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ORGANIC FLUORINE COMPOUNDS. PART XLV[1]

SYNTHESIS OF γ-FLUORO-β-HYDROXYCARBONYL COMPOUNDS

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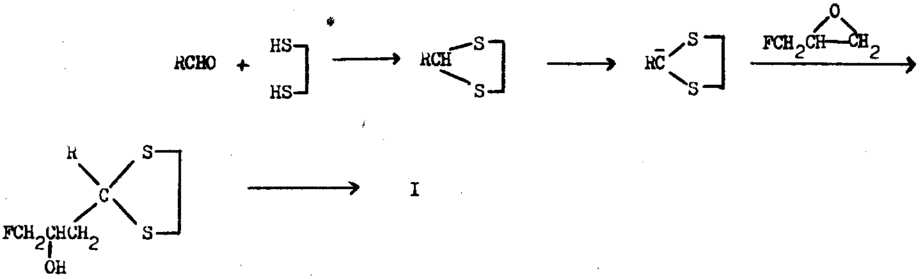
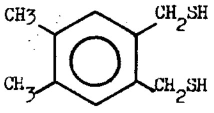
For a number of synthetic purposes, we were in need of a general method for the preparation of fluorinated keto-alcohols of the general formula $R.CO.CH_2.CH(OH)CH_2F$ (I). The method which seemed most suitable was based on the ability of 1,3-dithianes $-S-CHR-S-$ to give a carbanion $-S-\bar{C}R-S-$ [2-5], combined with the fact that the dithianes are masked forms of the aldehydes RCHO and their carbanions the masked forms of $R-\bar{C}=O$.



The dithianes usually employed are derived from 1,3 propanedithiol, but both starting material and end product often exhibit unpleasant properties. Thus we employed, following Shahak and Bergmann[6], 1,2-dimethyl-4,5-bis(mercaptomethyl)benzene (II) as point of departure for our syntheses. In the dithianes III studied, R was hydrogen, phenyl, p-tolyl-, 3-cyclohexenyl, styryl and n-nonyl (Table I).



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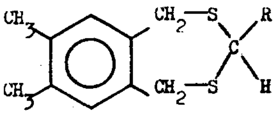

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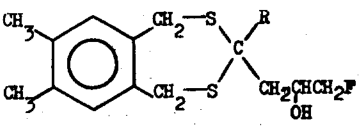
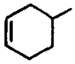


IV

IIIa, IVa : R = H

Ib, IIIb, IVb : R = C_6H_5

Ic, IIIc, IVc : R = $p\text{-}C_6H_4CH_3$

IIId, IVd : R = 

Ie, IIIe, IVe : R = $C_6H_5CH{=}CH$

IIIf, IVf : R = $n\text{-}C_9H_{19}$

Table I.

Synthesis of Compounds III

Compound	m.p.(°C)	yield(%)	nmr spectrum (δ (ppm))[7]
IIIa[a]	178°	65	δ= 3.93 (s, 4H, benzilic H) δ= 3.90 (s, 2H, CH_2 between the S atoms)
IIIb	200°[6]	90	AB pattern for 4 benzylic H; δ_A = 4.15, δ_B = 3.93, J_{AB} = 15 Hz. δ= 5.30 (s, 1H, CH between the S atoms)
IIIc	173°[6]	90	AB pattern for 4 benzylic H; δ_A = 4.30; δ_B = 4.10, J_{AB} = 16 Hz. δ= 5.50 (s, 1H, CH between the S atoms)
IIId	145°	75	δ = 4.13 (s, 4 benzylic H); δ= 4.47 (d, 1H, J = 2 Hz, CH between the S atoms); δ= 5.93 (broad s, 2 vinylic H)
IIIe	185°	70	δ= 4.13 (s, 4 benzylic H); δ= 5.10 (d, 1H, J = 6 Hz, CH between the two S atoms)
IIIf	89°	20	δ= 3.88 (s, 4 benzylic H); δ= 4.20 (t, 1H, J = 6 Hz, CH between the two S atoms)

[Note: (a) Prepared in 1,2 dimethoxyethane at room temperature; 12 hours]

THF solutions of compounds III were treated with n-butyl lithium in hexane to give the corresponding anions. These solutions were treated with a small excess of epifluorohydrin[1] at -20° in a nitrogen atmosphere, and the mixtures kept at 0° for seven days. They were then acidified with aqueous acetic acid and extracted with chloroform. The residues obtained by evaporation of these solutions were extracted again with boiling methanol and some unreacted starting material , undissolved in this solvent, **was** filtered. Evaporation of the clear methanol solutions gave residues which were chromatographed on silica-gel using 30% benzene in hexane as eluent.[8)]

Our results are summarized in Table II.

Table II.

Synthesis of Compounds IV

Compound	m.p.(^{o}C)	Yield(%)	III recovered,%	nmr of the CH_2F protons (δ (ppm))
IVa	175^{o}	55	21	4.55 (d,d,2H, J_{HF}= 50 Hz, J_{HH}= 5 Hz)
IVb	110^{o}	48	25	4.37 (d,d,2H, J_{HF}= 44 Hz, J_{HH}= 5 Hz)
IVc	108^{o}	43	23	4.40 (d,d,2H, J_{HF}= 46 Hz, J_{HH}= 6 Hz)
IVe	45^{o}	52	31	4.47 (d,d,2H, J_{HF}= 52 Hz, J_{HH}= 5 Hz)
IVf	oil	30	37	4.60 (d,d,2H, J_{HF}= 47 Hz, J_{HH}= 5 Hz)

The transformation IV $\longrightarrow$ I was best carried out with mercuric chloride-mercuric oxide in methanol; the fluorinated keto-alcohols were isolated as DNP's (some examples appear in Table III); the latter were purified by preparative TLC (eluent 1% methanol in benzene). The DNP's were found to be contaminated by small quantities of the derivatives of the methyl ethers of the hydroxy ketones; they were removed by the chromatography.

It is noteworthy that no dehydration of these β-hydroxy ketones took place even under the strongly acidic conditions required to form the DNP derivatives. This is obviously due to the presence of the fluorine atom. Indeed, when IIIa was treated with mercuric oxide and boron trifluoride etherate according to Vedejs[9)], γ-fluorocrotonaldehyde $FCH_2.CH{=}CH.CHO$ was isolated in 40% yield as its DNP, m.p. 165^{o}; $\lambda_{max.}^{ethanol}$ 370 mμ (ε = 2.5 x 10^4); mol. wt. 268 (mass spectrum); nmr: δ (ppm) = 6.90 (centre of m, 2 olefinic H); 5.38 (d,d,2H of CH_2F; J_{HF} 50 Hz, J_{HH} 4 Hz); 11.30 (d, 1 H of $CH{=}N$).

Table III

DNP's of keto alcohols I

Compound	m.p.(^{o}C)	yield (%)	nmr spectrum of the CH_2F protons (δ(ppm))
Ib	155^{o}	80	4.66 (d,d,2H, J_{HF}= 45 Hz, J_{HH}= 6 Hz)
Ic	160^{o}	40	4.70 (d,d,2H, J_{HF}= 47 Hz, J_{HH}= 5 Hz)
Ie	170^{o}	45	4.63 (d,d,2H, J_{HF}= 44 Hz, J_{HH}= 4 Hz)

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7) Satisfactory elemental analyses were obtained for all new compounds. Spectral data were in accord with the structural assignments made. The nmr spectra were recorded on a "Varian T-60", $CDCl_3$ served as solvent and TMS as internal reference.

8) The oily product IVd could not be obtained in pure form and was not further investigated.

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