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FURTHER STUDIES ON THE STRUCTURES OF LUTEOSKYRIN RUBROSKYRIN AND RUGULOSIN

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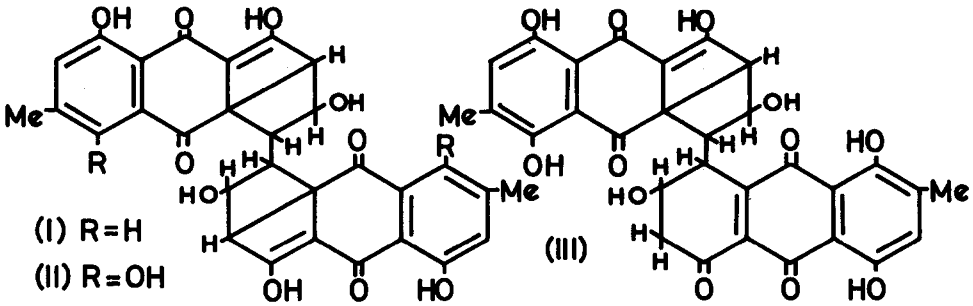
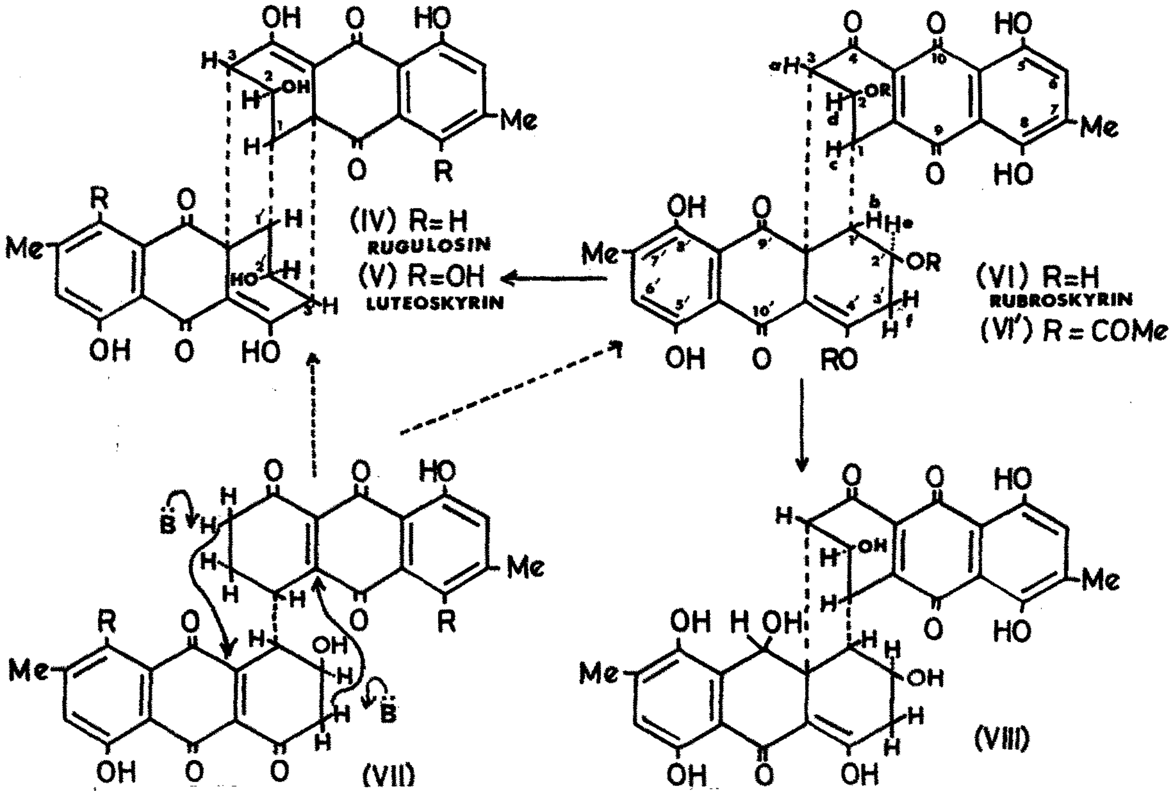
Recently we proposed (1) new structures of rugulosin (I), a pigment of <u>Penicillium rugulosum</u> Thom and some other fungi, luteoskyrin (II) and rubroskyrin (III), the pigments of <u>P. islandicum</u> Sopp. The evidence for the structural formulae was provided mostly by the NMR spectral analysis of these compounds and their derivatives.



(I) R=H
(II) R=OH
(III)

However, an alternative structure (VI) for rubroskyrin has now been forwarded on the basis of NMDR experiments on rubroskyrin triacetate, $C_{36}H_{28}O_{15}$, m.p. 262-263°(decomp.),$[\alpha]^{31}_{D}$ − 333° (dioxane), $IR^{CHCl_3}_{max}$ ν cm^{-1}: 1770 (sh) (enolic acetate C=O), 1745 (alcoholic acetate C=O), 1705 (six-membered ring C=O), 1655 (sh), 1640 (chelated C=O), 1620 (benzene ring), from which rubroskyrin is recovered readily on treatment with 10% NaOH.

On the basis of this finding, a renewed interpretation of the NMR spectra of rugulosin and luteoskyrin (see Fig.I in the previous report (1)) has led to the conclusion that they should be represented by structures (IV) and (V), respectively.



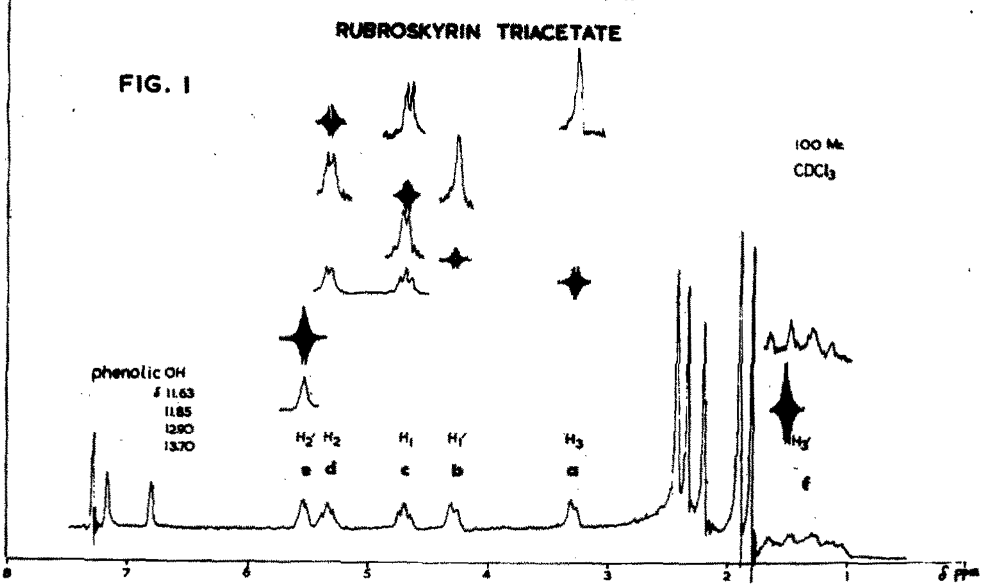
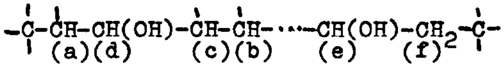


FIG. I

In the NMR spectrum of rubroskyrin triacetate (in $CDCl_3$)(Fig.I) signals (e) (δ 5.53, br.s) and (d) (δ 5.34, br.t) are attributed to protons on the carbon bearing acetoxyl.

The spin decoupling experiments demonstrated the following coupling correlations of the protons: e ↔ f, a ↔ d ↔ c and c ↔ b. Accordingly the sequence and relation of protons can be illustrated as follows:



$$-\overset{|}{\underset{|}{C}}-\underset{(a)}{\overset{|}{C}}\underset{(d)}{H}-CH(OH)-\underset{(c)}{\overset{|}{C}H}-\underset{(b)}{\overset{|}{C}H}-\cdots-\underset{(e)}{CH(OH)}-\underset{(f)}{CH_2}-\overset{|}{\underset{|}{C}}-$$

On the other hand, it would not be so unreasonable to assume a biogenetical intermediate (VII)* from which rugulosin, luteoskyrin and rubroskyrin can be derived by a Michael-type reaction. The structural formulae (I,II and III) proposed in the previous paper (1) for these compounds, respectively, were deduced in considering that such a reaction had occurred within each monomeric half of the precursor molecule (VII). However,there is an alternative possibility of occurrence of such a reaction between different molecular halves to result in the multi-bonded structures, IV, V and VI.

Adopting this biogenetical concept, the NMR spectra of rubroskyrin triacetate (VI') and dihydrorubroskyrin (VIII) (see Fig.III of the previous paper(1)) can reasonably be explained by the revised assignments (Table I).

The dihedral angle between $H_{(1')}$and $H_{(2')}$ measured from the Dreiding model of rubroskyrin triacetate (VI') is about 90°, which is in agreement with the non-coupling relation of signals (b) and (e). The dihedral angles (30~45°) observed at $H_{(1'\sim 1)}$,$H_{(1\sim 2)}$and $H_{(2\sim 3)}$ also agree the coupling constant(J:ca. 5 cps) of the signals (b),(c),(d) and (a).

The NMR spectra of rugulosin and luteoskyrin (cf.Fig.I in the previous paper (1)) can be interpreted satisfactorily based on the revised structures,(IV) and (V), respectively, by altering the former assignment of the proton signals at 1(1') and 3 (3') (Table II)**

The protons (δ3.38) at 1 and 1' of rugulosin are subjected to a strong deshielding effect of the carbonyls at 9 and 9' positions. The proton (δ4.29) at the 1-position of rubroskyrin triacetate is also in the same situation. Reduction of the carbonyl at the 9 and 9'-positions of rugulosin and that of the 9'-position of rubroskyrin caused a remarkable up-field shift of the above proton signals to δ2.70 and δ3.40, respectively.

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* (-)Rugulosin has recently been obtained during the preparation of (-)flavoskyrin from *P. islandicum* Sopp NRRL 1175, while (+)rugulosin was isolated from other various fungi (lit.cit. in(1)). The stereochemistry of VII must be reverse in the latter case. ------ ** The fused four-membered ring structures of rugulosin(I),luteoskyrin(II) and rubroskyrin(III) would have the same stereochemical dispositions of protons at 1,2 and 3 positions, which should give the same NMR coupling relation. However,rubroskyrin triacetate differs from rugulosin,luteoskyrin and their acetates with respect to the coupling relations of these protons. This also favours the multi-bonded structures of rugulosin(IV),luteoskyrin(V) and rubroskyrin (VI).

TABLE I

The NMR Spectra of Rubroskyrin Triacetate (VI') and Dihydrorubroskyrin (VIII)

Position of proton	Chemical Shift (δ ppm)	
	Rubroskyrin triacetate(VI') (in $CDCl_3$)	Dihydrorubroskyrin(VIII) (in d_6-DMSO)
(f) 2H (3')	1.21, 1.56(a pair of AB doublets, J: 17.5 cps)	1.22, 2.09(a pair of AB doublets,J: 20 cps)
(e) H (2')	5.53 (br.s)	4.31 (br.s)
(b) H (1')	4.29 (br.d. J: 5 cps)	3.40 (br.)
(c) H (1)	4.70 (br.t. J: 5 cps)	4.07 (br.)
(d) H (2)	5.34 (br.t. J: 5 cps)	4.84 (br.)
(a) H (3)	3.29 (br.d. J: 5 cps)	3.07 (br.d.)
$\mathrm{C\underline{H}_3}$ (7')	2.33 (s)	2.17 (s)
(7)	2.20 (s)	2.12 (s)
Arom.H (6')	7.15 (s)	7.00 (s)
(6)	6.80 (s)	6.72 (s)
Acetyl $\mathrm{C\underline{H}_3}$ (4')	2.42 (s)	----
(2)or(2')	1.91 (s), 1.79(s)	----
Phenolic $\mathrm{O\underline{H}}$ (5,5',8,8')	11.63, 11.85, 12.90, 13.70;	10.33, 11.45, 12.82, 13.00
Enolic $\mathrm{O\underline{H}}$ (4')	----	14.14
Alcoholic $\mathrm{O\underline{H}}$ (2')	----	5.06 (br.)
(2)	----	3.40 (br.)
H (9')	----	5.37 (d)
Alcoholic $\mathrm{O\underline{H}}$ (9')	----	8.07 (d)

TABLE II

The NMR Spectra of Rugulosin (IV) and Luteoskyrin (V) (in d_6-DMSO)

Position of proton	Chemical Shift (δ ppm)	
	Rugulosin (IV)	Luteoskyrin (V)
(a)* H (3,3')	2.78 (d. J: 5.5 cps)	2.96 (d. J: 5.5 cps)
(b)* H (1,1')	3.38 (br.s)	3.36 (br.s)
(c)* H (2,2')	4.38 (br.d. J: 5.5 cps)	4.53 (br.d. J: 5.5 cps)
$\mathrm{C\underline{H}_3}$ (7,7')	2.42 (s)	2.28 (s)
Arom.H	7.16 (d. J: 1 cps) 7.43 (d. J: 1 cps)	7.28 (s) ----
Phenolic $\mathrm{O\underline{H}}$ (5,5')	11.37 (s) ----	11.28 (s) 12.38 (s)
Enolic $\mathrm{O\underline{H}}$ (4,4')	14.54 (s)	14.53 (s)
Alcoholic $\mathrm{O\underline{H}}$ (2,2')	5.38	5.48

* See Fig.I in the previous paper (1)

An X-ray crystallographical analysis of a bromination product of tetrahydrorugulosin is now under progress, on which we will report soon.

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