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CONFIGURATION AND TOTAL ASSIGNMENT OF THE ^{1}H- AND ^{13}C-NMR SPECTRA OF THE ALKALOID HOLSTIINE

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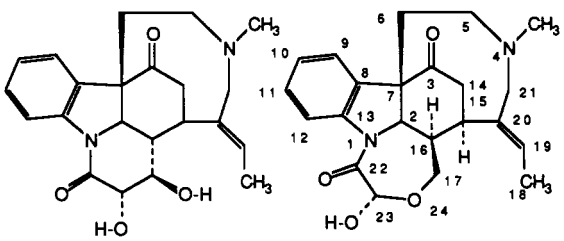
ABSTRACT.—The alkaloid holstiine [**2**] was reisolated from *Strychnos henningsii* and subjected to a total structural assignment through the concerted application of a number of two-dimensional nmr techniques that included COSY, HC-COSY, HOHAHA, NOESY, and proton-detected long-range heteronuclear chemical shift correlation (HMBC). The revised structure of holstiine proposed by Bisset *et al.* was rigorously confirmed by these methods. Unequivocal assignments of the ^{1}H- and ^{13}C-nmr spectra of holstiine are reported. The stereochemistry of the 23-hydroxyl group is finally established as α on the basis of NOESY data.

Bosly (1) reported in 1951 the isolation from *Strychnos holstii* of four new alkaloids, one of which was holstiine [**1**]. In the intervening years, *S. holstii* has been reclassified and is now included in the species *Strychnos henningsii* Gilg (Breviflorae) (2). More recently, Bisset *et al.* (3) have suggested a revision of the structure of holstiine, which is shown by **2**, based on the structures of *O*-demethylstilanine and related alkaloids isolated from *S. henningsii*.

At present, the accepted structure of holstiine [**2**] hinges upon relatively low-field (90 MHz) ^{1}H-nmr data. A computer search of the literature from 1975 to the present failed to uncover any studies at high field. Likewise, there have been no 2D nmr studies of this interesting alkaloid. Finally, the stereochemical orientation of the hydroxyl group at the 23 position also remains in question. Because *S. henningsii* is one of the most intensively studied of the African *Strychnos* species and has been shown to contain a wealth of structurally important alkaloids (4), we felt it important to reisolate holstiine and to establish, finally and unequivocally, the stereochemical orientation of the 23-hydroxyl group and the total assignment of the ^{1}H- and ^{13}C-nmr spectra of the molecule. Thus, we describe the results of a concerted 2D nmr study of holstiine that has confirmed the structure of the compound as **2**, providing, in the process, an unequivocal



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total assignment of the ^{1}H- and ^{13}C-nmr spectra of the molecule in conjunction with the orientation of the 23-hydroxyl group.

ASSIGNMENT OF THE ^{1}H-NMR SPECTRUM.—As with strychnine (5,6), the aliphatic portion of the ^{1}H-nmr spectrum of holstiine is subdivisible into four essentially isolated spin systems at 300 MHz. Constituents of these spin systems are readily established using the H-19 vinyl proton resonating at 5.51 ppm and the H-2 indole proton resonating at 4.84 ppm as starting points in the analysis of the COSY spectrum (7) of holstiine.

The H-19 vinyl proton is readily correlated with a methyl doublet resonating at 1.65 ppm, which may be assigned as the Me-18 group, and a geminal pair of protons resonating at 3.56 and 3.42 ppm, which can be assigned as the anisochronous C-21 methylene protons.

Beginning from the H-2 indole proton resonating at 4.84 ppm, we first established a correlation to the H-16 methine proton, which resonates at 2.33 ppm. The H-16 methine proton was correlated, in turn, to a geminal methylene pair resonating at 4.15 and 3.85 ppm, which we assigned to the C-17 methylene protons, and to a further methine proton resonating at 3.21 ppm, which may be assigned as H-15. Finally, the H-15 methine resonance was correlated with the C-14 methylene protons, which resonate at 2.49 and 2.27 ppm.

The connectivity network just established was independently assembled in a series of HOHAHA spectra (8,9) recorded with mixing times ranging from 20 to 100 msec. [This experiment is also referred to using the acronym TOCSY (TOtal Correlation SpectroscopY) after the work of L. Braunschweiler and R.R. Ernst (10). For a discussion on the implementation of this experiment on Nicolet NT-series instruments, see Johnston *et al.* (11). Details may also be obtained from the authors upon request.] In the latter spectra in this series, we were looking for potential long-range couplings which would bridge the quaternary carbons in the molecule, thereby linking larger structural fragments together. These responses were not, however, observed and it was thus necessary to resort to long-range heteronuclear shift correlations, which are discussed below.

At this point it should be noted that the series of operations described previously, when evaluated in light of a heteronuclear chemical shift correlation spectrum (HC-COSY) (12,13) to confirm the geminal character of the C-17 methylene protons, establishes **2** as the correct structure for holstiine. This observation was made by ruling out the possibility of successive hydroxyl methines required if **1** were the correct molecular structure.

For the protons of the 5,6-ethylene bridge, no convenient entry point into the assignment of these resonances is available from either the COSY spectrum or chemical shift arguments. Hence, these protons, which resonate at 3.10, 2.80, 2.66, and 1.95 ppm, were left unassigned for the moment. It should be noted, however, that the HC-COSY spectrum does allow the association of the protons resonating at 3.10 and 1.95 ppm with the carbon resonating at 45.76 ppm; the remaining protons resonating at 2.80 and 2.66 ppm were correlated with the carbon resonating at 53.47 ppm.

Finally, the H-23 methine proton appeared as a singlet resonating at 5.34 ppm which directly correlates with the carbon resonating at 92.75 ppm.

ASSIGNMENT OF THE ^{1}C-NMR SPECTRUM.—Where proton resonance assignments could be unequivocally made, protonated carbon resonance assignments directly followed from the HC-COSY spectrum (Table 1). In all cases, it was possible to confirm independently all of the carbon resonance assignments from a series of proton-detected long-range heteronuclear chemical shift correlation spectra (HMBC) acquired using the sequence described by Bax and Summers (14). Modifications to the spectrometer to

allow the performance of this experiment are described in our previous work (15). The HMBC experiment was also compared to conventional heteronuclear-detected long-range correlation experiments in a review by Martin and Zektzer (16).[2]

The most important correlations extracted from the wealth of information contained in the HMBC spectra were those which bridged quaternary carbons, heteroatoms, and functional groups that separate the isolated proton spin systems. These we considered in some detail. Long-range correlations observed in the HMBC experiment performed are summarized in Table 1.

Key substituents separating the aliphatic spin systems were: the C-3 carbonyl moiety, the *N*-methyl group at the 4-position, the C-7 quaternary carbon, the C-20 quaternary vinyl carbon, the C-22 amide carbonyl, and the O-24 ether linkage. There were also two bridgehead carbons in the indole nucleus which required assignment. We considered each of these features of the molecular structure in turn.

TABLE 1. Proton and Carbon Resonance Shift Assignments and Long-range Correlation Responses for Holstiine [**2**].

Position	δ ^{1}H	J_{HH} (Hz)[a]	δ ^{13}C (±0.02 ppm)	Long-range Responses in HMBC	
				10 Hz	6 Hz
3			191.01	14α/β	2, 6, 14α/β, 15
22			167.87	23	2, 23
13			139.93	2, 9, 11	2, 9
20			135.62	14α, Me-18	14α, 15, Me-18
8			132.72	2, 10, 12	2, 10 12
11	7.31	dt; 7.9, 1.0	128.76	9	9
19	5.51	q; 6.8	125.81	Me-18, 21α/β	15, Me-18, 21α/β
10	7.14	dt; 7.5, 0.5	125.38	12	12
9	7.52	dd; 7.9, 0.5	124.94	11	11
12	8.22	dd; 7.9, 0.5	116.89	10	10
23	5.34	—	92.75	17α/β	17β
17α	4.15	dd; 12.6, 3.6	74.30	2, 23	2, 23
17β	3.85	dd; 12.6, 10.4			
21α	3.56	dd; 14.9, 1.5	69.40	15, 19, N-Me	15, 19, N-Me
21β	3.42	d; 14.9			
2	4.84	d; 10.4	67.24	6, 15, 17α	6, 15, 17β
7			55.78	2, 5b, 6a, 14β	2, 5b, 6α/β, 14β
5α	2.80		53.47	N-Me	6a, N-Me
5β	2.66	ddd; 14.2, 8.6, 0.5			
6α	3.10	dd; 13.4, 8.6	45.76	2	2
6β	1.95	ddd; 13.4, 7.4, 0.5			
14α	2.49	dd; 16.9, 6.5	43.50	—	15, 16
14β[b]	2.27	dd; 16.9, 1.7			
16	2.33	ddd; 10.4, 3.6, 0.8	42.38	14β	14β, 15
N-Me	1.91		40.04	5b, 21a/b	21α/β
15	3.21		34.11	14α, 21β	14α, 21β
18	1.61	dd; 6.8, 1.5	12.98	—	—

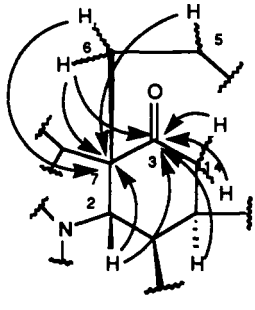
[a]Coupling constants were extracted from a resolution-enhanced 64K proton spectrum.

[b]Assignment of the stereochemistry in this case is based on the location of the two protons relative to the carbonyl. H-14β, which is in the plane of the carbonyl, would be expected to be somewhat more shielded than H-14α. Hence, H-14α is assigned as the downfield member of the geminal pair, resonating at 2.49 ppm.

[2]An invited review by G.E. Martin and R.C. Crouch will appear at a later date in *J. Nat. Prod.*

Linking structural fragments flanking the C-3 carbonyl attached to the C-7 quaternary carbon presented an interesting structural challenge. The 10 Hz optimized HMBC spectrum was not particularly illuminating with regard to the C-3 carbonyl. The only responses correlated with C-3 were the $^2J_{CH}$ couplings to the anisochronous C-14 methylene protons. Fortunately, in contrast, the 6 Hz optimized spectrum was much richer in correlations to the carbonyl. In particular, correlations were observed to both C-14 methylene protons as well as to H-2, H-15, and H-6b. The latter couplings to the H-6b resonance allowed the assignment of the C-5 and C-6 resonances and their respective protons. Extending our consideration to the long-range couplings to the C-7 quaternary carbon resonance, we observed that it exhibits couplings to the H-2, H-5b, H-6a, and H-14β protons in the 10 Hz optimized HMBC spectrum and to the H-2, H-5b, H-6α/β, and H-14β protons in the 6 Hz optimized HMBC spectrum. Long-range correlations to C-3 and C-7 are denoted by arrows in **3**. When combined with the connectivity information from the COSY spectrum, this established unequivocally the structure of the carbonyl-containing six-membered ring and assigned the protons and carbons of the C-5, C-6 ethylene bridge in a fashion which is completely consistent with the structure proposed by Bisset *et al.* (3).

Next it was necessary to establish unequivocally the structure of the oxazepine ring proposed by Bisset *et al.* (3), which is the major structural difference in **2** from the structure **1** proposed by Bosly (1). Correlations within the oxazepine ring are shown by **4**.



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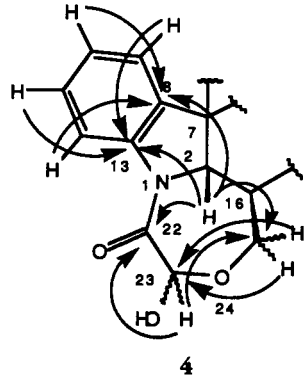

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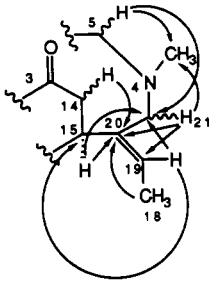
Importantly, the carbonyl, C-22, was correlated with the H-23 methine proton, which was in turn correlated with C-17 across the O-24 ether linkage in the 10 Hz HMBC spectrum. The amide carbonyl was also linked to the H-2 resonance in the 6 Hz optimized HMBC spectrum. Further, the H-2 resonance was long-range coupled to C-17 in the 10 Hz spectrum, while conversely the H-17b proton was long-range-coupled to C-2 in the 6 Hz optimized HMBC spectrum. These correlations effectively establish the structure of the oxazepine skeletal moiety and position it within the molecular framework in a manner consistent with the proposed structure of Bisset *et al.* (3).

Recognizing that C-7 generally resonates furthest upfield of the aromatic carbons in the ^{13}C-nmr spectrum of indole alkaloids (C-12 here because of the numbering system), C-12 and hence H-12 may be readily assigned from the HC-COSY data. Given these assignments as a starting point, the balance of the protonated carbon and proton assignments in the aromatic ring follow directly. Using this information the 10 Hz HMBC spectrum then readily afforded the unequivocal assignment of the C-8 and C-13 quaternary carbon resonances at 132.72 and 139.93 ppm, respectively. Long-range correlations observed to these quaternary carbons are also shown by **4**.

The remaining breaks in the proton-proton connectivity network at this point were associated with the *N*-methyl group at the 4 position and the C-20 vinyl quaternary carbon. Because these sites in the molecular framework are noncontiguous, they may be bridged independently of one another.

Two means of establishing the connectivity network across the *N*-methyl substituent at the 4 position are available. The 10 Hz optimized HMBC spectrum afforded a correlation between H-5a and C-21, thus directly establishing the correlation pathway required. A less direct means of linking structural entities through the *N*-methyl substituent was afforded by responses correlating H-5b, H-21a, and H-21b with the *N*-methyl carbon resonance. Both of these sets of correlations are shown by **5**.

The remaining site to be considered was the C-20 vinyl quaternary carbon. Here again responses were observed which correlate to C-20 as well as across this quaternary center to the flanking carbons. Responses were observed in the 10 Hz optimized HMBC spectrum that correlated H-15 with C-21 and conversely H-21b with C-15. Responses were observed in the 6 Hz optimized spectrum linking both H-15 and H-21b to the C-20 quaternary carbon via $^2J_{CH}$ coupling pathways in both cases. Several three-bond long-range couplings into C-20 were also observed; these are contained in Table 1. Once again, these coupling pathways are shown by **5**.



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STEREOCHEMICAL ASSIGNMENTS.—At this point, the ^{13}C-nmr spectrum of holstiine had been unequivocally assigned and the structure independently generated and shown to be consistent with that proposed by Bisset *et al.* (3). All of the proton identities had been established, but the stereochemical orientations of the protons remained to be assigned in the case of the geminal methylene pairings. The sole remaining major structural feature which remained to be determined was the stereochemical orientation of the 23-hydroxyl substituent. Although such information could presumably be obtained from a one-dimensional nuclear Overhauser difference (nOeds) spectrum, it seemed more useful to establish some of the geminal methylene stereochemical assignments via a NOESY experiment.

Though there is a relative dearth of NOESY data for small to medium-sized organic molecules, there have been some successful applications reported (17–20). One major concern in applying the NOESY experiment to small to medium-sized molecules is the suppression of responses due to scalar coupling (21,22). Ellena *et al.* (17) have surmounted this problem with a modified NOESY sequence in which a 180° pulse is successively repositioned during the mixing time to disrupt coherent (scalar) transfer of magnetization. Using the Hutton NOESY sequence, a series of spectra were recorded for holstiine [**2**] using mixing times which ranged from 200 msec to 1 sec.

Biogenetically, we have a convenient starting point from which the stereochemical assignments can be made in the form of the proton at the 15 position, which is always α. Given the orientation of the 15α proton as a starting point, we could establish the

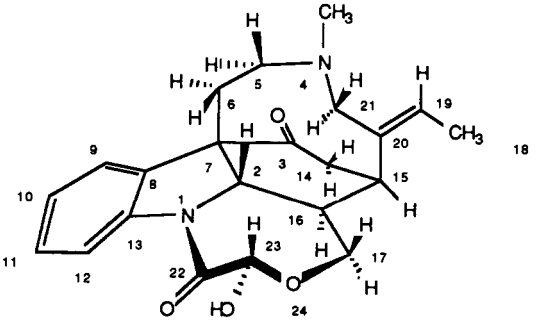
orientation of the key proton at the 2 position as β because it fails to exhibit an nOe response correlating it with 15α. Given this key position, we next embarked upon the stereochemical assignment of the oxazepine ring and with it, the determination of the orientation of the 23-hydroxyl substituent, which has remained equivocal since the proposal of the correct structure by Bisset *et al.* (3).

Thus, a strong nOe response was observed in spectra with mixing times ranging from 400 to 800 msec, which correlated the H-2 and H-23 resonances. This response resolves, finally, the question of the stereochemical orientation of the 23-hydroxyl substituent. To account for an nOe response between H-2 and H-23, the 23-hydroxyl substituent must be in the α orientation, leaving H-23 in the β orientation to account for the observed nOe. A similarly intense nOe response was observed between H-23 and the H-17 resonance at 3.85 ppm, which establishes the orientation of the latter resonance in the β orientation. The stereochemistry of the oxazepine ring is internally consistent, because an nOe response was also observed between H-2 and the upfield H-17 proton, which was hence assigned as H-17α. Further confirmation of this assignment was provided by an nOe linking H-15 and H-17α.

One other structural feature confirmed by the NOESY data was the orientation of the methyl group of the ethylidene structural unit as proposed by Bisset *et al.* (3). A strong nOe response between the H-15 proton and the Me-18 group confirmed the orientation of the ethylidene subunit. The H-19 vinyl proton also exhibited an nOe response to one of the H-21 protons, specifically that resonating at 3.42 ppm, which was thus established as H-21β. Conversely, the proton, which must now be assigned as H-21α, exhibited nOe responses to both H-2 and H-17β.

Further useful correlations partially established the stereochemical assignments of the 5/6 ethylene bridge. Beginning from the H-19 vinyl proton, we observed an nOe to the *N*-methyl group, which also exhibited an nOe to the H-21β resonance. There was a further nOe response to the H-5 proton resonating at 2.66 ppm, which was thus assignable as H-5β, which left its counterpart resonating at 2.80 ppm assignable as H-5α. Unfortunately, there were no nOe responses in any of the spectra recorded which gave any information about the stereochemical identity of the H-6/H-6′ protons. The COSY spectrum, however, shows a strong coupling response between H-5α and H-6 resonating upfield at 1.95 ppm. By examining a Dreiding model, the dihedral angle between H-5α and H-6β is essentially 180°, which would account for a large coupling. In contrast, the dihedral angle between H-5 and H-6 is essentially 90°, and only a very weak coupling response was observed in the COSY spectrum. Hence, H-6β was assigned as the proton resonating at 1.95 ppm while H-6α was assigned to the resonance at 3.10 ppm.

A perspective drawing of holstiine showing the stereochemical orientations of the protons as deduced from the nOe study just described is presented by **6**.



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EXPERIMENTAL

INSTRUMENTATION.—All spectra were recorded using a Nicolet NT-300 wide-bore spectrometer controlled by a Model 293-C pulse programmer and sample of 30 mg of holstiine dissolved in 0.5 ml of $CDCl_3$ in a 5-mm nmr tube at 30°. The sample of holstiine [**2**] used in this study was isolated from the root bark of *S. henningsii* using the procedure described in the work of Massiot *et al.* (23). The spectrometer was equipped for all experiments with a 5-mm $^1H/^{13}C$ dual tuned probehead with normal geometry (i.e., the ^{13}C coil closest to the sample). The spectrometer was modified as described in our previous work (15) to deliver ^{13}C pulses from the decoupler necessary for the performance of the Bax/Summers HMBC experiment (14). Pulse widths were calibrated as follows: 90° ^1H observe pulse = 17.1 μsec; ^{13}C observe pulse = 19.0 μ sec; ^1H decoupler 90° pulse = 24.6 μsec; ^{13}C 90° decoupler pulse = 9.8 μsec calibrated using a sample

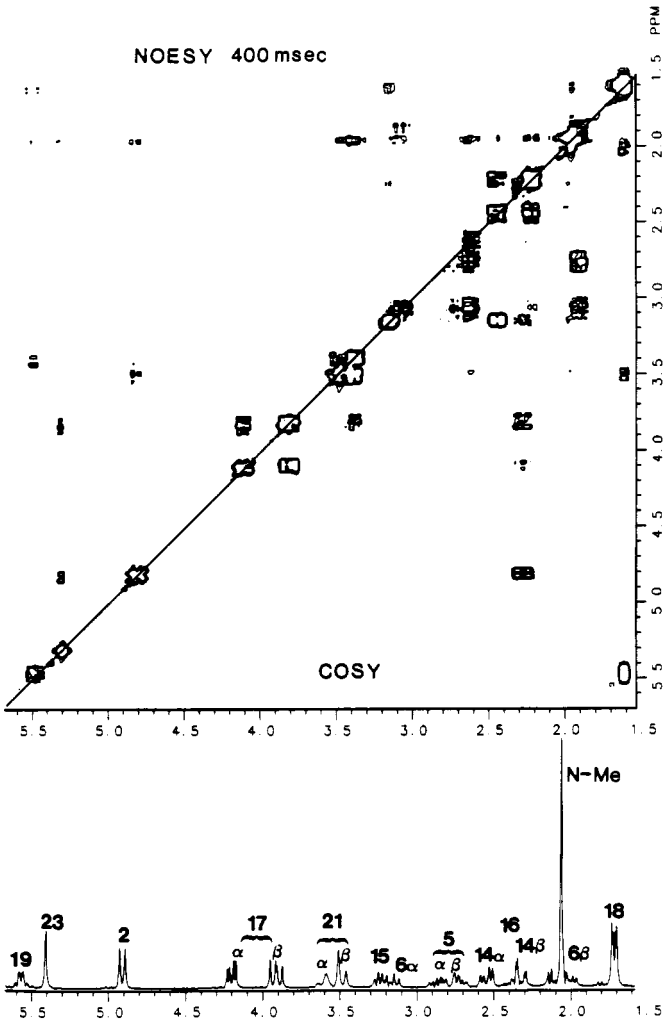

FIGURE 1. Composite contour plot showing the COSY spectrum of holstiine [**1**] below the diagonal and the 400 msec NOESY spectrum above the diagonal to facilitate comparison. Both spectra were taken as 200 × 1K complex points and were processed identically using sinusoidal multiplication prior to both Fourier transforms and zero filling prior to the second to afford final data matrices consisting of 512 × 512 real points, which were symmetrized prior to plotting. Proton identities are labeled on the high resolution reference spectrum plotted beneath the contour plot.

of 99% ^{13}C enriched 2-^{13}C-acetate; 90° ^{1}H decoupler pulse for HOHAHA sequence = 52.5 μsec. Spectral widths for all experiments were $^{1}H = \pm 1131$ Hz, $^{13}C = \pm 6450$ Hz unless otherwise noted.

COSY DATA ACQUISITION.—The COSY data were acquired using the normal pulse sequence and a sixteen-step phase cycle to afford quadrature detection in both frequency domains (6). The data were collected as 200 × 1K complex points and were processed using sinusoidal multiplication prior to both Fourier transformations with zero filling sufficient to afford a final magnitude calculated spectrum consisting of 512 × 512 real points. Sixteen acquisitions were taken for each experiment, giving an accumulation time of slightly less than 2 h. These data are plotted below the diagonal in the composite contour plot shown in Figure 1.

HOHAHA DATA ACQUISITION.—The HOHAHA data were acquired using the pulse sequence of Bax and Davis (8) with modifications and phase cycling as described in our previous work (9). The data were collected as 200 × 1K complex points and were processed using sinusoidal multiplication prior to both Fourier transformations and zero filling prior to the second to afford a final data matrix consisting of 512 × 512 real points. Data were magnitude-calculated and symmetrized prior to plotting. Mixing times used ranged from 20 to 80 msec. The pulse sequence employed an MLEV-17 sequence flanked by 2.5 msec

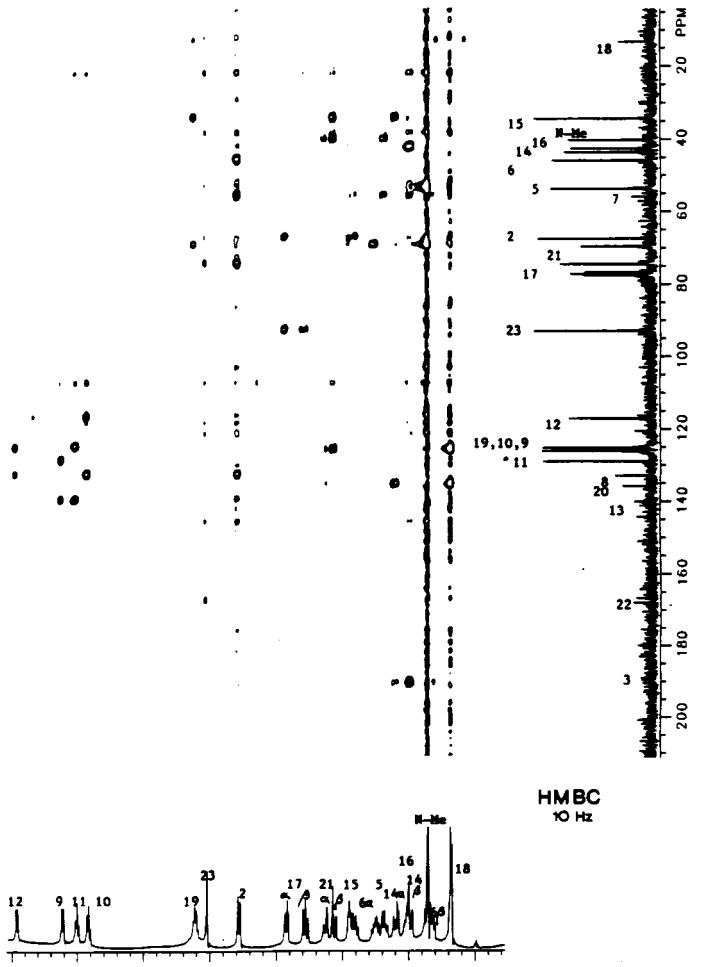

FIGURE 2. Proton-detected long range heteronuclear chemical shift correlation (HMBC) spectrum of holstiine [2] recorded with long range delays optimized for 10 Hz using the method of Bax and Summers (14). High resolution proton and carbon reference spectra flank the F_2 and F_1 axes, respectively. Data were taken as 160 × 1K complex points and were zero filled to afford a final matrix consisting of 512 × 512 real points.

trim pulses. To correct for phase imperfections, an even number of cycles of the MLEV-17 sequence was used in each case.

NOESY DATA ACQUISITION.—NOESY spectra were acquired using the pulse sequence described by Ellena *et al.* (17). Mixing times employed ranged from 400 msec to 1 sec. The data were acquired as 200 × 1K complex points and were processed using sinusoidal multiplication prior to both Fourier transforms and zero filling prior to the second to afford a final matrix consisting of 512 × 512 real points. The data were magnitude-calculated and symmetrized prior to plotting.

HC-COSY DATA ACQUISITION.—HC-COSY data were acquired using the pulse sequence of Freeman and Morris (12) with phase cycling according to Bax and Morris (13). Further, the received phase was cycled to record the coherence transfer echo necessitating spectral rotation prior to presentation (24,25). Data were collected as 160 × 1K complex points and were processed using exponential multiplication and zero filling prior to both Fourier transformations to give a final matrix consisting of 256 × 1K real points. The F_2 (^{13}C) spectral width was restricted to the protonated carbon resonances, giving a sweep width of ±4338 Hz.

ACQUISITION OF HMBC DATA.—The pulse sequence used was that of Bax and Summers (14) with modifications to the spectrometer as described in our previous work (15). The experiment was optimized for long-range couplings of 10, 6, and 4 Hz, giving fixed delays, $\Delta = 50$, 83.3, and 125 msec. The low pass J-filter in the experiment to eliminate responses from direct ($^1J_{CH}$) pairs was optimized for 145 Hz (3.44 msec). The sample was not spun, and 4 dummy scans were collected and discarded prior to the accumulation of each individual block of data. The data were acquired as 160 × 1K complex points and were processed using sinusoidal or double exponential apodization prior to both Fourier transforms with zero filling prior to the second to afford a final data matrix consisting of 512 × 512 real points (Figure 2). Data from the 10- and 6-Hz experiments were used in the assignment of the spectra of **2** and are presented in Table 1 and illustrated graphically on **3–5**. Data from the 4-Hz experiment were quite noisy and were not employed in the analysis. The complete set of three spectra were acquired over a weekend.

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ERRATUM

For the paper by Ghosh *et al.* entitled "Acidissimin, a New Tyramine Deviative from the Fruit of *Limonia acidissima*," *J. Nat. Prod.*, **52**, 1323 (1989), the authors request a name change in the title compound due to the earlier use of the name acidissimin. The new tyramine deviative in thus renamed acidissiminin [**1**].

For the paper by Kingston *et al.* entitled "The Chemistry of Taxol, a Clinically Useful Anticancer Agent," *J. Nat. Prod.*, **53**, 1 (1990), the authors have requested the following corrections:

Page 4, Structure **9**: The AcO group in the 2′-position of the side-chain should be an HO group.

Page 5, Table 2: References 16, 15, 18, and 13 cited in footnotes a–d should be 18, 17, 16, and 14 respectively.

Page 5 line 10: Reference 17 should be 19.