O. House, R. W. Giese, K. Kronberger, J. P. Kaplan, and J. F. Simeone, *ibid.*, **92**, 2800 (1970).
(18) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
(19) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules", Wiley, New York, N.Y., 1956, pp 40–42.
(20) B. M. Trost and T. N. Salzmann, *J. am. Chem. Soc.*, **95**, 6840 (1973).
(21) E. J. Corey, C. S. Shiner, R. P. Volante, and C. R. Cyr, *Tetrahedron Lett.*, 1161 (1975).
(22) Boiling points are uncorrected. Infrared (ir) spectra were determined on a Perkin-Elmer 237B grating infrared spectrometer and nuclear magnetic resonance (NMR) spectra were recorded using a Varian T-60 spectrometer. Chemical shifts are reported as δ values in parts per million relative to Me_4Si (δ Me_4Si 0.0 ppm) as an internal standard. Deuteriochloroform for NMR and chloroform for ir spectra were filtered through neutral alumina before use.

Vapor phase chromatographic (VPC) analyses were determined on either a Hewlett-Packard 5750 equipped with a flame ionization detector or a Varian 920 equipped wihh a thermal conductivity detector using helium as the carrier gas under the indicated conditions. The indicated liquid phase was absorbed on 60–80 mesh Chromosorb W AW DMCS.

Silica gel columns used the 0.05–0.2-mm silica gel manufactured by E. Merck & Co. Darmstadt, Germany. Acidic silica gel refers to Silicar CC-4 special "for column chromatography", sold by Mallinckrodt Chemical Works, St. Louis, Mo. Preparative medium-pressure chromatography was performed using glass columns of the indicated length and diameter with fittings supplied by Laboratory Data Control, Riviera Beach, Fla., and an instrument minipump supplied by Milton Roy Co., St. Petersburg, Fla. (instrumentation designed by R. H. Mueller, these laboratories, and copies are available on request). The columns were packed with silica gel H "for TLC acc. to Stahl" (10–40 μ) manufactured by E. Merck & Co., Darmstadt, Germany. Solvents were degassed under water aspirator vacuum prior to use.

Analytical thin layer chromatography was conducted on 2.5 × 10 cm precoated TLC plates, silica gel 60 F-254, layer thickness 0.25 mm, manufactured by E. Merck & Co., Darmstadt, Germany.

"Dry" solvents were dried immediately prior to use. Ether and tetrahydrofuran (THF) were distilled from lithium aluminum hydride; pyridine, triethylamine, diisopropylamine, *N*-isopropylcyclohexylamine, trimethylchlorosilane (TMSCl), hexamethylphosphoramide (HMPA), benzene, and toluene were distilled from calcium hydride; dimethylformamide (DMF) was dried over 4A molecular sieves and fractionally distilled at reduced pressure; methanol was dried over 3A molecular sieves; ammonia was distilled from a blue solution of sodium directly into the reaction flask; dichloromethane, methyl iodide, and hexane was distilled from phosphorus pentoxide. Petroleum ether refers to the Analyzed Reagent grade hydrocarbon fraction, bp 30–60 °C, which is supplied by J. T. Baker Co., Phillipsburg, N.J., and was not further purified.

Diisobutylaluminum hydride (DIBAH) was used as a standard solution in benzene (ca. 1.0 M). Lithium isopropylcyclohexylamide (LICA) and lithium diisopropylamide (LDA) were prepared as described previously.[3] Standard solutions of *tert*-butyldimethylchlorosilane (TBSCl) in hexane (ca. 3.3 M) or HMPA (ca. 1.5 M) were employed.

Reactions were run under an argon atmosphere arranged with a mercury bubbler so that the system could be alternately evacuated and filled with argon and left under a positive pressure.

Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.
(23) In cases where the products were isolated "by solvent extraction", the procedure generally followed was to dilute the reaction mixture with the indicated solvent or to extract the aqueous solution with several portions of the indicated solvent; then the combined organic layers were washed with several portions of water followed by saturated brine. The organic layer was dried over anhydrous sodium or magnesium sulfate, then filtered, and the solvent was evaporated from the filtrate under reduced pressure (water aspirator) using a rotary evaporator. The use of the terms "base wash" or "acid wash" indicate washing the organic solution with saturated aqueous sodium bicarbonate solution or with dilute aqueous hydrochloric acid, espectively, prior to the aforementioned wash with water.
(24) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, p 584.
(25) M. Gouge, *Ann. Chim. (Paris)*, **6**, 648 (1951).
(26) N. H. Anderson, *J. Lipid Res.*, **10**, 316 (1969).
(27) Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, H. Kakoi, *J. Chem. Soc., Chem. Commun.*, **64**, (1972).
(28) E. Andre and J. Henry, *C. R. Acad. Sci.*, **263**, 1084 (1966).
(29) H. M. Fales, T. M. Jaouni, and J. F. Babashak, *Anal. Chem.*, **45**, 2302 (1973).

Carbon-13 Nuclear Magnetic Resonance Spectra of Morphine Alkaloids[1]

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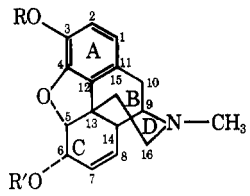
Carbon-13 chemical shifts were measured for 25 morphine, 14-hydroxymorphine, and 6,14-*endo*-etheno- and 6,14-*endo*-ethanotetrahydrothebaine compounds. The signal due to each carbon was assigned. The ^{13}C assignments of the protonated carbons were aided by single frequency off-resonance decoupling experiments and were confirmed in questionable cases by deuterium labeling experiments. Substituent effects were used to assign chemical shifts to nonprotonated as well as protonated carbons. Comparison of the chemical shifts of the morphine and 14-hydroxymorphine systems to those of the 6,14-*endo*-etheno- and 6,14-*endo*-ethanotetrahydrothebaine systems showed that the spatial configuration of rings A, B, and D of the two systems was similar. The ^1H and ^{13}C NMR data for the various compounds were compared.

It has been demonstrated that natural abundance carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy is an extremely useful physical method for the structure elucidation of alkaloids. Although several papers have presented correlations of structure with ^{13}C NMR spectra for many classes of alkaloids,[3] only limited studies have been reported for the physiologically and sociologically important morphine series of alkaloids.[4,5]

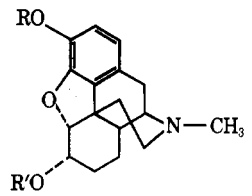
As a result of the continuing interest in the chemistry and pharmacology of the morphine class of alkaloids, we have synthesized many of the more active morphine type narcotics and narcotic antagonists as well as several of their biotransformation products. In this paper we present a study of the ^{13}C NMR spectra of the morphine alkaloids **1–11** shown in Chart I. The structures shown in Chart I are planar representations of the various morphine systems and illustrate the numbering used throughout this paper.

X-ray analysis of morphine (**1a**) hydriodide has shown that ring B is rigidly held in a distorted half-chair form and that rings C and D possess a boat and a chair form, respectively, with the 6α substituent in a bowsprit orientation.[6] ^1H NMR studies have shown that morphine as well as other Δ^7-morphine type alkaloids including 14-hydroxy analogues possess a similar conformation.[7] In contrast the ^1H NMR data[7] and chemical behavior[8] show that ring C of the C-7, C-8 saturated compounds such as **2a, 2b, 7a,** and **7b** exists in a chair conformation in which the 6α substituent is axial. The absolute stereochemistry of 19-propylthevinol (**9c**) hydrobromide has been established by an x-ray crystallographic study and shown to be as represented in struc-

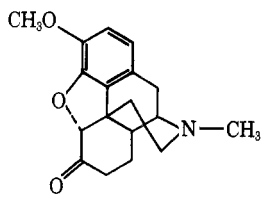
Chart I



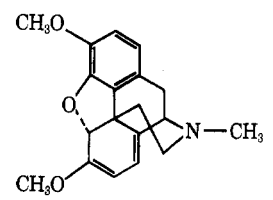
1a, R = R′ = H
b, R = CH_3; R′ = H
c, R = R′ = CH_3CO
d, R = H; R′ = CH_3CO



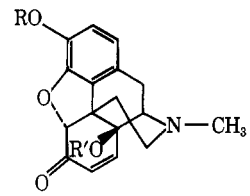
2a, R = R′ = H
b, R = CH_3; R′ = H



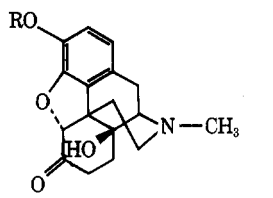
3



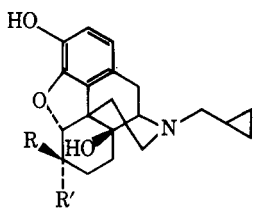
4



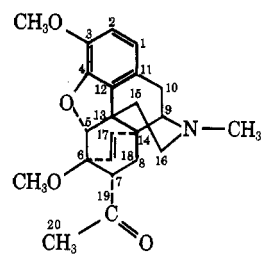
5a, R = R′ = H
b, R = CH_3; R′ = H
c, R = R′ = CH_3CO
d, R = CH_3; R′ = CH_3CO



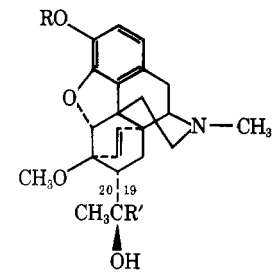
6a, R = H; R′ = $CH_2CH{=}CH_2$
b, R = H; R′ = CH_2-c-C_3H_5
c, R = CH_3; R′ = H



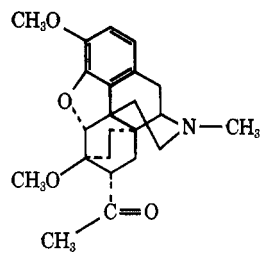
7a, R′ = OH; R = H
b, R = OH; R′ = H



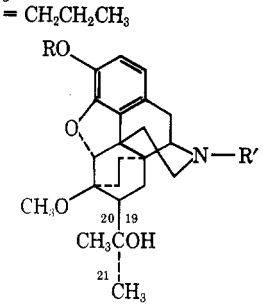
8



9a, R = H; R′ = $CH_2CH_2CH_3$
b, R = R′ = CH_3
c, R = CH_3; R′ = $CH_2CH_2CH_3$



10



11a, R = H; R′ = CH_2-c-C_3H_5
b, R = R′ = CH_3
c, R = CH_3; R′ = CN

ture **9c**.[9] The stereochemistry of **9c** as well as several other 6,14-*endo*-etheno- and 6,14-*endo*-ethanotetrahydrothebaine derivatives such as **10** and **11** has been confirmed by ^1H NMR studies.[10]

Results and Discussion

The structural and stereochemical information available from the x-ray and ^1H NMR studies described above was considered along with the application of ^{13}C NMR chemical shift theory,[3b,11] single frequency off-resonance decoupling (sford) experiments, deuterium labeling experiments, and comparisons to structurally related compounds[4,12,13] to arrive at the complete ^{13}C NMR chemical shift assignments of compounds **1–11** listed in Tables I–III.

Morphine Systems (Table I).[14] The two aromatic protonated carbons, C-1 (d)[15] and C-2 (d), of morphine (**1a**) and codeine (**1b**)[16] were easily differentiated from the olefinic carbons C-7 (d) and C-8 (d) by the upfield shift of the latter resonances on reduction of the double bond. Carbon 1 and C-2 were distinguished by the larger ortho effect from the C-3 hydroxyl substituent compared to the para effect from the C-4 *O*-alkyl moiety. Likewise, the even larger ortho effect of the C-3 methoxyl substituent caused the C-2 resonance in **1b** (and **2b**) to appear upfield relative to that in **1a** (and **2a**). Carbon 7 and C-8 of **1a** (and **1b**) were differentiated by the upfield shift of the C-7 resonance on going from **1a** to either 3,6-diacetylmorphine (**1c**) or 6-acetylmorphine (**1d**). The upfield shift was due to the γ effect of the C-6 acetoxyl group.[17]

The assignment of the C-3 (s) and C-4 (s) resonances was accomplished by comparing the compounds possessing a C-3 hydroxyl group to those containing a C-3 methoxyl group. On changing the hydroxyl group to the methoxyl group, substituent constants for methine carbons in substituted benzenes predict that the C-3 resonance should be shifted downfield by ca. 3–4 ppm while the C-4 resonance should go upfield by ca. 2 ppm owing to the larger ortho effect of the C-3 methoxyl substituent.[18] This was observed not only in going from **1a** to **1b** but also in going from **1a** and **2a** (C-3 hydroxyl) to dihydrocodeinone (**3**) and thebaine (**4**) (C-3 methoxyl). In addition, the C-3 resonance in heroin (**1c**) was upfield relative to **1a** and **1b** owing to the expected smaller α effect of the C-3 acetoxyl group.[18] In all the compounds the C-5 (d) signal appeared as a downfield resonance due to oxygen substitution. The C-6 signals of **1** and **2** appeared in the sford spectra as doublets in the 66–68-ppm range (due to hydroxyl substitution) that were replaced by a downfield singlet in the spectrum of **3** (C-6 carbonyl).

In compounds **1–4** the C-9 (d) and C-16 (t) resonances were downfield due to nitrogen substitution and easily distinguished from the carbons not attached to a heteroatom. In going from compounds **1–4** to the 14-hydroxy series (see Table II), the C-9 resonances were shifted downfield 2–4 ppm due to the additional β effect. Carbon 16 was distinguished by its consistency throughout the series. Carbon 10 (t) and C-15 (t), the two remaining methylenes, were distinguished by the fact that C-15 possessed more α and β substituents and fewer γ substituents than C-10 and thus appeared at lower field. (These assignments were also supported by the deuterium labeling experiments described below.) The C-10 methylene is at unusually high field in all the compounds except **4**. This is due to the combined γ effects from C-8, C-16, and the NCH_3. In the case of **4**, the skew relationship between C-8 and C-10 is prevented by the C-ring diene system.[19] Carbon 11, C-12, and C-13 all gave singlets in the sford spectra. The C-13 singlet was distinguished from the C-11 and C-12 signals by its high field position. Differentiation of the C-11 and C-12 singlets was

Table I. Carbon-13 NMR Chemical Shifts of Morphine Systems[a,b]

Identification of carbon[c]	1a[d]	1b[e]	1c[e]	1d[e]	2a[d]	2b[e]	3[e]	4[e]
1	118.60	119.39	119.10	119.34	118.08	118.75	119.73	118.85
2	116.36	112.81	121.63	117.20	116.77	112.90	114.63	112.26
3	138.45	142.12	132.02	138.41	138.03	141.18	142.82	142.45
4	146.30	146.17	149.14	145.53	146.08	145.97	144.75	144.40
5	91.49	91.15	88.47	87.88	90.04	90.22	90.95	88.81
6	66.38	66.18	67.89	68.27	66.19	66.86	207.26	152.15
7	133.43	133.39	129.24	129.78	25.71	26.72	39.21	95.59
8	128.50	127.83	128.21	128.02	19.61[f]	19.70[b]	25.21	111.19
9	58.09	58.76	58.67	58.62	59.02	59.40	59.40	60.47
10	20.20	20.38	20.43[f]	20.33	19.61[f]	18.92[b]	19.70	29.17
11	125.53	126.71	131.48	125.09	125.30	126.70	125.02	127.33
12	131.04	131.10	131.24	129.29	130.13	130.02	126.12	131.96
13	42.97	42.90	42.57	42.62	42.10	41.88	45.60	45.70[f]
14	40.63	40.33	40.38	39.94	38.24	40.08	40.33	132.94
15	35.56	35.40	34.92	34.71	37.27	37.06	34.61	36.73
16	46.05	46.28	46.28	46.33	46.10	46.48	46.83	45.70[f]
NCH_3	42.83	42.76	42.77	42.38	42.83	42.66	42.30	42.09
3 OCH_3		56.18				56.08	56.58	56.09
6 OCH_3								54.58
3 CH_3CO			20.43					
3 CH_3CO			168.16					
6 CH_3CO			20.43[f]	20.67				
6 CH_3CO			170.20	170.36				

[a] Chemical shifts are in parts per million relative to tetramethylsilane. [b] Signals in any one column may be reversed. [c] Numbering of carbons is shown in Chart I. [d] In dimethyl sulfoxide-d_6 solution. [e] In chloroform-d solution. [f] These resonances were twice as intense as those of other similar carbons.

Table II. Carbon-13 NMR Chemical Shifts of 14-Hydroxymorphine Systems[a,b]

Identification of carbon[c]	5a[d]	5b[e]	5c[e]	5d[e]	6a[e]	6b[e]	6c[e]	7a[e]	7b[e]
1	119.54	119.33	119.50	119.38	119.65	119.70	119.21	118.94	118.89
2	117.45	114.80	122.97	114.86	117.89[f]	117.92	114.63	117.63	117.53
3	139.15	142.47	132.13	144.23	138.81	138.77	142.65	137.37	139.81
4	142.91	144.06	147.35	146.41	143.45	143.41	144.65	145.57	142.30
5	86.57	86.89	87.66	87.01	90.21	90.36[g]	90.13	90.51[h]	95.78[i]
6	194.80	194.00	192.29	193.05	209.67	209.86	208.21	66.77	72.62
7	132.81	134.37	134.07	133.84	35.97	36.02[g]	35.90	22.97[b,h]	26.00[i]
8	150.61	147.29	145.94	145.94	31.04	31.20	31.20[b]	28.64	30.53
9	62.92	63.93	58.05	57.93	62.00	61.87	64.34	61.94	62.14
10	22.05	22.22	22.74	22.28	22.57	22.51	21.69	22.69[b]	22.63
11	124.08	124.79	130.48	125.61	123.76	123.85	124.67	125.23	123.72
12	130.86	130.25	131.07	129.90	128.82	128.84	129.14	130.84	131.38
13	46.38	46.42	46.77	46.65	50.78	50.88	49.94	47.26	47.26
14	67.70	67.57	76.56	76.73	70.53	70.27	70.10	69.89	70.38
15	28.92	29.74	28.73	28.86	30.27	30.44[j]	30.26[b]	33.22	29.56
16	45.12	44.95	45.13	45.24	43.20	43.48[j]	45.01	43.07	43.90
NCH_3	42.33	42.37	42.54	42.54			42.48		
OCH_3		56.64		56.58			56.58		
14 CH_3CO			169.91	169.79					
14 CH_3CO			21.50[b]	21.45					
3 CH_3CO			168.03						
3 CH_3CO			20.56[b]						
NCH_2					57.48	59.05		59.40	59.06
CH_2=CH					117.89[f]				
CH_2CH					134.98				
						9.23		9.18	9.23
						3.88 3.65		3.82 3.62	3.91[f]

[a-f] See footnotes to Table I. [g] The ^{13}C NMR spectrum of a sample of naltrexone which was partially deuterated in the 5 and 7 positions showed reduced intensities for the 90.36 and 36.02 ppm resonances. [h] The ^{13}C NMR spectrum of a sample of 6α-naltrexol which was partially deuterated in the 5 and 7 positions showed reduced intensities for the 90.51 and 22.97 ppm resonances. [i] The ^{13}C NMR spectrum of a sample of 6β-naltrexol which was partially deuterated in the 5 and 7 positions showed reduced intensities for the 95.78 and 26.00 ppm resonances. [j] The ^{13}C NMR spectrum of a sample of naltrexone which was partially deuterated in the 15,16 position showed reduced intensities for the 30.44 and 43.88 ppm resonance.

accomplished by comparing **1a** to **1c**. As shown in Chart I, C-11 is para to C-3 while C-12 is meta to C-3. Consequently, on changing the C-3 substituent from hydroxyl to acetoxyl, the C-11 resonance should be shifted downfield by ca. 5–6 ppm while that of C-12 should remain unchanged.[18] This type of shift was noted in going from **1a** to **1c** as well as from **5a** to **5c** (Table II). In addition, C-12 is bonded to C-13, a tertiary carbon, while C-11 is bonded to C-10, a primary carbon. Consequently, the C-11 singlet was broader than that of C-12 owing to long-range coupling to the

Table III. Carbon-13 NMR Chemical Shifts of 6,14-*endo*-Etheno- and 6,14-*endo*-Ethanotetrahydrothebaine System[a,b]

Identification of carbon[c]	8[e]	9a[e]	9b[e]	9c[e]	10[e]	11a[e]	11b[e]	11c[e]
1	119.15	119.44	119.05	119.00	119.05	119.34	118.95	119.59
2	113.39	116.27	113.69	113.63	113.83	116.66	114.03	114.76
3	141.59	137.58	141.58	141.53	141.63	137.58	141.49	142.22
4	147.76	146.60	147.92	147.87	146.60	145.60	146.80	147.05
5	95.00	98.81	98.61	98.61	94.47	97.05	96.76	96.22
6	81.02	83.98	83.98	83.93	77.40	80.42	80.18	79.64
7	50.47	46.43	48.48	46.52	49.40	47.69	47.65	47.45
8	29.74	30.42	30.86	30.43	30.23	32.14	32.23	31.45[b]
9	59.76	59.83	59.83	59.79	61.21	58.33	61.16	59.40
10	22.21	22.13	22.09	22.04	21.84	22.77	21.75	28.87
11	127.96	127.19	128.22	128.22	128.56	127.54	128.61	125.73
12	133.78	133.73	134.12	134.12	132.31	132.17	132.32	130.22
13	47.24	47.20	47.01	46.94	45.60	47.06	46.04	45.60
14	43.01	42.67[b]	42.71	42.62	35.41	35.94	35.89	35.30
15	33.26	33.31[g]	33.40	33.40	35.02	35.35	35.36[h]	33.30
16	45.24	45.40[g]	45.35	45.30	45.06	43.70	45.01[h]	41.35
17	125.73	124.60	124.71	125.00	17.36	17.50	17.41	17.02
18	135.66	135.14	135.05	134.99	28.46	29.55[b]	29.75	31.55[b]
19	208.68	75.25	73.25	74.67	210.54	74.57	74.18	73.89
20	30.23	23.89	25.16[b]	23.89	33.60	24.77[b]	24.72[b]	24.72[b]
21		42.87[b]	28.57[b]	43.06		29.79[b]	29.75[b]	29.55[b]
22		15.65		15.70				
23		14.53		14.58				
3 OCH_3	56.46		56.72	56.62	56.62		56.77	56.67
6 OCH_3	53.24	55.06	55.06	54.92	52.09	52.52	52.57	52.67
NCH_3	43.31	43.35	43.40	43.35	43.36		43.35	
NCH_2						59.79		
>CH						9.11		
						3.99 3.31		
N—CN								117.88

[a-f] See footnotes to Table I. [g] The ^{13}C NMR spectrum of etorphine which was partially deuterated in the 15,16 positions showed reduced intensities for the 33.31 and 45.40 ppm resonances. [h] The ^{13}C NMR spectrum of a sample of diprenorphine which was partially deuterated in the 15,16 positions showed reduced intensities for the 35.36 and 45.01 ppm resonances.

methylene protons of C-10. In the case of codeine Wehrli has shown that C-11 had a smaller T_1 value than C-12.[20] The C-14 resonance was a doublet in the sford spectrum which shifted downfield in the 14-hydroxy derivatives (Table II). The *N*-methyl and *O*-methyl resonances appeared in the expected regions as quartets in the sford spectra.

Dihydromorphine (**2a**) and dihydrocodeine (**2b**) differ from **1a** and **1b** only in having the C-7, C-8 double bond reduced. The resulting methylenes were differentiated by comparing the spectra to the data obtained on alkylcyclohexanes.[21] The rather large shift difference between the C-7 (t) and C-8 (t) signals was due to the γ effect of the axial C-6 α-hydroxyl substituent as well as C-10 methylene on C-8. Dihydrocodeinone (**3**) possesses a C-6 carbonyl function in addition to the C-7 and C-8 methylenes. The C-6 singlet was easily identified as the lowest field resonance in the spectrum. The C-7 (t) and C-8 (t) of **3** were now differentiated by comparison to alkylcyclohexanones.[22] In this case, the C-8 and C-12 signals were further upfield than expected. This is probably due to conformational changes in ring C of **3**. Except for C-6, C-7, C-8, C-10 (see comments above), and C-14, the chemical shifts for thebaine (**4**) were essentially identical with those of **2**. In the sford spectrum C-6 and C-14 appeared as singlets in the expected low-field region. Carbon 7 and C-8 gave doublets in the olefinic region. The C-7 doublet was upfield from the C-8 doublet owing to the γ effect of the C-6 methoxyl substituent and the electron-donating effect of the oxygen at C-6.

14-Hydroxymorphine Systems (Table II). All of the compounds in Table II were characterized by possessing a C-14 singlet at 67–77 ppm due to the C-14 hydroxyl or acetoxyl substituent. These substituents also caused a downfield shift (β effect) of the C-8, C-13, and C-9 resonances and an upfield shift (γ effect) of C-7 and C-15 resonances relative to similar compounds in Table I that do not contain a C-14 substituent. The aromatic carbons followed a pattern similar to the compounds in Table I. The larger downfield shift for C-2, C-4, and C-11 in the case of **5c** was due to the larger ortho and para effects of the C-3 acetoxyl function compared to the hydroxyl or methoxyl groups.[18] The C-3 resonance of 3,14-diacetoxymorphinone (**5c**) was again upfield relative to the other compounds owing to the expected smaller α effect of the C-3 acetoxyl group.[18] As before, C-5 (d) appeared at low field owing to oxygen substitution. Surprisingly, there is only a small γ interaction between C-5 and the C-14 hydroxyl substituent. In the case of naltrexone (**6b**), the fact that the 90.36-ppm resonance was reduced in intensity in the spectrum of a naltrexone-5,7,7-d_3 confirms this assignment for C-5.

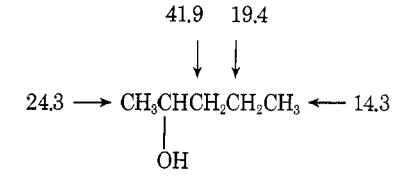
The carbonyl carbon (C-6) of **5a–d** and **6a–c** was easily identified as the lowest field resonance in the spectra. The C-6 singlet of **5a–d** appeared at higher field relative to **6a–c** owing to the conjugation of C-6 with the C-7, C-8 double bond of **5a–d.** This downfield singlet (sford) was replaced by a doublet in the 66–73-ppm region in the case of 6α-naltrexol (**7a**) and 6β-naltrexol (**7b**). The C-6 doublet of **7a,** in which the hydroxyl group is axial, appeared at a higher field than that of **7b,** which possesses an equatorial hydroxyl group. The C-8 (d) resonance of **5a–d** was at considerably lower field than the C-7 (d) resonance owing to conjugation with the C-6 carbonyl group.[23]

In 6α-naltrexol (**7a**) and 6β-naltrexol (**7b**) the assignment of the C-7 and C-8 resonances was confirmed by examining the spectra of samples containing deuterium on

C-5 and C-7. In these compounds, the C-7 signal now appeared upfield from the C-8 signal, in contrast to their relative positions in dihydromorphine (**2a**) and dihydrocodeine (**2b**). This shift is due to the effect of the axial C-14 hydroxyl substituent. In addition, the C-8 signal of **7a** appeared at higher field relative to **7b.** This was attributed to the larger γ effect on C-8 from the axial C-6 hydroxyl group of **7a.**

Compounds **5a–d** and **6c,** all of which possess NCH_3 groups, showed similar resonances for C-16 (t). Naloxone (**6a**), naltrexone (**6b**), and the naltrexols (**7a** and **7b**), all of which contain a larger *N*-alkyl substituent, showed resonances at slightly higher field for C-16 owing to the additional γ effects. The *N*-methyl, *O*-methyl, and acetyl methyl groups appeared as quartets (sford) in the expected region. The chemical shifts of the methylene carbon (t) and the two olefinic carbons (d) of the *N*-allyl group of naloxone (**6a**) were assigned by comparison to other allyl compounds.[24] The chemical shifts for the cyclopropyl groups in **6b, 7a,** and **7b** appeared at very high field. The cyclopropyl methine (d) came at ca. 9 ppm and the cyclopropyl methylene (t) appeared at ca. 3–4 ppm.

6,14-*endo*-Etheno- and 6,14-*endo*-Ethanotetrahydrothebaine Systems (Table III). The assignments for C-1–C-5, C-9–C-13, C-15, C-16, and the *N*-methyl, *N*-cyclopropylmethyl, and *O*-methyl followed the same reasoning presented for the compounds listed in Tables I and II. In the case of etorphine (**9a**) and diprenorphine (**11a**) the correctness of the C-15 and C-16 assignments was verified by demonstrating that **9a** and **11a** which were partially deuterated in the 15,16 position showed reduced intensities for these resonances. These results combined with the constancy of the C-15, C-16 resonances in all the compounds listed in Tables I–III support the C-15 and C-16 assignments in these cases as well. Carbon 6 and C-14 appeared as singlets (sford) which were shifted upfield on reduction of the C-17, C-18 double bond. Carbon 7 gave a new downfield doublet in the sford spectrum not present in the first two classes of compounds. The C-8 signal was the only remaining triplet in the case of thevinone (**8**), 19-methylthevinol (**9b**), and dihydrothevinone (**10**). It was also noted that the chemical shift of C-8 was affected by changing the substituent on the nitrogen which is γ to C-8 (compare **11b** to **11c**). Carbon 17 (d) and C-18 (d) were easily recognized by their low-field positions in the case of **8** and **9.** These doublets (sford) were replaced by two new triplets in the case of **10** and **11,** in which the C-17, C-18 double bond had been reduced. The C-17 and C-18 atoms are comparable to the C-8 and C-7 atoms, respectively, in the morphine systems. Thus, C-17 in compounds **8–11** was shifted upfield by a large γ interaction with C-10 similar to C-8 in the case of the morphine compounds listed in Tables I and II. Reduction of the C-17, C-18 double bond also resulted in a large downfield shift of C-14 and a smaller downfield shift of C-9 and C-8. Fulmor and co-workers[10] have noted that the C-9 and C-8 protons are also affected by reduction of the C-17, C-18 double bond. Carbon 19 was a singlet in all the compounds. In the case of **8** and **10** this resonance appeared at very low field owing to the oxo group, and in the case of the other compounds it was observed as a new peak in the C–O region. In compounds **8** and **10,** C-20 gave a quartet which appeared in the region expected for a methyl next to a carbonyl group. In the case of **9b** and **11a–c,** C-20 and C-21 were nonequivalent methyl groups that were easily distinguished by their multiplicities. The C-20, C-21, C-22, and C-23 carbons of **9a** and **9c** could be assigned by comparison to the assignments of 2-pentanol.[25] The C-21 and C-22 resonances were at slightly lower and higher field, respectively, in our compounds owing to the additional β and γ effects in these compounds.



The x-ray crystallographic studies[1] of van den Hende and Nelson[9] on the 6,14-*endo*-etheno analogue **9c** indicated that the spatial configuration of rings A, B, and D of this compound resembled that of codeine and morphine. Owing to the added C-7, C-8 bridge, ring C had a different conformation. The close similarities of the chemical shifts of C-10, C-16, and the aromatic carbons of 8–11 to comparable compounds listed in Tables I and II showed that the conformations of rings A, B, and D of the 6,14-*endo*-etheno- and 6,14-*endo*-ethanotetrahydrothebaine systems were similar to the simple morphine systems in $CDCl_3$.

The chemical shift of C-5 in **8** and **10,** which possess a C-19 keto group, was upfield ca. 3 ppm relative to **9** and/or **11** derivatives which contain a C-19 hydroxyl substituent. Apparently the conformation of the methyl of the C-6 methoxy group, which is γ to C-5, was different in the two cases. This arises from the fact that the C-19 hydroxyl proton of **9** and/or **11** can form an intramolecular hydrogen bond to the oxygen of the C-6 methoxyl group.[9]

Experimental Section

Morphine (**1a**), dihydrocodeine (**2b**), thebaine (**4**), and **6c** were obtained from S. P. Penick and Co., Lyndhurst, N.J. Codeine (**1b**) was purchased from Merck Chemical Co., Rahway, N.J. Naloxone (**6a**) and naltrexone (**6b**) were supplied by Endo Laboratories, Inc., Garden City, N.J.

3,6-Diacetylmorphine (**1c**) was prepared from **1a** by acetylation with acetic anhydride.[26] 6-Monoacetylmorphine (**1d**) was synthesized in three steps from **1a** using procedures described for the corresponding *N*-nor compound.[27] Catalytic hydrogenation of **1a** afforded dihydromorphine (**2a**). Dihydrocodeinone (**3**) was obtained in two steps from **4** by literature procedures.[28,29]

Treatment of **4** with *m*-chloroperbenzoic acid in acidic media afforded 14-hydroxycodeinone (**5b**),[30] which was acetylated to get 14-acetoxycodeinone (**5d**).[31] O-Demethylation of **5b** by the method of Weiss[32] gave 14-hydroxymorphinone (**5a**), which was subsequently acetylated to get 3,6-diacetoxymorphinone (**5c**).[33] 6α-Naltrexol (**7a**) was obtained by reducing **6b** with either $NaBH_4$ in THF or L-Selectride.[34] The 6β-alcohol **7b** was prepared by the formidinesulfinic acid reduction of **6b**.[35]

The Diels–Alder reaction of thebaine (**4**) with methyl vinyl ketone afforded 7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine (thevinone, **8**).[36] Treatment of **8** with the appropriate Grignard reagent afforded 19-methylthevinol (**9b**) and 19-propylthevinol (**9c**), while catalytic hydrogenation of **8** gave dihydrothevinone (**10**).[37] Addition of MeMgI to **10** provided dihydro-19-methylthevinol (**11b**).[37] 3-O-Demethylation of **9c** with KOH at 210 °C yielded 7α-(1-hydroxy-1-methylbutyl)-6,14-*endo*-ethenotetrahydrooripavine (etorphine, **9a**).[38] N-Demethylation of **11b** with CNBr gave *N*-cyano-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethanotetrahydronorthebaine (**11c**).[38] Subsequent treatment of **11c** with KOH at 225–230 °C removed the *N*-cyano group and effected 3-O-demethylation. The resultant *N*-nor compound was N-alkylated in DMF with cyclopropylmethyl bromide in the presence of excess $NaHCO_3$ to get *N*-cyclopropylmethyl-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethanotetrahydronororipavine (diprenorphine, **11a**).

Naltrexone-*5,7,7-d*$_3$ was prepared by heating **6b** at 80 °C in a sealed tube with potassium *tert*-butoxide and D_2O–DMF.[39] Reduction of naltrexone-*5,7,7-d*$_3$ provided samples of 6α-naltrexol-*5,7,7-d*$_3$ and 6β-naltrexol-*5,7,7-d*$_3$. Naltrexone-*15,16-d*$_2$, etorphine-*15,16-d*$_2$, and diprenorphine-*15,16-d*$_2$ were obtained by reducing the corresponding 15,16-didehydro compounds with deuterium gas over a 10% Pd/C catalyst. The 15,16-didehydro compounds were prepared by oxidation of the respective bases with $Hg(OAc)_2$ in HOAc.[40,41]

The ^{13}C NMR spectra were determined at 25.03 MHz on a modified JEOL JNM-PS-100 FT NMR interfaced with a Nicolet 1085 Fourier-transform computer system. The samples were spun in 10 mm o.d. tubes. The spectra were recorded at ambient temperature by using the deuterium resonance of the solvent as the internal lock signal. Chloroform-*d* or dimethyl sulfoxide-d_6 were used as the solvent and all δ values reported in the tables were in parts per million downfield from Me_4Si: $\delta^{Me_4Si} = \delta^{CDCl_3} + 76.91 = \delta^{Me_2SO\text{-}d_6} + 39.56$. All proton lines were decoupled by a broad band (~2500 Hz) irradiation from an incoherent 99.538-MHz source. Interferograms were stored in 8K of computer memory (4K output data points in the transformed phase corrected real spectrum), and chemical shifts were measured on 5000 Hz sweep width spectra. Typical pulse widths were 12.5 μs (45° flip angle), and the delay time between pulses was fixed at 1.0 s. Normally 1012 (twice as many for single frequence off-resonance experiments) data accumulations were obtained on a 100 mg/2 ml of solvent sample. The precision of the chemical shifts is ±0.05 ppm.

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Registry No.—**1a,** 57-27-2; **1b,** 76-57-3; **1c,** 561-27-3; **1d,** 2784-73-8; **2a,** 509-60-4; **2b,** 125-28-0; **3,** 125-29-1; **4,** 115-37-7; **5a,** 41135-98-2; **5b,** 508-54-3; **5c,** 50798-31-7; **5d,** 978-76-7; **6a,** 465-65-6; **6b,** 16590-41-3; **6c,** 57664-96-7; **7a,** 20410-98-4; **7b,** 49625-89-0; **8,** 15358-22-2; **9a,** 14521-96-1; **9b,** 16180-23-7; **9c,** 16180-26-0; **10,** 16196-82-0; **11a,** 14357-78-0; **11b,** 16196-64-8; **11c,** 16671-47-9.

References and Notes

(1) This work was supported under Contract HSM-42-73-228 with the National Institute on Drug Abuse, Division of Research, Biomedical Research Branch.
(2) (a) Research Triangle Institute; (b) North Carolina State University.
(3) (a) E. Wenkert, J. S. Bindra, C. J. Chang, D. W. Cochran, and F. M. Schell, *Acc. Chem. Res.*, **7**, 46 (1974); (b) C. G. Moreland, A. Philip, and F. I. Carroll, *J. Org. Chem.*, **39**, 2413 (1974), and references cited therein.
(4) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley-Interscience, New York, N.Y., 1972.
(5) Y. Terui, K. Tori, S. Maeda, and Y. K. Sawa, *Tetrahedron Lett.*, 2853 (1975).
(6) M. Mackay and D. C. Hodgkin, *J. Chem. Soc.*, 3261 (1955).
(7) S. Okuda, S. Yamaguchi, Y. Kawazoe, and K. Tsuda, *Chem. Pharm. Bull.*, **12**, 104 (1964).
(8) H. L. Holmes and G. Stork in "The Alkaloids", Vol. II, Part II, R. H. Manske, Ed., Academic Press, New York, N.Y., 1952, Chapter 8.
(9) J. H. van den Hende and N. R. Nelson, *J. Am. Chem. Soc.*, **89**, 2901 (1967).
(10) W. Fulmor, J. E. Lancaster, G. O. Morton, J. J. Brown, C. F. Howell, C. T. Nora, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **89**, 3322 (1967).
(11) G. E. Maciel in "Topics in Carbon-13 NMR Spectroscopy", Vol. 1, G. C. Levy, Ed., Wiley, New York, N.Y., 1974, Chapter 2.
(12) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, and references cited therein.
(13) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, and references cited therein.
(14) Terui and co-workers[5] have reported ^{13}C NMR spectral data for some of the compounds listed in Tables I and II. Their assignments are in agreement with ours; however, their method of establishing the assignments as well as the interpretation of unusual chemical shifts differ from ours.
(15) The letter in parenthesis refers to the signal multiplicity obtained from single frequency off-resonance experiments; s = singlet, d = doublet, t = triplet, and q = quartet.
(16) Johnson and Jankowski have reported the ^{13}C NMR spectrum of co-*deine phosphate* (Spectra 479 in ref 4). However, they were able to make assignments to only 8 of the 18 carbons. Taking into account that their spectrum was of the salt in D_2O, our assignments are in agreement with theirs.
(17) See E. Wenkert, M. J. Gasić, E. W. Hagaman, and L. D. Kwart, *Org. Magn. Reson.*, **7**, 51 (1975), and references cited therein, for effect of ^{13}C NMR chemical shifts on acylation of allyl alcohols.
(18) Reference 13, p 196.
(19) The γ effect of the NCH_3 group on C-10 is exemplified by the downfield shift of C-10 on going from **11b** (NCH_3) to **11c** (NCN) (see Table III). In the case of the model compounds 3-methoxymorphinone (NH) and 3-methoxy-*N*-methylmorphinone (NCH_3) Terui and co-workers[5] noted that the C-10 resonance was at higher field in the latter compound.
(20) F. W. Wehrli, *J. Chem. Soc., Chem. Commun.*, 379 (1973).
(21) Reference 13, p 163.
(22) Reference 13, p 173.
(23) Reference 12, p 67.
(24) Reference 13, p 188.
(25) Reference 13, p 141.
(26) C. R. Wright, *J. Chem. Soc.*, **27**, 1031 (1874).
(27) K. C. Rice and A. E. Jacobson, *J. Med. Chem.*, **18**, 1033 (1975).
(28) L. Small, H. M. Fitch, and W. E. Smith, *J. Am. Chem. Soc.*, **58**, 1457 (1936).
(29) M. Freund and E. Speyer, *Ber.*, **53**, 2250 (1920).
(30) F. M. Hauser, T. Chen, and F. I. Carroll, *J. Med. Chem.*, **17**, 1117 (1974).
(31) R. E. Lutz and L. Small, *J. Org. Chem.*, **4**, 220 (1939).
(32) U. Weiss, *J. Org. Chem.*, **22**, 1505 (1957).
(33) J. Fishman, M. L. Cotter, and B. I. Norton, *J. Med. Chem.*, **16**, 556 (1973).
(34) Aldrich Chemical Co. We are grateful to Dr. R. Reuning for calling this reagent to our attention.
(35) N. Chatterjie, C. E. Inturrisi, H. B. Dayton, and H. Blumberg, *J. Med. Chem.*, **18**, 490 (1975).
(36) K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, **89**, 3267 (1967).
(37) K. W. Bentley, D. G. Hardy, and B. Meek, *J. Am. Chem. Soc.*, **89**, 3273 (1967).
(38) K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, **89**, 3281 (1967).
(39) (a) D. H. R. Barton, A. J. Kirby, and G. W. Kirby, *J. Chem. Soc. C*, 929 (1968); (b) D. H. R. Barton, R. James, G. W. Kirby, D. W. Turner, and D. A. Widdowson, *J. Chem. Soc. C*, 1529 (1968).
(40) J. W. Lewis, M. J. Rance, and G. R. Young, *J. Med. Chem.*, **17**, 465 (1975).
(41) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, **77**, 439 (1955).

Alkaloids of *Vinca rosea* L. (*Catharanthus roseus* G. Don). XXXVII. Structure of Vincathicine[1]

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The structure of the dimeric alkaloid vincathicine is deduced from physical and chemical methods. The conversion of leurosine to vincathicine under acidic conditions is described.

Vincathicine (1), a dimeric indole alkaloid showing moderate oncolytic activity in experimental animals, was first isolated by Svoboda and Barnes.[2] On the basis of ultraviolet, infrared, and ^1H nuclear magnetic resonance (NMR) spectroscopies, these authors suggested that vincathicine included an oxindole moiety. Since this initial report, no further work on the structure of vincathicine has been published. The more recent discovery that vincathicine is chemically related to leurosine[3] has rekindled interest in this alkaloid.