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THE STRUCTURE OF QUASSIN

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THE constituents of Quassia amara have been thoroughly investigated by Robertson[1-5]. He found that the bitter extract consists of quassin, $C_{22}H_{28}O_6$, and neoquassin, $C_{22}H_{30}O_6$, which are in a lactone-hemiacetal relationship. Quassin contains two methoxyl groups, at least three C-methyl groups and no active hydrogen. The infrared (ν_{max} 1745, 1695, 1680, 1640 cm^{-1}) and ultraviolet spectra (λ_{max}

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[1] E. London, A. Robertson and H. Worthington, J. Chem. Soc. 1950, 3431.

[2] R.J.S. Beer, D.B.G. Jaquiss, A. Robertson and W.E. Savige, J. Chem. Soc. 1954, 3672.

[3] K.R. Hanson, D.B. Jaquiss, J.A. Lamberton, A. Robertson and W.E. Savige, J. Chem. Soc. 1954, 4238.

[4] R.J.S. Beer, K.R. Hanson and A. Robertson, J. Chem. Soc. 1956, 3280.

[5] R.J.S. Beer, B.G. Dutton, D.B. Jaquiss, A. Robertson and W.E. Savige, J. Chem. Soc. 1956, 4850.

255 mμ, ε 11650) of quassin showed the presence of two α,β-unsaturated ketones in the molecule[3,6]. Furthermore, the results of an acidic hydrolysis of various quassin derivatives indicated that both chromophores are probably diosphenol methyl ethers[3,7].

On the basis of the fact that the selenium dehydrogenation of neoquassin yields 3,4,5-trimethylguaiacol[2], while 1,2,8-trimethylphenanthrene is obtained from the dehydrogenation of the Clemmensen reduction product of neoquassin, Beer et al. have considered the terpenoid partial structures I and II for quassin[5].

Our own investigation has established the partial structure III for quassin. The NMR spectra of quassin and neoquassin clearly show the presence of four C-methyls, with singlets at 8.15, 8.45 and 8.94, and a doublet at 8.86 (J = 7 cycles/sec). Treatment of neoquassin with $NaOCH_3$ in

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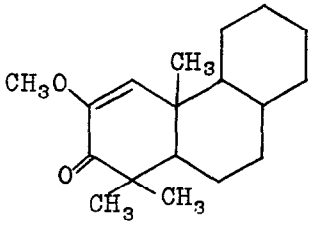
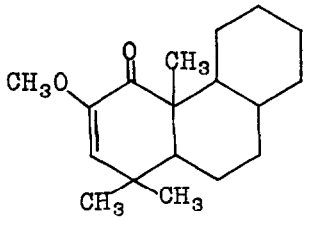
[6] Treatment of quassin with zinc and acetic acid saturates one double-bond to give dihydroquassin ($\lambda_{max.}$ 252 mμ, ε 8400)(ref. 3).

[7] Acidic hydrolysis of quassin gives norquassin, $C_{21}H_{26}O_6$ (λ_{max} 258 mμ, ε 11200; λ_{max} (KOH) 258 mμ, ε 8200; 312 mμ, ε 3300), which on treatment with base undergoes a benzilic acid rearrangement to norquassinic acid, $C_{21}H_{28}O_7$ (λ_{max} 259 mμ, ε 9640). Vigorous acid treatment of norquassinic acid hydrolyses the remaining methoxyl group and yields isobisnorquassinic acid, $C_{20}H_{26}O_7$ (λ_{max} 282 mμ, ε 7910; λ_{max} (KOH) 340 mμ, ε 6000) which can be reconverted to norquassinic acid on treatment with dimethylsulphate (ref. 3).

CH_3OD for 6 hours under reflux incorporates 5.5 atoms of deuterium[8]. The NMR spectrum of the deuterated neoquassin no longer contains the peak at 8.15 and the doublet at 8.86 is replaced by a triplet. Thus, one methyl group is converted to CD_3 and a $CHCH_3$ grouping to $CDCH_3$ during the treatment. The NMR spectrum of quassin shows the presence of one vinylic hydrogen (doublet at 4.77; J = 2 cycles/sec). The signal at 4.77 disappears when quassin and its derivatives are reduced to the corresponding dihydrocompounds with zinc



I



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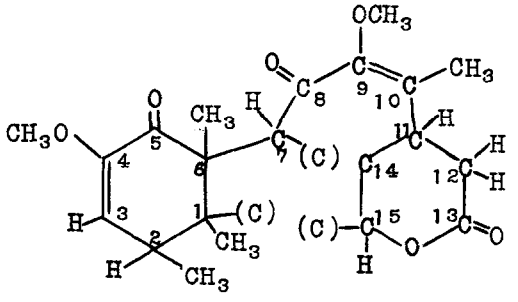
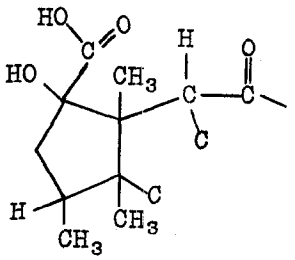


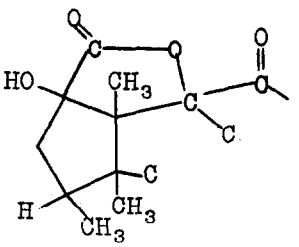
III

[8] The compound can be recovered quantitatively after a similar treatment in CH_3OH.

and acetic acid. The reflux of dihydrodesoxoquassin[9] (no vinylic H in NMR) with CH_3ONa in CH_3OD yields a deuterated product which, according to its NMR spectrum, contains the $CHCH_3$ grouping intact (doublet at 9.10)[8]. Since the vinylic hydrogen also disappears in the formation of norquassinic acid (partial formula IV), these findings clearly define the C_2-C_5 chain in quassin (see formula III).



IV



V

According to Hanson <u>et al.</u>[3], the treatment of norquassinic acid IV, $C_{21}H_{28}O_7$, with acetic anhydride - sodium acetate yields a neutral acetate, $C_{23}H_{28}O_7$, with a modified UV spectrum (λ_{max} 224 mμ, ε 6000; 284 mμ, ε 4200), υ_{IR} ($CHCl_3$) 1770, 1740 cm^{-1}, which can be reconverted to IV on basic hydrolysis. It is clearly an enol-lactone and its IR frequency indicates a 1,5-relationship of the carboxyl and ketone carbon atoms. Oxidation of IV with lead tetraacetate in acetic acid at room temperature gives the lactone V,

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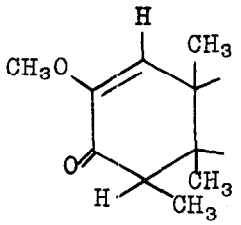
[9] In the desoxo-series, the quassin lactone ring has been replaced by a cyclic ether (ref. 4).

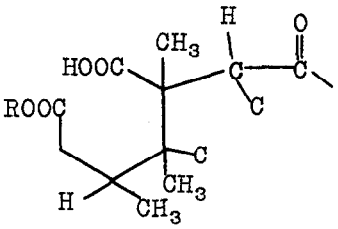
m.p. 210-214°, (Found: C, 64.64; H, 6.70; O, 29.06. $C_{21}H_{26}O_7$ requires: C, 64.59; H, 6.73; O, 28.68), (λ_{max} 269 mμ, ε 8000; ν_{IR} (KBr) 1785, 1735, 1670, 1630 cm^{-1}). Both the enol-lactone and compound V show the four C-methyl groups, including the $CHCH_3$ group, in their NMR spectra. Furthermore, the spectrum of V contains no hydrogens unshielded by the newly created lactone ring which must therefore have closed at a tertiary carbon atom. The formation of V, which is best explained by an oxidative attack at a position α to the ketone in IV, together with the deuteration results, eliminates the alternative partial formulation VI for quassin. Treatment of desoxonorquassinic acid[9] (partial formula IV) with conc. H_2SO_4 eliminates the elements of formic acid and gives an oily ketone (Found: C, 72.24; H, 8.43; O, 19.17. $C_{20}H_{28}O_4$ requires: C, 72.25; H, 8.51; O, 19.24). Its IR spectrum (1740, 1680, 1645 cm^{-1}) shows that the newly formed keto-group is in a 5-membered ring and the corresponding ring in quassin is therefore 6-membered.

Beer et al.[4] prepared the desoxodicarboxylic acid VII (R =H) by an oxidation of desoxonorquassin with alkaline hydrogen peroxide[9]. They reported that one of the carboxyl groups is very likely tertiary, since treatment of the diacid with methanol - HCl yielded a monoester, while the corresponding diester, prepared with diazomethane, gave a different monoester on prolonged basic hydrolysis. We find that the

monoester VII (R = CH_3), $C_{22}H_{32}O_7$, which is stable under the usual decarboxylating conditions, undergoes an oxidative decarboxylation on treatment with lead tetraacetate to give a doubly unsaturated ketone VIII, m.p. 102-106° (Found: C, 69.42; H, 8.48; O, 22.51. $C_{21}H_{30}O_5$ requires: C, 69.58; H, 8.36; O, 22.06); λ_{max} 267 mμ infl. (ε 6900), 295 mμ (ε 8500); ν_{IR} (KBr) 1740 (ester), 1645 (ketone), 1580 cm^{-1}. The NMR spectrum of this ketone shows no vinylic hydrogens and contains methyl singlets at 7.95, 8.16 and 8.94 and a doublet at 9.21. One methyl group must therefore be situated on the newly created double-bond. This unusual oxidation[10] completes the definition of the substitution of the C_5-C_8 chain in quassin (see formula III). It follows that quassin cannot contain a <u>geminal</u> dimethyl group.



VI

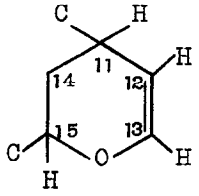


VII

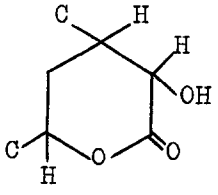
[10] The reaction can be formulated as a 'vinologous 1,2-diol' oxidation of the corresponding enol-acid. We are at present investigating whether it is generally applicable for degradation of γ-ketoacids.

The remaining features of the environment of the ketone at C_8 follow unambiguously. It is α,β-unsaturated and since C_7 has been defined by the formation of V and VIII, the double-bond must be at C_9-C_{10}. The complete deuteration of one methyl group on treatment of neoquassin with CH_3ONa in CH_3OD places the fourth methyl at C_{10}. The second methoxyl group must be at C_9, since the acid hydrolysis product of norquassinic acid (IV) shows diosphenolic properties.

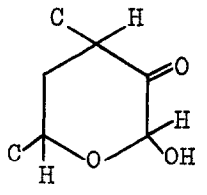
The detailed structure of the lactone ring has been established in the following way. Oxidation of anhydroneoquassin (IX)[11] with $KMnO_4$ in acetone yields three products:



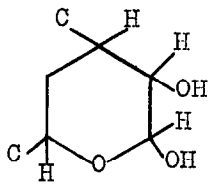
IX



X



XI



XII

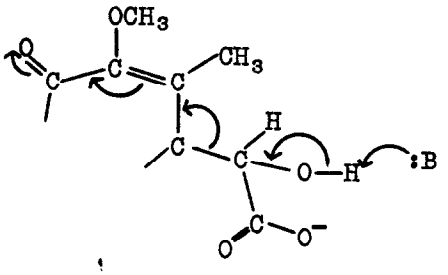
(1) hydroxyquassin X, m.p. 268-270° (Found: C, 65.28; H, 6.98; O, 27.83. $C_{22}H_{28}O_7$ requires: C, 65.34; H, 6.98; O, 27.68), ν_{IR} (KBr) 1740, 1695, 1685 and 1640 cm^{-1}; (2) the ketone XI, m.p. 242-244° (Found: C, 65.03; H, 6.96; O, 27.92), ν_{IR} (KBr) 1710 infl., 1695 and 1640 cm^{-1}; (3) the

[11] Anhydroneoquassin is prepared by the treatment of neoquassin with acetic anhydride-sodium acetate. The newly created double-bond is not in conjugation with either one of the quassin chromophores (ref. 3).

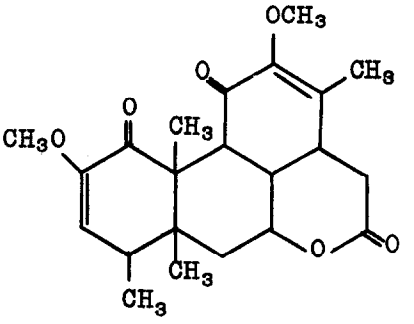
alcohol XII, m.p. 235-239° (Found: C, 64.90; H, 7.48; O, 27.28. $C_{22}H_{30}O_7$ requires: C, 65.01; H, 7.44; O, 27.55). Oxidation of XII with Ag_2O in boiling ethanol converts it to X. The formation of XI shows the presence of two hydrogens at C_{12} in quassin. In agreement, the NMR spectrum of anhydroneoquassin (IX) shows, in addition to the hydrogen at C_3, two vinylic hydrogens as doublets at 3.67 and 5.48 (J = 7 cycles/sec). The presence of one hydrogen at C_{15} follows from the fact that the NMR spectra of all quassin derivatives containing the lactone ring show a triplet (1 H) at 5.75 which shifts to a higher field when the lactone carbonyl group is reduced. Oxidation of XII with periodic acid followed by basic hydrolysis and oxidation with CrO_3 in pyridine yields a γ-lactone, m.p. 266-268° (Found: C, 67.03; H, 6.86; O, 26.12. $C_{21}H_{26}O_6$ requires: C, 67.36; H, 7.00; O, 25.64), ν_{IR} (KBr) 1775, 1700, 1690 and 1635 cm^{-1}. Thus, the lactone in quassin must be 6-membered. The amorphous aldehyde-formate, obtained as an intermediate in this degradative series, shows a doublet at 0.31 (J = 6 cycles/sec.; aldehyde) and a singlet at 2.17 (formate) in its spectrum. The splitting of the aldehyde peak leaves no doubt about the presence of one hydrogen at C_{11}.

Treatment of hydroxyquassin X, $C_{22}H_{28}O_7$, with aqueous base under reflux eliminates two carbon atoms and gives a nonlactonic compound, m.p. (184)-221° (Found: C, 69.00; H,

8.06; O, 22.88. $C_{20}H_{28}O_5$ requires: C, 68.94; H, 8.10; O, 22.96), ν_{IR} (KBr) 1690, 1660 and 1630 cm^{-1}. This elimination which can be visualized as shown in formula XIII establishes the relative position of the lactone ring and the ketone at C_8 in quassin[12].



XIII



XIV

On the basis of the above evidence, we propose formula XIV as the representation of quassin. It contains partial formula III and explains satisfactorily the transformation of neoquassin to the reported dehydrogenation products, 3,4,5-trimethylguaiacol[2] and 1,2,8-trimethylphenanthrene[5]. Biogenetically, its carbon skeleton can be derived from the pimarane skeleton by two 1,2-shifts.

Acknowledgements - One of us (A.H.G.) gratefully acknowledges the receipt of a National Research Council of Canada studentship. We are greatly indebted to Dr. R. S. Stuart, Merck and Co. Limited for the supply of crude quassin.

[12] The alternative attachment of the lactone ring at C_7 can be eliminated on the basis of evidence already presented.