The Synthesis of Oosponol and Oospoglycol

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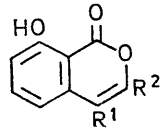
Summary Oosponol and (−)-oospoglycol (of about 66% optical purity) have been synthesized from 8-hydroxyisocoumarin-4-carboxylic acid (= oospoic acid).

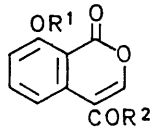
OOSPONOL (I), oospoglycol (II), and oospolactone (III) have been isolated as metabolites of a fungus, *Oospora astringenes*, which was obtained from the air of a bronchial asthma patient's room. Of these metabolites, (I) and (II) have been found to have biological activity in guinea pigs.[1] Structures for these compounds have been suggested by Yamamoto and his co-workers.[2] Oosponol and oospoglycol are the first naturally occurring 4-substituted isocoumarins to be isolated.[3] Although a synthesis of oosponol diacetate has been claimed previously, the yield of the compound was reported as only a trace.[4] We have now performed the total synthesis of oosponol and (−)-oospoglycol by the obvious route.

Oospoic acid[2] (IV) was acetylated and then treated with oxalyl chloride to give an acid chloride (V). The chemical properties of (V) seemed somewhat unusual. For example, reaction of (V) with diazomethane followed by the treatment with acetic acid in the presence of cupric chloride gave a complex mixture, from which oosponol diacetate was isolated in 0·3% yield by previous workers.[4] Condensation of (V) with diethyl ethoxymagnesium-malonate in chlorobenzene afforded the expected product (VI), (60% yield), m.p. 81°, ν_{max} (Nujol) 1770, 1750, and 1680 cm^{-1}, which was hydrolysed and decarboxylated by heating under reflux with dilute sulphuric acid in acetic acid for 6 h to give (VII), (90% yield), m.p. 111°, ν_{max} (Nujol) 1690 and 1630 cm^{-1}, δ($CDCl_3$) 2·5 (s, 3H), 8·0 (s, 1H), and 10·9 (s, 1H). A minor product was the isocoumarin aldehyde (VIII), (5%), m.p. 141°. Compound (IX), the product of acetylation of (VII), was treated with bromine (1·1 equiv.) in acetic acid at 50° in the presence of a trace of benzoyl peroxide to afford the ω-bromo-compound (X), m.p. 138°. Oosponol diacetate (XI) was obtained in almost quantitative yield by heating (X) under reflux with anhydrous sodium acetate in acetic acid for 4 h. Attempted hydrolysis of (XI) to oosponol was unsuccessful under various acidic or basic conditions, but the reaction proceeded enzymatically in high yield. The diacetate (XI) was suspended in acetate buffer (pH, 5·0, 0·05M) and incubated with a commercial enzyme, cellulosin (*Aspergillus niger*), at 20° for 26 h. The isolated product, m.p. 176°, was completely identical with natural oosponol with regard to i.r. spectrum ($CHCl_3$), m.p., mixed m.p.

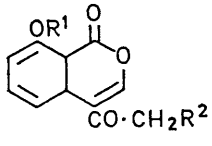
Reduction of oosponol diacetate with sodium borohydride (0·5 equiv.) in absolute methanol, followed by silica gel chromatography ($CHCl_3$ as solvent), gave two hydroxyacetates, (XII) (12% yield; m.p. 102°) and (XIII) (22% yield; m.p. 122°). Compound (XII) was converted into the triacetate (XIV), m.p. 140°, (Ac_2O–py) and compound (XIII) into a benzoate (XV), m.p. 142°, (PhCOCl–py) in good yield. The hydroxy-acetate (XIII) was hydrolysed with dilute sulphuric acid in acetic acid or with 2% cellulosin in acetate buffer (pH, 5·0; 0·05M) for 7 h to give (±)-oospoglycol, the i.r. and u.v. spectra of which were identical with those of natural (−)-oospoglycol.

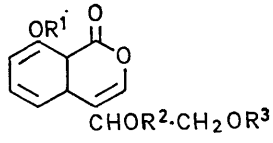


(I) R^1 = CO·CH_2OH, R^2 = H
(II) R^1 = CHOH·CH_2OH, R^2 = H
(III) R^1 = R^2 = Me
(VIII) R^1 = CHO, R^2 = Me



(IV) R^1 = H, R^2 = OH
(V) R^1 = Ac, R^2 = Cl
(VI) R^1 = Ac, R^2 = $CH(CO_2Et)_2$





(VII) R^1 = R^2 = H
(IX) R^1 = Ac, R^2 = H
(X) R^1 = Ac, R^2 = Br
(XI) R^1 = Ac, R^2 = OAc

(XII) R^1 = R^2 = H, R^3 = Ac
(XIII) R^1 = R^3 = Ac, R^2 = H
(XIV) R^1 = R^2 = R^3 = Ac
(XV) R^1 = R^3 = Ac, R^2 = CO·Ph

Optical resolution of (±)-oospoglycol was achieved as follows. When the triacetate (XIV) was partially hydrolysed with 0·1% cellulosin in acetate buffer (pH, 5·0) at 20° for 26 h, there was obtained preferentially in 33% yield one antipode, (−)-oospoglycol,† $[\alpha]_D$ −12·5° (*c* 0·4, EtOH), by silica gel chromatography. The residual hydrolysed mixture was further treated with 2% cellulosin for 39 h to afford in 35% yield the other antipode, (+)-oospoglycol $[\alpha]_D$ +20°.

It is interesting that under similar condition (0·5% enzyme concentration, 20 h), the benzoate (XV) was hydrolysed preferentially to (+)-oospoglycol, $[\alpha]_D$ +10°.

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† Natural oospoglycol; $[\alpha]_D$ −40° (*c* 0·46, EtOH). Authentic samples of natural oosponol and oospoglycol were provided by Dr. Y. Abe, Takeda Chemical Industries Ltd., whom we thank.

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