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A CORRECTION OF
THE STRUCTURE OF PEREZONE

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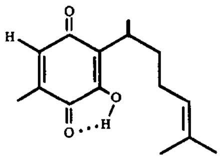
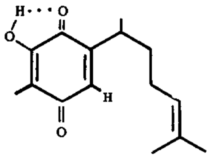
The recent publication of the structures of α- and β-pipitzols by Walls et al. (1) has prompted us to present the evidence we have obtained concerning the structure of perezone, the sesquiterpenoid, quinone precursor of the pipitzols. NMR evidence suggested that perezone has structure I rather than structure II proposed by Kögl and Boer (2) in 1935. Therefore, we had also determined the structure of pipitzol, hoping this information might confirm the correction of the structure of perezone.


I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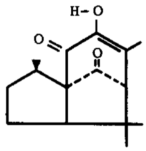
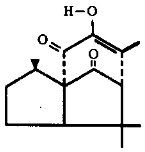

IIIα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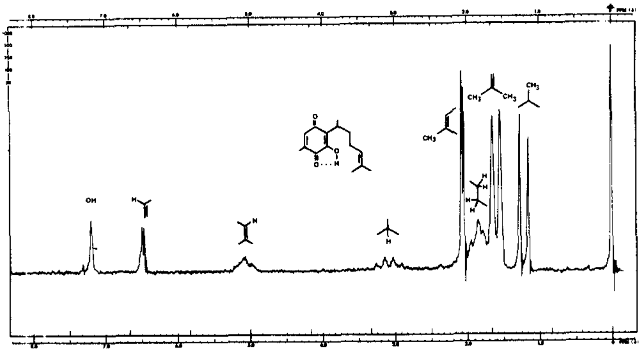

The NMR Spectrum of Perezone

The perezone studied was isolated from Perezia reticulata and possessed properties which corresponded exactly to those reported by Kögl,[1] including the melting point of an anilido derivative and the unique formation of the pipitzols (III α and β). However, during the characterization of perezone, it was noticed that the NMR* splitting patterns of the ring methyl group and the ring proton indicated they were on adjacent carbon atoms, ortho and not meta as in structure II. (See spectrum above). The methyl group at 2.05 ppm was coupled (J = 1.7 cps, a doublet), with the ring proton at 6.41 ppm (J = 1.7 cps, a quartet). A similar coupling constant and splitting pattern was seen in a number of quinones studied (see TABLE 1) and particularly in 6-hydroxythymoquinone IV, but not in 3-hydroxythymoquinone V. In

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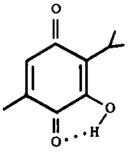
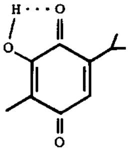
*All NMR spectra were measured on a Varian A-60 spectrometer in CCl_4 with tetramethylsilane as internal reference. Some reference quinone samples also were run in $CDCl_3$ for stronger spectra to confirm spectral structure.

V the methyl group at 1.88 ppm was unsplit and the ring proton at 6.36 ppm appeared as a doublet (J = 1.5 cps), obviously coupled with the single tertiary proton of the isopropyl group.



IV



V

Further supporting spectral evidence was supplied by comparison of the infrared spectra* of perezone and the thymoquinones (3) (see TABLE 2). The relative positions of the various bands were closer in perezone and IV than perezone and V; especially significant were the relative intensities in the carbonyl region, and the frequency of the ring out-of-plane CH bending vibration near 890 cm-1.

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*All infrared spectra were obtained on a Beckman KBr fore-prism grating spectrometer, Model IR-9.

TABLE 1.

A Comparison of NMR Spectra of Substituted Toluquinones

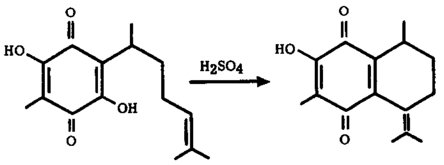
Compound	Chem Shift (ppm) in CCl_4	Coupling Constant (cps)
p-toluquinone	CH_3(2) 2.05 doublet	$J=1.52$
	H(3) 6.54 distorted quintet	$J\sim1.5$
	H(5,6) 6.66 small structure	~3 cps wide
2,5-dimethyl-*p*-benzoquinone	CH_3(2,5) 2.01 doublet	$J=1.58$
	H(3,6) 6.52 quartet	$J=1.58$
		$\leq.3$ to any other
2,6-dimethyl-*p*-benzoquinone	CH_3(2,6) 2.03 distorted doublet	$J=1.55$ (width)
	H(3,5) 6.46 septet	width ~5 cps
thymoquinone	CH_3(2) 1.99 doublet	$J=1.7$
	H(3) 6.52 quartet	$J\sim1.7$
	H(6) 6.43 doublet	$J\sim1.5$ to isopropyl
3-hydroxy-2,5-dimethyl-*p*-benzoquinone	CH_3(2) 1.93 singlet	
	CH_3(5) 2.06 doublet	$J=1.65$
	H(6) 6.53 quartet	$J=1.7$
3-hydroxythymoquinone (V)	CH_3(2) 1.88 singlet	
	H(6) 6.36 doublet	$J=1.2$
6-hydroxythymoquinone (IV)	CH_3(2) 2.03 doublet	$J=1.7$
	H(3) 6.38 quartet	$J=1.7$
perezone (I)	CH_3(2) 2.05 doublet	$J=1.7$
	H(3) 6.41 quartet	$J=1.7$

TABLE 2.

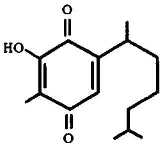
Infrared Comparison of Thymoquinones and Perezone (All frequencies from dilute solution in CCl_4, 4000 - 1333 cm^{-1}; dilute solution in CS_2, 1333 - 400 cm^{-1})

3-hydroxy-thymoquinone (V)	Perezone (I)	6-hydroxy-thymoquinone (IV)
3425m	3415m	3415m
1657m	1658m	1660s
1645s	1647s	1648s
1625w	1623m	1627m
1400m	1400s	1402s
----	1379s	1380s
1352s	1335s	1322s
1296w	1282m	1288m
1265m	1258w	1258w
1212m	1210m	1215m
1168m	----	----
1131m	----	----
----	1050m	1050m
----	980m	980m
900m	891m	891m
709vw	700w	700w
580vw	580m,br	580m,br

Kögl assigned the position of the hydroxyl group from the fact that perezone decomposed in warm, concentrated sulfuric acid, while oxyperezone VI, cyclized to perezinone VII in that reagent. However, the sulfuric acid treatment of the two hydroxythymoquinones shows that V is quite stable and can be recovered while IV is converted rapidly to an amorphous dark solid. Thus, it is conceivable that structure II would form some sort of cyclized product. This evidence in itself is insufficient since the presence of the unsaturated side chain is a complicating factor, but combined with the infrared and NMR data, presents a consistent argument for I.



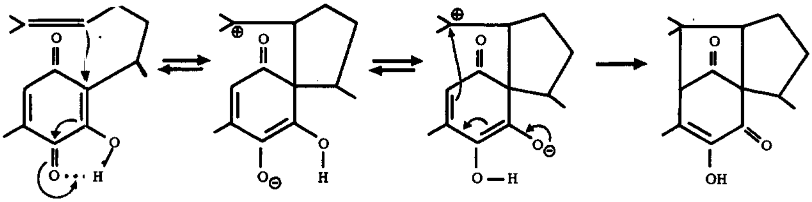
VI VII



VIII

A further point regarding a reported synthesis (4) of dl-dihydroperezone VIII must be considered. Though the synthesis of VIII is unequivocal, a detailed analysis of the paper indicates that, unfortunately, an inadequate comparison was made with the authentic perezone derivative. Only the ultraviolet spectra of the two were compared and shown to be similar (the synthetic material was racemic, so the melting points did not correspond). However, the ultraviolet spectra of IV and V are also essentially identical (5) and the only valid spectral comparison would be via the infrared solution spectra (6).

Our pipitzol studies fully support the cedrenoid skeleton (III α and β) as determined by Walls. The formation of this rare skeleton from a quinonoid precursor is without precedent.* We have found that this thermal rearrangement can be accomplished, slowly, even at temperatures as low as 80°C., suggesting a facile transformation. Structure I for perezone would allow a much more direct route to III than does structure II. From I, a direct cyclization would be possible via a Michael addition of the side-chain double bond to the quinone, followed by a proton transfer and an apparently irreversible electron shift to form the strained tricyclic system. From Kögl's structure, devious rearrangements are required to reach pipitzol (1).



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*Dr. Francis Johnson has suggested that this might be the biogenetic route to cedrene confirming Stork's (7) observation that cedrene is a formal cyclization product of β-curcumene. Professor R. B. Woodward in his lecture in the Symposium on Physical Organic Chemistry at the Sept. 14, Meeting of the American Chemical Society in Atlantic City suggested that the formation of pipitzol may also be considered as a sigmatropic change of order $\boxed{1,9}$.

A final confirmation of this structural assignment will have to await the synthesis of perezone itself, but spectral comparisons leave no doubt that perezone actually has structure I rather than structure II.

Soon after the submission of our manuscript, a communication by D.A. Archer and R. H. Thomson (8) was brought to our attention. They described the synthesis of compound VIII and also corrected the structure of perezone. Our paper is added as further proof.

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