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A CYCLOHEXADIENONE AND A CYCLOHEXENONE FROM *HALLERIA LUCIDA*

I MESSANA, M SPERANDEI*, G MULTARI*, C GALEFFI* and G B MARINI BETTOLO

Centro CNR di Chimica dei Recettori e delle Molecole Biologicamente Attive, Istituto di Chimica, Università Cattolica del Sacro Cuore, I go Francesco Vito 1, 00168 Roma, Italy and Dipartimento di Biologia Vegetale, Università di Roma 'La Sapienza', *Laboratorio di Chimica del Farmaco, Istituto Superiore di Sanità, v le Regina Elena 299, 00161 Roma, Italy

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Key Word Index—*Halleria lucida*, Scrophulariaceae cyclohexanones, ^{13}C NMR

Abstract—Two new compounds, a cyclohexadienone, hallerone and a cyclohexenone, halleridone, were isolated from *Halleria lucida* Their structures were established on the basis of spectroscopic data and by chemical behaviour Hallerone was converted into halleridone

INTRODUCTION

Halleria lucida L is utilized for magic purposes (against evil, wizards and bad weather) and in folk medicine in Southern Africa Its dried leaves were moistened with water by the Zulu, and the juice is put into the ear for the relief of earache [1]

The genus *Halleria* has never been phytochemically examined hitherto As a part of our investigations on African medicinal plants, we now report the isolation from the leaves of *H lucida* of two new compounds, a cyclohexadienone, hallerone (**1**) and a cyclohexenone, halleridone (**2**)

RESULTS AND DISCUSSION

Substance **1** (0 16% of the leaves) was obtained as a runny oil Its molecular formula was $C_{10}H_{12}O_4$ and it showed a UV maximum (MeOH) at 231 nm (log ε 3 92) and IR bands ($CHCl_3$) at 3400, 1730 and 1670 cm^{-1} A cyclohexan-2,5-dienone structure was indicated for **1** on the basis of the aforementioned data and the ^1H NMR signals ($CDCl_3$) at δ6 17 (2H, *d*, J = 10 Hz, H-2 and H-6) and at 6 97 (2H, *d*, J = 10 Hz, H-3 and H-5)

A hydroxyl group (δ4 25, *s* (*br*), exchangeable with D_2O) and the sequence $-CH_2-CH_2OAc$, deduced from the NMR signals at δ2 14 (2H, *t*, J = 6 Hz, H_2-1′), 4 17 (2H, *t*, J = 6 Hz, H_2-2′) and 2 03 (3H, *s*, Ac), were located on C-4 Taken together these data are in agreement with structure **1** In agreement with the presence of a free hydroxyl group hallerone was readily acetylated with pyridine and acetic anhydride to give the acetyl derivative $C_{12}H_{14}O_5$ (**3**) That acetylation of the tertiary alcoholic group had occurred was confirmed by the downfield shift of C-4 ($\Delta\delta$6 8 ppm) and the upfield shift of C-3 and C-5 ($\Delta\delta$3 9 ppm) on comparison of the ^{13}C NMR spectra of **3** and **1** (see Table 1) The mass spectra of **1** and **3** did not contain parent peaks due to the easy loss of 42 amu (ketene) from the acetyl group of the primary alcohol

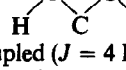
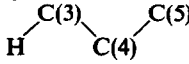
Halleridone (**2**) (0 26% of the leaves) was a runny oil Its molecular formula was $C_8H_{10}O_3$, $[M]^+$ at m/z 154 (9%), and it had a UV maximum (MeOH) at 234 nm (log ε3 37) and IR bands ($CHCl_3$) at 3400 and 1670 cm^{-1} In contrast to hallerone the ^1H NMR spectrum of halleridone showed only two olefinic protons mutually coupled (J = 10 Hz) at δ6 02 and 6 86 (H-6 and H-5, respectively) The latter signal showed an additional long-range W coupling (CH–C–CH, J = 1 5 Hz), which was confined to a planar zig-zag configuration  , with H-3 (δ4 28, *dt*) which was further coupled (J = 4 Hz) with two hydrogens at C-2 (δ2 70, *m*). As in hallerone the quaternary C-4 bears a hydroxyl group and the sequence $-CH_2-CH_2O-$[δ2 30, *t*(*br*), J = 7 Hz, H_2-1′ and 3 96, *t*(*br*), H_2-2′] which was cyclized onto C-3 giving rise to a tetrahydrofuran ring The structure **2** for halleridone was thus assigned unambiguously

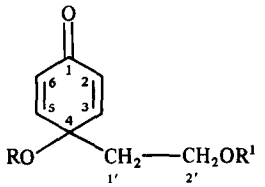
Table 1 ^{13}C NMR chemical shift assignments for **1**–**4** (25 2 MHz, $CDCl_3$, TMS as int standard)

C	1	2	3	4
1	185 5	197 7	184 3	195 4
2	127 4	39 2*	128 2	39 6
3	151 4	80 8	147 5	79 5
4	68 0	74 7	74 8	80 7
5	151 4	149 2	147 5	144 1
6	127 4	127 6	128 2	129 0
1′	38 8	39 7*	38 0	38 6
2′	59 6	65 9	58 7	65.5
$COCH_3$	20 8		20 4, 20 8	21 1
$\underline{C}OCH_3$	170 7		168 6, 169 9	169 7

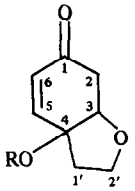
*These signals may be reversed

As in hallerone acetylation of the tertiary hydroxyl group of halleridone to give **4**, $C_{10}H_{12}O_4$ ($[M]^+$ at m/z 196, 5%), shifted the signal of C-4 downfield ($\Delta\delta$6 0 ppm) and the signal of β carbons C-3, C-5 and C-1′ upfield (see Table 1)

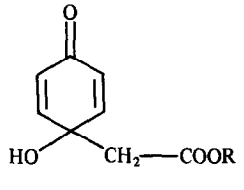
The strain of the Dreiding model, and much more so the planarity of the sequence  , rules out the possibility of the *trans* junction between the two rings in **2** Moreover, the lack of significant rotatory power of **2**



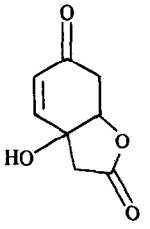
	R	R^1
1	H	Ac
3	Ac	Ac
5	H	H
6	H	β–D–glucopyranosyl



	R
2	H
4	Ac



	R
7	Me
9	Et
10	H



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and **4** in different solvents shows that halleridone is a racemic mixture of the *cis* form This suggests that **2**, whose presence in the original source has been confirmed, may be formed by the non stereospecific cyclization of **5**

On alkaline hydrolysis **1** was directly converted into **2** The latter, in turn, by reaction with semicarbazide hydrochloride and sodium acetate gave the corresponding semicarbazone ($C_9H_{11}N_3O_2$, mp 125–126°) with simultaneous dehydration between the tertiary hydroxyl group and H-3

Hallerone and halleridone represent two new cyclohexenones with a quinol structure Although described, natural cyclohexadienones and cyclohexadienols [2] are so far rather rare in the literature The β-glucoside of **5** (**6**) has been isolated from the leaves of *Cornus femina* Miller (Cornaceae) [3] After enzymic hydrolysis **5** was not isolated but was transformed into the corresponding diacetate **3** Another similar quinol, which by rearrangement has biogenetic potential for the formation of aromatic rings, is jacaranone **7**, a methyl ester isolated by Ogura *et al* from leaves and branches of *Jacaranda caucana* Pittier (Bignoniaceae) [4] which displays cytotoxic and antitumour activities and which occurs also in other *Jacaranda* species [5] Closely related to halleridone (**2**) is lactone **8**, patented for its anti-ulcer activity [6], which was obtained by acidic hydrolysis of the synthetically prepared ester **9** It was also obtained by acidic hydrolysis of an unusual mixture of esters, resulting from two or three residues of the corresponding acid of **9**, **10**, on positions 2, 3, 4 or 6 of glucose, isolated from *Senecio ambavilla* (Compositae) [7]

The presence of these cyclohexanones and related quinols in the metabolism of plants of different families (Cornaceae, Scrophulariaceae, Bignoniaceae, Compositae) indicates that these products may not be specific secondary metabolites but may represent an aspect of primary metabolism connected with the prephenic–shikimic–chorismic acids route as evidenced by the close structural similarity of these products with prephenic acid

EXPERIMENTAL

^1H and ^{13}C NMR $CDCl_3$, TMS as internal reference, separations were monitored by TLC on silica gel F_{254} (eluent EtOAc) The spots were detected by spraying with anisaldehyde–H_2SO_4 reagent

Plant material Leaves of *Halleria lucida* L were collected in the Botanical Garden of Rome in June 1983

Extraction and separation The fresh leaves of *H lucida* (420 g) were ground and extracted (× 3) with EtOAc The residue, after evaporation under vacuum, amounted to 19 g A portion (7 g) of the residue was submitted to counter-current distribution in a Craig Post apparatus (10 10 ml, upper and lower phase) using the solvent system H_2O–EtOH–EtOAc–cyclohexane (5 2 5 2) Two main substances were obtained hallerone (**1**) (K_r = 0 55, 252 mg, 0 16% of the starting material) and halleridone (**2**) (K_r = 0 25, 400 mg, 0 26%)

Hallerone (**1**) Oil (Found C, 60 88, H, 6 22 $C_{10}H_{12}O_4$ requires C, 61 21, H, 6 17%) UV λ_{max}^{MeOH} 231 nm (log ε 3 92), IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3400, 1730 and 1670, ^1H NMR see text, MS *m/z* (rel int) 154 (8), 136 (47), 110 (46), 109 (89), 88 (99), 43 (100)

Acetylation of **1** Compound **1** was acetylated with Ac_2O–C_5H_5N at room temp overnight After evaporation of the reagents under vacuum and CCD of the residue between H_2O–EtOH–EtOAc–cyclohexane (5 2 3 4) **3** (K_r = 0 7) was obtained Oil UV and ^1H NMR data in agreement with those reported in literature [3] MS *m/z* (rel int) 196 (24), 154 (43), 137 (56), 136 (100), 123 (36), 119 (85), 110 (66), 108 (95), 43 (100)

Halleridone (**2**) Oil (Found C, 61 95, H, 6 60 $C_8H_{10}O_3$ requires C, 62 32, H, 6 54%) UV λ_{max}^{MeOH} 234 nm (log ε 3 37), IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3400 and 1670, ^1H NMR δ 2 30 (2H, *t(br)*, *J*

= 7 Hz, H_2-1'), 2 70 (2H, *m*, J_{gem} = 16 Hz and J_{2-3} = 4 Hz, H_2-2), 3 96 (2H, *t*(*br*), H_2-2'), 4 28 (1H, *dt*, J_{3-5} = 1 5 Hz, H-3), 6 02 (1H, *d*, *J* = 10 Hz, H-6), 6 86 (1H, *dd*, H-5), MS *m/z* (rel int) 154 $[M]^+$ (9), 112 (33), 110 (81), 82 (100), 68 (53), 54 (40) *Semicarbazone of* **2**, *with simultaneous dehydration* Orange crystals from H_2O, mp 125–126° (Found C, 56 17, H, 5 82, N, 21 70 $C_9H_{11}N_3O_2$ requires C, 55 95, H, 5 74, N, 21 75%) ^{1}H NMR (CD_3OD) δ2 94 (2H, *t*(*br*), *J* = 7 Hz, H_2-1'), 3 32 (2H, *s*(*br*), H_2-2), 3 84 (2H, *t*(*br*), H_2-2'), 6 54 (1H, *d*, *J* = 8 Hz, H-6), 6 98 (1H, *d*, H-5)

Acetylation of **2** Compound **2** was acetylated as reported for **1** After CCD of the residue between H_2O–EtOH–EtOAc–cyclohexane (5 2 4 3) an oily compound was obtained (K_r = 0 6) (Found C, 61 07, H, 6 26 $C_{10}H_{12}O_4$ requires C, 61 21, H, 6 17%) IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1740 and 1680, ^{1}H NMR δ2 10 (3H, *s*, Ac), 2 45 (2H, *t*, *J* = 7 Hz, H_2-1'), 2 80 (2H, *m*, J_{gem} = 16 Hz and J_{2-3} = 4 Hz, H_2-2), 3 90 (2H, *t*, H_2-2'), 4 36 (1H, *dt*, J_{3-5} = 1 5 Hz, H-3), 6 00 (1H, *d*, *J* = 10 Hz, H-6), 6 92 (1H, *dd*, H-5), MS *m/z* (rel int) 196 $[M]^+$ (5), 154 (17), 136 (100), 124 (18), 119 (21), 108 (32), 43 (100)

Conversion of **1** *into* **2** Compound **1** (50 mg) was dissolved in 0 1 M aq Na_2CO_3 (5 ml) at room temp Next day the soln was extracted with $CHCl_3$ and the residue of the organic phase was submitted to CCD as for **2** The compound was identified as **2** by direct comparison

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