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THE STRUCTURE OF CACALONE

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Structures 1-4 have been proposed for cacalone[1-7], a sesquiterpene isolated from Cacalia species[1,2]. However, neither its known chemical behaviour, nor its spectral properties agree with the above formulae. Recently, a total synthesis of cacalol 5, a companion of cacalone, has been reported[8] by a route which unequivocally locates the three methyl groups on the same side of the molecule. Thus, as cacalone has been converted in cacalol by methods which do not change this distribution, structures 1 and 2 should be discarded. On the other hand, structure 3 was prepared[8] as intermediate in the above cacalol synthesis and shown to be different to the natural product. The uncommon structure 4[7] (tautomer of 3) did not appear very probable as long as there should be no apparent reason for stabilization of tautomer 4 over phenolic structure 3.

In this paper we wish to suggest that all the available data for cacalone can be explained by the p-quinol formula 6[9]. Thus, the "abnormal" C=O ir absorption at 1660 cm^{-1} and the nmr chemical shift of the OH proton and the tertiary CH_3 group at 3.86 and 1.62 ppm in cacalone[1,10], are easily accommodated in this formula. On the other hand, the ms reported for cacalone and its acetate[7], agree with this new formula (6 = $C_{15}H_{18}O_3$) rejecting the older one ($C_{15}H_{16}O_3$). The ms also gives further information about the tertiary nature of the OH group, because of the important contribution of M^+-H_2O and M^+-CH_3COOH in cacalone and its acetate respectively.

To disprove also structure 7 (a position isomer of 6) the following experiments were performed[11] : The known p-quinone 8[1] was treated with about one equivalent of CH_3Li (ether, 0°, nitrogen) to give a complex mixture of products. After tlc purification, a compound with close but clearly distinct spectroscopic properties of cacalone was isolated (ir 3450, 1660 cm^{-1}; nmr δ 1.29 (d, J=7 Hz, 3H), 1.63 (s, 3H), 2.23 (broad s, 3H), 7.20 (broad s, 1H)). However, $NaBH_4$ reduction (methanol, rt, 1 hour) of this material gave cacalol 5, further characterized as its acetate 10. As the conversion cacalone ⟶ cacalol according with structure 6 involves the loss of one asymmetric center, the above isolated compound should be an epimer at C-4 of cacalone

(4-epi cacalone 9). Furthermore, because of the known 1,4 relationship of the oxygenated function in the starting quinone, structure 7 was rejected.

The stereochemistry at C-4 in cacalone was proved in the following manner : Treatment of cacalol 5 with benzoyl peroxide in chloroform, gave in quantitative yield a mixture of C-4 epimeric benzoates 11 and 12 (ir of the mixture 1720 and 1660 cm^{-1}), ratio 5:1 calculated by nmr analysis of the secondary CH_3 group. The major isomer 11 could be isolated by fractional crystallization (anhydrous methanol) of the mixture (mp 175°; nmr δ 1.32 (d, J=7 Hz, 3H), 1.86 (s, 3H), 2.03 (d, J=2 Hz, 3H), 7.00-8.20 (complex signals, 6H)). Methanolysis of this isomer (sodium methoxide, methanol, rt) gave cacalone 6 identified by standard methods (mp 138°; $[\alpha]_D$ = +89°). The cacalone thus obtained gave the already described conversions to cacalol 5 and desoxicacalol 13[1], and gave negative test with sodium metaperiodate.

The aforementioned stereochemical results can be explained if one assumes preferential attack by methyllithium or benzoyl peroxide opposite to the known[3] to be β secondary methyl group of quinone 8 or cacalol 5, to give 4-epi cacalone 9 and cacalone benzoate 11 respectively.

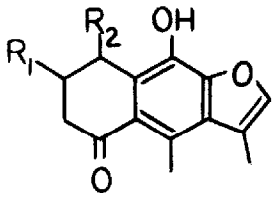
Interestingly, the benzoate of 4-epi cacalone (the minor isomer 12) could not be converted in 4-epi cacalone by the same reaction conditions used for its epimer. This observation can be rationalized as increased hindrance in the benzoate carbonyl of this epimer (12), which is an additional proof for the suggested stereochemistry at C-4 of cacalone.

Another interesting although low yield conversions of cacalol into cacalone, involved oxygenation (sodium amide, diethylamine, rt)[12] and sodium periodate (chloroform-water). Both reagents have been suggested as efficient methods for the conversions of p-substituted phenols into p-quinols.

The "abnormal" reactions for cacalone can now be easily explained by structure 6. Thus, reducing agents or Wolff-Kishner conditions give intermediates 14 and 15 respectively, rapidly transformed to the aromatic structures of cacalol 5 and desoxicacalol 13.

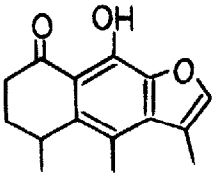
Therefore, cacalone is a biogenetic link between the furanoeremophilane (e.g. decompostine)[13] and the furonaphthalene sesquiterpenes[14] found in the same plant.

Finally, is worth to mention that as cacalol has been totally synthesized[8], the conversion cacalol ⟶ cacalone here reported constitutes a formal total synthesis of this compound.

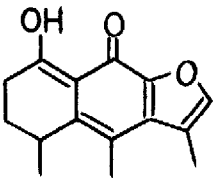


1 $R_1 = CH_3$, $R_2 = H$

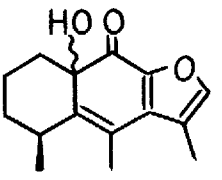
2 $R_1 = H$, $R_2 = CH_3$

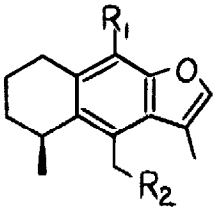


3



4

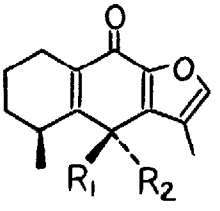




5 $R_1 = OH$, $R_2 = H$

10 $R_1 = OAc$, $R_2 = H$

13 $R_1 = R_2 = H$



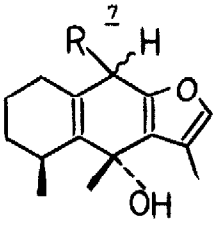
6 $R_1 = CH_3$, $R_2 = OH$

8 R_1, $R_2 = O$

9 $R_1 = OH$, $R_2 = CH_3$

11 $R_1 = CH_3$, $R_2 = OBz$

12 $R_1 = OBz$, $R_2 = CH_3$



14 R = OH

15 R = H

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