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^{13}C-NMR STUDIES OF ANTITUMORAL ALKALOIDS. II. CRYPTOPLEURINE

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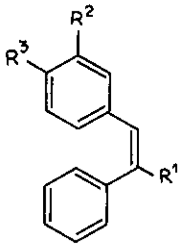
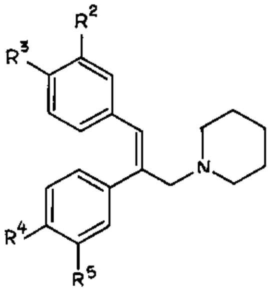
Abstract- For sixteen compounds related to cryptopleurine the carbon-13 chemical shifts and some first-order coupling constants were measured. Excepting the case of very close signals (less than 0.3 ppm of separation) all the signals were assigned. For cis-stilbene and phenanthrene series some useful SCS for methoxy and carboxy groups were calculated.

Our interest for antitumoral alkaloids led us to study colchicine and its derivatives.[1] In the present paper we wish to report the results obtained in the study of cryptopleurine and some related substances. Cryptopleurine (from *Cryptocarpa pleurosperma*)[2] is one of the rare phenanthroquinolizidine alkaloids whose unusual skeleton and interesting antitumor properties[3] explain the great effort devoted to its synthesis,[4] including our (M.S. and G.T.T.) own contribution.[5] However, no ^{13}C-nmr data about phenanthroquinolizidine alkaloids could be found in the literature.

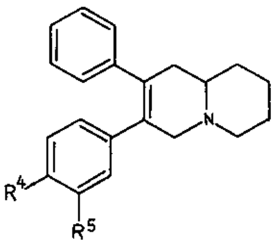
The following sixteen compounds were studied in deuteriochloroform solutions at 20.115 MHz (Bruker WP-80-DS).[6] Cryptopleurine itself 6b was also measured at 62.9 MHz (Bruker WM 250). The compounds chosen are analogues or precursors of cryptopleurine,[5] excepting the commercial *cis*-stilbene 1a and phenanthrene 4a. N-benzylpiperidine 5a was prepared specially for this study.[7] Carbon atoms of these compounds were numbered as in cryptopleurine itself (see table).



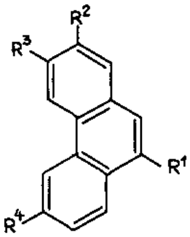
1a, $R^1 = R^2 = R^3 = H$
1b, $R^1 = CH_2OH$, $R^2 = R^3 = OMe$



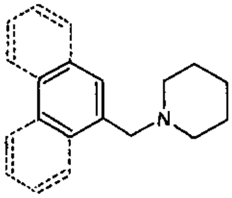
2a, $R^2 = R^5 = H$, $R^3 = R^4 = OMe$
2b, $R^2 = R^3 = OMe$, $R^4 = R^5 = H$
2c, $R^2 = H$, $R^3 = R^4 = R^5 = OMe$
2d, $R^2 = R^3 = R^4 = R^5 = OMe$



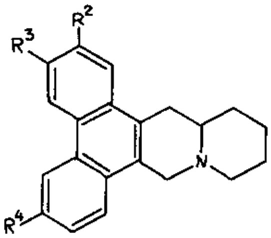
3a, $R^4 = R^5 = H$
3b, $R^4 = R^5 = OMe$



4a, $R^1 = R^2 = R^3 = R^4 = H$
4b, $R^1 = CH_2OH$, $R^2 = R^3 = R^4 = H$
4c, $R^1 = CO_2H$, $R^2 = R^3 = R^4 = H$
4d, $R^1 = CO_2H$, $R^2 = R^3 = R^4 = OMe$



5a, benzo
5b, phenanthro



6a, $R^2 = R^3 = R^4 = H$
6b, $R^2 = R^3 = R^4 = OMe$
(Cryptopleurine)

The almost symmetrical structure of several compounds, 2a, 2d, 3a, 4b, 4c, 5b, 6a, made difficult the assignment of the different carbons. Thus, many pairs of carbon signals separated by less than 0.3 ppm (marked in the table with *, §, or †) could not be assigned with certainty. The techniques used for the assignment are :

- Multiplicity of the signals (SFORD spectra) ;
- Coupling constants, mainly aromatic ^3J constants ;[8]
- Literature results ;
- Internal coherence.

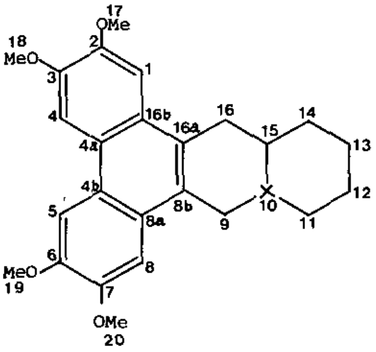
Compounds 1a and 4a have already been reported : our values are consistent with those of Hansen and his assignment has been followed.[10,11]

Quartets. The methoxy signals appearing around 55 ppm are difficult to assign ; if two methoxy groups occupy contiguous positions they are mutually deshielded, showing a downfield shift in relation to the third methoxy group (C_{18} in 2c, C_{19} in 4d, C_{19} in 6b).

Triplets. The β and γ CH_2 signals of the piperidine ring in compounds 2a, 2b, 2c, 2d, 5a, 5b, are easily assigned due to their relative intensities.[12] The CH_2 signals in the α position to the nitrogen (C_9 and C_{11}) were assigned in compound 2d where C_9 shows a ^3J coupling with the olefinic proton in position 16a (doublet of triplets) while C_{11} shows a complicated pattern. On the other hand, in all the six derivatives C_{11} appears around 55 ppm but the chemical shift of C_9 depends on the nature of the substituent, stilbene, ~55 ppm, benzene or phenanthrene, ~63 ppm. The CH_2 signals of the quinolizidine ring (3a, 3b, 6a, 6b) were assigned by analogy. In the stilbenic derivatives (3a, 3b) the carbons α to the double bond (C_9 and C_{16}) appear at higher frequencies than the corresponding carbons (C_{11} and C_{14}) of the saturated half-part. The coupled spectra show C_9 and C_{16} of compounds 3a and 3b as narrow triplets, whereas the signals corresponding to C_{11} and C_{14} have a complex pattern (long range couplings). This fact has been used to assign the very close signals of carbons C_9-C_{11} and C_{14}-C_{16} in compounds 6a and 6b.

Doublets. The only CH signal in the area of saturated carbons correspond to C_{15} of compounds 3a, 3b, 6a, and 6b. The other doublets belong to aromatic or ethylenic carbons. The ^3J coupling in compound 2d between the olefinic carbon C_{16a} and the two protons on carbon C_9 identifies unambiguously C_{16a} ; the coupling constant of 4.1 Hz has the same order of magnitude than those observed between *ortho* carbons and methyl protons (4 to 6 Hz)[11]. The aromatic CH signals were assigned using mainly two criteria : number of $^3J_{meta}$ couplings and SCS (substituent chemical shifts) of the carboxy and methoxy groups. The use of *meta* couplings is clearly illustrated in compounds 2d and 6b :

TABLE : *Chemical shifts in ppm and coupling constants in Hz.*



	1	2	3	4	4a	4b	5	6	7	8	8a	8b	9	11	12
	13	14	15	16	16a	16b	17	18	19	20					
1a	128.9	128.2	127.0	128.2	128.9	128.9	128.2	127.0	128.2	128.9	137.3	130.6	----	----	----
	----	----	----	----	130.6	137.3	----	----	----	----					
1b	112.1	148.4	148.4	111.0	122.7	129.2*	129.1*	126.5	129.1*	129.2*	139.4	129.5	68.8	----	----
	----	----	----	----	127.6	140.0	55.4†	55.7†	----	----					
2a	130.9	113.7*	158.9	113.7*	130.9	127.9	113.6*	158.9	113.6*	127.9	137.8	130.7	57.7	54.4	26.2
	24.5	26.2	54.4	----	131.0	136.6	----	55.3	54.4	----					
2b	113.2	148.4	148.9	111.1	122.8	128.2	128.2	127.0	128.2	126.9	144.7	133.0	58.2	54.6	26.2
	24.5	26.2	54.6	----	133.0	138.3	55.9	55.9	----	----					
2c	131.0	113.7	158.7	113.7	131.0	119.2	110.9	148.9	148.5	111.1	137.8*	131.0	57.9	54.4	26.3
	24.5	26.3	54.4	----	131.0	137.2*	----	55.3	56.0	56.0					
2d	113.1	148.3*	148.9†	111.2	122.6	119.1	110.8	148.8†	148.5*	111.2	137.8§	131.3	58.2	54.6	26.3
	24.5	26.3	54.6	----	131.8	137.6§	56.0	56.0	56.0	56.0					
3a	128.9	127.9*	126.2†	127.9	128.9	129.3	127.8	126.4†	127.8*	129.3	140.7	132.5§	60.4	55.7	26.0
	24.5	33.4	58.0	39.9	132.6§	141.9	----	----	----	----					
3b	128.9	127.9	126.1	127.9	128.9	120.9	110.7	147.6	148.2	113.6	132.2	131.9	60.1	55.6	26.0
	24.4	33.4	58.0	40.0	133.2	142.3	----	----	55.8*	55.7*					
4a	128.6	126.6	126.6	122.7	130.5	130.5	122.7	126.6	126.6	128.6	132.2	127.0	----	----	----
	----	----	----	----	127.0	132.2	----	----	----	----					
4b	128.6	126.8	126.4	122.6	130.5	130.4	123.1	126.4	126.8	125.1	130.1*	135.8	62.6	----	----
	----	----	----	----	124.4	131.7*	----	----	----	----					
4c	130.0	127.4	129.2	123.0	130.4	131.5	123.3	127.1	127.4	126.5	129.2	128.8	168.9	----	----
	----	----	----	----	131.6	129.9	----	----	----	----					
4d	109.5	149.9	151.1	103.5	125.9	131.8	104.2	158.1	115.9	128.8	123.3	126.7	169.9	----	----
	----	----	----	----	129.6	124.7	56.1*	55.9*	55.4	----					
5a	----	----	----	----	126.9	128.2	----	----	----	----	129.2	139.1	64.4	54.6	26.2
	24.5	26.2	54.6	----	129.2	128.2	----	----	----	----					
5b	128.5	126.6*	125.8	122.6†	130.4§	130.9§	122.9†	126.3	126.5*	126.4	132.0*	133.2	62.6	55.0	26.2
	24.6	26.2	55.0	----	127.8	131.8*	----	----	----	----					
6a	122.6	125.9*	126.8	122.9†	130.0	131.2	123.1†	126.8	125.8*	123.5	129.5§	N.O.	56.4	56.2	26.0
	24.4	33.8	57.5	34.8	N.O.	129.6§	----	----	----	----					
6b	104.0	148.3	149.4	104.0	126.6	130.1	104.7	157.4	114.8	124.0	123.8*	124.4	56.3	56.1	26.0
	24.4	33.8	57.5	34.7	125.7	123.4*	56.0†	55.8†	55.4	----					

TABLE : *continuation*

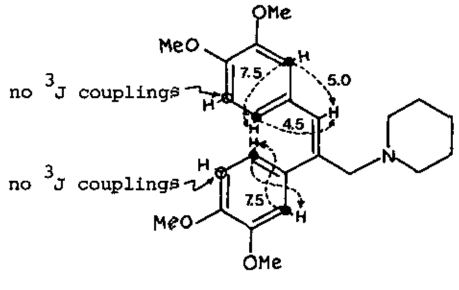
	1	2	3	4	4a	4b	5	6	7	8	8a	8b	9	11	12
	13	14	15	16	16a	16b	17	18	19	20					
2d	158 7.5 5.0[a]	N.M.	N.M.	158	161 7.5 4.5[a]	161 7.5	158	N.M.	N.M.	157 7.5	N.M.	N.M.	132 7.3[a]	131	125
	126	125	131	---	151 4.1[b]	N.M.	143	143	143	143					
3a	N.M.	N.M.	N.M.	N.M.	N.M.	N.M.	N.M.	N.M.	N.M.	N.M.	N.M.	N.M.	132	130	128
	128	126	130	127	N.M.	N.M.	----	----	----	----					
3b	159 7.0 8.0	160	160	160	159	160	158	N.M.	N.M.	156 8.0	N.M.	N.M.	133	130	128
	128	126	129	127	N.M.	N.M.	----	----	----	----					
5a	----	----	----	----	160 5.0 5.0	160 5.0	----	----	----	----	159 6.5 6.5	N.M.	132	131	125
	126	125	131	----	159 6.5 6.5 5.0[b]	160 5.0	----	----	----	----					
5b	N.M.	N.M.	N.M.	156 5.5	N.M.	N.M.	156 5.5	N.M.	N.M.	N.M.	N.M.	N.M.	133	131	126
	126	126	131	----	N.M.	N.M.	----	----	----	----					
6a	N.M.	161 8.5	159 8.5	N.M.	N.M.	N.M.	N.M.	160 9.0	161 8.5	N.M.	N.M.	N.M.	131	130	129
	128	126	130	128	N.M.	N.M.	----	----	----	----					
6b	155	N.M.	N.M.	155	6.5	N.M.	155 5.0	N.M.	161 6.0	157	N.M.	N.M.	132	130	128
	128	126	131	126	N.M.	N.M.	143	143	143	----					

N.O. Not observed

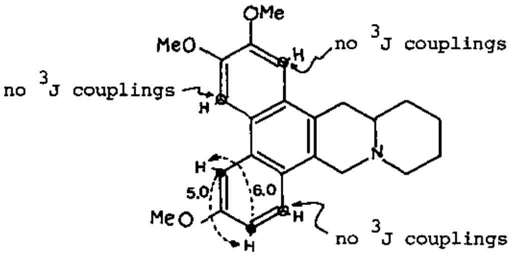
N.M. Not measured

[a] ^{3}J coupling with the C-H in position 16a

[b] ^{3}J coupling with the CH_2 in position 9

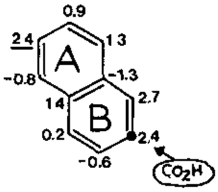


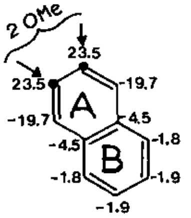
2d

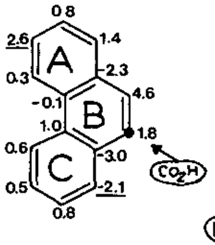


6b

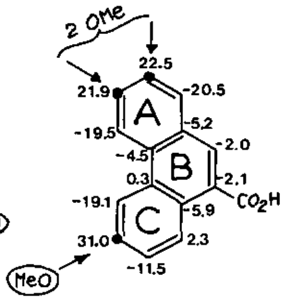
The methoxy and carboxy SCS are consistent with literature results on naphtalene derivatives ;[11] for instance :



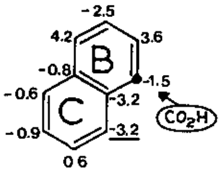


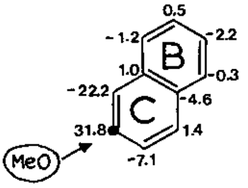


4c - 4a



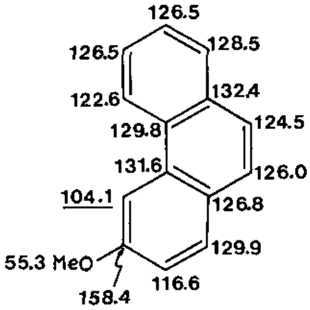
4d - 4c





Singlets. The assignment of singlets is the most difficult problem. In coupled spectra, the only well resolved quaternary carbon signal correspond to C_{4a} in compound 6b (doublet, J = 6.5 Hz, coupling with H_1), however the 'fingerprint'[14] of the different carbons is quite characteristic. This fact and the SCS, not only for phenanthrenes (see before) but also for stilbenes, conduced to the assignments of the table.

Concluding, we think chat our study will prove useful for the identification of the possible cryptopleurine metabolites and for the assignment of the signals of other related alkaloids,[4] like tylophorine, septicine, julandine, and antofine. Even other stilbenes and phenanthrenes could be assigned ; for instance, in the following methoxyphenanthrene only the signal at 104.1 ppm was already assigned.[15]



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