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CHEMICAL CONSTITUENTS OF THE BRIGHT ORANGE APHID, *APHIS NERII* FONSCOLOMBE. III. TWO NAPHTHAQUINONE METHIDES OF UNUSUAL STRUCTURE AND CHEMICAL BEHAVIOR *

Keith S. Brown, Jr. and Ulrich Weiss

Centro de Pesquisas de Produtos Naturais
Faculdade de Farmácia, U.F.R.J.
Praia Vermelha, Rio de Janeiro ZC-82, BRAZIL

NIAMD - LPB
National Institutes of Health
Bethesda, Maryland 20014, USA

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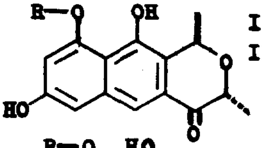
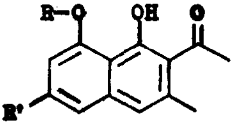
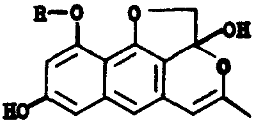
We have previously reported (1) the isolation from *Aphis nerii* of the polyketide glucosides neriaphin (I), 6-hydroxymusizin-8-O-β-D-glucoside (IV), glucoside B (VIII), fluoraphin (X), and acetylfluoraphin (XI). An additional small fraction of the polar pigments in the aphid extract has now been shown by NMR spectrometry to consist of a 2:1 mixture of the 6'-monoacetyl-glucosides II and V; this mixture was unchanged under conditions which gave a good yield of a 6'-monotritylate from neriaphin (I) (2). An interrelation of 6-hydroxymusizin (VI) with the plant product torachrysone (VII) (3) was also accomplished through partial methylation of the glucoside (IV) followed by acid hydrolysis (2). An elegant total synthesis of 6-hydroxymusizin itself has recently been achieved *via* barakol (XII) (4,5).



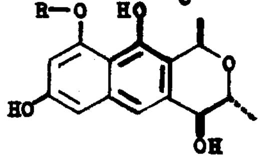
I. R=β-D-glucosyl
II. R=6-O-acetyl-β-D-glucosyl
III. R = H



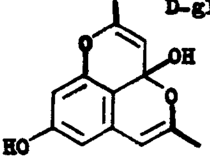
IV. R=β-D-glucosyl, R' = OH
V. R=6-O-acetyl-β-D-glucosyl, R' = OH
VI. R = H, R' = OH
VII. R = H, R'=OCH_3



X. R=β-D-glucosyl
XI. R=6-O-acetyl-β-D-glucosyl



VIII. R=β-D-glucosyl
IX. R = H



XII.

Repeated chromatography over Florisil and silica of the acetone extract of a large batch (405 g.) of *Aphis nerii* (prepared by Dr. Brent Acott in Tucson, Arizona) yielded trace amounts of two additional compounds, easily detected and followed on thin-layer plates by their brilliant red fluorescence.** These

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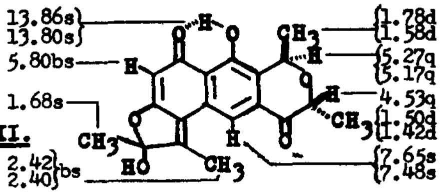
* Presented in part, including structure XIV, by U. Weiss at the Third Natural Products Symposium, Kingston, Jamaica, January 4-8, 1970.

** The presence of larger amounts of these two compounds was confirmed in a second large extract of *A. nerii* prepared in Tucson in 1971 by David Eckert.

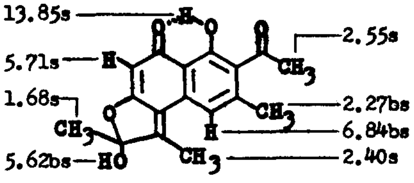
compounds, XIII [m.p. 118-122°(resolidifies and m. 215-218° dec.), λ_{max}^{EtOH} 216,244, 298,412 nm (log ϵ 4.59,4.65,4.45,4.28), ν_{max}^{KBr} 1700,1645,1600 cm.$^{-1}$] and XIV [m.p. 180-186°, λ_{max}^{EtOH} 216,240,297,395 nm (log ϵ 4.63,4.56,4.58,4.25), ν_{max}^{KBr} 1680,1650, 1600,1560 cm.$^{-1}$] were not reduced by aqueous sodium dithionite, but gave upon borohydride reduction material (not isolated) with UV absorption spectrum closely matching that of glucoside B (VIII). Their diagnostic NMR spectra (indicated alongside their structures, in δ-values below internal TMS, in $CDCl_3$ solution) showed that they were derived from neriaphigenin (III) and 6-hydroxymusizin (VI), respectively, by modification of the resorcinoid ring only, eliminating one aromatic proton and leaving the other in a more highly shielded position, and introducing two deshielded quaternary C-methyl groups with very different magnetic environments. The compounds could not be methylated with diazomethane, but still possessed a strongly hydrogen-bonded phenolic group (D_2O-exchangeable NMR signal near 14 ppm, and shift of the UV spectrum upon alkalinization).

The mass spectra of the two compounds revealed the addition of 68 mass units to the aglycones III and VI (M^+ 274 → 342, 232 → 300); the only significant fragmentations were loss of methyl and/or hydroxyl groups and water from the very stable molecular ions. The foregoing facts can best be accommodated by postulating a condensation of the aglycones with *biacetyl*, with elimination of water ($C_4H_6O_2$=86, $-H_2O$=68). Position 5 in compounds of this type is known to be highly reactive towards condensations with electron-poor atoms (6,7). The resulting structures, written as hemiacetals (XIII,XIV), are uniquely consistent with the physical and chemical data accumulated so far on these red-fluorescent entities.

In support of this formulation, it was shown to be possible to *synthesize* three representative compounds of this type. The two natural compounds XIII and XIV, and their analog XV [m.p. 180-185° dec., λ_{max}^{EtOH} 221,298,404 nm (log ϵ 4.53, 4.43,4.11), ν_{max}^{KBr} 1645,1580 cm^{-1}] were produced by the rapid, room-temperature condensation of one mole of biacetyl with the crude aglycones III, VI, and IX (from acid hydrolysis of I, IV, and VIII), in the presence of Florisil or triethylamine (yields about 50%). The synthetic materials XIII and XIV were in every way identical with those isolated from the aphid extracts. The unusual doubling of almost all peaks in the NMR spectra of XIII and XV may be related to slow interconversion of two conformers of the dihydropyran ring, or to diastereoisomer-

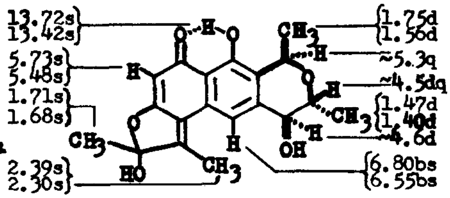


XIII.

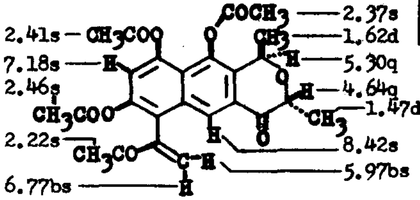


XIV.

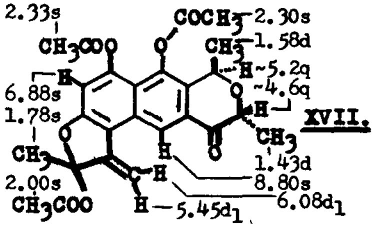
CODE:
s-singlet
bs-broad singlet
d-doublet, J≈7
q-quartet, J≈7
d_1-doublet, J=1.4



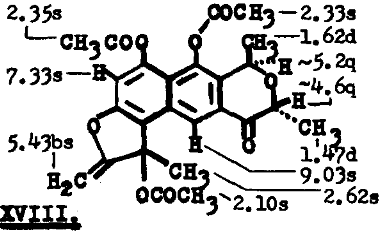
XV.



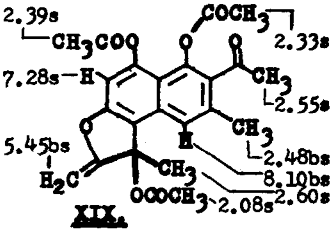
XVI.



XVII.



XVIII.



XIX.

ism due to the hemiacetal carbon; a solution of XIII in tetrachloroethylene showed partial coalescence of these doubled peaks in the spectrum measured at 115° (2).

Mild acetylation of XIII (Ac_2O-py, r.t.) gave a principal (70%) product XVI, m.p. 188-195°, with a simplified NMR spectrum (indicated beside structure), negligible fluorescence, and a UV spectrum nearly identical with that of peracetyl-I (1). The mass spectrum of this compound showed it to be triacetylated; the infrared spectrum revealed only phenolic acetate groups, and an unsaturated ketone band of greater intensity than that of the parent XIII. This principal product has evidently undergone the re-aromatization frequently observed in quinone methides (8); in view of its UV spectral characteristics, it should have the unsaturated ketone sidechain at C-5 twisted out of conjugation with the aromatic ring by steric pressure from the neighboring acetoxy group.

The acetylation of XIII gave, besides XVI, an inseparable mixture of two triacetates with very strong yellow-white fluorescence. The UV spectrum of this mixture indicated additional conjugation to the aromatic system; an aliphatic acetoxy group was evident from the IR (ν_{max}^{KBr} 1735 cm.$^{-1}$), mass (M^+ - 59), and NMR spectra. This latter spectrum strongly suggested the presence of a 2:1 mixture of the conjugated methylene-hemiacetal acetate XVII and the vinyl ether XVIII resulting from 1,6-addition of acetic acid. Clarification of the indicated NMR assignments and of the nature of the mixture was greatly aided by the use of synthetic model compounds, reported in the following communication (9). Acetylation of XIV apparently gave but two products (not yet fully purified), one corresponding to XVI and the other (XIX) to XVIII, unmixed with XVII-analogous material.

The possibility that XIII and XIV might be artefacts produced upon Florisil chromatography of the crude aglycone-containing aphid extracts (1) could be eliminated by the observation of their presence prior to chromatography in fresh extracts of *A. nerii* feeding on either *Asclepias curassavica* or *Nerium oleander*, and their detection on thin-layer plates in which live aphids were directly crushed on the origin. These compounds thus represent two of the very few known natural products (10) clearly related in part to biacetyl, rather than only to acetate units joined normally head-to-tail.

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