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THE EFFECT OF CO-SOLVENTS ON METAL IN AMMONIA REDUCTIONS. THE FORMATION OF DIMERIC STEROID HORMONES[1]

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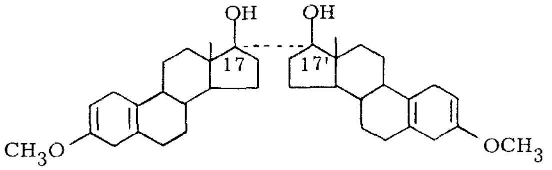
The reduction of organic compounds by metals in liquid ammonia in the presence of a proton source has become a major synthetic tool in recent years.(2, 3, 4) Of particular importance is the reduction of aromatic substrates first described by Wooster(5) and later extensively developed by A. J. Birch and his collaborators. Special recognition is also due Wilds and Nelson(6) for introducing a practical laboratory procedure involving the use of lithium. The majority of the numerous papers dealing with this reaction stresses the necessity of employing a co-solvent such as ether, dimethoxyethane, tetrahydrofuran or dioxane in order to improve the poor solubility properties of ammonia at -34° for many organic compounds. These agents have generally been considered to be inert and of no consequence on the course of the reaction. While this is probably true for most reductions involving the aromatic nucleus,(7) this view requires serious modification as far as the reduction of the carbonyl group is concerned. We have found that the exact nature of the "co-solvent" can have a decisive influence on the composition of the reaction products. Such an effect was first observed when the reduction of estrone methyl ether was conducted in a medium containing 10 parts of ammonia and 3 parts of ether(8) and there was isolated in addition to the expected 3-methoxy-$\Delta^{2,5(10)}$-estradiene-17β-ol a 30% yield of a more insoluble substance, m.p. 238-241°; $[\alpha]_D$ +112°;(9) λ_{max}^{KBr} 2.70 (OH), 5.88 and 5.98μ (enol ether);



I

Anal: Calcd. for $C_{38}H_{54}O_4$: 79.40; H, 9.47. Found: C, 79.33, H, 9.44; shown to be the pinacol (I) resulting from Birch reduction of ring A and reductive coupling of two steroid molecules at C17, on the basis of its mass spectrum,(10) (M^+ = 574), and the fact that the hydroxyl groups present in the molecule were resistant to acetylation. The n.m.r. spectrum of I showed signals identical with those for the monomeric reduction product at 279 c.p.s.(11) (vinyl protons), 213 c.p.s. (OCH_3) and 160.5 c.p.s. (C_1 and C_4 protons), but not for the 18 CH_3-group, which appeared at 55 c.p.s., 8 c.p.s. downfield with respect to the corresponding signal for the monomer. An identical chemical shift for the 18 CH_3-group (55.1) has been reported for 17α-methyl-testosterone.(12) Because of this correspondence in chemical shifts and of the well-known fact that bulky reagents approach C17 from the α-side the 17,17'-dimers are formulated as possessing the α, α'-attachment.

Hydrolysis of the enol ether I with acetic acid in dioxane at room temperature gave the dimeric $\Delta^{5(10)}$-3-ketone (II), m.p. 269-273°; $[\alpha]_D$ +226°; λ_{max}^{KBr} 2.85, 5.88μ, its n.m.r. showing the 18 and 18'-methyl signals at 58.5 and 55 c.p.s.(13) Hydrolysis of I with HCl in dioxane gave 17α, 17α'-di-19-nortestosterone (III), m.p. 214-217° and 255-260°; $[\alpha]_D$ +44°; λ_{max}^{KBr} 2.82, 5.97 and 6.19μ; λ_{max}^{alc} 240 mμ (ε = 30,420); n.m.r.: 47.5 and 62.5 c.p.s. (18 CH_3).

Dehydroisoandrosterone formed(8) an extremely difficultly soluble dimer (IV), m.p. 355-360°; $[\alpha]_D$ -97° (dioxane); λ_{max}^{KBr} 2.80, 2.98 and 6.14μ; (diacetate (IVa), m.p. 311-314°; $[\alpha]_D$ -114°; λ_{max}^{KBr} 2.72, 2.77 and 5.76μ; n.m.r. 54.5 c.p.s. (18 CH_3)), which on Oppenauer oxidation gave 17α, 17α'-ditestosterone, (V) m.p. 305-307°; $[\alpha]_D$ +43°; λ_{max}^{KBr} 2.81, 5.95 and 6.19μ; λ_{max}^{alc} 242 mμ (ε = 31,300); n.m.r.: 55 and 58.5 c.p.s. (18 CH_3).(14) Reduction of estrone gave 17α, 17α'-diestradiol (7.5% yield), m.p. 320-325°; $[\alpha]_D$ +48° (dioxane); λ_{max}^{alc} 282 mμ (ε = 3,960); λ_{max}^{KBr} 2.74, 2.83, 6.20, 6.30μ, 3,3'-diacetate (VII), m.p. 283-287°; $[\alpha]_D$ +18°; λ_{max}^{KBr} 2.75, 5.71, 6.22, 6.31 and 8.20μ; λ_{max}^{alc} 269 and 276.5 mμ (ε = 1,590); n.m.r. 55, 59.5 c.p.s. (18 CH_3)).

Chemical and spectral data indicate that individual 17α, 17α'-dimers exist in one of two preferred conformations, one, in which the 17- and 17'-hydroxyl groups are cis, and the other, in which they are trans to each other.(15) Thus, the IR-spectra of compounds I and IVa in 0.001M CCl_4 solution show hydroxyl absorption at 3638 and 3561 cm^{-1} and 3633 and 3556

cm^{-1}, respectively, ($\Delta\nu = 77\ cm^{-1}$), indicating strong intramolecular hydrogen bonding,(16) whereas compounds III and VII show only non-bonded hydroxyl absorption at 3615 cm^{-1} (shoulder at 3630 cm^{-1}) and at 3614 and 3636 cm^{-1}, respectively.(17) In harmony with these observations were the results of lead tetraacetate cleavage experiments, which showed a 70% recovery of unchanged *trans*oid III, and an 80% yield of the monomeric dehydroisoandrosterone acetate from the *cis*oid IVa after two hours at room temperature.(18) It is of considerable interest that the *cis*oid, conformers possess a single peak in the n. m. r. for the 18 and 18'-methyl groups, while all the *trans*oid conformers show two such peaks of 3 protons each. The influence of various factors on the extent of dimerization was studied with dehydroisoandrosterone, which gave the insoluble dimer IV.(8) Ether and dimethoxyethane two of the most popular "co-solvents" gave the best yields of dimer (7-10%) especially when the reaction time was extended to 1.5 hours.(19) The use of sodium in the presence of ether gave a significantly higher yield than that of lithium (20-24%), whereas calcium gave only 1%. Dimerization amounted to < 1% when no "co-solvent" was used,(20) or with tetrahydrofuran, 3-methoxy-*n*-propanol or dioxane. Diglyme was intermediate and furnished 2% of IV.

The complex equilibria postulated(2) to exist in liquid ammonia between unsaturated substrates and the products of progressive electron addition and subsequent protonation provide a ready basis for rationalization of dimer formation. Under conditions favoring maximum dissociation (NH_3 alone) the intermediate radical anions $>\dot{C}—O^{\ominus}$ will because of Coulombic interactions repel each other so as to avoid coupling. Suppression of dissociation by co-solvents could lead to ion pair formation between metal and radical-anion resulting in less repulsion and increased coupling. Precedent for this view may be seen in the behavior of the metal ketyl from benzophenone, which in NH_3 exists 85% as the radical anion(21) and in ether as the dimeric pinacol disodium salt.(22)

Dimerization was not confined to 17-ketones. Cholestan-3-one(8) gave the 3,3'-dimer, m.p. 320-325°; $[\alpha]_D$ +34°; λ_{max}^{KBr} 2.73 and 2.84μ; in 34% yield and androstan-17β-ol-3-one dimerized in 3% yield, m.p.>365°; $[\alpha]_D$ +25°; λ_{max}^{KBr} 2.73 and 2.84μ. On the other hand, the 4,4-dimethyl-3-ketone dipterocarpol(23) gave only the monomeric dammarenediol II.(23)

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(7) A. Streitwieser, Jr. and S. Suzuki, Tetrahedron, 16, 153 (1961) describe the dimerization of an aromatic nucleus, the fluoranthene radical-anion.

(8) The exact conditions are: To 500 mg of estrone methyl ether in 80 ml of distilled NH_3 and 24 ml of anhydrous ether was added 500 mg of Li over a 10 minute period. After 30 minutes 5 ml of absolute alcohol was added and the mixture worked up in the conventional manner. Other reductions not involving an aromatic A-ring were conducted with 270 mg of Li. These conditions are to be contrasted with those of C. Djerassi, L. Miramontes, G. Rosenkranz and Franz Sondheimer, (J. Am. Chem. Soc., 76, 4092 (1954)) who employed dioxane as a "co-solvent"

(9) Rotations in chloroform (c, 0.5-1.0) unless otherwise indicated. Microanalyses by J. Alicino, Metuchen, N. J. are omitted to conserve space.

(10) We wish to thank Professor C. Djerassi of Stanford University for the mass spectrum. Major peaks were also observed at M-1 and -2 and at 1/2 M+1, +2, -1, and -2.

(11) N.m.r. spectra were taken in $CDCl_3$-solution on a Varian A-60 spectrometer. Signals are reported as c.p.s. downfield from TMS (0.0 c.p.s.)

(12) R. F. Zürcher, Helv. Chim. Acta, 46, 2054 (1963).

(13) Other chemical shifts are omitted since they are identical with those for the corresponding monomers.

(14) The 17α, $17\alpha'$-dimers of androsterone (15%; m.p. 295-300°; $[\alpha]_D$ -20°; λ_{max}^{KBr} 2.73 and 283μ) and of isoandrosterone ((VI) 19%; m.p. 360° $[\alpha]_D$ 0° (dioxane); λ_{max}^{KBr} 2.73 and 2.83μ) were also prepared.

(15) Dreiding models show two potential energy minima when rotating the two halves about the C17, C17'-bond, corresponding to a *cis* and a *trans* conformation. In the cis-conformation the C17, O-bond essentially bisects the angle described by the $17\beta'$-O, C17', C13'-bonds and in the *trans*-conformation that described by the C13', C17', C16'-bonds. The alternative *cis*-conformation, in which the C17, O-bond bisects the angle between the $17\beta'$-O, C17', C16'-bonds is ruled out because of heavy non-bonded interactions between the two steroid nuclei.

(16) J. Kuhn, J. Am. Chem. Soc., 74, 2492 (1952), 76, 4323 (1954).

(17) We wish to express our sincere appreciation to Professor P. von R. Schleyer of Princeton University for the spectrum of compound III (Perkin-Elmer 421) and to Miss Barbara Keeler of the Squibb Institute for Medical Research for the remaining high resolution spectra (Perkin-Elmer 237).

(18) The dimer V gave a 40% recovery of starting material and 25% of Δ^4-androstene-3,17-dione after two hours. The dimers IV and VI were completely cleaved under these conditions. These compounds were too insoluble in CCl_4 for measurement of their IR spectra.

(19) The only previous report of dimerization in a lithium, ammonia reduction is by J. W. Huffmann, D. M. Alabran and T. W. Bethea, (J. Org. Chem., 27, 3381 (1962)), who isolated 40% of the pinacol of 12-cholanone when the reaction time was extended to one hour, but not otherwise. The pinacol was "characterized" only by melting point. Apparently ether and dioxane were used as co-solvents but no significance was ascribed to their presence.

(20) In our hands, even the insoluble estrone methyl ether was smoothly reduced in ammonia only, giving less than 0.5% of dimer.

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