Reaction of an α,β-Unsaturated Nitro-compound with Lithium Dimethylcuprate. A Novel Synthesis of a 3α,5α-Cyclosteroid

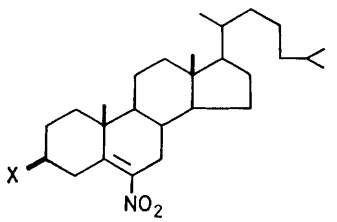
Shirley Stiver and Peter Yates*

Lash Miller Chemical Laboratories, University of Toronto, Toronto, Ontario, Canada M5S 1A1

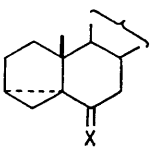
Treatment of 3β-acetoxy-6-nitrocholest-5-ene with an excess of lithium dimethylcuprate gives 3α,5α-cyclocholestan-6-one (*E*)-oxime; its Beckmann rearrangement product, 3α,5α-cyclo-6-aza-*B*-homocholestan-7-one, failed to undergo a 'retro-Beckmann' rearrangement.

Although examples of conjugate addition of lithium organocuprate reagents to α,β-unsaturated carbonyl compounds are numerous,[1] examples of such addition to α,β-unsaturated nitro-compounds are rare. Conjugate addition has been observed in the reactions of 1-(4-chlorophenyl)-2-nitropropene with both lithium dimethyl- and diphenyl-cuprate.[2] In the course of an investigation of the synthesis of 5-methyl-6-oxo-steroids we examined the reaction of 3β-acetoxy-6-nitrocholest-5-ene (**1**)[3] with lithium dimethylcuprate in diethyl ether. A product, m.p. 126—126.5 °C, was obtained in 65% yield whose elemental composition, $C_{27}H_{45}NO$, showed that reductive deacetylation rather than addition of the organocuprate reagent had occurred in spite of the fact that 5 equiv. of the reagent were used. The product was shown to be 3α,5α-cyclocholestan-6-one (*E*)-oxime (**2**)† by direct comparison with an authentic sample.[4,5] This structural assignment was corroborated by hydrolysis of the product from (**1**) with sodium bisulphite in aqueous ethanol[6] which gave the ketone (**3**),[7] identified by direct comparison. Comparison of the ^{13}C n.m.r. spectrum of (**2**) with that of (**3**)[8] in conjunction with data for (*E*)- and (*Z*)-oximes of cyclohexanones[9] confirmed the earlier assignment[5] of the (*E*)-configuration for (**2**). Several minor products were formed together with (**2**); one was identified as 3β-acetoxy-5α-cholestan-6-one (*E*)-oxime (**4**) by direct comparison.

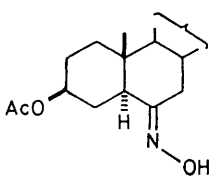
We suggest that the formation of (**2**) from (**1**) is initiated by one electron transfer from lithium dimethylcuprate to give the radical anion (**5**) (Scheme 1). House and Umen[10] have concluded that unsaturated systems with reduction potentials less negative than −2.4 V (in dimethylformamide) will accept an electron from this reagent and Sato and co-workers[11] have very recently reported that the reduction potential of (**1**) lies in the range −1.35 to −1.37 V. Internal displacement of the acetoxy-group in (**5**) would give the 3α,5α-cyclo-species (**6**). Displacement of an acyloxy-group is unusual, and while electrolysis of the toluene-*p*-sulphonate



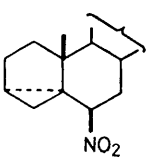
(**1**) X = OAc
(**7**) X = $OSO_2C_6H_4Me$-*p*



(**2**) X = (*E*)-NOH
(**3**) X = O

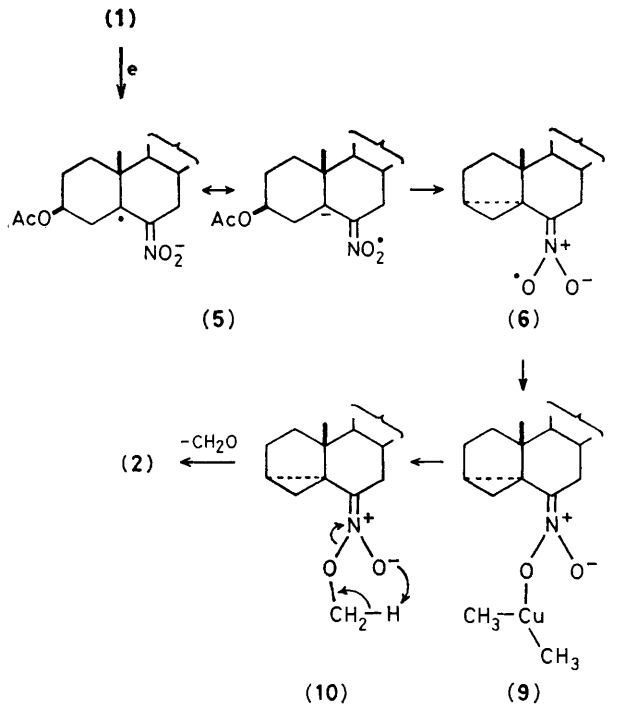


(**4**)



(**8**)

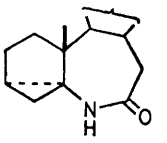
† Although the designation 3α,5α for the ring stereochemistry in (**2**) is in general use, since 1972 *Chemical Abstracts* have given it as 3β,5α.



Scheme 1

(7) gave (8), electrolysis of (1) gave no 3,5-cyclo-products.[11] In the present case the displacement of the acetate ion may be facilitated by complexation with lithium or copper species. In the electrolysis reactions reduction of the nitro-group does not occur; its occurrence with lithium dimethylcuprate is postulated to involve formation of an intermediate of type (9), which undergoes methyl insertion to give the nitronate ester (10).[10,12] The subsequent decomposition of (10) into (2) is not without precedent.[13] The stereochemical consequences of such a reaction sequence are uncertain; however, it is likely that the (*E*)- and (*Z*)-oximes equilibrate during work-up.‡

‡ A referee has suggested that (10) may be formed by an ionic mechanism; we cannot exclude this but favour the free-radical mechanism owing to its analogy with the electrolytic results.[11]



(11)

As the oxime (2) was available we took the opportunity to re-examine a remarkable 'retro-Beckmann' reaction that has been reported[14] to lead to the formation of (2) from the lactam (11), its Beckmann rearrangement product. Although (11) was obtained readily by rearrangement of the toluene-*p*-sulphonate of (2), it failed to give (2) upon treatment with hydrobromic acid in acetone.[14]

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