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

devised a synthesis which produced d,l-11β-methylestradiol-3-methyl ether in seven steps from 6-methoxy-1-tetralone. The key steps are the reaction of N-(2-(6-methoxy-3,4-dihydronaphthyl)propene-3-yl)trimethyl ammonium iodide with a salt of 2-methylcyclopentane-1,3-dione to produce 3-methoxy-11-methylene-8,14-secoestra-1,3,5(10),8,14-pentaene-17-one. After hydride reduction catalytic hydrogenation resulted in the uptake of 2 mol of hydrogen yielding predominately d,l-3-methoxy-11β-methylestra-1,3,5(10),8-tetraene-17β-ol. A sodium, aniline and ammonia reduction completed the synthesis. This synthesis is applicable to the preparation of 18-homologs of 11β-methylestradiol-3-methyl ether.

18. The total synthesis of 12-methyl-19-nor-steroids

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The total synthesis and structure determination of steroids incorporating the 12α-methyl-and 12β-methyl-19-nor moieties will be presented. Extension of the "Torgov Reaction" to the use of a propenyl carbinol in place of the normal vinyl carbinol gave two isomeric tetracyclic pentaenes, in a ratio of approximately 3:1, in rather low yield. These could be separated by chromatography and subjected to further reactions. Physical chemical investigations of the products using, in particular, n.m.r. and ultimately X-ray crystallography, indicated that the major isomer possessed the additional methyl group in the 12α stereochemistry. This new steric environment was seen to have a dramatic effect on the sterochemical outcome of the subsequent transformations and also to influence the reactivity of the neighbouring 17-carbonyl group. A further interesting finding of biological significance was that hormonal properties were modified, the 12α-methyl A-ring aromatic compound for example being devoid of estrogenic activity at a dose of 1000 μg in the standard rat assay.

19. The total synthesis of 2-azaestratrienes

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The interesting biological properties of (+)-2-azaestrone-3-methyl ether and its derivatives prompted work on the total synthesis of this series. Treatment of dihydroresorcinol with phosphorus trichloride produced 3-chloro-cyclohex-2-enone, which upon condensation with cyanoacetamide gave 3-(cyanoacetamido)cyclohex-2-enone. A one step reaction with dimethyl formamide diethyl acetal afforded the bicyclic product, 2,3,5,6,7,8-hexahydro-3,8-dioxo-4-isoquinolinecarbonitrile. Removal of the nitrile group with aqueous hydrobromic acid followed by alkylation with methyl iodide gave 7-aza-6-methoxy-1-tetralone, a key intermediate in the synthesis of 2-azaestratrienes. The three-step Torgov sequence gave the azasteroid skeleton which underwent desired catalytic hydrogenation of the 14,15-double bond. Chemical reduction of the tetrasubstituted double bond was accompanied by reduction of the aromatic ring. Subsequent treatment with DDQ produced (±)-2-aza-estradiol-3-methyl ether.

20. Total synthesis of the 8-azasteroids

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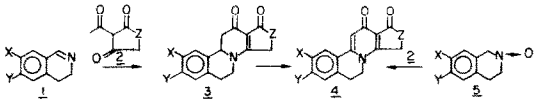
A simple method for the synthesis of heteroanalogs of steroids derived from azaestrane based on the reaction of dihydroisoquinolines 1 with triacylmethanes 2 was developed, compounds 3 with 50–70% yields thus being prepared. Condensation of 2 with N-oxide 5 leads to heterosteroids 4 identical to the products of dehydrogenation of 3. Compounds 3 and 4 and their derivatives are of pharmacological interest.



X,Y = H, OH, OMe; Z = CH_2, O NH

21. Stereospecific reduction of C = C bonds in steroids

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With the objective of preparing isomeric estrone and D-homoestrone methyl ethers we have studied hydrogenation of their $\Delta^{8(9)}$, $\Delta^{9(11)}$, $\Delta^{8(9),14(15)}$-dehydroderivatives and the stereochemistry of the reaction products. The double bond reduction was carried out either catalytically (with hydrogen gas or with isopropanol as hydrogen donating agent) or by ionic hydrogenation with triethylsilane in acidic medium. As a result we obtained 8α-; 9β-; 13α; 14β-; 8α,9β- and 9β,14β-methyl ethers of estrone and D-homoestrone. Employing ionic hydrogenation of $\Delta^{8(9)}$-dehydroestradiol we have worked out a new procedure for preparing D,L-estradiol. The total yield of the hormone was 37% with respect to the starting 6-hydroxytetralone.

22. Stereospecific synthesis of the 24-epimeric 5α-stigmast-22-en-3β-ols and 5α-stigmastan-3β-ols

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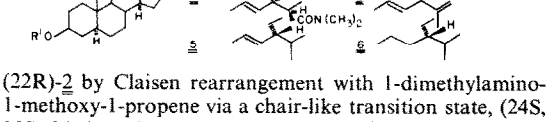
In a program to synthesize stereospecifically naturally occurring sterols, the epimeric title compounds 5 and 6 have been obtained starting from 3β-acetoxy-22,23-dinorcholanaldehyde 1 (preparation described) which was converted to 2 with butynyl magnesium bromide and Lindlar hydrogenation, the epimers being separated chromatographically. (24S, 25R)-3 was prepared from



(22R)-2 by Claisen rearrangement with 1-dimethylamino-1-methoxy-1-propene via a chair-like transition state, (24S, 25S)-3 being a by-product. The two can be reduced without separation and the amines subjected to Cope degradation to give pure (24S)-4, which by stepwise hydrogenation gave (24R)-5 and (24S)-6. The epimeric compounds were likewise obtained.