Study of some bisnorquassin derivatives

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The structures of several derivatives of bisnorquassin (**2***a*) are clarified. Chemical support for the mechanism of formation of this novel demethylation product of quassin (**1***a*) is provided, which together with the recent X-ray diffraction study of bisnorquassin *m*-bromobenzoate (**2***d*) offers an independent corroboration of the structure and stereochemistry of **1***a* deduced by Valenta.

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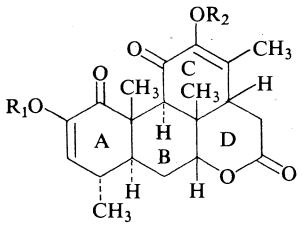
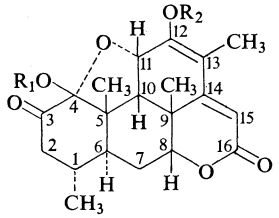
The complete structure and stereochemistry of quassin $C_{22}H_{28}O_6$ (**1***a*) a bitter principle from *Quassia amara*, was deduced by Valenta and coworkers (1) in 1962. It had been known for some time that quassin produced an abnormal demethylation product $C_{20}H_{24}O_6$ named bisnorquassin (2, 3) when treated with a mixture of concentrated hydrochloric and acetic acid. Recently we proposed structure **2***a* for this novel product and outlined a likely transformation mechanism (4). At that time the configuration of centers C-1, C-4, C-10, and C-11 remained unassigned. The X-ray diffraction study of Lynton (5) on bisnorquassin *m*-bromobenzoate **2***d* has now clarified the remaining stereochemistry and has corroborated in detail our proposal **2***a* for bisnorquassin.



1

a $R_1 = R_2 = CH_3$
b $R_1 = R_2 = H$



2

a $R_1 = R_2 = H$
b $R_1 = H$; $R_2 = COCH_3$
c $R_1 = H$; $R_2 = COC_6H_5$
d $R_1 = H$; $R_2 = COC_6H_5Br$ (*m*)

Prior to the conclusion of the X-ray study (5) we were seeking corroborative chemical evidence for structure **2***a* with a view also to determining additional stereochemical features of the molecule. This involved, in part, reexamining some of the derivatives of **2***a* reported by Robertson's group (2, 3). We now report our findings.

In one approach we have treated quassin (**1***a*) with concentrated DCl and CH_3COOD and obtained a polydeuterated bisnorquassin containing up to 7 deuterium atoms as evidenced by the mass spectrum which displayed ions of *m/e* 367, 366, 365, and 364, the latter two being the more abundant species. Examination of the nuclear magnetic resonance (n.m.r.) spectrum of this product indicated the absence of signals due to hydrogens at C-2, C-10, and C-11, all of which are clearly discernible in the corresponding spectrum of bisnorquassin at τ 7.7 (a multiplet, 2H), 7.4 (a doublet, 1H, J = 10 c.p.s.), and 5.0 (a doublet, 1H, J = 10 c.p.s.), respectively. In addition, the signal for the methyl group at C-13 (τ 8.1) is grossly diminished in the deuterated bisnorquassin spectrum. This result clearly supports structure **2***a* and the mechanism of formation proposed by us earlier (4) since all the hydrogens involved are potentially exchangeable via ketone-enol equilibria during the transformation of **1***a* to **2***a*.

An important feature of the n.m.r. spectrum of the polydeuterated bisnorquassin is that it displays a doublet at τ 9.1 (J = 5 c.p.s.) for the C-1 methyl group; a clear indication that C-1 has not epimerized in the quassin–bisnorquassin transformation. It follows then that the methyl group at C-1 must be α in bisnorquassin (**2***a*) corresponding to the same configuration at that site in quassin (**1***a*). This result, together with the X-ray solution of bisnorquassin *m*-bromobenzoate (**2***d*) allows for a complete and independent corroboration of the structure and stereochemistry

of quassin **1***a* (1) except for the centers C-10 and C-14.

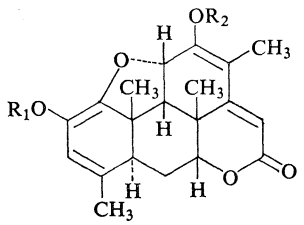
It is noteworthy that the coupling constant *J* for the mutual splitting of hydrogens at C-10 and C-11 in **2***a* and a number of derivatives, including the *m*-bromobenzoate **2***d*, is of the order of 9–10 c.p.s. The magnitude of this coupling constant suggests a *trans* relationship of the C-10 and C-11 hydrogens but this is clearly misleading in the light of the X-ray diffraction studies on **2***d* which show these hydrogens to be *cis* and β. From inspection of models it is evident that this *cis* arrangement confers greater strain-free planarity on the chromophoric system in rings C and D in **2***a* and also provides for a less strained 5-membered hemi-ketal ring than do alternate *trans* C-10, C-11 configurations.

In attempts to gain chemical insight to the configuration of the hydroxyl group at C-4 in **2***a* we have examined the n.m.r. spectra of a number of bisnorquassin derivatives some of which were first reported in Robertson's papers (2, 3).

In the n.m.r. spectrum of bisnorquassin itself the signal for the C-5 methyl is found at τ 9.1, while the C-9 methyl shows at τ 8.6, the low field position of the latter can be ascribed to deshielding caused by the adjacent extended chromophoric system. We have attempted to prepare derivatives of **2***a* in which the C-4 hydroxyl was acetylated or benzoylated with the expectation that the n.m.r. spectra of such might show shifts in the field position for signals due to protons at C-10, C-11 or for the methyl protons at C-5, should these hydrogens be *cis* to the introduced acetoxy or benzoyloxy group at C-4. Since earlier studies reported (3) the preparation of *O,O*-diacetyl bisnorquassin (m.p. 232°), our initial efforts were directed at obtaining this compound. While we had no difficulty in preparing a monoacetate **2***b* (m.p. 231–233°) by the procedure described for preparation of the presumed diacetate, the only diacetate we were able to prepare proved to be an anhydrodiacetate (m.p. 232–234°) and this was obtained by treatment of bisnorquassin with acetic anhydride and fused sodium acetate.

The n.m.r. spectrum of the monoacetate **2***b* differs little from that of **2***a* apart from the additional singlet (3H) at τ 7.74 (CH_3CO). Since the ultraviolet (u.v.) spectrum (λ_{max} 275 mμ, ε 20 000 in alcohol) of **2***b* displays a slow time dependent shift (to λ_{max} 373 mμ ε, > 25 000) in basic media there is no doubt that the acetoxy group is attached to C-12. The corresponding monobenzoate **2***c* is readily prepared by treatment of bisnorquassin with benzoyl chloride and pyridine.

We formulate the anhydrodiacetate of bisnorquassin as **3***a*. In the n.m.r. spectrum of this compound the signal for the C-1 methyl appears as a singlet near τ 8.2. Singlets (3H each) at τ 7.75 and 7.9 are assigned to the two acetate methyl groups. A slightly broadened singlet at τ 4.5 (1H) (C_2—H) attests to the location of a double bond between C-1 and C-2, while a broad multiplet (1H) at τ 7.4 is assigned to the C_6—H. The other features of the spectrum are unexceptional. Further support for formulation **3***a* comes from its infrared (i.r.) spectrum (KBr) which shows bands at 1780 (enol acetate), 1710 (lactone), 1650 and 1605 cm^{-1} (conjugated double bonds) and no hydroxylic absorption.



3

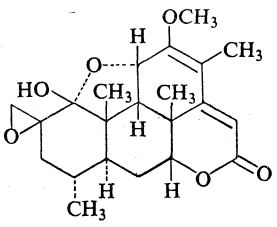
a $R_1 = R_2 = COCH_3$
b $R_1 = R_2 = COC_6H_5$

Formation of **3***a* can be visualized as occurring by 1,4-elimination via an intermediate enol acetate generated in the A ring. In attempting to obtain a dibenzoate of bisnorquassin we have encountered a parallel transformation leading to **3***b* which displays similar spectroscopic features to **3***a*.

Another interesting compound described (2, 3) earlier was obtained by prolonged treatment of bisnorquassin with diazomethane. This compound named α-*O*-methyl bisnorquassin (m.p. 210°) was initially believed to have the constitution $C_{21}H_{23}O_5 \cdot OMe$ (2) but was later amended to conform with $C_{20}H_{23}O_5 \cdot OMe$ (3). It displayed λ_{max} 315 mμ (ε 22 600) and did not appear to contain a hydroxyl group in view of the reported absence of hydroxylic bands in the i.r. spectrum and negative Zerewitinoff reaction.

In several attempts to prepare this compound with all the properties described we have been unsuccessful. However, by the same prolonged treatment of bisnorquassin with diazomethane

we have obtained a product with similar melting point (m.p. 206–208°) and u.v. spectrum (λ_{max} 312 mμ, ε 19 800). While the n.m.r. spectrum (*vide infra*) shows it to be a monomethyl ether, the mass spectrum displays a strong molecular ion of *m/e* 388, indicating a composition $C_{22}H_{28}O_6$. In addition this derivative displays hydroxylic absorption in the i.r. at 3600 cm^{-1} and responds positively to a Zerewitinoff determination and therefore does not appear to be identical with α-*O*-methyl bisnorquassin reported by Robertson and co-workers. We formulate this new derivative as **4** in the light of the following data. Its i.r. spectrum shows only one strong carbonyl band at 1700 cm^{-1} attributed to the enol lactone carbonyl. The n.m.r. spectrum displays a singlet (1H) at τ 4.3 (C_{15}—H), a doublet (1H) at 4.9 (J = 8 c.p.s.) (C_{11}—H), a triplet (1H) at 5.5 (J = 6 c.p.s.) (C_8—H) and a doublet (1H) centered at 7.5 (J = 8 c.p.s.) (C_{10}—H). The pattern of the low field signals is essentially the same as that in the bisnorquassin spectrum. The major difference is the appearance in the spectrum of **4** of a singlet (3H) at τ 6.15 (CH_3O) and a pair of doublets (1H each) at τ 7.0 and 7.5 (J = 4 c.p.s.), assigned to the hydrogens on the oxide bridge.



4

As chemical corroboration of structure **4** for the product of prolonged diazomethane treatment of bisnorquassin we have subjected it to treatment with concentrated hydrochloric acid and obtained the corresponding chlorohydrin (*m/e* 424) which on treatment with potassium carbonate solution refurnished the original oxide **4** in accord with expectation.

It should be noted that the simple bis demethylated quassin **1***b* can be prepared by treatment of quassin with aluminum chloride in hot nitrobenzene. The product **1***b* (m.p. 196–200°) is obtained in good yield and can be converted into quassin by treatment with ethereal diazomethane.[1] We have also succeeded in converting **1***b* into bisnorquassin (**2***a*) thus demonstrating the intermediacy of **1***b* in the quassin–bisnorquassin transformation as proposed by us recently (4).

[1]These two reactions were first carried out at the University of Liverpool. See ref. (6).

Experimental

General

The i.r. spectra were recorded on a Perkin–Elmer model 237B spectrophotometer. The mass spectra were determined on a Hitachi Perkin–Elmer model RMU-6D spectrometer. The n.m.r. spectra were recorded with a Varian 56.4 Mc/s instrument using tetramethylsilane as internal standard. A Köfler hot stage apparatus was employed to determine the melting points which are uncorrected.

Preparation of Bisnorquassin (2a)

Bisnorquassin was prepared from quassin (**1***a*) by the procedure described by London *et al.* (2) and was recrystallized to constant m.p. (250–253°) from 95% ethanol.

Preparation of Polydeuterated Bisnorquassin

A mixture of quassin (250 mg), CH_3COOD (2.5 ml) and concentrated DCl (0.75 ml) was heated on a steam bath for 1 h. The solution was concentrated, diluted with water, and cooled. A crystalline solid (180 mg) separated and was filtered off. After recrystallization from ethanol this material (m.p. 250–253°) showed no depression of melting point when admixed with bisnorquassin. The n.m.r. spectrum shows signals at τ 4.2 (singlet, 1H), 5.5 (multiplet, 1H), 8.2 (multiplet, 4H), 8.6 (singlet, 3H), 8.95 (singlet, 3H), and 9.1 (doublet, 3H, J = 5 c.p.s.). The mass spectrum displays abundant ions at *m/e* 367, 366, 365, and 364.

Preparation of Bisnorquassin Acetate (2b)

Bisnorquassin (100 mg) in dry pyridine (10 ml) was treated with acetic anhydride (10 ml) for 18 h at room temperature. After evaporation of the solution to dryness *in vacuo*, the residue was dissolved in glacial acetic acid (3 ml) from which the product (65 mg) crystallized on standing. After filtration and washing with water the product **2***b* was recrystallized from benzene and displayed m.p. 231–233°. The i.r. spectrum (CCl_4) shows bands at 3500, 1775, 1725, 1680, and 1600 cm^{-1}; λ_{max} (ethanol) 275 mμ (ε 20 000) shifts slowly in basic media to 373 (ε > 25 000). The mass spectrum displays a molecular ion of *m/e* 402 corresponding to $[C_{22}H_{26}O_7]^+$.

Preparation of Bisnorquassin Anhydrodiacetate (3a)

Bisnorquassin (1 g) in acetic anhydride (100 ml) was treated with sodium acetate (460 mg) and the solution was refluxed for 24 h. Evaporation *in vacuo* yielded a dark brown semi-solid mass which was taken up in hot ethanol. The cooled ethanolic solution yielded bisnorquassin anhydrodiacetate **3***a* (0.55 mg) which was recrystallized to constant melting point (232–234°) from ethanol. The i.r. spectrum (KBr) shows bands at 1780, 1710, 1650, and 1605 cm^{-1}; λ_{max} (ethanol) 268 mμ (ε 13 400) changes slowly on addition of base to λ_{max} 244 (ε 5600) and 380 mμ (ε 17 000). The n.m.r. spectrum displays signals at τ 4.1 (singlet, 1H), 4.5 (broad singlet, 1H) partly superimposed on a doublet centered near τ 4.6 (1H), 5.65 (multiplet, 1H), 7.4 (broad singlet, 1H), 7.75

(singlet, 3H), 7.9 (singlet, 3H), 8.2 and 8.25 (2 coalesced singlets, 6H), 8.7 (singlet, 3H) and 8.95 (singlet, 3H). The mass spectrum displays a molecular ion of *m/e* 426 corresponding to $[C_{24}H_{26}O_7]^+$.

*Preparation of Bisnorquassin Anhydrodibenzoate (**3b**)*

A mixture of bisnorquassin (1 g), dry pyridine (5 ml), and benzoyl chloride (2.5 ml) was heated at 70° for 24 h. The solution was evaporated to dryness and the residue taken up in ethyl acetate/ether (2:1). After washing this solution with dilute aqueous HCl it was dried over anhydrous magnesium sulfate and evaporated. The residue crystallized from ether/methanol yielding **3***b*, a crystalline solid (0.4 g) m.p. 243–244°. The i.r. spectrum (CCl_4) displays bands at 1750 (broad) and 1660 cm^{-1}; λ_{max} (ethanol) 231 (ε 12 900) and 267 mμ (ε 13 200) shifts slowly on addition of base to λ_{max} 380 mμ (ε 15 000). The n.m.r. spectrum shows signals at τ 1.93–3.30 (multiplets, 10H), 4.08 (singlet, 1H), 4.36 (singlet, 1H) partly superimposed on a doublet centered near τ 4.4, 5.45 (multiplet, 1H), 7.35 (broad based singlet, 1H), 7.7 (doublet, 1H, $J = 7.4$ c.p.s.), 8.1 (singlet, 3H), 8.2 (singlet, 3H), 8.5 (singlet, 1H) and 8.8 (singlet, 1H).

Anal. Calcd. for $C_{34}H_{30}O_7$: C, 74.30; H, 5.46; O, 20.19. Found: C, 74.22; H, 5.41; O, 20.29.

*Preparation of Bisnorquassin m-Bromobenzoate (**2d**)*

Bisnorquassin (0.2 g) in dry pyridine (3 ml) was treated with *m*-bromobenzoyl chloride (1.5 ml). After standing at room temperature for 18 h, the solution was evaporated to dryness. The crude product (0.23 g) was treated with carbon tetrachloride (10 ml) and the soluble portion was evaporated to dryness and chromatographed on a silica gel column. Bisnorquassin *m*-bromobenzoate **2***d* was eluted with $CCl_4/CHCl_3$ (1:1). The white crystalline product (40 mg) was recrystallized from ethanol to constant melting point (262–265°). The i.r. spectrum ($CHCl_3$) shows bands at 3600, 1750, 1725 (broad), 1670, 1600, and 1580 cm^{-1}. The mass spectrum displays a pair of molecular ions of approximately equal intensity at *m/e* 544 and 542 corresponding to $[C_{27}H_{27}O_7Br]^+$. The u.v. absorption spectrum displays λ_{max} 238 (ε 12 200) and 273 mμ (ε 18 700). The n.m.r. spectrum shows signals at τ 1.80–2.9 (multiplet, 4H), 4.0 (singlet, 1H), 4.9 (doublet, 1H, $J = 9.6$ c.p.s.), 5.4 (triplet, 1H, $J = 6$ c.p.s.), 7.4 (doublet, 1H, $J = 9.6$ c.p.s.), 7.65 (multiplet, 2H), 8.15 (singlet, 3H), 8.5 (singlet, 3H), 9.0 (singlet, 3H) and 9.1 (doublet, 3H, $J = 5$ c.p.s.).

*Preparation of **4***

Bisnorquassin (130 mg) in chloroform (5 ml) was treated with a large excess of ethereal diazomethane for a period of 12 h. After evaporation of solvent, the crude product was recrystallized from ethanol to furnish **4** (70 mg), m.p. 208–210°. The i.r. spectrum ($CHCl_3$) shows absorption maxima at 3600, 1700, 1640, and 1600 cm^{-1}; λ_{max} 312 mμ (ε 19 800). The mass spectrum displays a strong molecular ion of *m/e* 388 corresponding to $[C_{22}H_{28}O_6]^+$. The n.m.r. spectrum shows signals at τ 4.3 (singlet, 1H), 4.9 (doublet, 1H, $J = 8$ c.p.s.), 5.5 (triplet, 1H, $J = 6$ c.p.s.), 6.15 (singlet, 3H), 7.0 (doublet, 1H, $J = 4$ c.p.s.), 7.5 (doublet, 1H, $J = 4$ c.p.s.) superimposed on a signal at τ 7.6 (doublet, 1H, $J = 8$ c.p.s.), 8.2 (singlet, 3H), 8.7 (singlet, 3H), 8.9 (singlet, 3H) and 9.3 (doublet, 3H, $J = 4$ c.p.s.).

*Chlorohydrin of **4***

Compound **4** (79 mg) in anhydrous ether (5 ml) was treated with gaseous hydrochloric acid by bubbling a steady stream of gas through the solution for 1 h. The flask was then stoppered and the solution stirred for 18 h. Evaporation of the solvent gave a residue (89 mg) which was purified by preparative thin-layer chromatography on silica gel. The i.r. spectrum ($CHCl_3$) of the resulting chlorohydrin displays bands at 3680, 3520, 1695, and 1630 cm^{-1}. The n.m.r. spectrum shows signals at τ 4.35 (singlet, 1H), 4.9 (doublet, 1H, $J = 10$ c.p.s.), 5.45 (triplet, 1H, $J = 7$ c.p.s.), 6.1 (singlet, 3H), 6.45 (singlet, 1H), 6.7 (multiplet, 2H), 7.45 (doublet, 1H, $J = 10$ c.p.s.), 8.2 (singlet, 3H), 8.7 (singlet, 3H), 8.8 (singlet, 3H), and 9.25 (doublet, 3H, $J = 5$ c.p.s.). The mass spectrum displays a molecular ion of *m/e* 424 corresponding to $[C_{22}H_{29}O_6Cl]^+$. This compound was readily converted back to **4** by treatment with a solution of potassium carbonate in methanol/water.

*Preparation of **1b***

Aluminum chloride (1 g) was added to a solution of quassin (1 g) in nitrobenzene (25 ml) and the mixture was heated at 90° for 4 h. The solvent was removed by steam distillation and the residue taken up in chloroform. Crystallization of the chloroform soluble fraction from ethanol afforded **1***b* (650 mg), m.p. 196–200°. The mass spectrum displays a strong molecular ion of *m/e* 360 corresponding to $[C_{20}H_{24}O_6]^+$. The i.r. spectrum ($CHCl_3$) displays bands at 3500, 1740, 1690, and 1660 cm^{-1}; λ_{max} (ethanol) 273 mμ (ε 12 000) shifts in base to 315 mμ (ε 10 000).

*Conversion of **1b** to Bisnorquassin (**2a**)*

A mixture of **1***b* (100 mg), acetic acid (10 ml), and concentrated hydrochloric acid (3 ml) was heated on a steam bath for 1 h. The hot solution was diluted with water and on cooling yielded white crystalline needles (80 mg) which after recrystallization from ethanol proved to be identical with bisnorquassin (**2***a*) by m.p., mixed m.p., i.r., n.m.r., and mass spectra.

*Conversion of **1b** to Quassin (**1a**)*

Compound **1***b* (100 mg) in ether was treated with an excess of ethereal diazomethane for 1 h. After evaporation of ether the residue was recrystallized from acetone and ethanol to yield a product (55 mg) identical by m.p., mixed m.p., i.r., and u.v. spectrum with quassin **1***a*.

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