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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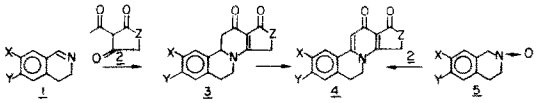
A simple method for the synthesis of heteroanalogs of steroids derived from azaestrane based on the reaction of dihydroisoquinolines 1 with triacylmethanes 2 was developed, compounds 3 with 50–70% yields thus being prepared. Condensation of 2 with N-oxide 5 leads to heterosteroids 4 identical to the 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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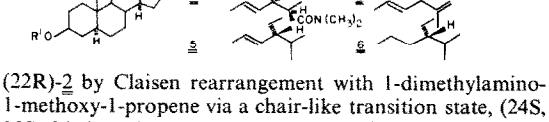
In a program to synthesize stereospecifically naturally occurring sterols, the epimeric title compounds 5 and 6 have been obtained starting from 3β-acetoxy-22,23-dinorcholanaldehyde 1 (preparation described) which was converted to 2 with butynyl magnesium bromide and Lindlar hydrogenation, the epimers 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.