When cholesterol-$[4\text{-}^{14}\text{C} + 7\beta\text{-}t]$ was used practically all the tritium remained in the cholic acid molecule. Mild oxidation of the isolated cholic acid to its 7-keto derivative resulted in complete loss of the tritium label. Consequently, 7α-hydroxylation involves displacement of the 7α-hydrogen with *at least* 93% and possibly complete specificity. The same stereochemical course has been observed for the hydroxylation of steroids at $C_{11}$, *i.e.*, displacement with retention of configuration.[8,9]

These data are reminiscent of the observation that hydroxylation of *cis*- and *trans*-decalin by ozone proceeds with retention of configuration to *cis*- and *trans*-9 hydroxydecalin, respectively,[10] and are in agreement with Bloom's evidence.[2] In addition, it seems relevant that *in chemical systems* electrophilic displacement at a saturated carbon atom has been found to occur preferentially with retention of configuration.[6a,11]

This work was supported by the National Institutes of Health (Grant H2842) and the Alfred P. Sloan Foundation.

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(8) M. Hayano, M. Gut and D. H. Peterson, private communication.

(9) E. J. Corey, G. A. Gregoriou and D. H. Peterson, THIS JOURNAL, **80**, 2338 (1958).

(10) J. R. Durland and H. Adkins, *ibid.*, **61**, 429 (1939).

(11) S. Winstein, T. G. Traylor and C. S. Garner, *ibid.*, **77**, 3741 (1955); S. Winstein and T. G. Traylor, *ibid.*, **77**, 3747 (1955), **78**, 2597 (1956).

DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY
UNIVERSITY OF LUND
LUND, SWEDEN
S. BERGSTROM
S. LINDSTREDT
B. SAMUELSON

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS
E. J. COREY
G. A. GREGORIOU

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## THE STEREOCHEMISTRY OF 11α-HYDROXYLATION OF STEROIDS

*Sir:*

The enzymatic hydroxylation of steroids at $C_{11}$, a reaction which is presently of considerable commercial and medical importance, is subject to the same sort of stereochemical analysis which has been utilized generally for the study of displacement reactions involving tetrahedral carbon, if the 11α- and 11β-hydrogens are differentiated isotopically.[1] The required stereospecific labelling has now been accomplished in the pregnane-3,20-dione series and the enzymatic 11α-hydroxylation by *Rhizopus nigricans* has been shown to proceed by *stereospecific* displacement of the *11α-hydrogen (or deuterium) substituent, i.e.*, with over-all retention of configuration.

Microbiological oxidation of pregnane-3,20-dione-11β-*d* containing one deuterium/molecule[2] was carried out with *Rhizopus nigricans* using the techniques previously described[3] and yielded 11α-hydroxypregnane-3,20-dione-11β-*d* containing 0.98 ± 0.02 deuterium/molecule. Similar oxidation of pregnane-3,20-dione-11α-*d* having additional deuterium at $C_9$ and $C_{12}$ and a total of 2.80 deuterium/molecule[4] resulted in complete loss of 11α-deuterium since the 11α-hydroxypregnane-3,20-dione which was produced possessed 1.77 deuterium/molecule.

Enzymatic hydroxylation of steroids at the 11β-[5] and 7α-positions[6] also has been found to proceed with retention of configuration, a course which, though under the control of specific enzymatic interactions as usual, may also be favored by the electrophilic nature of the displacing reagent.[6] All the data accumulated thus far[5,6] indicate a lack of hydrogen isotope effect on the rate of oxidation and permit an additional conclusion: either C–H bond rupture occurs after the rate determining step of the reaction or else chemical reaction is preceded by at least one slow physical step, *e.g.*, adsorption, which is insensitive to H isotope.

We take pleasure in thanking Mr. Josef Nemeth for the deuterium analyses, Dr. Robert Levin for gifts of steroids, and Mr. O. K. Sebek for experimental assistance and the Alfred P. Sloan Foundation for generous financial aid.

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(1) See E. J. Corey, M. G. Howell, A. Boston, R. L. Young and R. A. Sneen, THIS JOURNAL, **78**, 5036 (1956).

(2) Synthesized by the sequence: pregnane-3,11,20-trione → pregnane-3,11,20-trione-3,20-bis-ethylene ketal → pregnane-3,20-dione-11β-ol-11α-*d*-3,20-bis-ethylene ketal ($LiAlD_4$) → $\Delta^{9:11}$-pregnene-3,20-dione-11-*d*-($POCl_3$-$C_5H_5N$, followed by HOAc) → pregnane-3,20-diol-11β-*d* (Pt, $H_2$, HOAc followed by deacetylation with $LiAlH_4$) → pregnane-3,20-dione-11β-*d* ($CrO_3$-HOAc).

(3) D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, P. D. Meister and H. M. Leigh, *ibid.*, **74**, 5933 (1952).

(4) Prepared by the route: $\Delta^{9:11}$-pregnene-3,20-dione → $\Delta^{9:11}$-pregnene-3,20-diol ($LiAlH_4$) → pregnane-3,20-diol-9α,11α,12α-$d_{2.80}$ ($D_2$, DOAc, Pt) → pregnane-3,20-dione-9α,11α,12α-$d_{2.80}$ ($CrO_3$). The distribution of deuterium is probably: 9α:$d_1$, 11α:$d_1$ and 12α:$d_{0.8}$; see D. K. Fukushima and T. F. Gallagher, *ibid.*, **77**, 139 (1955).

(5) M. Hayano and M. Gut, private communication.

(6) S. Bergstrom, S. Linstedt, B. Samuelson, E. J. Corey and G. A. Gregoriou, *ibid.*, **80**, 2337 (1958).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS
E. J. COREY
G. A. GREGORIOU

RESEARCH DEPARTMENT
THE UPJOHN COMPANY
KALAMAZOO, MICHIGAN
D. H. PETERSON

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## CYCLIC 16α,17α-KETALS AND ACETALS OF 9α-FLUORO-16α-HYDROXY-CORTISOL AND -PREDNISOLONE

*Sir:*

9α-Fluoro-16α-hydroxy-cortisol and -prednisolone (triamcinolone) are potent glucocorticoids and anti-inflammatory agents devoid of salt retaining properties.[1] We have now found that certain cyclic 16α,17α-ketals[2] and -acetals derived from these steroids possess considerably greater glucocorticoid and anti-inflammatory activity than the parent compounds.

The cyclic derivatives are formed in excellent yield when a suspension of the steroid in the ketone or aldehyde[3] is agitated at room temperature with

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(1) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman and R. H. Blank, THIS JOURNAL, **76**, 5693 (1956).

(2) The preparation of the acetonide of triamcinolone was mentioned in a talk by Dr. Seymour Bernstein, Lederle Laboratories, at the Laurentian Hormone Conference, September, 1957.

(3) The acetaldehyde derivatives were prepared with paraldehyde. They were obtained in crystalline form only after acetylation and hydrolysis of the crystalline acetates.