Ring C Conformation of 6β-Naltrexol and 6α-Naltrexol. Evidence from Proton and Carbon-13 Nuclear Magnetic Resonance[1]

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A series of acetate derivatives of 6β-naltrexol and 6α-naltrexol were prepared and examined by ^1H and ^{13}C NMR. The results of this investigation indicated that ring C of these compounds was in the chair conformation. Moreover, spectral assignments were noted which should be useful in examining the ring C conformation of other 14-hydroxy-7,8-dihydroisomorphine and 14-hydroxy-7,8-dihydromorphine compounds.

Naltrexone (*N*-cyclopropylmethyl-14-hydroxy-7,8-dihydronormorphinone, **1**) is a potent narcotic antagonist[3] which currently shows considerable promise for the treatment of opiate dependence in man. Studies in several laboratories have shown that 6β-naltrexol (**2a**) is the major urinary metabolite of naltrexone in man[4-7] and six species of laboratory animals.[7-9] 6α-Naltrexol (**3a**), on the other hand, is present in only trace amounts in the urine of two species of laboratory animals.[7] However, in vitro reduction of naltrexone using the soluble fraction of chicken liver homogenates yielded only **3a**.[5] The pharmacology of **2a** and **3a** is presently under investigation in several laboratories.

Initial chemical[4] and ^1H NMR[5] examination of **2a** and **3a** suggested that ring C of each compound was in the chair conformation with the 6β-hydroxyl substituent being equatorial and the 6α-hydroxyl substituent being axial. This assignment was confirmed by a later ^1H NMR study of **2a** and **3a** and their respective 3,6,14-triacetates (**2e** and **3e**),[7] and by the ^{13}C NMR chemical shifts reported for **2a** and **3a**.[10] 6β-Naltrexol and 6α-naltrexol are, therefore, conformationally similar to other 7,8-dihydroisomorphine and 7,8-dihydromorphine compounds.

As a result of the continuing interest in naltrexone and its biotransformation products, we undertook a ^1H and ^{13}C NMR examination of several acetate derivatives of **2a** and **3a**. Our purpose was to correlate spectral assignments with the ring C conformation. We believe the results reported below to be of general applicability to other 14-hydroxy-7,8-dihydroisomorphine and 14-hydroxy-7,8-dihydromorphine compounds.

In a recent report Hahn and Fishmann presented a similar ^1H NMR study on the 3,6-diacetate and 3,6,14-triacetate derivatives (**5b** and **6b**) of 6β-naloxol (**5a**) and 6α-naloxol (**6a**).[11] We also prepared compounds **5b** and **6b**, examined the ^1H NMR spectra, and compared our results with the earlier ones.

Results and Discussion

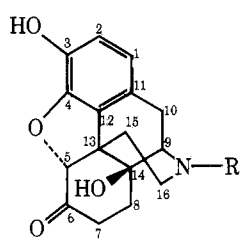
Sample Synthesis. 6β-Naltrexol (**2a**) was prepared by reducing naltrexone (**1**) with formamidinesulfinic acid in alkaline medium.[12] 6α-Naltrexol (**3a**) was obtained by reducing **1** with either sodium borohydride in tetrahydrofuran[13] or lithium tri-*sec*-butylborohydride[12,14] in tetrahydrofuran at −78 °C.[7] In our hands both reagents gave 6α-naltrexol (**3a**) contaminated with traces of the 6β epimer which could be removed by chromatography or recrystallization.

Acetylation of **2a** and **3a** with acetic anhydride and pyridine at room temperature overnight gave the corresponding 3,6,14-triacetates **2e** and **3e**. Acetylation with the same reagents at 0 °C for 1 h yielded the 3,6-diacetates **2d** and **3d**. In the case of **3a**, the 3,6-diacetate was contaminated with 15–20% of the 3,14-diacetate.[15] Hydrolysis of **2d** with 1 equiv of potassium carbonate in methanol afforded 6β-naltrexol 6-monoacetate (**2c**). Application of the same conditions to **3d** afforded only 6α-naltrexol. Sodium borohydride reduction of 14-acetoxynaltrexone gave 6α-naltrexol 14-monoacetate (**3c**). The two 3-monoacetates **2b** and **3b** were prepared by a standard procedure.[16,17]

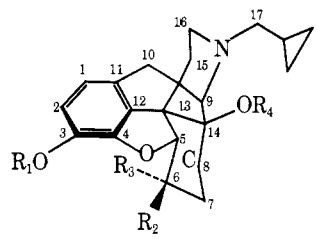
6β-Naloxol (**5a**)[12] and 6α-naloxol (**6a**)[11] were prepared by the reduction of naloxone (*N*-allyl-14-hydroxy-7,8-dihydronormorphinone, **4**) with respectively formamidinesulfinic acid and lithium tri-*sec*-butylborohydride. The corresponding 3,6,14-triacetates **5b** and **6b** were prepared by the same procedure used to make **2e** and **3e**.

The various compounds examined in our study are summarized in Chart I.

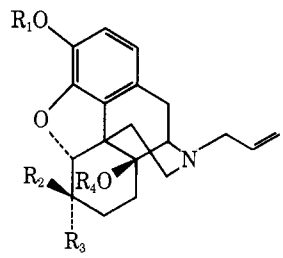
Chart I



1, R = $^{17}CH_2$-c-C_3H_5
4, R = $^{17}CH_2CH{=}CH_2$



2a, $R_1 = R_3 = R_4 = H$; $R_2 = OH$
b, $R_1 = Ac$; $R_2 = OH$; $R_3 = R_4 = H$
c, $R_1 = R_3 = R_4 = H$; $R_2 = OAc$
d, $R_1 = Ac$; $R_2 = OAc$; $R_3 = R_4 = H$
e, $R_1 = R_4 = Ac$; $R_2 = OAc$; $R_3 = H$
3a, $R_1 = R_2 = R_4 = H$; $R_3 = OH$
b, $R_1 = Ac$; $R_2 = R_4 = H$; $R_3 = OH$
c, $R_1 = R_2 = H$; $R_3 = OH$; $R_4 = Ac$
d, $R_1 = Ac$; $R_2 = R_4 = H$; $R_3 = OAc$
e, $R_1 = R_4 = Ac$; $R_2 = H$; $R_3 = OAc$



5a, $R_1 = R_3 = R_4 = H$; $R_2 = OH$
b, $R_1 = R_4 = Ac$; $R_3 = H$; $R_2 = OAc$
6a, $R_1 = R_2 = R_4 = H$; $R_3 = OH$
b, $R_1 = R_4 = Ac$; $R_2 = H$; $R_3 = OAc$

^1H NMR Examination. Summarized in Table I are the pertinent ^1H NMR data for compounds **2a–e** and **3a–e**, as well as the chemical shift values which we found for 6β-naloxol 3,6,14-triacetate (**5b**) and 6α-naloxol 3,6,14-triacetate (**6b**).

Table I. Pertinent ^{1}H NMR Chemical Shifts of 6β-Naltrexol, 6α-Naltrexol, and Their Respective Acetate Derivatives[a]

Compd	Acetate methyls 3	6	14	5β-H	6α-H	6β-H	$J_{5\beta\text{-}6}$[b]
2a				4.53 (d)	3.54 (m)		6.0
2b	2.26 (s)			4.51 (d)	3.53 (m)		6.0
2c		2.06 (s)		4.60 (m)			Nm
2d	2.25 (s)	2.07 (s)		4.64 (m)			Nm
2e[c]	2.26 (s)	2.07 (s)	2.14 (s)	4.63 (m)			Nm
5b[c]	2.25 (s)	2.07 (s)	2.12 (s)	4.64 (m)			Nm
7d[d]		2.07 (s)		4.43 (d)	4.5		6.5
3a				4.64 (d)		4.26 (m)	4.0
3b	2.27 (s)			4.63 (d)		4.14 (m)	5.2
3c			2.07 (s)	4.66 (d)		4.15 (m)	4.0
3d	2.28 (s)	1.90 (s)		4.78 (d)		5.40 (m)	5.0
3e[c]	2.27 (s)	1.94 (s)	2.13 (s)	4.80 (d)		5.30 (m)	5.0
6b[c]	2.27 (s)	1.94 (s)	2.10 (s)	4.78 (d)		5.2 (m)[e]	5.0
8[d]		1.81 (s)		4.59 (d)		5.2	5.7

[a] All experimental chemical shifts were obtained in $CDCl_3$ solution and are expressed in parts per million downfield from tetramethylsilane. Multiplicities are denoted by s (singlet), d (doublet), and m (multiplet). [b] Coupling constants are in cycles per second. Those cases in which the coupling constants were not measured are denoted by nm. [c] In the 3,6,14-triacetates the 9α-H appeared as a downfield doublet. The chemical shifts were 4.42 (**2e**), 4.26 (**5b**), 4.48 (**3e**), and 4.29 (**6b**). [d] Values are from ref 18. [e] The 6β proton was part of a three-proton multiplet that included two of the olefinic protons.

Also included in Table I are the corresponding literature values for 6-acetoxy-7,8-dihydroisocodeine (**7**) and 6-acetoxy-7,8-dihydrocodeine (**8**).[18]

The chemical shifts of the 5β and 6 protons of **2a** and **3a** were in excellent agreement with previously reported values.[5,7] In addition, the methyl chemical shifts of the 3,6,14-triacetates **2e** and **3e** (and hence **5b** and **6b**), which were unequivocally assigned by comparison with the respective mono- and diacetate values, agreed well with the chemical shifts found by Malspeis and co-workers.[7] The characteristic upfield shift of the 6-acetoxyl methyl in the 6α series, due to the increased shielding effect of the aromatic ring,[7,18] was clearly observed. The good agreement of the observed 6-acetoxyl methyl chemical shifts with those of compounds **7** and **8** provided strong evidence for the chair conformation of ring C in both the 6β and 6α series.

From the data in Table I it was apparent that acetylation of the 6-hydroxyl group of **2a** or **3a** consistently deshielded the corresponding 6 proton. The resultant downfield shift of approximately 1.1 ppm was of the magnitude expected for a secondary alcohol.[19] In contrast, Hahn and Fishman concluded from their ^{1}H NMR data that the 6-hydroxyl group of 6β-naloxol (**5a**) and 6α-naloxol (**6a**) could be acetylated without effecting any downfield shift of the proton.[11] However, our results with the 3,6,14-triacetates **5b** and **6b** closely paralleled those obtained for compounds **2e** and **3e**, as expected.[20]

In a previous ^{1}H NMR study on the morphine alkaloids, Okuda and co-workers[18] showed that the magnitude of $J_{5\beta\text{-}6}$ often yielded valuable information about the conformation of ring C. For compounds **2a** and **2b** the $J_{5\beta\text{-}6}$ value was in good agreement with the theoretical value[18,21] for the chair conformation. However, a complete analysis in the 6β series was impractical because acetylation of the 6-hydroxyl group caused the 5β and 6α protons to appear as a two-proton multiplet. In the 6α series the $J_{5\beta\text{-}6}$ value yielded conflicting information about the conformation of ring C. This was due partially to the qualitative nature and narrow range of the theoretical values,[18,21] and partially to intramolecular hydrogen bonding (vide infra).

^{13}C NMR Examination. The ^{13}C NMR chemical shifts for each series of compounds are given in Table II. The assignment of the ^{13}C resonances of 6β-naltrexol (**2a**) and 6α-naltrexol (**3a**) was described earlier, as were the procedures used to assign the ^{13}C resonances in the spectra of the corresponding acetates.[10]

The upfield shift of the C-6 resonance in going from **2a** to **3a** was clearly indicative of going from an equatorial to an axial alcohol[22] and was consistent with the chair conformation of ring C in these compounds. Moreover, the upfield positions of the C-5, C-7, and C-8 signals in the spectrum of **3a** reflected respectively the smaller β effect and the larger γ effect of the axial 6-hydroxyl group. Rerunning the spectra of **2a** and **3a** in dimethyl sulfoxide-d_6 solution produced only minor solvent effects on the chemical shift values.

The ^{13}C NMR spectra of the various 6β-naltrexol acetates were also consistent with a ring C chair conformation. As expected, acetylation of the phenolic hydroxyl group (compound **2b**) produced only changes in the aromatic chemical shifts. Acetylation of the 6-hydroxyl group (compound **2c**) caused a downfield shift of 3 ppm in the C-6 resonance and an upfield shift of 2–3 ppm in the C-5 and C-7 signals. These effects were again typical of an equatorial alcohol.[23] Acetylation of the 14-hydroxyl group (compound **2e**) produced the expected downfield shift of the C-14 signal[24] and a 5–7 ppm upfield move of the C-8 and C-9 resonances due to the γ effect of the axial 14-acetoxyl group.

The situation in the 6α-naltrexol series was slightly more complex. That acetylation of the phenolic hydroxyl group of **3a** affected the shape of ring C was suggested by the change in $J_{5\beta\text{-}6}$ in the ^{1}H NMR (vide supra). In addition to the expected changes in the aromatic resonances, the ^{13}C NMR spectrum of compound **3b** in deuteriochloroform solution showed an 0.83 ppm downfield shift for the C-7 resonance and a 2.45 ppm upfield shift for the C-8 signal. However, in dimethyl sulfoxide-d_6 solution the C-7 and C-8 signals showed no change due to acetylation. These observations suggested the existence of an intramolecular hydrogen bond between the axial 6-hydroxyl group and the 3-acetoxyl group which was disrupted in dimethyl sulfoxide-d_6 solution. The effect of the hydrogen bond was to distort ring C so that C-8 experienced increased shielding by the axial C-6 substituent.

The intramolecular hydrogen bonding observed in compound **3b** was possible only with ring C in the chair conformation. Moreover, the existence of the hydrogen bond undoubtedly contributed to the decreased reactivity of the axial 6-hydroxyl group toward derivatization with acetic anhydride or pentafluoropropionic anhydride.[25] In addition, the facile conversion of 3,6-diacetate **3d** to 6α-naltrexol (**3a**) was no doubt due to neighboring-group effects made possible by the close proximity of the 3- and 6-acetoxyl groups.

Acetylation of the 6-hydroxyl group of **3a** (compound **3d**)

Table II. Carbon-13 Chemical Shifts of 6β-Naltrexol, 6α-Naltrexol, and Their Respective Acetate Derivatives[a,b,c]

Carbon	2a	2b	2c	2d	2e	3a	3b[d]	3c	3d	3e
1	118.89	118.56	119.10	118.61	118.90	118.94	118.61	118.95	118.22	118.51
2	117.53	122.07	117.15	122.40	122.61	117.63	121.39	117.59	122.01	122.56
3	139.81	132.95	139.58	133.32	133.58	137.37	132.90	136.92	131.53	131.53[b]
4	142.30	147.00	141.87	146.09	146.26	145.57	148.31	144.93	149.00	149.34
5	95.78	96.27	92.66	92.39	92.22	90.51	91.49	90.26	87.88	87.69
6	72.62	71.79	75.59	75.35	74.91	66.77	66.42	66.62	68.22	67.89
7	26.00	25.12	23.31	23.22[c]	22.97[b]	22.97	23.80	23.46[c]	21.27	22.38
8	30.54	30.82	30.33	29.96[b]	24.97	28.64	26.19	25.69	27.24	23.80
9	62.14	61.79	62.08	61.91	55.45	61.94	62.13	55.79	62.05	55.50
10	22.63	22.82	22.53	23.22[c]	23.31[b]	22.69	22.92	23.46[c]	23.26	23.46[b]
11	123.72	130.46	124.32	129.29	131.00[b]	125.23	130.70[b]	126.04	131.04[b]	131.24[b]
12	131.38	132.51	131.10	131.58	131.10[b]	130.84	131.19[b]	129.49	130.31[b]	130.51
13	47.26	46.87	47.89	47.49	48.09	47.26	46.09	47.98	46.96	47.55
14	70.38	69.89	69.89	69.77	82.13	69.89	69.89	81.81	69.68	81.79
15	29.56	29.02	29.55	29.43[b]	29.55	33.22	31.89	33.22	32.25	31.99
16	43.90	43.45	43.79	44.19	43.94	43.07	43.40	43.56	43.61	43.50
17	59.06	59.06	59.06	59.00	59.11	59.40	59.16	59.63	59.34	59.40
3 CH_3CO		168.50		167.70	168.06		168.70		167.99	168.31
3 CH_3CO		20.58		20.89	20.58		20.53		20.84[b]	20.53[b,c]
6 CH_3CO			170.70	169.83	170.11[c]				169.69	170.16[c]
6 CH_3CO			21.26	21.38	21.12[b]				21.03[b]	20.53[b,c]
14 CH_3CO					170.11[c]			169.73		170.16[c]
14 CH_3CO					22.19[b]			22.73		20.78[b]
>CH	9.23	9.12	9.26	9.04	9.26	9.18	9.17	9.52	9.38	9.22
CH_2	3.91[c]	3.75	3.85[c]	4.38	3.66[c]	3.82	3.80	4.14	4.09[c]	3.75
CH_2		3.66		4.04		3.62	3.66	3.89		3.61

[a] Chemical shifts were obtained in $CDCl_3$ and are expressed in parts per million downfield from tetramethylsilane. [b] Signals in any one column may be reversed. [c] These resonances were twice as intense as other similar resonances. [d] In Me_2SO-d_6 the resonance for C-6 appeared at 65.26, C-7 at 22.93, C-8 at 28.10, and C-15 at 32.83.

produced a 1.4-ppm upfield shift of the C-8 resonance due to the larger γ effect of the axial 6-acetoxyl group. Acetylation of the 14-hydroxyl group (compounds **3c** and **3e**) caused the expected shifts of the C-8, C-9, and C-14 signals. In the 6α-naltrexol series the upfield shift of the C-8 resonance due to the 14-acetoxyl group was not as great as that in the 6β-naltrexol series.

An interesting difference between the two series of compounds was the appearance of the C-15 resonance at 2–4 ppm lower field in the 6α-naltrexol series. This difference was greatest for the parent compounds (**2a** and **3a**), was independent of solvent (except for compound **3b**), and was only slightly affected by acetylation. In addition, the C-3 and C-4 signals appeared respectively 1–2 ppm further upfield and 2–3 ppm further downfield in the 6α-naltrexol series. However, these changes were not as prominent as the shift of the C-15 resonance.

An examination of space-filling models indicated that the 6 substituent is more crowded by the ether oxygen and the aromatic ring in the α configuration than in the β configuration. One effect of this crowding could be the distortion of the carbon and oxygen substituents that are β and γ to C-15, thereby affecting the β and γ interaction between these atoms. The 6 substituent is also δ to both C-15 and C-4 (via the ether bridge). Although a δ interaction[26–28] could explain the shift of the C-4 resonance, the geometry between C-15 and the 6 substituent in either configuration is wrong for a δ interaction of much magnitude.[26,28] We are hopeful that the relationship between the chemical shift of C-15 and the configuration of C-6 will become clear upon examination of the ^{13}C NMR spectra of other ring C saturated compounds.

Experimental Section

NMR Spectral Measurements. ^1H NMR spectra were recorded in $CDCl_3$ solution on a Varian HA-100 spectrometer. ^{13}C NMR spectra were determined at 25.03 MHz on JEOL JNM-PS-100 FT NMR spectrometer interfaced with a Nicolet 1085 Fourier transform computer system under conditions previously described.[10] A 45° pulse of 12.5 μs was used, and the noise-modulated proton decoupling covered a bandwidth of 2500 Hz.

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Registry No.—**2a,** 49625-89-0; **2b,** 59888-59-4; **2c,** 59888-60-7; **2d,** 59888-61-8; **2e,** 59906-25-1; **3a,** 20410-98-4; **3b,** 59888-62-9; **3c,** 59888-63-0; **3d,** 59888-64-1; **3e,** 59888-65-2; **5b,** 53154-17-9; **6b,** 53154-16-8.

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Carbanions. 2.[1] Carbon-13 Nuclear Magnetic Resonance Study of Meisenheimer Complexes and Their Charge Distribution Pattern

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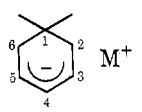
A series of 6-X,2,4-dinitroanisoles and their carbanionic methoxide addition products (Meisenheimer complexes) have been examined by ^{13}C NMR spectroscopy. Variation of X (CF_3, H, Cl, F, CH_3) does not affect the charge distribution pattern in the complexes as reflected by their ^{13}C NMR shifts. Only in the case where X is NO_2 can a change be observed. The ^{13}C NMR studies indicate that the cyclohexadienylic carbons carry about 0.3–0.4 e more negative charge than the corresponding carbons in their aromatic precursors. The additional charge is located on C_2, C_4, and C_6.

Intensive studies on the interaction of electron-deficient aromatic compounds with alkoxides culminated in 1902 with Meisenheimer's evidence that these complexes could be described by the structural formula 1.[2] These complexes, however, attracted little attention until 1964 when Crampton and Gold reported the first ^{1}H NMR spectrum of a Meisenheimer complex.[3a] Since then, numerous papers on the ^{1}H NMR studies of these complexes have been published,[3b] some of which also discussed aspects of their charge distribution pattern.[4] However, electron-withdrawing groups must occupy at least two and often three of the positions ortho and para (i.e., 2, 4, and 6) to the aliphatic center 1 in order to obtain stable complexes. As a result, the ortho and para positions, which are expected to carry most of the negative charge in cyclohexadienyl anions, cannot be studied by ^{1}H NMR spectroscopy, and the limitations of the ^{1}H NMR method of investigating charge distributions become evident.



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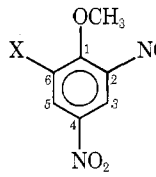
We now wish to report the first ^{13}C NMR spectroscopic study of Meisenheimer complexes, in which the obvious limitations of the ^{1}H NMR method are absent.

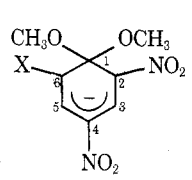
Results[5]

Substituted Anisoles. All ^{13}C NMR spectra showed a high-field absorption close to δ_C 65 (Table I), which was assigned to the methoxyl carbon based on the chemical shift and its quartet splitting in off-resonance spectra. Furthermore, off-resonance experiments allowed the separation of the C_3 and C_5 shifts from the other carbon shifts. δ C_3 and C_5 were found to be identical in anisoles **2** and **3**. In **6** these carbon shifts were characterized on the basis of the C–F couplings (J_{C_5F} = 14, J_{C_3F} = 8 Hz). In all other cases C_3 and C_5 were separated by more than 10 ppm, and their assignments were made possible by comparison of the observed shifts with calculated shifts.[6] The observed shifts showed a maximum deviation of 3.1 ppm from those which were determined from the substituent increments in monosubstituted benzenes.[6]

In accord with the calculations the most deshielded peaks were always ascribed to C_1. The only exception was **6** where C_6 was most deshielded, as indicated by the calculations and experimentally proved by its CF coupling of 231 Hz. The resonance at δ_C 127.6 was the only sp^2 carbon absorption of **3** showing CF coupling (6 Hz) and therefore could be assigned to C_6. Though the similarity between the calculated and observed C_1 and C_6 shifts in **5** and **7** is not outstanding, comparison with the resonances of the other singlets shows that no other assignment is possible.

In general, the nitro-substituted positions C_2 and C_4 show only slightly different chemical shifts. Though their assignments were not crucial to our present study, it was attempted on the basis of their intensities. If C_6, C_2, and C_4 in **2** had the





X		
NO_2	**2**	**2a**
CF_3	**3**	**3a**
H	**4**	**4a**
Cl	**5**	**5a**
F	**6**	**6a**
CH_3	**7**	**7a**