Phytochemistry, Vol. 26, No. 11, pp. 3085–3087, 1987.
Printed in Great Britain.

0031–9422/87 $3.00 + 0.00
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A NEW NEOQUASSIN DERIVATIVE FROM *QUASSIA AMARA**

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(*Revised received* 31 *March* 1987)

Key Word Index—*Quassia Amara*; Simarubaceae; quassinoids; dihydronorneoquassin.

Abstract—A new quassinoid, a dihydronorneoquassin, has been isolated from *Quassia amara* wood. In addition the known compounds, paraine and isoparaine, were also identified. Moreover, the known 4-methoxy-5-hydroxycantin-6-one was isolated for the first time from the same source. The structure and stereochemistry of 11-dihydro-12-nor-neoquassin were determined by spectroscopic methods as well as by means of chemical correlations.

INTRODUCTION

It is well known that many interesting biological properties are associated with the Simarubaceae bitter principles. Particularly, in the last decade, this family of plants has received renewed attention because of the anticancer activity shown by some quassinoids [1].

We have reported the isolation and the biological activity of novel quassinoids from *Ailanthus glandulosa* [2] and *Quassia amara* L. [3]. Further studies on the latter plant have now allowed us to detect a new minor bitter principle, a dihydronorneoquassin related to paraine, together with a number of other known quassinoids and cantinone derivatives, the occurrence of which in *Quassia amara* have not been observed previously. By means of spectral studies and chemical correlations, structure **1** was assigned to the novel compound.

RESULTS AND DISCUSSION

Elemental and mass spectral analyses (M^+ at m/z 378) indicated $C_{21}H_{30}O_6$ as the molecular formula. The IR [$\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 and 3430 (OH), 1730, 1690] and UV (λ_{max}^{MeOH} 268 nm, $\varepsilon = 3180$) spectra revealed characteristic absorptions for hydroxyl groups and two carbonyl groups, one of which was α,β-unsaturated. The multiplicity and chemical shift values of the carbon atoms (Table 1) in the ^{13}C NMR spectrum provided a corroboration for the elemental composition and suggested a quassinoid skeleton with a modified ring D structure. Details of the structure and stereochemistry of **1** were readily inferred from the high-field ^1H NMR spectrum (Table 1). From a comparison of the ^1H chemical shift values and J_{HH} coupling constants with those reported for quassinoids it became immediately evident that the lactone carbonyl group was replaced by a C(16)-HOH-function as in neoquassin (**3**). The C-16 hydroxy groups stereochemistry followed from the coupling constants of the proton at C-16 (Table 1). The proposed structure (**1**) was supported by acetylation experiments giving the 16-monoacetate and the 11,16-diacetates **2a** and **2b**, respectively, and by an unsuccessful reaction to form the acetonide of compound **1**.

A definitive verification of the structure of hemiacetal **1** was achieved by chemical correlation with paraine (**4**) (oxidation with Ag_2O) and quassin (**6**) (oxidation with CrO_3 to 12-norquassin [4] followed by methylation with CH_2N_2). It may be noted that, in contrast to the wide distribution of the quassinoids in plants of the Simarubaceae family, the occurrence of the neoquassin feature up to now has been observed only in a limited number of cases [5–7].

The physical and spectral data of 4-methoxy-5-hydroxycantin-6-one (**7**) were identical with the ones reported in the literature [8]. Moreover, its structure was confirmed by transformation into the known 4,5-dimethoxy derivative **8** [8] and by acetylation to **9** [9] as well as by oxidation with $KMnO_4$ to yield 1-methoxycarbonyl-β-carboline [10, 11], identical to a synthetic sample provided by Dr Gatta.

EXPERIMENTAL

General. Mps: uncorr. IR: $CHCl_3$. The MS were recorded on an LKB 2091 spectrometer at 70 eV. UV: MeOH soln. ^1H NMR spectra were recorded on 400, 100 and 90 MHz instruments using TMS as an int. standard. ^{13}C NMR spectra were recorded on a 20.15 MHz instrument. Merck's DC-Alufolien kieselgel 60 F_{254} and Merck's kieselgel 60 were used for TLC and CC. A voucher specimen of *Quassia amara* L. has been deposited at the Herbarium of the Institute of Vegetal Biology at the University of Perugia.

Extraction. Quassia wood from *Quassia amara* L. (chips, 100 kg) was exhaustively extracted with MeOH at room temp. and the extract evapd *in vacuo*. Water was then added to the residue and the mixture extracted with $CHCl_3$. The $CHCl_3$ soluble fraction was evaporated under red. pres. and extracted with petrol. The petrol insoluble residue (602 g) was repeatedly chromatographed on silica gel columns. Elution with solvents of

*Preliminary results were presented at the '2nd Convegno Nazionale della Società Italiana di Fitochimica', Roma, June 1984 and at the 'International Symposium on Organic Chemistry of Medicinal Natural Products', Shanghai, China, November 1985.

Table 1. ^{1}H NMR chemical shifts for compounds **1**, **2a**, **2b** (100*, 90** MHz, $CDCl_3$) and ^{13}C NMR chemical shifts for compound **1** (20.15 MHz, pyridine-d_5).

	Proton			
Carbon	**1***	**2a***	**2b****	**1**
1	–	–	–	211.3‡ *s*
2	–	–	–	148.7 *s*
3	5.36 *d*(3)	5.37 *d*(3)	5.11 *d*(3)	117.7 *d*
4	n.a.	n.a.	n.a.	41.3† *d*
5	n.a.	n.a.	n.a.	42.7† *d*
6	n.a.	n.a.	n.a.	26.1 *t*
7	3.45 *dd*(3,2)	3.55 *m*	3.49 *m*	75.2 *d*
8	–	–	–	37.3 *s*
9	2.68 *d*(12)	2.70 *d*(12)	3.10 *d*(12)	42.9† *d*
10	–	–	–	48.7 *s*
11	4.35 *ddd*(12, 11, 1)[a]	4.37 *dd*(12, 12)	5.22 *d*(12)	77.3 *d*
12	–	–	–	204.0‡ *s*
13	3.02 *m*	3.03 *m*	3.07 *m*	50.6 *d*
14	n.a.	n.a.	n.a.	44.4† *d*
15	(–)	(–)	(–)	31.2 *t*
16	4.73 *ddd*(10, 7, 3)[a]	5.67 *dd*(10, 3)	5.60 *dd*(10, 3)	97.0 *d*
17	1.12 *d*(6)	1.10 *d*(6)	1.12 *d*(6)	21.2 *q*
18	1.03 *d*(6)	1.05 *d*(6)	0.98 *d*(6)	11.0 *q*
19	1.50 *s*	1.50 *s*	1.42 *s*	12.3 *q*
30	1.38 *s*	1.38 *s*	1.30 *s*	19.2 *q*
2-OMe	3.58 *s*	3.60 *s*	3.52 *s*	54.9 *q*

Coupling constants (Hz) are in parentheses.

†‡The assignments of these signals may be reversed.

n.a. = Not assigned.

(–) = Overlapped signals.

[a] ^{1}H NMR chemical shifts of C-11 OH and C-16 OH are respectively at δ3.65(J = 11 Hz) and 3.02(J = 7 Hz).

increasing polarity yielded quassin (**6**) (33 g), neoquassin (**3**) (18 g), 4-OMe-5-OH-cantin-6-one (**7**), paraine (**4**) (12 g), isoparaine (**5**) (9 g) and the new dihydronorneoquassin (**1**) (9 g). The identifications of **3** and **6** were made by direct comparison with authentic samples.

11-Dihydro-12-norneoquassin (**1**). White prisms from MeOH, mp 227–9°. (Found: C, 66.77; H, 7.89. $C_{21}H_{30}O_6$ requires: C, 66.67; H, 7.93%). $[\alpha]_D^{20}$ + 21° (MeOH; *c* 0.19). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 and 3430 (–OH), 2960, 2940, 1730 (>C=O), 1690 (α,β-unsaturated >C=O), 1640 (olefinic unsaturation), 1395, 1380, 1350, 1260, 1240, 1200, 1180, 1130, 1100, 1050, 1000, 940, 845. UV $\lambda_{max}^{CH_3OH}$, nm: 268 (ε = 3180)., ^{1}H NMR (100 MHz, $CDCl_3$) see Table 1. ^{13}C NMR (20.15 MHz, pyridine-d_5) see Table 1. (For the assignments see refs [13, 14]). MS, *m/z* (rel. int.%): 378 (41) M^+, 360 (17) $M^+ - H_2O$, 332 (35), 318 (18), 165 (34), 154 (37), 153 (41), 152 (57), 12 (45).

Acetylation of compound **1**. A soln. of 11-dihydro-12-norneoquassin (**1**) (80 mg), pyridine (2 ml) and Ac_2O (0.5 ml) was kept at room temp. for 48 hr. Usual work-up gave a mixture of the mono- and di-OAc derivatives **2a** (25 mg) and **2b** (50 mg) which were easily separated by silica gel CC as white foam. If the reaction mixture was kept at room temp. for a week only the di-OAc derivative **2b** formed.

16-Acetoxy-11-dihydro-12-norneoquassin (**2a**). MS, *m/z*: 420 $[M]^+$. ^{1}H NMR (90 MHz, $CDCl_3$): see Table 1.

11,16-Diacetoxy-11-dihydro-12-norneoquassin (**2b**). White shining prisms from EtOAc, mp 230–232°. (Found: C, 64.86; H, 7.50. $C_{25}H_{34}O_8$ requires: C, 64.92; H, 7.41). MS *m/z*: 462 $[M]^+$. ^{1}H NMR (90 MHz, $CDCl_3$): see Table 1.

Oxidation of compound **1** by Ag_2O. A suspension of **1** (10 mg) in EtOH–H_2O (1/1) treated with Ag_2O was kept at 70° for 4 hr. After working up the crude product (20 mg) was crystallized from MeOH to afford colourless needles, mp 248–250, which were shown to be identical with paraine (**4**) [12] by IR, UV, ^{1}H NMR, and mass spectra.

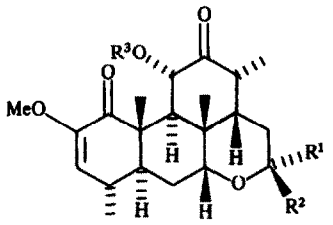
Oxidation of compound **1** *by* CrO_3 *and methylation to yield* **6**. Compound **1** (40 mg) was oxidized in Me_2CO by Jones reagent at room temp. The reaction yielded ~ 30 mg of crude mixture which was directly methylated by CH_2N_2 in the usual manner. After CC purification a pure product (20 mg) was recovered and identified as quassin (**6**) by direct comparison with an authentic sample.

Acetonylation of **1**: Compound **1** (30 mg) remained unreacted in Me_2CO in the dry $CuSO_4$ at reflux temp. for 2 weeks; about 25 mg of unreacted **1** were recovered.

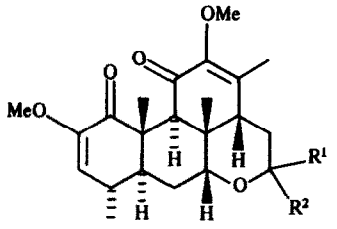
Paraine (**4**). White needles from MeOH, mp 245–246°. The spectral data were identical with those reported in the literature [12].

Isoparaine (**5**). White needles from MeOH, mp 259–261°. The spectral data were identical with those reported in the literature [12].

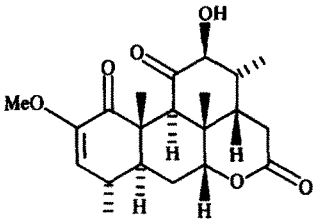
4-Methoxy-5-hydroxycantin-6-one (**7**) [4]. Yellow needles from MeOH, mp 232–235°. (Found: C, 67.72; H, 3.84; N, 10.38,



1 $R^1 = H$, $R^2 = OH$, $R^3 = H$
2a $R^1 = H$, $R^2 = OAc$, $R^3 = H$
2b $R^1 = H$, $R^2 = OAc$, $R^3 = Ac$
4 $R^1, R^2 = O$, $R^3 = H$



3 $R^1 = H$, $R^2 = OH$
6 $R^1, R^2 = O$



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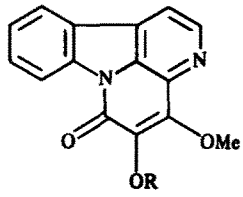

7 R = H
8 R = Me
9 R = Ac

Calc. for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.76; N, 10.52%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3405 (−OH), 2980, 1650 (α,β-unsaturated amide >C=O) 1620, 1580, 1560, 1470, 1400, 1325, 1315, 1295, 1270, 1145, 975. UV $\lambda_{max}^{CH_3OH}$, nm: 376, 359, 345, 298, 265, 249, 240, 231; (+NaOH): 421, 340, 328, 288, 258, 239, 233; (+HCl): 390, 373, 319, 310, 264, 252, 241, 235, 222, 216, 202. MS *m/z*: 266 $[M]^+$ (100%), 265, 251 $[M-Me]^+$, 248 $[M-H_2O]^+$, 237 $[M-CHO]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ4.40 (3H, *s*, 5-OMe), 7.45 (1H, *ddd*, J = 7.8, 7.8 and 1.8 Hz, 10-H), 7.63 (1H, *ddd*, J = 7.8, 7.8 and 1.8 Hz, 9-H), 7.76 (1H, *d*, J = 5.4 Hz, 1-H), 7.97 (1H, *d*, J = 7.8 Hz, 11-H), 8.39 (1H, *d*, J = 7.8 Hz, 8-H), 7.64 (1H, *d*, J = 5.4 Hz, 2-H). ^{13}C NMR (20.15 MHz, $CDCl_3$): δ157.0 (C-6), 144.8, 143.3, 140.3, 138.0, 134.0, 130.3, 125.4, 125.3, 124.8, 123.0, 115.8, 114.3, 60.8 (−OMe). The 4,5-dimethoxycantin-6-one (**8**) was obtained as described [8] and the spectral and physical-chemical properties proved to be identical to the data reported in the literature. The acetylderivative of **7**, 4-OMe-5-OAc-cantin-6-one, yellow needles from MeOH-H_2O, mp 199–200° (lit. [9] 190–192°).

Oxidation of **7** *by* $KMnO_4$. To soln of **7** (40 mg) in Me_2CO was added dropwise an aq. soln. of 5% $KMnO_4$ at room temp. After 1 hr of reaction, the work-up furnished 25 mg of 1-methoxycarbonyl-β-carboline [10], which was identical with a synthetic sample [11] thus confirming the proposed structure of 4-OMe-5-OH-cantin-6-one for **7**. ^1H NMR (90 MHz, $CDCl_3$): δ9.85 (1H, *br*, *s*, NH), 8.54 (1H, *d*, J = 6 Hz, 3-H), 8.10 (1H, *d*, J = 6 Hz, 4-H), 8.15 (1H, *m*, 8-H), 7.52 (2H, *m*, 5-H and 7-H), 7.25 (1H, *m*, 6-H) 4.12 (3H, *s*, −OMe).

Acknowledgements—This work was supported by the Ministero della Pubblica Istruzione of Italy. The authors are grateful to Dr Gatta, Istituto Superiore di Sanità, Rome, for supplying the synthetic sample of 1-methoxycarbonyl-β-carboline. Technical assistance given by Mr A. Rosini is also gratefully acknowledged.

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