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THE SYNTHESIS OF FLAVENSOMYCINIC ACID

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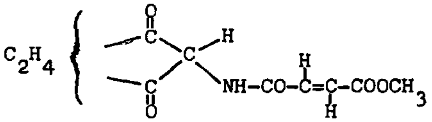
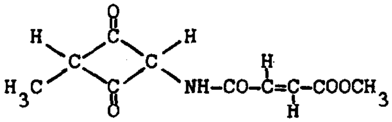
In the previous communications (1) the partial structure of flavensomycinic acid had been shown to be a 2-fumarylamino-1,3-cyclodione methyl ester (I).


(I)

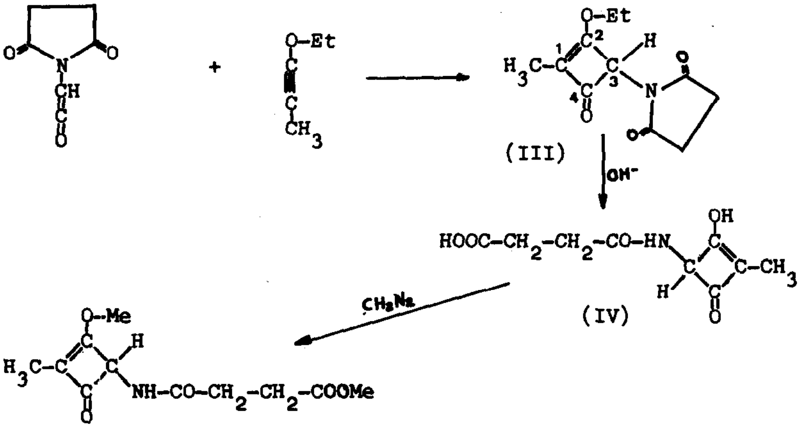
Some physical properties of the compound (the strong acidity shown by pK'_a and U.V. determinations; the hypsochromic effect of 10 mμ for the enolether of dihydroflavensomycinic acid with respect to its anion), some chemical properties (positive Kuhn-Roth determination and the identification on paper chromatography of propionic acid after strong alkaline hydrolysis) and, chiefly, an erroneus interpretation of N.M.R. spectra, impelled us to postulate for flavensomycinic acid the complete structure (II) in which the β-diketone is in a 4-membered ring.


(II)

Recently our investigation (2) of 2-acylamino-1,3-diketones of 5- and 6-membered rings, although confirmed the structure

(I), induced us to a new examination of the structure of flavensomycinic acid[a]; a conclusive evidence was achieved through the synthesis of 2-acylaminocyclobutan-1,3-diones.

The cycloaddition of ethoxypropine (3) to succinimidoketene (4) afforded compound (III) in 70% yield, m.p. 83°C after chromatography on Florisil and crystallization from ethyl ether; U.V. (CH_3OH) λ_{max} 240 (4.06); I.R. (nujol) ν_{max} 1765, 1706, 1625; N.M.R. ($CDCl_3$) 1.41 t (3H) and 4.38 q (2H)(CH_3-CH_2-O), 2.7 s (4H)(-CO-CH_2-CH_2-CO-), 1.78 d (3H; J 2.3)(CH_3-$C_{(1)}$), 5.4 q (1H; J 2.3)(H-$C_{(3)}$)[b].



(III)

(IV)

(V)

(a) For ex.: in the U.V. spectrum of 2-acetylaminocyclopentan-1,3-dione the hypsochromic effect enol ether → anion is 10 mμ.

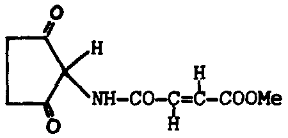
(b) λ_{max} of the U.V. spectra are in mμ (intensities as lg ε). ν_{max} of the I.R. spectra are in cm^{-1}. The chemical shifts of N.M.R. spectra are in δ=ppm (J in cps); TMS was used as internal reference; s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet.

By mild alkaline hydrolysis with NaOH 0.2N compound (IV) was obtained from (III); m.p. 182°C; U.V. (CH_3OH-NaOH) λ_{max} 251 (4.25); I.R. (nujol) ν_{max} 3300 and 3050, 2700–2300, 1736, 1695, 1656, 1543; N.M.R. (d_6-DMSO) 1.46 d (3H; J 2.3)(CH_3-$C_{(1)}$), 2.37 broad s (4H)(-CO-CH_2-CH_2-COO-), 5.16 double q (1H; $J_{H,NH}$ 9, J_{H,CH_3} 2.3)(H-$C_{(3)}$), 8.28 broad d (1H; $J_{NH,H}$ 9)(N-H), 10.6 broad (2H)(2 O-H).

Treatment of the acid (IV) with excess diazomethane gave the methyl ester methyl ether (V); m.p. 130°C; U.V. (CH_3OH) λ_{max} 240 (4.10); I.R. (nujol) ν_{max} 3250 and 3030, 1754, 1724, 1644, 1616, 1541; N.M.R. ($CDCl_3$) 1.63 d (3H; J 2.3)(CH_3-$C_{(1)}$), 2.59 m (4H)(-CO-CH_2-CH_2-COO-), 3.64 s (3H)(-$COOCH_3$), 4.07 s (3H) (=C-OCH_3), 5.42 double q (1H; $J_{H,NH}$ 9, J_{H,CH_3} 2.3)(H-$C_{(3)}$), 6.72 broad d (1H; $J_{NH,H}$ 9)(N-H).

The properties of the compound (V) are different from those of dihydroflavensomycinic acid methyl ether.

The reaction of 2-aminocyclopentan-1,3-dione hydrochloride(c) with fumaric acid methyl ester chloride (1b) afforded compound (VI), m.p. 232-3°C.



(VI)

The compound (VI) is identical with flavensomycinic acid as shown by mixed m.p. determination and U.V., I.R., N.M.R. comparison. Catalitic hydrogenation of (VI) furnished the dihydroderivative (VII), which on treatment with diazomethane gave the methyl ether (VIII).

The compounds (VII) and (VIII) are identical with the correspon-

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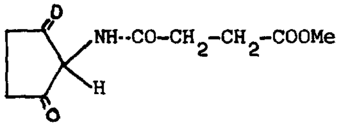
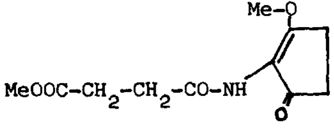
(c) The compound was obtained by reduction of 2-isonitrosocyclopentane-1,3-dione (2) with tin and hydrochloric acid.

ding derivatives of flavensomycinic acid (1).


(VII)


(VIII)

The previously reported (1b) N.M.R. spectra of dihydroflavensomycinic acid and of its methyl ether agree perfectly with the structures (VII) and (VIII). In fact N.M.R. spectrum of (VII) shows four protons at 152 cps and four at 164 cps as broad singlets ascribable to the two systems $-CO-CH_2-CH_2-CO-$; in the N.M.R. spectrum of (VIII) while the broad singlet of the group $-CO-CH_2-CH_2-CO-$ of the succinic chain is unchanged, the four protons of the cyclopentane ring are in the same region as multiplet.

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