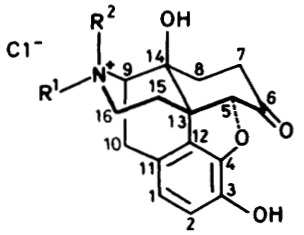
A ^{1}H and ^{13}C Nuclear Magnetic Resonance Study of Three Quaternary Salts of Naloxone and Oxymorphone†

Carel W. Funke* and Joop S. de Graaf
Organon International B.V. Scientific Development Group, P.O. Box 20, 5340 BH Oss, The Netherlands
Edward Buurman, Henk Thalen, and Pieter Vrijhof
Diosynth B.V., P.O. Box 407, 7300 AK Apeldoorn, The Netherlands

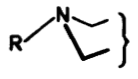
The information from ^{1}H–^{1}H and ^{1}H–^{13}C correlation n.m.r. spectra allowed a complete assignment of the ^{1}H and ^{13}C spectra of three *N,N*-dialkylmorphinanium chloride derivatives (one *N,N*-diallyl and two *N*-allyl-*N*-methyl diastereoisomers). In the case of the stereoisomers the configuration of the asymmetric N atom could be established on the basis of ^{1}H chemical shift data and nuclear Overhauser effects.

Quaternized analogues of opiate antagonists have been proposed for the alleviation of peripheral side effects in opiate-treated humans. On the other hand, these quaternary compounds have been compared with the corresponding tertiary amines in order to demonstrate alleged CNS efficacy of the latter.[1] Iorio and Frigeni have recognized[2] that diastereoisomeric pairs result if the quaternary nitrogen atom bears different substituents, and have compared biological activities on peripheral receptors. We report here a ^{1}H and ^{13}C n.m.r. study of the diastereoisomeric compounds (**1**) and (**2**), along with compound (**3**) which lacks a chiral nitrogen atom.

A quantitative comparison of the CNS effects of these compounds and naloxone will be reported separately.



(**1**) $R^1 = CH_2-CH=CH_2$, $R^2 = Me$
(**2**) $R^1 = Me$, $R^2 = CH_2-CH=CH_2$
(**3**) $R^1 = R^2 = CH_2-CH=CH_2$



(**4**) $R = CH_2-CH=CH_2$
(**5**) $R = Me$

Results and Discussion

Syntheses.—Quaternization of naloxone (**4**) with methyl iodide, of oxymorphone (**5**) with allyl bromide, and of naloxone with allyl bromide, followed by anion exchange, yielded the quaternized chlorides (**1**)—(**3**), respectively.

N.m.r. Spectra.—$(CD_3)_2SO$ was chosen as a solvent because of poor solubility in $CDCl_3$, and of partial deuteriation at C(7) in CD_3OD. Moreover $(CD_3)_2SO$ allows the detection of the hydroxy proton signals which are of diagnostic value (see later).

Assignment of the ^{1}H *and* ^{13}C *signals.* The ^{1}H and ^{13}C chemical shifts are listed in Table 1. The ^{1}H signal assignments are based on ^{1}H–^{1}H correlation spectroscopy (COSY) experiments; the high-field part of the COSY spectrum of (**1**) is shown in the Figure. The signals of H(7*ax*), H(8*ax*), H(15*ax*), and H(16*ax*) are easily recognized by their large (> 11 Hz) vicinal couplings. The assignment of the ^{13}C signals was based on *J*(CH)-modulated spin-echo experiments and comparison with the ^{13}C data of naloxone.[3a] Both assignments were finally checked by means of ^{1}H–^{13}C correlation spectra.

Configurational Information from the Spectral Parameters.—^{1}H *Chemical shifts.* The shifts of most backbone protons are similar for (**1**)—(**3**), suggesting similar skeletal structures. The large H(7*ax*), H(8*ax*) and H(15*ax*), H(16*ax*) couplings indicate antiperiplanar relations and thus confirm the chair-form cyclohexanone and piperidine rings also found for related compounds.[4] Remarkable shift differences amongst (**1**)—(**3**) are found for the *N*-methyl, *N*-allyl, and 14-hydroxy protons.

The ^{1}H shifts of axial and equatorial *N*-methyl groups in quaternary piperidinium salts[5] depend among other things on the presence of other substituents on the piperidine ring, but *cis*-1,1,2,3-tetramethylpiperidinium iodide, with its axial 2-methyl group, must be regarded as a good reference compound for (**1**) and (**2**). The axial and equatorial *N*-methyl groups of this compound resonate, in $(CD_3)_2SO$ solution, at δ 3.21 and 3.05, respectively.[6]

In (**1**) or (**2**), the axial *N*-methyl signal will be shifted *ca.* 0.25 p.p.m. further downfield by diaxial interaction[7] with the 14-hydroxy group. The *N*-methyl shifts thus predicted of δ 3.5 (axial) and 3.1 (equatorial) are consistent with the values found for compounds (**1**) (δ 3.60) and (**2**) (δ 3.11), and thus point to an *N*-methyl axial/*N*-allyl equatorial configuration for (**1**) and the reverse for (**2**).

The C(1′) and C(2′) protons of the *N*-allyl groups of (**1**) and (**2**) also follow the $\delta_{ax} > \delta_{eq}$ trend, and this accounts for the axial/equatorial assignment of the allyl proton signals of compound (**3**) in Table 1.

The chemical shift of the 14-hydroxy proton of compound (**3**) is similar to that of (**2**), but remarkably different from those of (**1**); this reflects a similar (allyl–hydroxy) diaxial interaction in (**2**) and (**3**) and a different (methyl–hydroxy) interaction in (**1**), and thus independently confirms the foregoing configurational assignment.

The COSY spectrum of (**1**) reveals a weak coupling (marked with an asterisk) between the *N*-methyl group and H(16*ax*); such a coupling is not detected for (**2**). The long-range couplings of axial protons are well known[8] for axial (angular) methyl groups in steroids; thus the axial assignment of the *N*-methyl group in (**1**) is supported.

Nuclear Overhauser measurements. Nuclear Overhauser difference spectra have been obtained for compounds (**1**) and (**2**); the results are summarized in Table 2. The proximity of 14-OH and the *N*-methyl group in (**1**), and of 14-OH and the *N*-allyl group in (**2**), confirms the configurations of the N atoms in these compounds.

† Naloxone is 17-allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one; oxymorphone is the 17-methyl analogue

Table 1. Chemical shifts (^{1}H and ^{13}C) of compounds (**1**)—(**3**)

	δ(^{1}H)[a]			δ(^{13}C)[b]		
Atom	(1)	(2)	(3)	(1)	(2)	(3)
1	6.68	6.64	6.68	120.3	120.1	120.4
2	6.73	6.76	6.75	118.2	118.3	118.2
3				140.6	140.8	140.7
4				143.7	143.9	143.7
5	4.95	5.01	4.98	88.6	88.6	88.6
6				207.5	207.7	207.7
7	2.94[c]/2.07[d]	2.97[c]/2.07[d]	2.98[c]/2.08[d]	35.0	35.0	35.2
8	1.52[c]/2.12[d]	1.52[c]/2.29[d]	1.55[c]/2.22[d]	32.0	31.6	32.1
9	3.89	3.92	4.09	70.8	69.6	70.1
10	3.01/3.57	2.98/3.47	3.03/3.58	27.2	27.3	27.3
11				119.8	120.0	120.0
12				127.8	128.0	128.0
13				48.4	48.4	48.7
14				71.7	72.0	72.3
15	2.78[c]/1.62[d]	2.81[c]/1.61[d]	2.75[c]/1.60[d]	24.6	24.6	24.5
16	2.83[c]/3.39[d]	2.85[c]/3.47[d]	2.78[c]/3.44[d]	56.8	57.2	53.6
NCH_3	3.60	3.11		53.0	52.5	
$NCH_2C{=}C$	3.98/4.38	4.19/5.42	4.67/5.03[e] 3.98/4.13[f]	69.1	68.1	62.9[e] 63.7[f]
$NCCH{=}C$	6.11	6.44	6.24[e] 6.11[f]	125.4	127.4	125.4[f] 126.9[e]
$NCC{=}CH_2$	5.71/5.79	5.67/5.71	5.66/5.68[e] 5.66/5.78[f]	127.4	127.8	127.1[f] 127.5[e]
3-OH	9.63	9.69	9.67			
14-OH	6.90	7.24	7.22			

[a] ±0.02 p.p.m. [b] ±0.1 p.p.m. [c] Axial proton. [d] Equatorial proton. [e] Axial allyl group. [f] Equatorial allyl group.

Table 2. Some through-space connectivities[a] in compounds (**1**) and (**2**) as established by nuclear Overhauser difference spectra[b]

	Nuclear Overhauser	
Proton irradiated	(1)	(2)
14-OH	7*ax*, 8*eq*, 9, NCH_3	5, 7*ax*, 8*eq*, 9, NCHC=C[c]
NCHC=C[c]	10[c], 16*ax*	9, 14-OH
NCHC=C[d]	NCH_3	16*eq*, NCH_3
NCH_3	9, 14-OH, NCHC=C[d]	9, 10[c], NCHC=C[d]

[a] Effects for protons connected *via* geminal, vicinal, or allylic couplings are omitted. [b] In CD_3SOCD_3 at 297 °C, pre-irradiation time 0.8 s. [c] Down-field signal. [d] Up-field signal.

^{13}C *Chemical shifts*. Table 1 reveals the lack of dependence of all carbon shifts on the configuration of the quaternary N atom. For the *N*-methyl carbon atoms in simple *N*,*N*-dimethylpiperidinium salts,[3b,3c] the difference $\delta_{eq} - \delta_{ax}$ is generally *ca.* 8 p.p.m. Apparently this equatorial–axial difference is offset in (**1**)—(**3**) by the 14-hydroxy group and the rest of the morphinan framework. Conclusions on the configuration of the quaternary N atoms in (**1**)—(**3**) can therefore not be drawn from the carbon shifts.

Experimental

(17R)-17-*Allyl*-4,5α-*epoxy*-3,14-*dihydroxy*-17-*methyl*-6-*oxomorphinanium Iodide* (**1**; I *for* Cl).—To a solution of methyl iodide (25 ml) in acetone (200 ml) naloxone base (**4**) (from naloxone hydrochloride, USP quality) (21 g) was added. The suspension was heated at 70 °C for 88 h in an autoclave. The precipitated solid was filtered off and dried to give the crude quaternary iodide (27.3 g, 90%).

(17R)-17-*Allyl*-4,5α-*epoxy*-3,14-*dihydroxy*-17-*methyl*-6-*oxomorphinanium Chloride* (**1**).—A suspension of anion-exchange resin (Dowex 21K; 310 g) was transferred into a column and washed with 1.4M-HCl (1.6 l) and water (2 l). Crude (**1**; I for Cl) (27.3 g) was dissolved in water (700 ml) and passed through the column, which was washed with water (250 ml). Evaporation left the crude chloride (**1**) (20.6 g), which was twice recrystallized from ethanol–water (yield 60%); m.p. 262—265 °C (decomp.); *m/z* 341.163 592 (*M* − HCl; calc. for $C_{20}H_{23}NO_4$: 341.162 697), 327 (*M* − CH_3Cl), and 301.133 071 (*M* − C_3H_5Cl; calc. for $C_{17}H_{19}NO_4$: 301.131 399); $\nu_{max.}$ (KBr) 3 154 and 3 115 (OH), 1 740 (C=O), and 1 500 cm^{-1} (C=C); $[\alpha]_D^{20}$ −198.3° (*c* 1 in water); t.l.c.: 100 γ spot homogeneous [silica 60 F-254, ethyl acetate–methanol–10% ammonia–propan-2-ol (1:2:2:1)].

(17S)-17-*Allyl*-4,5α-*epoxy*-3,14-*dihydroxy*-17-*methyl*-6-*oxomorphinanium Bromide* (**2**; Br *for* Cl).—A mixture of acetone, (185 ml), fresh distilled allyl bromide (36.4 ml), and oxymorphone (**5**) (20 g) was heated in an autoclave at 70 °C for 96 h. The precipitate was filtered off and dried to yield the crude bromide (25 g, 89%), containing *ca.* 5% oxymorphone.

(17S)-17-*Allyl*-4,5α-*epoxy*-3,14-*dihydroxy*-17-*methyl*-6-*oxomorphinanium Chloride* (**2**).—Crude (**2**; Br for Cl) (16 g) was dissolved in water (500 ml) and oxymorphone was removed by extraction at pH 8.8 with methylene dichloride (3 × 100 ml). The precipitate was filtered off and dissolved in dilute aqueous hydrochloric acid (pH 3). This phase was combined with the water phase, also adjusted to pH 3. The bromide was converted into the chloride (**2**) by passing through a column of anion-exchange resin (Dowex 1-X8, Cl^- form; 200 g); yield 9 g (63%) after two crystallizations from ethanol–water; water content (KF) 2.3%; m.p. 182.5—184.5 °C; *m/z* 341.167 665 (*M* − HCl; calc. for $C_{20}H_{23}NO_4$: 341.162 697), 327 (*M* − CH_3Cl), and 301.131 584 (*M* − C_3H_5Cl; calc. for $C_{17}H_{19}NO_4$: 301.131 399); $\nu_{max.}$ (KBr) 3 170 (OH), 1 720 (C=O), and 1 510 cm^{-1} (C=C); $[\alpha]_D^{20}$ −127.4° (*c* 1 in water); t.l.c. 100 γ spot homogeneous [silica 60 F-254, ethyl acetate–methanol–10% ammonia–propan-2-ol (1:2:2:1)].

17,17-*Dialkyl*-4,5α-*epoxy*-3,14-*dihydroxy*-6-*oxomorphinanium Chloride* (**3**).—The quaternization of naloxone with allyl

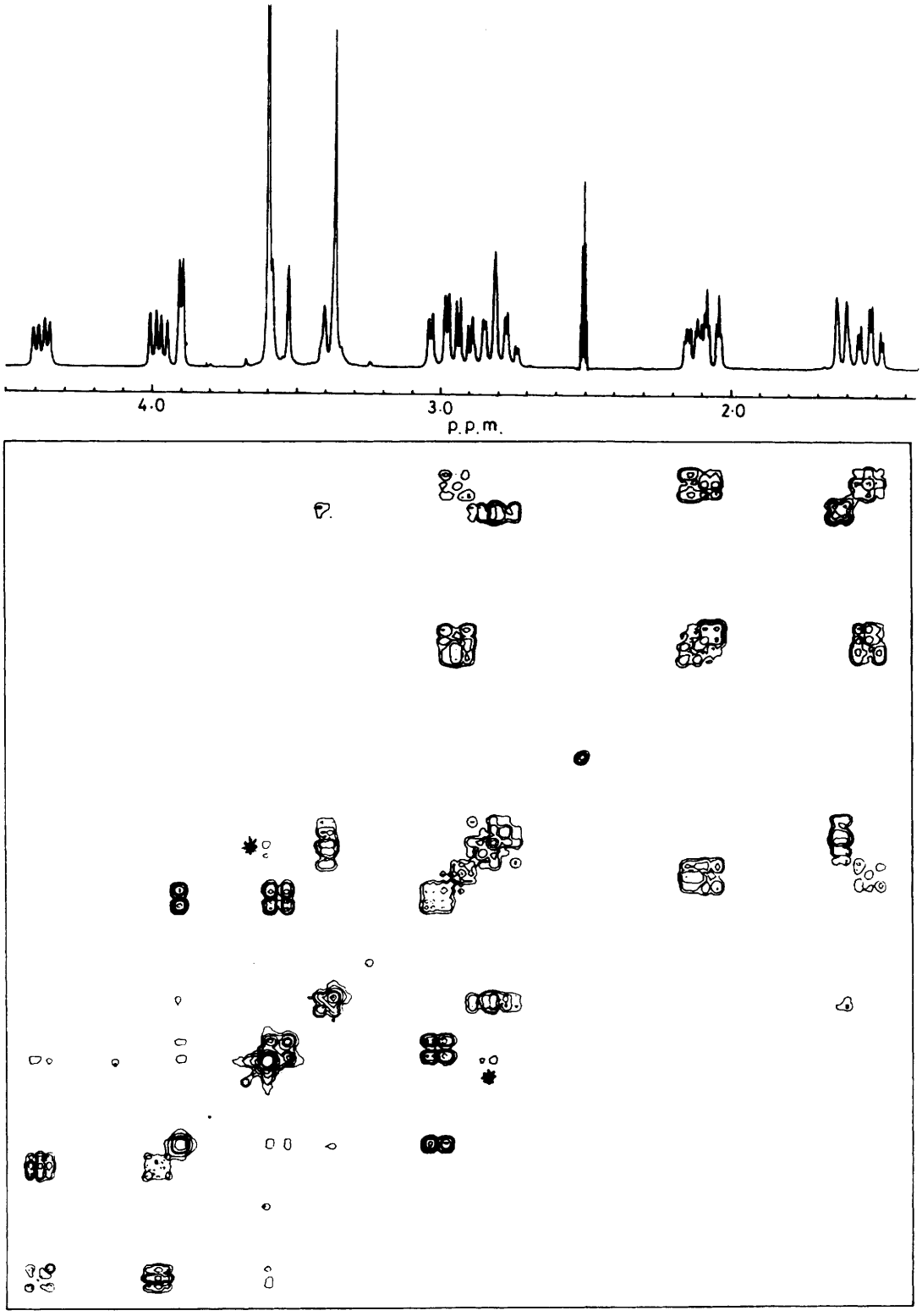


Figure. High-field part of the 360 MHz COSY spectrum of (1); the normal ^1H spectrum is plotted along the horizontal axis for reference purposes

bromide is a very slow reaction. We tried many solvents and reaction conditions and found mostly dissociation and formation of the 3-*O*-allyl compound. The following conditions gave us (3; Br for Cl): naloxone (35 g) was suspended in allyl bromide (35 ml) and DMF (350 ml) and the mixture was stirred for 9 days at room temperature (conversion *ca.* 10%). The reaction mixture was evaporated to 50 ml and poured into water. The precipitated naloxone (29 g) was filtered off and the filtrate

extracted with $CHCl_3$ to remove the last traces of naloxone. The water layer was evaporated to dryness and the residue triturated with methanol. The precipitated bromide was collected, recrystallized from ethanol and converted into (**3**) by passing through ion-exchange resin (Dowex 21 K; as before); yield (after crystallization from ethanol) 30% (calculated on converted naloxone); m.p. 211—213 °C; *m/z* 367.174 498 (M − HCl; calc. for $C_{22}H_{25}NO_4$: 367.178 347) and 327.145 177 (M − C_3H_5Cl; calc. for $C_{19}H_{21}NO_4$: 327.147 048); $\nu_{max.}$ (KBr) 3 420 and 3 220 (OH), 1 720 (C=O), and 1 510 cm^{-1} (C=C); $[\alpha]_D^{20}$ −176.3° (*c* 1 in water).

N.m.r. Spectra.—All n.m.r. spectra were recorded with a Bruker AM360 spectrometer. The 360 MHz ^1H and 90 MHz broad-band ^1H-decoupled ^{13}C spectra were taken for 0.05M-solutions in $(CD_3)_2SO$ (>99.8%; Merck) at 25 °C. Chemical shifts were referred to internal Me_4Si, and standard spectral parameters were used.

^1H Shift-correlated 2-D spectra,[9] (COSY-45, N-type selection), *J*-modulated spin-echo ^{13}C spectra,[10] and ^1H–^{13}C shift-correlated spectra[11] were recorded with the Bruker DISNMRP program, version 830701. Nuclear Overhauser difference spectra were obtained using the 'NOE difference series' microprogram (Bruker DISNMR software, version 850101).

Acknowledgements

We thank Professor J. L. Martinez Jr. (University of California, Irvine, USA) and Professor H. C. Beijerman (Technical University, Delft, The Netherlands) for ideas and discussions.

References

1 G. F. Koob, H. O. Pettit, A. Ettenberg, and F. E. Bloom, *J. Pharmacol. Exp. Ther.*, 1984, **229**, 481.
2 M. A. Iorio and V. Frigeni, *Eur. J. Med. Chem.-Chem. Ther.*, 1984, **19**, 301.
3 W. Bremser, L. Ernst, and B. Franke, Carbon-13 NMR Spectral Data, Verlag Chemie Weinheim, 1978, (*a*) NMR3051, (*b*) NMR1978, (*c*) NM22649.
4 S. D. Darling, V. M. Kolb, G. S. Mandel, and N. S. Mandel, *J. Pharm. Sci.*, 1982, **71**, 763, and references cited therein.
5 A. F. Casy, 'PMR Spectroscopy in Medicinal and Biological Chemistry,' Academic Press, London, 1971, p. 155.
6 M. Tsuda, M. Tsuda, Y. Kawozoe, A. F. Casy, and M. M. A. Hassan, *Chem. Pharm. Bull.*, 1974, **22**, 809.
7 G. Englert, W. Arnold, H. Els, A. Furst, A. Meier, and W. Meister, *Helv. Chim. Acta*, 1974, **57**, 1559.
8 L. D. Hall and J. K. M. Sanders, *J. Org. Chem.*, 1981, **46**, 1132.
9 A. Bax and R. Freeman, *J. Magn. Reson.*, 1981, **44**, 542.
10 C. Le Cocq and J. Lallemand, *J. Chem. Soc., Chem. Commun.*, 1981, 150.
11 A. Bax, Ph.D. Thesis, Delft, 1981.

Received 26*th June* 1985; *Paper* 5/1082