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THE STRUCTURE OF CHAPARRIN, AND A NOTE ON GLAUCARUBOL

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Chaparrin (I), the bitter lactone from the simaroubaceous plant Castela Nicholsoni Hook., has been described in a preliminary communication.[1] It is a compound with the composition $C_{20}H_{28}O_7$; it forms a triacetate, m.p. 191°, and a tetraacetate, m.p. 231-2°,[2] and undergoes the ready loss of one or two molecules of water by the action of dilute aqueous mineral acid. The products of this acid-catalyzed dehydration are anhydrochaparrin (III), $C_{20}H_{26}O_6$,[3] and chaparrol (II), $C_{20}H_{24}O_5$. Anhydrochaparrin is an α,β-unsaturated ketone (λ_{max} 230 mμ, ϵ 9700) and chaparrol contains an aromatic ring, a conclusion reached earlier[1] and now substantiated by additional evidence.

The presence of a carbonyl group in chaparrin was not recognized in the early studies[1] but has now been established by the reduction of chaparrin to a dihydro compound, $C_{20}H_{30}O_7$, with sodium borohydride, and by the appearance of a well-defined carbonyl peak (1720 $cm.^{-1}$) in the infra-red spectrum of the sodium salt of chaparrin. In chaparrin and most of its derivatives the infra-red absorption of the lactone and the ketone groupings are superimposed into a single peak.

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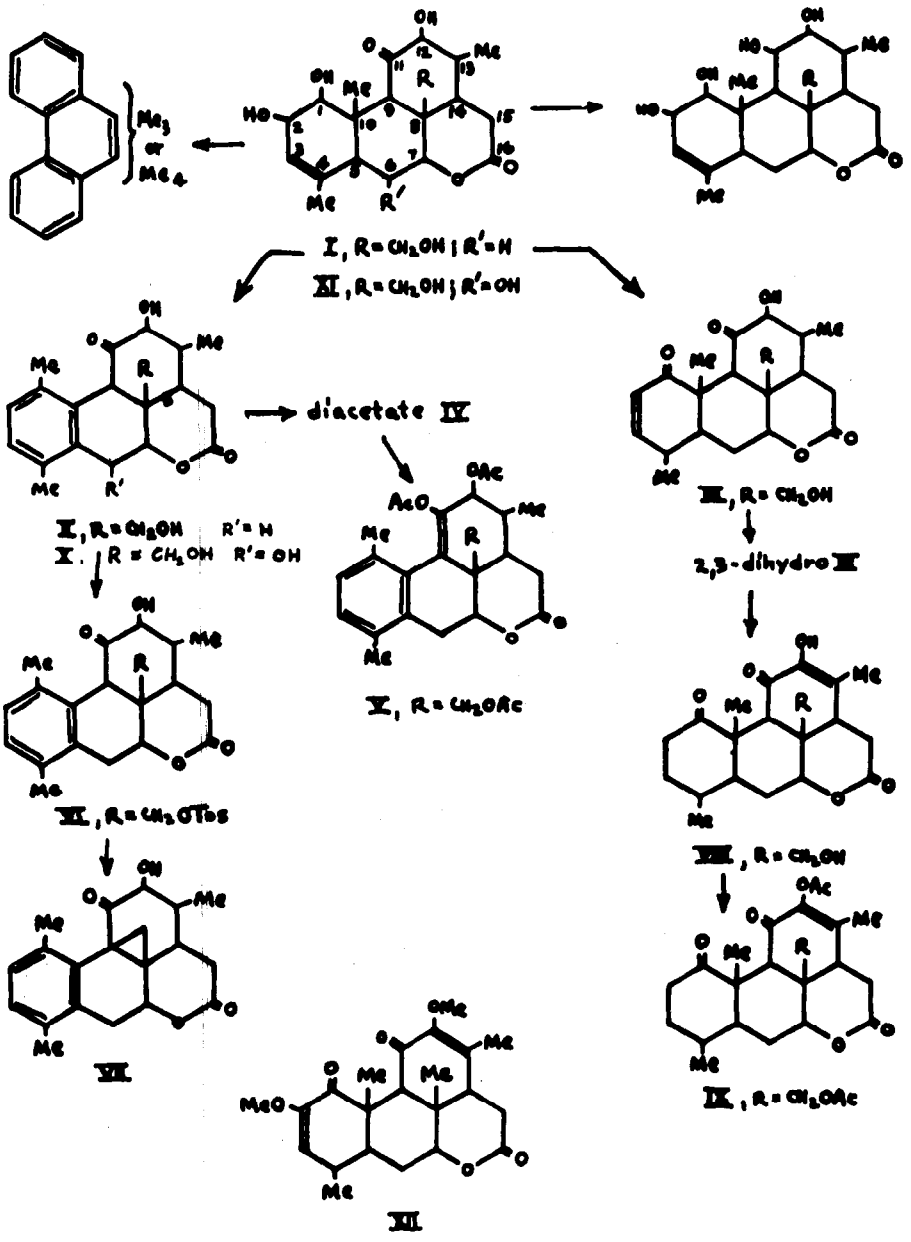
1) T. A. Geissman and K. R. Chandorkar, J. Org. Chem. 26, 1217 (1960).

2) Further studies on the acetates of chaparrin carried out since the first paper[1] with the aid of NMR spectra have shown that what appeared to be the pentaacetate, m.p. 232°, is in fact the tetraacetate. The triacetate is now known to form solvates of variable composition, and the acetate, m.p. 137°, reported earlier, is undoubtedly one of these. The solvent-free triacetate, m.p. 191°, solvates readily with various solvents to give crystalline materials with lower and non-reproducible melting points.

3) Carbon-hydrogen and, where applicable, O-acetyl analyses are in good agreement with all formulas given.


Me3 or Me4
I, R = CH2OH ; R' = H
II, R = CH2OH ; R' = OH
diacetate IV
I, R = CH2OH R' = H
II. R = CH2OH R' = OH
V, R = CH2OAc
III, R = CH2OH
2,3-dihydro III
VI, R = CH2OTos
VII, R = CH2OH
VIII, R = CH2OAc
XII

These observations establish the presence in chaparrin of four hydroxyl groups, one ketonic carbonyl group and a six-membered lactone ring. That two of the hydroxyl groups are vicinal is shown by the rapid consumption by chaparrin of one mole of periodic acid (followed by continuing, slower oxidation). Chaparrol does not consume periodate, an observation which, coupled with the fact that chaparrol contains two hydroxyl groups, indicates that the two hydroxyl groups lost in the dehydration of chaparrin are those that consume periodate, and are on the ring that becomes aromatic in chaparrol.

Chaparrol (II), the aromatic nature of which was at first suggested from the similarity of its ultraviolet absorption in the 270-280 mμ region with that of the tetrahydronaphthalene system, gives a nuclear magnetic resonance (NMR) spectrum that provides valuable evidence for a number of its structural features. The NMR spectrum of chaparrol shows a secondary methyl group (3H doublet, 8.91, J = 7),* two aromatic methyl groups (3H singlets, 7.72, 7.80), and a sharp vinyl proton signal (2H singlet, 3.10). Coupled with the NMR spectrum of chaparrin tetraacetate, which shows the three substituent methyl groups as the secondary methyl group (at C_{13}), the tertiary methyl group (at C_{10}) and the allylic methyl group (at C_4), this information leads to the formulation of the A ring as shown in the structures I and II, and the assignment of structure III to anhydrochaparrin. The NMR spectrum of the latter compound shows the expected two 3H doublets (methyl groups at C_4, C_{13}), the tertiary methyl group (at C_{10}) and the vinyl protons at C_2 and C_3 (3.17 (J = 1.5); 4.07 (J = 2.5)).

Chaparrol forms a diacetate (IV) upon acetylation under mild conditions, and a triacetate (V) under more vigorous acetylation. The diacetate shows no significant ultraviolet absorption except that for the benzene ring, shown by chaparrol itself. The triacetate, however, shows an ultraviolet absorption maximum at 242 mμ (ε 10000), due to the styrene-like chromophore shown in V. This is in excellent agreement with the ultraviolet spectrum shown by 3,11,17,21-tetraacetoxy-1-methyl-19-norpregna-1,3,5(10),9(11)-tetraen-20-one (242 mμ, ε 13000).[4]

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* NMR signals are expressed in tau values, J values in c.p.s.

4) E. J. Bailey, J. Elks, J. F. Oughton, and L. Stephenson, J. Chem. Soc., 4535 (1961).

This information provides a basis for the location of the carbonyl group at C_{11}, and, with the superimposition of the carbonyl and lactone infra-red absorption bands, suggests that the C ring of chaparrin has the 11-keto-12-hydroxy structure.

Support for the α-ketol nature of the C ring was obtained by the oxidation of 2,3-dihydroanhydrochaparrin to a diosphenol (VIII) with bismuth oxide. The crude product (uncrystallized; green ferric chloride reaction) was converted to a crystalline diacetate (IX), m.p. 275-276°, which had λ_{max} 241 mμ (ϵ 10,300). The ultraviolet absorption is in excellent agreement with that reported[5] for $\Delta^{9(11)}$-22a,5α-spirostene-3β,11-diol-12-one 3,11-diacetate (λ_{max} 244, ϵ 11200).

The NMR spectrum of the diosphenol acetate provided compelling evidence for the placing of the methyl group at C_{13}. Anhydrochaparrin (III), like many other derivatives in the series, shows two 3H doublets for the secondary methyl groups at C_4 and C_{13} (8.77, 8.97; J = 7). In the NMR spectrum of IX there is seen a sharp 1H singlet (5.4) assigned to the C_9 proton, but one of the 3H doublets has disappeared and has been replaced by a sharp 3H singlet (8.15) characteristic of the C=C-CH_3 system. This shows that the diosphenol is enolized in the manner shown in IX, and that the system -C(O)-C(OAc)=C-CH_3 is present in the acetate.

The placing of the CH_2OH group at position 8 at the B/C ring junction was first made on several grounds: 1) the close biogenetical relationship to quassin (XII)[6]; 2) the appearance of 2H NMR signals (usually a non-equivalence quartet, occasionally a singlet) for the grouping $\geqslant$C-CH_2-O- in the compounds studied, and 3) the sharp 1H singlet observed for the C_9 proton in many of the NMR spectra.

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5) C. Djerassi, H. J. Ringold, and G. Rosenkranz, J. Am. Chem. Soc. 76, 5533 (1954).

6) R. M. Carman and A. D. Ward, Tetrahedron Letters, no. 10, 317-320 (1961). In our view, the structure now established for chaparrin is strong support for Carman and Ward's structure for quassin, which differs in the placement of the C_8 (vs. C_5) methyl group from the structure of Z. Valenta, A. H. Gray, S. Papadopoulos and C. Podesva, Tetrahedron Letters, no. 20, 25-38 (1960).

Chemical confirmation of this assignment was obtained through the use of the mono-tosyl ester (VI) of chaparrol. The ease with which this ester is formed is an indication of the primary nature of the hydroxyl group involved. When VI is dissolved in alcoholic alkali, acidification yields a new compound, lacking the tosyl group, and having the composition ($C_{20}H_{22}O_4$; monoacetate, $C_{22}H_{24}O_5$) of a dehydrochaparrol. This compound shows no NMR signal for the C_9 proton, and shows a signal for a non-equivalent pair of protons as a well-defined non-equivalence quartet (2H) at 7.92 and 8.49 (J = 7.5). The elimination of the elements of p-toluenesulfonic acid and the formation of a cyclopropane ring between C_9 and the $-CH_2-$grouping at C_8 is clearly indicated by these results.

Selenium dehydrogenation of chaparrol has given results which, while useful, are not yet conclusive in providing additional support to the detailed structural assignments made possible by the evidence so far described. The product of the dehydrogenation is clearly a substituted phenanthrene (λ_{max} 259, 294, 308, 328, 343; log ϵ 4.95, 4.06, 4.10, 2.15, 2.20), the ultraviolet absorption curve of which is strikingly similar to those of 1,7-dimethyl-, 1,4,7-trimethyl-, and 1,2,8-trimethyl-phenanthrene. Its crystalline trinitrobenzene complex gives analytical figures in good agreement with those of a tetramethylphenanthrene, but has not yet been identified with a known compound.

The summary of the evidence at hand is that chaparrin is represented by I. Its close structural relationship to quassin (XII) is striking. The position of the lactone ring in chaparrin follows not only from its relationship to quassin but from the evidence for the positions of the other substituents. The lactone is saturated and six-membered (or greater) as shown by the infra-red absorption, and is in such a position as to permit its spontaneous reclosure upon acidification of an alkaline solution. These requirements leave no alternative position for the lactone ring. That the direction of the ring attachment (oxygen at C_7, CH_2 at C_{14}) is as shown in I, and not the reverse, is made certain by the recognition in NMR spectra of most of the compounds of the series of a symmetrical 1H triplet (about 5.5 in most cases) for the C_7 proton adjacent only to CH_2 at C_6. This feature is additional confirmation of the quaternary nature of C_8.

While certain features of the stereochemistry of chaparrin are known with reasonable certainty, more remains to be done to define the configuration of the molecule in all details.

Finally, the results of the studies on chaparrin permit us to propose a structure for glaucarubol,[7,8] the α-hydroxy-α-methyl-butyric acid ester of which, glaucarubin, is a bitter lactone found in Simarouba glauca. It will be recalled that among the compounds isolated from Castela Nicholsoni was a material suspected to be glaucarubol since it yielded glaucanol upon treatment with acid. Polonsky,[8] in her recent studies of glaucarubin, has examined the NMR spectrum of glaucanol acetate. The close correspondence of nearly all of the features of the NMR spectra of glaucanol ($C_{20}H_{24}O_6$) acetate and chaparrol ($C_{20}H_{24}O_5$) acetate leads us to conclude that glaucanol is hydroxychaparrol. While glaucanol (like chaparrol) does not consume periodate, isoglaucanol, in which the position of the lactone ring has evidently been altered by opening and reclosure, consumes a mole of periodate. These facts are readily accounted for if glaucanol is 6-hydroxychaparrol (X), and glaucarubol is 6-hydroxychaparrin (XI). Chaparrol, too, is isomerized by solution in alkali and acidification to yield isochaparrol. This compound has so far resisted purification and has been obtained only as the crystalline mono- and diacetates. Whether the chaparrol-isochaparrol change involves only relactonization (to the methylol group) or whether epimerization of the center at C_9 occurs, remains to be seen.[9]

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7) E. A. Ham, H. M. Schafer, R. G. Denkewalter, and N. G. Brink, J. Am. Chem. Soc. 76, 6066 (1954).

8) J. Polonsky and A. Gaudemer, Bull. Soc. Chim. Fr., 1432 (1961).

9) In a communication submitted simultaneously with this, Dr. P. deMayo reports on his studies of chaparrin. We and Dr. deMayo have been in correspondence during the course of our work and have agreed to present our results in this way, as separate letters.