Tetrahedron Letters No. 8, pp. 20-22, 1960. Pergamon Press Ltd. Printed in Great Britain.

ORGANIC FLUORINE COMPOUNDS[1]

FLUORINE DERIVATIVES OF MEVALOLACTONE

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(Received 17 March 1960)

THE substitution of hydrogen by fluorine transforms in some cases a metabolite into an anti-metabolite; in others, it produces a substance which can be incorporated by the cell instead of the "normal" compound. In view of the fundamental role of mevalonic acid and its lactone in biosynthetic processes, fluorine derivatives of mevalolactone would appear to be almost of equal interest if either of these two alternatives applies.

The diethyl ketal of ethyl γ-fluoroacetoacetate[2] [b.p. 63-64° (0.5 mm)] (Found: C, 54.2; H, 8.6. $C_{10}H_{19}FO_4$ requires C, 54.1; H, 8.6) was reduced by lithium aluminium hydride to the diethyl ketal of 4-fluoro-3-oxobutanol $FCH_2COCH_2CH_2OH$. The attempt to produce the free keto alcohol, however, led only to polymeric material. The alkali-catalysed condensation of fluoroacetone[3] with formaldehyde, on the other hand, gave in 43% yield a very stable fluoro-3-oxobutanol, b.p. 57-58° (0.5 mm) (Found: C, 45.8; H, 6.5; F, 18.2. C_4H_7FO

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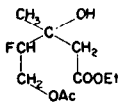
1 See E.D. Bergmann and I. Shahak, J. Chem. Soc. In press (1960).

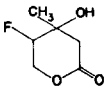
2 E.D. Bergmann, S. Cohen and I. Shahak, J. Chem. Soc. 3278 (1959).

3 E.D. Bergmann and S. Cohen, J. Chem. Soc. 2259 (1958).

requires: C, 45.3; H, 6.6; F, 17.9), which thus appears to be the 2-fluoro-derivative $CH_3CO.CHF.CH_2OH$. It is not unreasonable to assume that, as in many other cases, the methylene group of fluoro-acetone would react in preference to the methyl group, especially as this also applies to the parallel reaction of chloroacetone.[4] 2-Fluoro-3-oxobutylacetate [b.p. 54-55° (0.6 mm)] reacted normally with ethyl bromoacetate and zinc in ether to give in 55% yield ethyl δ-acetoxy-γ-fluoro-β-hydroxy-β-methylvalerate (I), b.p. 124-125° (0.4 mm) (Found: C, 51.0; H, 7.4; F, 8.4. $C_{10}H_{17}FO_5$ requires C, 50.9; H, 7.2; F, 8.0). Hydrolysis of (I) gave in 27% yield γ-fluoromevalolactone (II), b.p. 124-125° (0.4 mm) (Found: C, 49.2; H, 6.2; F. 13.4. $C_6H_9FO_3$ requires C, 48.6; H, 6.1; F, 12.9).[5,6]

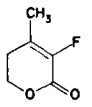


I

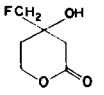


II

V



VI



VII

For the preparation of α-fluoromevalolactone (V) the observation has been utilized that the surprisingly stable enolate of ethyl fluoroacetate[7]

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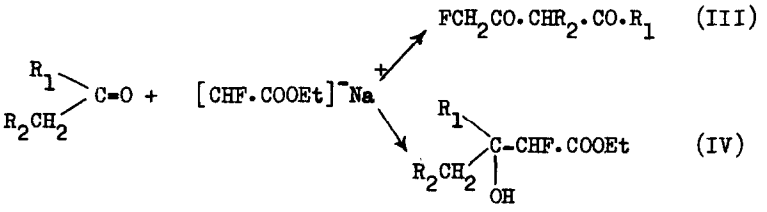
[4] E.R. Buchman and H. Sargent, J. Amer. Chem. Soc. 79, 400 (1945).

[5] So far, we have not determined whether the product is sterically homogeneous.

[6] This synthesis is modelled on the method of Folkers et al. for the preparation of mevalolactone. J. Amer. Chem. Soc. 79, 2316 (1957).

[7] E.D. Bergmann and S. Szinai, J. Chem. Soc. 1521 (1956).

reacts with ketones in two ways, viz., in a Claisen condensation, yielding 1-fluoro-2,4-diketones (III) and by a ketol condensation, yielding esters of α-fluoro-β-hydroxy acids (IV):



3-Oxobutyl acetate reacts according to the second mechanism, yielding directly α-fluoromevalolactone (V) via (IV, R_1 = $-CH_2CH_2OAc$, R_2 = H). Unfortunately, (V) could not be obtained in pure form; upon distillation [b.p. 120-123° (0.2 mm)] it loses water and gives the corresponding unsaturated lactone (VI) (Found: C, 55.8; H, 5.6; F, 14.3. C_6H_7FO requires C, 55.4; H, 5.4; F, 14.6).

The infra-red spectra, which will be reported in a more detailed communication, support the formulae of the substances described. The compounds (II) and (V) are now being studies as to their biological properties.

A third fluoromevalolactone (VII) has been studied by Singer et al.,[8] but its synthesis has not yet been published.

Acknowledgment - This study was initiated at the Biochemistry Department, College of Physicians and Surgeons, Columbia University, New York. One of us (E.D.B.) is deeply grateful to Professor David Rittenberg, Head of the Department, for the hospitality afforded to him.

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[8] F.M. Singer, J.P. Januszka and A. Berman, Proc. Soc. Exp. Biol.Med. 102, 170 (1959).