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BASIC STUDIES OF STEROID HORMONE METABOLISM

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ABSTRACT

Calculations based on several established pathways leading from cholesterol to pregnenolone account for only a small fraction of the total, experimentally found, pregnenolone, when calculated for an obligatory 20- or 22-hydroxy intermediate. Re-evaluation of our kinetic data may provide reasons for keeping the model cholesterol $\rightarrow$ (22*R*)-22-hydroxycholesterol $\rightarrow$ (20*R*,22*R*)-20,22-dihydroxycholesterol. However, we pursue actively the synthesis of (20*S*)-cholesterol-20-hydroperoxide in order to get experimental data pro or contra this hypothetical intermediate.

Synthesis of Isotopically Labeled Steroids

Studies involving the biosynthesis, secretion rates, catabolic studies and the elaboration of micro-analytical procedures required the syntheses of numerous ^{14}C and ^3H labeled steroids which are commercially not available.

We have produced labeled (20*S*)-20-hydroxydesmosterol, (22*R*)-22-hydroxydesmosterol and (20*R*,22*R*)-20,22-dihydroxydesmosterol, as well as tritiated and carbon-14 labeled desmosterol. Desmosterol does serve as precursor of pregnenolone (*in vitro* experiments with acetone powder preparations from adrenal mitochondria), however neither cholesterol nor any of the three hydroxylated desmosterol derivatives serve as intermediates. These three hydroxylated desmosterol derivatives can be metabolized to pregnenolone.

The synthesis of (20*S*)-cholesterol-20-hydroperoxide is progressing slowly. All attempts to introduce -OOH via a C-20 carbocation failed, yielding only the *trans*- $\Delta^{20(22)}$ -cholesterol. A new approach, based on the hydroboration of the appropriate $\Delta^{17(20)}$ -cholesterol (the Δ^5 -double bond protected) has progressed to the 22-hydroxy- $\Delta^{17(20)}$ -analog.

Syntheses of Sterols with Potential Biological Activities

The stereospecific syntheses of the two epimeric 22-amino-cholesterols from the two known epimeric 22-hydroxycholesterols via tosylate $\rightarrow$ azide $\rightarrow$ amine have been accomplished. The epimeric mixture of these amines can be obtained by the reduction of 22-ketocholesterol oxime.

List of Publications

1. Burstein, S. and Gut, M. Kinetic studies on the transformation of cholesterol to pregnenolone in adrenal tissue. Proc. Third Internat. Cong., Hamburg, Sept. 1970. Excerpta Med. Internat. Series 219, p. 277.
2. Nickolson, R.C. and Gut, M. Stereospecific synthesis of (20*S*,22*R*)-17 α ,20,22-trihydroxycholesterol and (20*S*,22*S*)-17 α ,20,22-trihydroxycholesterol. J. Org. Chem., 37: 2119 (1972).
3. Burstein, S., Dinh, J., Co, N., Gut, M., Schleyer, H., Cooper, D.Y. and Rosenthal, O. Kinetic studies on substrate-enzyme interaction in the adrenal cholesterol side-chain cleavage system. Biochemistry, 11: 2883, 1972.