Mass Spectrometry and Proton and Carbon-13 Nuclear Magnetic Resonance Spectroscopy in Assigning Stereochemistry to Derivatives of Des-*N*-morphinan and Des-*N*-isomorphinan

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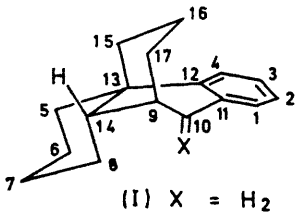
Summary Des-*N*-morphinan and des-*N*-isomorphinan derivatives can be differentiated by mass spectrometry or n.m.r. spectroscopy.

MASS spectrometry can be reliably used to differentiate between epimers[1] of certain des-*N*-morphinan (I) and des-*N*-isomorphinan (II) derivatives. When we synthesized 10-oxo-des-*N*-morphinan (III) and 10-oxo-des-*N*-isomorphinan (IV) for example, the pronounced differences observed in the mass spectra allowed us to assign structures readily.

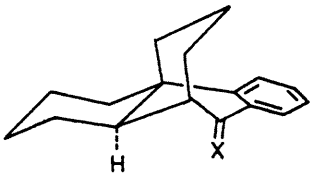
Compounds (III) and (IV) were synthesized in the following manner. Alkylation of $\Delta^{1,9}$-octalin-2-one with benzyl chloride in the presence of potassium t-pentyloxide in t-pentyl alcohol–benzene gave the monoalkylated product (V) (42%): b.p. 165—168° (0·3 mm.); λ_{max} (EtOH) 248 nm. (ϵ 10,470). Huang-Minlon reduction of (V) led to a mixture of benzyloctalins (80%), b.p. 132—133°, which cyclized[2] in polyphosphoric acid at 150° after 1 hr. to a 2 : 1 mixture of des-*N*-morphinan (I) and des-*N*-isomorphinan (II) (86%), b.p. 138—140° (0·6 mm.), λ_{max} (EtOH) 267 nm. (ϵ 870), 274 (780). The mixture of (I) and (II) was oxidized with chromium trioxide in aqueous acetic acid to a minor ketone, m.p. 72°, λ_{max} (EtOH) 255 nm. (ϵ 14,450), ν_{max} ($CHCl_3$) 1690 cm.$^{-1}$ and a major ketone, m.p. 118°, λ_{max} (EtOH) 254 nm. (ϵ 12,020), ν_{max} ($CHCl_3$) 1690 cm.$^{-1}$.

We had expected that the rigid des-*N*-morphinan and des-*N*-isomorphinan systems would show appreciable differences in their mass spectra to allow us to assign stereochemistry to the two ketones. This indeed turned out to be the case. In the spectrum (70 ev) of the ketone having m.p. 72° a very intense fragment peak is observed at *m/e* 198 with an accompanying metastable ion at *m/e* 163·5 for loss of propene from the molecular ion The *m/e* 198 ion is small in the spectrum of the ketone having m.p. 118°. The genesis of the *m/e* 198 ion to which we assign

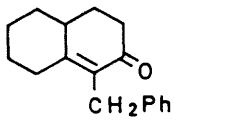
structure *a* is envisioned as cleavage of the trimethylene bridge at the benzylic position in the molecular ion followed by transfer of the C-14 proton to the radical site on C-15,

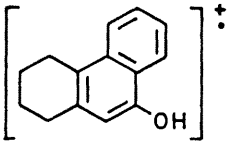


(I) X = H_2
(III) X = O

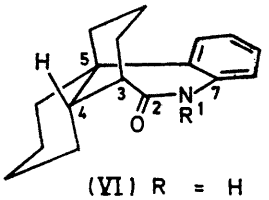


(II) X = H_2
(IV) X = O

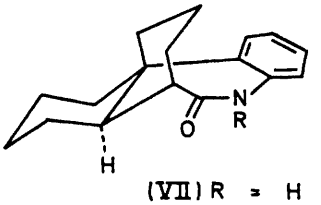




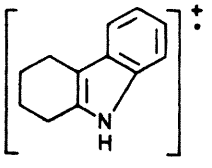
a, *m/e* 198



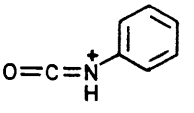
(VI) R = H
(VIII) R = D



(VII) R = H
(IX) R = D



b, *m/e* 171



c, *m/e* 120

and finally expulsion of propene *via* a McLafferty rearrangement. We concluded that formation of the methyl group in the elided propene would be facilitated in the isomer where the C-14 proton is *cis* to the trimethylene bridge. The minor ketone, m.p. 72°, therefore should have structure (III) and the major ketone, m.p. 118°, structure (IV).

More noteworthy are the dramatic differences observed in the mass spectra (Figure 1) of lactams (VI) [m.p. 199°; ν_{max} ($CHCl_3$) 1655, sh 1665 cm.$^{-1}$;[3] δ ($CDCl_3$) 8·99 (1H, broad), 6·95—7·50 (4H, m)] and (VII) [m.p. 223°; ν_{max} ($CHCl_3$ 1657 cm.$^{-1}$; δ ($CDCl_3$) 8·52 (1H, broad), 6·90—7·44 (4H, m)] obtained from treatment of ketones (III) and (IV) with sodium azide in benzene–sulphuric acid. The spectrum of (VI) shows its most intense fragment ion at *m/e* 171† [shifted to *m/e* 172 for (VIII)] and a metastable ion at *m/e* 114·8 which corresponds to the loss of propylketen from the molecular ion and formation of the tetrahydrocarbazole ion *b*. The *m/e* 171 ion is small in the spectrum of (VII), reflecting that formation of the methyl group in the elided propylketen is facilitated by the C-14 proton being *cis* to the trimethylene bridge. In the spectrum of (VII) there are a prominent fragment ion, actually the most intense one, at *m/e* 120† [shifted to *m/e* 121 for (IX)] and a metastable ion at *m/e* 56·5 which are absent in the spectrum of (VI).

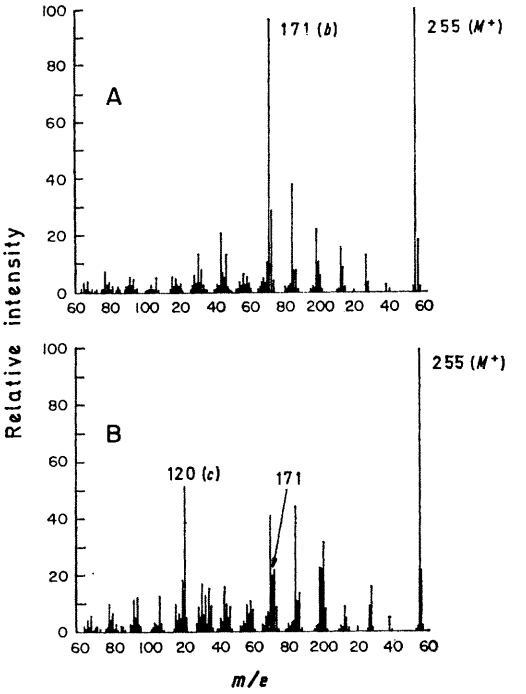


FIGURE 1. *Mass spectra of* (A) *lactam* (VI) *and* (B) *lactam* (VII).

The C-4 proton of (VII) is close to C-6 and presumably the *m/e* 120 ion is formed by transfer of the C-4 proton to C-6 in the molecular ion followed by cleavage of two bonds (between C-5 and C-6 and C-2 and C-3) to form an octalinyl radical and ion *c*.

To secure the structures, we next compared the proton and ^{13}C n.m.r. spectra‡ (Figure 2) of the epimeric ketones

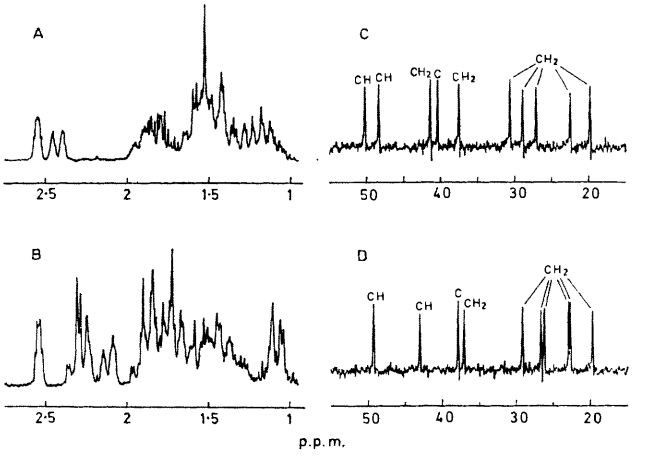


FIGURE 2. 220 MHz *N.m.r. spectra of* (A) 10-*oxo-des*-N-*morphinan* (III) *and* (B) 10-*oxo-des*-N-*isomorphinan* (IV). *Proton noise decoupled* 25·15 MHz ^{13}C *n.m.r. spectra of* (C) (III) *and* (D) (IV): 350 *mg.*/1·0 ml. *dioxan*, 8 mm. *tube*, 25 *scans with a* V-3530 *sweep unit. Aromatic and carbonyl absorptions are not shown.*

(III) and (IV). One would expect that the van der Waals interactions between the axial protons on C-6, C-8, C-15, and C-17 of (IV) should result in deshielding[4] of the protons and shielding[5] of the carbon atoms with respect to (III). Note in comparing the proton spectra that many of the methylene proton absorptions of (IV) are paramagnetically displaced compared to (III) whereas in comparing the ^{13}C spectra many of the methylene carbon absorptions of (IV) are diamagnetically shifted with respect to (III). Furthermore, there should be more proton absorption upfield for (III) as there are three protons (axial protons on C-6, C-8, and C-16) that lie in the shielding region of the aromatic ring whereas (IV) has only one proton (axial proton on C-16) in this region.

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‡ Chemical shifts are in p.p.m. relative to Me_4Si ($\delta = 0$). Quaternary, methine, and methylene carbons were identified by single frequency decoupling where the decoupler was turned to the exact frequency for irradiation of the dioxan protons. In this way quaternary carbons appeared as singlets, methine carbons as close-spaced doublets, and methylene carbons as close-spaced triplets.

[1] In only a few cases have the mass spectral differences of epimeric pairs of known structure been reported: A. Mandelbaum and D. Ginsburg, *Tetrahedron Letters*, 1965, 2479; K. Biemann, "Mass Spectrometry," McGraw-Hill, New York, 1962, p. 148; S. Meyerson and A. W. Weitkamp, *Org. Mass Spectrometry*, 1968, **1**, 659.

[2] Similar cyclizations have been studied extensively: R. Grewe, *Angew. Chem.*, 1947, **59**, 194; O. Schnider and A. Grüssner, *Helv. Chim. Acta*, 1949, **32**, 821; R. Grewe and A. Mondon, *Chem. Ber.*, 1948, **81**, 279; R. Grewe and W. Friedrichsen, *ibid.*, 1967, **100**, 1550; Y. K. Sawa, K. Kawasaki and S. Maeda, *Chem. Pharm. Bull. (Tokyo)*, 1960, **8**, 960; K. Kawasaki and H. Matsumura, *ibid.*, 1969, **17**, 1158. Recently Grewe's cyclization has been applied in the total synthesis of (±)-lycopodine [G. Stork, R. A. Kretchmer, and R. H. Schlessinger, *J. Amer. Chem. Soc.*, 1968, **90**, 1647].

[3] P. T. Lansbury and N. R. Mancuso, *J. Amer. Chem. Soc.*, 1966, **88**, 1205.

[4] S. Brownstein, *J. Amer. Chem. Soc.*, 1959, **81**, 1606.

[5] D. M. Grant and B. V. Cheney, *J. Amer. Chem. Soc.*, 1967, **89**, 5315.