Tetrahedron Letters No. 23, pp. 1089-1093, 1962. Pergamon Press Ltd.
Printed in Great Britain.

CHAPARRIN, THE BITTER PRINCIPLE FROM CASTELA NICHOLSONI

T.A. Davidson, T.R. Hollands and P. de Mayo

Department of Chemistry, University of Western Ontario, London, Canada.

(Received 10 August 1962)

IN 1922 Bosman[1] reported the presence in C. nicholsoni Hook (Chaparro amargosa) of two crystalline bitter principles. A search for these failed to reveal them, but instead a new substance was isolated. Whilst its characterisation and degradation was under study the isolation of the same substance was reported by Geissman and Chandorkar.[2] These authors applied the name 'chaparrin' to this compound and we are glad to accept this term.[3,4] We wish to report evidence leading to the structure (1) for this substance.

Chaparrin, m.p. 306-8° has the composition $C_{20}H_{28}O_7$. On acetylation a triacetate[3] and a tetraacetate[3] may be obtained from which chaparrin may be recovered on hydrolysis. Of the three remaining oxygen atoms two are involved in a δ-lactone and the third in a carbonyl group[3]. The presence of the carbonyl group is attested by the presence of a band at 1731 cm^{-1} in the infrared spectrum of the sodium salt of chaparrin[3], by the reduction of the tetraacetate ketone to the corresponding alcohol and by the presence of a band λ_{max} 308 mμ (ε 38) in the ultraviolet spectrum of the tetraacetate. In chaparrin and its derivatives the carbonyl and lactone carbonyl peaks

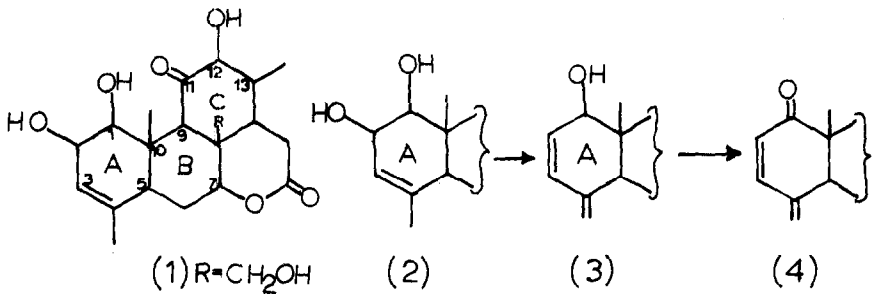
---

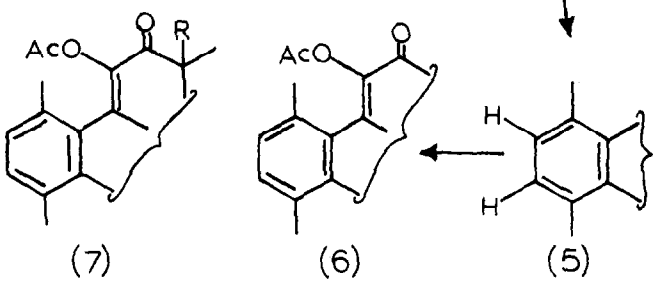
[1] L.P. Bosman, J. Chem. Soc. 121, 969 (1922); 123, 207 (1923).

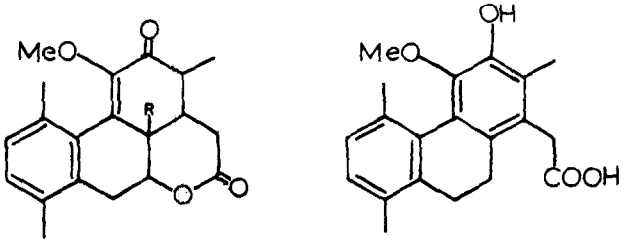
[2] T.A. Geissman and K.R. Chandorkar, J. Org. Chem. 26, 1217 (1960).

[3] Certain differences in the characterisation of chaparrin from that originally reported[2] were noted.

[4] Adequate analyses for all compounds reported have been obtained.


OH
HO
OH
A
B
C
R
(1) R=CH2OH
(2)
(3)
(4)


AcO
R
(7)
AcO
(6)
H
H
(5)


MeO
R
(8) R=CH2OH
MeO
OH
COOH
(9)

are superimposed in the infrared spectrum (~ 1726 cm^{-1}).

Chaparrin contains three methyl groups. One (τ 8.58, singlet) is attached to quaternary carbon whilst a band at τ 8.30 indicates vinylic methyl. The third appears as a doublet (τ 9.01, J ~ 5.4 c.p.s.).

Chaparrin consumes 1 mole of periodic acid rapidly, so that two of the hydroxyl groups must be vicinal. On refluxing in 0.1 N hydrochloric acid one molecule of water is lost to give, amongst other products, a diene, m.p. 258-60°C (acetate, m.p. 169-70°) which may be oxidised with manganese dioxide to a dienone. These transformations are accommodated in the change (2) → (3) → (4), and in agreement with this the appropriate changes in the n.m.r. spectrum are observed. Prolonged treatment of chaparrin with dilute acid, shorter treatment with strong acid or passage of the diene through alumina results in the loss of a further molecule of water and concomitant aromatisation. The product (5) shows benzenoid absorption in the ultraviolet[2], and the n.m.r. spectrum reveals that the angular methyl and the vinyl methyl groups have been replaced by aromatic methyl absorption (two singlets τ 7.72, 7.8). In addition two identical aromatic protons appear as a singlet at τ 3.02, as required in the formulation (5).

The presence of an α-ketol system in chaparrol was shown by its oxidation with bismuth trioxide in acetic acid or with bismuth triacetate in ethylenic glycol to a diosphenol characterised as the acetate, m.p. 183-185° [λ_{max} 288 mμ (ε 9,800)] and the methyl ether [λ_{max}298 mμ (ε 8,300)]. The ultraviolet absorption of the acetate clearly indicates conjugation of the aromatic ring with the enolised diosphenol and permits the expansion of (5) to (6). Bromination of the enol acetate (with the uptake of one atom of bromine) gave (7, R = Br) in which the former doublet methyl at C_{13} is now a singlet at τ 7.73. Further expansion of (6) to (7, R = H) can therefore be made for the enol acetate.

In the n.m.r. spectrum of a number of derivative a non-equivalence

quartet (2H) centered at about at $\tau \sim 5.02$ could be detected. This strongly suggested the presence of the grouping $\rangle C\text{-}CH_2OR$ in the molecule and its position at C_8 was suspected because of the presence of a singlet signal in chaparrin derivatives at τ 6.7 for the C_9 proton.[5] This was confirmed in the following way.

First, treatment of (7, R = H) with sulphuric acid gave formaldehyde (11%) estimated by the chromotropic acid procedure.[6] Secondly, when the enol ether, now to be represented as (8), was allowed to stand in 0.5 N alkali for 12 hours at room temperature formaldehyde was smoothly eliminated to give, after acidification, the diphenyl (9), m.p. 200-2°. This showed the expected ultraviolet spectrum [λ_{max} 250, 294 mμ (ε 9,600, 2,900) (neutral); λ_{max} 310 mμ (ε 3,800) (OH^-)] and the absence of carbonyl absorption (other than carboxyl) in the infrared spectrum. In agreement with this formulation no new aromatic protons were visible in the n.m.r. spectrum. The methyl doublet (at C_{13}) was however replaced by an aromatic singlet, and, in addition, a singlet (2H) at τ 6.20 was a clear indication of a phenylacetic acid methylene group.

The position of the lactonic ethereal oxygen is clearly demonstrated by its facile elimination under alkaline conditions. This is readily rationalised as a vinylogous β-elimination.

The general similarity between chaparrin and quassin[7] is obvious, and indeed the expected relationship was an important guide in our thinking.

Glaucarubin is a bitter lactone which occurs as an ester in Simarouba

---

[5] The presence of this singlet - absent in the borohydride reduction product - also establishes the 11-keto-12-hydroxy- as against the 11-hydroxy-12-keto system.

[6] R.L. Strong and K.O. Kutschke, Can. J. Chem. 37, 1456 (1959).

[7] Z. Valenta, S. Papadopoulos and C. Podesva, Tetrahedron 13, 100 (1961). See also R.M. Carman and A.D. Ward, Tetrahedron Letters, No. 10, 317 (1961).

glauca.[8] The reported features of its chemistry[7,8] and, in particular, the recorded n.m.r. spectrum of glaucanol acetate, the ring A aromatised derivative,[8] are indicative of a hydroxychaparrol structure, and this is supported by the isolation of glaucarubol from C. nicholsoni already reported.[8] Whereas glaucanol, like chaparrol, consumes no periodic acid, isoglaucanol[9] consumes one mole. This substance may be formed (at least) by opening and recyclisation of the lactone to the neopentyl hydroxyl group, and the periodate consumption is then rationalised by placing the 'extra' hydroxyl function at C_6. However, since an α-ketol system is present both in glaucanol and isoglaucanol which may also be involved in such oxidation this simple interpretation may not be correct and the alternative position α to the lactonic carbonyl must be considered.[10,11]

---

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

[9] J. Polonsky and A. Gaudemer, Bull. Soc. Chim. Fr., 1432 (1961).

[10] We are glad to acknowledge an exchange of correspondence with Dr. T.A. Geissman during the course of this work. We have agreed to present our results in separate communication simultaneously.

[11] The authors are indebted to the National Research Council of Canada, and Eli Lilly and Company for financial support.