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ON THE REDUCTION OF QUASSIN

PAOLO CECCHERELLI,*[a] MASSIMO CURINI,[b] MARCO DIAMANTINI,[a] MARIA CARLA MARCOTULLIO,[a] and GIULIANO GRANDOLINI.[b]

a) Istituto di Chimica Organica, Facoltà di Farmacia, Università di Perugia, Italy.
b) Istituto di Chimica Farmaceutica e Tecnica Farmaceutica, Università di Perugia, Italy.

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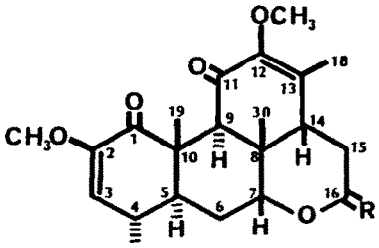
Abstract. The reduction of quassin (**1a**) with sodium borohydride in the presence of alkali was investigated. The process appeared to be regio- and stereo-selective leading to **2a**, which was utilized for the preparation of 2-epi-castelanolide-methylether (**4a**).

The structure of quassin, **1a**, the most famous member of the quassinoid family, was elucidated by Valenta[1], culminating a study started by Clark[2] on the isolated of Quassia wood. Despite the large amount of information accumulated defining most of the chemical properties of quassin, little is known on the reduction of this compound, except for its transformation into neoquassin, **1b**, by interaction with sodium borohydride or diisobuthyl-aluminium hydride.[3,4]

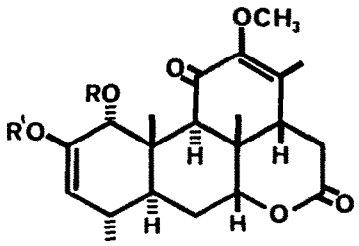
RESULTS and DISCUSSION

This report details attempts to achieve positional selectivity in the sodium borohydride reduction of the carbonyl groups of quassin, for the preparation of more complex quassinoids.[5] The carbonyl functions at C-1 and C-11 of **1a** proved to be unexpectedly inert toward sodium borohydride. When the reaction was carried out in the presence of aqueous base at 80°C and quenched with acetone prior to addition of acid, the C-1 carbonyl group was reduced. Competitive reduction of the C-11 carbonyl group and the lactone function was not observed under this conditions.[6] The reaction appeared to be completely steroselective and alcohol **2a** could be isolated in 50% yield after purification by silica gel chromatography. This compound was converted into monoacetate **2b** by treatment with acetic anhydride in pyridine. The ^{1}H NMR spectra of these products were in accord with the assigned structures, but not diagnostic for the C-1 stereochemistry. In the ^{13}C NMR spectra (Table) all carbon signals were nearly identical with those of quassin except for those of carbons 1, 2, 3, 5, 10. These shift alterations can be ascribed to the presence of an axially oriented hydroxyl group at C-1 which imposes a 1,3-diaxial interaction and hence a γ-effect on C-5 (up to 8 ppm). Surprisingly, carbon 9 is deshielded and this discrepancy may reflect subtle conformational modification of rings A and B perhaps due to a strong hydrogen bond between the alcohol function and the carbonyl group at C-11. The configuration at C-1 of **2a** was

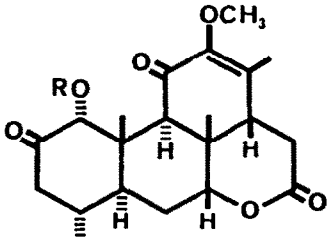
established by a NOE experiment, a strong enhancement of H-1 being observed upon irradiation of the C-10 methyl group. Unequivocal proof of the structure of 2a was obtained by single-crystal X-ray analysis of its acetate 2b (Figure).[7] In accord with literature reports on quassin[1], it could be predicted that the ring A enol ether of 2a should be hydrolyzed easily. The resultant product 2c probably existing as the more stable tautomer 3a, represents a potentially useful intermediate for the preparation of ring A substituted quassinoids. Treatment of alcohol 2a with



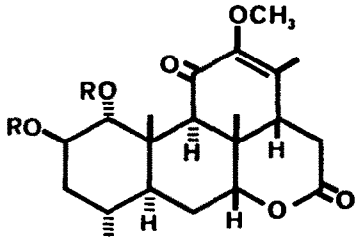
1a R = O
b R = H, OH



2a R = H R' = CH_3
b R = Ac R' = CH_3
c R = H R' = H



3a R = H
b R = Ac



4a R = H
b R = Ac

1N hydrochloric acid refluxing in ethanol led to keto alcohol 3a which on acetylation afforded the monoacetate 3b. Sodium borohydride reduction of ketoalcohol 3a gave diol 4a as the only product. The stereochemistry of this compound, expected to be as shown in 4a on the basis of approach of reducing agent from the less hindered side of the carbonyl group, was corroborated by the NMR spectra. Explicitly, the C-1 proton appeared at δ 4.48 as a doublet (J=3Hz) and the C-2 proton at δ 3.94 as a multiplet with very small coupling constants ($W_{1/2}$=6Hz), the C-1 and C-2 protons thus being diequatorially disposed. The ^{13}C NMR spectrum of 4a is in ful agreement with the predicted stereochemistry. Replacement of the C-2 carbonyl function of 3a with a β-axial hydroxy group (4a) induced characteristic shielding at C-4 (γ effect) and deshielding at C-19 (δ effect).It should be noted that the diol 4a has not been isolated to date and represents the C-2-epimer of natural castelanolide-methylether reported by Geissman.[8]

Table. ^{13}C NMR Data[a]

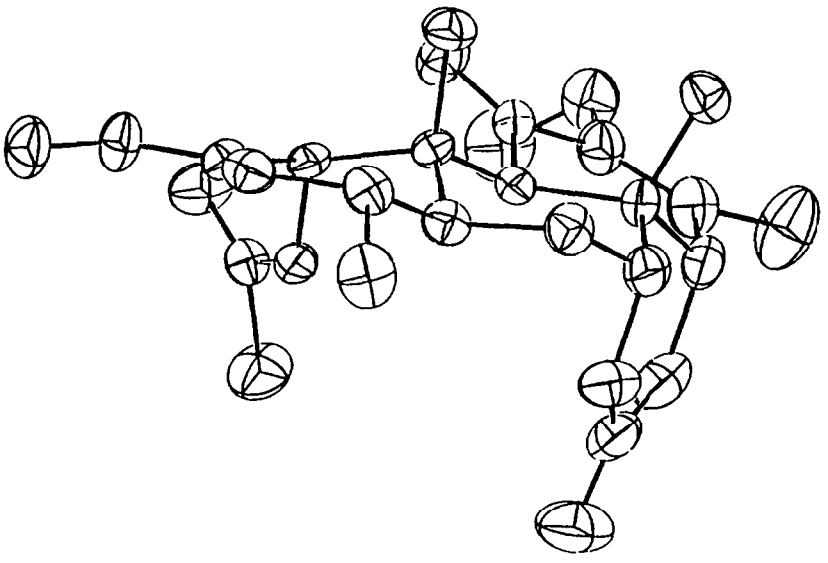
Carbon N°	1a	2a	2b	3a	3b	4a	4b
C(1)	197.5	71.8	73.3	77.3	80.2	74.2	73.4
C(2)	147.9	154.4	151.7	211.0	205.2	72.7	70.0
C(3)	116.3	101.4	103.2	44.9	45.3[d]	37.6	35.7
C(4)	30.7	30.6	31.9	31.0	32.1	25.2	25.0
C(5)	43.0	35.2	35.7	35.2	37.5	37.6	38.4
C(6)	25.4	26.4	26.2	25.0	25.7	26.0	25.6
C(7)	81.5	82.9	82.6	81.6	82.3	83.3	83.0
C(8)	36.7	36.8	37.3	36.5	37.1	37.0	37.5
C(9)	45.9[b]	47.1	46.5	44.4	46.5	47.7[e]	47.5[f]
C(10)	45.5	39.7	38.4	41.8	41.9	40.6	39.2
C(11)	190.7	194.0	191.9	193.2	191.8	195.2	192.3
C(12)	138.0	140.5	139.4	141.4	140.1	140.8	139.7
C(13)	147.6	148.2	147.9	147.3	148.0	148.5	148.3
C(14)	45.9[b]	47.5	45.4	45.2	46.0[d]	47.9[e]	47.2[f]
C(15)	31.2	31.5	30.5	30.9	31.5	31.4	31.9
C(16)	168.7	169.4	169.0[c]	168.8	168.8	169.5	169.3
C(18)	14.9	15.7	15.4	15.2	15.5	14.5	14.1
C(19)	12.3	13.5	13.1	12.8	12.7	15.7	15.6
C(30)	19.0	20.2	19.9	19.8	19.7	19.7	19.3
4-Me	21.8	22.7	22.2	21.8	22.6	23.7	23.5
2-OMe	54.6	54.3	54.3	-	-	-	-
12-OMe	58.9	59.8	59.6	59.2	59.6	60.0	59.5
1-OAc			168.9[c]-20.8		168.7-20.5		168.9[g]-20.5[h]
2-OAc							168.5[g]-21.3[h]

[a]The δ values are in parts per million downfield from Me_4Si.

[b-h]Signals within any vertical column may be reversed.

Figure

ORTEP stereoscopic projection of acetate 2b



EXPERIMENTAL

Melting points were taken on a Reichert micro hostage and are uncorrected. Elemental analyses were carried out on a Carlo Erba Model 1106 Elemental Analyzer. Proton NMR spectra were recorded at 90 MHz on a Varian EM390 instrument in $CDCl_3$ solutions (unless otherwise specified) using TMS as reference. Carbon-13 NMR spectra were recorded at 20.15 MHz on a Bruker WP80SY instrument, in the Fourier tranform mode with proton decoupling throughout, in $CDCl_3$ solutions (unless otherwise specified) using TMS as reference. Infrared spectra were obtained with a Perkin-Elmer 1320 spectrophotometer in $CHCl_3$ solutions. Column cromatography was carried out on 0.063-0.200 mesh Merck silica gel. All extracts were dried over Na_2SO_4.

1α-Hydroxy-2,12-methoxypicrasa-2,12-diene-11,16-dione, (2a). A solution of 100 mg (0.26 mmol) of quassin 1a in 4 ml of an aqueous solution of sodium hydroxide (10%) was treated with 300 mg of sodium borohydride (8 mmol) and the mixture stirred at 80°C. After 30 min. the reaction was cooled to room temperature. The reaction was quenched with acetone, acidified with 1% sulfuric acid to pH 2 and extracted with chloroform. The combined organic layers were washed with water, dried and evaporated under vacuum. Cromatography of the residue and elution with 99:1 chloroform-methanol gave 50 mg (50%) of alcohol 2a. m.p. ($CHCl_3$): 195-200°C; ^{1}H NMR δ 1.03 (d, 3, J=6Hz, C_4-Me), 1.10 (s, 3, C_{10}-Me), 1.23 (s, 3, C_8-Me), 1.5-2.4 (m, 4, H-5, H-6α, H-6β, H-15α), 1.88 (s, 3, C_{13}-Me), 2.6-3.2 (m, 3, H-4, H-14, H-15β) 3.38 (s, 1, H-9), 3.53 (s, 3, C_2-OMe), 3.60 (s, 3, C_{12}-OMe), 4.26 (m, 1, H-7), 4.50 (d, 1, J=3Hz, H-3), 4.55 (s, 1, H-1); Anal. Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.44. Found: C, 67.58; H, 7.61.

1α-Acetyloxy-2,12-methoxypicrasa-2,12-diene-11,16-dione, (2b). A solution of 50 mg of alcohol 2a and 1 ml of acetic anhydride in 3 ml of pyridine was kept at room temperature for 12 h. After the usual workup, the crude product, 60 mg, was chromatographed. Elution with 99:1 chloroform-methanol gave 48 mg (87%) of monoacetate 2b. m.p. (Et_2O): 215-219°C; ^{1}H NMR δ 1.08 (d, 3, J=6Hz, C_4-Me), 1.24 (s, 6, C_{10}-Me and C_8-Me), 1.6-3.2 (m, 7, H-4, H-5, H-6α, H-6β, H-14, H-15α, H-15β), 1.89 (s, 3, C_{13}-Me), 1.99 (s, 3, acetate), 2.82 (s, 1, H-9), 3.50 (s, 3, C_2-OMe), 3.58 (s, 3, C_{12}-OMe), 4.32 (m, 1, H-7), 4.60 (d, 1, J=3Hz, H-3), 5.83 (s, 1, H-1),; Anal. Calcd. for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.52; H, 7.51.

1α-Hydroxy-12-methoxypicrasa-12-ene-2,11,16-trione, (3a). A solution of N hydrochloric acid, 0.2 ml, was added to a stirring solution of 60 mg (0,15 mmol) of alcohol 2a in 2.5 ml of methanol and 1.1 ml of water and the solution refluxed for 1 h. The cooled mixture was poured into 10 ml of

water and extracted with chloroform. The extracted was washed with water, dried and evaporated under vacuum. Chromatography of the residue and elution with 99:1 chloroform-methanol gave 30 mg (52%) of alcohol **3a**. m.p. ($CHCl_3$): 242-247°C; ^1H NMR 1.00 (s, 3, C_{10}-Me), 1.00 (d, 3, J=6Hz, C_4-Me), 1.20 (s, 3, C_8-Me), 1.6-3.2 (m, 7, H-4, H-5, H-6α, H-6β, H-14, H-15α, H-15β), 1.87 (s, 3, C_{13}-Me), 3.30 (s, 1, H-9), 3.35 (s, 3, OMe), 4.25 (m, 1, H-7), 4.55 (s, 1, H-1). Anal. Calcd. for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50. Found C, 67.12; H, 7.46.

1α-Acetyloxy-12-methoxypicrasa-12-ene-2,11,16-trione, (**3b**). A solution of 25 mg of alcohol **3a** and 1 ml of acetic anhydride in 3 ml pyridine was kept at room temperature for 12 h. After the usual workup the crude product, 28 mg, was chromatographed. Elution with chloroform gave 22 mg (79%) of semisolid monoacetate **3b**. ^1H NMR δ 1.04 (d, 3, J=6Hz, C_4-Me), 1.14 (s, 3, C_{10}-Me), 1.28 (s, 3, C_8-Me), 1.6-3.3 (m, 7, H-4, H-5, H-6α, H-6β, H-14, H-15α, H-15β), 1.92 (s, 3, C_{13}-Me), 2.08 (s, 3, acetate), 2.92 (s, 1, H-9), 3.72 (s, 3, OMe), 4.40 (m, 1, H-7), 5.55 (s, 1, H-1). Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 66.12; H; 7.15.

1α,2β-Dihydroxy-12-methoxypicrasa-12-ene-11,16-dione, (**4a**). A solution of 70 mg (0.2 mmol) of alcohol **3a** in 3 ml of an aqueous solution of sodium hydroxide (10%) was treated with 200 mg of sodium borohydride (5 mmol) and the mixture stirred at room temperature for 30 min. Then the reaction was quenched with acetone, acidified with 1% sulfuric acid to pH 2 and extracted with chloroform. The combined organic layers were washed with water, dried and evaporated under vacuum. Chromatography of the residue and elution with 95:5 chloroform-methanol gave 35 mg (52%) of diol **4a**. m.p. ($CHCl_3$): 292-298°C; ^1H NMR δ 0.90 (d, 3, J=6Hz, C_4-Me), 1.25 (s, 3, C_{10}-Me), 1.33 (s, 3, C_8-Me), 1.5-2.9 (m, 9, H-3 , H-3 , H-4, H-5, H-6α, H-6β, H-14, H-15α, H-15β), 1.90 (s, 3, C_{13}-Me), 3.25 (s, 1, H-9), 3.60 (s, 3, OMe), 3.94 (m, 1, H-2), 4.25 (m, 1, H-7), 4.48 (d, 1, J=3Hz, H-1). Anal. Calcd. for $C_{21}H_{30}O_6$: C, 66.64; H, 7.99. Found: C, 66.52; H, 8.08.

1α,2β-Diacetyloxy-12-methoxypicrasa-12-ene-11,16-dione, (**4b**). A solution of 20 mg of alcohol **4a** and 1 ml of acetic anhydride in 3 ml of pyridine was kept at room temperature for 12 h. After the usual workup the crude product, 25 mg, was chromatographed. Elution with chloroform gave 13 mg (81%) of semisolid diacetate **4b**. ^1H NMR δ 0.90 (d, 3, J=6Hz, C_4-Me), 1.28 (s, 3, C_8-Me), 1.42 (s, 3, C_{10}-Me), 1.5-3.1 (m, 9, H-3 , H-3 , H-4, H-5, H-6α, H-6β, H-14, H-15α, H-15β), 1.90 (s, 3, C_{13}-Me), 1.98 (s, 3, C_2-acetate), 2.08(s, 3, C_1-acetate), 3.60 (s, 3, OMe), 4.29 (m, 1, H-7), 4.96 (m, 1, H-2), 5.64 (d, 1, J=3Hz,H-1). Anal. Calcd. for $C_{25}H_{34}O_8$: C, 64.92; H, 7.41. Found: C, 65.02; H, 7.34.

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4) Hemiacetal **1b** exists as a pair of isomers at C-16: the ^1H and ^{13}C NMR indicate a mixture 60:40 of 16-α-hydroxy (^1H NMR: δ 5.24,bm,1,H-16; ^{13}C NMR: δ 91.0,d,C-16) and 16-β-hydroxy (^1H NMR: δ 4.75,dd,1,J=3,9Hz; ^{13}C NMR: δ 95.6,d,C-16) respectively.

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7) Compound **2b** crystallizes in space group $P2_12_12_1$ with cell dimensions of a=17.279(3)Å, b=15.837(3)Å, c=8.160(3)Å, V=2232.96Å^3, D_{calcd}=1.286 g cm^{-3} (for Z=4). A total of 1860 reflections were measured, of which 1124 with $I>3\sigma(I)$ were considered as 'observed' and retained for calculations. The structure was solved by direct methods using the SIR package[10] and refined by full-matrix least-squares method with anisotropic temperature factors for all non-hydrogen atoms. The contribution of hydrogen atoms at computed positions was included. The final residuals are R(F)=0.0442 and R_w(F)=0.0473. (For experimental methods and data reduction details see: M. C. Burla and G. Polidori, Acta Cryst., submitted).

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