Tetrahedron Letters No.42, pp. 3697-3698, 1969. Pergamon Press. Printed in Great Britain.

# A NEW APPROACH TO THE TOTAL SYNTHESIS OF STEROIDS

U.K. Pandit*, F.A. van der Vlugt** and A.C. van Dalen,
Laboratory of Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, Amsterdam, The Netherlands.

(Received in UK 16 July 1969; accepted for publication 11 August 1969)

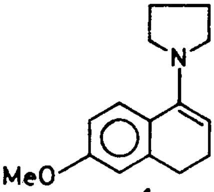
The simple three-step conversion of 6-methoxytetralone-1 to $\Delta^{8,14}$-steroids (5), initially developed by Torgov et.al.[1], has proved to be a versatile approach for the synthesis of natural estrogenic hormones or their ring A or B modified analogues[2]. In connection with our studies on the enamines derived from α-tetralones we have found that the corresponding iminium salts serve as valuable precursors for a convenient alternate route to 5. This communication present the transformation of enamine 1 to 8,14-bis-dehydroestrone methyl ether (5).

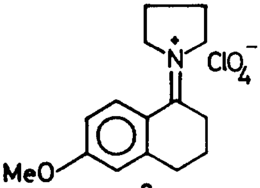
1-Pyrrolidyl-6-methoxy-3,4-dihydronaphthalene (1) was obtained from 6-methoxytetralone-1, in 80 p.c. yield, by the method of White and Weingarten[3]. Its structure followed from its IR ($\nu_{max}^{neat}$ 1615, N-C=C) and NMR ($\delta^{CDCl_3}$ 5.01, t, 1H, C=C-H, J=5 c/s). Treatment of 1 with $HClO_4$ in glacial acetic acid gave crystalline perchlorate 2 (80-90 p.c.), which could be stored under nitrogen without deterioration.

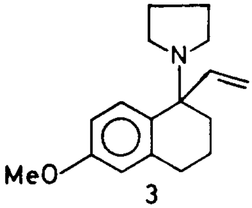
Addition of 2 to a ten-fold excess of vinylmagnesium bromide, in tetrahydrofuran, resulted in the formation of allyl amine 3, as an oil, in 82 p.c. yield (based upon recovered tetralone). Structure of 3 was attested by its spectral data and confirmed by conversion of the oily amine to its picrate, m.p. 103-104°. Found : C, 56.81; H, 5.49; N, 11.40. $C_{23}H_{26}N_4O_8$ requires : C, 56.78; H, 5.39; N, 11.52.

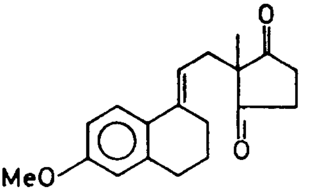
When a mixture of 2-methylcyclopentanedione-1,3 and allyl amine 3, in methanol, was refluxed for 16 hours, the seco-steroid 4 was formed in 80 p.c. yield. While no effort was spent on isolating 4 in its crystalline form, the IR and NMR spectra of the product were idential to those of a sample of 4 prepared according to the procedure of Ananchenko and Torgov[1]. Conventional acid-catalyzed cyclization of 4 gave the known 8,14-bisdehydroestrone methyl ether 5, m.p. 108-110°.

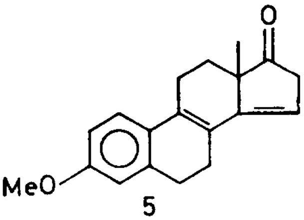
The condensation of methylcyclopentanedione with allyl amine 3 may follow the mechanism suggested for the analogous reaction with the corresponding allyl alcohol[4]. In the present case this would involve protonation of the amine by the di-


1

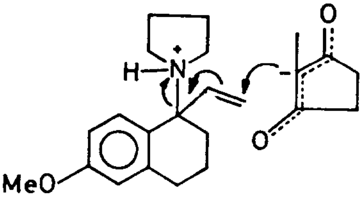

2

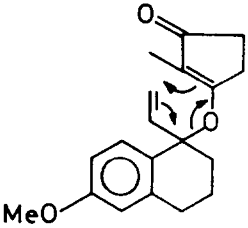

3


4


5

ketone, acting as an acid, to give presumably the ion-pair system 6, which collapses by an $SN_2$' displacement of pyrrolidine. An alternate mechanism[5] in which allyl ether 7 - initially formed from 3 and methylcyclopentanedione - undergoes a sigmatropic rearrangement under conditions of the reaction, to form 4, cannot, however, be excluded.


6


7

Acknowledgement :

We thank Professor Dr H.O.Huisman for his interest and encouragement.

* To whom all correspondence should be addressed.

** Taken in part from the forthcoming doctorate dissertation of F.A.van der Vlugt.

References :

1. S.N.Ananchenko and I.V.Torgov, Tetrahedron Letters, 1553 (1963)
2. (a) H.O.Huisman, Bull.Soc.Chim.Fr. 13 (1968); (b) J.H.Burckhalter and F.C. Sciavolino, J.Org.Chem., 32, 3968 (1967)
3. W.A.White and H.Weingarten, J.Org.Chem., 32, 213 (1967)
4. D.P.Strike, T.Y.Jen, G.A.Hughes, G.H.Douglas and H.Smith, Steroids, 8, 309 (1966)
5. This mechanism was suggested to the authors by Prof.Dr H.Schmid, University of Zürich, at the "Symposium on Heterocyclic Chemistry", sponsored by the Netherlands Foundation for Chemical Research (S.O.N.); Lunteren, The Netherlands, May 12-13 (1969).