#### **CYAN EXHIBIT 1002**

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6		to obtain
7		A PHYSICAL SCIENCES DOCTORATE
8		by
9		Rene GRANGAUD
10		Specialist Assistant Professor at the Algeria Faculty of Medicine and Pharmacy
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14		1 <sup>st</sup> THESIS – Research on Astaxanthin, a New Vitamin A Factor
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16		2 <sup>nd</sup> THESIS – proposals given by the school
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19		
20		Mr. CORDIERPresident
21		Mr. BERNARDExaminer
22		Mr. MEUNIERExaminer
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1 2 Chapter I 3 4 5 THE CONSTITUTION, CHEMICAL AND PHYSICAL PROPERTIES OF ASTACINE, ASTAXANTHIN AND THEIR 6 DERIVATIVES 7 8 A. - ASTACINE AND ITS DERIVATIVES 9 10 The carotenoid nature of astacine and the presence of oxygen in each of the  $\beta$ -ionone cores have been 11 recognized by Kuhn and Lederer (45). 12 13 In 1934, P. Karrer and colleagues (38) established the general formula,  $C_{40}H_{48}O_4$  and the constitution of the 14 pigment which is that of a  $\beta$ -carotene-tetrone. This constitution was deduced from the general formula and 15 oxygen group properties. Astacine, in fact, provides a dioxin with 4 active hydrogen atoms, two of which belong to oxime radicals, while the other two are fixed to two enolized carbonyls. The carotenoid has, 16 17 therefore, 4 ketonic groups which are not equivalent. Ortho-phenylenediamine reacts and creates bis-18 phenazine astacine which indicates that each  $\beta$ -ionone core encloses two carbonyl groups. Oxidation with 19 permanganate yields malonic dimethyl acid and oxidation of the diphenazine derivative leads to  $\alpha$ - $\alpha$ -dimethyl-20 succinate which establishes that the carbonyl groups occupy the 3, 4, 3', 4' positions. The formula for the 21 constitution of astacine is, therefore, as follows:

22 23



- 1 However, catalytic microhydrogenation reveals that there are not 11 but 13 double bonds. The extra two
- 2 double bonds establish the possibility of the enolic form represented by the following diagram:



4 5 6

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11

14



#### Astacine (enolic form)

8 In reality, free astacine is only very slightly enolized as demonstrated by the slow etherification speed with
9 diazo-methane and the determination of mobile hydrogens (Zerewitinoff). Astacine's acidic nature disappears
10 after hydrogenation.

Astacine crystallizes from a mix of pyridine and water into purple needles with metallic reflection which melt
at 228°C (Kuhn, Stene and Sorensen (48) (<sup>1</sup>).

Astacine is insoluble in water, is very difficult to dissolve in ether, petroleum ether or methane, is difficult to dissolve in benzene, ethyl acetate and acetic acid, is relatively easy to dissolve in carbon sulfur and is very easy to dissolve chloroform, pyridine (blood-red concentrated solution, diluted orangey solution) and dioxane.

18 19 When the solution is agitated in petroleum ether with 90% methanol, astacine transforms into the hydro-20 alcoholic phase but after dilution with water, the pigment is easily dissolved in petroleum ether. In contrast, it 21 remains in the aqueous phase if the latter is diluted with sodium or potassium after which it manifests its 22 acidic nature. After cooling, the pigment separates from the alkaline solution in the form of red flakes which 23 gather at the interphase. Acidification by acetic acid transforms the amorphous salt into shiny purple crystals 24 of free astacine.

Astacine dissolved in a mix of benzene and ligroin is absorbed rapidly in calcium carbonate. It is also absorbed in aluminum oxide from a benzene-ligroin or petroleum ether solution: it forms a purple area on the upper part of the column. The eluents are benzene and pyridine diluted with methanol as well as petroleum ether

- diluted with 5% potassium.
- 30

31 (1) Other possible temperatures are 240 - 243° C (Kuhn and Lederer [45]) and 241°C (Karrer and Benz [36]).

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The absorption spectrum of astacine is characteristic and present in a large band with a single peak (500 nm in pyridine and 510 nm in carbon-sulfur). The absorption spectrum and the pigment's behavior vis-à-vis sodium are the two main characteristics which identify it. Other, less specific, characteristics: in concentrated sulfuric acid, astacine dissolves into a deep blue color. The chloroform solution turns a blue-green color when diluted with antimony trichloride (R. de Carr and Price).

6 7 8

Astacine is very resistant to oxidation in air. Kuhn, Lederer and Deutsch (46) have obtained astacine diacetate. Dipalmitate (astacene) has also been produced (Kuhn and colleagues [48]).

10 B. – Astaxanthin and its Derivatives

11

9

12Kuhn and Sorensen (47) established that astaxanthin has four more hydrogen atoms than does astacine and13has a general formula of  $C_{40}H5_2O_4$ . In an alkaline solution in the presence of air, they have demonstrated that14astaxanthin transforms into astacine by means of an enediol auto-oxidation in which the enediol absorbs two15oxygen molecules and forms two molecules of oxygenated water. Deriving the structure of astaxanthin from16that of astacine, they assigned it the following formula which is that of 3,3'-dihydroxy-ß-carotene-4,4'-dione:17

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