Nuclear Magnetic Resonance Studies in the 6,14-*endo*-Ethenotetrahydrothebaine Series

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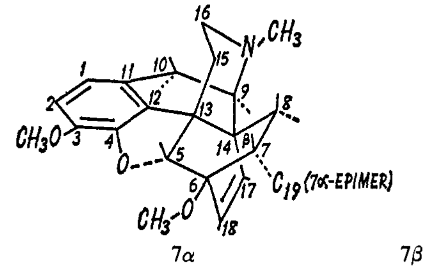
Abstract: Nuclear magnetic spectroscopy, including homonuclear field-sweep spin-decoupling techniques, has been used to determine the stereochemistry of the epimers and the configuration of some of the diastereomers formed by the Diels–Alder addition of electrophilic olefins to thebaine, followed by further transformations. Analyses of the nmr spectra include the comparisons of computed spectra with the observed spectra for the various spin–spin systems. Differences in chemical shift between similar protons in the various compounds have been explained in terms of the anisotropy of a phenyl substituent or the shielding parameters of the cyclic tertiary nitrogen atom and the bicyclo[2.2.2]octene double bond present in these structures.

The preceding papers[2] describe the preparation and chemical transformations of a variety of 6,14-*endo*-ethenotetrahydrothebaine derivatives containing the bicyclo[2.2.2]octene system, obtained by Diels–Alder addition of electrophilic olefins to thebaine followed by further transformations. This paper describes the application of nuclear magnetic resonance (nmr) spectroscopy, including homonuclear field-sweep spin-decoupling techniques, to the elucidation of the absolute configuration of asymmetric centers formed during these transformations. Included specifically are stereochemical assignments of epimers (at C-7) produced by the Diels–Alder reactions[2a] (and generally maintained during subsequent transformations) and a study of diastereomeric alcohols (at C-19) formed by stereoselective transformations of the Diels–Alder adducts.[2b] The structure below is a stereochemical representation of the 6,14-*endo*-ethenotetrahydrothebaine system and illustrates the numbering and designations for C-7 epimers used throughout these papers.[3]



	7α	7β
Ia	CN	H
Ib	H	CN
IIa	$COCH_3$	H
IIb	H	$COCH_3$
IIIa	$C(CH_3)_2OH$	H
IIIb	H	$C(CH_3)_2OH$
IV	COC_6H_5	H
V	$C(=NOH)CH_3$	H
VI	$C(=CH_2)CH_3$	H
VII	$C(=CH_2)C_6H_5$	H
VIII	$C(CH_3)_2OCH_3$	H
IX	$C(CH_3)_2OH$ (nor-IIIa NCN)	H
X	CH_2OH	H

Compounds Epimeric at C-7

A mixture of 7-cyano epimers (Ia and Ib) was obtained by repeating the synthesis of Bentley and Ball,[4] and these isomers were separated and isolated in approximately equal amounts by a combination of fractional crystallization and partition chromatography.[2a] At the outset, chemical data did not permit unequivocal assignment of the C-7 epimer configuration. However, the nmr data, including the results of spin decoupling, demonstrated that the more polar isomer, mp 183–184°, had the 7α-nitrile configuration (Ia) with the 6,14-etheno bridge disposed in the *endo* position "inside" the tetrahydrothebaine skeleton. The nmr spectrum of this epimer is shown in Figure 1 (with arrows indicating the spin systems established by decoupling experiments). Irradiation of the olefinic H-18 (δ 5.93) established that it was part of a four-spin system. Spin coupling was found between H-18 and H-17 (δ 5.61), $J_{17,18}$ = 9.0 cps (a typical AB pattern). Additionally, H-18 was coupled to both H-5β (δ 4.50), $J_{5\beta,18}$ = *ca.* 2 cps, and to H-7β (δ 2.85), $J_{7\beta,18} < 1.0$ cps. Examination of a Dreiding model of Ia showed that both H-5β and H-7β, together with H-18 and the intervening carbon atoms, approximate a plane in which the connecting bonds resemble a "W";[5] both protons would therefore be expected to couple with H-18.[6] These couplings are summarized in Figure 1. Decoupling experiments were also performed on the four-line pattern of the upfield proton (δ 1.50). This absorption, eventually assigned to H-8α, was established as part of a *three-spin system* involving H-7β and H-8β. Inspection of the H-8α pattern at δ 1.50 established that $J_{8\alpha,8\beta}$ = 12.0 cps (geminal coupling) and $J_{7\beta,8\alpha}$ = 4.5 cps (vicinal coupling, transoid). By using spin decoupling and observing the

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(1) Central Research Laboratories.

(2) (a) K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, **89**, 3267 (1967); (b) K. W. Bentley, D. G. Hardy, and B. Meek, *ibid.*, **89**, 3273 (1967); (c) K. W. Bentley and D. G. Hardy, *ibid.*, **89**, 3281 (1967); (d) K. W. Bentley, D. G. Hardy, and B. Meek, *ibid.*, **89**, 3293 (1967); (e) K. W. Bentley, D. G. Hardy, C. F. Howell, W. Fulmor, J. E. Lancaster, J. J. Brown, G. O. Morton, and R. A. Hardy, Jr., *ibid.*, **89**, 3303 (1967); (f) K. W. Bentley, D. G. Hardy, H. P. Crocker, D. I. Haddlesey, and P. A. Mayor, *ibid.*, **89**, 3312 (1967).

(3) H. Rapoport and P. Sheldrick, *ibid.*, **85**, 1636 (1963).

(4) K. W. Bentley and J. C. Ball, *J. Org. Chem.*, **23**, 1720, 1725 (1958).

(5) E. W. Garbisch, Jr., *Chem. Ind.* (London), 1715 (1964).

(6) (a) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964); (b) T. J. Batterham, K. H. Bell, and U. Weiss, *Australian J. Chem.*, **18**, 1799 (1965); (c) K. Tori, Y. Takano, and K. Kitahonoki, *Chem. Ber.*, **97**, 2798 (1964).

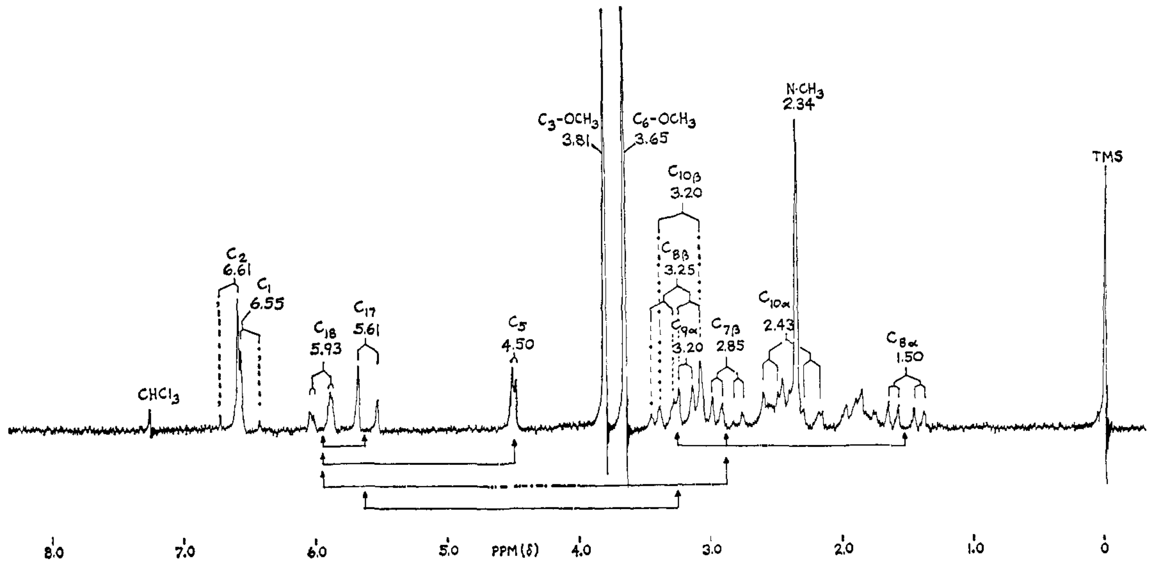

Figure 1. Proton nmr spectrum of the 7α-cyano epimer Ia.

perturbations of the four-line H-8α pattern, it was possible to locate both of the H-7β and H-8β multiplets in the region δ 2.5–3.5. However, owing to resonances from other protons in this region (H-9α and H-10β), identification of the individual resonance lines from these protons was difficult. Careful examination of the δ 2.8 region revealed a pair of doublets which had the same 4.5-cps vicinal splitting, but separated by 9.5 cps ($J_{7\beta,8\beta}$) in which the intensities of each component varied considerably. Careful spin decoupling then clearly indicated that the 4.5-cps doublets of H-8α were collapsed by irradiating these doublets at δ 2.8, and, moreover, it appeared that the upfield doublet of H-8α was collapsed by irradiating the *low-field* doublet of the pair at δ 2.8, and *vice versa*. This indicated that the two couplings, J = 12.0 cps and J = 9.5 cps, had opposite signs. This finding was consistent with the assigned arrangement of these protons, for it is known that the sign of J_{HH} (geminal) is negative while that for J_{HH} (vicinal) is positive.[7] Accordingly, the δ 2.8 doublets belonged to H-7β, and the H-8β pattern appeared partly hidden near δ 3.2.

To confirm the observed intensities of the H-7β doublets and to help locate the H-8β pattern, the expected spectrum was calculated using estimated chemical shifts (which approximated the true values) and the following J values: $J_{8\alpha,8\beta} = -12.0$ cps, $J_{7\beta,8\beta} = +9.5$ cps, and $J_{7\beta,8\alpha} = +4.5$ cps. The three spins were treated as an ABC system, following established mathematical procedures.[8,9] The line positions and intensities were calculated with the aid of a program written for a Burroughs 205 computer. The excellent agreement between the calculated and experimental spectra is shown in Figure 2, where the calculated H-8β set of lines fits under the observed lines. Two of the H-8β lines can be seen in the spectrum, while the other two are obscured. The three combination lines which result from an ABC treatment are omitted, as their intensities were near zero. The patterns for the H-9α and H-10β protons were also found in this region (δ 2.5–3.5) which integrates for four protons (H-7β, δ 2.8 and H-8β, δ 3.2 are also present). Using estimated chemical shifts for H-9α (δ 3.20), H-10β (δ 3.20), and H-10α (δ 2.43) with the observed coupling constants ($J_{9\alpha,10\alpha} = +6.2$ cps, $J_{10\alpha,10\beta} = -18.0$ cps, and $J_{9\alpha,10\beta} = ca.\ 0.0$ cps, which are in agreement with Rüll and Gagnaire[10]) the line positions and intensities of these proton patterns were calculated, and the agreement between these calculated and observed spectra is also shown in Figure 2. Thus, spin decoupling, together with the excellent agreement between the computed and observed spectra, confirmed the chemical shifts assigned for H-7β (δ 2.85) and H-8β (δ 3.25), as indicated in Figures 1 and 2, even though the complex patterns resulting from H-9α and H-10β resonance lines also appeared in this region.

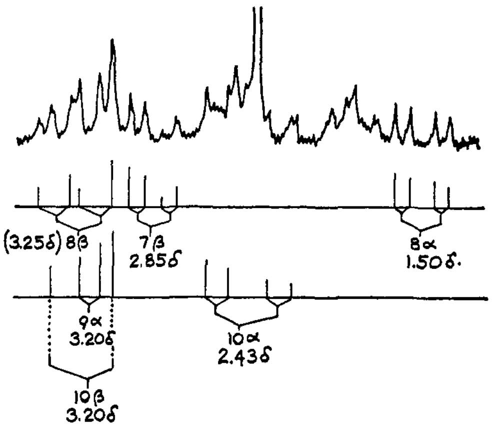

Figure 2. Calculated and experimental spectra (nmr) for the C-7β, C-8α, C-8β, C-9α, C-10α, and C-10β protons in the 7α-cyano epimer Ia.

Very small (<0.2 cps) long-range coupling between H-8β (δ 3.25) and H-17 (δ 5.61) was also detected by spin decoupling. These protons are sterically related to each other in the same sense that H-7β is related to

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(7) C. N. Banwell and N. Sheppard, *Discussions Faraday Soc.*, **34**, 115 (1962).

(8) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959.

(9) C. N. Banwell and N. Sheppard, *Mol. Phys.*, **3**, 351 (1960).

(10) T. Rüll and D. Gagnaire, *Bull. Soc. Chim. France*, 2189 (1963).

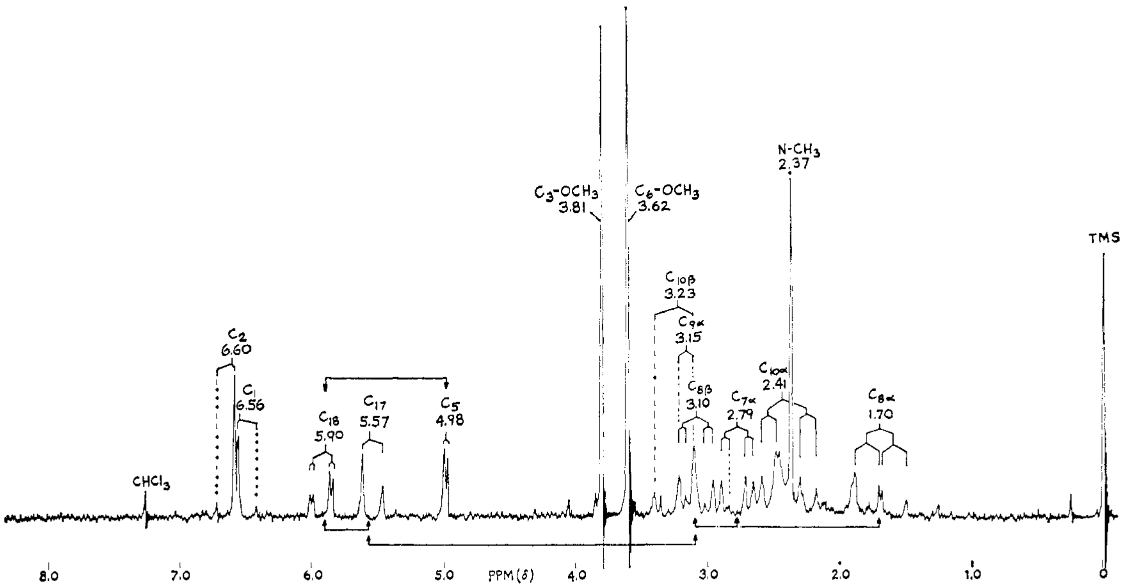

Figure 3. Proton nmr spectrum of the 7β-cyano epimer Ib.

H-18 (see structures I–X). The downfield chemical shift of H-8β (δ 3.25) compared with that of H-8α (δ 1.50) was somewhat surprising, since the corresponding protons in bicyclo[2.2.2]octene resonate at δ 1.50 and 1.27, respectively.[6c] The large difference in chemical shifts of the geminal protons H-8α and H-8β may be understandable upon consideration of the shielding (or the free electron pair) of the tertiary nitrogen atom held in proximity to H-8β (*ca.* 2.9 A)[11] by the rigid ring system (see structures I–X). The chemical shift of H-8β is similar to that observed for the *syn*-methylene bridge proton of sparteine,[12] which is also held in the proximity of a nitrogen atom (*ca.* 2.3 A away). Additional discussion of this point is included in the latter part of this paper, as this marked downfield shift for H-8β is evident in virtually all of the compounds examined in this series.

Assignment of the other isomer, mp 195–196°, as the 7β-cyano epimer (Ib) was based on equivalent decoupling experiments; this nmr spectrum is shown in Figure 3. In contrast to Ia, spin decoupling established that H-18 in this epimer was part of a *three-spin system.* Again, H-18 (δ 5.90) and H-17 (δ 5.57) formed a typical AB coupling pattern ($J_{17,18}$ = 9.0 cps), and the H-5β (δ 4.98), H-18 coupling ($J_{5β,18}$ = *ca.* 2 cps) was also similar to that found previously. However, no coupling was found between H-18 and any upfield proton in the area δ 2.8–3.1, where H-7α and H-8β were subsequently located by irradiation of H-8α (the upfield proton; δ 1.70 in this epimer). The absence of spin coupling between H-18 and H-7α in this isomer is as expected since the 7β position is now occupied by the nitrile group, and H-7α is not oriented correctly[5] for long-range coupling with H-18. The downfield shift of H-5β from δ 4.50 for the 7α-nitrile (Ia) to δ 4.98 for this epimer (Ib) was especially noteworthy. The chemical shifts for H-5β in virtually all of the related compounds (including II–XIV) appear to be diagnostic for assigning the configuration at C-7, and these ranges for both series of C-7 epimers are summarized in Table I. Indeed, mixtures of C-7 epimers (including Ia and Ib) were frequently recognized by examination of their nmr spectra (even of relatively crude products), as resonances from other protons (except for exchangeable hydroxyl protons) were generally not found in the δ 4.3–5.2 region. Confirmation of the C-7 epimer assignment based on the readily observed chemical shift for H-5β could then be established by spin decoupling.

Table I. Protons Diagnostic for C-7 Substituents

Proton	No. of examples	Av chem shift, δ	Exceptions
		7α Substituted	
H-5β	21	4.57 ± 0.05	XIIIa (4.47), b (4.47), c (4.37)
		7β Substituted	
H-5β	3	5.07 ± 0.12	
		7α or 7β Substituted (Ia–IX)	
H-8α	8	1.35 ± 0.15	IIIa (0.79), b (?), VIII (1.18), IX (0.93)
		7α-C-19 Carbinols	
H-8α	11	0.78 ± 0.05	XIb (1.20), XIIa (1.22), IIIb (?)

Close examination of the spectra and equivalent spin-decoupling experiments on the H-8α four-line pattern (δ 1.70) of Ib established that this proton was still part of a *three-spin system.* The high-field H-8α lines now showed nearly equal splittings of 11.2 cps (vicinal) and 12.2 cps (geminal). This increase in vicinal coupling would be expected for the *cis* relationship between H-7α and H-8α. Some of the H-7α and H-8β lines (in the δ 2.5–3.5 region) of this 7β epimer (see Figure 3) were more obvious than the corresponding lines in the spectrum of the 7α epimer (see Figure 1). This ABC system (H-8β, H-7α, H-8α) may be approximated by an ABX pattern where the AB part consists of two AB subspectra. One of these slightly perturbed AB subspectra was visible near δ 2.9 (Figure 3). The location of the other AB subspectrum followed from the couplings already determined; three of the four lines were identified near δ 3.1. The third coupling (3.6

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(11) Estimated from Dreiding models.

(12) F. Bohlmann, D. Schumann, and C. Arndt, *Tetrahedron Letters,* 2705 (1965).

Table II. Protons in Spin-Decoupled Systems[a,b]

Compd	Proton, chem shifts, δ H-5β	H-7α	H-7β	H-8α	H-8β	H-17	H-18	Coupling constants, J (cps)
Ia	4.49	. . .	2.85	1.50	3.26	5.60	5.93	5β,18 (<2.0), 7β,8α (+4.5), 8α,8β (−12.0), 7β,8β (+9.5), 17,18 (9.0), 7β,18 (<1.0), 8β,17 (<0.2)
Ib	4.99	2.79	. . .	1.70	3.10	5.57	5.90	5β,18 (<2.0), 7α,8α (+11.2), 8α,8β (−12.2), 7α,8β (+3.6), 17,18 (9.0), 8β,17 (<0.2)
IIa	4.53	. . .	2.90	1.34	2.91	5.54	5.85	5β,18 (<2.0), 7β,8α (+6.5), 8α,8β (−12.6), 7β,8β (+9.7), 17,18 (10.0), 7β,18 and 8β,17 (<0.2)
IIb	4.98	2.69	. . .	1.40	3.04	5.48	6.04	5β,18 (<2.0), 7α,8α (+13.9), 8α,8β (−15.6), 7α,8β (+5.0), 17,18 (9.0)

[a] General characteristics are in Table III. [b] These values are included in the averages in Table I.

cps) was evident by the splitting of the outer lines of each AB pattern. Using these chemical shifts and coupling constants and a negative value for the geminal coupling constant (−12.2 cps), the complete spectrum was calculated as before. By analogy with the 7α epimer (Ia), the four lines belonging to the upfield halves of each AB spectrum were assigned to H-7α (δ 2.79), and the lowfield halves to H-8β (δ 3.10). The agreement with the observed spectrum is shown in Figure 4 together with equivalent results for the H-9α, H-10α, and H-10β patterns. The very small long-range coupling (J = 0.2 cps) between H-17 and H-8β was also detected in this epimer by spin decoupling (analogous to that observed in Ia).

These nmr data pertaining to Ia and b, including the experimentally observed spin systems and coupling constants, and consideration of the anisotropic effects of the *t*-nitrogen on the C-8 protons independently confirm the conclusions of Bentley and co-workers[2a,4] that neither Ia nor Ib could be an 8-cyano derivative. They also confirm the assignment of the *endo* disposition of the 6,14-etheno bridge "inside" the tetrahydrothebaine system.[13] These conclusions, based upon nmr data, can generally be extended to other analogous Diels–Alder adducts (*e.g.*, IIa and IIb below), although our investigations of spin–spin couplings by double irradiation techniques (see Table II) and computed spectra produced the most definitive results with Ia and Ib of the several pairs of epimers studied. Other characteristic proton patterns recognized in the nmr spectra of Ia and b (and of II–XIV) are summarized in Table III.

The epimeric methyl ketones IIa and IIb[14] were similarly studied. The general characteristics of these nmr spectra were similar to those of the nitriles Ia and Ib (Table III). Detailed spin-decoupling experiments were also carried out to establish the appropriate spin systems for H-5β, H-7α, H-7β, H-8α, H-8β, H-17, and H-18, as before; these chemical shifts and coupling constants are included in Table II. However, additional difficulties in spin decoupling were encountered owing to the greater overlap of resonance patterns (*e.g.*, in IIa). Of particular interest was the pattern for H-8α in the spectrum of IIa. This was clearly seen between δ 1.1 and 1.6 (centered at δ 1.34), but it did not resemble the four-line pattern observed for H-8α in the spectra of Ia, Ib, and IIb. Instead, a five-line pattern was observed. Four of the five lines were narrow and symmetrically arranged, with the inner lines being stronger than the outer ones; the fifth line was somewhat broader and appeared in the center (see Figure 5). The two combination lines in the X pattern of an ABX system can become quite strong and appear in the center of the X pattern when the chemical shift of A is very close to that of B.[15] Indeed, decoupling

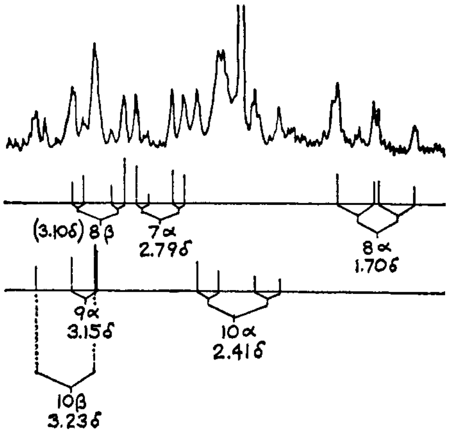

Figure 4. Calculated and experimental spectra (nmr) for the C-7α, C-8α, C-8β, C-9α, C-10α, and C-10β protons in the 7β-cyano epimer Ib.

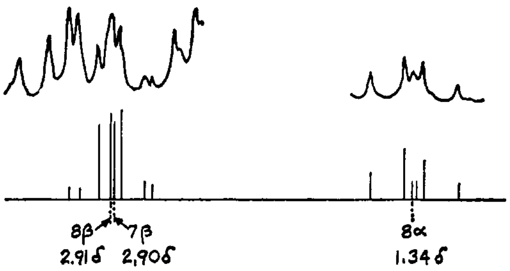

Figure 5. Calculated and experimental spectra (nmr) for the C-7β, C-8α, and C-8β protons in the 7α-methyl ketone epimer IIa.

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(13) In both 8-cyano epimers, H-18 would always be expected to be part of a *four-spin system* including H-7β which would have a geminal coupling constant as well. This was not observed in any compound examined. The possibility that Ib might be a 6,14-*exo*-etheno derivative may be dismissed because of the similarity of the H-17 and H-18 olefinic proton patterns to those of Ia, which had been assigned the *endo*-etheno configuration[2a,4] on the basis of chemical data.

(14) These epimers were obtained by repeating the synthesis of Bentley and coworkers;[2a,4] IIa, mp 115–118° (pure by nmr and tlc), was obtained in 80% yield (first crop), and IIb, mp 198–201°, was isolated in 1.8% yield by partition chromatography of the mother liquors.

(15) J. I. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1962).

Table III. General Characteristics of Compounds Studied[a]

Proton	No. of examples	Av chem shift, δ	Coupling constant, J (cps)	Exceptions
H-1	27	6.54 ± 0.03	1,2 (8 ± 0.5)	
H-8β	16	2.9 ± 0.15 (1)	8β,8α (2) (12 ± 2) 8β,7β (2) (8 ± 0.5) 8β,7α (2) (4.3 ± 0.7)	(1) IX (2.67), (2) known only for the compounds in Table II
H-9α	22	3.13 ± 0.04	9α,10α (6.5 ± 0.5)	XIa (2.94), IX (3.93), XIIIa (2.70), XIIIb (2.62), c (2.63), IIa·HCl (4.20)
H-10α	23	$\sim$2.4	10α,10β (18 ± 1)	IX (3.1)
H-10β	28	3.15 ± 0.05	...	IIa·HCl (?)
H-17	22	5.48 ± 0.06	17,18 (8.5 ± 0.5)	XIa (4.88), XIg (5.69), VIII (5.37), IIa·HCl (5.78)
H-18	21	5.91 ± 0.08	18,5β (≤ 2)	IIIb (6.15), XIIa (5.04), IIa·HCl (5.61)
3-OCH_3	25	3.81 ± 0.02		
6-OCH_3	27	3.65 ± 0.10	...	
N-CH_3	26	2.43 ± 0.02	...	XIa (2.17), IIa·HCl (3.05)
C-19 CH_3	21	1.1 ± 0.1	...	

[a] The nmr spectra were run on a Varian A-60 spectrometer equipped with a variable-temperature probe. Solutions were 20% (w/v) in deuteriochloroform except where noted otherwise. Tetramethylsilane was used as an internal reference, and the accuracy of the measurements is within δ 0.03 for the chemical shifts and 0.5 cps for the coupling constants. The spin-decoupling work was done on a Varian DP-60 equipped with a Varian integrator-decoupler.

experiments made while observing H-8α (δ 1.34) indicated that H-7β and H-8β were both near δ 2.9. With the values $J_{8\alpha,8\beta} = -12.0$ cps, $J_{8\alpha,7\beta} = +4.5$ cps, and $J_{8\beta,7\beta} = +9.5$ cps, obtained from the analogous isomer (Ia), trial three-spin spectra were computed. From these, an assignment of transitions could be made to the H-8α lines and four clearly visible lines assignable to H-7β and H-8β. The entire energy-level scheme could then be drawn up and the unobserved lines filled in. An exact Castellano–Waugh[16] calculation was carried out using the measured shift values. The spectrum was then exactly reproduced with the following parameters: H-8α, δ 1.34; H-7β, δ 2.90; H-8β, δ 2.91; $J_{8\alpha,8\beta} = -12.6$ cps; $J_{8\alpha,7\beta} = +6.5$ cps; $J_{8\beta,7\beta} = +9.7$ cps. The two combination lines in the H-8α pattern appeared at its center, separated by about 0.01 ppm, and could easily account for the central broad line (as shown in Figure 5).

Spin decoupling of the 7β-acetyl epimer IIb was similar to that of the 7β-nitrile Ib (see Tables I and III). The spin systems determined from the spectra of both IIa and IIb also confirmed the prior C-7 assignments of Bentley, *et al.*[2a,4] These assignments are: the configuration at C-7, that neither isomer could be an eight-substituted derivative, and that the 6,14-etheno bridge was in an *endo* disposition.

The epimeric tertiary carbinols IIIa[17] and IIIb,[18] synthesized from IIa and IIb, respectively, were also thoroughly investigated. In the 7α epimer IIIa, double-irradiation methods readily established that H-7β had moved upfield to δ 2.1 with respect to H-7β at δ 2.8 in its precursor, IIa. This upfield shift of the H-7β lines is as expected with the removal of the inductive and/or anisotropic effects of the 7α-cyano or -acetyl group. Observation of the spectrum showed that H-8α was also upfield at δ 0.79 (δ 1.32 in IIa) with the typical four-line pattern of an ABX system. Spin-decoupling experiments on this epimer gave completely analogous results to those obtained previously with Ia and IIa. The H-5β doublet ($J_{5\beta,18} =$ *ca.* 2.0 cps) was found at δ 4.50, as expected for a 7α epimer, and H-18 was part of a *four-spin system:* H-5β (δ 4.50), H-7β (δ 2.10), H-17 (δ 5.43), and H-18 (δ 5.92). H-8α was part of a *three-spin system:* H-8α (δ 0.79), H-8β (δ 2.88), and H-7β (δ 2.10). One additional spin-decoupling experiment on IIIa established that H-1 (δ 6.50) was coupled to at least one proton (probably H-10β) in the δ 3.0 region. This coupling ($J = <0.2$ cps) was apparent in the increased line width and lowered intensity of H-1, relative to H-2 in all compounds examined.

Spin-decoupling experiments on the epimeric 7β-carbinol IIIb were not successful. The 8α proton was not found in the region around δ 0.8 as in IIIa. This pattern was probably under the C-19-methyl resonances at *ca.* δ 1.25. Because of overlapping lines from other protons and lacking the H-8α handle, it was not possible to determine the chemical shifts and coupling patterns as in the spin systems previously investigated. The 5β proton was observed at δ 5.26 (a peak at δ 4.58 was assigned to the C-19 OH by exchange with D_2O). This was in accord with other 7β-substituted derivatives (Table I). Thus, although one might argue for the paramagnetic effects of the 7β-cyano[19] and -acetyl[20] moieties being responsible for the downfield shifts of H-5β in Ib and IIb (compared with Ia and IIa), these effects cannot be present in the 7β-carbinol IIIb, which showed an even larger downfield shift for H-5β. Probably steric compression is a better explanation.[21] It

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(16) S. Castellano and J. S. Waugh, *J. Chem. Phys.*, **34**, 295 (1961).

(17) This compound was synthesized by Grignard addition of methylmagnesium bromide to IIa as described by Bentley and co-workers.[2b]

(18) Obtained from the Reckitt and Sons Ltd., Laboratories through the courtesy of Dr. K. W. Bentley.

(19) A. D. Cross and I. T. Harrison, *J. Am. Chem. Soc.*, **85**, 3223 (1963).

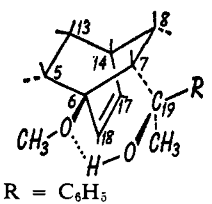
(20) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 112 ff.

is also of interest to note that the H-8α lines (δ 1.2) in IIIb had apparently moved downfield compared with their position (δ 0.79) in the spectrum of IIIa even though both IIIa and IIIb were C-19 tertiary carbinols (see Table I). Again, any rationale which invokes removal of the anisotropic effects of 7α-cyano or -acetyl groups to account for the marked upfield shift of H-8α to δ 0.79 in the 7α-*t*-carbinol IIIa (compared with δ 1.50 in Ia, and δ 1.32 in IIa) apparently does not apply in the equivalent changes (Ib and IIb to IIIb) for 7β substituents. Other factors must be involved (see Additional Studies of the C-8 Protons below).

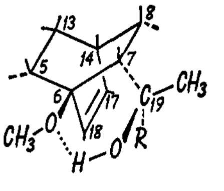
Compounds IV–X[22] are additional examples of C-7 epimers whose nmr spectra were entirely analogous to those just discussed in detail (Ia–IIIb). Chemical shift data from these spectra (all 7α epimers) are included in the summary data in Tables I and III. Of particular interest is the fact that the nmr spectrum (H-5β, δ 4.60) of nepenthone (IV; the precursor for C-19 diastereomer XIIa) confirmed its previous assignment as a 7α epimer.[2a,4] Compounds V, VI, and VII are additional derivatives in which C-19 bears an unsaturated moiety; these spectra were similar to the spectra of Ia and IIa. Compounds VIII, IX, and X are derivatives in which C-19 is a saturated carbon bearing a hydroxyl or ether moiety; their spectra were analogous to that of IIIa.

Compounds Diastereomeric at C-19

In the course of our investigations, it became apparent that spectral data (nmr and infrared) might provide a basis for assigning the configuration for the asymmetric carbon at C-19 in the appropriate derivatives. This expectation was realized in our study of the diastereomeric phenylmethyl tertiary carbinols XIa and XIIa. Two other pairs of diastereomers (XIb and XIIb; XIc and XIIc) were also studied, but their spectra did not provide such definitive conclusions.



XIa, R = C_6H_5
b, R = H
c, R = *n*-C_3H_7
d, R = *n*-C_3H_7 (3-OH)
e, R = *i*-C_5H_{11}
f, R = cyclohexyl
g, R = $CH_2CH_2C_6H_5$ (3-OH)



XIIa, R = C_6H_5
b, R = H
c, R = *n*-C_3H_7

The first pair of C-19 diastereomers studied in detail were XIa, obtained from the 7α-acetyl derivative IIa by addition of phenylmagnesium bromide,[23] and XIIa, obtained from the 7α-benzoyl derivative IV (nepenthone) by addition of methyllithium.[24] The nmr spectra of XIa and XIIa showed a number of general features consistent with those previously described (Table III), and the chemical shifts for H-5β in both of these C-19 diastereomers (Table I) indicated they were 7α epimers; the C-7 configuration had not been affected during their synthesis. However, in XIIa the upfield shift of both olefinic protons, H-17 (δ 4.88; $\Delta\delta$ = 0.55 ppm) and H-18 (δ 5.04; $\Delta\delta$ = 0.91 ppm), was striking and somewhat unexpected when compared with these chemical shifts in XIa and in virtually all analogous compounds (see Table III). These upfield shifts in XIIa are understandable if the phenyl moiety (R) in this diastereomer is held in a "down under" position in close proximity to the C-17 and C-18 protons of the *endo*-etheno bridge (as illustrated in XI and XII), thereby producing a shielding effect. Examination of models indicated this was possible, and the greater upfield shift of H-18 over that of H-17 was consistent with the closer proximity of H-18 to the phenyl group. There appeared to be considerable restriction of free rotation about the C-19 to C-7 bonds in both diastereomers (XIa and XIIa), and high-temperature nmr experiments provided experimental data consistent with these observations. In perdeuteriodimethyl sulfoxide the C-19-hydroxyl resonance of XIa was observed at δ 4.9 at ambient temperature and moved upfield to δ 4.7 at 180°. In XIIa, this hydroxyl absorption was found at δ 4.6 at ambient temperature, at δ 4.4 at 140°, and at 180° it was too diffuse to locate. There were no significant changes (more than δ 0.05) from the ambient temperature spectra for any other protons.

Intramolecular hydrogen bonding[25] of the C-19-*t*-hydroxyl proton was evident from the infrared spectra of both diastereomers XIa and XIIa (OH, 2.92 μ; not concentration dependent). This must involve the 6-methoxyl groups as indicated by the conformations shown in XI and XII. Hydroxyl resonances at δ 5.26 and 5.8 in the deuteriochloroform spectra of XIa and XIIa, respectively, also agreed with these hydrogen-bonded conformations.[26] The conformation shown for XIIa with the *t*-hydroxyl near the 6-methoxyl group and the phenyl group near the *endo*-etheno bridge thus fixed the configuration of this C-19 asymmetric center as 7α-(α-(*R*)-α-hydroxy-α-methylbenzyl).[27] The isomer XIa then had to have the opposite 7α-(α-(*S*)-α-hydroxyl-α-methylbenzyl) configuration as shown. These assignments for the C-19 diastereomer configurations in XIa and XIIa, obtained solely from spectral data, are entirely consistent with conclusions suggested by chemical data, including the high degree of stereoselectivity observed during the synthesis of a variety of C-19 diastereomeric alcohols.[2b]

Close inspection of the nmr spectra of XIa and XIIa revealed other relationships which appeared to be consistent with the assigned conformations of these diastereomers although they are probably less definitive. Models of XIIa indicated that the edge of the phenyl moiety is directed toward H-8α. Thus, a deshielding effect from the phenyl group *may* be responsible for the

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(21) W. Nagata, T. Terasawa, and K. Tori, *J. Am. Chem. Soc.*, **86**, 3746 (1964); D. R. Arnold, D. J. Trecker, and E. B. Whipple, *ibid.*, **87**, 2596 (1965).

(22) Compounds VI and VII were obtained through the courtesy of Dr. K. W. Bentley; the others were obtained by repeating the syntheses described by Bentley and co-workers as indicated: IV,[4] V,[2a] VIII,[2d] IX,[2c] X.[2]

(23) This compound, mp 210–212°, was synthesized by the Grignard addition of phenylmagnesium bromide to IIa. The crude product (mp 197–207°, 86%) had traces of the other diastereomer XIb (by tlc), and was purified by partition chromatography.

(24) This cmpound, mp 148–150°, was synthesized by the addition of methyllithium to IV. It was initially obtained as a glass (90% yield) and tlc indicated a trace amount of XIa. Purification by partition chromatography then gave crystalline material which was free from the diastereomer XIa (by nmr and tlc).

(25) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1954, p 89, gives 2.8–2.9 μ for intramolecularly hydrogen-bonded hydroxyl stretching.

(26) Reference 8, p 400.

(27) R. S. Cahn, *J. Chem. Educ.*, **41**, 116 (1964).

downfield position (δ 1.22) of this 8α proton in XIIa as compared with H-8α (δ 0.60) in XIa. There were other differences such as the C-19-methyl singlet in XIa which appeared at δ 1.42 compared with δ 1.52 in XIIa. In XIa, the H-8β pattern had apparently shifted slightly upfield (δ <2.7), since the δ 2.7–3.5 region integrated for only two protons, which were assigned as H-9α and H-10β. In the spectrum of XIIa and most other *carbinols*, this δ 2.7–3.5 region integrated for three protons, one of which was H-8β in addition to H-9α and H-10β. Another difference between the spectra of XIa and XIIa was found in the chemical shifts of the N-methyl groups. In the spectrum of XIIa, the N-methyl singlet (δ 2.36) appeared at a position consistent with the other compounds studied (see Table III). In contrast stood the upfield shift of the N-methyl singlet (δ 2.17) in the spectrum of XIa; a satisfactory explanation of these phenomena is not readily apparent.[28]

The second pair of C-19 diastereomers studied in detail (both nmr and infrared) were the secondary alcohols XIb[29] and XIIb,[18] obtained from the 7α-acetyl derivative IIa.[2b] These nmr spectra had general features in agreement with the values in Table I and Table III. The nmr spectrum of XIIb showed the C-19-hydroxyl proton resonance at δ 4.92, suggesting hydrogen bonding (with the 6-methoxyl) as discussed with the previous diastereomers XIa and XIIa. Infrared studies also indicated an intramolecular hydrogen bond in XIIb (2.90 μ, not concentration dependent) equivalent to the previous findings. In contrast, the C-19-hydroxyl resonance in the nmr spectrum of XIb was found at *ca.* δ 2.2. Parallel infrared studies with XIb showed maxima at both 2.78 and 2.86 μ (neither of which was concentration dependent) suggesting that this C-19 hydroxyl exists in two conformers, one with a weak hydrogen bond (2.86 μ) and one with a "free" hydroxyl (2.78 μ).[30] In addition to these indications of weaker hydrogen bonding, the H-8α lines were found at δ 1.20 in the nmr spectrum of XIb, while in its diastereomer XIIb, H-8α was observed at δ 0.69. In the previous pair of diastereomers XIa and XIIa (see above), the difference in chemical shifts for the H-8α protons could be ascribed to the deshielding edge of the "down under" phenyl group in XIIa directed toward H-8α and held rather firmly by steric constraints to rotation. An explanation for the opposite chemical shifts for H-8α in XIb and XIIb is not readily apparent. Comparative data were also obtained with the primary alcohol X in which the C-19 hydroxyl did not appear to be hydrogen bonded (infrared, 2.86 μ, not concentration dependent; nmr, δ 2.6). The location of H-8α (δ 0.52) in X, however, was similar to that of H-8α in the hydrogen-bonded secondary carbinol diastereomer XIIb. Thus, satisfactory interpretation of the range of chemical shifts (*ca.* δ 1.2–0.5) observed for H-8α in these very closely related structures was difficult (see below).

Although these detailed spectral studies showed interesting differences between the two secondary carbinol diastereomers XIb and XIIb, they did not provide definitive conclusions concerning the absolute configuration at C-19. Assignment of these configurations (shown in XIb and XIIb) was obtained from chemical data.[2b]

The third diastereomer pair studied were the propylmethyl tertiary carbinols XIc[31] and XIIc,[18] obtained from the 7α-acetyl (IIa) and 7α-propionyl derivatives, respectively. The nmr spectra of XIc and XIIc were completely in accord with all of the general features listed in Table III, and the H-5β chemical shifts (δ 4.52 in XIc; δ 4.55 in XIIc) were consistent with the 7α configuration. The C-19 hydroxyl appeared to be bonded in both diastereomers (δ 4.80 and 4.45, respectively), as in XIa and XIIa. Thus, the nmr spectra of these diastereomers were virtually indistinguishable from each other and provided no useful information for assignment of the absolute configuration at C-19. These were assigned by analogy with XIa and XIIa and assumption of similar stereochemistry in their synthesis[2b] (XIa–g, all obtained from IIa). An X-ray crystallographic analysis of XIc hydrobromide[32] has confirmed the configuration of XIc as that shown in configurations XI and XII, including the hydrogen-bonded conformation of the C-19-hydroxyl group.

Compounds XId–g,[33] inclusive, are additional C-19 diastereomers whose nmr spectra also show the general patterns previously discussed in detail (their chemical shift data are included in the summary ranges given in Tables I and III). These data (*i.e.*, the H-5β shifts) were consistent with the assigned 7α configuration, but did not permit conclusions concerning their C-19 diastereomeric configurations. These were assigned by chemical analogy.[2b] Compound XId was of particular interest as it is a very high potency oripavine derivative whose biological properties have been extensively studied;[34] its nmr spectrum was virtually identical with that of XIc (its synthetic precursor), but lacked the 3-methoxyl singlet observed in the spectrum XIc; this indicated that unexpected changes had not taken place during its synthesis (a high-temperature alkaline hydrolysis).[2b]

Additional Studies of the C-8 and C-9 Protons

As these nmr studies of the C-7 epimers and the C-19 diastereomers progressed, the unique nature of the C-8 protons became increasingly apparent, emphasized by the sometimes unexpected variations in their chemical shifts. The proximity of H-8β to the rigidly held *t*-nitrogen atom has already been noted (downfield shift of H-8β). Both C-8 protons may have their chemical shifts affected by the C-17–C-18 double bond which is part of the bicyclo[2.2.2]octene system. Variations of the *endo*- and *exo*-proton shifts known for this system[6b] may well apply to our compounds. Further, the C-8

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[28] The upfield shift of the N-methyl singlet and the apparent upfield shift of H-8β in this diastereomer are unique among all of the spectra examined, and may be due to the C-19 phenyl group held in an "up" position. However, any interpretation of these factors which may be related appears to be speculative in the absence of additional examples.

[29] This compound, XIb, mp 73–75°, was obtained as a Grignard reduction by-product from the reaction of IIa with propylmagnesium iodide as described by Bentley and coworkers;[2b] it was isolated by chromatography of the mother liquors after separation of XIc.

[30] Bentley and co-workers[2b] have attributed the band at 2.78 μ to a conformation with the C-19 hydroxyl bonded to the C-17–C-18 double bond.

[31] This compound was synthesized by the Grignard addition of propylmagnesium iodide to IIa as described by Bentley and co-workers.[2b]

[32] Private communication from J. H. van den Hende and N. R. Nelson, to be published.

[33] Compound XId was obtained by heating XIc with potassium hydroxide in diethylene glycol at 200–220° as described by Bentley and co-workers.[20] Compounds XIe–g, inclusive, were obtained from the Reckitt and Sons Ltd., Laboratories through the courtesy of Dr. K. W. Bentley.

[34] (a) R. E. Lister, *J. Pharm. Pharmacol.*, **16**, 364 (1964); (b) A. M. Harthoorn, *J. S. African Vet. Med. Assoc.*, **36**, 45 (1965).

Table IV. Chemical Shift of Protonated Species[a]

Compd	Changes (Δδ, ppm) observed *vs.* the bases			
	H-8α	H-8β	H-9α	N-Methyl[f]
IIa·HCl	−0.34		−1.1	−0.7
IIIa (CF_3COOH)[b,c]	−0.21		−1.0	−0.7
X (CF_3COOH)[c]	−0.31	*Ca.* +0.4	−1.0	−0.7
XIb (CF_3COOH)[c]	−0.10	?[d]	−1.0	−0.7
XIIb (CF_3COOH)[c]	*Ca.* −0.3	?[d]	−1.0	−0.7
VII[e]	−0.14	+0.21	−0.81	...

[a] In none of the experiments ($CF_3COOH–CDCl_3$) did additional increments of acid move either the H-9α or N-methyl lines farther downfield (indicating complete protonation of the *t*-nitrogen). [b] In the experiment on IIIa, the acid was added to the $CDCl_3$ solution in small increments and both the H-8α and N-methyl absorptions were observed moving downfield simultaneously as the acidity increased. [c] In each case, after recording the protonated spectra, the acid was neutralized with dilute $NaOD–D_2O$ until the spectra of the original bases were recovered (establishing the absence of decomposition). [d] In these spectra, the H-8β lines could not be located because of overlap with other proton lines, presumably H-16α and H-16β. [e] The N-cyano derivative (not protonated) is included for comparison. [f] The N-methyl absorption was a broadened singlet in all cases studied.

protons in our C-7 epimers and C-19 diastereomers are clearly influenced both by the nature of and the stereochemical orientations of the C-7 substituents. This section describes further studies of these apparently unique chemical shifts directed toward a better correlation of the observed chemical shifts with structural and environmental factors responsible for them.

The N-cyano derivative IX, obtained from IIIa, and an intermediate for N-substituted derivatives,[2c] is a compound in which the basicity of the nitrogen is diminished by the nitrile moiety. Although anisotropic effects of the nitrile group might distort some chemical shifts, spin-decoupling techniques were used to locate the H-8α,H-8β,H-7β spin system in IX (as in Ia–IIIa). The lines for H-8β in the spectrum of IX were located centered at δ 2.67, slightly upfield (Δδ = +0.21 ppm) from this pattern in IIIa, probably because of the reduced basicity of the ring nitrogen. The H-8α lines at δ 0.93, the upfield "handle" for the spin decoupling, were slightly downfield (Δδ = −0.14 ppm) from those in the precursor (IIIa). Both of these changes can be ascribed to the effects of the diminished electron availability on the ring nitrogen. The third proton in this spin system, H-7β, was found at δ 2.04, shifted slightly upfield (Δδ = +0.06 ppm) from its position in the spectrum of IIIa. Interestingly, the H-10α lines moved downfield (Δδ = −0.7 ppm) to about δ 3.1 and overlapped with the lines from H-10β (δ 3.16) which did not change from their position in the spectrum of IIIa. The H-9α absorption (δ 3.93) moved downfield (Δδ = −0.81 ppm from IIIa) as expected. All other proton absorptions maintained their positions (±0.05 ppm) compared with IIIa.

Since the nmr spectrum of IX (ring nitrogen with diminished electron density) indicated that the H-8α and H-8β lines had moved toward each other, further studies were undertaken with a number of protonated derivatives. These were carried out with an isolated hydrochloride or by the addition of trifluoroacetic acid to deuteriochloroform solutions of the free bases. The results are summarized in Table IV (Δδ shifts for H-8α, H-8β, H-9α, N-Me). In the spectrum of the hydrochloride of IIa (the 7α-acetyl epimer), H-8α had moved downfield about 0.3 ppm, but, unfortunately, the H-8β lines could not be observed because of overlap with other lines (H-16α and H-16β would be expected to shift downfield upon protonation of the ring nitrogen). H-1 and H-2 moved slightly downfield (Δδ = −0.15 and −0.14 ppm, respectively), as did H-17 (Δδ = −0.24 ppm). Both H-9α and the N-methyl resonance lines showed the expected downfield shifts (Table IV) and the N-methyl absorption was a broadened singlet in all cases. No other proton absorptions which could be identified by observation had moved, compared with the spectrum of the base.

The nmr spectrum of the primary alcohol X as the conjugate with trifluoroacetic acid showed similar shifts. The H-8α lines moved downfield by *ca.* 0.3 ppm (to δ 0.83) and the H-8β lines were tentatively identified at δ 2.5, an upfield shift of *ca.* +0.4 ppm compared with the base. In this case, then, the difference between the chemical shifts of the geminal pair, H-8α and H-8β, was reduced from *ca.* 2.4 to *ca.* 1.7 ppm upon protonation of the ring nitrogen.

Spectra of protonated conjugates of the following compounds were also studied: the dimethyl tertiary carbinol IIIa and the diastereomeric secondary carbinols XIb and XIIb. The results of these experiments were similar to those just described (with IIa and X). All of these protonation experiments (Table IV) indicated a downfield shift for H-8α which varied somewhat with different C-7 substituents. There is a possible progression for the tertiary carbinol IIIa, the secondary carbinol XIIb, and the primary carbinol X. In their nmr spectra, the H-8α lines were found at δ 0.79, 0.69, and 0.52, respectively. In the presence of CF_3COOH and in the same order, the H-8α lines were observed at δ 1.0, *ca.* 1.0, and 0.83, respectively. In the two cases where H-8β could be located, the lines for these protons were found to have shifted upfield. The constancy of the downfield shifts for H-9α and the N-methyl protons was also apparent (Table IV). These experiments clearly indicated that at least part of the large difference between the H-8α and H-8β chemical shifts is due to shielding by the ring nitrogen, rigidly held by the fused ring system. This effect is analogous to that found by Winstein and co-workers[35] for the hydroxyl group in half-cage hydrocarbons, but smaller in magnitude.

High- and low-temperature nmr experiments were performed on the tertiary carbinol IIIa, the secondary carbinol XIIb, and the primary carbinol X, and a low-temperature experiment only on XIb. The purpose was to investigate any observable effects on the H-8α chemical shifts by possibly inducing more rotation about the C-19 to C-7 bond, or the effects of any additional conformers. The high-temperature experiments were run using *o*-dichlorobenzene as the solvent. The probe temperature was raised to 180 ± 2° without any diagnostic changes occurring from the observed ambient temperature spectra (essentially the same as deuteriochloroform spectra). In each case, of course, the hydroxyl absorption moved upfield and usually became too diffuse to locate. In the low-temperature experiments, deuteriochloroform was used as the solvent, and the probe temperature was lowered to −50

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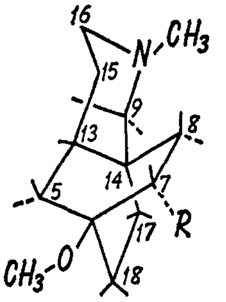
(35) S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, *J. Am. Chem. Soc.*, 87, 5247 (1965).

± 2°. It is probable that additional conformers were present as evidenced by line broadening, but in no case was a conformer obtained that was markedly different from that present in the ambient temperature spectrum, nor was there any diagnostic shift in any of the proton resonance lines.



XIIIa, R = $COCH_3$
b, R = $CH(OH)CH_3$
c, R = $C(CH_3)_2OH$

Three 17,18-dihydro (6,14-*endo*-ethano) derivatives XIIIa, b, and c,[36] formed by reduction of the C-17–C-18 double bond (or transformation of a reduced derivative) from IIa, XIIb, and IIIa, respectively,[2a,b] provided insight to a deshielding effect on H-9α. The lines for H-9α, normally found around δ 3.13 (Table III) in the unsaturated compounds, had moved upfield about 0.5 ppm in the nmr spectra of XIIIa, b, and c (to δ 2.70, 2.62, and 2.63, respectively) compared with the unsaturated analogs. Since H-9α (see configurations I–X) is rigidly held in its position relative to the C-17–C-18 double bond, this effect is an example of deshielding along the *z* axis of a double bond in accordance with Jackman's[37] hypothesis and in agreement with the findings of Yamaguchi, *et al.*[38]

The two dihydro carbinols XIIIb and c also provided evidence that more than just the shielding of the ring nitrogen atom is responsible for the upfield position of the H-8α lines. In the spectrum of XIIIb, the H-8α lines are obscured, but they could not be higher than about δ 0.9; this was *ca.* −0.2 ppm or more downfield from the H-8α lines (δ 0.69) in the unsaturated precursor (XIIb). This same situation was observed for the dihydro compound XIIIc; H-8α could not be higher than about δ 1.1, and was therefore *ca.* >0.3 ppm downfield from the corresponding lines (δ 0.79) in the unsaturated analog IIIa. The δ 0.9 region in the spectra of the dihydro compounds was obscured, probably by the C-17 and C-18 aliphatic proton patterns (which are absent from this region when H-17 and H-18 are olefinic). Coincidental decoupling of these aliphatic proton patterns prevented location of any H-8α lines by the usual spin-decoupling experiments. The upfield position of the H-8α resonances in the bicyclo[2.2.2]octene analogs XIIb and IIIa, compared with their saturated counterparts XIIIb and XIIIc, respectively ($\Delta\delta = +0.2$–0.3 ppm), is similar to that observed for simpler bicyclo[2.2.2]octene derivatives[6c] and demonstrates that the C-17–C-18 double bond may also be responsible, *in part*, for the upfield position of the H-8α lines observed in the spectra of the C-19 carbinols studied. However, these effects are not operable in the case of the carbinols IIIb and XIa (H-8α *ca.* δ 1.2 and 1.2, respectively).

In summary, considering the structural variations examined by nmr, the following additional conclusions are evident. There is only one major deshielding effect on H-9α in these 6,14-*endo*-ethenotetrahydrothebaine derivatives, along the *z* axis of the C-17–C-18 double bond. Saturation of the double bond allows H-9α to shift upfield to around δ 2.6 (a reasonable position for this type of proton). The magnitude of the various changes in the chemical shifts of H-8α and H-8β are undoubtedly significant, but the complexity of a number of competing effects makes a complete analysis of these shifts difficult. Particularly perplexing are explanations for the downfield shift to a more normal (bicyclo[2.2.2]octene) position of the H-8α lines in the 7α secondary carbinol diastereomer XIb (δ 1.20), the 7α tertiary ether VIII (δ 1.18), and the 7β tertiary carbinol IIIb. Although the marked separations of the shifts for the geminal 8α and 8β protons are clearly involved with both the nearby nitrogen atom and with the presence of the C-17–C-18 double bond, better interpretation of the observed shifts for H-8α has not been possible, partly due to uncertainties about the conformation of C-19 substituents. Additional investigations of these interesting variations are continuing.

Acknowledgment. We wish to thank Dr. K. W. Bentley for valuable discussions and for providing generous samples of compounds as noted. Microanalyses carried out by Mr. L. Brancone and group, partition column separations carried out by C. Pidacks and group, literature assistance by Dr. M. G. Howell, and editorial service by Mrs. D. Budd are gratefully acknowledged. We also wish to thank Dr. J. J. Denton for interest and encouragement throughout these investigations.

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[36] Compounds XIIIa and XIIIc were obtained from the Reckitt and Sons Ltd., Laboratories through the courtesy of Dr. K. W. Bentley. Compound XIIIb was synthesized by catalytic hydrogenation of XIIb and described by Bentley and co-workers.[2b]

[37] A. A. Bothner-By and J. A. Pople, *Ann. Rev. Phys. Chem.*, **16**, 43 (1965). The authors interpret Jackman's hypothesis as implying deshielding on the *z* axis of a carbon–carbon double bond.

[38] S. Yamaguchi, S. Okuda, and N. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **11**, 1465 (1963).