

THE STEREOCHEMISTRY AND ^{13}C NMR SPECTRA OF PROTOPINIUM SALTS

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ABSTRACT.—The ^{13}C nmr spectra for protopine (1), allocryptopine (4), 1-methoxyallocryptopine (5), hunnemanine (6), and thalicticine (7), were recorded in TFA-*d* solution. There is a predominance of the *cis* protopinium salt over the *trans* isomer, except in the case of thalicticine where the *trans* salt is the major isomer. The chemical shifts of C-6, C-13 and the *N*-methyl group are particularly diagnostic of the stereochemistry of the protopinium salts.

Sixteen naturally occurring protopines are presently known, and their physical and spectral characteristics have recently been summarized (1). They all possess the tricyclic skeleton represented by expression *A*.

The ^{13}C nmr spectra for five protopine bases had been recorded as early as 1973 in 5% cyclohexane in chloroform (2). Since this solvent is not presently a common one in ^{13}C nmr spectroscopy, and since some of the protopine alkaloids such as thalicticine (7) are only slightly soluble in neat CDCl_3 , it was decided to study the ^{13}C nmr spectra of a series of protopine alkaloids in TFA-*d*, a solvent in which all protopines are readily soluble. Concentrations of about 55 mg per 2 ml of solvent were used.

It was immediately recognized that in TFA solution, the protonated form of each alkaloid is present, which could *a priori* exist either in the tetracyclic *cis* form (*cis*-*A*) or the *trans* form (*trans*-*A*). In TFA-*d*, therefore, the deuterated salts corresponding to *cis*-*A* and *trans*-*A* should exist.

Inspection of the ^{13}C nmr spectrum of protopine (1) in TFA-*d* revealed that two species were present, corresponding to the *cis* and *trans* protopinium salts. The two sets of signals could be differentiated, since one was about twice as large, in terms of peak areas, as the other (65:35).⁴

In order to associate a specific stereochemistry with each of the two sets of signals, we had recourse to the fact that the ^{13}C nmr spectra in TFA-*d* for the related berbines *cis*- and *trans*-canadine oxide (*cis*-2 and *trans*-2), (3) and *cis*- and *trans*-canadine *N*-metho salts (*cis*-3 and *trans*-3) (4) had been recorded. The critical chemical shift values for these compounds have been reproduced here.

With the *N*-oxides *cis*-2 and *trans*-2, it is the chemical shift values for C-6 and C-13 which are diagnostic. The C-6 signal is upfield (59.42 ppm) in the *cis* *N*-oxide and further downfield (66.00 ppm) in the *trans* oxide, while C-13 is relatively downfield (36.88 ppm) for the *cis* isomer and upfield (31.08 ppm) for the *trans* compound. Exactly the same trend is apparent with *N*-metho salts *cis*-3 and *trans*-3, except that in this case the chemical shift of the *N*-methyl is also a good gauge; in the *cis* salt the signal for this group appearing further downfield (52.4 ppm) than in the corresponding *trans* isomer (40.6 ppm).

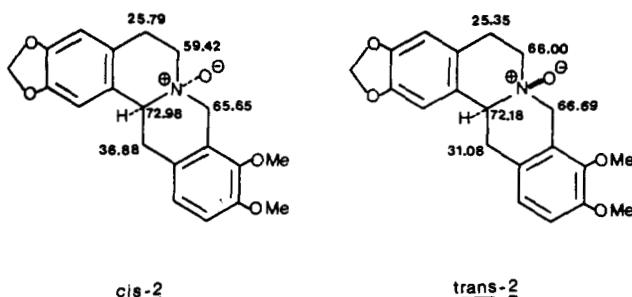
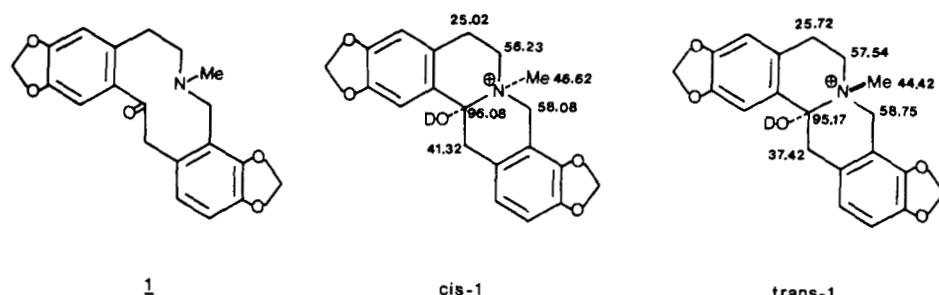
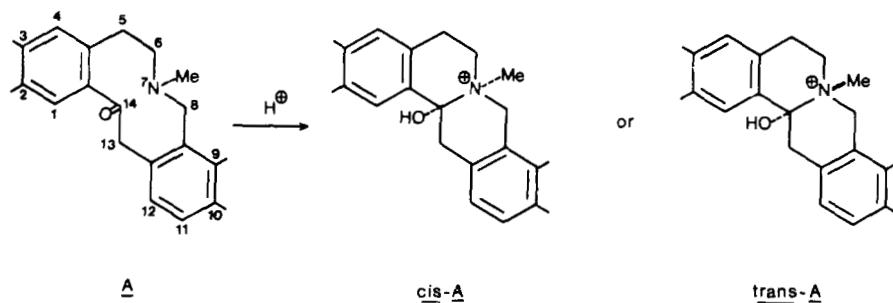
These criteria were next applied to the protopinium spectrum we had obtained in TFA-*d*. The more intense set of peaks can be assigned to the *cis* stereomer,

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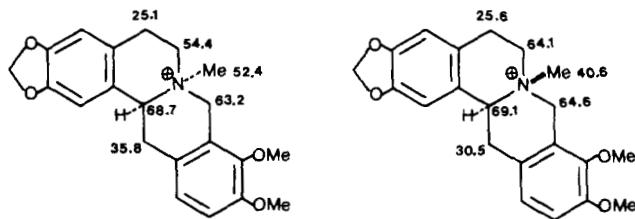
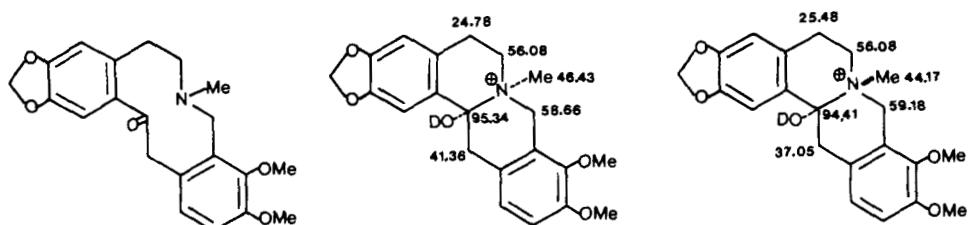
⁴The ^{13}C nmr spectra were also rerun for each compound after allowing the samples to stand at room temperature for 48 hours. The time factor did not significantly alter either peak areas or chemical shifts.



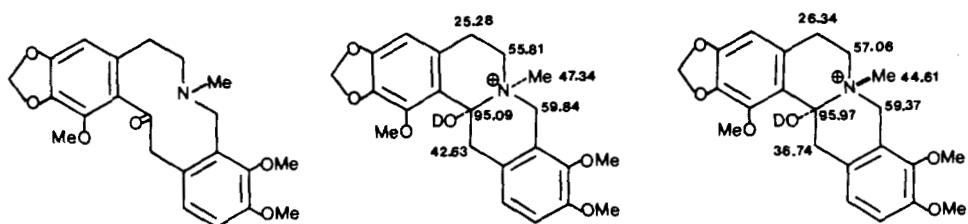
while the less intense one represents the *trans* isomer. These spectra have been summarized in expressions *cis*-1 and *trans*-1 below.

It will be noted that consonant with the *N*-oxides and the *N*-metho salts of the berbines, C-6 appears further upfield (56.23 ppm) in *cis*-1 than in *trans*-1 (57.54 ppm); while this trend is reversed for C-13 (41.32 ppm for the *cis*, and 37.42 ppm for the *trans* isomer). Furthermore, the *N*-methyl group appears further downfield in *cis*-1 (46.62 ppm) than in *trans*-1 (44.42 ppm).

The same trend as the above, *i.e.* a predominance of the *cis* over the *trans* salt, was also observed in the case of allocryptopine (4), 1-methoxy-allocryptopine (5), which we synthesized according to the method of Brossi and Trojánek (5) and hunnemanine (6). The ratios of *cis/trans* isomers calculated on the basis of peak areas were 83:17, 63:37 and 90:10, respectively. The spectral assignments have been summarized below.

cis-3trans-3

4

cis-4trans-4

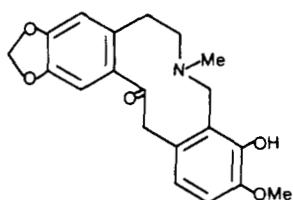
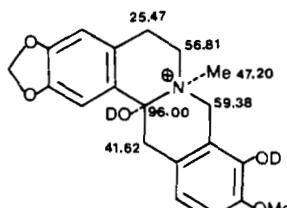
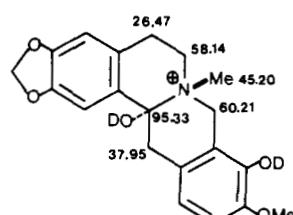
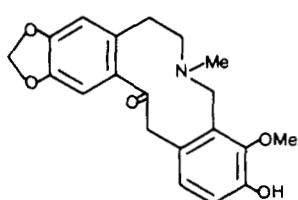
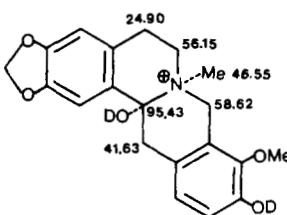
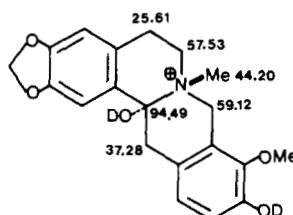
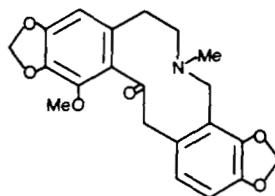
5

cis-5trans-5

Thalictropicine (7) was the one instance in which the *trans* isomer was found to be predominant. Peak areas in the spectrum of this material indicated a ratio of 16:84 in favor of the *trans*-7 salt. It is difficult to rationalize exactly why this should be the case, except to note that the thalictropicine is also the only protopine studied which incorporates a phenol at C-10.

Our present results, which indicate the usual predominance of the *cis* isomer in TFA-*d* solution, are also in accord with a study of the proton nmr spectrum of the alkaloid coulteropine (8) carried out some fifteen years ago by Stermitz, Coomes and Harris (6). They found that in CDCl_3 solution containing some TFA the salt of 8 exists as an equilibrium mixture of *cis* (major) and *trans* (minor) isomers.

It should be pointed out in conclusion that differences in percent composition (*cis* vs *trans*) for the protopinum salts studied are a reflexion of very small standard

6cis-6trans-67cis-7trans-78

free energy differences (ΔF°).⁵ It is not surprising, therefore, to find that variations in the substitution pattern can affect the *cis/trans* ratio.

EXPERIMENTAL

The ^{13}C nmr spectra were run at 90.56 Hz using a WM-360 instrument. The chemical shifts, in ppm, besides those listed above are as follows, with peaks due to the minor isomers indicated between parentheses. In some cases, these minor peaks were either too small to be observed, or else were situated underneath peaks due to the major isomers.

Protopine (**1**), 104.57 (104.49) (t), 107.84 (107.70) (t), 109.23 (109.63) (d), 111.01 (110.79) (d), 112.30 (112.18) (d), 124.35 (d), 122.74 (122.98) (s), 125.62 (125.99) (s), 126.08 (s), 128.57 (s), 146.70 (s), 149.33 (149.22) (s), 150.21 (150.90) (s), 152.09 (152.47) (s).

Allocryptopine (**4**), 57.42 (q), 62.84 (q), 103.99 (104.24) (t), 107.58 (107.50) (d), 110.76 (110.56) (d), 116.65 (d), 128.06 (d), 121.37 (121.88) (s), 122.36 (122.72) (s), 125.23 (125.68) (s), 128.61 (128.92) (s), 146.00 (s), 150.01 (150.59) (s), 151.83 (152.29) (s), 153.76 (153.68) (s).

⁵Using the well known relationship $\Delta F^\circ = -RT\ln K$, it is possible to calculate that a ratio of 65:35 for the two isomers represents a free energy difference of only 0.4 kcal at 25° between the *cis* and *trans* forms, while a ratio of 90:10 indicates again a small difference of 1.3 kcal.

1-Methoxyallocryptopine (5), 57.72 (57.06) (q), 62.62 (62.00) (q), 63.14 (q), 104.57 (t), 106.14 (d), 116.78 (d), 128.26 (129.28) (d), 119.44 (118.64) (s), 121.58 (122.06) (s), 122.84 (124.01) (s), 126.07 (127.69) (s), 138.64 (140.64) (s), 142.51 (144.57) (s), 146.03 (146.20) (s), 153.74 (s), 153.90 (153.99) (s).

Hunnemanine (6), 58.64 (q), 104.55 (105.22) (t), 108.24 (d), 111.37 (d), 115.54 (d), 123.30 (d), 114.42 (s), 122.57 (122.67) (s), 126.06 (s), 129.06 (s), 144.83 (s), 148.79 (s), 150.58 (s), 152.42 (s).

Thalicticine (7), 63.09 (62.97) (q), 104.37 (104.11) (t), 107.61 (108.29) (d), 110.69 (110.90) (d), 120.64 (120.85) (d), 122.14 (121.62) (d), 123.63 (123.23) (s), 125.76 (125.17) (s), 125.98 (125.42) (s), 129.09 (128.74) (s), 145.23 (145.75) (s), 149.22 (149.37) (s), 150.81 (150.12) (s), 152.40 (151.90) (s).

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