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METABOLITES OF PYRENOMYCETES XI.[1] STRUCTURE OF AUROCITRIN, A NEW ANTIBACTERIAL PIGMENT FROM *HYPOCREA CITRINA*.

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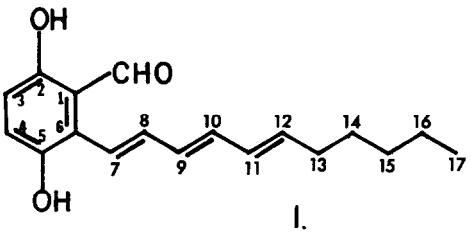
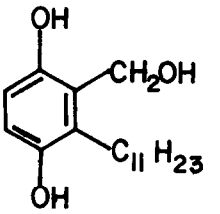
Isolation and structure elucidation of aurocitrin, a new antibiotic metabolite from two varieties of the hypocrealean fungus, *H. citrina*, is reported.

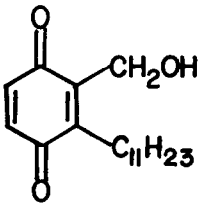
Hypocrea citrina (Fr.) Fr. var. *citrina* Fr. and *H. citrina* (Fr.) Fr. var. *americana* Canham, when grown in still cultures in a dextrose yeast medium in the dark at 25° produced red mycelial mats. From the extracts of the mycelia and the culture liquid, aurocitrin (I) was isolated as orange red crystals. Aurocitrin, its hydrogenation product II, and the quinone III, were active at concentrations less than 1 ppm against *Staphylococcus aureus* in serial dilution tests. We wish to report here the chemical and spectroscopic data based on which the all *trans*-structure I was assigned to aurocitrin.



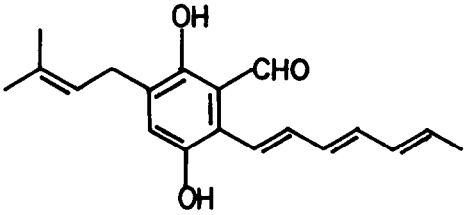
I.



II.



III.



IV.

Aurocitrin, $C_{18}H_{22}O_3$ MW 286.1557 had mp 106-7°, λ 413 (12,700), 314, (26,265) and 266 (35,750) nm; ν max 3200 (br) 1625, 1607 and 1570 cm^{-1}. The ^1H NMR spectrum showed an AB quartet at δ 6.83 and 7.19 (J = 8 Hz) for the C_3 and C_4 protons, a broad peak at δ 5.1 for the C_5-OH and two singlets at 10.01

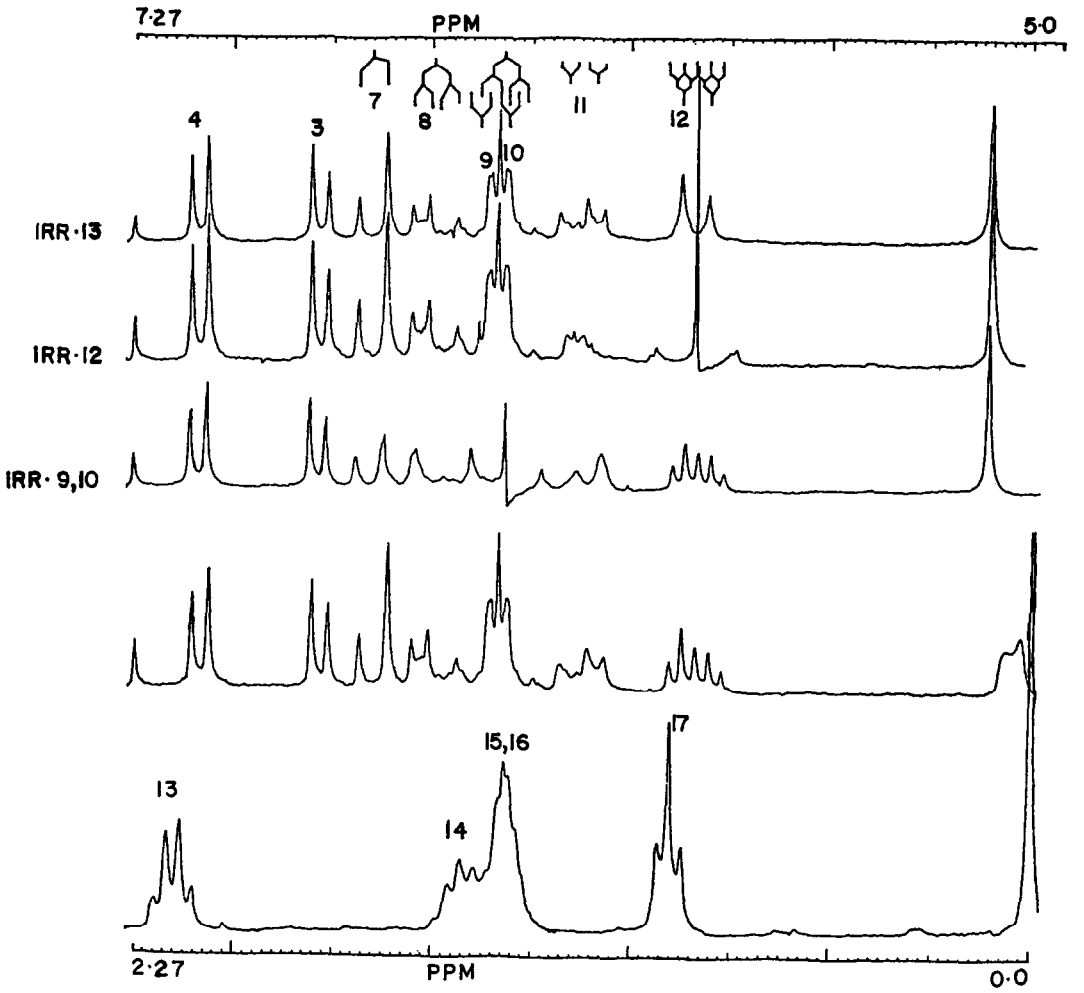

7·27
PPM
5·0
7
8
11
12
4
3
9
10
IRR·13
IRR·12
IRR·9,10
15,16
17
13
14
2·27
PPM
0·0

Fig. 1

for the CHO and 11.4 (chelated C_2-OH). It also showed the presence of a *trans*-undecatrienyl side chain (Fig. 1). The ^{13}C NMR spectrum showed signals at δ 12.8 (C_{17}), 21.6 (C_{16}), 28.1 (C_{14}), 30.6 (C_{15}), 32.1 (C_{13}), 116.2 (C_3), 117.6 (C_1), 122.4 (C_4), 125.2 (C_6), 126.1, 130.5, 130.9, 135.3, 136.7, 139.2 (C_7-C_{12}), 147.2 (C_5), 149.1 (C_2) and 196.6 (CHO).

On catalytic hydrogenation in ethanol over platinum catalyst, aurocitrin absorbed 4 molecules of hydrogen to yield the octahydro derivative II, $C_{18}H_{30}O_3$ MW 294.2193, m.p. 108-10°, λ max 295 nm (3,800) shifts to 280 nm on adding sodium hydroxide; ν max 3300 (br), 1620 and 720 cm^{-1}, 60 MHz ^1H NMR spectrum in acetone-d6 showed a triplet 1.02 (3H, J = 5.5) for the C_{17} protons, a broad peak at 1.27 (18 H) for the C_8-C_{16} protons, a multiplet at 2.6 for C-7 protons, a broad peak at 4.38 (1H) for the CH_2-OH, a singlet at 4.78 (2H for CH_2-OH, an AB quartet at 6.45 and 6.65 (J = 8) for the aromatic protons, and singlets at 7.48 and 8.02 (phenolic hydroxyls). The ^{13}C NMR spectrum showed signals at 58.6 (CH_2OH), 113.5 (C_3), 115.1 (C_4), 125.8 (C_1), 128.5 (C_6), 148.4 (C_5) and 150.2 (C_2). It also showed signals at δ 14.0-32.2 for the sp^3 carbons of the side chain. The blue shift of the UV maximum on adding alkali suggested the hydroxyls were *para* to each other in the benzene ring.[2] In confirmation, II was converted quantitatively to the quinone III by silver carbonate on celite. Quinone III, MW 292 (CI-MS) melted at 49-51°, had ν max 3300 (br), 1652, 1626 and 714 cm^{-1}. The ^1H NMR spectrum showed a triplet at δ 0.9 for the end methyl, a broad peak at 1.25 for the side chain methylenes, a doublet of a doublet at 2.55 for the C_7 methylene, a singlet at 4.55 for the CH_2OH and a singlet at 6.6 for the ring protons.

Thus, aurocitrin has an aromatic ring with two vicinal protons and two hydroxyls *para* to each other. This defines the substitution pattern as in structure I. Detailed analysis of 220 MHz ^1H NMR spectrum using decoupling (see Fig. 1) showed that $J_{7,8} = J_{9,10} = J_{11,12} = 15$ Hz and $J_{8,9} = J_{10,11} = 10$ Hz establishing the triene system as all *trans*.

Auroglaucin, a metabolite of *Aspergillus glaucus*[3] was shown to have structure IV, but the heptatrienyl side chain geometry has never been determined. The close resemblance of the UV spectra[4] of auroglaucin and aurocitrin makes it highly likely that the auroglaucin has also an all *trans* side chain.

A long hydrophobic side chain with a hydrophilic ring, here, a hydroquinone, usually renders a compound physiologically active. Further, the chromophore of aurocitrin can be looked at as a tetra-ene-aldehyde similar to 13-*cis*-retinal, derivatives of which have shown anticancer activity.[5,6]

Aurocitrin probably is a true polyketide, but the possibility that it is formed from a C_{18} fatty acid cannot be ruled out.

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Footnotes and References:

1. For Part X see *J. Natural Products* (1979) in press. Susan T. Carey and M. S. R. Nair.

2. M. S. R. Nair and M. Anchel, *Phytochemistry* 16, 390 (1977).

3. A. Quilico, C. Cardani and I. Lucattelli, *Gazz. Chim. Ital.* 83, 1083 (1953).

4. M. Simonetta and C. Cardani, *ibid.*, 80, 750 (1950).

5. M. B. Sporn, R. A. Squire, C. C. Brown, J. M. Smith, M. L. Wenk and S. Springer, *Science* 195, 487 (1977).

6. H. Mayer, W. Bollag, R. Hanni and R. Ruegg, *Experientia* 34, 1105 (1978).

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