6. Reactions of steroidal epoxides derived from 4, 5-, 5, 10- and 5, 6-enes

HORNING, E. C., THOMPSON, R. M. and LAU, S. S., Institute for Lipid Research, Baylor College of Medicine, Houston, Texas 77025, U.S.A.

Steroidal epoxides are of interest from several points of view. They may be metabolic intermediates formed from normal precursors or from steroidal drugs. Since epoxides are known to have cytotoxic, mutagenic, carcinogenic or teratogenic properties, this pathway is potentially hazardous. Routes of preparation (*m*-chloroperbenzoic acid) and separation (GC and t.l.c.), and reactions of epoxides from 4,5-, 5,10- and 5,6-enes will be compared. Possible metabolic pathways involving an epoxide include the aromatization of the A-ring and the formation of 10β-hydroxy metabolites from 19-nor-steroids.

7. Novel ^{75}Se-labelled steroids for use in saturation analysis

CHAMBERS, V. E. M., TUDOR, R. and RILEY, A. L. M., The Radiochemical Centre, Amersham, England

A new development in the radio-isotopic labelling of steroids for use in saturation analysis is described. For such analyses γ-emitting ^{75}Se-labelled steroids have proved to be novel practical alternatives to ^{125}I-labelled steroids. The methods for the preparation of alkylseleno- and diseleno-(^{75}Se) derivatives of several important steroidal hormones, including cortisol, testosterone and aldosterone are described. The structures of these compounds have been confirmed using chemical and spectroscopic techniques. The use of a ^{75}Se-labelled cortisol derivative in a competitive protein binding assay for cortisol is described. Some clinical results obtained with this assay are given.

8. Two novel syntheses of 18-hydroxy-deoxycorticosterone

GUZZI, U. and CIABATTI, R., Research Laboratories of Gruppo Lepetit S.p.A., Milano, Italy

18-Hydroxy-deoxycorticosterone has been synthesized by two different sequences of reactions. In both methods, the conversion of the 18-methyl to an 18-hydroxymethylene group was carried out by photolysis of the corresponding hypoiodite. In one case we started from 3β-hydroxy-5-pregnen-20-one acetate and in the other from 21-hydroxy-4-pregnene-3,20-dione acetate (DOCA). DOCA has not been used previously in the hypoiodite reaction. Identity of the synthetic product with an authentic sample was demonstrated by t.l.c., n.m.r. and mass spectroscopy.

1B. Synthesis of biologically active steroids and related compounds

9. Synthesis of biologically active D-homopregnanes

ALIG, L., FUERST, A., KELLER, P. and MUELLER, M., F. Hoffman-La Roche & Co. AG, Basle, Switzerland
KERB, U. and WIECHERT, R., Schering AG, Berlin, Germany

Various syntheses of a series of biologically active D-homo-pregnanes, starting from androstane derivatives, are described. The influence of the six-membered ring D on the steric course of some reactions at C-17a and on the elaboration of various pregnane side chains has been studied. A variety of reactions in rings A, B and C of D-homo-steroids and their steric implications have been investigated.

10. Synthesis of new D-homo-pregnanes

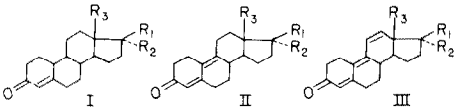
KERB, U., KIESLICH, K., PETZOLDT, K., WIECHERT, R., *FUERST, A. and *MUELLER, M., Schering AG, Berlin, Germany and *F. Hoffmann-La Roche & Cie. AG, Basle, Switzerland

The acid-promoted rearrangement of 16α, 17α-methylene-pregnenolone (1) provides a convenient synthesis of Δ^{17}-D-homo-pregnenolone (2), a key substance for the preparation of D-homo-progesterones and D-homo-corticoids. The ring enlargement reaction and the associated side reactions as well as the synthesis of various biologically-active D-homo-pregnanes from the D-homo-ketone (2) will be reported. Remarkable differences in the chemical reactivity and microbiological 11-hydroxylation of D-homo steroids as compared to normal D-C_5 ring steroids have been observed.

11. Active steroids without a 17-hydroxyl function. Synthesis of a new class of progestomimetic agents devoid of androgenic activity

BUCOURT, R., NEDELEC, L., GASC, J. C., ROUSSEAU, G., PHILIBERT, D. and TOURNEMINE, C., Centre de Recherches Roussel-Uclaf, Romainville, France

A new class of 19-nor steroids having an ethinyl group at C-17 but lacking the classical hydroxyl function at the same position have been prepared in three related series: the series of 19-nor testosterone I, and the dienic and trienic analogous series II and III.



a $R_1 = H, R_2 = -C\equiv CH, R_3 = -CH_3$
b $R_1 = -C\equiv CH, R_2 = H, R_3 = -CH_3$
c $R_1 = -C\equiv CH, R_2 = H, R_3 = -C_2H_5$

These new compounds retained the progestomimetic activity of 17α-ethinyl 17β-hydroxy 19-nor testosterone and lost its androgenic effect. There is one exception for compound Ia which still shows the same androgenic activity as the 17β-hydroxy compound. Thus, in this latter case, the 17β-hydroxyl function seems to have no physiological significance. The same phenomenon was also observed in a pure androgenic series: IIIa, with a methyl group ($R_2 = CH_3$) instead of the ethinyl, is a potent androgen.

12. A new class of long-acting hormonal steroid preparation: synthesis of oligomeric steroid derivatives

KUHL, H. and TAUBERT, H.-D., Abteilung für gynäkologische Endokrinologie, Zentrum der Frauenkrankheiten und Geburtshilfe, J. W. Goethe Universität, Frankfurt/Main, F. R. Germany

The synthesis of oligomeric steroid esters can be achieved by condensation of 2 or 3 steroid molecules with a dicarbonic acid by direct esterification of the hydroxy-group

of steroids with steroid hemi-dicarbonic 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-3β, 17β-diol in the presence of N,N′-carbonyldiimidazole. The estradiol oligomeres 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., RASMUSSON, 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 dimethyoxosulfoxonium methylide (DMSM) and 19-nor-4,6-dien-3-ones is reported for the first time and shown to yield a preponderance of the α 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 β-position is strongly activity-enhancing in the aldosterone antagonist series. The most interesting compounds resulting from the study are 3′-(6β,7β-methylene-17β-hydroxy-3-oxo-1,4-androstadien-17α-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 glycal method
STACHE, U., FRITSCH, W., HAEDE, W. and RADSCHEIT, 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 "glycal" 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-5β-lactone, a new partially synthesized cardiac steroid aglycone, with L- or D-diacetylrhamnal 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 glycal moiety. In each instance the α-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_2OH 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 17α-hydroxy-androstane-17β-carboxylic acids. Esterification either of the 17α-hydroxyl or of the 17β-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 17α-propionyloxy group and a 17β-methoxycarbonyl or halomethoxycarbonyl group. Fluoromethyl carboxylates appear to be a new class of compounds.

16. Synthesis of vitamin D_3 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_4. A 1α-hydroxy group was introduced into I and II affording 1α,24-dihydroxycholesterol (III) and 1α,24,25-trihydroxycholesterol (IV) by this sequence: (1) oxidation with DDQ; (2) epoxidation with H_2O_2-NaOH; and (3) reduction with Li-liq. NH_3. 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 11β-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 11β-methyl-19-norsteroids. Thus we have