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34. The Structure of C-Alkaloid-O, a Constituent of Calabash Curare

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Summary

The structure of C-alkaloid-O (**1** = his HCl-salt) was established on the basis of spectral data and comparison with the analogous compound **2**, synthesized from a natural product of known absolute configuration. Internally consistent ^{13}C-NMR. assignments are given for **1**, **2**, huntrabrine methochloride (**4**) and its diacetate derivative **5**.

The isolation of C-alkaloid-O, a quaternary indole alkaloid of calabash curare, was first reported in 1954 [2]. Microanalysis of the picrate and chloride salts suggested a molecular formula (for the cation) of $C_{20}H_{27}N_2O^+$, and indicated the presence of a methoxy group. The UV. spectrum of this compound suggested a simple indole chromophore. Optical rotation, melting points and behavior on paper chromatography were also reported, but the quantity isolated was insufficient for a rigorous structure elucidation. The results of a re-investigation of this alkaloid are presented in the following.

The determination of the molecular ion of C-alkaloid-O chloride by electron impact mass spectrometry (EI./MS.) was quite difficult. The peak at highest mass was found at *m/z* 616 (13% rel. intensity). Another intense signal appeared at *m/z* 308 (100%). As in the case of other quaternary alkaloids, prior to electron impact under EI. conditions thermal decomposition reactions must be expected [3]. With chloride as the anion, a thermal *Hofmann* degradation is most probable. In some cases, *e.g.* as shown in [4], the first formed *Hofmann* base may be dimerized. Therefore it is not clear if C-alkaloid-O has the molecular weight (616 + 2 HCl) or (308 + HCl). The ion *m/z* 308 loses 15 mass units to give *m/z* 293, but the peak at *m/z* 277 (loss of OCH_3 from the base peak) is not intense, casting doubt on the presence of an aromatic methoxy group. Further, in the mass spectrum of the iodide salt, the base peak at *m/z* 142 (CH_3I^+) is characteristic of the methiodide of a tertiary

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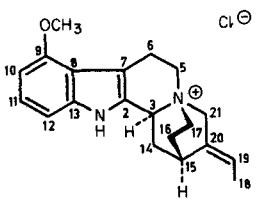

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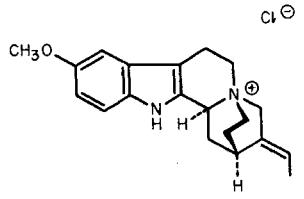

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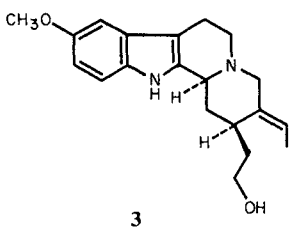

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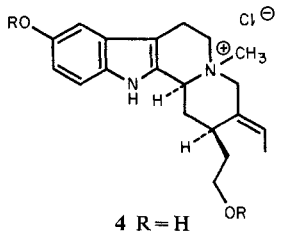

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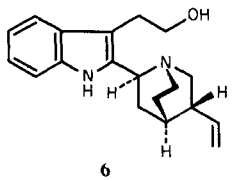
5 R = Ac



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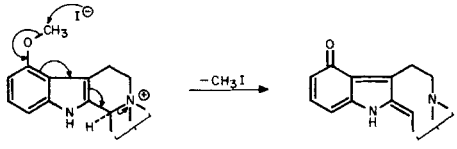
amine [5]. As the expected chemical shifts for an aromatic methoxy and a methyl group attached to a quaternary N-atom overlap in both the ^{1}H- and ^{13}C-NMR. spectra, inspection of these spectra could not resolve this ambiguity. However, irradiation of the 3 H *s* at 3.90 ppm in the ^{1}H-NMR. spectrum produced a 23% nuclear *Overhauser* enhancement (NOE) in the *d* at 6.52 ppm (H–C(10)), clearly establishing the presence of a methoxy group on the aromatic ring[3]), and therefore the absence of an N–CH_3-group. Also in agreement with these findings is the lack of change in the UV. spectrum of this compound in the presence of acid or base.

The aromatic substitution pattern was deduced from the ^{1}H- and ^{13}C-NMR. spectra. As both aromatic proton doublets show *ortho*-coupling to the $d \times d$ at 7.10 ppm, the aromatic ring should be 1,2,3-trisubstituted. Such a substitution

[3]) The intense CH_3I^+-peak at *m/z* 142 may be explained in the following manner: in a thermal reaction, $I^\ominus$ removes methyl of the methoxy group in **1** forming the tertiary base **i** containing an *o*-quinoid component.



i

pattern requires that the methoxy must be located at either C(9) or C(12). If the substituent were located at C(12), the ^{13}C-NMR. chemical shift of C(12) would be expected at 140–145 ppm, whereas, if it were located at C(9), C(9) would be expected to resonate downfield of 150 ppm. Furthermore, the chemical shift of C(13) is expected to be 135–140 ppm in the case of oxygenation at C(9), but 125–130 ppm in the case of substitution at C(12) [6]. The observed chemical shifts of C(9) and C(13), 155.2 and 139.7 ppm, respectively, agree with oxygenation at C(9). The remaining aromatic ring C-resonances (see *Table 1*) are also in agreement with calculated values for an indole nucleus oxygenated at C(9) [6].

From the ^{13}C-NMR. spectrum in the single-frequency off-resonance decoupled mode, the remainder of the molecule was found to consist of one methyl group, a trisubstituted C,C-double bond, two methine- and six methylene-groups, along with a positively charged N-atom. Irradiation of a broadened *qa* at 5.62 ppm (H–C(19)) in the ^{1}H-NMR. spectrum caused the collapse of the broadened $d \times d$ at 1.80 ppm (3 H–C(18)), indicating the presence of an ethylidene side chain. All four of these protons were further coupled to the protons giving rise to signals at 4.15 und 4.42 ppm (2 H–C(21)) *via* allylic and homoallylic pathways. The chemical shift of these protons which show only an additional geminal coupling indicates that they are bound to an allylic C-atom adjacent to the N-atom.

Table 1. *^{13}C-NMR. data for compounds* **1**, **2**, **4** *and* **5**

Atom	**1**[a])	**2**[a])	**4**[b])	**5**[b])
C(2)	127.4	126.8	127.2	127.0
C(3)	62.6	64.0	65.3	65.5
C(5)	49.9	50.2	49.2	49.2
C(6)	19.8	17.9	18.0	18.2
C(7)	105.0	105.4	104.6	105.8
C(8)	116.6	133.7	132.7	130.2
C(9)	155.2	101.8	103.6	111.7
C(10)	106.0	155.0	150.7	145.8
C(11)	124.6	113.4[c])	113.3[c])	118.0
C(12)	101.1	113.5[c])	113.4[c])	112.8
C(13)	139.7	130.0[d])	128.8	136.0
C(14)	32.0	31.9	30.8	31.1
C(15)	25.4	25.4	31.0	31.7
C(16)	24.5	24.6	36.1	32.8
C(17)	61.1	61.1	60.8	63.0
C(18)	13.0	12.9	13.8	13.8
C(19)	121.8	121.7	133.6	133.7
C(20)	130.0	130.1[d])	129.4	129.4
C(21)	66.0	66.1	63.5	63.8
OCH_3	56.0	56.9	–	–
NCH_3	–	–	59.9	60.7
CH_3COO	–	–	–	20.9, 21.1
CH_3COO	–	–	–	172.0, 172.5

[a]) Spectra run in $CD_3OD + D_2O$.

[b]) Spectra run in CD_3OD.

[c]) [d]) Assignments within each footnoted group may be interchanged.

Irradiation of the (1H)-*t* at 4.91 ppm (H–C(3)) causes simplification of the *m*'s at 2.07 and 2.65 ppm (2 H–C(14)). As C(5) and C(6) are unsubstituted, as indicated by the ^{13}C-NMR. chemical shifts of the CH_2-groups at 19.8 and 49.9 ppm, which are typical of these C-atoms in a tetrahydro-β-carboline skeleton [7], the remaining bridgehead C-atom must be C(15). Thus, the gross structure **1** could be proposed for C-alkaloid-O chloride which, by thermal decomposition in mass spectrometer, will give a *Hofmann* base with the molecular ion *m/z* 308.

To confirm the proposed skeleton and establish the absolute configuration of C(3), the analogous compound **2** was synthesized by known methods [8]. Treatment of 10-methoxygeissoschizol (**3**) of proven absolute configuration [9] with tosyl chloride/pyridine at 5° for 48 h directly afforded, after workup, the cyclized quaternary amine as its *p*-toluenesulfonate, which was then converted to the chloride **2** by ion exchange.

The mass spectrum of **2** differed from that of **1** only slightly in the intensity of some of the fragment ions, while the aliphatic regions of the ^{1}H-NMR. spectra were almost superimposable. The aliphatic regions of the ^{13}C-NMR. spectra of the two compounds also differ only slightly. The chemical shift of C(6) in **1** is 19.8 ppm, while in **2**, this resonance is shifted to 17.9 ppm. This change can be rationalized as being the result of a through-space deshielding of this C-atom in **1** by the O-atom at C(9), with which it is in a quasi-peri relationship. The resonance of C(3) is also shifted, but the cause of this shift is not readily apparent.

Comparison of the ^{13}C-NMR. spectra of **1** and **2** with those of the model compounds huntrabrine methochloride (**4**) and its diacetate derivative (**5**), prepared by treatment of **4** with acetic anhydride/pyridine, permits the proposal of an internally consistent assignment of the resonances for these compounds (see *Table 1*). In light of the proposed structure for C-alkaloid-O, the mass-spectral fragmentation of its chloride degradation product can be explained in terms of known tetrahydro-β-carboline alkaloids [5].

It has been shown [9] that the molecular optical rotations in pyridine solution of a number of *Corynanthe*-type alkaloids with a H_a–C(3) are all negative in sign, while those of their C(3)-epimers are uniformly positive. Conversion of **3**, having a

Table 2. *Optical rotations of compounds* **1** *and* **2**

	1[a])	**2**[b])
$[\alpha]_D^{22}$	– 150°	– 142°
$[\alpha]_{578}^{22}$	– 157°	– 150°
$[\alpha]_{546}^{22}$	– 178°	– 171°
$[\alpha]_{436}^{22}$	– 311°	– 293°
$[\alpha]_{365}^{22}$	– 520°	– 463°
$[M]_D^{22}$	– 489°	– 463°
$[\alpha]_D^{22}$ (MeOH)	– 124° (c = 1.265)	– 98° (c = 0.805)

[a]) Pyridine/water 19:1, c = 0.283.
[b]) Pyridine/water 10:1, c = 0.146.

molecular optical rotation of −212°, to **2** ($[M]_D = -463°$) does not change the sign of the molecular optical rotation, but increases its magnitude. As the molecular optical rotation of C-alkaloid-O chloride is similar in sign and magnitude to that of **2**, it can be inferred that the absolute configuration at C(3) is the same in both compounds. This is further supported by the similarity of optical rotations in MeOH and at five wavelengths in pyridine/water solution (see *Table 2*).

No formal proof of the absolute configuration at C(15) can be offered at this time. Regarding the great similarity in sign and magnitude of the optical rotation of model compound **2** and C-alkaloid-O chloride (**1**) and the fact that all known alkaloids of the *Corynanthe*-type have a H_α-atom at C(15), it is most likely that the absolute configuration is that shown in **1**.

Biogenetically, it would be attractive to speculate that C-alkaloid-O may represent a link between alkaloids of the *Corynanthe*-type and those related to cinchonamine (**6**). As the exact plant source of C-alkaloid-O is not known, and this compound may not be a natural product but rather an artefact formed during the preparation of calabash curare by the natives, such speculation is unfounded. Synthetic compounds with similar skeleta have been utilized to correlate the absolute configurations of these two classes of alkaloids [8].

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Experimental Part

General. Thin layer chromatography (TLC.) was performed on 0.2-mm layers of silica gel *$60F_{254}$ (Merck)* developed with propanol/formic acid 19:1 and visualized with either ceric sulfate/sulfuric acid or potassium iodoplatinate reagent [10]. Solvents used were of analytical reagent grade and distilled prior to use. Optical rotations were determined using a *Perkin-Elmer 241* polarimeter. Ultraviolet spectra (UV.) in 95% ethanol with a *Perkin-Elmer 555* instrument, absorptions in nm ($\log\varepsilon$). Infrared spectra (IR.) in KBr with a *Perkin-Elmer 297* spectrophotometer, absorption bands in wavenumber (cm^{-1}). ^{1}H-NMR. spectra were determined at 200 MHz with a *Varian XL-200* superconducting spectrometer, while ^{13}C-NMR. spectra were obtained at 25.2 MHz with a *Varian XL-100* instrument. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants *(J)* are reported in Hz. Signal multiplicities are abbreviated as: *s* = singlet, *d* = doublet, *t* = triplet, *qa* = quadruplett, *m* = multiplet, and br. = broad. Electron impact mass spectra (E.I./MS.) were obtained with a *Varian MAT-711* instrument coupled to a *Varian SS-100 MS* data system, important signals in *m/z* (rel. %).

Abbreviations: NOE = nuclear *Overhauser* enhancement, sh = shoulder.

C-Alkaloid-O chloride (**1**). M.p. 288–9° (dec.). Optical rotation: see *Table 2*. – UV.: max 291 (3.74), 281 (3.78), 267 (3.97), 223 (4.59); min 288 (3.68), 278 (3.77), 240 (3.50); sh 206 (4.38); unchanged in acid or base. – IR.: 3170, 2960, 1600, 1570, 1510, 1460, 1450, 1445, 1352, 1262, 1255, 1108, 775, 729. – ^{1}H-NMR. (CD_3OD): 7.10 (*d* × *d*, $J_1 = 7.7$, $J_2 = 7.8$, H–C(11)); 7.00 (*d*, $J = 7.7$, H–C(12)); 6.52 (*d*, $J = 7.8$, H–C(10)); 5.62 (br. *qa*, $J = 7.0$, H–C(19)); 4.91 (*t*, $J = 8.5$, H–C(3)); 4.42 (br. *d* × *qa*, $J_1 = 15$, $J_2 = 2.2$, H–C(21)); 4.15 (br. *d*, $J = 15$, H–C(21)); 3.90 (*s*, OCH_3); 3.85–3.20 (*m*, 2 H–C(5), 2 H–C(6), H–C(15), 2 H–C(17)); 2.65 (*m*, H–C(14)); 2.07 (*m*, H–C(14), 2 H–C(16)); 1.80 (br. *d* × *d*, $J_1 = 7.0$, $J_2 = 2.2$, 3 H–C(18)). – ^{13}C-NMR.: see *Table 1*. – MS.: 616 (13), 506 (12), 346 (11), 345 (20), 344 (31), 343 (41), 309 (51, M^+), 308 (100), 307 (59), 306 (16), 305 (25), 294 (12), 293 (37), 291 (15), 281 (23), 280 (18), 279 (39), 278 (10), 277 (13), 267 (12), 265 (17), 264 (12), 263 (10), 253 (18), 251 (11), 239 (14), 214 (35), 213 (23), 212 (13), 201 (19), 200 (41), 199 (42), 198 (30), 187 (10), 186 (39), 185 (19), 184 (26), 174 (15), 170 (15), 155 (10), 154 (14), 135 (29), 124 (18), 123 (47), 122 (29), 121 (13), 115 (11), 109 (10), 108 (24),

107 (24), 93 (14), 81 (10), 79 (12), 77 (14), 73 (13), 42 (15), 41 (15), 39 (10), 38 (27), 36 (85). – MS. of C-alkaloid-O iodide: 308 (18), 307 (12), 293 (10), 214 (10), 142 (100), 141 (14), 128 (6), 127 (37), 124 (12), 123 (30), 112 (9), 108 (10).

$C_{20}H_{25}ClN_2O$ (344.166)	Calc.	C 69.73	H 7.32	N 8.14%
	Found	„ 68.87	„ 7.12	„ 8.29%
	Lit. [2]	„ 69.24, 69.66	„ 7.42, 7.51	„ 8.00%

Synthesis of **2**. A solution of 10-methoxygeissoschizol (**3**) (300 mg) in pyridine (2 ml) was added to tosyl chloride (600 mg) in pyridine (10 ml), and the resulting mixture was allowed to stand 48 h at 5°. The cloudy solution was then poured into ice-cold 5% aq. NaOH-solution (20 ml) and extracted with CH_2Cl_2 (5 × 20 ml). The pooled org. phase was freed of solvent at ambient temperature under reduced pressure to yield an off-white solid residue which was crystallized from MeOH to yield off-white plates of the *p*-toluenesulfonate of **2** (180 mg, 41%). Ion exchange on *Amberlite IRA-400* (Cl^-) yielded the chloride salt of **2** which crystallized from MeOH as fine colorless plates (140 mg, 99%), m.p. > 300°. Optical rotation: see *Table 2*. – UV.: max 308 (3.63), 296 (3.73), 273 (3.98), 215 (4.52); min 307 (3.62), 294 (3.72), 245 (3.41); sh 206 (4.47); unchanged in acid or base. – IR.: 3110, 3060, 2970, 2950, 1630, 1491, 1474, 1440, 1220, 1190, 1149, 1030, 840, 802. – ^{1}H-NMR. ($CD_3OD + D_2O$): 7.38 (*d*, J = 9.0, H–C(12)); 7.09 (*d*, J = 2.5, H–C(9)); 6.90 (*d* × *d*, J_1 = 9.0, J_2 = 2.5, H–C(11)); 5.65 (br. *qa*, J = 7.0, H–C(19)); 4.43 (br. *d*, J = 15, H–C(21)); 4.15 (br. *d*, J = 15, H–C(21)); 3.88 (*s*, OCH_3); 3.80–3.15 (*m*, 2 H–C(5), 2 H–C(6), H–C(15), 2 H–C(17)); 2.68 (*m*, 1 H–C(14)); 2.07 (*m*, 1 H–C(14), 2 H–C(16)); 1.80 (br. *d*, J = 7.0, 3 H–C(18)). – ^{13}C-NMR.: see *Table 1*. – MS.: 616 (3), 506 (13), 345 (9), 344 (14), 343 (18), 309 (34), 308 (100, M^+), 307 (50), 306 (11), 305 (15), 293 (33), 281 (16), 280 (14), 279 (34), 265 (14), 253 (15), 239 (15), 225 (10), 214 (27), 213 (30), 212 (15), 201 (13), 200 (28), 199 (38), 198 (37), 187 (14), 186 (30), 185 (20), 184 (29), 183 (11), 174 (10), 170 (10), 156 (11), 155 (12), 154 (14), 135 (12), 124 (11), 123 (26), 122 (17), 109 (16), 108 (25), 107 (10), 94 (10), 79 (10), 77 (12), 42 (10), 41 (15), 39 (10), 38 (10), 36 (32).

$C_{20}H_{25}ClN_2O$ (344.166) Calc. C 69.73 H 7.32 N 8.14% Found C 69.82 H 7.20 N 8.00%

Acetylation of huntabrine methochloride (**4**). To a stirred solution of **4** (100 mg) [11] in pyridine (5 ml) was added acetic anhydride (3 ml). The mixture was then stirred 24 h at ambient temperature. The solvent was removed at ambient temperature under reduced pressure. Ion exchange of the oily residue on *Amberlite IRA-400* (Cl^-) afforded **5** as an oil (122 mg, 99%). – ^{13}C-NMR.: see *Table 1*.

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