636. *Quassin and* neo*Quassin. Part IV.*[1]

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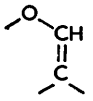
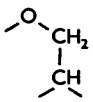
Like quassin and *neo*quassin, deoxoquassin, a dihydro-derivative of anhydro*neo*quassin, is readily demethylated, giving deoxonorquassin the properties and reactions of which are in agreement with the view that it is an enolic α-diketone.

Whereas anhydro*neo*quassin is converted by aqueous acetic acid into *neo*quassin and by methanolic hydrogen chloride into α- and β-*O*-methyl*neo*quassin,[1] the hydrogenation product of anhydro*neo*quassin, a dihydro-derivative formed with the aid of a Raney nickel catalyst, is stable to these reagents and has the same ultraviolet absorption as *neo*quassin. As it


(I)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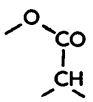

(III)

is obviously formed by hydrogenation of the αβ-unsaturated ether residue (I) in anhydro-*neo*quassin this dihydro-compound contains the partial structure (II) and may conveniently be termed deoxoquassin since quassin is the corresponding lactone (III).

[1] Part III, Hanson, Jaquiss, Lamberton, Robertson, and Savige, *J.*, 1954, 4238.

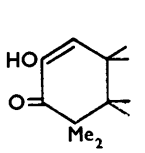
Starting with deoxoquassin, a number of experiments have been carried out, the results of which lend general support to the views expressed in Part III, particularly those which relate to chromophore (A). With hot dilute mineral acid deoxoquassin loses a methyl group, giving deoxonorquassin, analogous to norquassin and nor*neo*quassin. Deoxonorquassin behaves as an enol and can be remethylated with methanolic hydrogen chloride to deoxoquassin. In alkaline solution the ultraviolet absorption spectrum of deoxonorquassin shows a major peak attributed to chromophore (B) [1] and a minor peak at 314 mμ due to the enol ion derived from chromophore (A).

Oxidation of deoxonorquassin with alkaline hydrogen peroxide furnished a high yield of a non-enolic dibasic acid, $C_{20}H_{27}O_6 \cdot OMe$, the ultraviolet absorption of which is very similar to that of dihydroquassin. This spectrum is unchanged in alkaline solution and can therefore be attributed to chromophore (B).[1] Clearly, the dibasic acid is derived by oxidative fission of an α-diketone system, which is present in the enolic form in deoxonorquassin and as the enol ether (chromophore A) in deoxoquassin. Formulation of the enolic system as (IV) or (V), in agreement with previous results,[1] suggests for the dibasic acid partial structures (VI or VII; R = R′ = H), which are consistent with the behaviour of the acid on esterification. We shall employ formulæ (IV) and (VI) in subsequent discussion.

With diazomethane the dibasic acid gave rise to a dimethyl ester (VI; R = R′ = Me) whereas prolonged treatment with methanolic hydrogen chloride at room temperature gave only a monomethyl ester (A) (VI; R = Me, R′ = H). A second monomethyl ester (B) (VI; R = H, R′ = Me) is formed by mild hydrolysis of the dimethyl ester with alkali.

Attempts to convert the dibasic acid into a *cyclo*pentanone (VIII) by the action of heat were unsuccessful, giving only a neutral non-ketonic gum. Reduction of the dibasic acid with lithium aluminium hydride gave a non-crystalline product which had no significant ultraviolet absorption above 220 mμ, a result which supports the view that chromophore (B) is not a diene system but is an αβ-unsaturated ketone.

On reduction with zinc and acetic acid, deoxonorquassin is converted into an alkali-insoluble deoxodihydronorquassin (IX). As expected, this product has ultraviolet absorption characteristic of chromophore (B) and its infrared spectrum has a peak at 1710 cm.$^{-1}$ which may be attributed to a *cyclo*hexanone-carbonyl group. Periodate oxidation of



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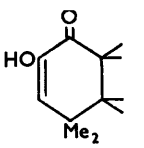

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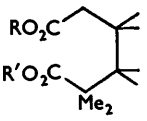

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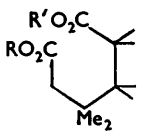

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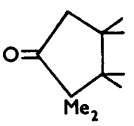

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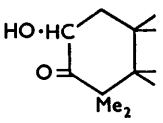
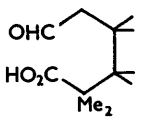


(IX)



(X)

dihydro-compound (IX) furnished an acid, presumably (X), which reacts immediately with Brady's reagent (the dihydro-compound reacts rather slowly with this reagent) and has infrared absorption peaks at 1737 (CHO group) and 1710 cm.$^{-1}$ (CO of CO_2H) and a broad shoulder at *ca.* 3050 cm.$^{-1}$ (CO_2H group).

The product obtained by reduction of deoxonorquassin with Raney nickel and hydrogen at room temperature and atmospheric pressure was amorphous but its properties clearly indicated that the enolic system derived from chromophore (A) had been reduced to a diol. Thus the reduction product was alkali-insoluble, gave no ferric reaction, and failed

to react with Brady's reagent, but was oxidised by sodium metaperiodate to a neutral non-crystalline substance which gave an immediate reaction with Brady's reagent.

Oxidation of deoxonorquassin by periodic acid yielded a non-enolic monobasic acid, $C_{20}H_{27}O_6 \cdot OMe$, and an enolic substance. The relation of these compounds to deoxonorquassin is not clear at present.

Deoxonorquassin is converted by the action of hot aqueous alkali into deoxonorquassinic acid, a reaction of the type previously encountered with nor- and nor*neo*-quassin, involving the addition of a molecule of water with the loss of the characteristic enol properties of the nor-compound. The ultraviolet absorption maxima of this acid and its methyl ester fall within the range 257—259 mμ already quoted for the analogous acids and esters derived from norquassin and nor*neo*quassin.[1] Methyl deoxonorquassinate has also been prepared from methyl nor*neo*quassinate by dehydration to methyl anhydronor*neo*quassinate and subsequent hydrogenation. The infrared absorption spectra of methyl anhydronor*neo*-quassinate and methyl deoxonorquassinate show sharp hydroxyl bands at 3440 and 3390 cm.$^{-1}$ respectively, thus providing further evidence that the conversion of the enolic nor-compounds into non-enolic acids with alkalis involves a transformation of the benzilic acid type. The newly formed hydroxyl group in these products is unreactive; thus *p*-nitrobenzazide is without action on methyl deoxonorquassinate and only the hemiacetal systems of nor*neo*quassinic acid and its methyl ester are readily oxidised by alkaline potassium permanganate and chromic acid respectively. Methyl deoxonorquassinate is also unaffected by dehydrating agents, *e.g.*, hot acetic anhydride and sodium acetate. Deoxonorquassinic acid is, however, oxidised by lead tetra-acetate at room temperature, giving a neutral non-crystalline product which reacts with Brady's reagent.

As in the conversion of norquassinic acid into the enolic *iso*bisnorquassinic acid [1] treatment of deoxonorquassinic acid with hot mineral acid gave a non-crystalline acid, deoxo*iso*bisnorquassinic acid, which with diazomethane affords a crystalline enolic methyl ester but on treatment with dimethyl sulphate and alkali gives the non-enolic methyl deoxonorquassinate. The latter reaction and the methylation experiments with *iso*-bisnorquassinic acid described in Part III [1] suggest that the *iso*bisnor-acids and the nor-acids are simply related as enols and enol ethers, but the considerable differences in the positions of the ultraviolet absorption maxima in the two series (nor-acid series, $\lambda_{max.}$ 257—259 mμ; *iso*bisnor-acid series, $\lambda_{max.}$ *ca.* 284 mμ) are then difficult to explain.

Experimental

Molecular rotations were measured in $CHCl_3$ and ultraviolet absorption spectra (Unicam spectrophotometer) in EtOH. Infrared 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°.

Deoxoquassin.—Reduced in methanol (50 ml.) with hydrogen at room temperature and atmospheric pressure in the presence of Raney nickel, anhydro*neo*quassin (2 g.) gave deoxoquassin which separated from aqueous methanol as the *hydrate* (1·6 g.) in colourless needles, m. p. 187—188°, $[M]_D^{22}$ +74° (*c* 1·00), λ_{max} 256 mμ (ε 12,630) (unchanged in 0·04% alcoholic potassium hydroxide) [Found: C, 67·3; H, 8·3. $C_{20}H_{24}O_3(OMe)_2,H_2O$ requires C, 67·3; H, 8·2. Found, in a specimen dried at 100° *in vacuo*: C, 70·4; H, 8·2; OMe, 16·5. $C_{20}H_{24}O_3(OMe)_2$ requires C, 70·5; H, 8·1; OMe, 16·6%]. Deoxoquassin was recovered unchanged after treatment with boiling acetic acid (8 hr.), boiling aqueous acetic acid (3 hr.), cold 5% methanolic hydrogen chloride (3 days), or with boiling aqueous-methanolic sodium hydroxide (2 hr.).

Deoxonorquassin.—Deoxoquassin (1 g.) was heated under reflux with a mixture of acetic acid (4 ml.), concentrated hydrochloric acid (4 ml.), and water (32 ml.) for 3 hr. and the hot colourless solution was decanted from undissolved oil and allowed to cool; deoxonorquassin separated in colourless needles (0·5 g.), m. p. 160—164°. The combined mother-liquor and the solidified oil were heated for 2 hr. and on cooling gave a second crop of crystals (0·25 g.), m. p. 159—162°. Recrystallised from aqueous methanol and then from ethyl acetate–light petroleum, *deoxonorquassin* formed colourless prisms and hexagonal plates, m. p. 164—165°, $[M]_D^{22}$ +126° (*c* 1·00), $\lambda_{max.}$ 257 mμ (ε 11,900) [254 mμ (ε 8500), 314 (ε 4200) in 0·04% alcoholic

potassium hydroxide] (Found : C, 69·7; H, 8·0; OMe, 8·6. $C_{20}H_{25}O_4$·OMe requires C, 69·9; H, 7·8; OMe, 8·6%). This product, which is readily soluble in aqueous sodium hydroxide but not in aqueous sodium hydrogen carbonate, has a deep violet-brown ferric reaction, reacts immediately with Brady's reagent, and gives a red precipitate with diazotised *p*-toluidine. On treatment with methyl sulphate and alkali, or with methanolic hydrogen chloride for 4 days at room temperature, deoxonorquassin yielded deoxoquassin hydrate, m. p. and mixed m. p. 187—188°.

With acetic anhydride (4 ml.), containing a trace of pyridine, at room temperature for 7 days deoxonorquassin (0·3 g.) was converted into the *acetate* (0·25 g.) which, on crystallisation from aqueous methanol and then from benzene–light petroleum, formed flat needles, m. p. 215—216°, $\lambda_{max.}$ 240 mμ (ε 12,000) [Found : C, 68·6; H, 7·4; OMe, 7·7. $C_{22}H_{27}O_5$·OMe requires C, 68·6; H, 7·5; OMe, 7·7%). The acetate, which had a negative ferric reaction, was readily hydrolysed with a hot dilute aqueous acetic acid solution of hydrochloric acid, giving deoxonorquassin.

Prepared with hydroxylamine hydrochloride and sodium acetate in hot aqueous methanol, the *oxime* of deoxonorquassin crystallised from aqueous methanol and then from ethyl acetate–light petroleum in colourless plates, m. p. 235—238° (decomp.), $\lambda_{max.}$ 249 mμ (ε 11,700) (Found : C, 67·6; H, 8·3; N, 3·8. $C_{21}H_{29}O_5N$ requires C, 67·2; H, 7·8; N, 3·7%).

Dibasic Acid from Deoxonorquassin.—To a solution of deoxonorquassin (0·5 g.) in ethanol (50 ml.) at 70°, a mixture of hydrogen peroxide (3 ml.; 100-vol.) and 2N-aqueous sodium hydroxide (6 ml.) was added portion-wise during 1 hr. After the addition of water (15 ml.), most of the ethanol was removed by distillation and the residual alkaline solution neutralised with concentrated hydrochloric acid, precipitating the *dibasic acid* as a white solid (0·5 g.), m. p. 280—282°. Recrystallised from aqueous methanol and then chloroform–light petroleum this acid formed colourless needles, m. p. 288—289°, which had a negative ferric reaction and did not react with diazotised *p*-toluidine; $[M]_D^{20}$ −319° (*c* 0·20), $\lambda_{max.}$ 253 mμ (ε 8900) (unchanged in alcoholic potassium hydroxide) (Found : C, 63·9; H, 7·6; OMe, 7·7%; equiv. wt., by titration, 206. $C_{20}H_{27}O_6$·OMe requires C, 63·9; H, 7·7; OMe, 7·6%; equiv. wt., 197). A solution of the acid (0·2 g.) in 2·5% methanolic hydrogen chloride (10 ml.), which had been kept at room temperature for 5 days, yielded an acidic *monomethyl ester* (A), which crystallised from aqueous methanol in hexagonal prisms (0·1 g.), m. p. 150—153°, $\lambda_{max.}$ 253 mμ (ε 9000) [Found : C, 64·8; H, 8·1; OMe, 14·7. $C_{20}H_{26}O_5(OMe)_2$ requires C, 64·7; H, 7·9; OMe, 15·2%]. On treatment of the acid (0·2 g.) in a little methanol with an excess of ethereal diazomethane for 30 min., the main product was a neutral *dimethyl ester* (0·1 g.), m. p. 80—82°, $\lambda_{max.}$ 254 mμ (ε 9000) [Found : C, 65·3; H, 8·0; OMe, 21·8. $C_{20}H_{25}O_4(OMe)_3$ requires C, 65·3; H, 8·1; OMe, 22·0%]. A solution of this ester (from 0·1 g. of dibasic acid) in a mixture of methanol (10 ml.) and 2N-aqueous sodium hydroxide was warmed for 10 min. and, after isolation with chloroform, the product was separated from a negligible amount of neutral material in the usual way. The acidic monomethyl ester (B) separated from aqueous methanol as a *hydrate* in rectangular plates, m. p. 90—92° [Found : C, 61·2; H, 7·8; OMe, 14·5. $C_{20}H_{26}O_5(OMe)_2,H_2O$ requires C, 62·0; H, 8·0; OMe, 14·5%]. Heated in nitrogen at 280° for 1 hr., the dibasic acid gave a brown non-ketonic gum which did not yield a crystalline product. Treatment of the dimethyl ester (from 0·4 g. of dibasic acid) with excess of lithium aluminium hydride (0·5 g.) in boiling ether for 2 hr. furnished a colourless gum with no significant ultraviolet absorption.

Deoxodihydronorquassin.—To a solution of deoxonorquassin (0·5 g.) in boiling acetic acid (10 ml.), zinc dust (1·0 g.) was added in four equal portions at intervals of 15 min. 45 Min. later the hot reaction mixture was filtered, the solid was washed with methanol and water, the combined filtrate and washings were extracted with chloroform, and the extract was freed from acidic material with 2N-aqueous sodium hydroxide and evaporated. Crystallised from ethyl acetate–light petroleum, the residue gave *deoxodihydronorquassin* in needles (0·2 g.), m. p. 240—245°, unchanged by further recrystallisation, $\lambda_{max.}$ 252 mμ (ε 8200) (Found : C, 69·4; H, 8·3; OMe, 8·6. $C_{20}H_{27}O_4$·OMe requires C, 69·6; H, 8·3; OMe, 8·6%). This compound reacted slowly with Brady's reagent and gave a negative ferric reaction.

Sodium metaperiodate (0·5 g.), in water (20 ml.), was added to a solution of deoxodihydronorquassin (0·3 g.) in methanol (10 ml.) and the mixture kept at 0° for 12 hr. On isolation with chloroform, the product was separated into a neutral and a main acidic fraction which on crystallisation from aqueous methanol slowly gave the *aldehydo-acid* (0·1 g.), m. p. 166—170°. Recrystallised from ethyl acetate–light petroleum, this had m. p. 176—178°, $\lambda_{max.}$ 253 mμ (ε 8300), and gave an immediate precipitate with Brady's reagent (Found : OMe, 8·2. $C_{20}H_{27}O_5$·OMe requires OMe, 8·2%).

When a solution of deoxonorquassin (0·2 g.) in methanol (50 ml.) containing Raney nickel was shaken with hydrogen at room temperature and atmospheric pressure the absorption of hydrogen almost ceased after 20 min. The product was a colourless gum, which was insoluble in aqueous sodium hydroxide, had a negative ferric reaction, failed to react with Brady's reagent and, on oxidation with sodium metaperiodate by the method used for deoxodihydronorquassin, gave a colourless amorphous product having ketonic properties.

Oxidation of Deoxonorquassin with Periodic Acid.—Sodium metaperiodate (0·5 g.) in 2N-sulphuric acid (10 ml.) was added to a solution of deoxonorquassin (0·5 g.) in methanol (10 ml.) at 0°. 2 Hours later the mixture was diluted with water (50 ml.) and the product isolated with chloroform and separated into neutral, " phenolic," and acidic fractions in the usual way, Acidification of a solution of the acidic fraction in aqueous sodium hydrogen carbonate gave an *acid* (0·15 g.), m. p. 175—178°, which separated from ethyl acetate–light petroleum in needles, m. p. 175—178°, with a negative ferric reaction (mixed m. p. with aldehydo-acid, m. p. 176—178°, from deoxodihydronorquassin was 150—165°), $\lambda_{max.}$ 256 mμ (ε 8700) (Found: C, 63·8; H, 7·3; OMe, 7·9%; equiv. wt., by titration, 397. $C_{20}H_{27}O_6$·OMe requires C, 63·9; H, 7·7; OMe, 7·9%; *M*, 394·5). This acid did not react with diazotised *p*-toluidine. Prepared with diazomethane, the methyl ester formed needles, m. p. 182—183°, from ethyl acetate–light petroleum [Found: OMe, 15·2. $C_{20}H_{26}O_5(OMe)_2$ requires OMe, 15·2%].

The " phenolic " fraction from the foregoing oxidation yielded an enolic substance, m. p. *ca* 210°, which has not yet been characterised.

Deoxonorquassinic Acid.—A solution of deoxonorquassin (0·3 g.) in aqueous 2N-sodium hydroxide (30 ml.) was boiled for 3 hr., cooled, and acidified with concentrated hydrochloric acid. Isolated with chloroform, the product was crystallised from aqueous methanol and treated in sodium hydrogen carbonate solution with charcoal, giving *deoxonorquassinic acid* which separated from ethyl acetate–light petroleum in colourless prisms, m. p. 194—196°, $[M]_D^{22}$ −90° (*c* 1·00), pK_a 4·90, $\lambda_{max.}$ 258 (ε 8750) [253 mμ (ε 9000) in 0·04% alcoholic potassium hydroxide] (Found: C, 66·4; H, 8·1; OMe, 8·1%; equiv. wt., by titration, 360. $C_{20}H_{27}O_5$·OMe requires C, 66·6; H, 8·0; OMe, 8·2%; *M*, 378·5). This acid, which had a negative ferric reaction and did not react with diazotised *p*-toluidine, gave *methyldeoxonorquassinate* with ethereal diazomethane, rhombs, m. p. 225° (from benzene–light petroleum), $[M]_D^{22}$ −66° (*c* 1·00), $\lambda_{max.}$ 259 mμ (ε 8550) [Found: C, 67·3; H, 8·2; OMe, 15·9. $C_{20}H_{26}O_4(OMe)_2$ requires C, 67·3; H, 8·2; OMe, 15·8%]. This ester, which was also prepared from deoxonorquassinic acid with methyl sulphate and alkali and with methanolic hydrogen chloride, regenerated the parent acid on hydrolysis with hot dilute methanolic sodium hydroxide.

*Methyl Anhydronor*neo*quassinate.*—A mixture of methyl nor*neo*quassinate (0·5 g.), sodium acetate (0·2 g.), and acetic anhydride (5 ml.) was heated under reflux for 2½ hr., cooled, and diluted with methanol (10 ml.). After distillation of the excess of methanol and methyl acetate the residue was treated with 2N-aqueous sodium hydroxide, and the granular buff product was purified in benzene with aluminium oxide. Recrystallised from ethyl acetate–light petroleum, the resulting *methyl anhydronor*neo*quassinate* formed plates (0·25 g.), m. p. 192—194°, $\lambda_{max.}$ 258 mμ (ε 7540) [Found: C, 67·7; H, 7·8; OMe, 15·7. $C_{20}H_{24}O_4(OMe)_2$ requires C, 67·6; H, 7·7; OMe, 15·9%]. Hydrogenation of this ester (0·1 g.) in methanol (30 ml.) with a Raney nickel catalyst at room temperature for 3 hr. gave methyl deoxonorquassinate (0·08 g.), m. p. and mixed m. p. 224°.

*Methyl Deoxo*iso*bisnorquassinate.*—The solution formed by heating deoxonorquassinic acid (0·5 g.), acetic acid (8 ml.), and concentrated hydrochloric acid (8 ml.) under reflux for 8 hr. was diluted with water (50 ml.) and extracted with chloroform, giving an amorphous product with a green-black ferric reaction. With ethereal diazomethane this gave *methyl deoxo*iso*bisnorquassinate* (0·4 g.) which separated from ethyl acetate–light petroleum and then aqueous methanol in hexagonal prisms, m. p. 204°, $\lambda_{max.}$ 284 mμ (ε 8500) [340 mμ (ε 5810) in 0·75% alcoholic potassium hydroxide] (Found: C, 66·4; H, 8·2; OMe, 8·3. $C_{20}H_{27}O_5$·OMe requires C, 66·6; H, 8·0; OMe, 8·2%). This ester gave an intense green-black ferric reaction in aqueous alcohol. Methylation of the amorphous deoxo*iso*bisnorquassinic acid with methyl sulphate in 2N-aqueous sodium hydroxide furnished methyl deoxonorquassinate, m. p. and mixed m. p. 223°.

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