Quassin and neo*Quassin. Part III.**

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It is shown that quassin does not contain a hydroxyl group, that its lactone system (γ- or δ-type) is not $\alpha\beta$- or $\beta\gamma$-unsaturated, and that the α-carbon atom of this system, which is not at a bridgehead, bears at least one hydrogen atom. Quassin and *neo*quassin contain two chromophoric systems, type (V) and (probably) type (VII). The demethylation of quassin to bisnorquassin, which contains a single ionisable, non-aromatic chromophore, is accompanied by an irreversible molecular rearrangement.

The conversion of norquassin and nor*neo*quassin with warm aqueous sodium hydroxide into the respective hydroxy-acids involves destruction of the enol derived from (V) and modification of the second chromophore. With norquassin this change does not involve the lactone system originally present.

Though still somewhat tedious and costly the modified technique for the isolation of pure quassin and *neo*quassin now described is an improvement on the earlier, elaborate procedures (Part I, *J.*, 1950, 3431; cf. Adams and Whaley, *J. Amer. Chem. Soc.*, 1950, **72**, 375). With more of these compounds available we have made a detailed examination of the functional groups present.

From the results of active-hydrogen determinations by the Zerewitinoff method (Part I, *loc. cit.*) it appeared that quassin contained a hydroxyl group but a reinvestigation of this has given values (0·46 and 0·39 atom) which do not support this view. The infra-red absorption spectra of quassin and *neo*quassin now recorded are in agreement with those recorded by Adams and Whaley (*loc. cit.*) and indicate that *neo*quassin contains a hydroxyl group (sharp absorption band at 3390 $cm.^{-1}$) which is absent in quassin, being replaced by a carbonyl group (band at 1745 $cm.^{-1}$).

The view expressed in Part I (*loc. cit.*) that quassin is a lactone has been further substantiated. Although the crystalline compound is but slowly soluble in cold aqueous sodium hydroxide it readily dissolves when wetted with a hydrophilic solvent, *e.g.*, methanol or acetone, or when pulverised. Quassin readily dissolves in warm alkalis and if the solution is rapidly cooled and neutralised the compound is recovered unchanged. A phenolic or enolic system is absent because quassin does not give a ferric reaction, is inert

* Part II, *J.*, 1954, 3672.

towards etherifying or esterifying reagents, and in alkaline solution does not show a displacement of its ultra-violet absorption curve. Further, the potentiometric titration curve of quassin is typical of a lactone. On addition of a small amount of aqueous sodium hydroxide to an aqueous-alcoholic solution of the compound the pH of the mixture rises, but as the lactone ring opens with accompanying ionisation the excess of hydroxyl ions is removed and the pH falls to an equilibrium value; if only the equilibrium titres are regarded then quassin behaves as a weak acid, of pK_a 9·6.

In view of the relation of quassin to *neo*quassin, *i.e.*, lactone to hemiacetal, the close similarity between the ultra-violet absorption spectra of the compounds indicates that the same chromophoric system is present in each and, on this basis, it appears unlikely that in quassin the lactone system is αβ-unsaturated. In agreement with this view and contrary to an earlier observation (Part I, *loc. cit.*), quassin has now been found to give a negative result in the Legal test for αβ-unsaturated lactones. As to whether the lactone system is of the γ- or the δ-type the available evidence is at present somewhat conflicting. The lactone and not the hydroxy-acid is obtained immediately on neutralisation or acidification of an alkaline solution and thus quassin resembles the γ-lactone from *cis*-1-hydroxy-2-indanylacetic acid (Peacock and Menon, *J.*, 1934, 1296). In failing to react with ammonia or *p*-toluidine, quassin behaves as a γ- rather than a δ-lactone (cf., *e.g.*, marrubiin; unpublished work in this laboratory and Cocker, Cross, Duff, Edward, and Holley, *J.*, 1953, 2540). On the other hand the infra-red carbonyl-stretching frequency associated with the lactone ring of quassin occurs at 1745 $cm.^{-1}$ and it therefore appears that the observed value corresponds to that of a δ-lactone ring (1740 $cm.^{-1}$) rather than to a γ-lactone ring (1770 $cm.^{-1}$) (cf. Grove and Willis, *J.*, 1951, 877). Since a hydroxyl-stretching frequency is not observed it cannot be assumed that the carbonyl frequency has been lowered by hydrogen bonding (cf. Cocker *et al.*, *loc. cit.*).

In boiling acetic acid, alcoholic hydrogen chloride at room temperature, or boiling acetic anhydride containing sodium acetate quassin is converted into an equilibrium mixture of quassin and an isomeride, which we have named *iso*quassin,* m. p. 292°; this mixture is produced from *iso*quassin under the same conditions but the nature of the change is at present obscure. *iso*Quassin resembles quassin in that (*a*) it is readily demethylated to give norquassin and bisnorquassin (Part I, *loc. cit.*), (*b*) it fails to react with acetylating agents or with aryl *iso*cyanates, (*c*) the optical rotation is of the same sign and magnitude, (*d*) the ultra-violet absorption spectrum closely resembles that of quassin, (*e*) it is soluble in aqueous sodium hydroxide and can be recovered unchanged by acidification of an alkaline solution, and (*f*) it decolorises dilute aqueous potassium permanganate at approximately the same rate. *iso*Quassin differs from quassin (i) in being less soluble in organic solvents and less stable in alkaline solution, (ii) in failing to react with 2 : 4-dinitrophenylhydrazine, (iii) in lacking the characteristic bitter taste, and (iv) in its infra-red absorption spectrum.

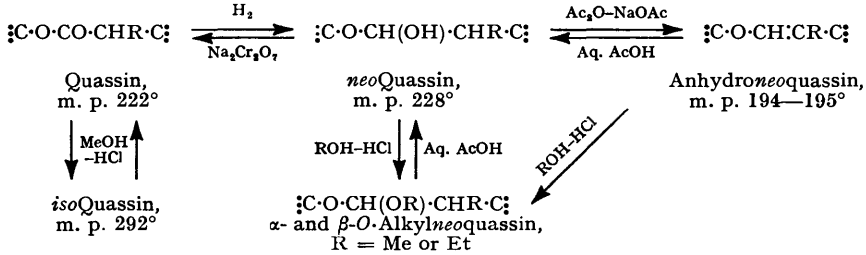
A more detailed examination of *neo*quassin confirms the presence of the hemi-acetal residue in this compound and consequently substantiates its relation to quassin defined in Part I (*loc. cit.*). The main additional support for this structure is derived from the close analogy between the *O*-alkyl ethers of *neo*quassin and, *e.g.*, the α- and β-methyl glucopyranosides. It was found in Part I (*loc. cit.*) that with methanolic and with ethanolic hydrogen chloride *neo*quassin gave respectively an *O*-methyl and an *O*-ethyl ether each of which was accompanied by small amounts of a second product. Re-examination of this reaction has shown that with each reagent *neo*quassin gives rise to an equilibrium mixture of pairs of isomerides, *viz.*, α- and β-*O*-methyl- and α- and β-*O*-ethyl-*neo*quassin, which, in agreement with the proposed acetal structure, can be readily de-alkylated to *neo*quassin with boiling acetic acid but are stable to boiling aqueous 2N-sodium hydroxide. The same equilibrium mixture is obtained by treatment of either the α- or the β-isomeride with the

* Adams and Whaley (*loc. cit.*) allocated the term quassin to denote the natural mixture of bitter principles and employed the name *iso*quassin for a pure component which in Part I (*loc. cit.*) was named quassin. The term *iso*quassin was originally proposed by Clark for an oxidation product from mixtures (*J. Amer. Chem. Soc.*, 1937, **59**, 927, 2511; 1938, **60**, 1146). The number of isomerides of quassin now obtained affords pertinent justification for retaining the designation employed in Part I.

appropriate alcohol containing hydrogen chloride, and, moreover, when either α- or β-*O*-ethyl*neo*quassin is treated with methanolic hydrogen chloride there is formed the α- and β-methyl*neo*quassin mixture. In both equilibrium mixtures the α-forms invariably predominate. From their optical rotations and by analogy with the D-series of sugars the anomer with the more positive rotation has been named "α" and the other isomeride "β." Alkylation of *neo*quassin in an aqueous-dioxan solution of sodium hydroxide with methyl or ethyl sulphate gives almost quantitative yields of the corresponding β-*O*-alkyl-*neo*quassin, results which suggest that *neo*quassin in the reaction mixture exists as the β-form. With ethanethiol in ethereal hydrogen chloride *neo*quassin rapidly forms ethylthio*neo*quassin which closely resembles the *O*-alkyl ethers but has not been resolved into α- and β-forms. It is possible that of respective pairs of *O*-alkyl*neo*quassins described one isomer may be derived from *neo*quassin and the second from an *isoneo*quassin corresponding to *iso*quassin, but so far the conversion of *neo*quassin into *isoneo*quassin has not been observed and a consideration of the molecular rotation differences, Δ(OMe–OEt), indicates that the analogy with the sugars is justified (cf. Gorin, Kauzmann, and Walter, *J. Chem. Phys.*, 1939, **7**, 327; Barton and Jones, *J.*, 1944, 659).

With hot acetic anhydride *neo*quassin is dehydrated to anhydro*neo*quassin, m. p. 194—195°, which may be identical with the incorrectly named anhydroquassin, m. p. 196°, which Clark (*loc. cit.*) prepared by heating impure quassin, or *neo*quassin, with sodium acetate and acetic anhydride. Although stable to warm aqueous sodium hydroxide anhydro*neo*quassin is readily hydrated to *neo*quassin with hot aqueous acetic acid and with alcoholic hydrogen chloride, and ethanethiol in ethereal hydrogen chloride gives, respectively, the equilibrium mixture of α- and β-*O*-ethyl*neo*quassin and ethylthio*neo*quassin. The compound differs from quassin and *neo*quassin in its lack of taste, greater solubilities, and more rapid reaction with aqueous potassium permanganate. The properties of anhydro*neo*quassin indicate that it is an αβ-unsaturated ether, formed by the elimination of the elements of water from the hemi-acetal residue, and comparable with dihydrofuran and dihydropyran (cf. Elderfield, "Heterocyclic Compounds," Wiley, New York, Vol. I, 1950, pp. 174, 348) or with the glycals (cf. Shafizadeh and Stacey, *J.*, 1952, 3608). In agreement with this the infra-red absorption spectrum of anhydro*neo*quassin does not show a hydroxyl-stretching band at 3390 cm.$^{-1}$. The similarity of the ultra-violet absorption spectra of anhydro*neo*quassin, quassin, and *neo*quassin indicates that the new double bond appearing in anhydro*neo*quassin is not conjugated and hence the lactone structure of quassin is neither αβ- or βγ-unsaturated. By Bredt's rule it follows that the α-carbon atom is not at a bridgehead (cf. Fawcett, *Chem. Reviews*, 1950, **47**, 219), thus systems of the type (I) or (II) are not present in quassin.

Consequently the annexed relations obtain.



Of the six oxygen atoms in quassin two have been accounted for in methoxyl groups, two in the lactone system, and one in a ketonic group. In the absence of a hydroxyl group in the molecule it seemed likely that the remaining oxygen atom is in a carbonyl or ether

system and from the following considerations it appears, *inter alia*, that the sixth oxygen atom is present in an αβ-unsaturated carbonyl group.

The reduction of quassin with zinc dust and acetic acid gives dihydroquassin, identical with the product obtained by the hydrogenation of quassin in alkaline solution with a palladium–charcoal catalyst (Part I, *loc. cit.*), and the absence of a hydroxyl band in the infra-red absorption spectrum of this derivative indicates that the reduction involves the saturation of a double bond rather than the conversion of a carbonyl into a hydroxyl group. The ultra-violet absorption spectrum of dihydroquassin has a maximum (252 mμ, ε 8400) at almost the same wave-length as has quassin but with the intensity reduced by almost one third. On the assumption that quassin contains two non-aromatic chromophoric groups (A) and (B), of which (A) has been destroyed on hydrogenation, then (B) will have the ultra-violet absorption characteristic of dihydroquassin and the curve obtained by subtracting the absorption curve of dihydroquassin from that of quassin will represent the absorption due to the chromophore (A), *viz.*, $\lambda_{max.}$ 264 mμ (ε 4500). Subtraction of the absorption curve for dihydro*neo*quassin acetate ($\lambda_{max.}$ 252 mμ; ε 9200), which is formed by the reduction of *neo*quassin with zinc and acetic acid, from that of *neo*quassin gives a second value for chromophore (A) ($\lambda_{max.}$ 264 mμ; ε 5000) in satisfactory agreement with that obtained from the quassin–dihydroquassin curves.

The validity of the assumption that quassin contains two chromophoric systems (A) and (B) is supported by a study of the demethylation products of quassin and *neo*quassin, *viz.*, nor- and nor*neo*-quassin. These compounds, which exhibit the properties of a phenol or acidic enol, regenerate respectively quassin and *neo*quassin on methylation. The ultra-violet absorption spectra of quassin, *neo*-, nor-, and nor*neo*-quassin in alcoholic solution closely resemble each other but the spectra of nor- and nor*neo*-quassin in alcoholic alkali exhibit minor peaks at 314 (ε 4000) and a main peak at approximately the same wave-length as in neutral solution with the intensity reduced by almost one-third. This behaviour can be explained on the two-chromophore hypothesis if chromophore (A) is the *O*-methyl ether of a weakly acidic enol. The major and the minor peak exhibited by the nor-compounds in alkaline solution then correspond respectively to chromophore (B), modified by local electrostatic fields and changed dielectric constant, and to the ion of the enol derived from chromophore (A), whilst in neutral solution the single peak will represent the superposition of the absorption due to (B) and the absorption of the enol derived from (A). The calculated values for (A) and its derivatives are given in the Table, [thus: $\lambda_{max.}$ in mμ ($\varepsilon_{max.}$), in EtOH].

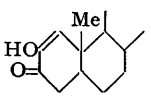
	Enol ether	Enol acetate	Enol	Enol ion
Quassin	264 (4500)	233 (5800)	271 (5300)	315 (3200)
*neo*Quassin	264 (5000)	—	268 (5700)	313 (4000)
Cholestane-2 : 3-dione enols	—	238 (7410) 237 (8910)	272 (5010) 270 (8510)	320 (3720)

Data concerning the ultra-violet absorption spectra of ethers of enols derived from α-diketones do not appear to have been recorded but the absorption characteristics of the cholestane-2 : 3-dione enols, (III) and (IV) (Stiller and Rosenheim, *J.*, 1938, 353), correspond closely to those of the enol derived from chromophore (A). The observed values +44 and +45 mμ for Δλ(enol ion − enol) lie between the value +50 mμ for cholestane-2 : 3-dione and the values +43 and +42 for 3-methyl*cyclo*hexanedione (French and Holden, *J. Amer. Chem. Soc.*, 1945, **67**, 1239) and the α-diketone system of the cevagenin oxidation product (Sundt, Jeger, and Prelog, *Chem. and Ind.*, 1953, 1365). The observed value −38 mμ for Δλ(enol acetate − enol) in respect of quassin is numerically greater than the values −34 and −33 mμ for cholestane-2 : 3-dione but identical with the value for 11 : 12-dioxocholanic acid (Wintersteiner and Moore, *J. Biol. Chem.*, 1946, **162**, 725); other reported values lie between these limits. It is also significant that all known α-diketone enol systems exhibit intense ferric reactions comparable with nor- and nor*neo*-quassin. Enols of α-diketones are incapable of conjugate chelation and therefore show an infra-red absorption band characteristic of a weakly bonded hydroxyl group. Thus, diosphenol has a strong, fairly sharp band at 3410 $cm.^{-1}$ (Nujol) (Le Fèvre, Maramba, and Werner, *J.*,

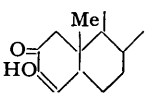
1953, 2496) whereas compounds capable of inter- or intra-molecular conjugate chelation show a weak broad band at lower wave-numbers (Rasmussen, Tunnicliff, and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1068). The sharp infra-red hydroxyl band of norquassin at 3390 cm.$^{-1}$ (Nujol) resembles that of diosphenol.

On the basis of this analogy we tentatively propose that quassin and *neo*quassin contain the residue (V), *i.e.*, chromophore (A), which in the dihydro-derivatives becomes (VI), thus accounting for the fact that dihydroquassin is not demethylated with hot dilute hydrochloric acid and that the infra-red spectrum of dihydro*neo*quassin acetate shows bands at 1748 cm.$^{-1}$ (acetate C=O) and 1715 cm.$^{-1}$ (*cyclo*hexanone-type C=O). A structure in which the *cyclo*hexanone system of (V) is substituted in the β-position by an alkyl group is considered to be improbable as all enols, or enol acetates derived from α-diketones, which are substituted in this manner appear to show absorption at wave-lengths higher than do the corresponding derivatives of cholestane-2 : 3-dione. The presence of a residue type (V) in quassin and *neo*quassin is in keeping with the production of 3 : 4 : 5-trimethylguaiacol when *neo*quassin is heated with selenium (Part II, *loc. cit.*).

With regard to chromophore (B) the evidence appears to support an αββ-trisubstituted, αβ-unsaturated ketone system since the ultra-violet absorption maximum (λ 253 mμ) falls within the range (254±5 mμ) characteristic of such chromophores (Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 76) Only a few examples of di-β-substituted, αβ-unsaturated ketones which show absorption in this region are known (Ruzicka, Nisoli, and Jeger, *Helv. Chim. Acta*, 1946, **29**, 2017). In the infra-red spectra of dihydroquassin and dihydro*neo*quassin acetate bands are observed at 1680 and 1675 cm.$^{-1}$ respectively, values which are comparable with the carbonyl-stretching band of *cyclo*hexen-3-one type systems



(III)



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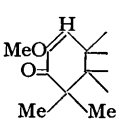

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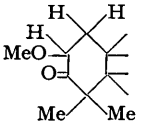

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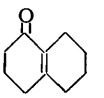
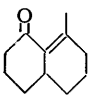


(VII)



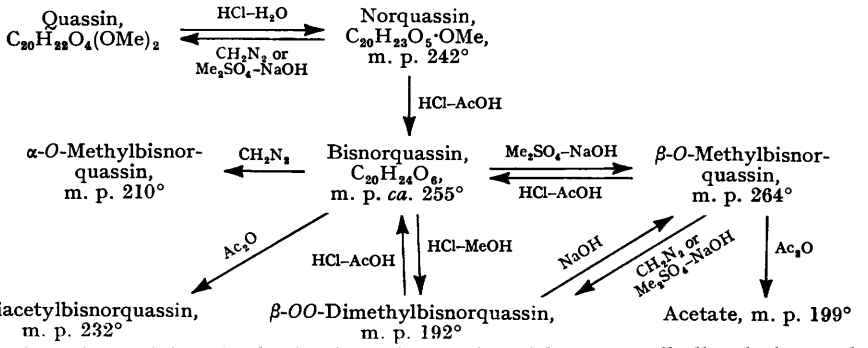
(VIII)

(typical value 1680 cm.$^{-1}$) but which are at a wave-number too low to be attributed to a *cyclo*penten-3-one system, or to a system in which the carbon–carbon double bond is exocyclic to a 5-membered carbonyl-bearing ring (Grove and Willis, *loc. cit.*). For a system analogous to (VII) ($\lambda_{max.}$ 255 mμ), the tetra-substituted carbon–carbon double bond, activated by conjugation, absorbs at 1583 cm.$^{-1}$ (C=O absorption at 1656 cm.$^{-1}$) (McGhie, Pradhan, and Cavalla, *J.*, 1952, 3176) while 1-acetyl-2-methyl*cyclo*hexene ($\lambda_{max.}$ 245 mμ) shows absorption at 1620 cm.$^{-1}$ (C=O absorption at 1686 cm.$^{-1}$) (Henbest and Woods, *J.*, 1952, 1150). As the dihydro-compound shows C=C absorption at higher wave-numbers (1635 and 1640 cm.$^{-1}$ respectively), it is possible that this double bond is exocyclic to the 6-membered ring as in (VIII) rather than endocyclic as in (VII). Certain variants of the partial structures (VII) and (VIII) are also under consideration (cf. Fieser and Fieser, " Natural Products related to Phenanthrene," Reinhold Publ. Corp., New York, 1949, p. 190).

A re-examination has shown that bisnorquassin (Part I, *loc. cit.*) and some of its derivatives tenaciously retain solvent of crystallisation and that, although solvated bisnorquassin is stable, the solvent-free compound decomposes to a brown amorphous product on being kept for several weeks. Further, on rigorous purification bisnorquassin does not give the weak green ferric reaction attributed to it and on methylation with diazomethane yields a monomethyl ether, $C_{20}H_{23}O_5$·OMe, α-*O*-methylbisnorquassin, which was incorrectly formulated as $C_{21}H_{23}O_5$·OMe (Part I, *loc. cit.*). From the absence of hydroxyl bands in the infra-red spectrum and its negative Zerewitinoff reaction this ether, which has the properties of a lactone, does not appear to contain a hydroxyl group. With methyl sulphate and alkali, however, bisnorquassin gives rise to β-*O*-methylbisnorquassin and then β-*OO*-dimethylbisnorquassin isomeric with quassin and analogous to the *OO*-diacetylbisnorquassin formed by the acetic anhydride–pyridine method. The mono- and di-β-methyl ether, which have negative ferric reactions and form oximes and 2 : 4-dinitrophenylhydrazones,

are demethylated with hot acetic–hydrochloric acid, regenerating bisnorquassin; with hot aqueous sodium hydroxide β-*OO*-dimethylbisnorquassin gives the β-*O*-methylbisnorquassin.

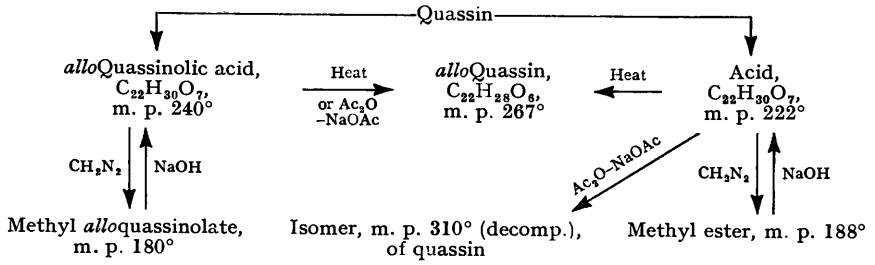
The ultra-violet absorption spectra of bisnorquassin and its methyl ethers closely resemble each other ($\lambda_{max.}$ *ca.* 313 mμ; ε 19,000) and are entirely different from that of quassin. The spectra of bisnor- and β-*O*-methylbisnor-quassin in alcoholic alkali show a single intense peak in the regions of longer wave-length (*ca.* 385 mμ; ε 48,000). Thus it seems that the conversion of quassin or norquassin into bisnorquassin is accompanied by a molecular re-arrangement where a single ionisable chromophore replaces the two chromophores originally present [cf. "3 : 7-diketocholestene" which shows $\lambda_{max.}$ 320 mμ (ε 24,300) in neutral and $\lambda_{max.}$ 392 mμ (ε 62,200) in alcoholic alkali (Greenhalgh, Henbest, and Jones, *J.*, 1952, 2375)]. In this connexion it is of interest that from crude bisnorquassin a second demethylation product (yield, 20%) has been isolated which is soluble in alkali and gives a ferric reaction. This appears to be a mixture of isomerides which on treatment with a warm mixture of acetic–hydrochloric acid gives bisnorquassin and are regarded as intermediates in the conversion of norquassin into bisnorquassin. Specimens with different melting points have similar absorption spectra—in alcohol, $\lambda_{max.}$ 273 mμ (ε 12,360) and in alcoholic alkali $\lambda_{max.}$ 316 mμ (ε 9000).



The product formed by the hydration of quassin with warm alkalis, designated *iso*-quassinic acid in Part I (*loc. cit.*), has been separated into two isomeric acids, m. p. 240° and m. p. 222°, which have been characterised as their methyl esters. Since these esters are readily hydrolysed with warm dilute aqueous sodium hydroxide the carboxyl groups are not tertiary. The ultra-violet absorption spectra of the acids and their esters are almost identical with that of quassin. The ester of the acid, m. p. 240°, which contains active hydrogen (1·01 atoms), shows a hydroxyl-stretching band at 3500 cm.$^{-1}$, whilst the parent acid shows a sharp band at 3400 cm.$^{-1}$ and a broad shoulder at 3040 cm.$^{-1}$. Therefore this acid has been termed *allo*quassinolic acid, and the names quassinolic and *iso*quassinolic acid are reserved for the unstable acids obtained as sodium salts from quassin and *iso*-quassin. On being heated alone or with sodium acetate in acetic anhydride, *allo*quassinolic acid lost the elements of water and furnished an *allo*quassin having almost the same ultra-violet absorption spectrum as quassin. The infra-red spectrum of this compound, however, shows a lactone carbonyl-stretching band at a lower wave-number than quassin, *viz.*, 1712 cm.$^{-1}$, whilst the molecular rotation is much higher. Since *neo*quassin is inert to aqueous sodium hydroxide it is almost certain that *allo*quassinolic acid and *allo*quassin arise by a stereochemical change involving the lactone system.

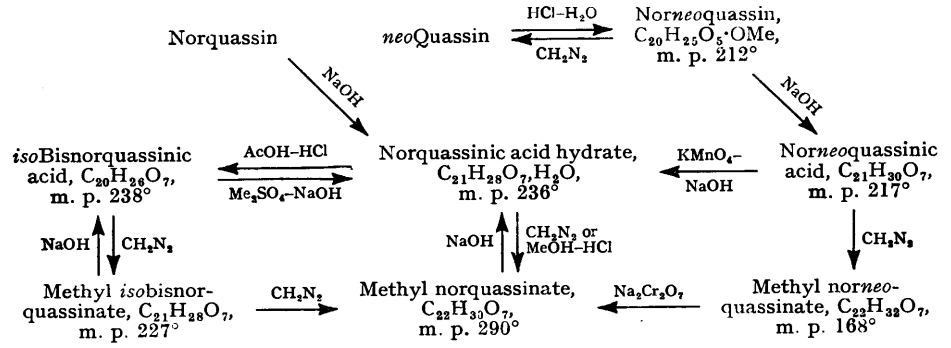
The methyl ester of the acid, m. p. 222°, does not show a hydroxyl-stretching band in the infra-red spectrum (0·46 atom of active hydrogen) and the parent acid shows only the broad shoulder at 3135 cm.$^{-1}$. On being heated this acid, which retains the bitter taste of quassin, gives *allo*quassin but with hot acetic anhydride and sodium acetate yields a second isomeride of quassin having a modified ultra-violet absorption spectrum. At present the relation of this acid to *allo*quassinolic acid is not clear.

Norquassin is converted by boiling dilute aqueous sodium hydroxide into a monobasic acid, norquassinic acid, which is obtained as an unexpectedly stable monohydrate. Esterification of this product with diazomethane, however, is accompanied by loss of a molecule of water. The potentiometric titration curves for this hydrate and the methyl ester show that both compounds retain a lactone system of stability comparable with that in quassin.



That the lactone group of norquassin is not concerned in the production of the carboxyl group in norquassinic acid is established by the fact that on treatment with hot alkalis nor*neo*quassin gives monobasic nor*neo*quassinic acid which on oxidation with potassium permanganate furnishes norquassinic acid. Similarly the oxidation of methyl nor*neo*-quassinate with chromic acid yields methyl norquassinate. In these conversions it is reasonably certain that the hemiacetal residue is oxidised to a lactone system. Although the ultra-violet absorption spectra of nor- and nor*neo*-quassinic acid and their respective methyl esters ($\lambda_{max.}$ 257—259 mμ; ε *ca.* 9000) differ somewhat from that of dihydroquassin, they are not displaced in alkaline media, indicating that the formation of the acids is accompanied by the destruction of the enol derived from the chromophoric group (A). In agreement with this view nor- and nor*neo*-quassinic acid do not give ferric reactions and are comparatively stable to neutral aqueous potassium permanganate. Although experimental information on the nature of the norquassin ⟶ norquassinic acid change is not available it is tentatively suggested that the change involves, *inter alia*, re-arrangement of the benzilic acid type. It may be noted in this connexion that the infra-red absorption spectrum of methyl norquassinate has a hydroxyl-stretching band (3450 cm.$^{-1}$).

Demethylation of norquassinic acid hydrate with hot hydrochloric–acetic acid gave *iso*-bisnorquassinic acid which, on short treatment with diazomethane, furnished methyl *iso*bisnorquassinate. The acid and its ester, which have strong ferric reactions, contain an enolic system which is independent of the carboxyl or ester group because both compounds show similar ultra-violet absorption characteristics, *viz.*, $\lambda_{max.}$ *ca.* 283 mμ in alcohol, $\lambda_{max.}$ *ca.* 340 mμ in alcoholic alkali. On methylation with methyl sulphate and aqueous sodium



hydroxide *iso*bisnorquassinic acid gave norquassinic acid hydrate and on prolonged treatment with diazomethane methyl *iso*bisnorquassinate furnished methyl norquassinate.

From the present evidence it is possible that the enolic system obtaining in *iso*bisnorquassinic acid and its ester derives from an α-diketonic residue, but a full discussion of this is reserved for a future communication.

Experimental

Unless otherwise stated, molecular rotations were measured in $CHCl_3$ and ultra-violet absorption spectra (Unicam spectrophotometer) in EtOH. Infra-red absorption measurements were made with a Grubb-Parsons double-beam spectrometer and a paste of the material in "Nujol." The light petroleum used had b. p. 60—80°.

Isolation of Quassin and neo*Quassin.*—The following improved procedure is now employed. Powdered wood of *Quassia amara* Linn. (25 kg.) was percolated with methanol (150 l.), and the extract concentrated to *ca.* 4 l.; the spongy wood was percolated with water to recover part of the methanol (*ca.* 30 l.) retained. After having been decanted from black tar (*ca.* 100 ml.), the cooled concentrate was diluted with water (6 l.) to precipitate a brown resin (*ca.* 100 ml.), kept for a short time, and then decanted or filtered through hessian or cotton-wool to remove more resin. A solution of the tar and resinous precipitate in hot methanol (*ca.* 500 ml.) was cooled, decanted from gum which had separated, diluted with water (750 ml.), and filtered. The combined aqueous methanolic, tar-free solutions (*ca.* 11 l.) were extracted with benzene in a continuous extractor, and the concentrated benzene extract (*ca.* 400 ml.) was poured through a column of aluminium oxide (20 × 3 cm.) which was washed with more benzene (1 l.). The concentrated pale yellow eluate and washings (*ca.* 300 ml.) were agitated with 10% aqueous sodium hydroxide (300 ml.), and the alkaline extract was washed with chloroform and saturated with carbon dioxide, giving crude quassin. Concentration of the washed benzene and chloroform liquors gave *neo*quassin; more *neo*quassin separated on addition of ethyl acetate to the benzene residue.

A solution of the crude quassin in chloroform–benzene (1 : 2) was poured through a column of aluminium oxide (2 × 5 cm.) (wash with same solvent), and the quassin recovered by evaporation; if this material gave a positive ferric test the chromatographic process was repeated. Recrystallised from ethyl acetate–light petroleum, quassin usually then had m. p. 222° (yield, 12 g.). If the product had m. p. <222°, it was best purified by re-precipitation from aqueous-methanolic sodium hydroxide with carbon dioxide. A phenolic impurity (*ca.* 1 g.), which appears to be a mixture, was eluted from the aluminium oxide column with methanol. Recrystallised from methanol and then chloroform–ether, this *substance* formed needles, m. p. 273—275° (Found: C, 63·7; H, 6·8; OMe, 8·7%).

*neo*Quassin was purified by precipitation from a solution in the minimum amount of hot methanol with 10% aqueous sodium hydroxide (5 ml.) followed by water (3 volumes). Recrystallised from ethyl acetate–light petroleum, it had m. p. 228° (yield, 20 g.). The *p-nitrophenylcarbamate* formed needles, m. p. *ca.* 180° (decomp.), from chloroform–ethyl acetate (Found: N, 5·0. $C_{29}H_{34}O_9N_2$ requires N, 5·0%).

Norquassin.—This has been prepared by the following improved method (cf. Part I, *loc. cit.*). A mixture of quassin (2 g.), 2N-hydrochloric acid (30 ml.), and acetic acid (10 ml.) was heated on the steam-bath for 1½ hr., cooled, partly neutralised with aqueous 2N-ammonia (30 ml.), and kept for 18 hr. The resulting crystalline precipitate (1·2 g.) was dissolved in aqueous 2N-sodium hydroxide, and the solution saturated with carbon dioxide, giving norquassin which separated from aqueous methanol and then chloroform–light petroleum in prisms (1·0 g.), m. p. 246—247°, with a deep purple ferric reaction in alcohol [$\lambda_{max.}$ 258 (ε 11,200) and 258 mμ (ε 8200) with minor peak at *ca.* 312 mμ (ε 3300) in alcoholic sodium hydroxide] [cf. Part I, *loc. cit.*, where the m. p. was found to be 241·5—242·5° (decomp.)]. The small, methanol-insoluble residue was recrystallised from alcohol, giving bisnorquassin (0·15 g.), m. p. *ca.* 255° (decomp.). Heated with concentrated hydrochloric acid (0·3 ml.) and acetic acid (1 ml.) on the steam-bath for 1 hr., norquassin (0·1 g.) gave bisnorquassin which was precipitated from the reaction mixture with water (2 ml.) and had m. p. and mixed m. p. *ca.* 255° (decomp.), after purification by precipitation from aqueous sodium hydrogen carbonate with mineral acid, followed by recrystallisation from ethyl acetate.

A mixture of norquassin (0·2 g.), hydroxylamine hydrochloride (0·4 g.), sodium acetate (0·5 g.), pyridine (2 ml.), and water (5 ml.) was kept at room temperature for 12 days and then warmed on the steam-bath until an oil separated. On being kept, this product solidified and was crystallised from aqueous alcohol, giving a compound in slender needles (0·2 g.), m. p.

228—230° (decomp.), which appears to be the *hydrate* of the oxime (Found: C, 61·5; H, 7·1; N, 3·1. $C_{21}H_{27}O_6N,H_2O$ requires C, 61·9; H, 7·2; N, 3·4%. Calc. for oxime, $C_{21}H_{27}O_6N$: C, 64·8; H, 7·0; N, 3·6%). This derivative, which gives a negative ferric reaction and is not dehydrated in a high vacuum at 160°, is soluble in aqueous sodium hydroxide and insoluble in aqueous sodium hydrogen carbonate.

On being heated with sodium acetate (0·1 g.) and acetic anhydride (2 ml.) at 160° for 1½ hr. norquassin gave the acetate, m. p. and mixed m. p. 236°, $\lambda_{max.}$ 240 mμ (ε 11,200). Methylation of norquassin, m. p. 246—247°, with ethereal diazomethane regenerated quassin, m. p. 222°, unaccompanied by a second product (cf. Part I, *loc. cit.*). Quassin was also obtained by methylation of norquassin with methyl sulphate and alkali or with methyl iodide and potassium carbonate in boiling acetone.

Dihydroquassin.—Zinc dust (2 g.) was added portion-wise in 2 hr. to a boiling solution of quassin (1 g.) in acetic acid (20 ml.), and the solution decanted, the zinc being washed with methanol. The combined solution and washings were concentrated, almost neutralised with aqueous sodium hydrogen carbonate, filtered, and extracted with chloroform. The product left on evaporation of the dried extracts was purified by chromatography from benzene on aluminium oxide and then from methanol, forming plates (0·4 g.), m. p. *ca.* 110°, $\lambda_{max.}$ 252 mμ (ε 8430), which retained solvent of crystallisation [Found: C, 65·2; H, 8·0; OMe, 21·1. $C_{20}H_{24}O_4(OMe)_2,MeOH$ requires C, 65·4; H, 8·1; OMe, 22·0. Found, in specimen dried in a vacuum at 80°: C, 67·6; H, 7·8. $C_{22}H_{30}O_6$ requires C, 67·7; H, 7·7%]. A specimen, crystallised from alcohol, behaved similarly [Found: C, 65·8; H, 8·1; Alkyl-O, 10·3. $C_{20}H_{24}O_4(OMe)_2,EtOH$ requires C, 66·1; H, 8·3; Alkyl-O, 11·0%].

iso*Quassin.*—On being kept at room temperature for 18 hr. a solution of quassin (2 g.) in 5% ethanolic or methanolic hydrogen chloride (50 ml.) slowly deposited a crystalline product (1·5 g.), m. p. *ca.* 260°, having a bitter taste. This product, which separated from alcohol in fine needles or plates, m. p. 260°, was a mixture of quassin and iso*quassin* which were separated by a prolonged fractional crystallisation from chloroform–light petroleum. Ultimately the less soluble isomeride, *iso*quassin, was obtained in needles (0·4 g.), m. p. 292° (slight decomp.) which varied slightly with the rate of heating, $[M]_D^{21}$ +167° (*c*, 1·0), $\lambda_{max.}$ 258 mμ (ε 12,700) [Found: C, 68·0; H, 7·1; OMe, 16·2. $C_{20}H_{22}O_4(OMe)_2$ requires C, 68·0; H, 7·3; OMe, 16·0%]. The same quassin–*iso*quassin mixture was obtained when the 5% alcoholic hydrogen chloride solution was kept at room temperature for 4 days or at 50° for 4 hr. and when a solution of quassin (1 g.) in acetic acid (20 ml.) was heated under reflux for 6 or 12 hr. Like quassin, *iso*quassin gives a negative ferric and Legal test, and decolorises potassium permanganate in aqueous acetone; it has solubility properties in organic solvents and in aqueous sodium hydroxide similar to those of quassin. If, however, the alkaline solution is heated the compound is converted into an amorphous, water-soluble acid. Unlike quassin, *iso*quassin is tasteless and does not react with 2 : 4-dinitrophenylhydrazine.

When a solution of *iso*quassin (0·2 g.) in acetic acid (10 ml.) was heated under reflux for 6 hr., the product consisted of a mixture (0·18 g.), m. p. 220—240°, of quassin and *iso*quassin. From this, part of the quassin (0·05 g.), m. p. and mixed m. p. 222°, was separated by the fractional crystallisation procedure, leaving the quassin–*iso*quassin mixture (0·7 g.), m. p. 262°.

A solution of *iso*quassin (0·1 g.) in a mixture of acetic acid (1 ml.) and 2N-hydrochloric acid was heated on the steam-bath for 2 hr., cooled, basified with aqueous sodium hydroxide, saturated with carbon dioxide, and extracted with chloroform. Evaporation of the dried extracts gave norquassin, m. p. and mixed m. p. 246—247°, after purification from aqueous methanol, having the characteristic ferric reaction. Acidification of the alkaline liquors to Congo-red followed by extraction with chloroform gave a little bisnorquassin, m. p. and mixed m. p. *ca.* 255° (decomp.), identical with an authentic specimen.

Bisnorquassin.—The m. p. *ca.* 255° (highest obtained, m. p. 263°) of this compound (Part I, *loc. cit.*) depends on the rate of heating and the nature of the solvent employed for purification, owing to retention of solvent of crystallisation. Although the crude compound had a pale green ferric reaction, this was negative in material purified by digestion with hot methanol followed by solution in aqueous sodium hydrogen carbonate and reprecipitation with acid, $\lambda_{min.}$ ~254 mμ (ε 1200), $\lambda_{max.}$ 312 mμ (ε 18,800) [$\lambda_{min.}$ ~290 mμ (ε 300), $\lambda_{max.}$ 384 mμ (ε 48,100) in alcoholic alkali]. The diacetate (Part I, *loc. cit.*), $\lambda_{max.}$ 276 mμ (ε 20,100), $\lambda_{min.}$ ~225 mμ (ε 2100), gave a 2 : 4-*dinitrophenylhydrazone* which separated from alcohol in yellow needles, m. p. 236—238° (Found: N, 9·2. $C_{30}H_{32}O_{11}N_4$ requires N, 9·0%).

α-O-*Methylbisnorquassin.*—With diazomethane in ether–methanol or ether–chloroform for 12 hr. bisnorquassin gave α-O-*methylbisnorquassin* which formed large prisms, m. p. 210°, from

methanol or chloroform–light petroleum, $\lambda_{max.}$ 315 mμ (ε 22,600), $\lambda_{min.}$ ~250 mμ (ε 2200) (Found: C, 67·5; H, 6·9; OMe, 8·5. $C_{20}H_{23}O_5$·OMe requires C, 67·4; H, 7·0; OMe, 8·3%). This compound, which does not form an acetate or carbanilate, is slowly soluble in warm aqueous sodium hydroxide and readily so in cold alcoholic sodium hydroxide from which it does not separate on dilution with water; carbon dioxide then precipitates the unchanged ether.

β-OO-*Dimethylbisnorquassin*.—A solution of bisnorquassin (0·2 g.) in methanolic hydrogen chloride (15 ml.) was kept for 3 days and concentrated on the steam-bath. Treatment of the residual liquor (5 ml.) with an excess of aqueous sodium hydrogen carbonate gave a precipitate which, on recrystallisation from aqueous methanol containing a drop of ammonia and then from light petroleum mixed with a little alcohol, furnished β-OO-*dimethylbisnorquassin* in small prisms, m. p. 192° (0·05 g.), $\lambda_{min.}$ ~257 mμ (ε 1400), $\lambda_{max.}$ 313 mμ (ε 19,500), insoluble in aqueous-alcoholic sodium hydroxide and having a negative ferric reaction [Found: C, 68·0; H, 7·2; OMe, 15·4. $C_{20}H_{22}O_4(OMe)_2$ requires C, 68·0; H, 7·3; OMe, 16·0%]. The 2 : 4-*dinitrophenylhydrazone* separated from chloroform–light petroleum in yellow plates, m. p. 274° (decomp.) (Found: N, 10·0. $C_{28}H_{32}O_9N_4$ requires N, 9·9%). From dilute alcohol and then chloroform–light petroleum, the oxime formed plates, m. p. 265°, retaining solvent of crystallisation.

With a hot mixture of acetic and hydrochloric acid β-*OO*-dimethylbisnorquassin gave bisnorquassin, m. p. and mixed m. p. *ca.* 255° (decomp.), after purification, whilst treatment with chloroformic perbenzoic acid at 0° for 2 days gave an *epoxide* which separated from acetone–light petroleum in rosettes of needles, m. p. 196—197°, readily soluble in ethyl acetate, $\lambda_{max.}$ 232 mμ (ε 11,400) [Found: C, 65·3; H, 6·8; OMe, 15·8. $C_{20}H_{22}O_5(OMe)_2$ requires C, 65·3; H, 7·0; OMe, 15·3%].

β-O-*Methylbisnorquassin*.—Methylation of bisnorquassin (1 g.) with aqueous 2N-sodium hydroxide (20 ml.) and methyl sulphate (5 ml.) (added gradually) gave an acidic mixture which was basified with more aqueous sodium hydroxide (3 ml.) at below 30°. Some time later the neutral product (0·5 g.) was collected, washed, and recrystallised from alcohol–light petroleum, giving β-*OO*-dimethylbisnorquassin, m. p. and mixed m. p. 192°. Acidification of the alkaline liquor (Congo-red) precipitated β-O-*methylbisnorquassin* (0·42 g.) which formed prisms, m. p. 264° (decomp.), from dilute methanol, with a negative ferric reaction, $\lambda_{min.}$ ~257 mμ (ε 1300), $\lambda_{max.}$ 314 mμ (ε 19,200) [$\lambda_{min.}$ ~275 mμ (ε 600), $\lambda_{max.}$ 389 mμ (ε 48,700) in alcoholic alkali] (Found: C, 67·1; H, 7·1; OMe, 8·4. $C_{20}H_{23}O_5$·OMe requires C, 67·4; H, 7·0; OMe, 8·3%). This ether was also formed by the dropwise addition of aqueous 2N-sodium hydroxide (10 ml.) to a solution of β-*OO*-dimethylbisnorquassin (0·5 g.) in boiling methanol (10 ml.) during 10 min. and then heating the mixture on the steam-bath for 40 min. to evaporate the greater part of the methanol. The compound (0·3 g.) was precipitated from the cooled residue with hydrochloric acid and, on purification by means of aqueous sodium hydrogen carbonate followed by crystallisation from acetone, had m. p. and mixed m. p. 264°. This ether is soluble in aqueous sodium hydrogen carbonate and, unlike bisnorquassin, in warm methanol. An acetone solution of the compound readily decolorised aqueous potassium permanganate. The 2 : 4-*dinitrophenylhydrazone* formed rosettes of needles, m. p. 208° (decomp.), from alcohol, retaining solvent of crystallisation (Found in specimen dried in a high vacuum at 105°: N, 9·6. $C_{27}H_{30}O_9N_4$ requires N, 10·1%). Prepared by pyridine–acetic anhydride, the *acetate* separated from ethyl acetate–light petroleum in rods, m. p. 199—200°, $\lambda_{max.}$ 277 mμ (ε 15,800) (Found: C, 66·3; H, 6·8; OMe, 8·2. $C_{22}H_{25}O_6$·OMe requires C, 66·3; H, 6·5; OMe, 7·4%).

Treatment of β-*O*-methylbisnorquassin with a warm mixture of acetic and concentrated hydrochloric acid furnished bisnorquassin, m. p. and mixed m. p. *ca.* 255° (decomp.), after purification, whilst methylation with methanolic-ethereal diazomethane gave β-*OO*-dimethylbisnorquassin, m. p. and mixed m. p. 192°.

allo*Quassinolic Acid*.—A solution of quassin (2 g.) in 10% aqueous sodium hydroxide was boiled for 40 min., cooled, acidified (Congo-red) with sulphuric acid, and decanted from a little resin (*ca.* 0·2 g.). The crude acids were isolated by repeated extraction with chloroform and triturated with ethyl acetate. The resulting crystalline mixture had m. p. 210—220° (decomp.) and did not depress the m. p. of "*iso*quassinic acid" described in Part I (*loc. cit.*). By fractional crystallisation from chloroform–ethyl acetate this mixture was resolved into a more soluble *acid* in short rods (0·8 g.), m. p. 222° (decomp.), $[M]_D^{22}$ −13° (*c*, 1·00), $\lambda_{max.}$ 257 mμ (ε 14,000) [Found: C, 64·3; H, 7·3; OMe, 15·8. $C_{20}H_{24}O_5(OMe)_2$ requires C, 65·0; H, 7·4; OMe, 15·3%], and a less soluble isomeride, allo*quassinolic acid*, in short needles (0·1 g.), m. p. 240° (decomp.), $[M]_D^{23}$ +78° (*c*, 0·166), $\lambda_{max.}$ 258 mμ (ε 13,200) [$\lambda_{max.}$ 259 mμ (ε 15,200) in alcoholic alkali (Found: C, 64·9; H, 7·3; OMe, 15·3%). Increasing the time of hydrolysis appeared to favour the yield of *allo*-quassinolic acid at the expense of the acid, m. p. 222°. The acid, m. p. 222°, is readily soluble in

water or alcohol, sparingly soluble in ether or light petroleum, and moderately soluble in other solvents. *allo*Quassinolic acid is readily soluble in alcohol, but sparingly soluble in water and most organic solvents including chloroform. Both acids dissolve in aqueous sodium hydrogen carbonate with effervescence and are reprecipitated on acidification of their solutions. The acid, m. p. 222°, which has a bitter taste, instantaneously decolorises dilute aqueous sodium permanganate whilst the tasteless isomeride does so more slowly.

Prepared with ethereal diazomethane, the *methyl ester* of the acid, m. p. 222°, separated from ethyl acetate in prisms, m. p. 188° [Found: C, 66·0; H, 7·9; OMe, 22·5. $C_{20}H_{23}O_4(OMe)_3$ requires C, 65·7; H, 7·7; OMe, 22·1%]. *Methyl* β-allo*quassinolate* formed needles, m. p. 180°, from ethyl acetate–ether–light petroleum (Found: C, 66·6; H, 7·9%). A mixture of the two esters had m. p. 160—170°.

When heated with acetic acid (1 g.) and concentrated hydrochloric acid (0·3 g.) on the steam bath for 1 hr. either acid (0·1 g.) gave bisnorquassin (*ca.* 0·05 g.), m. p. and mixed m. p. 253° (decomp.), after purification from chloroform–light petroleum. On being heated at 220°/0·05 mm. the acid, m. p. 222° (0·4 g.), gave a mixture from which allo*quassin* was isolated by repeated crystallisation from methanol, forming needles (0·12 g.), m. p. 267—268°, tasteless, insoluble in cold aqueous sodium hydroxide, having a negative ferric reaction, and readily decolorising aqueous potassium permanganate, $[M]_D^{22}$ +705° (*c*, 1·00), $\lambda_{max.}$ 262 mμ (ε 12,600 (Found: C, 68·3; H, 7·2. $C_{22}H_{28}O_6$ requires C, 68·0; H, 7·3%). Heated at 220°, *allo*-quassinolic acid (0·1 g.) gave a product which on crystallisation from methanol gave *allo*quassin (0·05 g.), m. p. and mixed m. p. 267—268°; heating the acid at 260°/0·4 mm. caused it to sublime.

The acid, m. p. 222° (0·45 g.), was heated under reflux with acetic anhydride (10 ml.) and sodium acetate (0·5 g.) for 1¼ hr., the cooled mixture was treated with methanol (10 ml.), the methyl acetate and excess methanol were evaporated, and the residual liquor was partially neutralised. After being triturated with aqueous sodium hydrogen carbonate, water, and then hot ethyl acetate, the solid crystallised from chloroform–ethyl acetate, giving a third *isomeride* of quassin in prisms (0·2 g.), m. p. 310—312° (decomp.), depressed on admixture with *allo*quassin, and having properties similar to this compound, $\lambda_{max.}$ 258 mμ (ε 8400) [Found: C, 67·6; H, 7·1; OMe, 16·2. $C_{20}H_{22}O_4(OMe)_2$ requires C, 68·0; H, 7·3; OMe, 16·0%]. Under the same conditions *allo*quassinolic acid yielded *allo*quassin, m. p. and mixed m. p. 267—268°.

neo*Quassin Derivatives*.—A solution of *neo*quassin (0·5 g.) in 3% methanolic hydrogen chloride (20 ml.) was kept at room temperature for 4 days and neutralised with aqueous sodium hydrogen carbonate. The resulting product separated from aqueous methanol in prisms (0·4 g.), identical with the compound described as *O*-methyl*neo*quassin, m. p. 156°, in Part I (*loc. cit.*). This product (0·8 g.) was adsorbed from benzene (6 ml.) on a column of aluminium oxide (1 × 40 cm.). Elution with benzene (160 ml.) gave α-O-*methyl*neo*quassin* which separated from benzene–ether in prismatic needles (0·15 g.), m. p. 173—174°, $[M]_D^{21}$ +260° (*c*, 0·98), unchanged on repeated chromatography [Found: C, 67·7; H, 7·9; OMe, 23·5. $C_{20}H_{23}O_3(OMe)_3$ requires C, 68·3; H, 8·0; OMe, 23·0%]. Subsequent elution of the aluminium oxide column with benzene–ethyl acetate (1 : 1) gave β-O-*methyl*neo*quassin* (0·07 g.) which, on recrystallisation from benzene–ether, had m. p. 210° and was slightly impure. The pure β-ether was prepared by methylation *of neo*quassin (0·5 g.), dissolved in dioxan (5 ml.), with methyl sulphate (2·5 ml.) and 10% aqueous sodium hydroxide (30 ml.) or by methyl sulphate and potassium carbonate in boiling acetone. Crystallisation of the product (0·45 g.) from ethyl acetate–light petroleum gave β-*O*-methyl*neo*quassin in prismatic needles, m. p. 212—213°, $[M]_D^{21}$ −181° (*c*, 0·99) (Found: C, 68·7; H, 8·0; OMe, 22·4%). This ether sublimed unchanged at 200°/0·3 mm.

The ethyl ether, m. p. 190—192°, of *neo*quassin described in Part I (*loc. cit.*) is α-*O*-ethyl*neo*-quassin, m. p. 194—196°, $[M]_D^{21}$ +137° (*c*, 1·0). With ethyl sulphate and aqueous sodium hydroxide, *neo*quassin (1 g.) yielded a product (0·87 g.) which on recrystallisation from ethyl acetate–light petroleum gave β-O-*ethyl*neo*quassin* in square prisms, m. p. 203—204·5°, $[M]_D^{21}$ −69° (*c*, 1·0) [Found: C, 68·8; H, 8·1; Alkyl-O, 10·5. $C_{20}H_{23}O_3(OMe)_2(OEt)$ requires C, 68·9; H, 8·2; Alkyl-O, 11·9%]. Except for their lack of taste the *O*-alkyl*neo*quassins closely resemble quassin and *neo*quassin, being extremely soluble in chloroform or acetic acid, readily in methanol or alcohol, and sparingly in dioxan, ethyl acetate, or benzene. The ethers are stable to warm alcoholic sodium hydroxide. With 3% methanolic hydrogen chloride during 4 days β-*O*-methyl-*neo*quassin (0·2 g.) was converted into α-*O*-methyl*neo*quassin (0·15 g.), m. p. and mixed m. p. 172—173°, after purification from ether–ethyl acetate (2 : 1). When boiled with acetic acid for 2 hr., α- or β-*O*-ethyl*neo*quassin (0·1 g.) reverted to *neo*quassin (0·07 g.). Treatment of the methyl or ethyl ether (0·1 g.) with warm acetic acid (1 ml.) and hydrochloric acid (1 ml.) on the

steam-bath for 1 hr. gave nor*neo*quassin, m. p. and mixed m. p. 212° after purification from ethyl acetate–light petroleum (Part I, *loc. cit.*).

Saturated ethereal hydrogen chloride (20 ml.) was added to a mixture of *neo*quassin (1 g.) and ethanethiol (2 ml.) and 5 minutes later rosettes of *ethylthioneoquassin* began to separate. Half an hour later the mixture was evaporated in a vacuum at room temperature and the product recrystallised from alcohol, light petroleum, and then chloroform–light petroleum, forming needles, m. p. 172—174° [Found: C, 66·1; H, 8·0; S, 6·5; OMe, 13·9. $C_{22}H_{38}O_3S(OMe)_2$ requires C, 66·3; H, 7·9; S, 7·3; OMe, 14·3%]. This tasteless derivative is stable to warm aqueous sodium carbonate and is decomposed with hot dilute acetic acid (odour of thiol).

*Anhydro*neo*quassin.*—A mixture of *neo*quassin (2 g.), sodium acetate (1 g.), and acetic anhydride (10 ml.) was heated under reflux (oil-bath at 160°) for 2 hr., part of the anhydride distilled, and the cooled residue mixed with methanol (10 ml.). After removal of the excess of methanol and methyl acetate in a vacuum, the slow addition of water (30 ml.) gave *anhydro*neo*quassin* (1·5 g.) which crystallised from aqueous alcohol and then ethyl acetate in short rods, m. p. 194—195°, $[M]_D^{21}$ −155° (*c*, 0·99), $\lambda_{max.}$ 255 mμ (ε 11,430) [Found: C, 70·3; H, 7·5; OMe, 15·4. $C_{20}H_{22}O_3(OMe)_2$ requires C, 70·9; H, 7·6; OMe, 16·7%]. This tasteless compound readily decolorised aqueous potassium permanganate and gave an amorphous product with 2 : 4-dinitrophenylhydrazine. On being refluxed with 2N-acetic acid (10 ml.) anhydro*neo*quassin (0·11) was almost quantitatively hydrated to *neo*quassin, m. p. and mixed m. p. 227—228°, whilst with 3% alcoholic hydrogen chloride at room temperature for 3 days it gave α-*O*-ethyl*neo*quassin. Boiled with a mixture of 3% hydrochloric acid (5 ml.) and dioxan (0·1 ml.) for 3 hr., anhydro*neo*quassin furnished nor*neo*quassin, m. p. and mixed m. p. 212° after purification from ethyl acetate–light petroleum, and having the characteristic ferric reaction.

*Dihydro*neo*quassin Acetate.*—Reduction of *neo*quassin (3 g.) with zinc dust (10 g.) and acetic acid (25 ml.) by the method employed for the preparation of dihydroquassin furnished *dihydro*neo*quassin acetate* (0·8 g.) which separated from alcohol–light petroleum and then dilute alcohol in needles, m. p. 227°, $\lambda_{max.}$ 252 mμ (ε 9200) [Found: C, 66·1; H, 8·2; OMe, 14·2; OAc, 13·5. $C_{20}H_{35}O_3(OMe)_2(OAc)$ requires C, 66·3; H, 7·8; OMe, 14·3; OAc, 13·6%].

*Nor*neo*quassin.*—This compound (Part I, *loc. cit.*), $[M]_D^{21}$ +179° (*c*, 1·0), had $\lambda_{max.}$ 257 mμ (ε 12,000) [$\lambda_{max.}$ 254 mμ (ε 8950) with minor peak $\lambda_{max.}$ 310 mμ (ε 4130) in 0·5% alcoholic sodium hydroxide] and formed a 2 : 4-*dinitrophenylhydrazone* which separated from aqueous acetone in rosettes of pale yellow needles, m. p. 190° (Found: N, 8·9. $C_{27}H_{30}O_9N_4$ requires N, 10·1%). With ethereal diazomethane or with methyl iodide (3 ml.) and potassium carbonate (5 g.) in boiling acetone (25 ml.) for 4 hr. nor*neo*quassin (0·5 g.) gave *neo*quassin (0·35 g.), m. p. and mixed m. p. 212°, after purification from ethyl acetate. Methylation of nor*neo*quassin with methyl sulphate and 10% aqueous sodium hydroxide gave β-*O*-methyl*neo*quassin, m. p. and mixed m. p. 212—213°.

*Nor*neo*quassinic Acid.*—A solution of nor*neo*quassin (1·7 g.) in 10% aqueous sodium hydroxide (30 ml.) was heated on the steam-bath for 2 hr., cooled, and saturated with carbon dioxide to remove a trace of unchanged compound. From the acidified aqueous liquor *nor*neo*quassinic acid* was isolated with chloroform and crystallised from ethyl acetate–light petroleum and then ethyl acetate, forming prisms (1·2 g.), m. p. 217—218° (decomp.), $\lambda_{max.}$ 259 mμ (ε 8430), $[M]_D^{20}$ +107° (*c*, 1·0), pK_a 5·75 [Found: C, 64·2; H, 7·5; OMe, 8·9; equiv. (by titration), 394. $C_{20}H_{27}O_6{\cdot}OMe$ requires C, 64·0; H, 7·7; OMe, 7·9%; *M*, 394]. This compound has a negative ferric reaction and does not react with aqueous potassium permanganate, with benzenediazonium chloride, or with 2 : 4-dinitrophenylhydrazine. Prepared by use of diazomethane, the *methyl ester* separated from ethyl acetate–light petroleum in prisms, m. p. 168—170°, $[M]_D^{23}$ +40° (*c*, 0·096), $\lambda_{max.}$ 259 mμ (ε 9110) (Found: OMe, 16·5. $C_{20}H_{26}O_5(OMe)_2$ requires OMe, 15·2%].

Norquassinic Acid.—Oxidation of nor*neo*quassinic acid (1 g.), dissolved in 1% aqueous sodium hydroxide (25 ml.), with a slight excess of 1% aqueous potassium permanganate (added dropwise) and clarification of the acidified mixture with sulphur dioxide gave the *hydrate* of norquassinic acid which separated from methanol–ethyl acetate (1 : 9) in needles (0·6 g.), m. p. 236—237°, unchanged on sublimation at 200°/0·001 mm., $[M]_D^{22}$ −120° (*c*, 0·2), $\lambda_{max.}$ 259 mμ (ε 9640), pK_a 5·4 [Found, in specimen dried in a vacuum at 60°: C, 61·4; H, 7·4; equiv. (by titration), 410, 434. $C_{20}H_{25}O_6{\cdot}OMe,H_2O$ requires C, 61·4; H, 7·4%; *M*, 410]. This compound has a negative ferric reaction and does not react with 2 : 4-dinitrophenylhydrazine. Prepared from the acid by means of diazomethane or 3% methanolic hydrogen chloride at room temperature for 3 days, *methyl norquassinate* separated from ethyl acetate–light petroleum in needles, m. p. 290—292° (decomp.), $[M]_D^{22}$ −119° (*c*, 0·42), $\lambda_{max.}$ 257 mμ (ε 9950) [Found: C,

65·0; H, 7·4; OMe, 16·1. $C_{20}H_{24}O_5(OMe)_2$ requires C, 65·0; H, 7·4; OMe, 15·2%]. In warm aqueous 2N-sodium hydroxide the ester regenerated the parent acid.

A mixture of methyl nor*neo*quassinate (0·2 g.), sodium dichromate (0·2 g.), sodium acetate (0·5 g.), acetic acid (5 ml.), and water (3 ml.) was heated under reflux for 2 hr., cooled, and diluted with water (20 ml.), giving methyl norquassinate (0·2 g.) in needles, m. p. and mixed m. p. 295° after purification from methanol.

Norquassinic acid was also prepared by heating a solution of norquassin (1 g.) in 10% aqueous sodium hydroxide (20 ml.) on the steam-bath for 1 hr. On isolation from the cooled, acidified solution with chloroform the acid separated as the hydrate, m. p. and mixed m. p. 236—237°, from methanol–ethyl acetate (Found: C, 61·4; H, 7·4; OMe, 8·6%), and with diazomethane gave the methyl ester, m. p. and mixed m. p. 290—292°.

On being heated under reflux for 45 min. and treated with water, a mixture of norquassinic acid (0·2 g.), acetic anhydride (4 ml.), and sodium acetate gave a neutral acetylation *product* which separated from aqueous methanol in short lustrous needles, m. p. 203°, $\lambda_{max.}$ ~224 and 284 mμ (ε 6000 and 4200) (Found: C, 66·1; H, 6·6. $C_{23}H_{28}O_7$ requires C, 66·3; H, 6·8%). This compound, which is insoluble in aqueous sodium hydrogen carbonate, gives the hydrate of norquassinic acid, m. p. and mixed m. p. 236—237°, on treatment with warm alcoholic sodium hydroxide on the steam-bath.

iso*Bisnorquassinic Acid.*—Norquassinic acid (0·5 g.) was heated with acetic acid (10 ml.) and concentrated hydrochloric acid (1·5 ml.) on the steam-bath for 7 hr. On isolation from the diluted mixture with chloroform, the resulting iso*bisnorquassinic acid* was triturated with a little acetic acid and then crystallised from dilute methanol, forming small prisms, m. p. 238—240° (decomp.), with a dark green ferric reaction, $[M]_D^{20}$ −33° (*c*, 1·0), $\lambda_{max.}$ 282 mμ (ε 7910) [$\lambda_{max.}$ 340 mμ (ε 6000) in 0·9% alcoholic potassium hydroxide] (isosbestic point 305 mμ, ε 3350), pK_a 4·8 (Found: C, 63·5; H, 6·7; OMe, negative. $C_{20}H_{26}O_7$ requires C, 63·5; H, 6·9%). Esterification of this acid in ether with a slight excess of diazomethane for 1 min. gave *methyl* iso*bisnorquassinate* which separated from ethyl acetate–light petroleum in needles, m. p. 227—228°, with a dark green ferric reaction, $[M]_D^{23}$ −30° (*c*, 1·0); $\lambda_{max.}$ 284 mμ (ε 8500) ($\lambda_{max.}$ 294, 335 mμ (ε 4200, 3900) in 0·04% alcoholic potassium hydroxide and $\lambda_{max.}$ 342 mμ (ε 6200) in 0·2% alcoholic potassium hydroxide (isosbestic point 307 mμ, ε 3700)] (Found: C, 64·1; H, 7·1; OMe, 8·0. $C_{20}H_{25}O_6$·OMe requires C, 64·3; H, 7·2; OMe, 7·9%). In aqueous 2N-sodium hydroxide on the steam-bath for 20 min. this ester regenerated the parent acid. On treatment with an excess of diazomethane for 4 days *iso*bisnorquassinic acid gave rise to methyl norquassinate, m. p. and mixed m. p. 290—292° after purification from methanol–ethyl acetate. When a solution of *iso*bisnorquassinic acid (0·05 g.) in aqueous 2N-sodium hydroxide (3 ml.), containing methyl sulphate (0·6 ml.), was agitated for ½ hr. and acidified, the hydrate of norquassinic acid was obtained having m. p. and mixed m. p. 233°.

By the pyridine method methyl bisnorquassinate gave an *acetate* which separated from aqueous methanol and then ethyl acetate–light petroleum in needles, m. p. 203°, $\lambda_{max.}$ 247 mμ (ε 10,000), having a negative ferric reaction (Found: C, 63·6; H, 7·2; OMe, 7·2. $C_{22}H_{27}O_7$·OMe requires C, 63·6; H, 7·0; OMe, 7·1%).

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