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THE STRUCTURE OF HYPERFORIN

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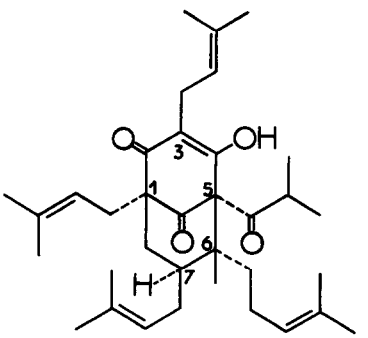
Hyperforin, $C_{35}H_{52}O_4$, is an antibiotic from St.-John's wort (Hypericum perforatum L.) active against Gram positive bacteria (1). We have found it to possess the structure and stereochemistry I.



I

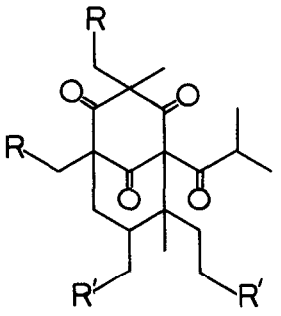
Hyperforin has the UV spectra of an enolized cyclic β-diketone [λ_{max} 278 nm (ε 8400) and 298 nm (ε 12000) in 0.05 N ethanolic HCl and NaOH, respect.] and forms a C-methyl derivative [λ_{max} 294, 303 nm (ε 142, 138)] on alkylation with MeI + NaH in DMSO. Oxidation of this derivative by $KMnO_4$ + $NaIO_4$ yielded 4 moles of Me_2CO and a tetracarboxylic acid (II) whose tetramethyl ester (III) underwent isomerisation when heated at 180°. The thermolysis product (IX) gave Me_2CHCO_2H on acid hydrolysis and had the chromophore of a cross conjugated triketone [λ_{max} 240, 281 nm (ε 10900, 12800) and 280 nm (ε 18800) in acid and basic solution, respectively]. Thereby followed the partial structure $O{=}\underset{|}{C}\text{-}\underset{|}{C}{=}C(OH)\text{-}\underset{|}{C}(COPr^i)\text{-}\underset{|}{C}{=}O$ for hyperforin, which led to the tentative formulation of this bicyclic tetraketone as a 1,3-bridged 3,5-dialkylphloroisobutyrophenone.

To corroborate this formulation, a C-benzyl analog (X) of IX was prepared

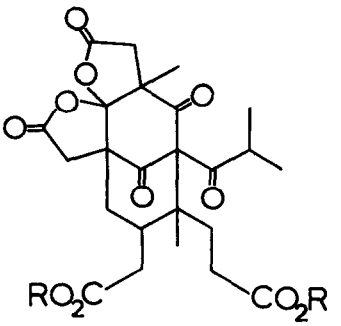
from hyperforin in a similar way and de-benzylated by hydrogenation on Pd in methanolic HCl. The UV spectra of the hydrogenolysis product (XII) in acid, neutral and basic solutions were found to be identical with those of 3,3,5-trimethylated phloroacetophenone thus proving the substitution pattern in the phloroglucinol ring.

In order to elucidate the structure of the substituents the tetracarboxylic acid II was converted via dilactones (VII and VIII) into a diester diacid (IV) (1 mole of DCC, then CH_2N_2 and 5% $NaHCO_3$ aq.). The latter was bromo-decarboxylated by treatment with Br_2 + HgO and the resultant dibromide (V) reduced with Zn + AcOH to yield two products. The main product (VI) was found by NMR to contain four methyls on quaternary carbons, while only two were present in the parent acid II; hence isopentenyl structures in positions 3 and 5 of the phloroisobutyrophenone moiety were deduced for the two alkyl groups that gave rise to the methyls in the above degradation. An analogous conversion XIII → XIV revealed the presence of a third isoprenyl but attached to the methine of the C_1-C_5 bridge of the ring. Cleavage of the bridge occured to a small extent in the Zn-reduction of the dibromide V yielding an unsaturated monocyclic tetraketone (XI) as a minor product. Oxydation of XI by $KMnO_4$ + $NaIO_4$ afforded methyl levulate (detected by GLC), thus demonstrating the fourth side chain of the antibiotic to be homo-isoprenyl and to be attached to a quaternary carbon carrying a methyl group. Thereby followed structure I for hyperforin.

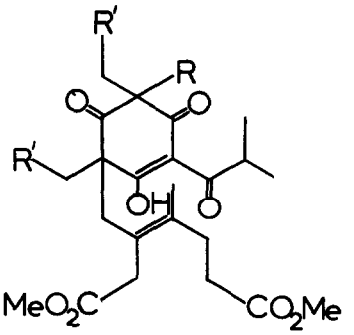
Biogenetically, formation of the bicyclo[3,3,1]nonane structure I could be accounted for by the concerted intramolecular addition of a phloroisobutyrophenone anion and electrophilic attack by isopentenyl pyrophosphate on the internal olefinic bond of a geranyl containing precursor (XV); this should result in a trans arrangement of the homo-isoprenyl and isopentenyl residues in the 6 and 7 positions of the antibiotic. To verify this hypothesis, the triketone ring and the isopropylidene groups of hyperforin were cleaved by hydrolysis with $Ba(OH)_2$ followed by oxidation with $KMnO_4$ + $NaIO_4$. The resultant acid (XVI) was converted via a five membered anhydride diacid into the diacid diester (XVII) (DCC, then CH_2N_2 and $NaHCO_3$ aq.) and the latter was oxidized on a Pt anode to give the olefinic diester (XVIII). After $NaBH_4$ reduction followed



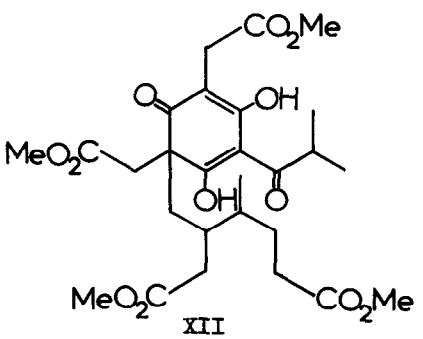
II R = R′ = CO_2H
III R = R′ = CO_2Me
IV R = CO_2H, R′ = CO_2Me
V R = Br, R′ = CO_2Me
VI R = H, R′ = CO_2Me



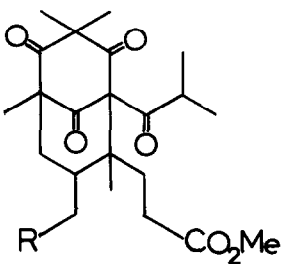
VII R = H
VIII R = Me



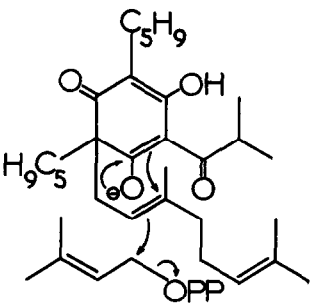
IX R = Me, R′ = CO_2Me
X R = $PhCH_2$, R′ = CO_2Me
XI R = Me, R′ = H



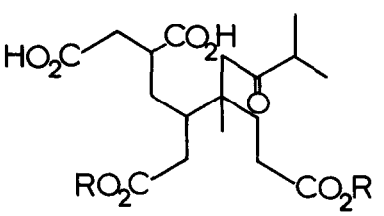
XII



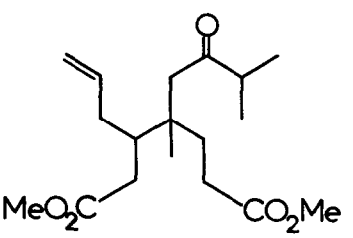
XIII R = CO_2H
XIV R = H



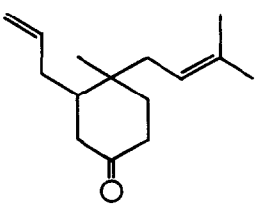
XV



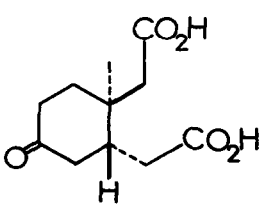
XVI R = H
XVII R = Me



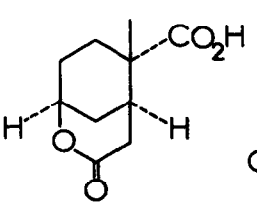
XVIII



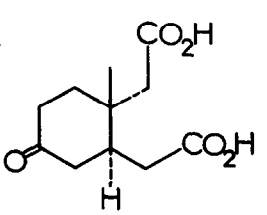
XIX



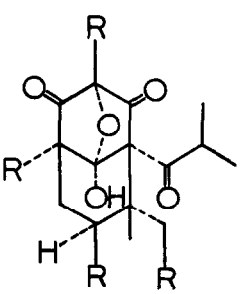
XX



XXI



XXII



XXIII
R = $Me_2C{=}CHCH_2$

by dehydration with $POCl_3$, Beckmann cyclisation, and hydrolysis, the trisubstituted cyclohexanone (XIX) was obtained that yielded the dicarboxylic ketoacid (XX) on oxidation by $KMnO_4$ + $NaIO_4$. On the other hand, the lactone acid (XXI) prepared from cholesta-7,9-diene-3-ol (2) was converted by the Arndt-Eistert procedure into an ester of the homologous lactone acid. Alkaline hydrolysis of this ester lactone followed by CrO_3 oxidation afforded the keto acid (XXII), enantiomeric to the degradation product XX of the antibiotic; hyperforin is therefore of the 6S,7R configuration.

The only enolized β-diketone group of hyperforin is readily α-hydroxylated on $NaIO_4$ oxidation, the product being a bridged hemiketal (XXIII) with the exocyclic carbonyl fixed syn to the hemiketal hydroxyl by an intramolecular H-bond. NMR studies of this substance have shown that saturation of its H(O) signal has no effect on the 6-methyl resonance while significant NOE's are observed between the H(O) and some other protons. Therefore the trans configuration has been assigned to the hydroxyl (and consequently to the angular C-1 and C-5 side chains) with respect to the 6-methyl group, as shown in formula I. Independent proof of the absolute configuration I was furnished by the CD spectrum of XXIII which, like that of 5S-spiro-[4,4]-nonane-1,6-dione (3), exhibited a negative longwave Cotton effect indicative of the left hand helicity of the β-dicarbonyl chromophore $-\overset{\overset{O}{\|}}{C_4}-C_5-\overset{\overset{O}{\|}}{C}-Pr^i$.

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