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(*1R, 2S*)-(-)-MANGOCHININE, A NATURALLY-OCCURRING DIBENZOPYRROCOLINE ALKALOID FROM *MANGLIETIA CHINGII*

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Abstract: (*1R, 2S*)-(-)-Mangochinine (**1**), a third member of an unusual naturally-occurring quaternary dibenzopyrrocoline alkaloid, was isolated from the bark of *Manglietia chingii* Dandy (Mangnoliaceae), its structure was determined on the basis of extensive 1D- and 2D-NMR (DQF-COSY, ROESY, HMQC, and HMBC) spectral analysis on its diacetylated derivative and the absolute configuration was also assigned using optical rotation measurement.

In 1932, Robinson and Sugasawa[1] and Schöpf and Thierfelder[2] independently prepared a rare dibenzopyrrocoline type alkaloid, dehydrolaudanosoline, from the oxidative cyclization of laudanosoline. Since the oxidation proceeded so readily and smoothly, Schöpf and Thierfelder therefore concluded that these tetracyclic alkaloids may one day be found in nature. Two decades later, the natural dibenzopyrrocoline alkaloids, (-)-cryptaustoline and (-)-cryptowoline were isolated as their iodides from *Cryptocarya bowiei*,[3] a plant indigenous to Queensland. These alkaloids were shown to cause neurological paralysis by acting as respiratory poisons.[4] The absolute configurations at C-1 erroneously assigned to the ***S*** configuration on the basis of chemical transformation by oxidative coupling of (+)-laudanosoline[5] using chloranil or horseradish peroxidase were revised to ***R*** by Meyers *et al.*[6] through detailed asymmetric synthesis studies, and discovered that the discrepancy arose from the unexpected configuration inversion during oxidative coupling.[5]

Manglietia chingii Dandy (Magnoliaceae) is a tall tree indigenous to the Guanxi and Guangdong Provinces of the People's Republic of China. Its bark has been used locally in Southwest and South China under the name of "Tu-Hou-Po" as a substitute for the official crude drug "Hou-Po", *Manglietia officinalis* Rehd. et Wils. for the purposes of anti-ulcer, analgesic, muscle relaxant and anti-bacterial therapy.[7, 8] The presence of magnolol (0.008 %), honokiol (0.004 %), mangocurarine (0.817 %) and silicifoline (0.004 %) in the bark, as determined by HPLC analysis, is the only phytochemical study reported to date.[9]

As part of our search for novel chemical compounds with potential biological activity, the present phytochemical investigation of the bark of *Manglietia chingii* Dandy led to the isolation and identification of

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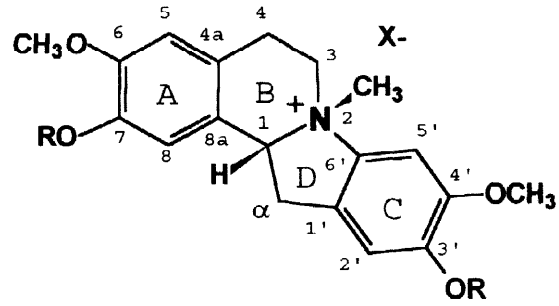
(1R, 2S)-(-)-**mangochinine (1), a third naturally-occurring** dibenzopyrrocoline alkaloid. The present report describes the isolation and structure elucidation of **1** by means of 1D- and 2D-NMR techniques.



1 R = H, X unspecified
1a R = H, X = OH
1b R = H, X = Cl
1c R = Ac, X = OH

Air-dried and milled bark of *M. chingii* (5 kg) was extracted with EtOH, and the concd. extract was then stirred with dilute HCl (2%) and filtered. On basification of the acidic extract, the mixture was partitioned against $CHCl_3$ and then n-BuOH. The concentrated n-BuOH extract furnished **1a**[10] after removal of the solvent under reduced pressure followed by crystallization from MeOH.

Mangochinine hydroxide (**1a**) was isolated as light-gray needles, $[\alpha]_D$ -164° (c 0.4, MeOH), its UV absorption at 211 (log ε 4.27) and 287 (log ε 3.83) nm suggested the presence of a benzyltetrahydroisoquinoline backbone. The ^{13}C DEPT experiment revealed a total of 19 carbon signals of which three are attributable to methyl, three to methylene carbons, five to methine and eight to quaternary carbons, consistent with the molecular formula of $C_{19}H_{22}O_4N$ (MW = 328), which was based on pseudo-molecular ions at *m/z* 328 $[M]^+$ and *m/z* 326 $[M-2H]^-$ from the positive and negative mode Electronspray and FAB mass spectra. The unusual behavior of its mass spectra of positive and negative modes in which 2 a.m.u difference was observed may be accounted for by the chemical nature of its being a quaternary alkaloid. Such a mass spectral pattern was observed for a model compound, chelerythrine chloride (M. F. $C_{21}H_{18}NO_4$•Cl), in which the molecular ion *m/z* 348 (cationic ion) was detected in the positive ionization mode Electronspray mass spectrum.

The foregoing inference was also strengthened by the presence of characteristic signals consisting of four non-splitted aromatic protons at δ 6.76, 6.86 (2H from the integration), and 7.57, as well as one N-methyl signal at δ 3.50 and two methoxyl group signals resonating at δ 3.78 and 3.87, respectively, in the ^1H NMR spectrum. It also showed additional proton signals for two phenolic hydroxyl groups (δ 9.22, 7-OH; and δ 9.78, 3'-OH), Furthermore, three non-equivalent methylene proton pairs appeared as overlapping multiplicities in the ^1H NMR spectrum which could only be distinguished with the aid of DQF-COSY and HMQC experiments.

The interpretation of the through-bond connectivity information derived from DQF-COSY and HMBC spectra led to the initial structure of **1**. Starting with the typical H-1 signal at δ 5.28 (t, J = 9.3 Hz), the methylene protons resonating at δ 3.69 and 3.06 could be easily assigned to H_2-α based on their coupling correlations observed with H-1 in the DQF-COSY spectrum. The differentiation between H_2-3 and H_2-4 could be achieved using a HMBC spectrum in which a cross peak was observed between N-$C\underline{H}_3$ and a methylene carbon signal at δ 57.46, assignable to C-3, which led to the remaining methylene carbon resonating at δ 23.54 be assigned to C-4. HMBC revealed further connectivities between C-1/ N-$C\underline{H}_3$ and N-$\underline{C}H_3$/H-1.

Thus, the assignments of C-α, C-1, H_2-3 and H_2-4 were relatively straightforward by means of a HMQC experiment. Moreover, the two sharp singlet phenolic hydroxyls detected at δ 9.22 and 9.78 could be located at C-7 and C-3', respectively, from the HMBC spectrum.

There remained, however, some uncertainties on the connecting position of the N atom to ring C, since the expected ^{13}C-^{1}H long-range correlations were not observed between the N-C$\underline{H_3}$ and C-6', and the $\underline{H_2}$-3 and C-6' in both the FLOCK and HMBC spectra. These uncertainties were probably due to the severe overlapping of the proton signals of interest. The assignment of the stereochemistry of 1 was also difficult from the ROESY and NOED spectral evidence based on spatial relationships, although the *ortho*- relationships between 6-OCH_3 and H-5, 4'-OCH_3 and H-5' were evident.

It was anticipated that more highly resolved NMR spectra were needed to remove the ambiguities surrounding the structure of 1. Thus, derivatives of 1 were subjected to NMR analysis. Mangochinine chloride (1b), however, afforded only a slightly improved ^{1}H NMR spectrum in which most of the signals at high field remained overlapped. Acetylation of 1a with Ac_2O/Py afforded diacetylmangochinine (1c) [11] as confirmed by

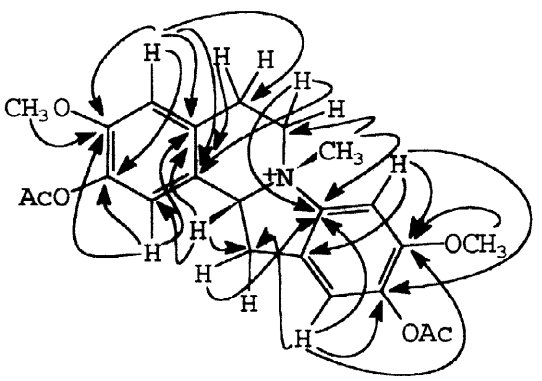


Figure 1. Key long-range ^{13}C-^{1}H-NMR (HMBC) correlations for Compound **1c**

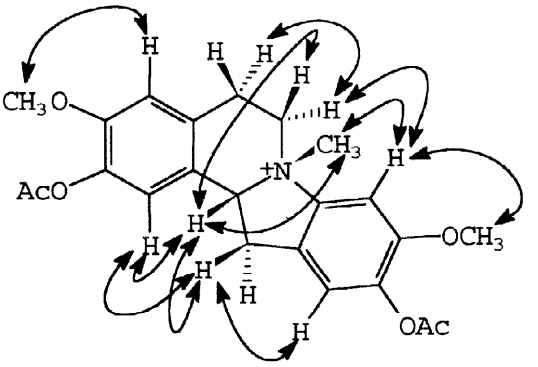


Figure 2. Significant ROE correlations of compound **1c** observed in ROESY spectrum

the observation of a pseudo-molecular ion at *m/z* 412 $[M]^+$ from the positive mode Electronspray mass spectrum. The acetate 1c gave satisfactorily well-resolved ^{1}H and ^{13}C NMR spectra in $CDCl_3$, in which all the non-equivalent methylene proton pairs were differentiated and suitable for further spectral delineation of the structure of 1. The ^{13}C-^{1}H long-range correlations observed between C-6'/N-C$\underline{H_3}$, C-6'/$\underline{H_2}$-α, and C-6'/$\underline{H_2}$-3 (Figure 1) in the HMBC spectrum constituted the conclusive evidence for the covalent structure of 1. The stereochemistry at the stereogenic centers at C-1 and position 2 (N) remain to be addressed. The ROE cross peak of H-1/N-CH_3 in the ROESY spectrum (Figure 2) indicated that they are *cis*-disposed. It also followed that the ROE correlations between H-1/H-8 and H-5/N-C$\underline{H_3}$ suggested the absolute configuration of 1 as being 1***R***, 2***S*** from the examination of the Dreiding model. This result is consistent with the expected configuration based on optical rotation, biogenetic pathways and mechanics calculations for compounds of this type,[6] which

showed that the stereocenter NMe anchors the absolute configuration of C-1 and furnishes the more stable *cis*-fused-ring and the formation of ***R*** enantiomer with levorotatory rotation.

To the best of our knowledge, (*1R, 2S*)-(-)-mangochinine (**1**) represents the third natural member of the unusual dibenzopyrrocoline alkaloid, and the first one whose NMR signals and stereochemistry were unambiguously assigned by 2D NMR experiments. Its biogenesis may proceed through carbon-nitrogen coupling of a benzylisoquinoline alkaloid precursor such as mangocurarine,[3] which has also been found in this plant.

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REFERENCES AND NOTES

1. Robinson, R.; Sugasawa, S. *J. Chem. Soc.* **1932**, *135*, 789-805.
2. Schopf, C.; Theirfelder, K. *Liebigs Ann. Chem.* **1932**, 498, 22.
3. Ewing, J.; Hughes, G. K.; Ritchie, E.; Taylor, W. C. *Nature* **1952**, *169*, 618-619.
4. Ewing, J.; Hughes, G. K.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1953**, *6*, 78.
5. Brossi, A.; Ramel, A.; O'Brien, J.; Teitel, S. *Chem. Pharm. Bull.* **1973**, *8*, 1839-1840.
6. Meyers, A. I.; Sielecki, T. M.; Crans, D. C.; Marshman, R. W.; Nguyen, T. H. *J. Am. Chem. Soc.***1992**, *114*, 8483-8489.
7. Song, W.-Z.; Chen, J.-M.; Ji, C.-Y. *Acta Pharm. Sinica* **1984**, *19* (3), 213-219.
8. Song, W-Z.; Cui, J.-F.; Zhang, G.-D. *Acta Pharm. Sinica* **1989**, *24* (4), 295-299.
9. Tao, Z.; Xia, Z.; Li, Z. *Chinese Pharm. Bull.* **1983**, *18* (11), 663-664.
10. Mangochinine hydroxide (**1a**). Light-gray needle (18 mg) was obtained from EtOH/Et_2O, light-gray, easily soluble in MeOH, warm EtOH and warm Me_2CO, hardly in $CHCl_3$ and Et_2O; mp 162-164 °C; $[\alpha]_D$ -164° (c 0.4, MeOH). IR (KBr) ν_{max} (cm^{-1}): 3200 (OH), 1600. 1500, 1450, 1230, 1020, 840, 820. ^1H NMR (300 M Hz, DMSO-d_6) δ: 2.91 (1H, m, 4-Ha), 3.06 (1H, m, α-Ha), 3.12 (1H, m, 4-Hb), 3.50 (3H, s, N-CH_3), 3.69 (1H, m, α-Hb), 3.71 (1H, m, 3-Ha), 3.78 (3H, s, 6-OCH_3), 3.87 (3H, s, 4'-OCH_3), 3.93 (1H, m, H-3b), 5.28 (1H, t, J = 9.3, 1-H), 6.76 (1H, s, 8-H), 6.86 (2H, s, 5-H and 2'-H), 7.57 (1H, s, 5'-H), 9.22 (1H, s, exchangeable, 7-OH), 9.78 (1H, s, exchangeable, 3'-OH); ^{13}C NMR (75.48 M Hz, DMSO-d_6) δ: 23.54 (t, C-4), 35.84 (t, C-α), 49.32 (q, N-CH_3), 55.70 (q, 6-OCH_3), 56.46 (q, 4'-OCH_3), 57.64 (t, C-3), 102.13 (d, C-5'), 111.67 (2C, d, C-5 and C-2'), 113.09 (d, C-8), 119.58 (s, C-4a), 122.26 (s, C-8a), 124.52 (s, C-1'), 137.69 (s, C-6'), 146.05 (s, C-7), 147.69 (s, C-6), 148.20 (s, C-4'), 148.82 (C-3'). Relevant NMR nOes are 6-OCH_3 to H-5 (4.8%), 4'-OCH_3 to H-5' (5.0%), H-1 to H-8 (4.3%) and H-1 to N-CH_3 (6.0%).
11. Diacetylmangochinine hydroxide (**1c**). ^1H NMR (300 M Hz, $CDCl_3$) δ: 2.31 (6H, s, 2 x Ac), 3.12 (1H, dt, J = 14.5, 5.6, H-4α), 3.21 (1H, dd, J = 9.0, 16.2, H-αβ), 3.35 (1H, ddd, J = 14.5, 5.6, 8.5, H-4β), 3.82 (1H, Obsc, H-3β), 3.85 (3H, s, 6-OCH_3), 3.89 (1H, Obsc, H-αα), 3.91 (1H, s, N-CH_3), 4.05 (3H, s, 4'-OCH_3), 4.76 (1H, dt, J =12.5, 5.6, H-3α), 5.41 (1H, t, J = 8.2, H-1), 6.92 (1H, s, H-5), 7.02 (1H, s, H-8), 7.08 (1H, s, H-2'), 8.26 (1H, s, H-5'); ^{13}C NMR (75.48 M Hz, $CDCl_3$) δ: 20.49 (q, Ac), 20.51 (q, Ac), 24.47 (t, C-4), 36.48 (t, C-α), 51.0 (q, N-CH_3), 56.23 (q, 6-OCH_3), 58.10 (t, C-3), 58.67 (q, 4'-OCH_3), 74.57 (t, C-1), 104.31 (d, C-5'), 112.44 (d, C-5), 120.28 (d, C-2'), 120.64 (s, C-8a), 121.05 (d, C-8), 122.28 (C-1'), 127.29 (s, C-4a), 139.69 (s, C-7), 141.91 (s, C-3'), 144.23 (s, C-6'), 151.41 (s, C-6), 153.00 (s, C-4'), 168.47 (s, Ac), 168.73 (s, Ac).