Total Synthesis of Fulvic Acid

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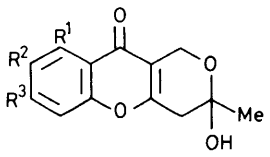
Synthesis of fulvic acid (**1a**) was accomplished by a route involving selective ozonization of 9-propenylpyranobenzopyran (**1c**), obtained by a regioselective cyclization of the 2-methylsulphinylmethyl 1,3-dione (**3c**).

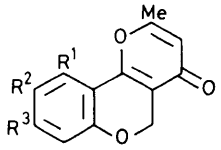
In earlier preliminary studies[1] aiming at the syntheses of fungal metabolites such as fulvic acid (**1a**)[2] and citromycetin (**2a**),[3] we have shown that both the basic skeletons in (**1a**) and (**2a**), 4,10-dihydro-3-hydroxy-3-methyl-1*H*,3*H*-pyrano[4,3-*b*]-[1]benzopyran-10-one (**1b**) and 2-methyl-4*H*,5*H*-pyrano-[3,2-*c*][1]benzopyran-4-one (**2b**), were derived from a common intermediate (**3b**) corresponding to the biogenetic intermediate (**3a**) for (**2a**).[4] We describe here the first total synthesis of (**1a**) *via* the sulphinylmethyl dione (**3c**), which may be regarded as an equivalent of (**3b**), by use of the synthetic strategy for (**1b**).

The acetophenone (**4**), chosen as a starting material, was prepared from vanillin *via* 9 steps (32% total yield) by a modification of Dean's method.[5] The hydroxyketone (**6**), obtained by aldol condensation of (**4**) and the aldehyde (**5**),[6] was converted into the diketone (**8**) by treatment with *N*-chlorosuccinimide and dimethyl sulphide followed by reduction with zinc dust and acetic acid in 83% yield from (**4**).† Alkylation of (**8**) using methylthiomethylpiperidine hydrochloride[7] in dioxane afforded the thiomethyl dione (**9**) in 87% yield, which was converted into the sulphinylmethyl dione (**3c**) by treatment with sodium metaperiodate. Acid treatment [5% H_2SO_4–AcOH–tetrahydrofuran (THF) (1 : 1 : 4), reflux, 3 h][1c] of (**3c**) caused regioselective cyclization to give the dihydropyrone (**10**) as an unstable oily product (positive $FeCl_3$ test). Application of Fujita's debenzylation method[8] to the BF_2-complex (**11**) of the dihydropyrone (**10**) gave the phenol (**12**). Acid catalysed cyclization [conc. HCl–AcOH (1 : 6), room temp., 24 h] of (**12**) afforded the pyrano[4,3-*b*][1]benzopyran (**13**) in 22% total yield from (**9**). Ozonization of (**13**) gave unidentified complex products owing to the presence of the various double bonds. However prior hydration [5% HCl–acetone (1 : 2), room temp., 4 days][9] of the pyrone (**13**) to give the alcohol (**1c**) and ozonization of (**1c**) in the presence of a dye (Oil Violet) as an internal indicator[10] followed by reduction with dimethyl sulphide yielded the aldehyde (**1d**) (m.p. 172—174 °C) in 64% yield from (**13**). Oxidation of (**1d**) with sulphamic acid and sodium chlorite[11] afforded the unstable *O*,*O*-dimethylfulvic acid (**1e**), which was converted into the anhydro compound (**14**) on chromato-



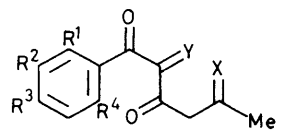
(**1**)

a; $R^1 = CO_2H$, $R^2 = R^3 = OH$
b; $R^1 = R^2 = R^3 = H$
c; $R^1 = CH{=}CHMe$, $R^2 = R^3 = OMe$
d; $R^1 = CHO$, $R^2 = R^3 = OMe$
e; $R^1 = CO_2H$, $R^2 = R^3 = OMe$



(**2**)

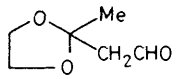
a; $R^1 = CO_2H$, $R^2 = R^3 = OH$
b; $R^1 = R^2 = R^3 = H$



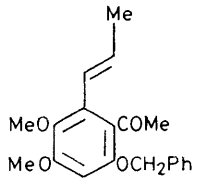
(**3**)

a; $R^1 = CO_2H$, $R^2 = R^3 = R^4 = OH$, $X = O$, $Y = CH_2$
b; $R^1 = R^2 = R^3 = H$, $R^4 = OCH_2Ph$, $X = OCH_2CH_2O$, $Y = CH_2$
c; $R^1 = CH{=}CHMe$, $R^2 = R^3 = OMe$, $R^4 = OCH_2Ph$, $X = OCH_2CH_2O$, $Y = H$, $CH_2S(O)Me$

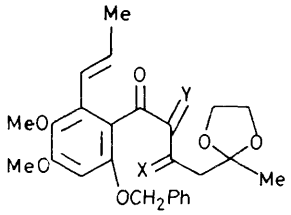
† The structure of the intermediate diacyl-*S*-ylide (**7**) was confirmed by i.r., ^1H n.m.r., and ^{13}C n.m.r. spectral data.



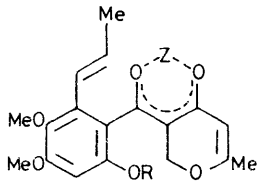
(5)



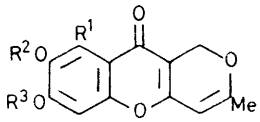
(4)



(6) X = H, OH, Y = H,H
(7) X = O, Y = SMe_2
(8) X = O, Y = H,H
(9) X = O, Y = H, CH_2SMe



(10) R = CH_2Ph, Z = H
(11) R = CH_2Ph, Z = BF_2
(12) R = H, Z = BF_2



(13) R^1 =CH=CHMe R^2=R^3= Me
(14) R^1 = CO_2H, R^2 = R^3 = Me
(15) R^1 = CO_2H, R^2,R^3= H,Me
(16) R^1 = CO_2H, R^2 = R^3 = H

graphy on silica or recrystallization. On treatment with conc. H_2SO_4–acetone (1:250) the alcohol (**1e**) was converted into anhydro-*O*,*O*-dimethylfulvic acid (**14**) [74% yield from (**1d**)]. Demethylation of (**14**) with BBr_3 gave anhydro-*O*-monomethylfulvic acid (**15**) in low yield, whereas treatment with $AlCl_3$ (10 equiv.) and dimethyl sulphide in anhydrous CH_2Cl_2 at −10 °C furnished anhydrofulvic acid (**16**) (m.p. 236—239 °C) in 52% yield. Finally conversion of (**16**) into fulvic acid (**1a**)‡ was achieved by treatment with acid [5% HCl–acetone (1:2), 55 °C, 24 h] (68% yield). The physical and spectral data for (**1a**) [m.p. 242—244 °C; *m/z* 308.0543 ($C_{14}H_{12}O_8$ requires 308.0531); $\nu_{max.}$ 3430, 1635, 1552, 1480, 1450, and 1175 cm^{-1}; $\lambda_{max.}$ (log ε) (EtOH) 224 (4.50), 317 (4.07), and 343 nm (4.06); ^1H n.m.r., [$(CD_3)_2SO$], δ 1.45 (s, CH_3), 2.72 (AB q, *J* 17.6 Hz, 4-H), 4.43 (s, 1-H), 6.22 (s, 3-OH), 6.89 (s, 6-H), 9.74 and 11.22 (br. s, 7,8-OH), and 13.27 (br. s, 9-CO_2H)] were identical with that of natural fulvic acid.

‡ The interconversion of (**16**) and (**1a**) is known (see ref. 2c), but our attempts to use this method led to unsatisfactory results.

We thank Professor S. Sakamura of Hokkaido University for kindly providing natural fulvic acid, methyl *O*,*O*-dimethylfulvate, and their spectroscopic data.

Received, 2nd July 1984; Com. 943

References

1 (a) T. Watanabe, S. Katayama, Y. Nakashita, and M. Yamauchi, *J. Chem. Soc., Chem. Commun.*, 1981, 761; (b) M. Yamauchi, S. Katayama, Y. Nakashita, and T. Watanabe, *ibid.*, 1983, 335; (c) *J. Chem. Soc., Perkin Trans. 1*, 1984, 503; (d) *ibid.*, in the press.
2 (a) For isolation see A. E. Oxford, H. Raistrick, and P. Simonart, *Biochem. J.*, 1935, **29**, 1102; T. Sakai, A. Ichihara, and S. Sakamura, *Agric. Biol. Chem.*, 1981, **45**, 1275; (b) for structure determination see F. M. Dean, R. A. Eade, R. A. Moubasher, and A. Robertson, *Nature (London)*, 1957, **179**, 366; (c) *J. Chem. Soc.*, 1957, 3497.
3 For isolation see A. C. Hetherington and H. Raistrick, *Philos. Trans. R. Soc. London, Ser. B*, 1931, **220**, 209; for structure determination see J. B. D. Mackenzie, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1950, 2965.
4 (a) W. B. Whalley, *Chem. Ind. (London)*, 1958, 131; T. Money, *Nature (London)*, 1963, **199**, 592; R. Thomas, *Biochem. J.*, 1961, **78**, 748; (b) I. Kurobane and C. R. Hutchinson, *Tetrahedron Lett.*, 1981, **22**, 493; G. E. Evans and J. Staunton, *J. Chem. Soc., Chem. Commun.*, 1976, 760.
5 F. M. Dean, D. R. Randell, and G. Winfield, *J. Chem. Soc.*, 1959, 1071.
6 Z. Horii, H. Hakusui, T. Shigeuchi, M. Hanaoka, and T. Momose, *Yakugaku Zasshi*, 1972, **92**, 503.
7 M. Yamauchi, S. Katayama, and T. Watanabe, *Synthesis*, 1982, 935.
8 K. Fuji, T. Kawabata, and E. Fujita, *Chem. Pharm. Bull.*, 1980, **28**, 3662.
9 J. Ficini, P. Kahn, S. Falon, and M. Touzin, *Tetrahedron Lett.*, 1979, 67.
10 T. Veysoglu, L. A. Mitscher, and J. K. Swayze, *Synthesis*, 1980, 807.
11 B. O. Lindgren and T. Nilsson, *Acta Chem. Scand.*, 1973, **27**, 888.