

THE METHYLENE SIGNATURE OF REDUCED ISOQUINOLINES: A PMR STRUCTURAL CORRELATION

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The ring B methylene proton signals in the pmr spectra of reduced isoquinolines appear as symmetrical triplets when nitrogen inversion is precluded, and as complex multiplets when the nitrogen atom can undergo inversion. The chemical shifts for the ring B protons on the carbon adjacent to nitrogen are dependent on the state of that nitrogen atom, and are in the following order of increasing δ values: Amines < protopines < enamines < amides < imines < imides < pyridones < N-oxides < pyridinium salts.

The 3,4-dihydro- or 1,2,3,4-tetrahydroisoquinoline systems are present in a large number of naturally occurring alkaloids. Over the years, studies of the pmr spectra of these natural bases have yielded a number of useful pmr structural correlations.^{1,2} However, the shifts of the ring B isoquinoline methylene protons have been largely ignored or relegated to a position of minor importance. This is due in part to the fact that the ring B protons in the tetrahydrobenzylisoquinolines, the proaporphines, the aporphines, the emetines, and related alkaloids, cannot be readily differentiated from some of the other protons present.

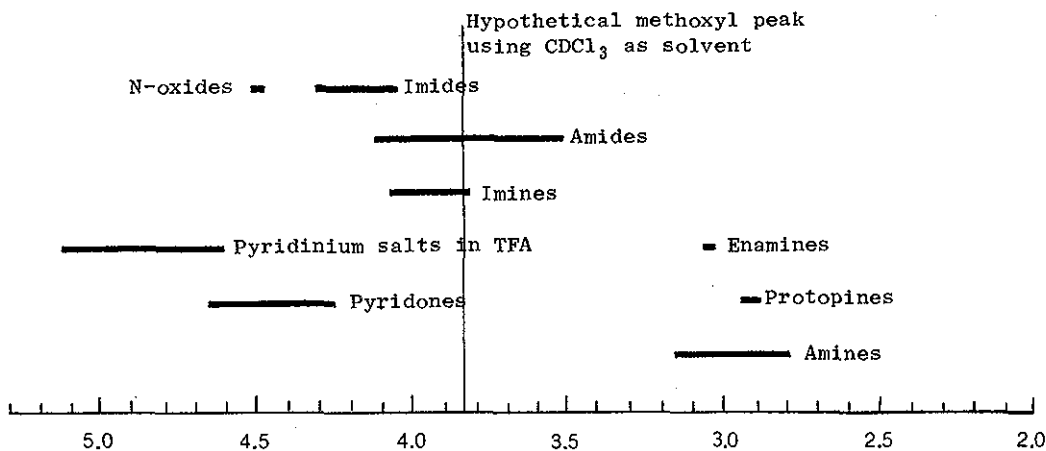
With the advent of a large number of reports describing synthetic, oxidative, and degradative, derivatives of reduced isoquinoline alkaloids, a more significant diagnostic value can be ascribed to the ring B methylene proton signals. It can be

stated that the pmr chemical shifts and splitting patterns of the ring B methylene protons adjacent to the nitrogen atom are a clear signature of the state of that nitrogen.

This empirical correlation presents two facets. Firstly, the ring B methylene proton signals appear as symmetrical triplets when nitrogen inversion is precluded (amides and quaternary salts), and as complex multiplets when the nitrogen atom can undergo inversion. Secondly, the proton chemical shifts of the ring B methylene attached to nitrogen appear over a broad range of δ values depending upon the state of the nitrogen. As a general approximation, the ranges are as follows using deuteriochloroform as solvent except where indicated otherwise: amines δ 2.79-3.17, protopines δ 2.88-2.95, enamines δ 3.03-3.05, amides δ 3.50-4.10, imines δ 3.82-4.05, imides δ 4.04-4.29, pyridones δ 4.23-4.66, N-oxides \approx δ 4.48, and pyridinium salts in trifluoroacetic acid δ 4.60-5.12 (see chart).

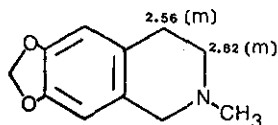
CHART

Approximate Chemical Shifts for the Ring B Methylene Protons Adjacent to Nitrogen in Reduced Isoquinoline Derivatives

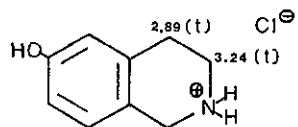


The examples shown below to illustrate the above correlation are mostly from our own collection of compounds with a few culled from the literature.

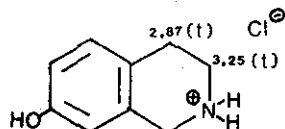
Amines



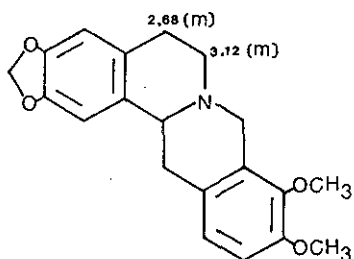
O-Methylcorypalline



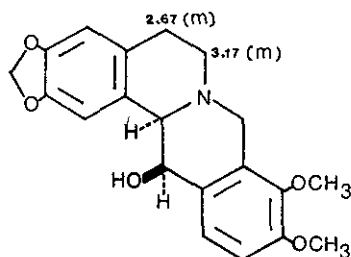
6-Hydroxytetrahydro-
isoquinoline.HCl³
(DMSO-d₆)



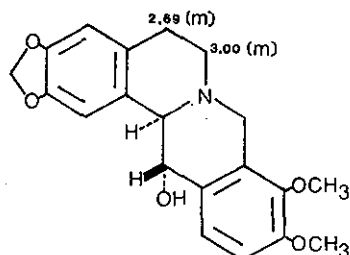
7-Hydroxytetrahydro-
isoquinoline.HCl³
(DMSO-d₆)



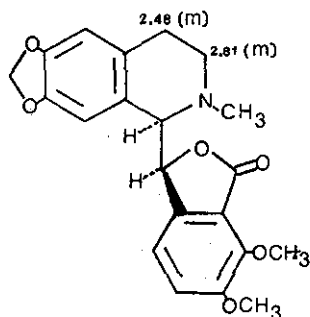
Canadine



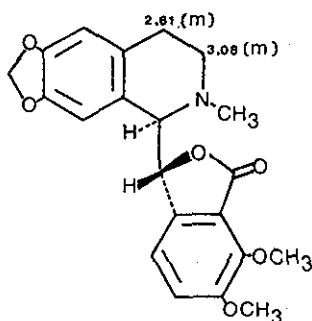
Ophiocarpine



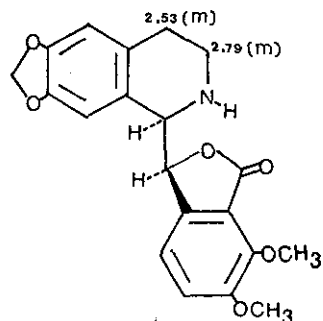
13-Epiophiocarpine



β -Hydrastine

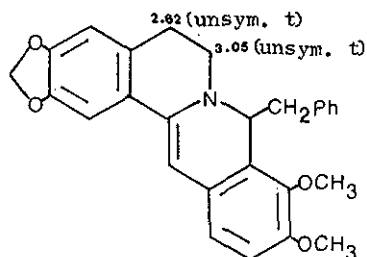
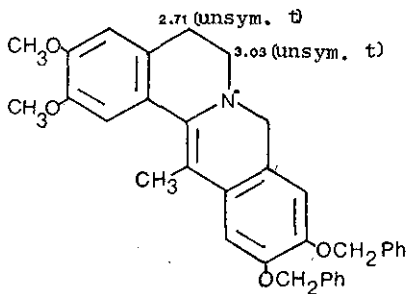


α -Hydrastine



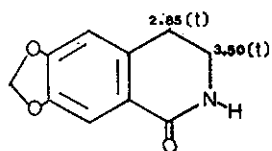
β -Norhydrastine

Enamines

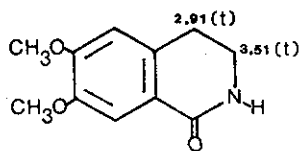


Amides

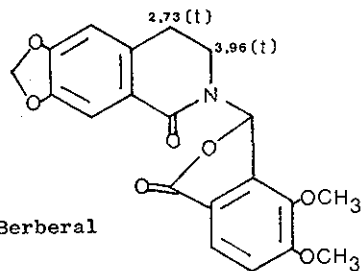
Amides present a somewhat complex picture, but if they are broken down into sub-groupings such as lactams and carbinol lactams, the ranges can be seen to be quite narrow.



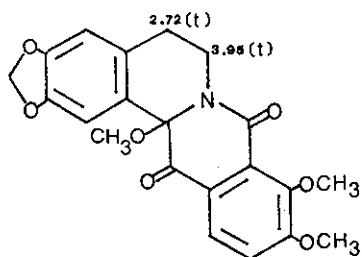
Noroxyhydrastinine



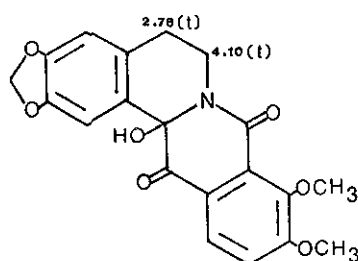
Corydaldine



Berberal

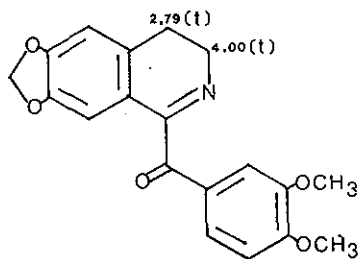
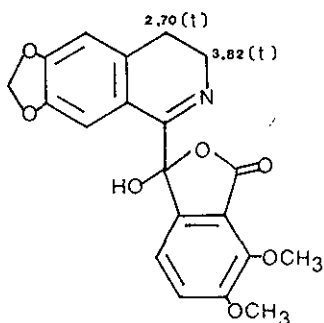
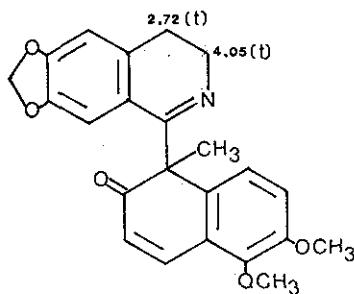
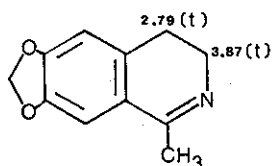


8,13-Dioxo-14-methoxycanadine



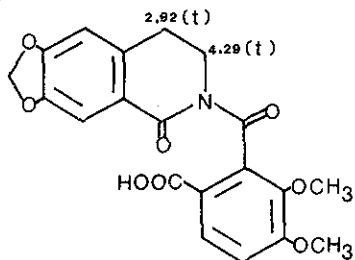
8,13-Dioxo-14-hydroxycanadine

Imines

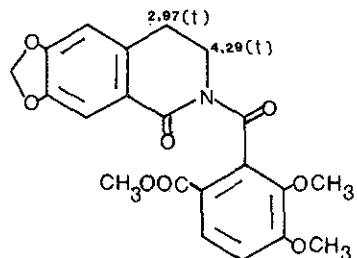


3,4-Dihydropapaveraldine

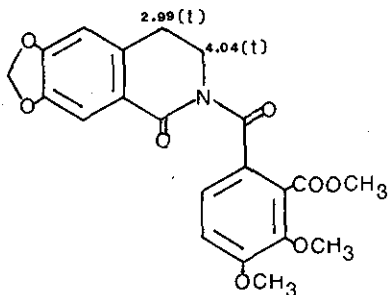
Imides



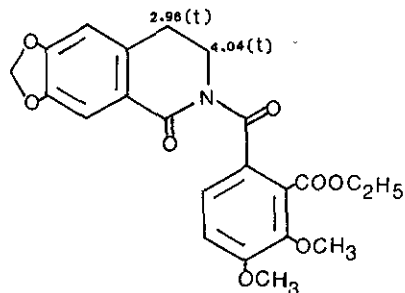
Anhydroberberilic acid



Methyl anhydroberberilate



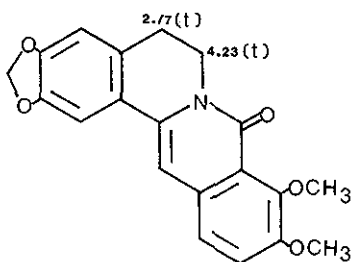
Methyl isoanhydroberberilate



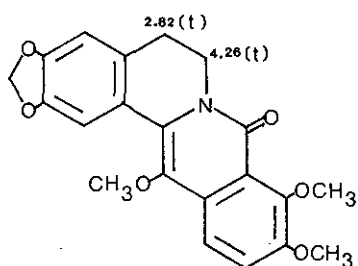
Ethyl isoanhydroberberilate

Pyridones

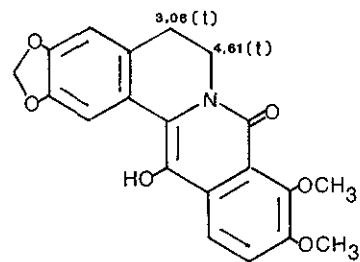
If ring C is a pyridone, the C-5 and C-6 methylenes will be present near δ 2.80 and 4.24, respectively. However, in the case of 13-hydroxyoxyberberine which is insoluble in deuteriochloroform and was, therefore, run in trifluoroacetic acid, protonation on the carbonyl oxygen occurred, so that both sets of values shifted downfield to δ 3.08 and 4.61, respectively; thus approximating those for the pyridinium salts given below. The case of synthetic compounds 1 and 2 are interesting since these species can be considered to be homologous pyridones, and indeed their chemical shifts point towards such an approximation.



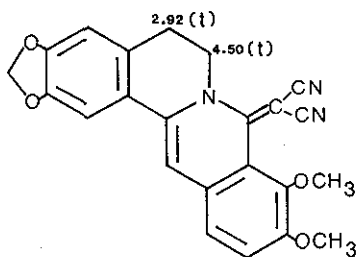
Oxyberberine



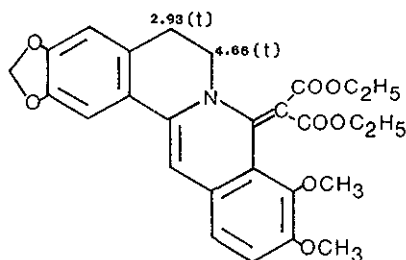
13-Methoxyoxyberberine



13-Hydroxyoxyberberine
(TFA)



1

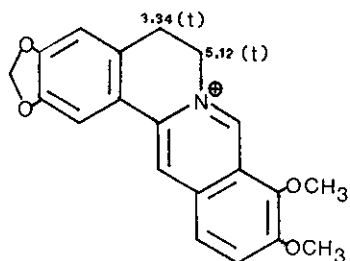


2

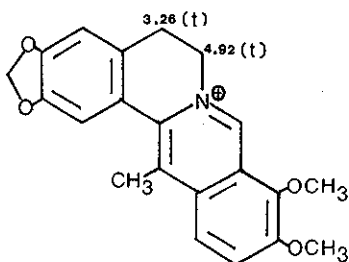
Pyridinium Salts

The range of values for the methylene adjacent to nitrogen in pyridinium salts is the furthest downfield for any of the categories of compounds considered in the present study. It should be noted, however, that trifluoroacetic acid is the solvent of choice for pyridinium salts, and that it tends to move chemical shifts downfield. An aromatic methoxyl peak falls around $\delta 4.1$ rather than near $\delta 3.84$ when that solvent is used.

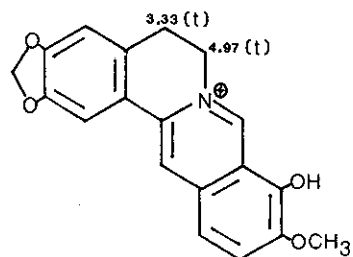
In the case of canadine N-oxide (\equiv tetrahydroberberine N-oxide) where a net plus charge is present on the nitrogen atom, the C-5 methylene protons appear as an overlapped triplet centered at $\delta 3.56$, while the C-6 methylene is present downfield at $\delta 4.48$.



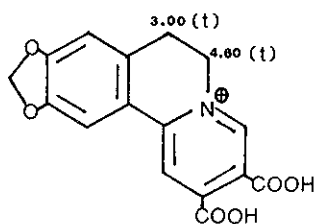
Berberine (TFA)



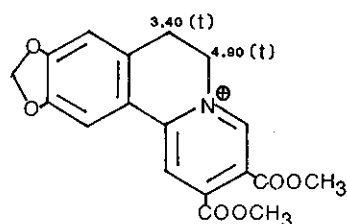
13-Methylberberine (TFA)



Berberrubine (TFA)



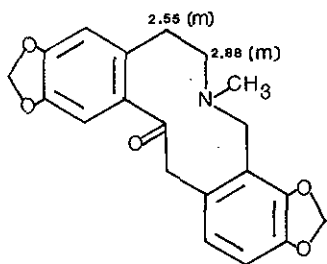
(TFA)



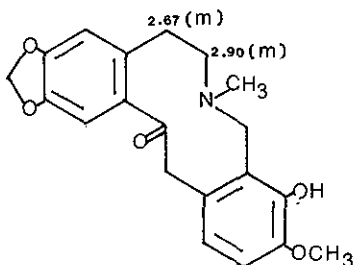
(TFA)

Protopines

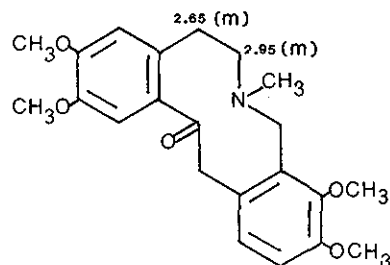
The protopines present an interesting case. The spectrum of protopine itself possesses a multiplet at $\delta 2.88$ and another at $\delta 2.55$, and these had been assigned previously to the C-5 and C-6 protons, respectively.⁴ However, the above discussion clearly indicates that in every single instance considered the C-6 protons are found downfield from the benzylic C-5 protons. Such should also be the case for the protopines where it has been clearly demonstrated by infra-red spectroscopy that there is a ground-state interaction between the carbonyl carbon and the basic nitrogen, so that the carbonyl group is appreciably of the amide type.⁵ This transannular effect imparts a partial positive charge to the nitrogen, which in turn induces a downfield shift of the neighboring C-6 protons. It follows that the assignments for the C-5 and C-6 protons for protopine should be reversed, with the downfield multiplet now ascribed to the C-6 methylene.



Protopine



Protothalipine⁶



Muramine⁶

In conclusion, it is suggested that future reports presenting spectral data for reduced isoquinoline derivatives include a listing of the chemical shifts and splitting patterns of the ring B methylene groups when possible, since this information can be of diagnostic value.

Acknowledgments. This project was supported by Grant HL-12971 from the National Institutes of Health.

References

1. M. Shamma, The Isoquinoline Alkaloids, Academic Press, New York (1972).
2. M. Shamma and J.L. Moniot, Isoquinoline Alkaloids Research 1972-1976, Plenum Press, New York (1978).
3. F. Schenker, R. Schmidt, T. Williams and A. Brossi, J. Heterocycl. Chem., **8**, 665 (1971).
4. N.S. Bhacca, L.F. Johnson and J.N. Shoolery, NMR Spectra Catalog, Vol. 1, Varian Associates, Palo Alto (1962), spectrum No. 339.
5. F.A.L. Anet, A.S. Bailey and R. Robinson, Chem. Ind. (London), 944 (1953).
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The values quoted for the C-5 and C-6 methylene protons have been reversed.

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