142. Structural Modifications of Chaparrinone Using Benzeneseleninic Anhydride

Preliminary Communication

by **Nguyên Khôi** and **Judith Polonsky**

Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France

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Summary

Treatment of chaparrinone triacetate with benzeneseleninic anhydride afforded in addition to the $\Delta^{14,15}$-dehydro compound two products arising from angular hydroxylation at C(5). The mechanism of this reaction is discussed. The corresponding deacetylated compounds do not display significant antineoplastic activity.

Part of our continuing work on the quassinoids [1], the *Simaroubaceae* bitter principles, has been concerned with the preparation of antineoplastic quassinoids (or quassinoid analogues of interest for biological evaluation) from inactive but relatively abundant precursors.

Previous studies [2] of structure/activity relationships for several quassinoids have established some of the structural requirements for *in vivo* antileukaemic activity against the murine lymphocytic leukemia P-388. Among them are the following: a Δ^3-oxo moiety in ring A (as in chaparrinone **1**), an epoxymethano bridge between C(8) and C(11) and an ester group at C(15) and/or at C(6). Thus, chaparrinone **1** [3], which possesses these structural features but lacks an ester side chain, does not display any significant antineoplastic activity [4].

In our search for direct methods of quassinoid functionalization we were attracted by benzeneseleninic anhydride in the hope of introducing an additional degree of unsaturation in ring D of chaparrinone. The versatility of benzeneseleninic anhydride has been demonstrated by *Barton et al.:* Thus, among the wide variety of reactions due to this reagent one can cite *ortho*-hydroxylation of phenols [5], oxidation of a number of alicyclic alcohols to carbonyl derivatives and oxidation of enolisable ketones to enones [6].

We herein report that chaparrinone triacetate (**2**) [3] upon exposure to benzeneseleninic anhydride afforded in addition to the $\Delta^{14,15}$-dehydro compound **3** two products (**4** and **5**) arising from angular hydroxylation at C(5) *(Scheme 1)*.

A solution of chaparrinone triacetate ($C_{26}H_{32}O_{10}$, **2**) (0.5 mmol) in chlorobenzene was heated with benzeneseleninic anhydride (0.75 mmol) at 125° for 4 h. The reaction was monitored by TLC. revealing the nearly simultaneous appearance

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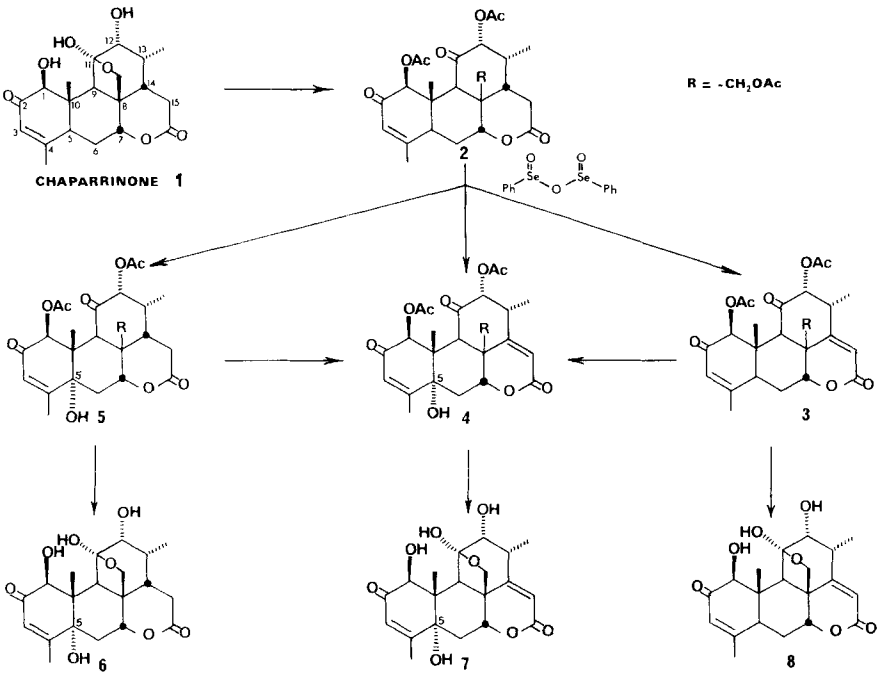
of three products in addition to the starting material. Preparative TLC. (silica gel, $CHCl_3$/MeOH 97:3) of the reaction mixture afforded in order of increasing polarity compounds **3**, **2**, **4** and **5**, in 19, 13, 16 and 20% yield, respectively *(Scheme 1)*.

Scheme 1



$\Delta^{14,15}$-Dehydro chaparrinone triacetate (**3**) ($C_{26}H_{30}O_{10}$, MS.: M^+ 502). Double m.p. 185° and 230–231°, $[\alpha]_D^{22} = -19°$ ($c = 0.96$, $CHCl_3$). The UV. spectrum showed a maximum at 228 nm ($\log\varepsilon = 3.93$) due to both the α,β-unsaturated ketone and the α,β-unsaturated lactone moieties. The structure of **3** was further supported by its ^{1}H-NMR. spectrum *(Table 1)* which was very similar to that of chaparrinone triacetate (**2**). A downfield signal (1 H) at δ 5.90 was assigned to H–C(15); the H_3C(13) is slightly deshielded.

$\Delta^{14,15}$-Dehydro-5α-hydroxy-chaparrinone triacetate (**4**) ($C_{26}H_{30}O_{11}$, MS.: M^+ 518). M.p. 265–268°, $[\alpha]_D^{22} = -33.6°$ ($c = 1.0$, $CHCl_3$). The UV. spectrum showed a maximum at 224 nm (log4.36) and the IR. spectrum showed OH-absorption (3490 cm^{-1}). These data suggested that **4** differs from **3** by an additional OH-group. The 250-MHz-^{1}H-NMR. spectrum *(Table 1, Fig. 1)* of **4** gave a substantial amount of structural information. It was ascertained that the OH-function in **4** is located at C(5) and is axial. A signal (1 H, exchangeable with D_2O) at δ 3.72 is due to the OH-group and the expected signals are found for the H_3C-groups and for the protons H–C(1), H–C(3) and H–C(15). Double resonance experiments identified most of the other signals and in particular those due to the 2 H–C(6). These give rise to two double doublets (centered at δ 2.41) which collapse to a clear *AB*-quartet (*Fig.*, part A) upon irradiation of the signal assigned to H–C(7) (δ 4.78). The α-configuration of the OH at C(5) was indicated by the pronounced downfield shifts of H–C(1) and H–C(9) with respect to those of chaparrinone triacetate (**2**) (1,3 diaxial to OH). The *trans* fusion of rings A/B in **4** was further substantiated by its circular dichroism curve ($\lambda_{max} = 337$ nm; $\Delta_\varepsilon = +0.6$, dioxane) with a *Cotton* effect similar to that of chaparrinone triacetate.

Table 1. *^{1}H-NMR. spectra of compounds* **2–5** *in $CDCl_3$ solution and of* **6–8** *in solution $CDCl_3$/pyridine-d_5 95:5*[a])

	2	**3**	**4**	**5**	**6**	**7**	**8**
H–C(1)	5.07	4.97	5.91	5.93	4.05	5.11	5.07
H–C(3)	5.92	5.87	6.03	5.93	6.14	6.00	6.04
H–C(6)			2.47 *d*×*d* (16; 2.3)	2.42 *d*×*d* (~ 13)		2.47 *d*×*d* (16; 2.4)	2.14 *d*×*d* (16; 2.3)
			2.35 *d*×*d* (16; 3.4)	2.33 *d*×*d* (~ 13)		2.32 *d*×*d* (16; 3.7)	2.36 *d*×*d* (16; 3.6)
H–C(7)	4.50 *t*	4.57 *t* (3)	4.78 *d* (2.6)	4.66 *t*-like	4.45 *t* (2.7)	4.55 *d* (2.6)	4.46 *t* (2.3)
H–C(9)	3.37	3.26	4.04	4.26	2.76	3.42	3.41
H–C(12)	4.87 *d* (3)	4.90 *d* (2.6)	5.03 *d* (3.4)	5.00 *d* (3)	3.86 *d* (5.5)	3.96 *d* (4.4)	3.62 *d* (4.5)
CH_2O	3.82 *d* (13)	3.87 *d* (12)	4.01 *d* (13)	3.90 *d* (12)	3.75 *d* (9.1)	3.45 *d* (9.1)	3.73 *d* (8.3)
	4.52 *d*	4.60 *d*	4.51 *d*	4.36 *d*	3.88*d*	3.83 *d*	3.95*d* (10)
H–C(15)		5.90	5.91		5.78 *d* (2.1)	5.81 *d* (2)	
H_3C(4)	1.95	1.97	2.07	2.00	2.05	2.00	1.98
H_3C(10)	1.41	1.31	1.40	1.46	1.27	1.46	1.34
H_3C(13)	1.05 *d* (7)	1.19 *d* (7)	1.21 *d* (7)	1.08 *d* (6.5)	1.23 *d* (7)	1.25 *d* (6.5)	1.06 *d* (6.8)
CH_3COO	2.00	1.97	2.09	2.00			
	2.12	2.02	2.09	2.12			
	2.08	2.06	2.15	2.18			

[a]) Spectra were recorded at 250 MHz, except those of **3** and **5** at 60 MHz. Chemical shifts in ppm, coupling constants in Hz.

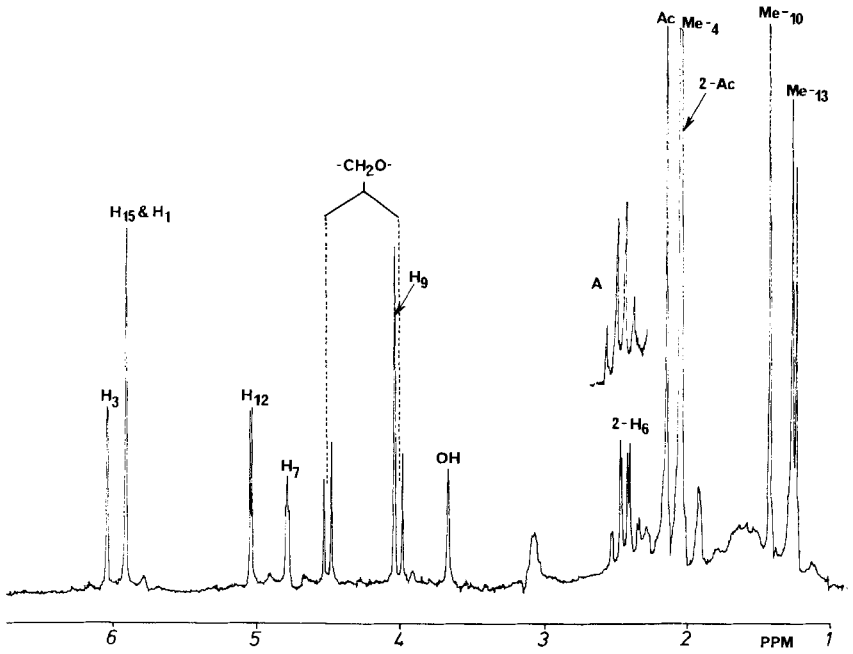
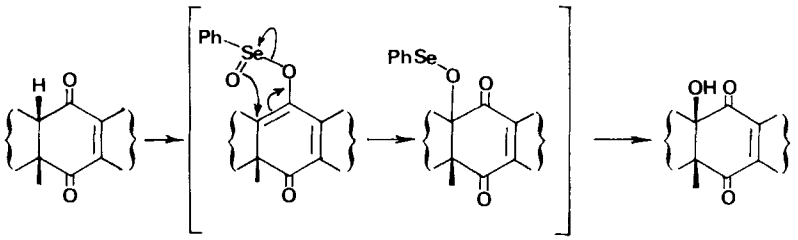


Figure. *250-MHz-^{1}H-NMR. spectrum of $\Delta^{14,15}$-dehydro-5α-hydroxychaparrinone triacetate* (**4**)

5α-Hydroxy-chaparrinone triacetate (**5**) ($C_{26}H_{32}O_{11}$, MS.: M^+ 520). M.p. 258–259°, $[\alpha]_D^{22} - 25.9°$ ($c = 0.11$, $CHCl_3$). – UV.: $\lambda_{max} = 237$ nm ($\log\varepsilon$ 3.87). The ^{1}H-NMR. spectrum supports fully structure **5** and shows in particular the double doublets centered at 2.37 assigned to the 2 H–C(6) and the H–C(1) and H–C(9) which are deshielded with respect to chaparrinone triacetate (**2**).

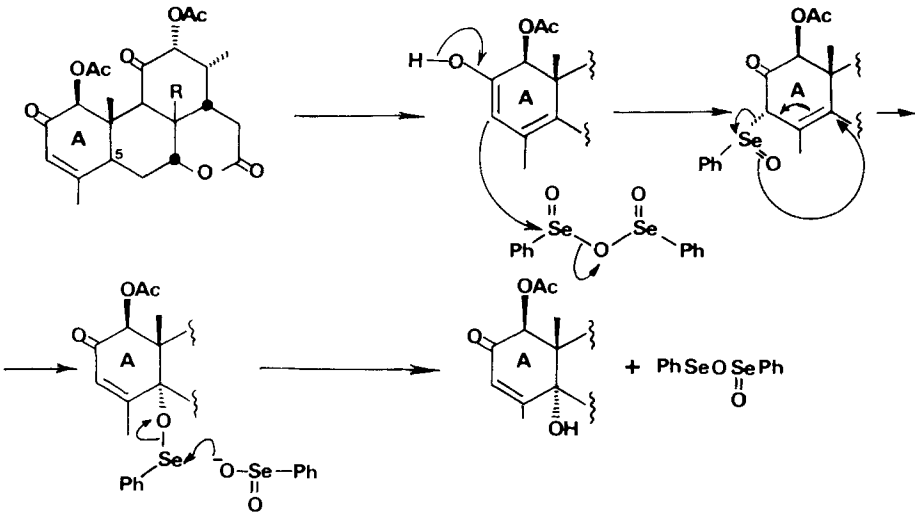
Further oxidation of **5** as well as of **3** with benzeneselininic anhydride afforded $\Delta^{14,15}$-Dehydro-5-hydroxy-chaparrinone triacetate (**4**).

Introduction of a double bond *α* to an enolisable lactone group with benzeneselininic anhydride was expected, although only one example has so far been reported [7]. As far as the angular hydroxylation is concerned, a recent publication by *Yamakawa et al.* [8] reported the introduction of a OH-group into the angular position of some tricyclic ketones (such as 3,3-ethylenedioxy-6,9-dioxofuranoeremophilane). The following mechanism was proposed for these sterically hindered ketones.



The 3-keto group in chaparrinone triacetate (**2**) is relatively unhindered and the attack by the anhydride on the enol should occur at the C- and not at the O-atom [6]. The mechanism outlined in *Scheme 2* seems therefore most likely; it explains both the position and the configuration of the introduced OH-group.

Scheme 2



Treatment of compounds **3**, **4** and **5** with methanolic ammonia and purification by preparative TLC. afforded the corresponding deacetylated products whose structures were confirmed by mass and ^{1}H-NMR. spectra.

$\Delta^{14,15}$-Dehydro-chapparrinone (**6**, $C_{20}H_{24}O_7$, MS.: M^+ 376). M.p. 239–242°. Its ^{1}H-NMR. spectrum *(Table 1)* shows one downfield signal at δ 5.78 assigned to H–C(15) with long-range allylic coupling with H–C(13).

$\Delta^{14,15}$-Dehydro-5-hydroxy-chaparrinone (**7**, $C_{20}H_{24}O_8$, MS.: M^+ 392). Decomposes above 250°. The 250-MHz-^{1}H-NMR. spectrum *(Table 1)* reveals the expected signals for most of the protons and shows the HO-resonance superimposed on that of H–C(9) (δ 3.42). The circular dichroism curve of **7** was very similar to that of chaparrinone (**1**) (λ_{max} = 323 nm, $\Delta\varepsilon$ = +2.6, in dioxane) thus proving that no isomerization occured during deacetylation.

5-Hydroxy-chaparrinone (**8**, $C_{20}H_{26}O_8$, MS.: M^+ 394). M.p. 233–237°. The ^{1}H-NMR. data *(Table 1)* support its structure.

The deacetylated compounds **6**, **7** and **8** did not display significant *in vitro* cytotoxic activity against the murine lymphocytic cell line P-388. Other chemical modifications of chaparrinone, and in particular the introduction of an ester chain at C(15) and/or at C(6) may be necessary to confer antineoplastic activity to this molecule.

It is interesting to note that the first two natural $\Delta^{14,15}$-unsaturated quassinoids have been isolated only recently [9] [10].

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