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FORMYLATION OF ETHYLENE KETALS. SYNTHESIS OF α-MONOALKYL KETALS AND KETONES

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IT is frequently difficult to effect the mono-alkylation of ketones, in view of the occurrence of poly-alkylation. The brilliant discovery of Stork[1] on the alkylation of enamines has been useful in overcoming this difficulty in many cases. We now wish to report a novel method of alkylation of ethylene ketals, which results in a two-step synthesis of α-monoalkyl ketals and hence of α-monoalkyl ketones. This new synthetic method is remarkable for its mildness and for the ease with which monoalkylation can be achieved in a rather high yield.

Treatment of ethylene ketals with a Vilsmeier reagent[2] at room temperature for one hour followed by base or acid hydrolysis leads to α-formylketals or α-formylketones, respectively.[3] Wolff-Kishner reduction of the α-formylketals gives the corresponding α-methylketals which upon acid hydrolysis yield the α-methylketones.

Recently, we have introduced a new and relatively easy method for the acylation of ketals, which resulted in a one-step synthesis of α-acetylketals.[4] These α-acetylketals on Wolff-

Kishner reduction are similarly converted to α-ethylketals, which on acid treatment give α-ethylketones.

Treatment of cholestan-3-one ethylene ketal (1 g) (I) in ethylene chloride (5 ml) with a mixture of dimethylformamide (1.4 g), phosphorous oxychloride (1 g) and ethylene chloride (10 ml) for one hour at room temperature yielded 84% of 2-formyl-3-(β-formoxy) ethoxy-Δ^2-cholestene (II) [m.p. 127°; $(\alpha)_D^{CHCl_3}$ +88; λ_{max}^{EtOH} 275 mμ (ε 12700); ν_{max}^{KBr} 5.79(s), 6.06(m), 6.20(s), 8.40(s)μ. Anal. Found: C, 76.26; H, 10.50], and 4% of 2-formyl-3-(β-hydroxy) ethoxy-Δ^2-cholestene (III) [m.p. 144-5°; $(\alpha)_D^{CHCl_3}$ +93°; λ_{max}^{EtOH} 277 mμ (ε 13100); ν_{max}^{KBr} 2.9(m), 6.04(m), 6.18(s)μ. Anal. Found: C, 78.35; H, 11.01].

In a similar manner, androstan-17β-ol-3-one ethylene ketal (IV) and androstan-17β-ol-3-one ethylene ketal acetate (V) yielded 22% of androstan-17β-ol-3-one formate[5,6] (VI) [m.p. 143-145°; $(\alpha)_D^{CHCl_3}$ +24°; ν_{max}^{KBr} 5.8(s), 8.4(s)μ. Anal. Found: C, 75.40; H, 9.43], 67% of 2-formyl-3-(β-formoxy) ethoxy-Δ^2-androstene-17β-ol-formate (VII) [m.p. 132-4°; $(\alpha)_D^{CHCl_3}$ +82; λ_{max}^{EtOH} 275 mμ (11,800); ν_{max}^{KBr} 5.80(s), 6.04(m), 6.18(s), 8.45(s)μ. Anal. Found: C, 68.75; H, 8.19] and 4% of 2-formyl-3-(β-hydroxy) ethoxy-Δ^2-androstene-17β-ol-formate (VIII) [m.p. 155-8°; $(\alpha)_D^{CHCl_3}$ +97; λ_{max}^{EtOH} 277 mμ (13,300); ν_{max}^{KBr} 2.98(m), 5.82(s), 6.07(m), 6.18(s), 8.5(s)μ. Anal. Found: C, 70.53; H, 8.70]; and 3% of androstan-17β-ol-3-one acetate (IX)[5] and 92% of 2-formyl-3(β-formoxy) ethoxy-Δ^2-androstene-17β-ol acetate (X) [m.p. 140-1°; $(\alpha)_D^{CHCl_3}$ +79; λ_{max}^{EtOH} 277 mμ (12,900); ν_{max}^{KBr} 5.78(s), 5.80(s), 6.05(m), 6.17(s), 8.0(s)μ. Anal. Found: C, 69.33; H, 8.86], respectively.

The n.m.r. spectrum[7] of VIII indicated a broad band at 3.05 ppm due to one hydroxylic proton, an A_2B_2 type multiplet centered at 3.96 ppm related to the four neighbouring side chain protons, a broad triplet at 4.70 ppm due to the 17-H neighbouring the C-17 formate group. Two singlets appeared at 8.09 and 10.2 ppm which are ascribed to formate and aldehydic protons, respectively.

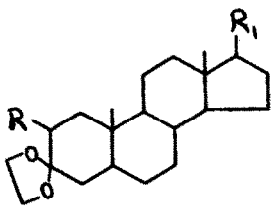
Acid hydrolysis of II and X gave 2-hydroxymethylene cholestan-3-one[8] (XI) [m.p. 170-2°; λ_{max}^{EtOH} 283 mμ (8600); $\lambda_{max}^{EtOH-NaOH}$ 314 mμ (ε 18,800); ν_{max}^{KBr} 6.4(broad), 8.25(s)μ. Anal. Found: C, 81.07; H, 11.07] and 2-hydroxymethylene androstan-17β-ol-3-one acetate (XII)[9] [m.p. 189-190°; $(\alpha)_D^{CHCl_3}$ +49; λ_{max}^{NaOH} 285 mμ (8400); $\lambda_{max}^{EtOH-NaOH}$ 314 mμ (19,100); ν_{max}^{KBr} 5.76(s), 6.4(broad), 8.0(s), 8.25(s)μ. Anal. Found: C, 73.08; H, 8.88], respectively.

Hydrolysis of II and X with methanolic sodium bicarbonate solution yielded 2-formylcholestan-3-one ethylene ketal (XIII) [m.p. 162-4°; $(\alpha)_D^{CHCl_3}$ -25; ν_{max}^{KBr} 5.8(s), 8.61(m), 9.31(m)μ. Anal. Found: C, 78.44; H, 10.96] and 2-formylandrostan-17β-ol-3-one acetate ethylene ketal (XIV) [m.p. 197-8°; $(\alpha)_D^{CHCl_3}$ -47; ν_{max}^{KBr} 5.78(s), 5.8(s), 8.0(s), 8.6(m), 9.20(m), 9.35(m)μ.

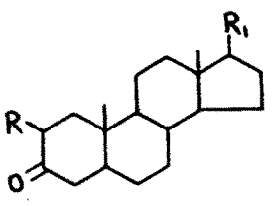
Anal. Found: C, 71.10; H, 8.99], respectively.

Wolff-Kishner reduction of XIII and XIV led to 2-methylcholestan-3-one ethylene ketal (XV) [m.p. 116-7°; $(\alpha)_D^{CHCl_3}$ +22; ν_{max}^{KBr} 9.1(m) and 9.2(m)μ. Anal. Found: C, 80.77; H, 11.70] and 2-methylandrostan-17β-ol-3-one ethylene ketal (XVI) [m.p. 220-1°; $(\alpha)_D^{CHCl_3}$ +20; ν_{max}^{KBr} 2.8(m), 9.1(m) and 9.42(m)μ. Anal. Found: C, 76.13; H, 10.47], which were converted to 2α-methylcholestan-3-one[8,10] (XVII) [m.p. 121-3°; $(\alpha)_D^{CHCl_3}$ +51; ν_{max}^{KBr} 5.84(s)μ. Anal. Found: C, 83.52; H, 12.02] and 2α-methylandrostan-17β-ol-3-one[11,12] (XVIII) [m.p. 152-3°; $(\alpha)_D^{CHCl_3}$ +27; ν_{max}^{KBr} 2.87(m), 5.86(s)μ], respectively, by an acid solution.

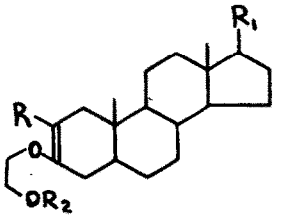
Analogous Wolff-Kishner reduction of 2-acetyl cholestan-3-one ethylene ketal[4] (XIX) and 2-acetyl androstan-17β-ol-3-one acetate ethylene ketal[4] (XX) yielded 2-ethylcholestan-3-one ethylene ketal (XXI) [m.p. 117-9°; $(\alpha)_D^{CHCl_3}$ +24; ν_{max}^{KBr} 9.05(m) and 9.15(m)μ. Anal. Found: C, 81.10; H, 12.00] and 2-ethylandrostan-17β-ol-3-one ethylene ketal (XXII) [m.p. 166-7°; $(\alpha)_D^{CHCl_3}$ +17; ν_{max}^{KBr} 2.9(m), 9.1(m), 9.5(m), 9.76(m)μ. Anal. Found: C, 76.00; H, 10.81], which upon acid hydrolysis gave 2α-ethylcholestan-3-one (XXIII) [m.p. 112-4°; $(\alpha)_D^{CHCl_3}$ +42; ν_{max}^{KBr} 5.85(s). Anal. Found: C, 83.46; H, 12.10] and 2α-ethylandrostan-17β-ol-3-one[11] (XXIV) [m.p. 169-170°; $(\alpha)_D^{CHCl_3}$ +29; ν_{max}^{KBr} 2.8(m), 5.85(s)μ. Anal. Found: C, 79.29; H, 10.90], respectively.



I R = H, R_1 = C_8H_{17}
IV R = H, R_1 = OH
V R = H, R_1 = OAc
XIII R = CHO, R_1 = C_8H_{17}
XIV R = CHO, R_1 = OAc
XV R = CH_3, R_1 = C_8H_{17}
XVI R = CH_3, R_1 = OH
XIX R = CH_3CO, R_1 = C_8H_{17}
XX R = CH_3CO, R_1 = OAc
XXI R = C_2H_5, R_1 = C_8H_{17}
XXII R = C_2H_5, R_1 = OH



VI R = H, R_1 = OCHO
IX R = H, R_1 = OAC
XI R = CHO, R_1 = C_8H_{17}
XII R = CHO, R_1 = OAc
XVII R = CH_3, R_1 = C_8H_{17}
XVIII R = CH_3, R_1 = OH
XXIII R = C_2H_5, R_1 = C_8H_{17}
XXIV R = C_2H_5, R_1 = OH



II R = CHO, R_1 = C_8H_{17}, R_2 = CHO
III R = CHO, R_1 = C_8H_{17}, R_2 = H
VII R = CHO, R_1 = OCHO, R_2 = CHO
VIII R = CHO, R_1 = OCHO, R_2 = H
X R = CHO, R_1 = OAc, R_2 = CHO

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REFERENCES

1. G. Stork and S.R. Dowd, J. Am. Chem. Soc. 85, 2180 (1963), and references cited there; J. Szmuszkovicz, in "Advances in Organic Chemistry", Vol. IV, R.A. Raphael, E.C. Taylor and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N.Y., 1963, p.1.

2. Houben-Weyl, "Methoden der Organische Chemie", 4th ed., 1954, Vol. 7(1), p. 29; H.H. Bosshard and Hch. Zollinger, Helv. Chim. Acta 42, 1659 (1959), and references there cited.

3. Formylation of dialkyl acetals and ketals to α-dialdehydes and β-aldehydo-enol ethers have been reported recently. Z. Arnold and J. Zemlijcka, Coll. Czech. Chem. Comm. 24, 786 (1959); and references there cited; D. Burn, G. Cooley, J.W. Ducker, B. Ellis, D.N. Kirk, V. Petrow, Tetrahedron Letters 13, 733 (1964), and references there cited; D. Bertin, L. Nedelec and J. Mathieu, Compt. rend. 253, 1219 (1961).

4. R.D. Youssefyeh, J. Am. Chem. Soc. 85, 3901 (1963).

5. K. Miescher, H. Kagi, C. Scholz, A. Wettstein and E. Tschopp, Biochem. Z. 294, 39 (1937); C. Djerassi, J. Org. Chem. 12, 823 (1947).

6. Formylation of alcohols by means of Vilsmeier reagent have been reported recently, Z. Arnold, Coll. Czech. Chem. Comm. 26, 1723 (1961), and references there cited.

7. The n.m.r. spectrum was measured in deuterated chloroform solution of 5-10% concentration with tetramethylsilane as internal standard.

8. C. Djerassi, N. Finch, R.C. Cookson and C.W. Bird, J. Am. Chem. Soc. 82, 5488 (1960).

9. S.H. Burstein and H.J. Ringold, J. Org. Chem. 26, 3084 (1961).

10. Y. Mazur and F. Sondheimer, J. Am. Chem. Soc. 80, 5220 (1958); B. Fuchs and H.J.E. Loewenthal, Tetrahedron 11, 199 (1960).

11. H.J. Ringold, E. Batres, O. Halpern and E. Necoechea, J. Am. Chem. Soc. 81, 427 (1959); Upjohn Co., Brit. 889, 330 [C.A. 57, 2289 (1962)].

12. Syntex, S.A., Brit. 853, 291 [C.A. 56, 8800 (1962)].