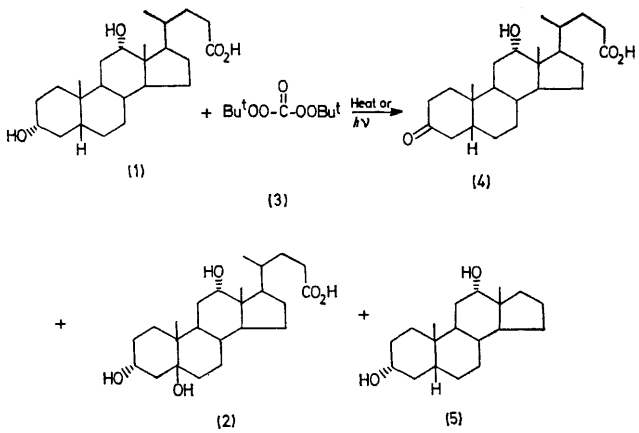
Reactions in Inclusion Molecular Complexes. A One-step Regiospecific and Stereospecific Hydroxylation of Deoxycholic Acid[1]

By NOGA FRIEDMAN, MEIR LAHAV,* LESLIE LEISEROWITZ,* RONIT POPOVITZ-BIRO, CHIA-PIN TANG, and ZEEV (V. I.) ZARETZKII†

(*Department of Structural Chemistry and †Department of Organic Chemistry, Laboratory for Mass Spectrometry, The Weizmann Institute of Science, Rehovot, Israel*)

Summary Solid-state thermolysis at 90 °C or photolysis at ambient temperature of the molecular complex of deoxycholic acid with di-t-butyl diperoxycarbonate leads to a one-step regiospecific and stereospecific hydroxylation at position 5 of the acid.

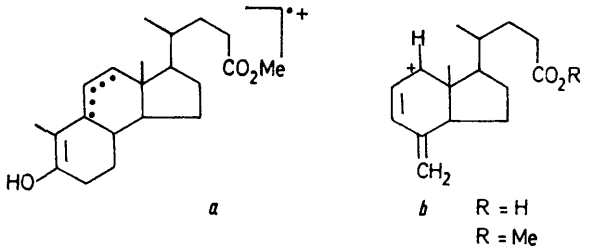
RECENTLY there have been various attempts to increase the power of synthetic chemistry by mimicking the enzymatic reactions of Nature.[2] In certain systems crystalline molecular complexes might be a convenient vehicle for such reactions, since in them, as in an enzyme, the geometrical contacts between reacting centres of guest and host are strictly defined. As models, we have investigated the solid-state functionalisation of steroids, which are known to form well defined complexes with a large variety of guest molecules.[3]



SCHEME

We report a one-step regiospecific and stereospecific hydroxylation of deoxycholic acid (**1**) which yields 3α,5β,12α trihydroxycholanic acid (**2**). A 4:1 molecular complex is formed by mixing (**1**) with stoicheiometric amounts of di-t-butyl diperoxycarbonate (**3**).[4] Heating of the complex at 90 °C for 120 h or photolysis with $\lambda > 300$ nm at 25 °C for 2 weeks leads to complete decomposition of the guest (i.r. analysis) followed by a reaction with the host to give two major products (**2**) (15%) and (**4**) (15%), and traces of (**5**)‡ (Scheme). After recycling the process, the yield of (**2**) could be doubled.

The structure of (**2**) follows from the high-resolution mass spectrum of its methyl ester: *m/e* (rel. int., %), 422(1) (M^+), 404(7) ($M - H_2O$), 386(51) ($M - 2H_2O$), 368(49) ($M - 3H_2O$), 115(40) [side chain (s.ch.) fragment[5]], 289(28) ($M - H_2O$ — s.ch.), 271(100) ($M - 2H_2O$ — s.ch.) 253(99) ($M - 3H_2O$ — s.ch.), 332(80) (ion *a*, characteristic of 5-hydroxy-steroids[6]), 261(69) (ion *b*, R = Me), and 247(50) (ion *b*, R = H). The intense formation of ion *b* is evidence



for the 5β-configuration in (**2**). Indeed, it was shown recently that while 3α,5β- dihydroxy-steroids eliminate ring A together with the C-6 atom, their 3α,5α- and 3β,5β-isomers do not exhibit such fragmentation. The 5β-configuration assignment of (**2**) is strongly supported by the 10-Me chemical shift (δ 0·87), which is 4 Hz upfield from 10-Me in deoxycholic acid.[7]

Compound (**4**) was identified as 3-oxo-12α-hydroxycholanic acid, by m.p. and mixed m.p. with an authentic sample.[8] Compound (**5**) was obtained in traces and identified by high-resolution mass spectrometry: *m/e* 292(1) (M^+), 274(40) ($M - H_2O$), 256(100) ($M - 2H_2O$), and 241(64) ($M - 2H_2O$ — Me). Compound (**2**) could not be detected when (**1**) was irradiated with as much as a three-fold excess of (**3**) in methanol solution.§

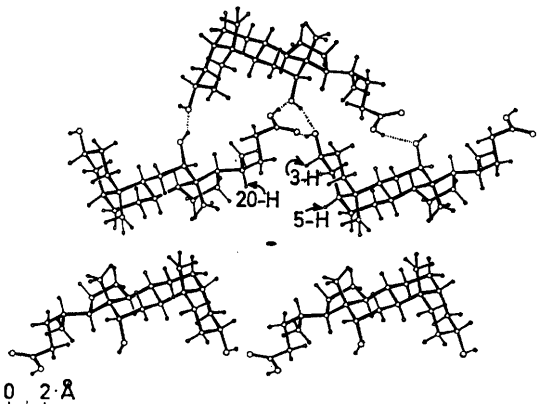


FIGURE. Host structure viewed along *c*. The inclusion channel in which the guest lies is clearly evident. The tertiary hydrogens 5-, 3-, and 20-H are labelled.

‡ 1—5 g samples were used. Products were separated by column chromatography on Kieselgel G with CH_2Cl–MeOH as eluant. Each compound was repurified by preparative t.l.c. (CH_2Cl_2–MeOH 9:1).

§ Oxidation of androstane di-acetate with di-t-butyl trioxide in MeCl at −30 °C is very unselective and leads to the formation of seven different oxidation products (M. Lahav, Y. Mazur, and R. Popovitz-Biro, unpublished results).

An *X*-ray crystal structure analysis of the complex was carried out at room temperature, on crystals obtained from MeOH. *Crystal data*:¶ $a = 27{\cdot}16$, $b = 13{\cdot}48$, $c = 14{\cdot}17$ Å, space group $P2_12_12$. The unit cell contains 8 molecules of (**1**) and 2 molecules of (**3**). The structure of the steroid fragment has been determined and refined, including its hydrogen atoms. The molecular structure compares most favourably with that of other reported deoxycholic acids.[9] However, the guest molecule has not yet been located presumably since it lies in the inclusion channel on a two-fold axis about which it is disordered. The hydrogen bonding structure of the steroid is similar to that of other reported deoxycholic acid complexes[9] (Figure). The host channel structure shows that only a limited number of tertiary hydrogens of the steroid (**3**-,**5**-, and **20**-H) lie on the inner wall of the channel and are thus exposed to the guest for abstraction; consequently only these sites are oxidised. The tertiary hydrogens at positions **12** and **14**, which are not exposed to the guest, remained unaffected by the oxidation process. The observation that the reaction takes place in the absence as well as in the presence of molecular oxygen suggests that the alcoholic oxygen is derived from the peroxy-ester.

Specific labelling of the oxygen atoms of the guest and a low-temperature *X*-ray diffraction study of this complex [to help locate the disordered guest (**3**) in the channel] are presently being undertaken.

We thank the Israel Academy of Science and Humanity for support, Professor Y. Mazur for discussions, and Professor M. D. Cohen for interest.

(*Received*, 30*th June* 1975; *Com.* 738.)

¶ There is reason to believe that the crystalline complex includes methanol which may complicate the crystal structure analysis.

[1] This work is part of the Ph.D. Theses of R.P.B. and C.P.T., to be submitted to the Feinberg Graduate School.
[2] R. Breslow, *Chem. Soc. Rev.*, 1972, **1**, 553; D. J. Cram and J. M. Cram, *Science*, 1974, **183**, 308.
[3] For a review on molecular inclusion complexes of deoxycholic acid see W. C. Herdon, *J. Chem. Educ.*, 1967, **44**, 724.
[4] For the synthesis of (**3**) and its solid-state photolysis see: M. M. Martin, *J. Amer. Chem. Soc.*, 1961, **83**, 2869; P. D. Bartlett and M. Lahav, *Israel J. Chem.*, 1972, **10**, 101.
[5] L. O. Severina, I. V. Torgov, G. K. Skrjabin, N. S. Wulfson, V. I. Zaretskii, and I. B. Papernaja, *Tetrahedron*, 1969, **25**, 485.
[6] A. Rotman, A. Mandelbaum, and Y. Mazur, *Tetrahedron*, 1973, **29**, 1303, J. Jovanovic and G. Spiteller, *ibid.*, p. 4017.
[7] In the 5α-hydroxy-derivative, the difference in chemical shift is generally +3·5 Hz compared to the unhydroxylated sample (N. S. Bhacca and D. H. Williams in 'Applications of N.m.r. Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964, p. 22 and references cited therein).
[8] B. Riegel and A. V. McIntash, Jr., *J. Amer. Chem. Soc.*, 1944, **66**, 1099.
[9] B. M. Craven and G. T. DeTitta, *J.C.S. Chem. Comm.*, 1972, 530; S. C. de Sanctis, E. Giglio, V. Pavel, and C. Quagliato, *Acta Cryst.*, 1972, **B28**, 3656.