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QUASSIN AND *NEO*QUASSIN[1]

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Abstract—Structure XIX (R_1 = H; R_2 = CH_3) was derived for quassin on the basis of extensive chemical and physical evidence.

THE existence of bitter substances in quassia wood (*Quassia amara*) was reported in 1835.[2] Several unsuccessful attempts to purify the chemical constituents culminated, a century later, in their isolation and partial purification by Clark.[3]

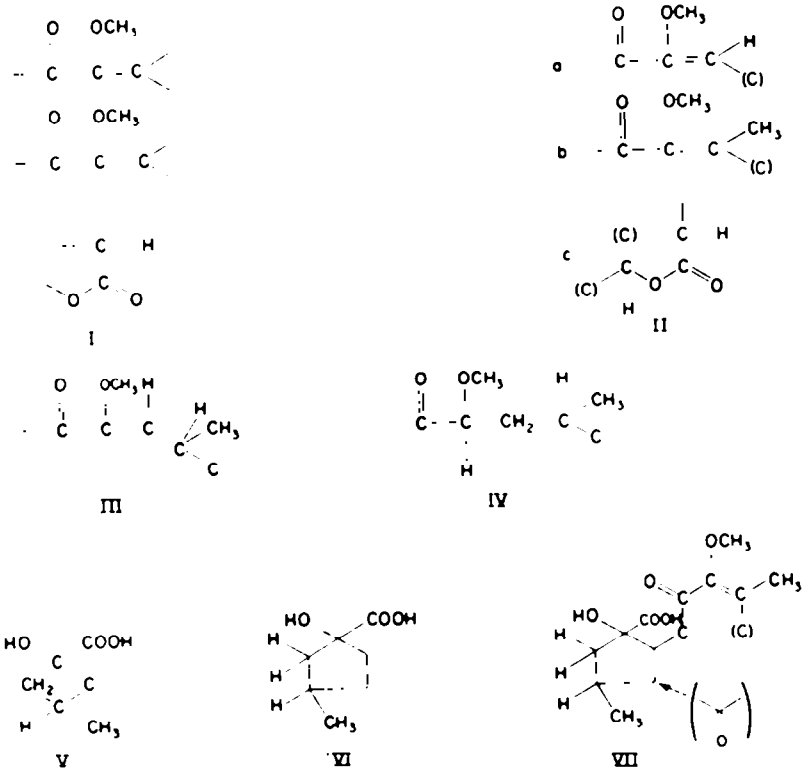
The first extensive investigation of the bitter substances was performed by Robertson and his co-workers[4]. They were able to achieve a clean separation and characterization of the two major constituents, quassin, $C_{22}H_{26}O_6$, and *neo*quassin, $C_{22}H_{30}O_6$, and to define their functionality. Quassin was found to be a lactone, and *neo*quassin the corresponding hemiacetal. The compounds contain two methoxyl groups, at least three C-methyl groups, and no active hydrogen in addition to the hemiacetal hydroxyl group. Acidic degradation indicated the presence of two diosphenol methyl ethers in the molecule.[4c] Acidic hydrolysis of quassin (IR_{max} 1745, 1695, 1680, 1640 cm^{-1}; λ_{max} 255 mμ, ε 11650) yielded 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 diazomethane was reconverted to quassin. Norquassin on treatment with base underwent a benzilic acid rearrangement to give norquassinic acid, $C_{21}H_{28}O_7$ (λ_{max} 259 mμ, ε 9640), which could be further hydrolysed with acid to *iso*bisnorquassinic acid, $C_{20}H_{26}O_7$ (λ_{max} 282 mμ, ε 7910; λ_{max} (KOH) 340 mμ, ε 6000). The last step could be reversed by treatment with dimethylsulphate. It is clear from the above evidence that neither of the acidic reactions involved a skeletal rearrangement and, on that basis, the spectroscopic properties of the nor-compounds provide a strong indication of the presence of two methylated diosphenols in quassin.

The hemiacetal ring of *neo*quassin was further defined by a reaction with acetic anhydride, which yielded anhydro*neo*quassin, $C_{22}H_{28}O_5$, a cyclic enol-ether.[4c] This fact was established by the reformation of *neo*quassin on treatment with aqueous acetic acid. According to the ultraviolet spectra, the newly formed double-bond of anhydro*neo*quassin is not conjugated with either one of the diosphenol methyl ethers.

The quoted results of Robertson *et al.* can be summarized by the partial structure I for quassin. On the basis of infrared evidence, the two ketones and the lactone are situated in six-membered (or larger) rings.

[1] For a preliminary report, see Z. Valenta, A. H. Gray, S. Papadopoulos and C. Podešva, *Tetrahedron Letters* No. 20, 25 (1960).
[2] F. L. Winckler, *Rep. Pharm.* **4**, 85 (1835).
[3] E. P. Clark, *J. Amer. Chem. Soc.* **59**, 927, 2511 (1937).
[4a] E. London, A. Robertson and H. Worthington, *J. Chem. Soc.* 3431 (1950); [b] R. J. S. Beer, D. B. G. Jaquiss, A. Robertson and W. E. Savige, *Ibid.* 3672 (1954); [c] K. R. Hanson, D. B. G. Jaquiss, J. A. Lamberton, A. Robertson and W. E. Savige, *Ibid.* 4238 (1954); [d] R. J. S. Beer, K. R. Hanson and A. Robertson, *Ibid.* 3280 (1956); [e] R. J. S. Beer, B. G. Dutton, D. B. G. Jaquiss, A. Robertson and W. E. Savige, *Ibid.* 4850 (1956).

Our own investigation started with the assumption that a molecule with a relatively large number of unsaturated functions must be particularly well suited for an investigation by nuclear magnetic resonance spectroscopy. The spectrum of quassin[5] revealed the presence of one vinylic hydrogen and four C-methyl groups. Of these, two are tertiary (singlets at 8·45 and 8·79 p.p.m.), one secondary (doublet at 8·86), and one (singlet at 8·15 p.p.m.) is situated on a double-bond. Furthermore, the shift of a signal for one hydrogen at 5·70 p.p.m. in quassin to 6·15 p.p.m. in *neo*quassin indicates the secondary nature of the ether oxygen of the lactone ring. The partial formula I for quassin can therefore be extended to II.



Both quassin and *neo*quassin can be reduced with zinc and acetic acid to the corresponding dihydroderivatives.[4c] On the basis of their NMR spectra, the two dihydrocompounds no longer contain a vinylic hydrogen and the secondary methyl group becomes more shielded during the reduction (a shift of the methyl doublet from 8·86 to 9·10 p.p.m.). This change is best explained by the reduction of III to IV. This postulate was confirmed in the following way. *Neo*quassin and dihydro*neo*quassin were found to be resistant to vigorous treatment with sodium methoxide in methanol; the two compounds were therefore separately treated under similar conditions in CH_3OD. The NMR spectrum of deuterated *neo*quassin shows that the $CHCH_3$ group has been replaced by $CDCH_3$ (triplet at 8·85 p.p.m.) and that one methyl group has

[5] The NMR signals of important compounds are given in Table 1 in the experimental section. For interpretation, see e.g. L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*. Pergamon Press, London, New York (1959).

been completely deuterated (disappearance of the singlet at 8·15 p.p.m.). In contrast, treatment of dihydro*neo*quassin again deuterated one methyl group completely, but left the $CHCH_3$ grouping intact. Since only hydrogens α or vinylogously α to carbonyl groups can be replaced by deuterium under these conditions, partial formulae IIb, III and IV give a satisfactory explanation of these results.[6]

We next turned our attention to the size of the ring containing the grouping III and its position in relation to the remaining oxygen functions. An infrared maximum at 1715 cm^{-1} in the spectra of the dihydrocompounds indicates that the saturated ketone is in a six-membered or larger ring. A definite decision was reached by the investigation of norquassinic acid, the benzilic acid rearrangement product of norquassin.[4c] Since this acid, according to its NMR spectrum, does not contain a vinylic hydrogen, it must be formed by the hydrolysis and rearrangement of the chromophor III and can, therefore, be represented by the partial formula V. Desoxonorquassinic acid,[7] $C_{21}H_{30}O_6$, which must also contain the grouping V, lost the elements of formic acid on treatment with concentrated sulfuric acid, and gave a ketone, $C_{20}H_{28}O_4$, with infrared bands (in $CHCl_3$) at 1740, 1680 and 1645 cm^{-1}. The maximum at 1740 cm^{-1} shows that the newly formed keto-group is in a five-membered ring and the partial formula of norquassinic acid can therefore be extended to VI.

It proved to be relatively easy to establish the relationship of the grouping VI to the remaining diosphenol methyl ether. According to Hanson *et al.*[4c], treatment of norquassinic acid, $C_{21}H_{28}O_7$, with acetic anhydride-sodium acetate yielded a neutral acetate, $C_{23}H_{28}O_7$, with a modified ultraviolet spectrum (λ_{max} 224 mμ, ε 6000; 284 mμ, ε 4200) and infrared bands (in $CHCl_3$) at 1770 and 1740 cm^{-1}. This acetate could be reconverted to norquassinic acid on basic hydrolysis. The compound is clearly the acetate of an enol-lactone and the maximum at 1770 cm^{-1} indicates a 1,5-relationship of the carboxyl and ketone carbon atoms. The partial formula VI can therefore, with some assurance, be extended to VII, since the only other possible extension (see arrow in VII) would lead to a highly strained enol double-bond.

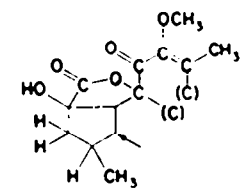
Two additional reactions are of importance for the partial formulation VII. Oxidation of norquassinic acid with lead tetraacetate in acetic acid at room temperature gave a neutral compound, $C_{21}H_{26}O_7$, showing infrared maxima (in $CHCl_3$) at 1785 (γ-lactone), 1735 (lactone), 1670 (unsaturated ketone) and 1630 (double-bond) cm^{-1}. Its NMR spectrum contains signals for all four C-methyl groups, including the $CHCH_3$ group, and shows no hydrogens unshielded by the newly created lactone ring. This high-yield reaction is best explained by an oxidative attack at a position α to the ketone to give VIII, although the attack at one alternate position (see arrow in VIII) cannot be completely excluded.

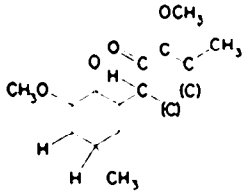
On that basis, quassin can be represented by the partial structure IX, in which the substitution of the two carbons connecting both keto-groups is not rigorously defined. This final point was clarified by the degradation of the desoxodicarboxylic acid (partial formula X, R = H),[7] obtained following the procedure of Beer *et al.*[4d] by the alkaline hydrogen peroxide oxidation of desoxonorquassin. It had been established that one of the carboxyl groups of the diacid is probably tertiary since treatment with methanolic hydrochloric acid gave a monoester, while the corresponding diester,

[6] *Neo*quassin incorporated 5·4 atoms of D, while the value for dihydro*neo*quassin was 6·62 D. Possible reasons for this difference and other deuteration results will be discussed in a separate communication.

[7] Desoxoquassin, $C_{19}H_{26}O_4$, is prepared by the catalytic reduction of anhydro*neo*quassin.[4d] It therefore contains a cyclic ether ring in place of the quassin lactone ring.

prepared with diazomethane, gave a different monoester on prolonged basic hydrolysis.[4d] The monoester X (R = CH_3), $C_{22}H_{32}O_7$, which was found to be stable under the usual decarboxylating conditions, lost the elements of formic acid on treatment with lead tetraacetate in boiling benzene to give a doubly unsaturated ketone, $C_{21}H_{30}O_6$. 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 p.p.m. One methyl group must therefore be situated on the newly created double-bond. These data and the modified ultraviolet[8] (λ_{max} 267 mμ infl., ε 6900; 295 mμ, ε 8500) and infrared spectra[9] (I.R.$_{max}$ 1740, ester; 1645, ketone; 1580 cm^{-1}, double-bond) are in good agreement with the partial structure XI for the unsaturated ketone. Since the infrared intensity of the double-bond band is comparable with that of the keto-group, a *cisoid* arrangement of one enone group in XI is indicated.[9,10] This interesting γ-keto acid oxidation can be assumed to proceed through a transition state of the type XII or its non-cyclic equivalent.[10a]


VIII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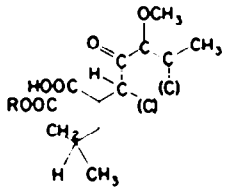
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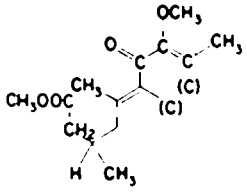
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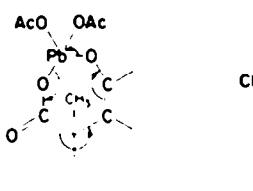
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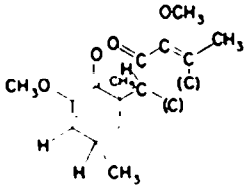
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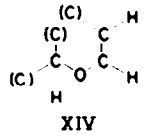
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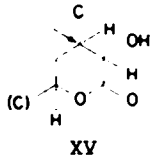
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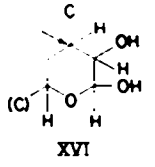

XVI

The chemical and physical properties of the compounds discussed thus lead to the partial structure XIII for quassin and *neo*quassin. It remains to establish the position of the lactone ring and the fourth C-methyl group and to close two carbocyclic rings. An oxidative study of anhydro*neo*quassin completely clarified these structural features. Anhydro*neo*quassin, $C_{22}H_{28}O_6$, is a cyclic enol-ether prepared by the dehydration of

[8] The anomalous ultraviolet spectrum compares with that of the similarly constituted chromophor in diosterol-II: L. F. Fieser, M. Fieser and S. Rajagopalan, *J. Org. Chem.* 13, 800 (1948).

[9] The unusually low infrared frequency of the keto-group finds its analogy in the spectrum of lactucin: D. H. R. Barton and C. R. Narayanan, *J. Chem. Soc.* 963 (1958).

[10] R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey and N. L. Wendler, *J. Amer. Chem. Soc.* 76, 4013 (1954).

[10a] However, the keto-group need not be mechanistically involved. The formation of olefins on treatment of tertiary carboxyl-groups under comparable conditions has been reported: W. A. Mosher and C. L. Kehr, *J. Amer. Chem. Soc.* 75, 3172 (1953); L. L. McCoy and A. Zagalo, *J. Org. Chem.* 25, 824 (1960); G. Büchi, R. E. Erickson and N. Wakabayashi, *J. Amer. Chem. Soc.* In press (G. Büchi, personal communication).

*neo*quassin with acetic anhydride.[4c] In addition to the vinylic hydrogen present in XIII, its NMR spectrum shows two vinylic hydrogens with signals at 3·67 and 5·48 p.p.m. These positions are in good agreement with those of α- and β-hydrogens, respectively, of model enol-ethers. In addition to XIII, anhydro*neo*quassin therefore contains the grouping XIV (*cf.* IIc).

As anticipated, only the strongly nucleophilic enol-ether double-bond was attacked during a mild potassium permanganate oxidation of anhydro*neo*quassin in acetone. Three crystalline products were thus obtained in a high yield: a lactone A, $C_{22}H_{28}O_7$ (I.R.$_{max}$ 1740, 1695, 1685 and 1640 cm^{-1}), its non-lactonic isomer B, $C_{22}H_{28}O_7$ (I.R.$_{max}$ 1695 and 1640 cm^{-1}), and a diol C, $C_{22}H_{30}O_7$. Diol C was converted to compound A on treatment with silver oxide. Oxidation of C with periodic acid gave an amorphous aldehyde-formate which on basic hydrolysis followed by chromium trioxide oxidation yielded a crystalline γ-lactone, $C_{21}H_{26}O_6$ (I.R.$_{max}$ 1775, 1700, 1690 and 1635 cm^{-1}). This degradation, involving the loss of the formate carbon atom, clearly defines the six-membered nature of the oxygen ring in quassin and *neo*quassin. Compounds A and C thus can be represented by partial structures XV and XVI, respectively. The substitution of the carbon atom indicated by the arrow in these formulae was deduced on the basis of the NMR spectrum of the intermediate aldehyde-formate. It contains an aldehyde doublet at 0·31 p.p.m. (J 6 cycles/sec) and a formate singlet at 2·17 p.p.m; the splitting of the aldehyde peak leaves no doubt about the presence of one hydrogen atom in the α-position.

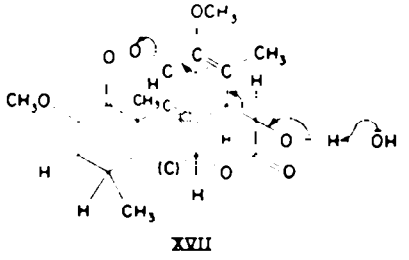
Treatment of lactone A, $C_{22}H_{28}O_7$, with hot aqueous base eliminated two carbon atoms and gave a non-lactonic compound, $C_{20}H_{28}O_5$, with infrared bands (in KBr) at 3450 (OH), 1690, 1660 (unsaturated ketones) and 1630 (double-bonds) cm^{-1}. Partial formulation XVII for lactone A represents the only way in which groupings XIII and XV can be connected, and which at the same time gives a rational explanation of the elimination (see arrows in XVII). The secondary nature of the hydroxyl group in the product of elimination (XVIII), was confirmed by a chromium trioxide oxidation to a ketone, $C_{20}H_{26}O_5$. The absence of any carbonyl maximum above 1715 cm^{-1} in the infrared spectrum of this ketone shows that the newly formed keto-group is located in a six-membered or larger ring.

The complete structure of quassin can now be discussed. The formulation XIX is a unique consequence of all the physical and chemical data described above. On the basis of extensive infrared evidence, ring C cannot be five-membered, and no structure with a seven-membered ring can be constructed which would satisfy all the requirements. The only remaining uncertainty is the position of the fourth methyl group, which can be attached at C_6 or C_9.[11] The sharp NMR singlet corresponding to this methyl group appears at 8·79 p.p.m. in quassin and at 8·94 p.p.m. in *neo*quassin. This shift, associated with the change of the lactone ring to a hemiacetal ring, favors the attachment at C_9.

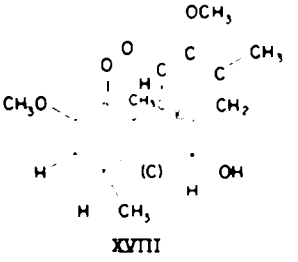
In addition to anhydro*neo*quassin, the treatment of *neo*quassin, $C_{22}H_{30}O_6$, with acetic anhydride-sodium acetate yielded dehydro*neo*quassin (XX), $C_{22}H_{28}O_6$. This unusual dehydrogenation was first reported by Clark[3] and must involve oxidation by air or peroxides. Dehydro*neo*quassin shows infrared bands (in KBr) at 3400, 1697, 1680, 1640 and 1605 cm^{-1} and an ultraviolet maximum at 280 mμ (ε 10500). Oxidation of XX with silver oxide gave dehydroquassin (XXI), $C_{22}H_{26}O_6$, with infrared bands

[11] Only structure XIX (R_1 = CH_3; R_2 — H) was discussed in our preliminary communication.[1]

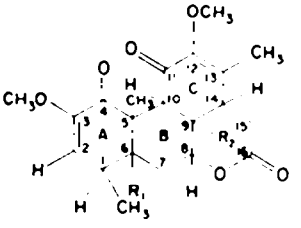
(in KBr) at 1727 (conjugated lactone), 1700, 1690 (ketones), 1635, 1616 and 1590 (double-bonds) cm^{-1}. Ultraviolet maxima at 305 mμ (ε 8600), 268 mμ (ε 7000) and 228 mμ (ε 7000) indicate that one of the chromophores has been extended. The NMR spectra of the two compounds are in good agreement with the assigned structures and again show an unshielding of one methyl group by the lactone ring (singlet at 8·75 p.p.m. in XXI).



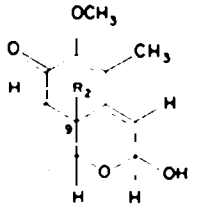
XVII



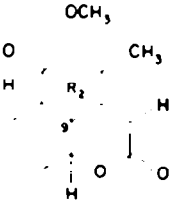
XVIII



XIX



XX



XXI

Clearly, the fact that dehydro*neo*quassin (XX) does not aromatize under the conditions of its formation provides a strong indication that ring C must be blocked. In addition, XX and XXI could not be converted to a phenol on treatment with acid or base, and all attempts to obtain a phenol by a mild dehydrogenation of quassin proved unsuccessful. A vigorous dehydrogenation of quassin with chloranil yielded a small amount of a non-aromatic isomer of XXI. This compelling evidence places the last methyl group at C_9, and the structure of quassin must therefore be XIX (R_1 = H, R_2 = CH_3).

A surprising confirmation of this assignment came from the study of the previously mentioned compound B, $C_{22}H_{28}O_7$, one of the permanganate oxidation products of anhydro*neo*quassin. The infrared spectrum of a carefully purified sample of B shows the absence of any lactone or unconjugated ketone, while the ultraviolet and NMR spectra exclude the presence of a new double-bond. The compound liberates iodine on treatment with potassium iodide in acetic acid and must therefore contain an

epoxide ring activated by a keto-group. Structure XXII[12] explains the described properties and the following transformations. Treatment of XXII with formic acid in acetone hydrolysed one methoxyl group and gave the yellow compound XXIII, $C_{21}H_{28}O_7$. Its functionality follows from the infrared bands (in KBr) at 3400 (hemiacetal), 1730 (unconjugated ketone), 1690, 1680 (conjugated ketones), 1635 and 1622 (double bonds) cm^{-1}, and from the normal ultraviolet maximum at 264 mμ (ε 9400). The normally very stable methoxyl group in ring C is clearly activated for acid hydrolysis by the epoxide ring as indicated by arrows in XXII.

The hydrolysis of XXIII with methanolic potassium hydroxide yielded the phenol XXIV, $C_{20}H_{24}O_6$. Its NMR spectrum shows the presence of two aldehyde groups (signals at $-0{\cdot}44$ and $+0{\cdot}60$ p.p.m.), one secondary methyl group (doublet at 9·00 p.p.m.), one tertiary methyl group (singlet at 8·59 p.p.m.), and two strongly and about equally unshielded aromatic methyl groups (7·46 and 7·53 p.p.m.). In agreement with structure XXIV are infrared bands (in KBr) at 3100 (OH), 1715 (aldehyde), 1675 (aromatic aldehyde), 1595 (infl.) and 1583 (aromatic ring), and ultraviolet maxima at 239 mμ (ε 8500) and 296 mμ (ε 8500), shifting to 261 mμ (ε9950) and 314 mμ (ε 5800), respectively, in ethanolic potassium hydroxide. The presence of a hemiketal in ring A follows from the ultraviolet spectrum and from the position of the vinyl hydrogen signal (5·19 p.p.m.).

The aromatization is best rationalized as proceeding through the stages XXIII→XXV→XXVI→XXIV. It was found that no phenol was formed in an alkaline hydrolysis of XXIII in an inert atmosphere. The transformation thus involves an air oxidation which can take place before[13] or after the C_8—C_9 bond-cleavage.

The possibility of an acid catalyzed skeletal rearrangement during the transformation of XXII to XXIV is excluded by the fact that the phenol XXIV was also obtained by the reaction of XXII with sodium metaperiodate and sodium bicarbonate in aqueous methanol followed by basic hydrolysis. These remarkable transformations of the epoxide XXII thus confirm that ring C in quassin is six-membered and that aromatization is possible only after the cleavage of the C_8—C_9 bond. Furthermore, the NMR spectrum of the phenol XXIV reveals the position of the elusive angular methyl group.

The reported formation of 3,4,5-trimethylguaiacol[14b] and 1,2,8-trimethylphenanthrene[14c] in the selenium dehydrogenation of *neo*quassin and its Clemmensen reduction product, respectively, can be easily rationalized on the basis of the proposed structure.

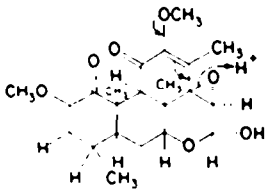
Two fundamentally different biogenetic hypotheses can be formulated for the formation of quassin and *neo*quassin. The compounds could arise from the diterpenoid pimarane skeleton by a series of C-methyl shifts and a shift of a two-carbon fragment. However, the distribution of oxygen atoms and the obvious structural symmetry strongly favor an oxidative coupling of two identical C_{10}-units (XXVII).[14]

The stereochemistry of quassin and additional transformations in the quassin series will be discussed in separate publications.

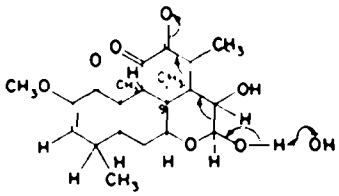
[12] This unusual formation of an epoxide in a permanganate oxidation finds its formal analogy in the well-known epoxidation of α,β-unsaturated ketones with alkaline hydrogen peroxide. The survival of the epoxide is explained by the mild reaction conditions (several minutes in acetone at room temperature).

[13] For air-oxidation of 1,4-diketones to enediones in alkaline solution, *cf.* W. G. Dauben, G. A. Boswell and W. Templeton, *J. Org. Chem.* **25**, 1853 (1960).

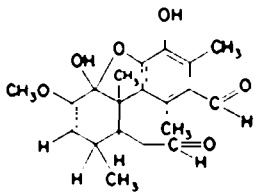
[14] For an authoritative summary on the role of phenol oxidations in biogenesis, see D. H. R. Barton and T. Cohen, *Festschrift Arthur Stoll*. Birkhauser Verlag, Basel (1957).



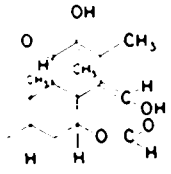
XXII



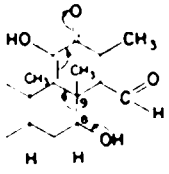
XXIII



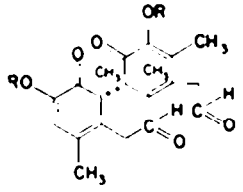
XXIV



XXV



XXVI



XXVII

EXPERIMENTAL

Preparation of pure quassin. Crude quassin supplied by Merck Co. of Canada was found to consist of a mixture of quassin and *neo*quassin. Silver oxide proved to be the most efficient oxidizing agent. The mixture (10 g), m.p. 229°, was dissolved in 200 ml of ethanol and 150 ml of water, and treated with freshly prepared silver oxide (from 40 g of $AgNO_3$) for 15 hr under reflux. The warm reaction mixture was filtered through Celite, the filtrate was diluted with an equal volume of water and extracted with five 50 ml portions of $CHCl_3$. Evaporation yielded a foam (8·3 g) which was purified by a treatment with charcoal in CH_3OH and crystallized from aqueous CH_3OH (total yield 5·8 g); recrystallized product melted at 221°. (Found: C, 67·71; H, 7·28; O, 25·18; C—CH_3, 8·02; OCH_3, 15·81. $C_{22}H_{30}O_6$ requires: C, 68·02; H, 7·26; O, 24·72; 4 C—CH_3, 15·4; 2 OCH_3, 16·0%.)

Preparation of pure neo*quassin*[46]. "Crude quassin" was treated with aqueous KOH at room temperature, *neo*quassin was extracted with $CHCl_3$ and recrystallized from aqueous CH_3OH, m.p. 231°. Quassin could be recovered from the aqueous solution by saturation with CO_2 and extraction with $CHCl_3$.

Deuteration of neo*quassin.* A solution of *neo*quassin (300 mg) and Na (150 mg) in 6 ml of CH_3OD was heated under reflux for 4 hr. Special precautions were taken to exclude moisture before and during the reaction, which was run under purified and dried N_2. The reaction mixture was poured into $CHCl_3$ (200 ml) and washed with ice-cold aqueous HCl and with ice-water. The solution was evaporated and the residue crystallized from ethyl acetate–pet. ether to give pure product, m.p. 220–222°. Isotopic analysis revealed the presence of 5·4 atoms of D. The same isotopic content was found in a reaction run for 10 hr. Pure *neo*quassin was recovered when CH_3OH was used in place of CH_3OD.

Deuteration of dihydroneoquassin. Dihydro*neo*quassin acetate was prepared by the reduction of *neo*quassin with Zn and acetic acid.[4c] The acetate (200 mg) was treated with a solution of Na (100 mg) in 6 ml of CH_3OH and refluxed for 5 hr under N_2. The solution was poured into $CHCl_3$ washed with cold aqueous HCl followed by ice-water, evaporated, and the residue crystallized from ethyl acetate to give pure dihydro*neo*quassin, m.p. 204–206°. (Found: C, 66·85; H, 8·50; O, 24·79. $C_{22}H_{32}O_6$ requires: C, 67·16; H, 8·26; O, 24·58%.)

An identical treatment of dihydro*neo*quassin acetate (190 mg) with Na (110 mg) in 6 ml of CH_3OD yielded deuterated dihydro*neo*quassin, m.p. 205–207°, containing 6·62 atoms of D per molecule.

Deformylation of desoxonorquassinic acid. Desoxonorquassinic acid[4d] (100 mg), m.p. 190–194°, was dissolved in 3 ml of conc H_2SO_4 and allowed to stand for 4 hr at room temperature. The solution was extracted with $CHCl_3$. Evaporation yielded a colorless oil (80 mg) which was chromatographed and sublimed for analysis. (Found: C, 72·24; H, 8·43; O, 19·17. $C_{20}H_{28}O_4$ requires: C, 72·26; H, 8·49; O, 19·25%.)

Oxidation of norquassinic acid with lead tetraacetate. Norquassinic acid[4c] (190 mg), m.p. 228–232°, was treated with 200 mg of $Pb(OAc)_4$ in glacial acetic acid (10 ml) for 15 hr at room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in $CHCl_3$. The

solution was shaken with aqueous $NaHCO_3$ and evaporated to dryness. The neutral residue (80 mg) was recrystallized from chloroform–benzene to give the γ-lactone VIII, m.p. 210–214°. (Found: C, 64·64; H, 6·68; O, 29·06. $C_{21}H_{36}O_7$ requires: C, 64·59; H, 6·71; O, 28·70%).

Oxidation of desoxodicarboxylic acid monoester (X; R = CH_3) *with lead tetraacetate.* The oily monoester (780 mg), prepared by methylation of desoxodicarboxylic acid X (R = H),[44] m.p. 275–280°, with methanolic HCl, was reacted with 1·1 g of $Pb(OAc)_4$ in boiling dry benzene (100 ml) for 15 hr. The solvent was evaporated, the residue suspended in chloroform and the suspension was extracted repeatedly with aqueous $NaHCO_3$. Evaporation of $CHCl_3$ gave a neutral fraction (580 mg) which was hydrolyzed with boiling methanolic NaOH (1%) for 30 min. A conventional separation gave an acidic fraction (350 mg), which was subjected to a chromatography on silicic acid (silica gel, Light and Co). Fractions eluted with benzene–ether (1:1) (170 mg) were distributed in 9 funnels between $CHCl_3$ and a phosphate–citrate buffer (pH 7) (50 ml in each phase). The peak fraction (105 mg) was esterified with diazomethane and crystallized from ether to give the unsaturated ketone XI, m.p. 102–106°. (Found: C, 69·42; H, 8·48; O, 22·32; OCH_3, 16·90. $C_{31}H_{50}O_8$ requires: C, 69·58; H, 8·34; O, 22·08; 2 OCH_3, 17·1%.)

Oxidation of anhydroneoquassin with $KMnO_4$. Anhydro*neo*quassin, m.p. 196°, was prepared according to the method of Clark[8] and Robertson[4]. To the stirred solution of anhydro*neo*quassin (2·0 g) in pure acetone (250 ml) and dist. H_2O (100 ml), a solution of $KMnO_4$ (2·06 g) in dist. H_2O (100 ml) was added dropwise at room temperature over a period of about 15 min. After filtration of the reaction mixture through Celite and washing of the cake with acetone, the combined filtrate was partially evaporated *in vacuo*. Epoxide XXII, which separated during the evaporation, was filtered (240 mg) and recrystallized from ethyl acetate–chloroform, m.p. 222–224°. (Found: C, 65·07; H, 6·94; O, 27·52. $C_{21}H_{28}O_7$ requires: C, 65·34; H, 6·98; O, 27·68%.)

The mother liquor was made strongly basic by the addition of 10% KOH(10 ml) and exhaustively extracted with chloroform. Evaporation of the combined extracts left a white foam (520 mg) which was crystallized from a minimum amount of ethyl acetate. Two subsequent recrystallizations from methanol–isopropyl ether yielded pure XVI, m.p. 213°. (Found: C, 64·90; H, 7·48; O, 27·28. $C_{21}H_{30}O_7$ requires: C, 65·01; H, 7·44; O, 27·55%), I.R.$_{max}$ 3400, 1705 (infl.), 1685 and 1637 cm^{-1}; U.V.$_{max}$ 258 mμ, ε 12,000.

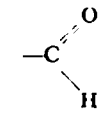
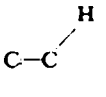
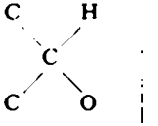
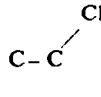
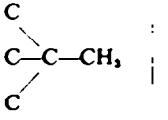
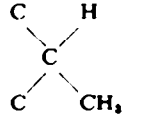
Extraction of the acidified (HCl) aqueous solution with chloroform and evaporation of the solvent yielded a foam which on treatment with ethyl acetate deposited crystals of XV, recrystallized from methanol, m.p. 254–260° (dec.). (Found: C, 65·28; H, 6·98; O, 27·83. $C_{21}H_{28}O_7$ requires: C, 65·34; H, 6·98; O, 27·68%.)

Oxidation of XVI *with* H_5IO_6. A mixture of XVI (300 mg), pure acetone (50 ml), H_5IO_6 (115 mg) and H_2O (5 ml) was stirred overnight at room temperature. After partial evaporation of acetone and dilution of the reaction mixture with dist. H_2O, the reaction products were extracted with chloroform. The foamy product obtained after evaporation of the solvent was kept for 30 min in aqueous methanolic KOH. The solution was diluted with H_2O, extracted with $CHCl_3$, the solvent removed *in vacuo* and the resulting oil (160 mg) refluxed overnight in 70% ethanol in the presence of freshly prepared Ag_2O (from 1·0 g $AgNO_3$). After filtration through Celite, the reaction mixture was evaporated to a small volume, diluted with H_2O, made alkaline with NaOH (100 mg) and extracted with $CHCl_3$. Evaporation of the solvent yielded a neutral fraction (89 mg) which was dissolved in pyridine (20 ml). CrO_3 (90 mg) in pyridine (20 ml) was then added and the mixture left standing overnight. Evaporation of the reaction mixture *in vacuo* and extraction of the residue with $CHCl_3$, followed by decoloration of the solution with charcoal and removal of the solvent, yielded the γ-lactone which was crystallized from methanol and then from methanol isopropyl ether, m.p. 266–268°. (Found: C, 67·13; H, 6·77; O, 26·15. $C_{21}H_{28}O_6$ requires: C, 67·36; H, 7·00; O, 25·64%.)

Acidification of the aqueous layer from the Ag_2O oxidation followed by extraction with $CHCl_3$ yielded crystalline XV (identical m.p., I.R.).

Treatment of XV *with aqueous* KOH. A solution of XV (70 mg) in 5% aqueous KOH (20 ml) was left standing for 3 days at room temperature. Neutral material was extracted with $CHCl_3$, the solvent removed *in vacuo*, the residue redissolved in aqueous methanolic KOH (1:1, 5%, 20 ml) and refluxed for 3 hr. After dilution with H_2O, the reaction product was extracted with $CHCl_3$. Removal of the solvent *in vacuo* gave an oily residue (38 mg), which was crystallized from ethyl acetate isopropyl ether. Pure XVIII decomposed at 183–208°. (Found: C, 68·94; H, 8·06; O, 23·05. $C_{30}H_{48}O_8$ requires: C, 68·94; H, 8·10; O, 22·96%), I.R.$_{max}$ (KBr) 3450, 1695, 1675, 1650 and 1635 cm^{-1}.

TABLE I.—IMPORTANT NMR SIGNALS OF QUASSIN AND ITS DERIVATIVES*

Compound				OCH_3			
Quassin		4·71*d* (2)	5·70*t*	6·38 6·44	8·15	8·45 8·79	8·86*d* (5·6)
*Neo*quassin		4·75*d* (2)	5·26*t* 6·15*m*	6·38 6·41	8·15	8·46 8·94	8·89*d* (5·6)
Deuterated *neo*quassin		4·72*d* (2)	5·26*m*; 0·5H 6·15*m*	6·36 6·45		8·45 8·89	8·85*t* (5·4)
Dihydro*neo*quassin			4·61*t* 5·52*m* 6·10*m*	6·40 6·59	8·16	8·50 8·95*d* (1·1)	9·10*d* (5·6)
Deuterated dihydro*neo*quassin			5·20*m*; 0·5H 6·07*m*	6·36 6·56		8·58 8·94 (1·1)	9·10*d* (5·6)
Norketone (XI)			6·3*m*	6·35; 6H	7·95 8·16	8·94	9·21*d* (6·3)
Anhydro*neo*quassin		3·67*m* 4·77*d* (2) 5·48*m*	6·25*m*	6·40 6·46	8·13	8·58 8·88	8·90*d* (5·4)
Dehydro*neo*quassin (XX)		4·43*d* (4·5) 4·72*d* (2)	4·22*d* (4·5) 6·05*m*	6·27 6·44	8·05	8·48 8·89	8·84*d* (5·6)
Dehydroquassin (XXI)		3·97 4·61*d* (2)	5·72*m*	6·22 6·41	7·98	8·48 8·75	8·90*d* (5·6)
Phenol (XXIV)	−0·44 0·60*m*	5·19*d* (2)		6·27	7·46 7·53	8·59	9·00*d* (5·6)

* The spectra were determined in $CDCl_3$ with a Varian instrument at 56·4 Mc/sec. The values are given in p.p.m. relative to $(CH_3)_4Si$ as an internal reference. Unless specified, all signals in the first three columns correspond to 1 H, all those in the last four columns to 3 H atoms. Singlets are unmarked, while multiplets are described by the following abbreviations: *d*, doublet; *t*, triplet; *m*, incompletely resolved multiplet. Numbers in brackets denote splitting constants in cycles/sec.

An isomeric product showing I.R. bands (in KBr) at 3450, 1690, 1660 and 1630 cm^{-1}, m.p. 184–221° (dec.), was obtained when XV was treated with 5% aqueous KOH for 4 hr under reflux. (Found: C, 69·00; H, 8·06; O, 22·88. $C_{30}H_{38}O_6$ requires: C, 68·94; H, 8·10; O, 22·96%.)

The two compounds are probably epimers.

Dehydroneoquassin (XX). The compound was obtained from the mother liquors of anhydro*neo*-quassin by evaporation to dryness and crystallization of the residue from CH_3OH. In contrast to Clark's results,[8] the pure product, m.p. 194–196°, crystallized as a monohydrate. (Found: C, 65·26; H, 7·17; O, 27·41. $C_{22}H_{28}O_6 \cdot H_2O$ requires: C, 65·02; H, 7·43; O, 27·55%.)

Oxidation of XX *with* Ag_2O. A mixture of XX (0·5 g), 70% ethanol (75 ml) and freshly prepared Ag_2O (from 2 g of $AgNO_3$) was refluxed overnight. After filtration through Celite, partial evaporation of the alcohol and dilution with H_2O, unchanged XX was removed from the basified solution (10% NaOH, 5 ml) by extraction with $CHCl_3$. The reaction product was then extracted from the acidified aqueous solution with $CHCl_3$. Removal of the solvent *in vacuo* left a foam which was crystallized from ethyl acetate. Crystalline XXI decomposed at 210–221°C even after repeated recrystallization from CH_3OH. (Found: C, 68·72; H, 7·07; O, 24·78. $C_{22}H_{28}O_6$ requires: C, 68·38; H, 6·78; O, 24·84%.)

Demethylation of XXII *with* HCOOH *in acetone*. A mixture of XXII (100 mg), pure acetone (50 ml) and 90% HCOOH (1·2 ml) was left standing at room temperature for 48 hr. After partial evaporation of acetone *in vacuo* and dilution of the reaction mixture with H_2O, the reaction product was extracted with $CHCl_3$. Yellow foam (100 mg) obtained after solvent evaporation was crystallized from ethyl acetate–chloroform to give pure XXIII, m.p. 230–234° (dec.). (Found: C, 64·60; H, 6·65; O, 28·86; OCH_3, 7·95. $C_{21}H_{26}O_7$ requires: C, 64·61; H, 6·71; O, 28·68; 1 OCH_3, 7·95%.)

Treatment of XXIII *with* KOH. Treatment of XXIII with aqueous methanolic KOH for 30 min at room temperature converted it to phenol XXIV, which was extracted from the diluted and acidified solution with chloroform. Two recrystallizations from ethyl acetate gave pure XXIV, m.p. 229–230°. (Found for a dried sample: C, 66·03; H, 6·52; O, 27·34; OCH_3, 8·74; for a sublimed sample: C, 66·69; H, 6·92; O, 26·16. $C_{20}H_{24}O_6$ requires: C, 66·65; H, 6·61; O, 26·92; 1 OCH_3, 8·61%.)

The identical product (U.V., I.R., m.p.) was obtained when a mixture of XXII (100 mg), CH_3OH (50 ml), H_5IO_6 (113 mg), $NaHCO_3$ (100 mg) and H_2O (20 ml) was stirred at room temperature overnight, then concentrated *in vacuo* and the separated crystalline intermediate treated with aqueous methanolic KOH. XXIV was then extracted from the reaction mixture with chloroform.

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