A Useful Homologation Reaction for the Preparation of Fluoro-ketones[1]

By P. CRABBE,* H. CARPIO, A. CERVANTES, J. IRIARTE, and L. TÖKES

(*Research Laboratories, Syntex S.A., Apartado Postal* 2679, *Mexico, D.F., Mexico*)

IN connection with Syntex' effort[2] in the field of difluorocarbene chemistry,[3] we report here the addition of difluorocarbene to 5β-pregn-17(20)-ene-3α,20-diol diacetate (I) [m.p. 140—141°; ν_{max} 1745 (OAc) cm.$^{-1}$; n.m.r. 0·88 (18-H), 0·93 (19-H), 1·88 (21-H) 2·00, 2·07 p.p.m. (3- and 20-acetate)],† and further reactions. It was noted that hydrolysis of the adduct constitutes a new route to $\alpha\alpha$-difluoroketones, as well as to α-fluoro-$\alpha\beta$-unsaturated ketones.

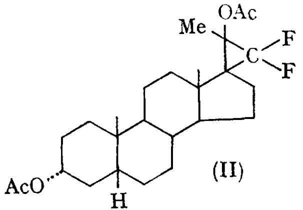
Addition of difluorocarbene[4] to enol acetate (I) provided the amorphous compound (II) [n.m.r. 0·93 (18-H), 0·99 (19-H), 1·40 (21-H), 1·99 and 2·03 p.p.m. (3 and 20-acetate)]. Reaction of (II) with acid or base afforded three compounds. The first substance isolated in 13% yield was assigned structure (III) [m.p. 151—152°; ν_{max} 1750 (C=O) cm.$^{-1}$; n.m.r. 0·83 (18-H) triplet ($J_{H,F}$ = 2 c./sec.,),[5] 0·92 (19-H), 2·27 p.p.m. (22-H)]. The other two products from hydrolysis were obtained in 5% and 48% yield respectively and have structures (IV) [m.p. 176—177°; λ_{max} 252 mμ (log ϵ 3·99); n.m.r. 0·93 (18-H and 19-H), doublet (22-H) centred at 2·25 p.p.m. ($J_{H,F}$ = 5 c./sec.)] and (V) [m.p. 150—151°; λ_{max} 250 mμ (log ϵ 4·11); n.m.r. 0·93 (18-H and 19-H), doublet (22-H) at 2·24 p.p.m. ($J_{H,F}$ = 5 c./sec.)].[6] The assignment of the isomeric structures (IV) and (V) is based on the higher extinction coefficient of the ultraviolet maximum of (V) which has less distortion from planarity of the enone chromophore, lacking the 12-methylene-22-methyl interaction.

Lithium aluminium hydride reduction of (II) afforded a mixture of epimeric alcohols at C-21 (VIa) [m.p. 160—162°; n.m.r. $(CD_3)_2SO$ 0·88 (18-H and 19-H), doublet (22-H) at 1·17 p.p.m. ($J_{H,F}$ = 6 c./sec.) (22-H)] and its isomer (VIb) [m.p. 148—149°; n.m.r. $(CD_3)_2SO$ 0·80 (18-H), 0·90 (19-H), doublet (22-H) at 1·19 p.p.m. ($J_{H,F}$ = 5 c./sec.)]. The structure of these isomers was

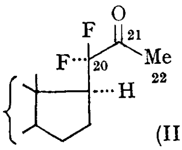
---

† Infrared spectra were determined in potassium bromide discs and n.m.r. spectra with a A-60 spectrometer, in deuteriochloroform solution containing tetramethylsilane as an internal reference (unless stated otherwise). We express our thanks to Dr. L. Throop and Mr. J. Murphy, Syntex Research, Palo Alto, California, for physical determinations of compounds herein reported. Satisfactory elemental analyses were obtained for all new compounds described herein.

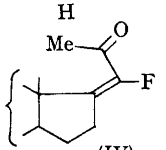
confirmed when reduction of the unsaturated ketone (V) provided a mixture of (VIa) and (VIb).



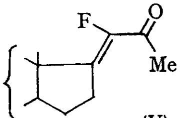
(II)



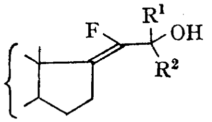
(III)



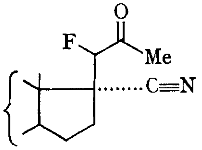
(IV)



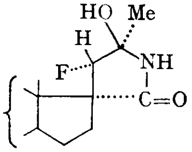
(V)



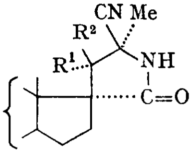
(VIa) R^1=H, R^2=Me
(VIb) R^1=Me, R^2=H
(VIc) R^1=R^2=Me



(VII)



(VIII)



(IXa) R^1=F, R^2=H
(IXb) R^1=H, R^2=F

Whereas Grignard reaction of the ketone (V) with methylmagnesium bromide, in the presence of cuprous chloride, afforded only the tertiary alcohol (VIc) [m.p. 168—170°; n.m.r. 0·86, 0·93 (18-H, 19-H), 1·36, 1·41 p.p.m. (22-H), 6 protons)], cyanide addition, in the presence of ammonium chloride,[7] gave the expected 1,4-addition compound (VII) [m.p. 178—179°; λ_{max} 288 mμ (log ε 1·79); ν_{max} 2250 (C≡N), 1740 (C=O) cm.$^{-1}$; n.m.r. 0·91, 0·94 (18-H, 19-H), a three proton doublet (22-H) at 2·41 p.p.m. ($J_{H,F}$ = 5 c./sec.), doublet (CHF) centred at 4·82 p.p.m. ($J_{H,F}$ = 49 c./sec.)].

Besides the cyano-derivative (VII), three lactams were isolated, resulting from hydrolysis of the 17α-cyano-group, followed by lactam formation (VIII), and by addition of a second mole of hydrogen cyanide to the 21-ketone prior to cylization to afford (IXa) and (IXb). The ready hydrolysis of the nitrile function is attributed to vicinal participation of the carbonyl group.[8] One of these lactams is compound (VIII) [m.p. 210—212°; n.m.r. $(CD_3)_2SO$) 0·88 (18-H, 19-H), a three proton doublet (22-H) centred at 1·36 p.p.m. ($J_{H,F}$ = 4 c./sec.), due to long-range coupling with the fluorine at C-20,[6] doublet (CHF) at 4·58 p.p.m. ($J_{H,F}$ = 51 c./sec.), 8·15 p.p.m. (NH)]. The other two products are the fluoro-cyano-lactams (IXa) [m.p. 287—289°; ν_{max} 3250 (NH), 1710 (C=O) cm.$^{-1}$; n.m.r. 0·92 (18-H), 0·96 (19-H), 1·69, 1·74 (22-H, doublet, $J_{H,F}$ = 3 c./sec.), attributed to coupling with C-20–F,[6] 4·58, 5·41 (CHF, doublet, J = 50 c./sec.), 7·63 p.p.m. (23-NH)] and (IXb) [m.p. 281—283°; ν_{max} 3230 (NH), 1710 (C=O) cm.$^{-1}$; n.m.r. 0·76, 0·81 (18-H doublet, $J_{H,F}$ = 3·5 c./sec.), 0·92 (19-H), 1·77 (22-H), 2·18 (3-OH), 4·18, 5·06 (CHF, doublet, $J_{H,F}$ = 52 c./sec.), 6·96 p.p.m. (23-NH)], of which structure and configuration are supported by the n.m.r. properties. This route thus constitutes an attractive new synthesis of halogeno-lactams.

We thank Dr. A. D. Cross and Dr. J. Fried for helpful discussions.

(*Received, October 23rd, 1967; Com.* 1130.)

---

[1] Part of the series on Steroids, previous Paper, P. Crabbé, P. Anderson, and E. Velarde, submitted for publication.

[2] *Inter alia* (a) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, P. W. Landis, and A. D. Cross, *J. Amer. Chem. Soc.*, 1963, **85**, 1851, and related papers; (b) C. Beard, N. H. Dyson, and J. H. Fried, *Tetrahedron Letters*, 1966, 3281, and references therein; (c) P. Anderson, P. Crabbé, A. D. Cross, J. H. Fried, L. H. Knox, and E. Velarde, submitted for publication.

[3] (a) W. Kirmse, "Carbene Chemistry", Academic Press, New York, 1964, ch. 8; (b) J. Herold and P. P. Gaspar, "Möglichkeiten der Carben-Chemie", Springer Verlag, Berlin, 1965; (c) J. Hine, "Divalent Carbon", Ronald Press Co., New York, 1964.

W. M. Wagner, *Proc. Chem. Soc.*, 1959, 229; J. M. Birchall, G. W. Cross, and R. N. Haszeldine, *Proc. Chem. Soc.*, 1960, 81.

[5] A. D. Cross and W. Landis, *J. Amer. Chem. Soc.*, **1962**, **84**, 1736, 3784; *ibid.*, 1964, **86**, 4005.

[6] See also: W. E. Parham and J. F. Dooley, *J. Amer. Chem. Soc.*, 1967, **89**, 895, and related papers.

[7] W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *Annalen*, 1961, **641**, 196.

[8] The formation of a lactam under such conditions has some precedent, see A. Lapworth, *J. Chem. Soc.*, 1904, **85**, 1214; W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *J. Org. Chem.*, 1961, **26**, 196.