m, C-7 CHOAc), 7.32 and 7.76 (each 2 H, d, J = 9 Hz, *p*-disubstituted phenyl).

Anal. Calcd for $C_{36}H_{52}N_2O_8S$ (mol wt 672.79): C, 64.26; H, 7.79. Found: C, 63.91; H, 7.88.

From the methanolic mother liquor a second crop of crystals was obtained, 1.42 g (10%), mp 144.0–146.0 °C.

Methyl Chenodeoxycholate Diacetate (1a). To a magnetically stirred solution of acetic acid (80 mL) containing 4.04 g (0.006 mol) of **3** was added 2.27 g (0.06 mol) of $NaBH_4$ (pellets) at a rate which did not allow the reaction temperature to exceed 60 °C (ca. 1 h). Stirring was continued at room temperature for 3 h, and then with the flask immersed in an ice bath, ice chips were gradually stirred in. The precipitated and filtered solid, after being washed with water, crystallized from aqueous methanol as fine needles: 1.58 g (53%; mp 133.0–133.5 °C (lit.[4d] mp 130–132 °C); IR ($CHCl_3$) 5.80 (C=O), 9.38, 10.33 μm (C—O); NMR δ 0.64 (3 H, s, C-18 Me), 0.92 (3 H, s, C-19 Me), 2.00 and 2.02 (each 3 H, s, OCO**Me**), 3.63 (3 H, s, OMe), 4.56 (1 H, br m, C-3 CHOAc), 4.88 (1 H, m, C-7 CHOAc).

Anal. Calcd for $C_{29}H_{46}O_6$: C, 70.98; H, 9.45. Found: C, 71.30; H, 9.24.

(5) The method of Sato and Ikekawa[4c] differs from the others in the use of Raney nickel for reduction of the thioketal of the ketone. Hofmann[4e] discusses the shortcomings of this method.
(6) R. O. Hutchins and N. R. Natale, *J. Org. Chem.*, **43**, 2299 (1978).
(7) Calculated overall yield when crystalline second crops of **3** and **1a** are included would be 49%.
(8) The reaction rate at which **3** is formed at room temperature was unexpected; in previous work[9] refluxing in ethanol with acetic acid as catalyst required longer than 6.5 h for complete conversion to the tosylhydrazone.
(9) F. C. Chang, *J. Org. Chem.*, **30**, 2053 (1965).
(10) (a) E. H. Mosbach, G. Nicolau, and R. W. Nichols, *Lancet*, 111 (1974); (b) P. Van Straelin, H. A. P. DeJongh, and F. H. Jansen, *ibid.*, 1518 (1974); (c) G. P. Van Birge-Henegouwen, A. F. Hofmann, and T. S. Gaginella, *Gastroenterology*, **73**, 291 (1977); (d) S. Macke and P. Rambacher, German Patent 2,613,346, (1978); *Chem. Abstr.* **88**, 41664 (1978).
(11) We thank Dr. A. F. Hofmann for a generous sample of **1**.

A second crop of crystals from the mother liquor weighed 0.20 g (7%), mp 127.5–130.5 °C.

Chenodeoxycholic Acid (1). **1a** (2 g) refluxed in 40 mL of 10% methanolic KOH for 12 h was processed by evaporation of the solvent, solution of the residue in water, and acidification (3 N H_2SO_4) of the ice-cooled solution. The precipitated solid was washed with water, dried at 100 °C, and crystallized from ethyl acetate–hexane as fine needles, 1.60 g, mp 119.5-121.0 °C (96%).[12] The latter recrystallized from acetonitrile had mp 167.5–172.5 °C (lit. mp 140–142,[4a] 145–146,[4c] 125–146,[4d] 119, 146,[4e] 138–141,[4f] 168–171 °C[10d]): IR (KBr) 5.92 (C=O), 9.34, 10.25 μm (C—O).[13] TLC: 121 °C crystals, 172 °C crystals and precipitated 1 (dried at 100 °C, without crystallization) all exhibited single spots (R_f 0.80; developing system $CHCl_3$–EtOAc–HOAc, 45:45:10, 2×) and were identical (cospot) with an authentic sample of chenodeoxycholic acid.[11]

Anal. Calcd for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found: C, 73,70; H, 10.60.

Acknowledgment. This work was supported by a National Cancer Institute (PHS) grant as part of the National Large Bowel Cancer Project program. Dr. James D. Henderson performed some preliminary experiments. Ms. Susan Brannan contributed able technical assistance.

Registry No. 1, 474-25-9; **1a**, 2616-71-9; **2c**, 28535-81-1; **3**, 76927-60-1.

(12) Calcd for $C_{24}H_4O_4 \cdot 0.2C_6H_{14}$: C, 73.48; H, 10.85. Found: C, 73.61; H, 10.74.

(13) D. H. Small in "The Bile Acids", Vol. I, P. P. Nair and D. Kritchevsky, Eds., Plenum Press, New York, 1971, p 259 (Table I).

Stereochemistry of the Conversion of Sulfoxides into Aminosulfonium Salts

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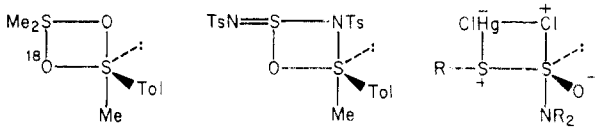
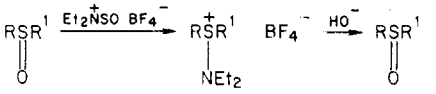
Received August 4, 1980

The mechanism of nucleophilic substitution reactions at the tricoordinate sulfur atom has been a subject of considerable interest for the past few years.[1] One of the most important questions is whether such reactions occur synchronously according to a S_N2-S mechanism or stepwise by an addition–elimination (A–E) mechanism involving a tetracoordinate sulfurane intermediate. The second, closely related problem concerns the relationship between the structure of a transition state or intermediate and the stereochemical course of nucleophilic substitution at sulfur. Since the first reported example of inversion at sulfinyl sulfur in the transesterification of chiral sulfinates,[2] numerous instances of nucleophilic substitution reactions have been demonstrated to occur with inversion of configuration at sulfur.[1] However, only in a few cases was the retention mechanism at tricoordinate sulfur observed. Oae et at.[3] found that chiral methyl *p*-tolyl sulfoxide containing ^{18}O exchanged oxygen with dimethyl sulfoxide without racemization, i.e., with retention. The retention of configuration was observed in the conversion of chiral sulfoxides into the corresponding sulfimides using *N*-sulfinyl-*p*-toluenesulfonamide,[4a] bis(*N*-tosylsulfurdiimine),[4b] and *p*-toluenesulfinylnitrene[4c] as reagents. Recently, the reaction of chiral amidothiosulfite with mercury(II) chloride leading to optically active aminosulfinyl chloride was shown to proceed with retention of configuration at the sulfinyl center.[5] It is believed that the formation in these reactions of the trigonal bipyramidal intermediates A, B, and C with the four-membered ring occupying the apical-equatorial position is the main factor responsible for the retention mechanism.[6]



A B C

In this paper we report that the conversion of sulfoxides into aminosulfonium salts by means of *N*-sulfinyldialkyl immonium salts—a reaction described recently by Kresze and Rössert[9]—is accompanied by retention and/or racemization at chiral sulfur, depending on the structure of the starting sulfoxide. We found that optically active sulfoxides (**1a–c**) gave the corresponding optically active aminosulfonium salts (**2a–c**) on treatment with *N*-sulfinyldiethylimmonium tetrafluoroborate (**3**). On the contrary, the reaction of optically active phenyl *p*-tolyl sulfoxide (**1d**) with **3** resulted in the formation of the salt **2d** which exhibited no measurable optical rotation.



1 2 1

a, R = Me, R^1 = *i*-Bu; **b**, R = Me, R^1 = *n*-Bu; **c**, R = Me, R^1 = *p*-Tol; **d**, R = Ph, R^1 = *p*-Tol

In order to establish the stereochemical course as well as the degree of stereospecificity of the **1** → **2** conversion, the base-catalyzed hydrolysis of aminosulfonium salts **2** was carried out. It gave back optically active sulfoxides **1a-c**, however, with the opposite sign of optical rotation to that of the starting **1**. Hydrolysis of **2d** gave completely racemic sulfoxide **1d**. The results of all experiments are collected in Table I.

Since alkaline hydrolysis of aminosulfonium salts has been demonstrated[10] to proceed with inversion of config-

(1) For a review see J. G. Tillet, *Chem. Rev.*, **76**, 747 (1976).

(2) H. Phillips, *J. Chem. Soc.*, 2552 (1925); M. Mikolajczyk, J. Drabowicz, and H. Slebocka-Tilk, *J. Am. Chem. Soc.*, **101**, 1302 (1979).

(3) S. Oae, M. Yokoyama, M. Kise, and N. Furukawa, *Tetrahedron Lett.*, 4131, (1968).

(4) (a) B. W. Christensen and A. Kjaer, *J. Chem. Soc.* D, 934, (1969); F. G. Yamagishi, O. R. Rayner, E. T. Zwicker, and D. J. Cram, *J. Am. Chem. Soc.*, **95**, 1916 (1973); (b) B. W. Christensen, *J. Chem. Soc. D*, 597, (1971); (c) T. J. Maricich and V. L. Hoffman, *Tetrahedron Lett.*, 5309 (1972); *J. Am. Chem. Soc.*, **96**, 7770 (1974).

(5) M. Mikolajczyk and J. Drabowicz, *J. Chem. Soc., Chem. Commun.*, 775 (1974).

(6) In this context, however, it is interesting to note that the alkaline hydrolysis of cyclic *cis*- and *trans*-1-ethoxy-3-methylthietanium salts proceeds with complete inversion at sulfur[7] in spite of the fact that the four-membered ring is present in the molecule. The formation of two intermediates, in which either entering and leaving groups occupy equatorial positions or the ring spans two equatorial positions with the leaving and entering groups axial, may account for inversion. The latter possibility is quite probable in view of the fact that the four-membered ring in the difluorosulfurane derived from thiacyclobutane has been shown by Denney[8] to occupy equatorial positions. Therefore, one can suppose that the four-membered rings containing heteroatoms (O, N, S) with their lone electron pairs show much higher preference for the apical-equatorial arrangement.

(7) R. Tang, and K. Mislow, *J. Am. Chem. Soc.*, **91**, 5644 (1969).

(8) D. B. Denney, D. Z. Denney, and Y. F. Hsu, *J. Am. Chem. Soc.*, **95**, 4064 (1973).

(9) G. Kresze, and M. Rössert, *Angew. Chem.*, **90**, 61 (1978); *Angew. Chem., Int. Ed. Engl.*, **17**, 64 (1978).

(10) O. Bohman, and S. Allenmark, *Chem. Scripta*, **4**, 202 (1973); C. R. Johnson and J. T. Rigau, *J. Org. Chem.*, **33**, 4340 (1968).

0022-3263/81/1946-2788$01.25/0