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Naturally Occurring Rubiadins. A Caveat

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A number of typical rubiadins have been prepared by unambiguous means, and their characteristics reveal that the structures of most natural products so designated are erroneous.

During the last twenty odd years, a number of substances (about twenty-five) considered to be substituted rubiadins (i.e. 1,3-dihydroxy-2-methyl-anthraquinones) have been isolated from plants belonging in general to the families Rubiaceae and Leguminosae. The structural determinations were mainly based on spectroscopic data and colour reactions, more rarely on degradations or not unambiguous syntheses. Evidence for these proposals is therefore rarely compelling and in some cases obvious inconsistencies become quite apparent. That these structures have now found their way into reviews$^{1)}$ and standard reference books$^{2)}$ urgently requires that rigorous criteria for this type of structure be provided.

Syntheses of some representative members of this series by reliable methods and identification of certain characteristics attributable to common features would conveniently confirm or invalidate the status of these products. The methodology$^{3,4)}$ for regiospecific and unequivocal syntheses of this nature is now available and requires only that a 2-methylacetoacetate (1) be converted by double enolsilylation to the desired dienic reactant (2). Cycloaddition of the latter to appropriate halonaphthoquinones followed by acid hydrolysis and aromatization of the resultant adducts would then provide the corresponding rubiadins (Scheme 1). Originally attempts to prepare these pigments by oxidation of analogous intermediates$^{5)}$ obtained using 2-methyl-1,3-bistrimethylsilylbutadiene were unsuccessful, elimination in all cases occurring at the expense of the expected process.

In a typical example, a mixture of the naphthoquinone (3-8) (1.00 mmol) in benzene (2-10 mL) and diene 2 (1.75-3.00 mmol) in the same solvent (1-6 mL) (added in 2 or 3 portions) was stirred at room temperature for 20-72 h and evaporated. Treatment of the residue with concd. HCl (2 mL) in THF (10 mL) at r.t. (1-3 h) and then under reflux (1-5 h) provided the crude anthraquinone (9-14) which was then purified by dry-column chromatography on silica gel using CH_2Cl_2 and CH_2Cl_2 -ether 1:1 as eluants.

As expected the synthetic rubiadins 9-14 showed a number of characteristics resulting from the common denominator, the 1,3-dihydroxylated portion and found to be quite independent of the nature and position of substituents in the other ring. All of these compounds gave high melting points, near or above 300 °C, and were quite insoluble in $CDCl_3$. More significant results were provided by the NMR spectra taken in DMSO-d_6 and established that the protons of the 2-CH_3 group resonate within very narrow limits, i.e. δ 2.00-2.05 and that the same is true for the one in the 4-position (δ 7.16-7.24). In rubiadin the 3-OH substituent provides a signal at δ ≈ 11.16 as does galyprenylin[6)] but was not observed with other such compounds (Table 1).

Among those natural products considered to be rubiadins, only four present any or all of these features: rubiadin, galyprenylin[6)], 6-hydroxyrubiadin[7)] and 3-hydroxymorindone[8)] (6-hydroxyrubiadin however has a suspiciously low mp). Rubiadin (9) prepared in this manner shows physical characteristics in excellent agreement with those described in numerous sources (e.g. Ref. 8).

The non natural 5-hydroxyrubiadin (10) was next obtained from 2-chlorojuglone acetate (4) in 73% yield after treatment of the crude product with a mixture of 48% HBr in AcOH at reflux temperature. The mp of 298-299 °C is nearly 20 °C higher than the one recorded for a previously prepared material later converted to nor-juzunol[9)]. However the two substances are undoubtedly identical since their triacetates, mp 242-243 °C (lit.[9)] 239.5-240.5 °C) and trimethyl ethers, mp 184-185 °C (lit.[9)] 184-185 °C) are quite comparable (all original samples are no longer available).

A compound described as 8-hydroxyrubiadin (12) has been isolated or otherwise obtained from natural sources on numerous occasions.[10-16)] Most of the recorded physical characteristics, the mp's of the natural product (≈ 229-232 °C) and of its triacetate (≈ 205-206 °C) as well the IR and UV spectra are reasonably consistent. However the NMR spectra taken either in $CDCl_3$[14,16)] or DMSO-d_6 appear to be largely incompatible. Synthetic 8-hydroxyrubiadin obtained in 56% yield from 3-chlorojuglone (6), melts at 310 °C, is totally insoluble in $CDCl_3$, gives NMR signals (DMSO-d_6) at δ 2.05 (3H, s, 2-CH_3) and δ 7.23 (1H, s, 4-H) among others and is obviously quite different from the natural product in spite of an apparently fortuitous similarity in the mp's of their acetates (i.e. 205-206 °C). Unfortunately the NMR spectrum of this acetate has not previously been published and requests for samples of the authentic substance from three of the originators have been disregarded. Until proper comparisons can be carried out, the proposed structure must be considered to be in error.

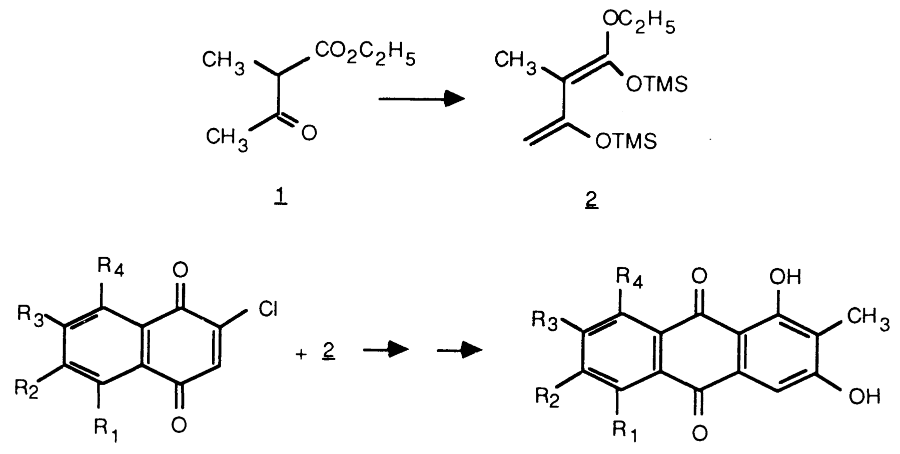
Another substance isolated on at least two occasions[17,18)] and held to be 8-hydroxy-6-methoxyrubiadin (13) had a mp of 250 °C and in the NMR spectrum ($CDCl_3$) showed signals at δ 2.10 (2-CH_3) and 7.89 (4-H). The synthetic material obtained from 3-chloro-7-methoxyjuglone (7) melts above 300 °C and gives characteristic signals at δ 2.04 and 7.22 (DMSO-d_6). However the corresponding triacetate, mp 204-205 °C (lit.[17)] 213 °C) provided NMR data in fairly good agreement with the published ones.[18)] It would seem that in the original paper the spectrum of the triacetate was confused with that of the natural product. The structure of this compound, in spite of the low mp must tentatively be considered correct until comparisons with the authentic substance (as yet unavailable) can be made.

Finally yet another natural product identified as 8-hydroxy-6- or 7-methoxyrubiadin[19)] had a mp of 220 °C. It is obviously not the 6-methoxy isomer (13) described above. The 7-substituted compound (14) was prepared from 3-chloro-6-methoxyjuglone (8), shows the usual characteristics of other authentic rubiadins and therefore is quite different from the natural product.

Table 1. ^{1}H-NMR Spectra of Compounds 9-14 (Recorded at 200 MHz)

Compound[a]	Substituent							
	1	2	3	4	5	6	7	8
9	13.03s	2.00	11.16s	7.17s	8.02-8.16m	7.79-7.90m	7.79-7.90m	8.02-8.16m
10	13.06a	2.02s	-	7.21s	12.40s	7.30dd (1.2; 8.2)	7.75~t (7.6; 8.2)	7.65dd (1.2; 7.6)
11	13.03s	2.05s	-	7.16s	3.93s	7.56t (4.8)	7.83d (5.1)	7.83d (5.1)
12	12.48s	2.05s	-	7.23s	7.64dd (1.5; 7.3)	7.74~t (7.3; 8.2)	7.32dd (1.5; 8.2)	12.08s
Acetate of 12	2.45 or 2.48s	2.15s	2.39s	7.92s	8.21dd (1.5; 8.0)	7.75t (8.0)	7.40dd (1.5; 8.0)	2.45 or 2.48s
13	12.50s	2.04s	-	7.22s	7.13d (2.6)	3.90s	6.82d	12.27s
Acetate of 13	2.44 or 2.48s	2.14s	2.39s	7.90s	7.66d (2.6)	3.96s	6.89d (2.6)	2.44 or 2.48s
14	12.43s	2.05s	-	7.24s	7.68d (8.4)	7.38d (8.4)	3.92s	12.43s

a) Spectra of hydroxylated cpds were recorded in DMSO-d_6; those of acetates in $CDCl_3$. Coupling constants are in parentheses.



	R1	R2	R3	R4
3	H	H	H	H
4	OAc	H	H	H
5	OCH3	H	H	H
6	H	H	H	OH
7	H	OCH3	H	OH
8	H	H	OCH3	OH

	R1	R2	R3	R4
9	H	H	H	H
10	OH	H	H	H
11	OCH3	H	H	H
12	H	H	H	OH
13	H	OCH3	H	OH
14	H	H	OCH3	OH

Scheme 1.

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