NMR Study of 6-Azabicyclo[3.2.1]octene Derivatives, By-products of Catharanthine Synthesis

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The structures and stereochemistries of several 6-azabicyclo[3.2.1]octene derivatives, obtained by rearrangement reactions of the catharanthine synthesis, were determined by various NMR methods. Long-range ^{13}C–^{1}H coupling constants were measured by selective two-dimensional INEPT experiments. The dependence of $^{3}J(C,H)$ and $^{2}J(C,H)$ coupling constants on the dihedral angles and on the position of an electronegative substituent along the coupling path was studied.

During our efforts aimed at synthesizing catharanthine and its derivatives, the formation of several rearranged products was observed.[1,2] These rearrangements, depending on the reaction conditions and the substituents on the isoquinuclidine moiety, afforded a variety of products, a few of them having the 6-azabicyclo[3.2.1]octene skeleton.

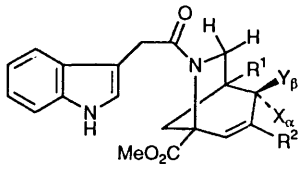
The liability to rearrangement of compounds with the isoquinuclidine skeleton has been noted by others before.[3,4] Mangeney and Langlois[5] observed the rearrangement of catharanthinic acid into a 6-azabicyclo[3.2.1]oct-2-ene derivative. In the course of a mechanistic study of the above reaction, these authors assumed an intermediate with a 6-azabicyclo-[3.2.1]oct-3-ene structure. In our case, both types of rearranged products (structures **A** and **B**) were isolated, confirming the proposed mechanism.

Attempts to obtain other 6-azabicyclo[3.2.1]octene derivatives, by changing the reaction conditions of the photochemical reactions and the eluent during the work-up procedure, afforded the new compounds **10**, **11** and **15**–**18**. The structures and stereochemistries of the products were established by NMR spectroscopy.

The number and variety of derivatives differing in the type and stereochemistry of their substituents, moreover the conformational rigidity of the bicyclic skeleton, allowed us to study the effect of stereochemical factors and electronegative substituents on the vicinal and geminal ^{13}C–^{1}H coupling constants. While most of the $^{3}J(C,H)$ couplings followed a Karplus-type relationship, there were some unexpected values worthy of note. The correlation of $^{2}J(C,H)$ coupling constants with the hybridization state of the carbon atom taking part in the coupling is also reported.

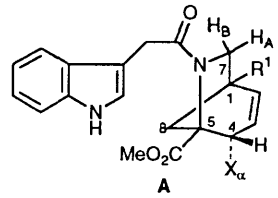
Results and Discussion

Synthesis and Isolation of the Rearrangement Products.— Catharanthine (**4a**) is one of the major alkaloids of *Catharantus roseus*. By coupling **4a** with vindoline, a vinblastine-type antitumor diindole alkaloid can be obtained. Using the route **1**→**3**→**5**→**4** (Scheme 1), catharanthine (**4a**), allocatharanthine (**4b**) and deethylcatharanthine (**4c**) were synthesized.[1,2]



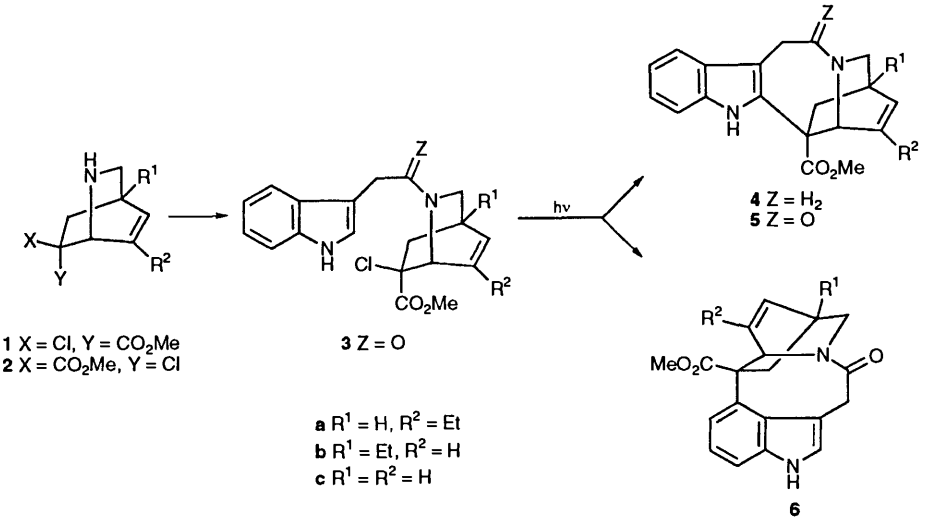
B

7 $R^1 = Y = R^2 = H$, X = Cl
8 $R^1 = Y = R^2 = H$, X = Br
9 $R^1 = Y = R^2 = H$, X = OH
10 $R^1 = X = R^2 = H$, Y = Cl
11 $Y = R^2 = H$, X = Cl, R^1 = Et
12 $X = R^2 = H$, Y = Cl, R^1 = Et
13 $Y = R^1 = H$, X = Cl, R^2 = Et
14 $Y = R^1 = H$, X = Br, R^2 = Et



A

15 R^1 = H, X = Cl
16 R^1 = H, X = Br
17 R^1 = Et, X = OMe
18 R^1 = H, X = OMe



1 X = Cl, Y = CO_2Me
2 X = CO_2Me, Y = Cl

3 Z = O

4 Z = H_2
5 Z = O

a R^1 = H, R^2 = Et
b R^1 = Et, R^2 = H
c $R^1 = R^2$ = H

6

Scheme 1

Following the above reaction sequence, several intermediates were isolated. The isoquinuclidine skeleton exhibited various unexpected rearrangements depending on the reaction conditions and the substituents on the 2-azabicyclo[2.2.2]oct-5-ene skeleton. The isoquinuclidine skeleton was particularly susceptible to rearrangements when the chlorine substituent was in the *endo* position (**2a–c**). Thus, when starting from the HBr salt of **2c**, the 6-azabicyclo[3.2.1]oct-3-enes **7** and **8** were obtained as major products in a simple acylating reaction under mild conditions, as reported earlier.[1,2] A careful choice of the eluent in column chromatography (see Experimental) allowed us to isolate a small amount of by-product **10**, an epimer of **7**, as well as the 6-azabicyclo[3.2.1]oct-2-ene derivatives **15** and **16**.

When the above described acylation reaction was applied to the isoquinuclidines **2a** and **b**, the corresponding 6-azabicyclo-[3.2.1]oct-3-ene derivatives (**12–14**) were obtained.[2] During repeated work-up of the above reaction mixture, we also obtained **11**, the epimer of **12**.

In the photochemical reactions, irradiation of the 2-indolyl acetyl-2-azabicyclo[2.2.2]oct-5-ene derivatives **3a–c** led to **5a–c**, **6a–c** and, depending on the solvent, some other rearranged by-products with the 6-azabicyclo[3.2.1]octene skeleton. Thus when **3c** was irradiated in a mixture of tetrahydrofuran and water, a by-product (**9**) with the 6-azabicyclo[3.2.1]oct-3-ene skeleton was found.[1] The presence of the hydroxy group in the molecule can be explained by a Cl–OH exchange. Unlike the deethyl and 6-ethyl derivatives (**3c** and **a**), irradiation of the 4-ethyl compound **3b** gave the by-product **17** with a 6-azabicyclo[3.2.1]oct-2-ene skeleton.

Irradiation of the mixture of **7** and **8** resulted in **18** as the main product, among other by-products. The halogen–OCH_3 exchange can be attributed to the presence of methanol used as the solvent.

NMR Spectroscopy.—Distinction between 2- (**A**) *and* 3-*octene* (**B**) *derivatives.* The structures of the 6-azabicyclo[3.2.1]octene derivatives were established by NMR. The ^1H and ^{13}C NMR chemical shifts and proton–proton coupling constants for compounds **7–18** are collected in Tables 1 and 2, the structurally important carbon–proton coupling constants are given in Table 3.

Of the several structures that have been considered,[1,2] we propose the 6-azabicyclo[3.2.1]octene skeleton for molecules **7–18** on the basis of the results of INAPT,[6] 2D INEPT[7] and NOE[8] techniques. The characteristic feature of this structure in comparison with the other rearranged systems formed in the same reactions[1,2] is the relatively large olefinic coupling constant values ($^3J_{HH}$ = 9–9.5 Hz) while the other NMR data (chemical shifts and proton couplings) were not informative of the ring size.

Distinction between structures **A** and **B** was also made by applying long-range hetero-correlation and NOE difference methods. In the selective INAPT experiment of the **B**-type molecules, irradiation of the downfield olefinic proton (4-H) gave response in the carboxy carbon resonance, among others, while no such correlation was found with C-1. On the other hand, the selective INAPT spectrum obtained by irradiation of the higher field olefinic proton (3-H) had responses at C-1 and -5. These observations are in agreement with the 6-azabicyclo-[3.2.1]oct-3-ene structure for compounds **7–14**, where the double bond is located between carbons C-3 and -4 and the halogen or hydroxy substituent is at C-2.

The NOE difference experiments provided additional information. Irradiation of 4-H gave NOE enhancement of the signal due to carbomethoxy protons, while saturation of 2-H resulted in enhancement of the signals of 1-H (or C-1 ethyl) and 3-H in both the C-2α and -2β substituted derivatives. Since proton–proton couplings were of little value, the relative orientation of the C-2 substituent was also determined by NOE experiments. Irradiation of 2α-H in **10** and **12** gave NOE response on the signal of 8α-H proton, while in the C-2α substituted derivatives (**7–9**, **11**, **13**, **14**), NOE enhancement was observed between 2β- and 7_A-H (7_A-H was always identified by its W coupling with 8α-H). As a consequence of different γ-*gauche* effects in C-2α and -2β substituent cases, the chemical shifts of C-7 and -8 also reflect the stereochemical differences.

In **11** and **12**, the C-1 location of the ethyl substituent followed from long-range connectivities between the ethyl protons and skeletal C-1, -2, -7 and -8. In compounds **13** and **14**, one of the olefinic carbons was quaternary. The substitution pattern as depicted in **A** and **B** was chosen on the basis of selective INAPT connectivities between the olefinic proton and carbon atoms C-5, carboxy and ethyl CH_2.

^1H and ^{13}C chemical shift values and electron impact mass spectral data indicated the presence of a chlorine atom in **15**, a bromine atom in **16**, methoxy and C-1 ethyl substituents in **17**, and a methoxy group in **18**. The results of selective INAPT spectra and NOE difference experiments have led to structure **A** for these compounds. Thus, irradiation of the proton geminal to the substituent (4-H) revealed connectivities between this proton and the C-5 and carboxy carbons. In the NOE experiment, irradiation of one of the olefinic protons (assigned to 2-H) exerted NOEs on 1-H (or C-1 ethyl) and 7_A-H. In all four compounds, saturation of 4-H enhanced the resonance of the 3-H olefinic proton only.

The orientation of the C-4 substituent did not follow from the characterless coupling constants of 4-H ($^3J_{3,4} \approx 4$ in **15–18**). The apparent absence of an NOE on the signal of 8α-H upon irradiation of 4-H, however, is consistent with the α orientation of the C-4 substituent. Moreover, in a manner similar to cases with C-2α substitution, the upfield shift of C-8 may be attributed to the γ-*gauche* effect of the C-4α substituent.

Multiple bond ^{13}C–^1H *coupling constants and their stereochemical implications.* Long-range carbon–proton coupling constants were inferred from selective 2D INEPT experiments. Since sign information for the coupling constants was not available from the applied 2D INEPT experiment, absolute values are given for the ^2J(C,H) and ^3J(C,H) couplings in Table 3. However, based on quantum chemical calculations and experimental results reported for structurally related compounds,[9] a positive sign can be expected for vicinal C,H couplings, while both positive and negative signs have been reported for geminal C,H coupling constants.

There are various factors which may influence the magnitude of geminal and vicinal couplings. Although the measured data generally reflect the cumulative effect of these factors, appropriate comparison of data may single out one predominant effect on the coupling constant values. For our molecules, the stereochemical and electronegative substituent effects on coupling values are discussed only.

(*a*) Vicinal ^{13}C–^1H coupling constants. The Karplus-type dihedral angle dependence of the ^3J(C,H) coupling constant values have been widely used[10] for stereochemical assignment in substituted rigid bicyclic systems. The Dreiding model of the molecules studied here shows that 8α-H and C-7 assume a nearly planar (~ 180°) steric arrangement, while the dihedral angle between 8β-H and C-7 is about 90° in both **A**- and **B**-type structures. The differences observed are reflected well in the experimental coupling values (5.9–7.2 and < 0.5 Hz, respectively).

Similar steric dependence can be presumed for ^3J(C-8,2-H), ^3J(C-7,2-H) and ^3J(C-2,8-H) couplings in the **B**-type compounds **7–14**, and for ^3J(C-4,8-H) couplings in **A**-type compounds **15–18**. However, electronegative substituents at

Table 1 ^{1}H NMR chemical shifts (δ_H, referenced to internal tetramethylsilane) and relevant coupling constants (Hz)

	7[a]	8[a]	10[a]	11[b]	12[b]	13[b]	14[b]	9[a]	15[a]	16[a]	17[b]	18[b]
1-H	2.90	2.99	2.86	—	—	2.92	3.03	2.63	2.88	2.87	—	2.80
2-H	4.39	4.59	4.97	4.40	4.91	4.22	4.44	3.93	5.93	5.83	5.83[c]	6.01
3-H	5.69	5.79	5.58	5.75	5.63	—	—	5.65	5.69	5.79	5.86[c]	5.81
4-H	6.88	6.79	6.85	6.84	6.85	6.60	6.61	6.74	4.98	5.12	4.19	4.19
7_A-H	3.29	3.30	4.09	3.27	4.12	3.22	3.22	3.26	3.37	3.36	3.19	3.27
7_B-H	3.87	3.85	3.73	3.73	3.43	3.84	3.79	3.79	3.64	3.63	3.34	3.58
8β-H	2.13	2.17	2.34	1.93	2.19	2.16	2.13	1.93	2.14	2.18	1.83	2.02
8α-H	2.29	2.37	2.09	2.15	2.05	2.31	2.39	2.14	2.44	2.55	2.17	2.24
2′-H	7.05	7.04	6.99	6.94	7.03	7.03	7.02	7.04	7.05	7.06	7.00	6.99
4′-H	7.52	7.51	7.55	7.50	7.55	7.53	7.52	7.48	7.49	7.50	7.51	7.52
5′-H	7.07	7.08	7.09	7.08	7.10	7.10	7.11	7.00	7.03	7.02	7.08	7.10
6′-H	7.16	7.14	7.16	7.15	7.17	7.19	7.18	7.09	7.16	7.13	7.16	7.17
7′-H	7.36	7.35	7.31	7.30	7.32	7.34	7.34	7.32	7.36	7.35	7.35	7.35
3′-CH_2	3.64 3.68	3.66 3.70	3.69 3.74	3.60 3.65	3.67 3.72	3.65	3.64	3.58 3.64	3.64 3.68	3.66 3.68	3.63 3.66	3.65 3.69
CO_2CH_3	3.78	3.73	3.74	3.76	3.75	3.81	3.80	3.70	3.69	3.67	3.74	3.75
NH	9.25	9.30	8.48	8.60	8.38	8.20	8.18	10.30	10.10	10.11	8.58	8.38
OH	—	—	—	—	—	—	—	4.98	—	—	—	—
CH_2CH_3	—	—	—	1.51 2.04	1.52 1.80	2.01 2.15	2.02 2.19	—	—	—	1.50 1.58	—
CH_2CH_3	—	—	—	0.89	0.92	0.91	0.89	—	—	—	0.92	—
OCH_3	—	—	—	—	—	—	—	—	—	—	3.57	3.57
J(1,2)	2.0	2.0	5.0	—	—	1.8	1.8	2.0	6.1	5.8	—	6.1
J(1,7_A)	1.0	1.0	1.0	—	—	1.0	1.0	1.0	0.5	0.5	—	0.5
J(1,7_B)	6.0	6.0	5.0	—	—	6.0	5.2	6.1	4.0	4.0	—	4.0
J(1,3)	1.5	1.5	1.3	—	—	—	—	1.2	—	—	—	—
J(1,8β)	4.8	4.0	5.0	—	—	4.9	5.0	4.5	3.5	3.5	—	3.8
J(1,8α)	1.5	1.5	1.5	–	—	1.0	1.0	1.5	1.0	1.0	—	0.8
J(2,3)	3.5	3.5	2.8	4.0	3.0	—	—	3.8	9.2	9.2	9.5	9.3
J(2,4)	1.2	1.2	1.6	1.5	1.5	0.5	0.5	1.0	0.5	0.5	0.5	0.5
J(2,7_B	—	—	1.5	—	1.7	—	—	—	—	—	—	—
J(2,8β)	—	—	—	—	—	—	—	—	1.0	1.0	1.8	1.0
J(3,4)	9.5	9.5	9.5	9.5	9.5	—	—	9.3	4.3	3.9	4.5	4.1
J(4,8β)	1.0	1.0	1.6	0.8	1.4	1.0	1.0	1.0	0.8	0.8	0.5	0.6
J(7_A,7_B)	−10.5	−10.5	−10.5	−10.5	−10.5	−10.5	−10.5	−10.2	−9.0	−9.0	−9.0	−9.0
J(7_A,8α)	1.0	1.0	1.0	1.0	1.0	0.8	0.8	1.0	1.7	1.7	1.6	1.7
J(8α,8β)	−11.5	−11.5	−11.0	−11.5	−11.5	−11.1	−11.1	−11.0	−11.4	−11.5	−11.0	−11.0
J(3′,3′)	−15.1	−15.1	−15.5	−15.5	−15.5	—	—	−15.0	−15.5	−15.5	−15.5	−15.5
J(2,OH)	—	—	—	—	—	—	—	5.6	—	—	—	—

[a] In $CDCl_3$ and [$^2H_6$]dimethylsulfoxide solution. [b] In $CDCl_3$ solution. [c] Assignments may be interchanged.

Table 2 ^{13}C NMR chemical shifts (δ_C, referenced to internal tetramethylsilane)

	7[a]	8[a]	10[a]	11[b]	12[b]	13[b]	14[b]	9[a]	15[a]	16[a]	17[b]	18[b]
C-1	41.70	41.71	42.00	47.56	49.76	42.53	43.04	40.28	35.73	35.75	45.53	35.61
C-2	58.09	51.30	60.82	61.49	64.24	61.20	54.44	68.95	129.66	128.49	134.88	130.97
C-3	126.59	127.72	127.17	127.49	127.85	138.89	139.63	129.09	127.53	128.57	126.25	126.29
C-4	133.00	131.92	133.93	131.62	133.33	126.71	126.52	131.88	53.80	46.21	74.08	74.26
C-5	62.63	62.20	62.13	64.53	63.17	63.06	63.20	62.52	68.04	67.51	68.73	67.84
C-7	50.61	50.68	48.43	54.91	53.06	50.39	51.02	49.35	54.06	54.90	57.73	53.29
C-8	34.68	34.68	41.61	39.99	44.58	35.06	35.33	34.79	34.18	34.66	39.08	35.15
C-2′	122.90	123.22	122.97	122.89	123.14	122.54	122.83	123.18	123.04	123.01	122.09	122.74
C-3′	107.07	107.06	107.87	107.46	107.02	108.03	107.48	107.45	106.87	106.80	108.29	108.22
C-3a′	127.07	127.14	127.22	128.04	127.17	127.04	127.05	127.27	127.02	127.00	127.21	127.20
C-4′	118.42	118.36	118.59	118.33	118.58	118.53	118.40	118.33	118.36	118.30	118.59	118.50
C-5′	118.94	118.57	119.29	119.33	118.59	119.59	119.38	118.61	118.79	118.82	119.40	119.39
C-6′	121.64	121.62	121.94	121.99	121.26	122.28	122.06	121.04	121.47	121.50	122.08	122.05
C-7′	111.43	111.28	111.29	111.44	111.28	111.26	111.42	111.28	111.43	111.40	111.24	111.27
C-7a′	136.35	136.21	136.19	136.19	136.33	136.16	136.23	136.27	136.32	136.36	136.27	136.13
3′-CH_2	32.02	31.40	31.91	31.59	31.63	31.96	31.96	31.52	32.60	32.56	32.23	32.43
NCO	169.21	168.61	169.39	169.45	168.80	168.97	169.06	168.74	170.62	170.62	170.34	170.63
CO_2	170.56	170.26	170.70	170.45	170.33	170.94	170.94	170.01	169.79	169.70	171.75	171.83
OCH_3	52.45	51.96	52.65	52.65	52.17	52.67	52.65	51.72	52.03	52.03	52.22	52.23
CH_2CH_3	—	—	—	30.03	27.25	26.04	26.94	—	—	—	27.53	—
CH_2CH_3	—	—	—	8.13	8.68	11.46	11.51	—	—	—	9.32	—
4-OCH_3	—	—	—	—	—	—	—	—	—	—	58.80	58.71

[a] In $CDCl_3$ and [$^2H_6$]dimethylsulfoxide solution. [b] In $CDCl_3$ solution.

Table 3 Selected ^nJ(C,H) values[a]

	7	8	10	11	12	13	14	15	17	18
^2J(C-1,2-H)	1.4	1.8	2.7	1.5	2.4	1.8	*c*	3.2	4.1	4.8
^3J(C-1,3-H)	5.0	5.0	5.2	4.6	4.7	—	—	8.4	8.7	9.1
^2J(C-1,8α-H)	*b*	*b*	*b*	2.4	1.7	*b*	*b*	*b*	2.5	1.5
^2J(C-1,8β-H)	*b*	*b*	*b*	3.3	3.3	*b*	*b*	*b*	3.1	3.4
^2J(C-2,1-H)	5.2	4.5	4.4	—	—	5.5	4.8	4.0	—	4.0
^2J(C-2,3-H)	2.3	2.8	2.0	2.1	*c*	—	—	*c*	*c*	*c*
^3J(C-2,4-H)	11.8	12.4	12.0	11.8	12.2	11.5	11.6	5.0	5.7	5.0
^3J(C-2,8α-H)	*b*	*b*	*b*	2.9	2.8	*b*	*b*	*b*	2.0	1.4
^3J(C-2,8β-H)	*b*	*b*	*b*	7.1	8.8	*b*	*b*	*b*	6.6	7.4
^3J(C-3,1-H)	5.5	5.0	6.3	—	—	5.6	5.4	6.0	—	5.5
^3J(C-3,2-H)	4.7	4.0	6.0	4.6	5.7	4.2	4.4	1.4	0.8	*c*
^2J(C-3,4-H)	*c*	0.9	0.5	0.5	0.5	*c*	*c*	4.5	3.6	3.3
^3J(C-4,2-H)	5.2	5.4	5.8	5.0	5.4	4.4	4.6	10.2	9.9	9.8
^2J(C-4,3-H)	0.5	*c*	0.5	*c*	*c*	—	—	2.8	3.2	3.3
^3J(C-4,8α-H)	*b*	*b*	*b*	1.2	1.3	*b*	*b*	*b*	1.5	1.4
^3J(C-4,8β-H)	*b*	*b*	*b*	5.5	6.0	*b*	*b*	*b*	4.1	4.3
^3J(C-5,1-H)	4.8	4.8	4.7	—	—	5.2	5.2	5.0	—	5.5
^3J(C-5,3-H)	9.2	9.3	9.0	9.1	9.9	—	—	4.9	6.0	6.0
^2J(C-5,4-H)	3.4	2.9	3.2	3.2	3.1	3.0	3.0	3.8	4.3	4.4
^2J(C-5,8β-H)	*b*	*b*	*b*	4.4	4.3	*b*	*b*	*b*	4.7	4.7
^3J(C-7,2-H)	1.9	2.0	6.1	1.4	5.0	1.9	*c*	*c*	*c*	*c*
^3J(C-7,8α-H)	*b*	*b*	*b*	6.0	6.0	*b*	*b*	*b*	5.9	7.2
^2J(C-8,1-H)	*c*	*c*	2.7	—	—	*c*	*c*	*c*	—	1.5
^3J(C-8,2-H)	3.9	4.0	1.0	3.0	0.8	4.2	4.2	2.6	3.3	3.6
^3J(C-8,4-H)	*c*	2.2	2.8	2.2	3.1	2.0	2.0	3.2	2.8	3.0
^3J(CO_2,4-H)	2.2	1.6	2.2	1.8	1.9	2.4	1.9	0.9	1.6	1.5
^3J(CO_2,8β-H)	*b*	*b*	*b*	2.6	2.5	*b*	*b*	*b*	3.5	3.6

[a] Absolute values of coupling constants are shown. [b] Not measured. [c] < 0.5 Hz or not found. [d] The ^2J(C-5,8α-H), ^3J(C-7,8β-H) and ^3J(CO_2,8β-H) values are less than 0.5 Hz.

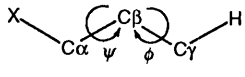
carbons C-2 or -4 are expected to alter the magnitude of vicinal couplings, since in the $^{13}C_\alpha$–C_β–C_γ–^1H fragment, an electronegative substituent in the γ-position was reported[11] to decrease the ^3J(C,H) values, while α-substitution increased these values. Although this tendency is evident also for our compounds [*cf.* ^3J(C-8,4β-H) with ^3J(C-4,8β-H) values in the **A**-type molecules, and ^3J(C-8,2β-H) with ^3J(C-2,8β-H) couplings in the **B**-type molecules], the stereochemistry can be unambiguously deduced from the corresponding ^3J(C,H) coupling values. Thus, for the nearly planar arrangements (C-7–2α-H, C-8–2β-H, C-2–8β-H, C-4–8β-H), the vicinal couplings observed have values at least 3 Hz higher than ^3J(C-7,2β-H), ^3J(C-8,2α-H), ^3J(C-2,8α-H) and ^3J(C-4,8α-H).

While we had both C-2α and -2β substituted cases for structure **B**, only one stereoisomer was found for the **A**-type compounds (**15**–**18**). Examination of the Dreiding models suggests that C-8 and 4β-H have about the same stereochemical arrangement in **A**-type molecules as C-8 and 2β-H in **B**-type molecules. In agreement with this, the values observed for ^3J(C-8,4-H) discriminate clearly between α and β configurations. This coupling in **15**, **17** and **18** (2.8–3.2 Hz) shows closer correlation with the ^3J(C-8,2β-H) values (3.0–4.2 Hz in compounds **7**, **8**, **13**, **14** and **11**) than with ^3J(C-8, 2α-H) values (0.8–1.0 Hz in **10** and **12**), which corroborates our stereochemical assignment for **15**–**18** based on NOE observations.

The ^3J(C-8,4β-H) values in **A**-type molecules fit much better with ^3J(C-8,2β-H) couplings in **B**-type molecules if we consider the different substitution pattern at C-1 and -5. As is known,[12] electronegative substituents at the intervening carbon of the coupling pathway reduce the ^3J(C,H) values. The presence of carbomethoxy and NCO groups at the quaternary C-5 may be responsible for the fact that ^3J(C-8,4β-H) in **15**, **17** and **18** has about 1–1.5 Hz lower values than the corresponding ^3J(C-8,2β-H) values in **7**, **8**, **13** and **14** where the bridgehead C-1 is not substituted.

Branching, caused by an aliphatic unit at the intervening carbon, may also influence the ^3J(C,H) couplings.[13] Comparison of ^3J(C-8,2β-H) in **11** (3.0 Hz) with that of **7**, **8**, **13** and **14** (3.9–4.2 Hz) shows that C-1 ethyl substitution definitely reduces this vicinal coupling. A similar decrease was found in the ^3J(C-7,2α-H) value of **12** when compared with **10** and in the ^3J(C-7,8α-H) value of **17** in comparison with **18**.

In addition to the Karplus-type behaviour of ^3J(C,H) couplings described above, we have found experimental verification of the predicted[14] effect of electronegative C_α-substituent orientation in the fragment. Thus far, the only experimental corroboration of the theoretical predictions was given by measurement of ^3J(C,H) in *cis*- and *trans*-4-*tert*-butylcyclohexanol.[15] In spite of the fact that the dihedral angle between the 8β-H proton and C-2 carbon (φ_{CH}) is 180° in both **11** and **12**, the pertinent ^3J(C-2,8β-H) coupling values are



markedly different (7.1 and 8.8 Hz, respectively). In this pair of compounds, Ψ_{XC} is the only angle that takes different values ($\Psi_{Cl,C}$ is approximately 180° in compound **12**, while it is *ca.* 60° in **11**). The observed 1.7 Hz difference in ^3J(C-2,8β-H) compares favourably with the values calculated by INDO methods. These calculations also show that when Φ_{CH} is about 60°, the orientation of the substituent at the α-carbon has negligible effect on the ^3J(C,H) coupling.[15] The experimental ^3J(C-2,8α-H) values (2.8 in **12** and 2.9 Hz in **11**) are in support of calculated results.

Steric effects also prevail on ^3J(C,H) couplings even if the carbon atom is olefinic. Comparison of the ^3J(C-4,8α-H) couplings (1.2–1.3 Hz) with ^3J(C-4,8β-H) couplings (5.5–6.0 Hz) in molecules **11** and **12** of structure **B**, and similarly, the ^3J(C-

2,8α-H) couplings with ^3J(C-2,8β-H) couplings in **A**-type molecules **17** and **18** (1.4–2.0 and 6.6–7.4 Hz, respectively) reveals that, irrespective of the s-character of the participating carbon, the magnitude of the vicinal coupling definitely follows Karplus-type angular dependence and the values are similar to the aliphatic vicinal ^3J(C,H) couplings. The situation is entirely different when the proton is the olefinic and the carbon is the saturated partner in the coupling path. Although both C-8–4-H atoms in the **B**-type and C-8–2-H atoms in the **A**-type molecules are in almost planar arrangement, their vicinal coupling constants have substantially lower values (2.2–3.6 Hz) than in the case of olefinic carbons. This peculiarity deserves attention since it may result in erroneous steric assignments.

In agreement with literature observations,[16] we have found that vicinal couplings are larger for coupling paths that traverse the entire olefin. For instance, in compound **18**, ^3J(C-8,2-H) is 3.6 Hz, while ^3J(C-1,3-H), where the entire olefinic bond takes part in the coupling, is 9.1 Hz. We have also found that external substitution on the sp^3 carbon by an ethyl, a carbomethoxy or methoxy group essentially does not affect the above coupling value [^3J(C-1,3-H) is 8.7 Hz in **17**, ^3J(C-5,3-H) in **7**–**12** is 9.1–9.9 Hz and ^3J(C-4,2-H) is 9.8 and 9.9 Hz in **17** and **18**]. By contrast, external substitution with halogens on the sp^3 carbon substantially increased the vicinal couplings [^3J(C-2,4-H) is 11.8–12.4 Hz in **7**–**12**].

(*b*) Geminal ^{13}C–^1H coupling constants. The ^2J(C,H) values in saturated rigid bicyclic systems, whenever measured, were found to be negative.[10] However, electronegative substituents at either the observed or the intervening carbon atom may alter the ^2J(C,H) coupling values in different ways. In addition, not only the magnitude but also the sign of geminal couplings depends on the dihedral angle defined by the C–H and C–X bonds in the X–^{13}C–C–^1H fragment.

Cyr *et al.*[17] have established for carbohydrate derivatives that an oxygen *anti* to the proton makes a positive contribution, and a *gauche* oxygen a negative contribution to ^2J(C,H). (A similar trend was presumed for other electronegative substituents such as chlorine.)

Since for C-2–C-1–1-H arrays both the α and the β oriented halogen is *gauche* to 1-H in the **B**-type molecules, the observed sizeable ^2J(C-2,1-H) couplings (4.4–5.5 Hz) are presumed to be of negative sign. Much lower values and a slight dependence on the substituent orientation were found for the ^2J(C-1,2-H) couplings (1.4–1.8 Hz for **7**, **8**, **11**, **13** and 2.4–2.7 Hz for β-substituted **10** and **12**, respectively). The similar arrangement in **A**-type **15**, **17** and **18** compounds resulted in higher absolute values [^2J(C-5,4-H) is 3.8–4.4 Hz]. In these latter cases, the β-oriented 4-H is in a *gauche* relation to the electronegative NCO unit, thus the increase in the absolute value suggests a negative sign for this coupling.

Signs for geminal couplings, when one or both of the coupled nuclei are olefinic, may be either negative or positive. Thus for propene,[18] the coupling between the aliphatic (methyl) proton and olefinic carbon atom was −6.75 Hz, while it was +4.95 Hz between the saturated carbon and olefinic proton. It appears reasonable to assume the same signs of couplings for the similar arrangements in the **A**-type molecules [−4 Hz for ^2J(C-2,1-H) and +3.2 to +4.8 Hz for ^2J(C-1,2-H) couplings]. In all the other cases the sp^3 partner—either the proton-bearing carbon or the carbon taking part in the ^2J(C,H) coupling—is substituted with electronegative substituents such as chlorine, bromine or methoxy.

Comparison of the ^2J(C-2,1-H) couplings of **15** and **18** with the ^2J(C-3,2-H) values of **B**-type molecules reveals that in the latter compounds, the electronegative substituents at C-2 do not alter significantly the magnitude of ^2J(sp^2 C, sp^3 H)-type couplings. These observations, together with those found for aliphatic ^2J(C-5,4β-H) couplings, support the presence of a negative sign for all ^2J(C,H) couplings where the proton partner is geminal to the electronegative substituent. At the same time, by analogy with the entirely aliphatic ^2J(C-1,2-H) couplings, the ^2J(C-3,2-H) values exhibit slight dependence on the substituent stereochemistry (−4.0 to −4.7 Hz for α-substituted **7**, **8**, **11**, **13**, **14** and −5.8 to −6.0 Hz for β-substituted **10** and **12**). The ^3J(C-3,4-H) values (−3.3 to −4.5 Hz) of **A**-type **15**, **17** and **18** fit well with the α-substituted cases of the **B**-type structures. Finally, the ^2J(C-2,3-H) couplings in **B**-type and the ^2J(C-4,3-H) values of **A**-type molecules are quite similar (2.0–2.8 and 2.8–3.3 Hz, respectively), and no correlation with substituent orientation can be recognized, which is in agreement with the result obtained for purely aliphatic ^2J(C-2,1-H) couplings.

The parallel behaviour of ^2J(sp^3 C, sp^3 H) and ^2J(sp^2 C, sp^3 H) couplings toward substituent stereochemistry allows generalizations. Accordingly, different orientation of the substituent at the terminal carbon hardly affects ^2J(C,H), while in those cases where the coupled proton is geminal to the substituent, some correlation has been observed between ^2J(C,H) values and the orientation of the substituent. The difference in the ^2J(C,H) values for α and β substitution may be even more pronounced than in the corresponding ^3J(H,H) values [*cf.* ^2J(C-3,2-H) and ^3J(3-H,2-H) values of **B**-type molecules].

In summary, we have presented that geminal and vicinal carbon–proton couplings appear to portray accurately the orientation of an electronegative substituent, therefore, these values serve as suitable complements to proton couplings and NOE results in the stereochemical studies of rigid bicyclic systems.

Experimental

Compounds.—Syntheses of compounds **7**–**9** and **12**–**14** have been reported previously.[1,2]

(±)-*Methyl* 6-{1-[2-(*indol*-3-*yl*)-1-*oxoethyl*]}-2β-*chloro*-6-*azabicyclo*[3.2.1]*oct*-3-*ene*-5-*carboxylate* **10**, (±)-*methyl* 6-{1-[2-(*indol*-3-*yl*)-1-*oxoethyl*]}-4α-*chloro*-6-*azabicyclo*[3.2.1]*oct*-2-*ene*-5-*carboxylate* **15** *and* (±)-*methyl* 6-{1-[2-(*indol*-3-*yl*)-1-*oxoethyl*]}-4α-*bromo*-6-*azabicylo*[3.2.1]*oct*-2-*ene*-5-*carboxylate* **16**. The mother liquor of **7** and **8** (ref. 1) was purified by silica gel column chromatography (eluent hexane–ethyl acetate–triethylamine, 3:3:1) to afford three other products. (*a*) **10** (oil, 8.0%). The analytical sample was crystallized from acetone–hexane, m.p. 154–157 °C; ν_{max}(KBr)/cm^{-1} 1650 (amide C=O) and 1745 (ester C=O); *m*/*z* 360,* 358 (M^+), 327, 323, 295, 264, 227, 196, 186, 157, 156, 130, 105, 103, 102, 93, 91, 77, 59, 51, 50, 38 and 36. NMR data are summarized in the Tables. (*b*) Mixture of **15** and **16** (oil, 2.9%). The analytical sample was crystallized from acetone–hexane, m.p. 174–179 °C; ν_{max}(KBr)/cm^{-1} 1620 (amide C=O) and 1750 (ester C=O); *m*/*z* 404,* 402 (M^+, **16**), 392,* 390, 360,*, 359*, 358 (M^+, **15**), 340, 324, 322, 307, 293, 265, 261, 228, 200, 157, 130, 113, 112, 77, 71 and 57. NMR data are summarized in the Tables.

(±)-*Methyl* 6-{1-[2-(*indol*-3-*yl*)-1-*oxoethyl*]}-1-*ethyl*-4-*methoxy*-6-*azabicyclo*[3.2.1]*oct*-2-*ene*-5-*carboxylate* **17** *and* (±)-*methyl* 10-*ethyl*-7-*oxo*-6,7,9,10,12a,13-*hexahydro*-10,13-*methano*-4H-*pyrido*[2,1-b]*pyrrolo*[4,3,2-fg][3]*benzazocine*-13-*carboxylate* **6b**. (±)-Methyl 2-{1-[2-(indol-3-yl)-1-oxoethyl]}-4-ethyl-7-*exo*-chloro-2-azabicyclo[2.2.2]oct-5-ene-7-*endo*-carboxylate **3b** (500 mg, 1.292 mmol) was dissolved in dry methanol (1.5 dm^3) to which $NaBH_4$ (45 mg, 1.190 mmol) and tributyltin chloride (0.05 cm^3, 60 mg, 0.184 mmol) were added. The solution was stirred with a magnetic stirrer, purged with N_2

* Isotopic peak.

and irradiated with a low pressure mercury lamp (Tungsram 250 W) for 3 h until TLC showed no remaining starting material. The methanolic solution was evaporated and the residue dissolved between chloroform and water. The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (eluent toluene–acetone–triethylamine, 40:20:1) to afford three main products, listed in order of increasing polarity. (*a*) 5-Oxoallocatharanthine (124 mg, 0.354 mmol, 27.39%), **5b** (see ref. 2). (*b*) **17**, oil (140 mg, 0.366 mmol, 28.33%) ν_{max}(film)/cm^{-1} 1650 (amide C=O) and 1750 (ester C=O); *m/z* 382 (M^+), 367, 353, 350, 323, 266, 224, 196, 195, 188, 166, 165, 164, 157, 130, 92, 85 and 83. NMR data are summarized in the Tables. (*c*) **6b**, oil (90 mg, 0.256 mmol, 19.88%). The analytical sample was crystallized from acetone–hexane, m.p. 280–288 °C, ν_{max}(KBr)/cm^{-1} 1632 (lactam C=O) and 1740 (ester C=O); *m/z* 350 (M^+), 322, 292, 291, 243, 234, 215, 214, 211, 204, 201, 184, 154, 149, 130, 121, 108, 100, 86 and 80; δ_H(400 MHz, $CDCl_3$, room temp.) 1.02 (3 H, t, *J* 6.7, CH_2CH_3), 1.64 (2 H, q, *J* 6.7, CH_2CH_3), 1.67 (1 H, d, *J* 13.5, 14_A-H), 2.94 (1 H, dd, *J* 11, 2.5, 9_A-H), 3.11 (1 H, dd, *J* 13.5, 2.5, 14_B-H), 3.22 (1 H, d, *J* 11, 9_B-H), 3.55 (3 H, s, CO_2Me), 3.66 (1 H, d, *J* 14.5, 6_A-H), 4.30 (1 H, d, *J* 14.5, 6_B-H), 5.71 (1 H, d, *J* 5.5, 12_A-H), 6.40 (1 H, dd, *J* 8.2 and 5.5, 12-H), 6.44 (1 H, d, *J* 8.2, 11-H), 6.92 (1 H, s, 5-H), 7.0 (1 H, d, *J* 8, 3-H), 7.09 (1 H, t, *J* 8, 2-H), 7.30 (1 H, d, *J* 8, 1-H) and 9.10 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$, room temp.) 8.55 (CH_2CH_3), 27.89 (CH_2CH_3), 34.94 (C-6), 39.01 (C-10), 41.41 (C-14), 52.80 (OMe), 52.89 (C-9), 53.18 (C-12a), 59.64 (C-13), 107.91 (C-5a), 111.37 (C-3), 121.27 (C-1), 121.94 (C-2), 121.86 (C-13b), 126.60 (C-5), 128.46 (C-12), 134.74 (C-3a), 139.12 (C-13a), 141.00 (C-11), 172.83 (C-7) and 173.78 (CO_2).

(±)-*Methyl* 6-{1-[2-(*indol*-3-*yl*)-1-*oxoethyl*]}-4α-*methoxy*-6-*azabicyclo*[3.2.1]*oct*-2-*ene*-5-*carboxylate* **18**. The mixture of **7** and **8** (600 mg) (see ref. 1) was dissolved in dry methanol (1.5 dm^3) to which $NaBH_4$ (720 mg, 19.03 mmol) and tributyltin chloride (984 mg, 3.023 mmol) were added. The solution was irradiated for 3.5 h in a similar way to that described for **17**. After the usual work-up and chromatography, **18** was isolated as the main product (oil, 103 mg, 0.2908 mmol, 18.5%), which was crystallized from acetone–hexane, m.p. 177–178 °C; ν_{max}(KBr)/cm^{-1} 1627 (amide C=O) and 1756 (ester C=O); *m/z* 354 (M^+), 324, 295, 224, 196, 165, 130, 103 and 77. The NMR data are in Tables 1, 2 and 3.

Spectra.—Mass spectra were measured on an AEI MJ-902 (70 eV) spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ and $CDCl_3$–[$^2H_6$]dimethylsulfoxide solutions at ambient temperature using a Varian XL-400 spectrometer operating at 400.4 MHz for ^1H and 100 MHz for ^{13}C. The chemical shifts were referenced to internal tetramethylsilane.

Two-dimensional carbon–proton heteronuclear correlation spectra were measured using the standard Varian microprogram HETCOR. Solution concentrations for the 2D spectra were 21–50 mg in 0.6 cm^3 $CDCl_3$ (**11**–**14**, **17** and **18**) or $CDCl_3$–[$^2H_6$]dimethylsulfoxide **7**–**10**, **15** and **16**).

NOE difference spectra were obtained using the procedure described in ref. 8. The INAPT spectra were measured according to ref. 6. The timing delays Δ_1 and Δ_2 were 60 and 25 ms, respectively. The soft proton 180° pulse length was set to 25 ms, while the selectivity of the decoupler pulse was 20 Hz.

Long-range proton–carbon coupling constants were obtained by the selective two-dimensional INEPT experiment,[7] which is a 2D extension of the refocused INEPT. The low concentration of solutions did not allow these experiments for compounds **9** and **16**. Typically, data matrices of 4 K × 32 in size were created in the time domain with 256–1024 acquisitions per block and 1 s repeat time. The initial matrices were zero filled and Fourier transformed to spectra with frequency resolution of 0.156 Hz in the f_1 direction (*J* axis) and 4 Hz in the f_2 direction (δ axis). The spectral widths were 20 and 16 000 Hz, respectively. A 10–20 ms soft pulse was used for the selective ^1H 180° pulse, and the delay time prior to the data acquisition was set to 100 ms.

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