A Convenient Method for Replacing the *N*-Methyl Group of Morphine, Codeine, and Thebaine by Other Alkyl Groups

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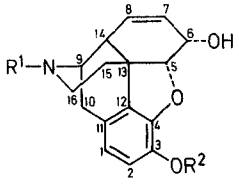
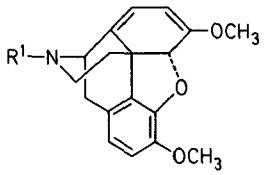
A large number of compounds have been prepared by structural modifications of morphine-type alkaloids to study the relationship between structure and analgesic activity[1,2]. One of the common modifications, i.e., the replacement of the *N*-methyl group of the alkaloids by various other alkyl groups, is usually achieved by *N*-demethylation to the *N*-nor compounds, followed by realkylation with the appropriate alkyl halide. The required *N*-normorphine **(1a)** and *N*-norcodeine **(1c)** have been obtained from morphine **(1b)** and codeine **(1d)** by the von Braun reaction with cyanogen bromide[3] or by reaction with alkyl carbonochloridates[4-8] and subsequent cleavage of the resultant cyanamide or carbamate. However, these reactions are not suitable for the preparation of *N*-northebaine **(2a)**, which has been obtained by reaction of thebaine **(2b)** with ethyl diazenedicarboxylate, followed by hydrolysis[9,10]. *N*-Northebaine **(2a)** was first prepared by suitable transformations of derivatives of dihydro-*N*-norcodeinone[11] or *N*-norcodeinone[12]. All these methods involve several steps. Photochemical demethylation[13] was observed only in the case of codeine.

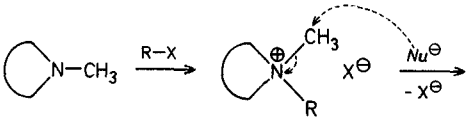


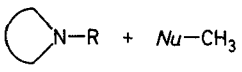
1a $R^1 = H$; $R^2 = H$
1b $R^1 = CH_3$; $R^2 = H$
1c $R^1 = H$; $R^2 = CH_3$
1d $R^1 = CH_3$; $R^2 = CH_3$



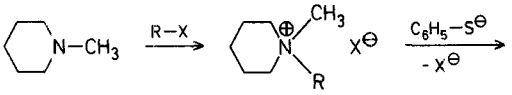
2a $R^1 = H$
2b $R^1 = CH_3$

We present here a simple two-step technique for the replacement of the *N*-methyl group of **1b, 1d,** and **2b** by other alkyl groups which consists of quaternization of the tertiary *N*-methyl compound with an alkyl halide, followed by selective removal of the methyl group by a nucleophile.

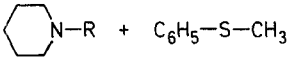




Demethylation of trialkylmethylammonium halides has been achieved by a variety of methods: heating in high boiling aprotic solvents[14] which, however, is too drastic for many compounds; boiling with nucleophiles[15] such as triphenylphosphine, thiourea, sodium thiosulphate, or sodium azide in dimethylformamide, with lithium propylmercaptide[16] in hexamethylphosphoric triamide, with lithium trialkylborohydride[17,18] or benzenethiolate[19] in butanone. The last-named method[19] seemed particularly suitable for our purpose. It had already been shown for triethylmethylammonium chloride as an aliphatic model compound that demethylation is strongly preferred over deethylation; it had further been shown that alkoxy groups present in the molecule are not cleaved, that demethylation occurs via an S_N2 reaction, and that 3-*O*-ethylmorphine methochloride is smoothly converted to the tertiary base. We first studied this method using *N*-methylpiperidine as a cyclic model compound, to establish whether methyl would also be removed preferentially in competition with alkyls higher than ethyl. *N*-Methylpiperidine was quaternized with 1-bromopropane, 1-iodobutane, and 2-iodopropane and the resultant salts **3a, 3b,** and **3c** were converted into the tertiary bases **4a, 4b,** and **4c,** respectively, by reaction with benzenethiolate anion. We found that demethylation is strongly favoured over removal of the two unbranched alkyls, while **3c** underwent demethylation and deisopropylation to about equal extents.



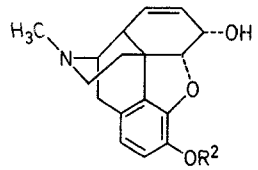
3a $R = n\text{-}C_3H_7$; $X = Br$
3b $R = n\text{-}C_4H_9$; $X = J$
3c $R = i\text{-}C_3H_7$; $X = J$



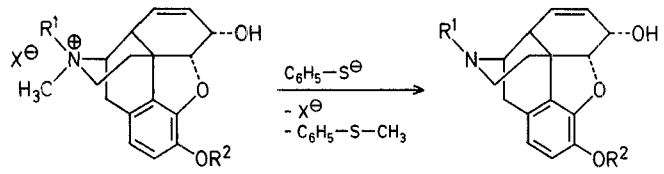
4a $R = n\text{-}C_3H_7$
4b $R = n\text{-}C_4H_9$
4c $R = i\text{-}C_3H_7$

Having found this approach successful with *N*-methylpiperidine, we applied the method to morphine **(1b),** codeine **(1d),** and thebaine **(2b).** Morphine **(1b)** was quaternized with 1-iodopropane and 1-iodobutane and the resultant compounds **5a** and **5b** were demethylated to *N*-propylnormorphine **(6a)** and *N*-butylnormorphine **(6b),** respectively, by treatment with sodium benzenethiolate. An attempt to quaternize morphine with isopropyl iodide failed. According to a report[20], even the direct alkylation of *N*-normorphine with isopropyl halide in alkaline ethanolic solution resulted only in *O*-alkylation. Codeine **(1d)** and thebaine **(2b)** were quaternized with 1-bromopropane or 1-iodopropane, 1-iodobutane, and 2-iodopropane; the resultant quaternary compounds **5c, d, e, 7a, b, c** were demethylated to *N*-propylnorcodeine **(6c),** *N*-butylnorcodeine **(6d),** *N*-isopropylnorcodeine **(6e),** *N*-propylnorthebaine **(8a),** *N*-butylnorthebaine **(8b),** and *N*-isopropylnorthebaine **(8c),** respectively (see Tables 1 and 2).

As can be seen from Table 1, thebaine **(2b)** is quaternized more rapidly than morphine **(1b)** and codeine **(1d).** It has been shown that the quaternization of morphine **(1b)** and codeine **(1d)** with alkyl halides[21,22,23] takes place predominantly by axial attack. Since 14-H in morphine and codeine is axial, this approach of the alkyl halide can give rise to considerable 1,3-steric interaction with 14-H. The rapid quaternization of thebaine is readily understandable since 14-H is absent in this alkaloid. The ease with which demethylation occurs in the case of quaternary compounds of morphine, codeine, and thebaine, may be due to release of strain by demethylation.

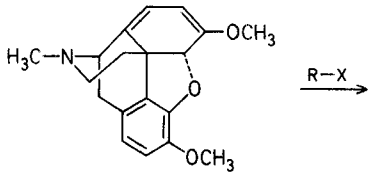


1b,d

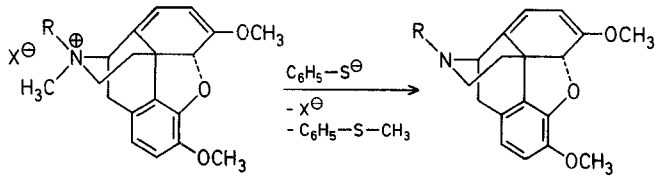


5a $R^1 = n\text{-}C_3H_7$; $R^2 = H$; X = J
5b $R^1 = n\text{-}C_4H_9$; $R^2 = H$; X = J
5c $R^1 = n\text{-}C_3H_7$; $R^2 = CH_3$; X = Br
5d $R^1 = n\text{-}C_4H_9$; $R^2 = CH_3$; X = J
5e $R^1 = i\text{-}C_3H_7$; $R^2 = CH_3$; X = J

6a $R^1 = n\text{-}C_3H_7$; $R^2 = H$
6b $R^1 = n\text{-}C_4H_9$; $R^2 = H$
6c $R^1 = n\text{-}C_3H_7$; $R^2 = CH_3$
6d $R^1 = n\text{-}C_4H_9$; $R^2 = CH_3$
6e $R^1 = i\text{-}C_3H_7$; $R^2 = CH_3$



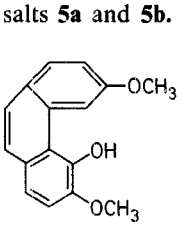
2b



7a R = $n\text{-}C_3H_7$; X = J
7b R = $n\text{-}C_4H_9$; X = J
7c R = $i\text{-}C_3H_7$; X = J

8a R = $n\text{-}C_3H_7$
8b R = $n\text{-}C_4H_9$
8c R = $i\text{-}C_3H_7$

The formation of the hitherto unknown *N*-alkylnorthebaines **8a, b, c** from the quaternized thebaine derivatives **7a, b, c** could not have been predicted to proceed with such ease since this reaction should be assumed to compete with aromatization via elimination to give thebaol[28] **(9)**. This product **(9)** is in fact observed in 40% yield together with a 40% yield of the elimination product *N*-isopropyl-*N*-methyl-2-phenylthioethanamine **(10)** in the demethylation of **7c**, the yield of the desired product **8c** still being 40%, however. The *N*-alkylnorthebaines **8a** and **8b** are obtained in higher yield (~70%), showing that demethylation competes favorably with thebaol **(9)** formation. In the demethylation of the quaternary salts **5c** and **5d**, compounds **11a** and **11b**, respectively, are obtained as by-products in 20% yields. Analogous elimination products could not be observed in the demethylation of the quaternary salts **5a** and **5b**.



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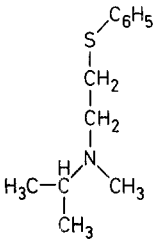

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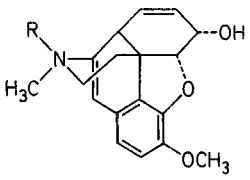

11a R = $n\text{-}C_3H_7$
11b R = $n\text{-}C_4H_9$

Quaternization of *N*-Methylpiperidine and Alkaloids 1 and 2; General Procedure:

N-Methylpiperidine is quaternized by mixing it with a slight excess of the alkyl halide in chloroform and stirring the mixture at 60°C. Morphine, codeine, and thebaine are quaternized by refluxing with a large excess of the alkyl halide in chloroform; see Table 1 for reaction times and yields. All quaternary compounds are chromatographed on neutral alumina using chloroform/methanol as eluent, and recrystallized from chloroform/methanol.

[No attempt was made to separate the diastereoisomers which may be formed in the case of morphine, codeine, and thebaine.]

Table 1. Quaternization Products **3**, **5**, and **7** prepared

Product	Reaction time [h]	Yield [%]	m.p.[a] [°C]	I.R.[b] (Nujol) ν [cm^{-1}]	^{1}H-N.M.R.[c] δ [ppm]
3a	5–6	100	250–252°		0.9 (t, 3H); 1.8 (m, 8H); 3.0 (s, 3H); 3.3 (m, 6H)
3b	5–6	100	205–207°		1.0 (br t, 3H); 1.7 (m, 10H); 3.0 (s, 3H); 3.4 (m, 6H)
3c	6–8	100	248–250°		1.5 (d, 6H); 2.0 (br m, 6H); 3.0–4.4 (m, 5H); 3.1 (s, 3H)
5a	72	60	255–258°	3300	1.0 (t, 3H); 1.6–2.4 (m, 4H); 2.9 (m, 3H); 3.2 (m, 7H); 4.2 (m, 2H); 4.8–5.8 (m, 3H); 6.6 (br s, 2H)
5b	72	60	178–180°	3300	1.0 (m, 3H); 1.4–2.2 (m, 6H); 3.0 (m, 3H); 3.4 (m, 7H); 4.3 (m, 2H); 4.9–5.8 (m, 3H); 6.6 (m, 2H)
5c	48	90	140–145°	3400	1.0 (t, 3H); 1.8–2.2 (m, 3H); 2.7 (m, 1H); 3.1 (m, 2H); 3.3–3.5 (s, 3H; m, 5H); 3.8 (s, 3H); 4.3 (m, 2H); 5.0 (br, 1H); 5.2–5.8 (m, 2H); 6.8 (q, 2H)
5d	48	90	220–223°	3400	1.0 (br t, 3H); 1.2–2.0 (m, 4H); 2.7–2.9 (m, 2H); 3.3 (m, 10H); 3.8 (s, 3H); 4.2 (m, 2H); 4.8–5.8 (m, 3H); 6.6 (q, 2H)
5e	96	60	250–252°	3400	1.5 (d, 6H); 2.1 (m, 1H); 2.6–3.0 (m, 1H); 3.2 (m, 4H); 3.5 (m, 4H); 3.9 (s, 3H); 4.4 (m, 3H); 5.0–5.9 (m, 3H); 6.8 (q, 2H)
7a	12	95	170–172°		1.1 (t, 3H); 1.7–2.2 (m, 6H); 3.4–3.7 (m, 8H); 3.6 (s, 3H); 3.8 (s, 3H); 5.0–6.2 (m, 3H); 6.7 (s, 2H)
7b	12	95	hygroscopic		1.0 (br t, 3H); 1.4–2.4 (m, 8H); 3.4–3.7 (m, 8H); 3.6 (s, 3H); 3.8 (s, 3H); 5.0–6.2 (m, 3H); 6.7 (s, 2H)
7c	12	95	196–197°		1.4 (d, 6H); 1.6–2.7 (m, 3H); 3.0 (s, 3H); 3.2 (br, 3H); 3.4 (m, 1H); 3.6 (s, 3H); 3.8 (s, 3H); 4.2 (m, 1H); 5.0–6.2 (m, 3H); 6.7 (s, 2H)

[a] Melting points were determined by using capillary melting point apparatus; they are uncorrected.

[b] All I.R. Spectra were recorded on a Perkin-Elmer 397 Spectrometer.

[c] All N.M.R. spectra were recorded on a Varian T-60 Spectrometer. TMS was used as internal standard except when D_2O was the solvent in which cases DSS was used instead. D_2O was used for **3a, 3b, 5a, 5c,** and **5e**, $CDCl_3$ for **3c, 7a,** and **7b**, DMSO-d_6 for **5b, 5d,** and **7c**.

Table 2. Products Obtained on Demethylation of Quaternary Salts **3**, **5**, and **7**

Product	Reaction time [h]	Yield [%]	b.p. [°C]/torr or m.p. [°C]	Molecular formula[a] or Lit. data	M.S. *m/e* (M^+)	I.R. ($CHCl_3$) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[b] δ [ppm]
4a	24–26	75	b.p. 148–150°/700	b.p. 152.1°[24]			0.8 (t, 3H); 1.5 (m, 8H); 2.3 (m, 6H)
4b	24–26	70	b.p. 171–173°/700	b.p. 175.8°[24]			1.0 (br t, 3H); 1.5 (m, 10H); 2.4 (m, 6H)
4c	24–26	45	b.p. 138–140°/700	b.p. 143°[25]			1.1 (d, 6H); 1.5 (m, 6H); 2.2–3.0 (m, 5H)
6a	6	55	m.p. 198–199° (hydrochloride)	m.p. 195–198°[26]	313	3400	1.0 (t, 3H); 1.3–2.3 (m, 5H); 2.3–3.2 (m, 6H); 3.4 (m, 1H); 4.2 (m, 1H); 4.8–5.7 (m, 3H); 6.5 (q, 2H)[b]
6b	6	55	m.p. 194–196°	m.p. 193–195°[20]	327	3400	1.0 (br t, 3H); 1.5 (m, 4H); 1.7–2.1 (m, 3H); 2.3–3.1 (m, 6H); 3.4 (m, 1H); 4.1 (m, 1H); 4.8–5.7 (m, 3H); 6.4 (q, 2H)[b]
6c	5–6	60	m.p. 274–276° (hydrochloride)	m.p. 276–278°[26]	327	3500	0.9 (t, 3H); 1.4 (m, 2H); 1.7–2.2 (m, 3H); 2.4–2.8 (m, 6H); 2.9, 3.2 (2br s, 1H); 3.4 (m, 1H); 3.8 (s, 3H); 4.2 (m, 1H); 4.8 (br, 1H); 4.9–5.8 (m, 2H); 6.6 (q, 2H)
6d	5–6	60	m.p. 96–98°	m.p. 100°[27]	341	3500	0.9 (br t, 3H); 1.5 (m, 4H); 1.8–2.2 (m, 3H); 2.4–2.8 (m, 6H); 2.9, 3.2 (2br s, 1H); 3.5 (m, 1H); 3.8 (s, 3H); 4.2 (m, 1H); 4.9 (br d, 1H); 5.2–5.8 (m, 2H); 6.6 (q, 2H)
6e	5–6	70	m.p. 234–236° (hydrobromide)	m.p. 237–238°[26]	327	3500	1.2 (d, 6H); 1.8–2.3 (m, 3H); 2.4–2.9 and 3.6 (m, 7H); 3.8 (s, 3H); 4.2 (m, 1H); 4.8–5.8 (m, 3H); 6.6 (q, 2H)
8a	6	70	m.p. 138–140°	$C_{21}H_{25}NO_3$ (339.4)	339		1.0 (t, 3H); 1.3–2.0 (m, 4H); 2.1–3.3 (m, 6H); 3.5–3.8 (m, 1H); 3.7 (s, 3H); 3.9 (s, 3H); 5.0 (d, 1H); 5.3 (s, 1H); 5.6 (d, 1H); 6.7 (s, 2H)
8b	6	70	m.p. 78–79°	$C_{22}H_{27}NO_3$ (353.4)	353		0.9 (br t, 3H); 1.1–1.7 (m, 4H); 1.8–2.3 (m, 2H); 2.4–3.4, 3.7 (m, 7H); 3.6 (s, 3H); 3.8 (s, 3H); 5.0 (d, 1H); 5.3 (s, 1H); 5.6 (d, 1H); 6.6 (s, 2H)
8c	6–8	40	m.p. 120–123°	$C_{21}H_{25}NO_3$ (339.4)	339		1.2 (d, 6H); 1.8–2.6 (m, 2H); 2.7–3.4 (m, 5H); 3.6 (s, 3H); 3.8 (s, 3H); 4.0 (m, 1H); 5.0 (d, 1H); 5.3 (s, 1H); 5.6 (d, 1H); 6.6 (s, 2H)
10	5–6	40	b.p. 145–150°/30	$C_{12}H_{19}NS$ (209.3)	209		1.0 (d, 6H); 2.2 (s, 3H); 2.5–3.9 (m, 5H); 7.3 (m, 5H)
11a	5–6	20	gum	$C_{21}H_{27}NO_3$ (341.4)	341	3450	0.9 (t, 3H); 1.2–1.6 (m, 2H); 1.8–2.1 (m, 2H); 2.2 (s, 3H); 2.4 (m, 4H); 3.0 (m, 2H); 3.8 (s, 3H); 4.3 (m, 1H); 5.2–5.4 (m, 2H); 5.7–6.5 (m, 3H); 6.6 (s, 2H)
11b	5–6	20	gum	$C_{22}H_{29}NO_3$ (355.5)	355	3450	0.9 (br t, 3H); 1.4 (m, 4H); 1.8–2.1 (m, 2H); 2.2 (s, 3H); 2.3–3.0 (m, 6H); 3.8 (s, 3H); 4.2 (m, 1H); 5.2–5.4 (m, 2H); 5.7–6.4 (m, 3H); 6.6 (s, 2H)

[a] Satisfactory microanalyses obtained: C, ±0.32; H, ±0.20; N, ±0.31. [b] DMSO-d_6 was used for **6a** and **6b**.

Table 3. Conditions of T.L.C. of Products **6**, **8**, **10**, and **11**

Compound	T.L.C. Solvent System	R_f
6a, 6c, 6d, 11a, 11b, 6e, 8a	ethyl acetate / methanol / aq. ammonia (85 / 15 / 1)	0.45, 0.70, 0.71, 0.59, 0.55, 0.48, 0.63
6b	ethyl acetate / methanol / aq. ammonia (85 / 15 / 7)	0.60
8b	4% methanol in chloroform	0.70
8c, 10	ethyl acetate / aq. ammonia (100 / 0.3)	0.37, 0.59

Demethylation of the Quaternary Compounds 3, 5, and 7; General Procedure:

A mixture of the quaternary compound (0.6 mmol), sodium benzenethiolate (0.238 g, 1.8 mmol), and butanone/acetonitrile (1/1; 20 ml) is refluxed with stirring under dry nitrogen; for reaction times, see Table 2. The solvent is evaporated under reduced pressure, the residue is dried in vacuo, and water (15 ml) is added. The product is extracted with chloroform (3 × 150 ml) and with 5% methanol in chloroform (150 ml). After evaporation of the solvent, the product is purified by T.L.C. (silica Gel G); see Table 3 for solvent systems or chromatographed on neutral alumina, using chloroform/methanol as eluent.

The demethylation products **4** of the *N*-alkyl-*N*-methylpiperidinium salts **3** are purified in the usual manner by extracting with 10% hydrochloric acid and liberating the amine with aqueous 50% sodium hydroxide. The amine is distilled at atmospheric pressure.

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