Tetrahedron Letters No. 5, pp. 1-5, 1960. Pergamon Press Ltd. Printed in Great Britain.

A NEW REACTION OF DIAZOMETHANE WITH α,β-UNSATURATED KETONES

William S. Johnson, M. Neeman and S. P. Birkeland

Department of Chemistry, University of Wisconsin,

Madison, Wisconsin

(Received 29 January 1960)

THERE are no reported instances of a true α,β-unsaturated aldehyde or ketone reacting with an aliphatic diazo compound to effect linear homologation.[1] The reactions instead involve attack of the olefinic linkage to produce pyrazoline derivatives as with benzalacetone,[2] or, if the olefinic bond is unreactive, as in the case of steroid 4-ene-3-ones, no reaction at all is observed.[3]

We have discovered that fluoboric acid, in catalytic amounts, promotes the reaction of diazomethane with α,β-unsaturated ketones to effect homologation, probably by attack at the carbonyl group. Prima facie evidence for the occurrence of this unprecedented reaction was provided when testosterone was submitted to the fluoboric acid-catalyzed diazomethane treatment in

---

[1] C.D. Gutsche in Adams' Org. Reactions VIII, 384 (1954); R. Huisgen, Angew. Chem. 67, 439 (1955).

[2] E. Azzarello, Gazz. Chim. Ital. 36, II, 50 (1906); L.I. Smith and K.L. Howard, J. Amer. Chem. Soc. 65, 165 (1943).

[3] A. Wettstein, Helv. Chim. Acta 27, 1803 (1944); C. Djerassi and C.R. Scholz, J. Org. Chem. 14, 660 (1949); A.L. Nussbaum and F.E. Carlon, J. Amer. Chem. Soc. 79, 3831 (1957).

order to effect methylation of the 17-hydroxyl group.[4] The resulting mixture contained, in addition to the desired methyl ether, a significant proportion of material exhibiting unconjugated carbonyl absorption in the infrared spectrum. Similar results were obtained in the experiment with desoxycorticosterone.[4]

These preliminary findings prompted us to study this reaction with 4-cholestene-3-one. When an excess (4 mole equivalents) of diazomethane in methylene chloride solution was slowly added to a stirred solution of pure[5] cholestenone in methylene chloride containing about 6 mole % of concentrated[4] fluoboric acid, vigorous evolution of nitrogen ensued, and the ultraviolet spectrum of the crude product exhibited relatively weak absorption (ε 6,500) at 241 mμ. Chromatography readily afforded, in 40% yield, a new ketone, m.p. 94-95°, $[\alpha]_D^{25}$ +47.8° (CCl_4), (C, 84.4; H, 11.59), $\lambda_{max}^{CH_2Cl_2}$ 5.84 μ (C=O), 6.1 μ (weak, C=C). The ultraviolet spectrum exhibited only end absorption.

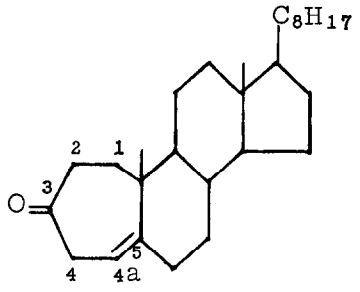
The new ketone gave a yellow color with tetranitromethane, formed a yellow 2,4-dinitrophenylhydrazone, m.p. 189-190° (C, 70.34; H, 8.79), and absorbed 1 mole-equivalent of hydrogen in the presence of palladium catalyst. The nmr spectrum at 60 mc. of a solution of the new ketone in carbon tetrachloride, with benzene as an external standard, gave signals indicating the partial structure $-CH_2COCH_2CH=C$: triplet (J=6) at +80 cps (one vinyl

---

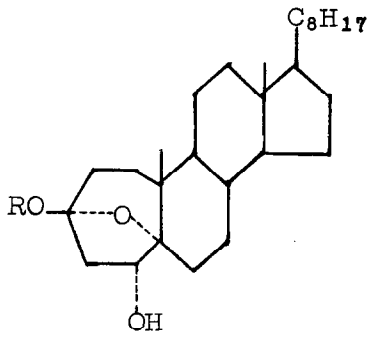
[4] M. Neeman, M.C. Caserio, J.D. Roberts and W.S. Johnson, Tetrahedron 6, 36 (1959).

[5] Material was prepared by the procedure of J.F. Eastham and R. Teranishi, Org. Synth. 35, 39 (1955) from cholesterol purified as described by L.F. Fieser, Ibid. 35, 43 (1955). Cholestenone prepared from commerical cholesterol was contaminated with cholestanone and gave difficultly separable mixtures in the diazomethane reaction.

hydrogen, split by two adjacent hydrogens); unresolved multiplet at +208 cps (two hydrogens, allylic to double bond and α to carbonyl); multiplets at +253 and +266 cps (two hydrogens, α to carbonyl group, one showing axial and the other equatorial properties, both split by adjacent hydrogens). The remaining significant features of the nmr spectrum included sharp signals at +324 cps (C_{19} methyl), +333 cps (C_{26} and C_{27} methyls), +339 cps (C_{21} methyl), and +348 cps (C_{18} methyl). Confirmation of the β,γ-unsaturated ketone system was afforded by the appearance of a new band at 6.0 μ in the infrared spectrum of the ketone after it was heated overnight in benzene solution containing a trace of p-toluene sulfonic acid; thus the olefinic bond apparantly was partially isomerized into conjugation with the carbonyl group. It is noteworthy, however, that the equilibrium seems to be in favour of the β,γ-tautomer.



I



II

The foregoing results are consistent with an A homo compound I or the isomeric 4-one-5-ene structure. The latter formulation was excluded by the following experiments. Hydroxylation with osmium tetroxide gave, in high yield, a crystalline product, which was stable to periodic acid and showed no carbonyl stretching absorption in the infrared spectrum. This hydroxylation

product accordingly was formulated as the hemiketal II (R=H). Confirmation of this structure was afforded by its facile conversation, with methanolic hydrogen chloride, into a hydroxy lactol ether (II, R = CH_3), m.p. 177.5-178.5° (C, 77.75; H, 11.17; OCH_3, 6.94). The hydroxyl group of this derivative was shown to be secondary (rather than tertiary as required by the alternative structure mentioned above) by oxidation with chromium trioxide in acetic acid to a keto lactol methyl ether. m.p. 115-116° (C, 78.67; H, 10.83; OCH_3, 7.40). The new ketone, m.p. 94-95°, accordingly may be formulated as A-homo-4a-cholestene-3-one (I).

We have also examined, in a preliminary way, the behaviour of benzalacetone and of benzalacetphenone under these new reaction conditions. Benzalacetone, λ_{max}^{EtOH} 286 mμ (ε 23,500), 220 (12,000), $\lambda_{max}^{CHCl_3}$ 5.98 μ (strong C=O), 6.14, 6.20, was treated for 1 hr with a methylene chloride solution containing 4 mole-equivalents of diazomethane. The significant spectral properties of the crude product were, λ_{max}^{EtOH} 312 mμ (ε 8,100); $\lambda_{max}^{CHCl_3}$ 3.04 μ (N-H), 5.98 (strong, C=O), 6.20, which are indicative of the Δ^2-pyrazoline.[2] When the reaction was repeated as above except that 6 mole % of fluoboric acid was added, the significant spectral properties of the crude product were, λ_{max}^{EtOH} 287 mμ (ε 9,600), 255 (8,700); $\lambda_{max}^{CHCl_3}$ 5.85 μ (strong, C=O), 5.98, 6.14, 6.20 μ. It is clear that in the latter experiment, the carbonyl group was attacked by diazomethane to effect homologation without significant pyrazoline formation. The product clearly contains an unconjugated keto group while the olefinic bond remains largely in conjugation with the benzene nucleus. Similar results were obtained with benzalacetophenone. In the fluoroboric acid-catalyzed experiment no pyrazoline formation was observed, and the extinction coefficient of the absorption maximum at 308 mμ in the

ultraviolet spectrum of the starting material dropped by 25% after the reaction.

Preliminary experiments indicate that comparable results are realized when boron trifluoride is used in place of fluoboric acid.[6]

---

[6] This work is being supported by grants from the U.S. Public Health Service and the National Science Foundation.