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SYNTHESIS OF A STEROIDAL CYCLOPROPANOL

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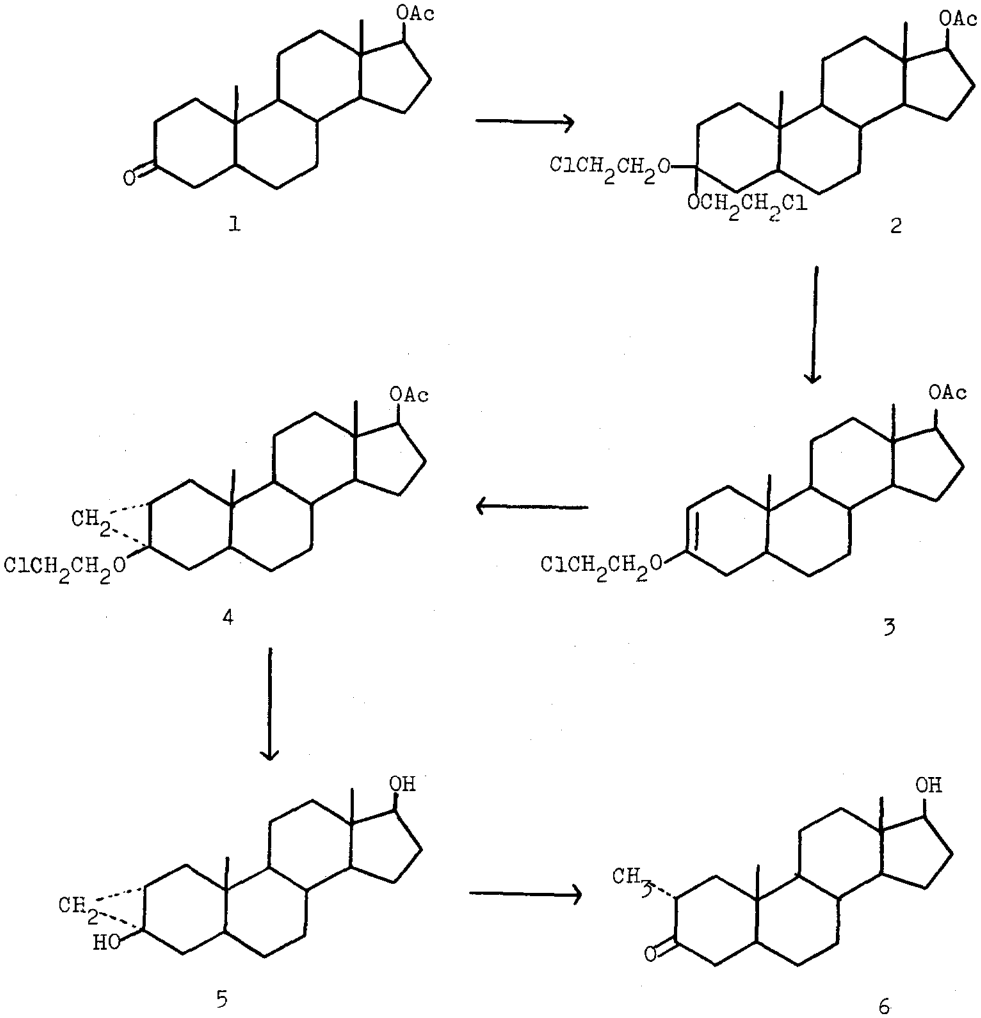
Recently a number of synthetic methods have been developed for the preparation of cyclopropanol derivatives[1,2]. However, none are readily applicable to the formation of a fused cyclopropanol ring containing an existing oxygen atom of a parent molecule. Although some steroidal cyclopropane ether derivatives have been prepared by dihalocarbene addition to an enol ether[3,4], these substances can not be converted into a halogen free cyclopropanol.

Steroidal 3-ketones are readily converted into the corresponding acetal derivatives[5a]. Azeotropic removal of water from a solution of 17-acetoxy-5α-androstan-3-one(1) in 10% v/v 2-chloroethanol in dry benzene containing 0.1% w/v p-toluenesulfonic acid gave 17β-acetoxy-3,3-bis(2-chloroethoxy)-5α-androstane (2) m.p. 94-5° $[\alpha]_D$ + 11° ($CHCl_3$). Pyrolysis of 3-dimethoxysteroid acetals gives the 2,3-unsaturated enol ether[6]. Pyrolysis of the acetal(2) at reduced pressure yielded the 2-chloroethoxy enol ether(3) m.p. 130-131°, $[a]_D$ + 44° ($CHCl_3$). Treatment of the crude pyrolysis product with an excess of the Simmons-Smith reagent[7] gave the 2-chloroethoxycyclopropane ether(4) m.p. 129-130°, [α] + 23° ($CHCl_3$). Normal addition to the steroidal 2,3-double bond occurs from the α-face[5b].

Schollkopf[1] has shown that removal of the 2-chloroethyl group readily occurs with n-butyl lithium. Brief treatment of 4 with excess n-butyl lithium at room temperature yielded the heat labile product 2β,3-dihydro-2'H-cyclopropa [2,3]-5α-androstan-3β,17β-diol(5) m.p. 145-155°, $[\alpha]_D$ + 18° (dioxane) as a hemihydrate. The melting point is dependent upon the rate of heating. The product showed only one substance on thin layer chromatography (four systems). Material from



OAc
O
1
OAc
ClCH$_2$CH$_2$O
OCH$_2$CH$_2$Cl
2
OAc
ClCH$_2$CH$_2$O
3
OAc
CH$_2$
ClCH$_2$CH$_2$O
4
OH
CH$_2$
HO
5
OH
CH$_3$
O
6

a melt showed two substances on t.l.c. corresponding to the starting material(5) and 17β-hydroxy-2α-methyl-5α-androstan-3-one(6). Gas liquid chromatographic analysis of 5 gave one peak corresponding to 17β-hydroxy-2α-methyl-5α-androstan-3-one(6). The infrared spectrum of 5 showed cyclopropyl C-H stretching, strong hydroxylic and no carbonyl absorption. The proton magnetic resonance spectrum had high field signals characteristic of cyclopropyl C-H resonance.

Treatment of 5 with dilute methanolic potassium hydroxide gave 17β-hydroxy-2α-methyl-5α-androstan-3-one(6) identified by mixed melting point and infrared spectrum. This compound demonstrates that addition of methylene occurred to the 2,3-double bond.

All reactions gave yields of 50-60%. All of the above substances showed spectroscopic properties (IR, PMR, MS) and elemental analyses (C,H) consistent with the structures indicated.

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REFERENCES

1. U. Schollköpf, Angew.Chem.Internat.Edn., 7, 588 (1968).
2. C.H. DePuy, Accounts of Chem.Res., 1, 33 (1968).
3. A.B. Font, Bull.Soc.Chim.(Fr.), 419 (1964).
4. G. Stork, M. Nussim and B. August, Tetrahedron, Supp. 8, 105 (1966).
5. D.N. Kirk and M.P. Hartshorn, "Steroid Reaction Mechanisms", 1968, Elsevier Publishing Company, Amsterdam. (a) p.130 (b) ch. 3.
6. G. Karmas, J.Org.Chem., 33, 2436 (1968).
7. H.E. Simmons and R.D. Smith, J.Am.Chem.Soc., 81, 4256 (1959).