Carbon-13 Magnetic Resonance Spectra of Cocaine Metabolites and Derivatives

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The carbon-13 nmr spectral assignments of cocaine, *O*-benzoylecgonine, ecgonine, norcocaine, *O*-benzylnorecgonine, norecgonine, and *N*-allylnorcocaine were made. The assignments were primarily based on the correlation of substituent effects within series and selective proton irradiation studies.

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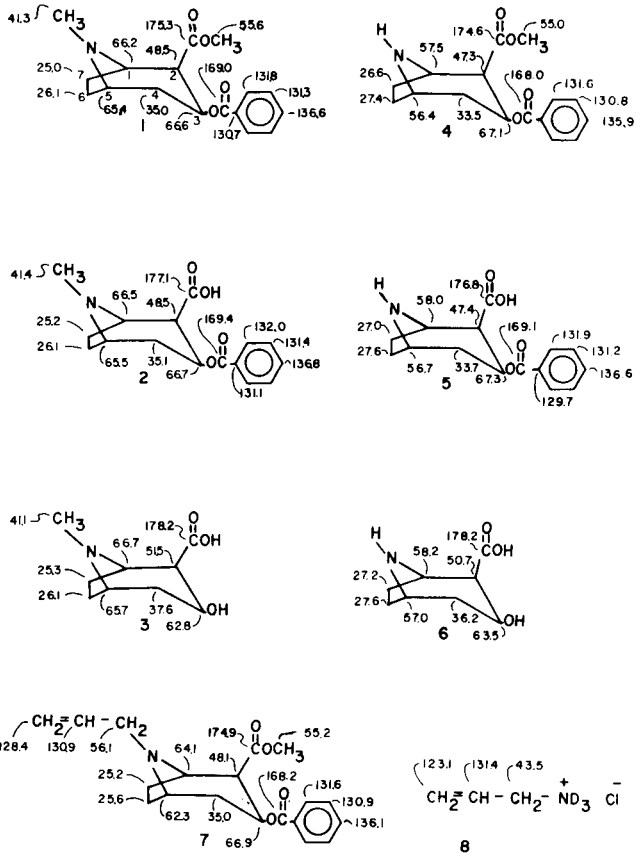
In conjunction with our work on the chemistry and pharmacological activity of cocaine metabolities and derivatives (1,2) we undertook a C-13 nmr study of these compounds in order to confirm their structures and to aid in the structure elucidation of new metabolities and derivatives.

The recent report by Stenberg, *et al.*, (3) prompts us to report our assignments for the C-13 nmr spectra of cocaine (**1**) and the assignments of six other cocaine metabolites and derivatives; *O*-benzoylecgonine (**2**), ecgonine (**3**), norcocaine (**4**), *O*-benzoylnorecgonine (**5**), norecgonine (**6**), and *N*-allylnorcocaine (**7**).

Most of the spectral assignments for **1** were readily made from the observed chemical shifts and peak multiplicities in off-resonance H-1 decoupling experiments. The two quartets that were observed at 41.3 and 55.6 ppm were assigned to the *N*-methyl and *O*-methyl, respectively. This assignment was consistent with the usual observation of *O*-methyl groups at a more downfield location, with the *N*-methyl chemical shift reported for atropine (4), and with the observation that the peak at 55.6 ppm collapsed to a singlet when the protons of the *O*-methyl group were irradiated.

The assignments of the two carbonyl singlets of **1** at 175.3 and 169.0 ppm are in agreement with the earlier assignments (3) which were based on a comparison of the carbonyl chemical shifts of methylacetate (170.7 ppm) and methyl benzoate (167.0 ppm). The assignments were also substantiated in the present study in that only the methyl ester carbonyl peak shifted on conversion of **1** to **2**. The assignments of the aromatic carbons are also in agreement with the earlier work of Stenberg, *it al.*, (3).

However, the assignments of the three doublets that were observed for C_1, C_3 and C_5 were not well substantiated by Stenberg, *et al.*, (3) and our assignments were not in agreement. As a means of aiding in the assignment, the proton on C_3 was irradiated and it was observed that the peak at 66.6 ppm collapsed to a singlet. It was also observed that when the two methine protons alpha to the nitrogen were irradiated, the two peaks at 66.2 and 65.4 ppm collapsed to singlets. In order to determine which of these latter peaks corresponded to C_1 and C_5, it was necessary to draw on two arguments. If acyclic hydrocarbons were used as models, one would expect the ester



group to move the chemical shift of C_1 9.0 ppm downfield (5). If 2-substituted norbornanes were used as models, one would expect a 5.1 ppm downfield shift (5). Based on these arguments, C_1 was assigned to the peak at 66.2 ppm and C_5 to the one at 6.4 ppm. As an additional argument in favor of this assignment, it can be seen that the conversion of **1** to **2** or **3** has a slightly greater effect on the adadjacent carbon as would be expected.

Triplets were also observed at 25.0, 26.1, and 35.0 ppm for **1**. The peak at 35.0 was assigned to C_4 because methylenes alpha to a hydroxyl are usually more downfield and because of the change of these peak positions in analogs **2** and **3**. From a comparison to 2-substituted norbornanes (5), it was predicted that C_7 would be 1.3 ppm upfield from C_6 which lead to our assignments of C_7 at 25.0 and C_6 at 26.1 ppm. As an additional argument for the assignment, in compounds **1**, **2**, and **3** the C_6 peak of each ap-

pears at 26.1 ppm while the C_7 peak was slightly upfield in **1** compared to that in **2** and **3**. Stenberg *et al.* (3) had assigned the upfield peak to C_6.

The assignments of the chemical shifts of **2** followed those of **1** in a very direct manner. All of the peaks of **2** were nearly identical except that the methyl group of the ester was missing and the methyl ester carbonyl showed a slight downfield shift. The spectrum of **3** was found to be nearly identical to **2** except the benzoyl peaks were missing. Removal of the benzoyl group also produced slight downfield shifts for C_2 and C_4 while an upfield shift was observed for C_3. A nearly identical change was also observed following the conversion of **5** to **6**.

Following the conversion of **1** to **4**, nearly the identical spectrum was observed except the *N*-methyl peak was missing and two of the three methine peaks that had been closely grouped (65.4-66.6 ppm) had moved upfield considerably. The peaks for C_1 and C_5 nearly overlapped the methyl peak but they could easily be distinguished in the single frequency off-resonance decoupling experiments.

Nearly the identical spectra were observed for **5** and **4** except for the absence of the methyl signal. Only the slight changes in the chemical shifts of C_1 and C_7, and the methyl ester carbonyl were significant. These subtle changes were also the same that had been observed for the corresponding groups in **1** and **2**. The spectrum of **6** was found to be nearly identical to that for **5** except that the benzoyl peaks were missing. As had been observed for **2** and **3**, C_2 and C_4 were slightly more downfield and C_3 more upfield as would be expected in the comparison of an alcohol and its ester.

The assignments for **7** were made primarily through comparison of the spectra of **1** and **8**. The major difference in the upfield spectrum of **7** was a peak missing at 41.3 (quartet) and the appearance of a peak at 56.1 ppm (triplet) that was assigned to the alpha carbon of the allyl group. The two olefinic carbons overlapped the peaks for the aromatic carbons which increased the experimental difficulties in determining the peak multiplicities. From a comparison to **8**, it was possible to assign the peaks at 128.4 and 130.9 ppm for **7** to the gamma and beta carbons.

In conclusion, the three *nor*-metabolites could easily be characterized and distinguished from the three *N*-methyl compounds by the chemical shifts of the C_1 and C_5 carbons. Within each of these series, the three compounds were easily distinguished by the presence or absence of the two ester groups. In identification of these metabolites, care should be taken to avoid the facile interconversion of **5** and *N*-benzoylnorecgonine (6). Though the spectrum of the latter compound was not obtained as a part of this study, it would propably have considerably different chemical shifts for C_1 and C_5.

EXPERIMENTAL

The ^{13}C nmr spectra were obtained using a JOEL FX-60 Fourier transform spectrometer operating at 15 MHz for carbon spectra and 59.75 for proton spectra. All spectra of the compounds were obtained as their hydrochloride salts in deuterium oxide (100 mg./0.5 ml.) using 5 mm sample tubes a 25°. All chemical shifts were measured relative to the trimethylsilyl group of sodium 2,2-dimethyl-2-silapentane-5-sulfonate that was added to each sample.

Decoupled spectra were obtained using a 1.0 KHz noise modulated carrier centered approximately 300 Hz downfield from the proton resonance of the trimethylsilyl group. Partially coupled spectra were obtained using the single frequency off-resonance technique where the proton irradiation frequency was placed 300 Hz upfield from the ^1H trimethylsilyl peak.

Specific proton group irradiation experiments were conducted using a RF oscillator whose frequency was controlled relative to the deuterium lock oscillator and the observation RF oscillator. The irradiation frequency was determined by direct measurement of the proton spectra obtained from the identical sample used for obtaining the carbon spectra.

Cocaine hydrochloride was obtained from Mallinckrodt Chemical Works. *O*-Benzoylecgonine was obtained from Syvia Corporation. Ecgonine hydrochloride was obtained by the hydrolysis of cocaine hydrochloride with 10% hydrochloric acid as previously described (7). Norcocaine hydrochloride was prepared as previously described (1) as was *N*-allylnorcocaine hydrochloride (2). *O*-Benzoylnorcocaine was prepared by the aqueous hydrolysis of norcocaine (6). The spectrum was obtained by the addition of deuterium chloride to an aqueous solution of the free base. Norecgonine was obtained by the subsequent hydrolysis of this free base with hydrochloric acid.

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REFERENCES AND NOTES

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