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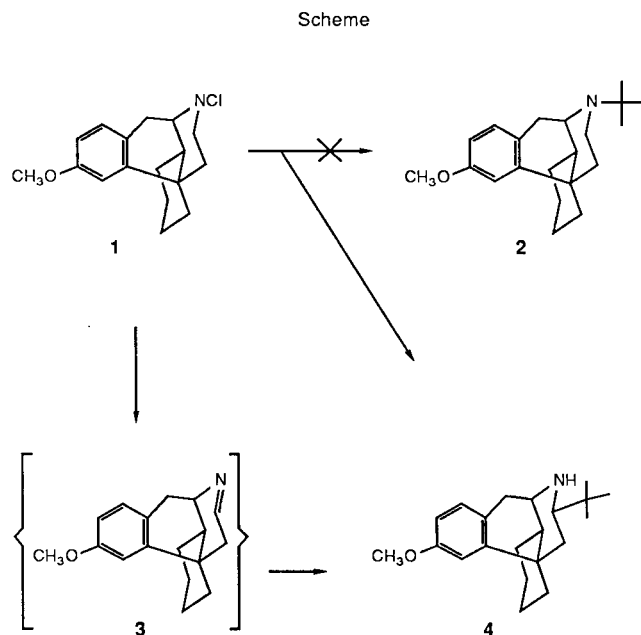
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Preparation of (\pm)-3-methoxy-16-*t*-butylmorphinan (**4**) by reaction of *t*-butyl lithium with (\pm)-3-methoxy-*N*-chloromorphinan (**1**) is described. The structure of **4** was confirmed by X-ray crystallography.

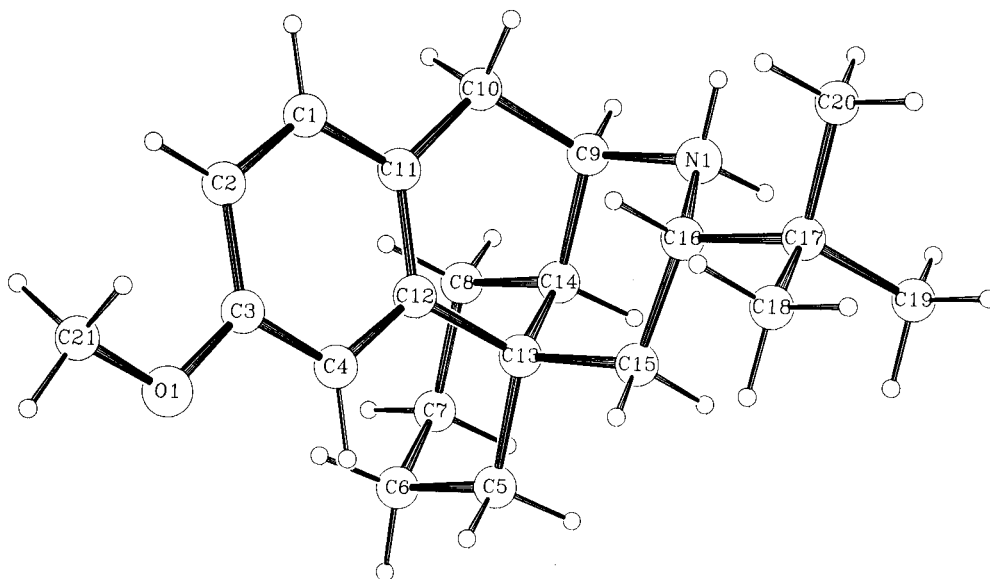
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In a previous paper [1] we have described the synthesis of metabolically stable *t*-butyl ethers of morphine and levorphanol. From this result it appeared attractive to attempt to replace the vulnerable *N*-methyl group in (\pm)-3-methoxy-*N*-methylmorphinan with a *t*-butyl substituent in order to reduce rapid *in vivo* metabolic inactivation, and to prolong the analgesic activity.

In this connection, we have recently examined the reaction of *t*-butyl lithium with (\pm)-3-methoxy-*N*-chloromorphinan (**1**) [2] as a possible route to (\pm)-3-methoxy-*N*-*t*-butylmorphinan (**2**). When *N*-chloromorphinan (**1**) [2] was allowed to react with *t*-butyl lithium in ether at ice-bath temperature, followed by warming to room temperature, chromatography of the crude reaction mixture yielded a colorless solid, mp 101-103° (Scheme). The mass spectrum of this compound shows the molecular ion peak as anticipated at *m/e* 313. The nmr spectrum (deuteriochloroform) features a characteristic ABX pattern for the three aromatic protons, namely two doublets centered at δ 7.00 ($J = 8.5$ Hz) and 6.75 ($J = 2.5$ Hz) and a quartet of 6.66 ($J = 8.5$ Hz). This compound shows, among other signals, a three-proton singlet at δ 3.77 for the aromatic methoxy protons and a nine-proton singlet for the *t*-butyl protons at 0.75.



Analysis of spectral data including nmr was not sufficient to unambiguously assign structure **2** or **4** to this compound. Consequently, various aspects of the chemical be-



Figure

Table I

Final Atomic Parameters for **4** with Standard Deviations in Parentheses

Atom	X	Y	Z	Beqv/Biso
Br	0.07854(4)	0.60324(10)	0.44827(3)	6.42(2)
O(1)	0.2108(3)	0.4802(6)	0.8788(3)	9.5(2)
N(1)	0.0604(2)	0.5649(7)	0.5911(2)	4.7(2)
C(1)	0.0945(3)	0.3121(8)	0.7635(4)	4.9(2)
C(2)	0.1249(4)	0.3444(9)	0.8212(3)	5.4(2)
C(3)	0.1765(4)	0.4416(9)	0.8249(4)	5.8(2)
C(4)	0.1970(3)	0.5012(8)	0.7739(4)	6.1(2)
C(5)	0.2597(4)	0.5764(9)	0.6617(3)	7.5(2)
C(6)	0.3005(4)	0.4385(11)	0.6616(4)	8.8(3)
C(7)	0.2812(4)	0.3477(10)	0.6048(4)	9.0(3)
C(8)	0.2092(4)	0.3098(8)	0.5997(3)	7.2(2)
C(9)	0.0960(3)	0.4204(8)	0.5983(3)	4.6(2)
C(10)	0.0771(3)	0.3321(7)	0.6510(3)	5.1(2)
C(11)	0.1137(3)	0.3727(9)	0.7118(3)	4.3(2)
C(12)	0.1664(4)	0.4669(8)	0.7159(3)	4.7(2)
C(13)	0.1867(3)	0.5408(9)	0.6594(4)	5.2(2)
C(14)	0.1686(4)	0.4513(9)	0.6014(3)	5.6(2)
C(15)	0.1502(3)	0.6896(8)	0.6500(3)	5.6(2)
C(16)	0.0767(3)	0.6726(8)	0.6419(3)	5.0(2)
C(17)	0.0373(4)	0.8155(9)	0.6305(4)	6.2(2)
C(18)	0.0504(3)	0.9072(9)	0.6882(3)	8.5(2)
C(19)	0.0547(4)	0.9007(9)	0.5760(3)	9.1(2)
C(20)	-0.0352(4)	0.7787(8)	0.6237(4)	10.1(3)
C(21)	0.1867(4)	0.4382(10)	0.9339(4)	11.7(3)
HN(1)A	0.071	0.608	0.554	5.0
HN(1)B	0.015	0.546	0.589	5.0
H(1)	0.057	0.242	0.760	5.0
H(2)	0.110	0.299	0.859	5.5
H(4)	0.234	0.571	0.778	6.5
H(5)A	0.267	0.636	0.625	8.0
H(5)B	0.273	0.633	0.700	8.0
H(6)A	0.347	0.466	0.662	9.0
H(6)B	0.294	0.380	0.699	9.0
H(7)A	0.307	0.256	0.607	9.5
H(7)B	0.290	0.404	0.568	9.5
H(8)A	0.200	0.246	0.634	7.5
H(8)B	0.197	0.258	0.560	7.5
H(9)	0.084	0.363	0.560	5.0
H(10)A	0.086	0.227	0.643	5.5
H(10)B	0.030	0.346	0.654	5.5
H(14)	0.177	0.512	0.565	6.0
H(15)A	0.162	0.753	0.686	6.0
H(15)B	0.164	0.738	0.613	6.0
H(16)	0.064	0.628	0.680	5.0
H(18)A	0.024	0.999	0.684	8.5
H(18)B	0.098	0.932	0.695	8.5
H(18)C	0.038	0.851	0.724	8.5
H(19)A	0.028	0.992	0.572	9.5
H(19)B	0.046	0.841	0.538	9.5
H(19)C	0.102	0.926	0.582	9.5
H(20)A	-0.061	0.871	0.619	10.5

Table I (continued)

Atom	X	Y	Z	Beqv/Biso
H(20)B	-0.046	0.726	0.661	10.5
H(20)C	-0.046	0.717	0.587	10.5
H(21)A	0.217	0.474	0.969	12.0
H(21)B	0.184	0.330	0.935	12.0
H(21)C	0.143	0.481	0.936	12.0

Table II

Bond Lengths (Å) in **4** with Standard Deviations in Parentheses

O(1)-C(3)	1.367(10)	C(8)-C(14)	1.552(11)
O(1)-C(21)	1.412(11)	C(9)-C(10)	1.501(10)
N(1)-C(9)	1.522(9)	C(9)-C(14)	1.524(10)
N(1)-C(16)	1.507(9)	C(10)-C(11)	1.517(9)
C(1)-C(2)	1.391(11)	C(11)-C(12)	1.390(11)
C(1)-C(11)	1.363(11)	C(12)-C(13)	1.513(12)
C(2)-C(3)	1.388(12)	C(13)-C(14)	1.534(11)
C(3)-C(4)	1.357(13)	C(13)-C(15)	1.569(11)
C(4)-C(12)	1.403(11)	C(15)-C(16)	1.522(10)
C(5)-C(6)	1.525(13)	C(16)-C(17)	1.554(11)
C(5)-C(13)	1.542(11)	C(17)-C(18)	1.528(11)
C(6)-C(7)	1.523(13)	C(17)-C(19)	1.507(12)
C(7)-C(8)	1.524(12)	C(17)-C(20)	1.532(11)

havior of this substance were examined. The failure of this compound to undergo *N*-alkylation [3], -acetylation [4], -formylation [5] and reductive methylation [6] is compatible with **2**, but does not rule out the possibility that the inertness of this compound could conceivably be attributed to the bulky *t*-butyl group in the α -position in **4**. Finally, an X-ray analysis of the hydrobromide derivative [7] of this sample identified the compound as (\pm)-3-methoxy-16-*t*-butylmorphinan (**4**, Figure [7]). The conversion of **1** to **4** appears to involve initial formation of imine **3**, followed by *C*-alkylation of this intermediate to yield the observed product **4**. This reaction is analogous to the conversion of cyclic secondary amines to their 2-cyano derivatives by addition of hydrogen cyanide to the imine derived from the *N*-chloroamines [8].

Attempts to dehydrohalogenate **1** with methanolic sodium hydroxide failed to give the expected imine **3** and the starting material **1** was recovered unchanged.

EXPERIMENTAL

Melting points were taken in capillary tubes with a Thomas Hoover melting point apparatus and are uncorrected. Ultraviolet spectra were measured in 95% ethanol with a Carey Model 14 spectrophotometer. Infrared spectra were determined with a Beckman Model IR-9 spectro-

Table III

Bond Angles (°) in **4** with Standard Deviations in Parentheses

C(3)-O(1)-C(21)	118.5(6)
C(9)-N(1)-C(16)	115.4(5)
C(2)-C(1)-C(11)	122.1(6)
C(1)-C(2)-C(3)	117.8(7)
O(1)-C(3)-C(2)	123.2(7)
O(1)-C(3)-C(4)	115.8(7)
C(2)-C(3)-C(4)	121.0(7)
C(3)-C(4)-C(12)	120.9(7)
C(6)-C(5)-C(13)	111.4(7)
C(5)-C(6)-C(7)	111.0(7)
C(6)-C(7)-C(8)	111.1(7)
C(7)-C(8)-C(14)	109.5(6)
N(1)-C(9)-C(10)	113.1(5)
N(1)-C(9)-C(14)	107.9(6)
C(10)-C(9)-C(14)	113.6(5)
C(9)-C(10)-C(11)	113.7(5)
C(1)-C(11)-C(10)	118.4(6)
C(1)-C(11)-C(12)	119.7(6)
C(10)-C(11)-C(12)	121.9(6)
C(4)-C(12)-C(11)	118.5(7)
C(4)-C(12)-C(13)	120.6(7)
C(11)-C(12)-C(13)	120.6(6)
C(5)-C(13)-C(12)	115.0(6)
C(5)-C(13)-C(14)	107.2(6)
C(5)-C(13)-C(15)	106.0(6)
C(12)-C(13)-C(14)	112.2(6)
C(12)-C(13)-C(15)	109.3(6)
C(14)-C(13)-C(15)	106.6(6)
C(8)-C(14)-C(9)	112.1(6)
C(8)-C(14)-C(13)	112.6(6)
C(9)-C(14)-C(13)	107.1(6)
C(13)-C(15)-C(16)	112.8(6)
N(1)-C(16)-C(15)	107.5(5)
N(1)-C(16)-C(17)	111.3(5)
C(15)-C(16)-C(17)	115.7(6)
C(16)-C(17)-C(18)	106.7(6)
C(16)-C(17)-C(19)	113.9(7)
C(16)-C(17)-C(20)	108.7(6)
C(18)-C(17)-C(19)	109.8(7)
C(18)-C(17)-C(20)	107.1(7)
C(19)-C(17)-C(20)	110.4(6)

photometer. Nuclear magnetic resonance spectra were measured with a Varian A-60 or HA-100 spectrometer and recorded in δ values with deuteriochloroform as the solvent and tetramethylsilane as an internal reference. The proton signals are designated as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra (70 eV, direct inlet system) were determined with a CEC type 21-110 spectrometer. Crystallographic data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu K α radiation, θ - 2θ scans, pulse-height discrimination).

(\pm)-3-Methoxy-16-*t*-butylmorphinan (**4**).

A 250 ml, 1-necked round-bottomed flask is fitted with a magnetic stirring bar and a rubber septum. After the system is flushed with nitrogen, the flask is charged with 100 ml ether (anhydrous) and 3.0 g (0.01 mole) of (\pm)-3-methoxy-*N*-chloromorphinan (**1**) [2]. The flask is immersed in an ice-bath and 11.0 ml of a 2.1 M solution of *t*-butyl lithium in pentane is added to the stirred solution with the aid of a syringe over a period of 10 minutes. The mixture is stirred at ice-bath temperature overnight, then allowed to warm to room temperature, and quenched carefully with water (6.0 ml). The organic phase is separated, washed with water, then dried over magnesium sulfate and concentrated *in vacuo* to give 3.01 g of a yellow oil. Reaction products as described above are combined (5.5 g) and chromatographed on 150.0 g Alumina Act. III. Elution is carried out with benzene-hexane (4:1) taking 150 ml fractions. The progress of the purification is monitored by thin layer chromatography (silica gel and 60% ethyl acetate in hexane). Fractions 1-15 containing the product are combined and the solvents are removed under reduced pressure. The residue is crystallized from benzene to give 1.5 g (47%) of **4** as a colorless solid, mp 101-103°; ir (potassium bromide): 3345 (NH) cm⁻¹; uv (95% ethanol): max 220 m μ (ϵ 7560), max 280 (2440) and max 287 (2220); ms: m/e 313 [M⁺]; nmr (deuteriochloroform): δ 7.00 (d, 1H, J = 8.5 Hz, ArH), 6.75 (d, 1H, J = 2.5 Hz, ArH), 6.66 (q, 1H, J = 8.5 Hz, ArH), 3.77 (s, 3H, ArOCH₃) and 0.75 [s, 9H, C(CCH₃)₃].

Anal. Calcd. for C₂₁H₃₁NO: C, 80.46; H, 9.97; N, 4.46. Found: C, 80.57; H, 9.95; N, 4.46.

A portion of the above base **4** is treated with hydrogen bromide (anhydrous) in ethyl acetate and the crude **4**·HBr is recrystallized from 2-propanol, mp 286-287°; nmr (deuteriochloroform): δ 7.10 (d, 1H, J = 8.5 Hz, ArH), 6.80 (d, 1H, J = 2.5 Hz, ArH), 6.60 (q, 1H, J = 8.5 Hz, ArH), 3.80 (s, 3H, ArOCH₃) and 1.07 [s, 9H, C(CH₃)₃].

Anal. Calcd. for C₂₁H₃₁NO·HBr: C, 63.95; H, 8.18; N, 3.55. Found: C, 63.86; H, 8.28; N, 3.40.

Crystal Data and Structure Determination.

Formula C₂₁H₃₁NO·HBr, M = 394.34, crystal selected from a sample recrystallized from 2-propanol, of approximate dimensions 0.06 x 0.10 x 0.20 mm, space group A2/a, cell dimensions a = 20.706, b = 9.205, c = 22.022 Å, β = 95.83°, Z = 8, μ = 30.0 cm⁻¹, ρ_{calcd} = 1.255 g cm⁻³, max θ = 48°, 2118 unique reflections, of which 1323 were considered observed [$I > 2.5 \sigma(I)$].

The structure of **4** was solved by the heavy-atom method and was refined by full-matrix least squares. In the final refinement, anisotropic thermal parameters were used for the nonhydrogen atoms and isotropic temperature factors were used for the hydrogen atoms. The positions of the hydrogen atoms were calculated based on the local molecular geometry. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are R = 0.043 and wR = 0.024, for 217 parameters. The difference map has no peaks greater than $\pm 0.3 e \text{ \AA}^{-3}$.

The cation is depicted in the figure showing that the structure is that of **4**. The final atomic parameters, bond lengths, and bond angles of **4** are listed in Tables I through III, respectively.

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