

of steroids with steroid hemi-dicarboxylic acid esters in the presence of *N,N'*-carbonyldiimidazole. This method was used for the preparation of several dimeric, trimeric, and one tetrameric estradiol derivative, and of some compounds containing estradiol and other steroids. Dimeric derivatives of ethynodiol, nortestosterone, and testosterone were also prepared. A trimeric compound consisting of 2 molecules of testosterone and 1 molecule androstenediol, and 2 other combinations of testosterone and androstenediol were obtained by allowing excess testosterone hemisuccinate to react with 5-androstene-3 $\beta$ , 17 $\beta$ -diol in the presence of *N,N'*-carbonyldiimidazole. The estradiol oligomers were found to have a rather protracted estrogenic effect in the Allen-Doisy test using rats. Dimeric ethynodiol proved to be a long-acting depot-progestagen when tested for its anti-estrogenic effect in rats. Dimeric testosterone was shown to have a period of effectiveness which equalled at least that of testosterone enanthate. (This study was supported in part by a grant from the WHO).

- 13. 6,7-methylenated steroids. Structure-activity relationships in the androgens and aldosterone antagonist series**  
ARTH, G. E., REYNOLDS, G. F., RASMUSSEN, G. H., CHEN, A., PATCHETT, A. A. and GLITZER, M. S., Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065, U.S.A.

The syntheses of 6,7-methylenated steroids in the testosterone and derived aldosterone antagonist series are described. Reaction of dimethyloxosulfoxonium methylide (DMSM) and 19-nor-4,6-dien-3-ones is reported for the first time and shown to yield a preponderance of the  $\alpha$  isomer in contrast to results obtained in the 19-methyl series. An explanation for these stereochemical results is discussed. The 6,7-methylene function is shown not to enhance androgenic or myotrophic activity. In contrast, evidence is presented which demonstrates that this function in the  $\beta$ -position is strongly activity-enhancing in the aldosterone antagonist series. The most interesting compounds resulting from the study are 3'-(6 $\beta$ ,7 $\beta$ -methylene-17 $\beta$ -hydroxy-3-oxo-1,4-androstadien-17 $\alpha$ -yl)propanoic acid lactone and salts therefrom, potent, orally active aldosterone antagonists, diuretics, and hypotensive agents, devoid of anti-androgenic activity at massive doses in rats. An hypothesis to explain the paradoxical "androgen-like" and "estrogen-like" clinical properties of spironolactone is offered.

- 14. New cardiac glycosides obtained by the glycol method**  
STACHE, U., FRITSCH, W., HAEBE, W. and RADSCHET, K., Farbwerke Hoechst AG, Frankfurt/Main, West Germany

Taking a range of cardiac-steroid aglycones of natural or synthetic origin as an example, the use of the so called "glycol" method for the synthesis of new kinds of highly active cardiac glycosides with previously unknown structures in the sugar component is illustrated in detail. Acid catalyzed treatment of digitoxigenin or 19-carboxymethylene-periplogenin-5 $\beta$ -lactone, a new partially synthesized cardiac steroid aglycone, with L- or D-diacetyl-rhamnal or triacetylglucal leads to the corresponding 2', 3'-dehydro-glycosides with the 3'-acetate group being eliminated and with simultaneous allylic rearrangement of the 1', 2'-double bond in the glycol moiety. In each instance the  $\alpha$ -anomers are obtained (n.m.r.-spectra). In addition,

with the aid of spectroscopic methods, an explanation is given of the conformational relationship in the sugar moiety of the newly synthesized 2', 3' dehydro glycosides and their secondary products obtained by functionalization of the 2', 3'-double bond (1. selective catalytic hydrogenation, 2. addition of HOBr and elimination of Br, 3. epoxydation) or some other modifications in the sugar moiety (1. reactions in the 6'-CH<sub>2</sub>OH group. 2. Introduction of amino groups). This is of decisive importance for structure-activity relationships.

- 15. Anti-inflammatory esters of steroidal carboxylic acids**  
BAIN, B. M., MAY, P. J., PHILLIPPS, G. H. and WOOLLETT, E. A., Glaxo Research Ltd., Greenford, Middlesex, England

Oxidation of the 17-dihydroxyacetone side chains of anti-inflammatory steroids with periodic acid gives the inactive 17 $\alpha$ -hydroxy-androstane-17 $\beta$ -carboxylic acids. Esterification either of the 17 $\alpha$ -hydroxyl or of the 17 $\beta$ -carboxyl does not generate useful anti-inflammatory activity, but esterification of both groups gives potent compounds showing high topical activity in the McKenzie vasoconstriction assay. Activity is comparable to that of the 17-esters and 17,21-diesters of normal corticoids. The best compounds are usually those with a 17 $\alpha$ -propionyloxy group and a 17 $\beta$ -methoxycarbonyl or halomethoxycarbonyl group. Fluoromethyl carboxylates appear to be a new class of compounds.

- 16. Synthesis of vitamin D<sub>3</sub> metabolites and their analogs**  
IKEKAWA, N., MORISAKI, M., SEKI, M., RUBIO-LIGHTBOURN, J. and SAWAMURA, M., Laboratory of Chemistry for Natural Products, Tokyo Institute of Technology, Meguro-ku, Tokyo, Japan.  
ISHIMOTO, S., YOSHIDA, T., TAKESHITA, T. and KATO, Y., Central Research Institute, Teijin Limited, Hino-shi, Tokyo, Japan

Fucosterol, an abundant sterol in brown algae, was converted to 24-hydroxycholesterol (I) via ozonolysis. Dehydration of I gave desmosterol which in turn was transformed to 24,25-dihydroxycholesterol (II) by oxidation with OsO<sub>4</sub>. A 1 $\alpha$ -hydroxy group was introduced into I and II affording 1 $\alpha$ ,24-dihydroxycholesterol (III) and 1 $\alpha$ ,24,25-trihydroxycholesterol (IV) by this sequence: (1) oxidation with DDQ; (2) epoxidation with H<sub>2</sub>O<sub>2</sub>-NaOH; and (3) reduction with Li-liq. NH<sub>3</sub>. Fractional crystallization or column chromatographic separation of benzoates of I, II, III and IV afforded epimers of C-24 (24R and 24S). After their absolute configuration at C-24 was determined, they were converted into the corresponding Vitamin D derivatives by the established procedures.

### 1C. Total and stereospecific synthesis of steroids

- 17. Total synthesis of 11 $\beta$ -methyl-19-norsteroids**  
GARLAND, R. B. and PAPPO, R., Department of Chemical Research, Searle Laboratories, a Division of G. D. Searle & Co., Chicago, Illinois 60680, U.S.A.

The Smith-Torgov synthesis is unsatisfactory for the direct total synthesis of 11 $\beta$ -methyl-19-norsteroids. Thus we have