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THE CLEMMENSEN REACTION OF TIGOGENIN. A REINVESTIGATION[1].

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Summary: The reaction of tigogenin (1b) with amalgamated zinc yields tetrahydrotigogenin (2b) and the furostan 3. While 2b undergoes acid catalyzed elimination to give the rearranged product 7, 3 spontaneously decomposes to a mixture of 4 and 5.

One of the early evidences in favor of the presence of a spiroketal system in some steroidal sapogenins was provided by the study of the Clemmensen reaction which gives, in all cases so far investigated, a tetrahydroderivative[2]. Thus, diosgenin (1a) gave the triol 2a which could be correlated with cholesterol establishing in this manner the stereochemistry of 1a including the α orientation of the methyl group at C$_{20}$[3]. Eventhough 2a could be reduced to tetrahydrotigogenin (2b, mp. 195-7°)[3] the latter could not be obtained by Marker by the Clemmensen reduction of tigogenin (1b) itself. Under forcing conditions 1b was reported to give a low yield of an unidentified compound (C$_{27}$H$_{46}$O$_2$, mp. 152°)[4]. More recently however the formation of 2b from 1b was reported.[5]

In our hands when 1b was allowed to react with amalgamated zinc in acid medium[2] and the reaction stopped when ~70% of 1b had been consumed, two main unstable products could be detected by thin layer chromatography[6]. These were separated and identified as the triol 2b (∿63%) and the furostan 3 (∿37%)[7].

Compound 3 could not be obtained pure. Attempts to purify it by column chromatography using silica gel, always yielded fractions containing 3 and a mixture of the olefin-triols 4 and 5. Support for the structure of 3 was provided by analysis of the ^{13}C NMR spectrum of a mixture containing ∿75% of 3 and ∿25% of 4 + 5 and by observing the spontaneous and almost quantitative transformation (>95%) of mixtures containing 3, 4 and 5 in 4 + 5 only (vide infra).

In the ^{13}C NMR spectrum of 3 C$_{22}$ appeared at 90.1 ppm while C$_{16}$ resonated at 83.2 ppm (73.1 ppm in 2b[7]) thus strongly suggesting that the ether bond C_{16}-O-C_{22} was intact[8]. Further support for the presence of the tetrahydrofuran moiety in 3 was obtained by noting that the above spectrum was almost completely superimposable on that of the furostan 6 made by catalytic hydrogenation of 1b.[4,9]

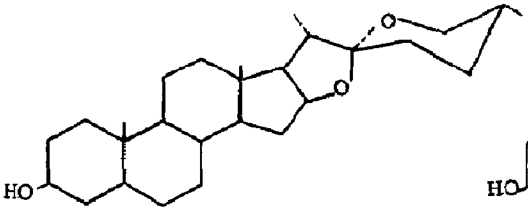
While a $CHCl_3$ solution of 6 remains almost unchanged for several weeks at room temperature, a similar solution of 3 (containing $\sim$20% of 4 + 5) gave after two weeks a quantitative yield (>95%) of 4 + 5. The latter mixture could not be separated by the normal low pressure chromatographic procedures but their spectral and chemical properties are in complete agreement with the structures as proposed. The IR spectrum showed bands at 1695, 1305, 990 and 971 cm^{-1} suggesting the presence of *trans* disubstituted olefins. The ^1H NMR spectrum showed, besides a multiplet at 4.20 ppm (H-16), another multiplet centered at 5.45 ppm (2H) and the absence of methyls on a double bond thus locating the unsaturation between C_{22} and C_{23} and/or C_{23} and C_{24}. In the ^{13}C NMR spectrum, C_{16} appeared at 73.4 ppm while a doublet at 71.6 ppm and two triplets at 68.1 and 67.7 ppm were attributed to C_3 and C_{26} of both isomeric olefins respectively. The olefinic carbons were doublets at 140.2, 138.5 and 127.9 ppm, the width of the latter clearly indicating superposition of two signals.[10] Further, catalytic hydrogenation of 4 + 5 gave exclusively 2b, identical in all respects with that obtained by the Clemmensen reduction of 1b.

This latter finding strongly suggests that the absolute configuration at C_{20} in 4 and 5 is identical with that of 2b, that is R as depicted. On the other hand, assuming no changes around C_{20} during the formation of 4 and 5 from 3, we may assign the absolute configuration at C_{20} in 3 as being S as shown. The same configuration (S) at C_{20} is also found in 6^{9b}. Since 3 and 6 have identical configuration at C_{20} but differ greatly in reactivity as we have shown, we suggest that the difference in stability is due to them having opposite configuration at C_{22}. Knowing that the latter is R in 6^{9b}, it follows that C_{22} in 3 is S as depicted.[11] These assignments suggest that the origen of the observed unstability of 3 is due to eclipsing of the methyl group at C_{20} and the bulkier group attached to C_{22}.[12]

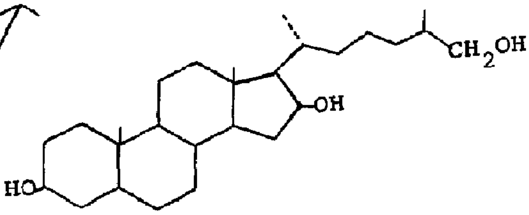
The identification of 2b and 3 as the primary products of the Clemmensen reaction of 1b and the demonstration that 3 yields 4 and 5, indicated that the unidentified product isolated by Marker[4] (vide supra)was derived from 2b. In fact, treatment of the latter with p-toluenesulfonic acid in benzene under reflux gave an excellent yield of 7 (mp 152-3°). As expected, the most abundant fragment in its mass spectrum appeared at m/e 273 resulting from the allylic cleavage of the C_{17}-C_{20} bond. The ^1H NMR spectrum did not show signals for olefinic protons nor for H-16 but the methyl at C_{17} appeared at 0.98 ppm and the C_{20}-CH_3

suffered an upfield shift resonating at 0.71 ppm. These latter assignments definitely located the double bond between C_{13} and C_{14}. The ^{13}C NMR spectrum further supported the structure of 7 showing two olefinic carbons as singlets at 140.6 and 137.9 ppm while the signal corresponding to C_{16} had disappeared from the low field region.[13]

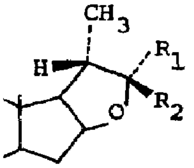
The facile conversion of 3 into 4 and 5 seems an appropiate starting point for the search of alternative synthetic procedures for the obtention of the increasingly important C_{22} and C_{23} alcohols[14] such as the recently identified plant growth promoter brassinolide (8)[15].



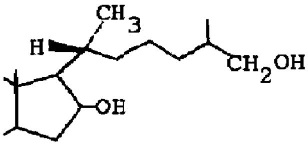
1a, 5,6-dehydro
1b, 5α,6-dihydro



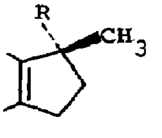
2a, 5,6-dehydro
2b, 5α,6-dihydro



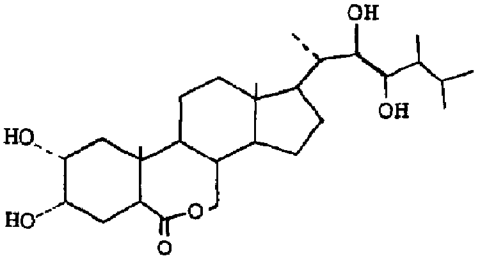
3, $R_1 = C_5H_{11}O$; $R_2 = H$
6, $R_1 = H$; $R_2 = C_5H_{11}O$



4, $\Delta^{22,23}$
5, $\Delta^{23,24}$



7, R = $C_8H_{17}O$



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REFERENCES AND NOTES

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3. R.E. Marker and D.L. Turner, J. Am. Chem. Soc., 63, 767 (1941).
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5. R. Tschesche, Y. Saito and A. Töpfer, Tetrahedron Letters, 967 (1974).
6. It usually took 5 to 6 hours for the reaction to get to this stage. Longer periods of time resulted in the appearance of many secondary products suggesting the relative sensitivity of the primary products to acids.
7. All compounds reported gave analytical data in complete agreement with the structures as proposed. Compound 1b: mp 196-8^0; ^{1}H NMR (100 MHz, $CDCl_3$) δ 4.30 (1, m, H-16), 3.67 (1, m, H-3), 3.47 (2, d, J = 6 Hz, H_2-26), 1.54 (3, broad s, C_3, C_{16} and C_{26} hydroxyls), 0.97 and 0.91 (3 each, d, J $\sim$6 Hz, C_{20}-CH_3 or C_{25}-CH_3), 0.86 and 0.82 (3 each, s, C_{10}-CH_3 or C_{13}-CH_3); ^{13}C NMR (25.2 MHz, $CDCl_3$) δ 73.1 (d, C_{16}), 71.9 (d, C_3), 68.9 (t, C_{26}).
8. In 1b C_{22} and C_{16} appear at 109.0 and 80.7 ppm respectively. H. Eggert and C. Djerassi, Tetrahedron Letters, 3635 (1975).
9. a) G.R. Pettit and W.J. Bowyer, J. Org. Chem., 25, 84 (1960).
   b) A.H. Albert, G.R. Pettit and P. Brown, J. Org. Chem., 38, 2197 (1973).
10. Calculated values for the olefinic carbons are 138.6 and 129.6 ppm for C_{22} and C_{23} of 4 and 128.1 and 140.1 ppm for C_{23} and C_{24} of 5. G.C. Levy and G.L. Nelson in "C-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, N.Y., 1972, ch. 3.
11. This result is most interesting as it sheds some light into the possible mechanism of the Clemmensen reaction. It suggests that the formation of the organometallic intermediate and the transfer of the proton to C_{22} (probably from the solvent) occur from opposite sides. Since the metal most likely attacks the oxonium ion at C_{22} (resulting from the acid catalyzed opening of ring F) from the α face, the orientation of the proton in the final product is β.
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