1- AND 2-CHLOROMORPHINE. HALOGENATION OF MORPHINE META TO THE FREE PHENOLIC HYDROXYL GROUP.

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Abstract - Treatment of morphine in aqueous HCl at 70° with KIO_3 yields a monochloromorphine, identified as 1-chloromorphine by spectroscopic means and by the fact that it, and its methyl ether 1-chlorocodeine, are different from 2-chloromorphine and 2-chlorocodeine prepared from 2-aminomorphine of unequivocally established structure. Formation of 1-chloromorphine and the previously known 1-bromomorphine involves entry of the halogen into the position meta to the free phenolic hydroxyl. Possible mechanistic interpretations of this unusual orientation are discussed.

The chemistry of morphine (1) and its congeners has been studied extensively for almost 100 years. It is striking, however, that, to the best of our knowledge, no chloromorphine carrying the halogen on the aromatic ring has been reported to date. We wish to describe the preparation of both possible isomers of this type and the unusual orientation involved in the halogenation of (1).

The reaction of (1) with iodic acid was first observed as early as 1830,[1a] and has been used for titrimetric assay,[1b] but the chemistry of the underlying reaction(s) appears not to have been studied. We have now found that treatment of (1) in aqueous hydrochloric acid with one equivalent of KIO_3 produces small amounts of a compound, mp 240-244°C (dec.), which has been characterized by spectroscopic techniques as a monochloromorphine (2) substituted in the aromatic ring. The initial low yield of (2) is improved to >50% by dilution of the reaction mixture with about 3

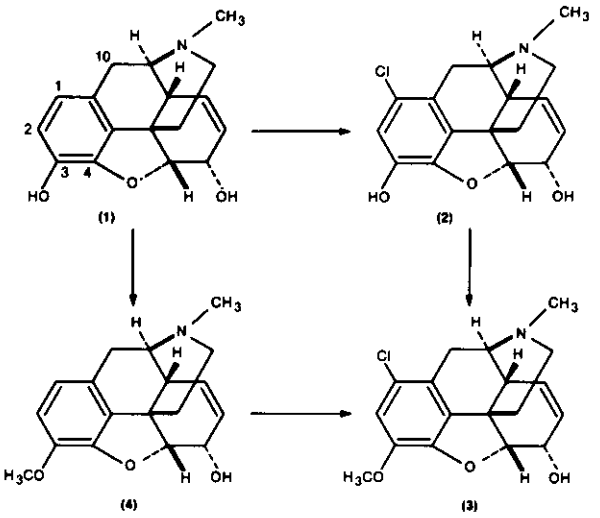
vols. of acetone, and by working at higher temperature (70-75°). The effect of acetone was found empirically; we have no explanation for it. The yield of isolated product is probably a minimum; no attempt to maximize it has been made so far.

The identification of (2) as a monochloromorphine rests on the mass-spectrometric (C.I.) molecular weight (NH_3 as carrier gas): $(M+1)^+$ 320 and 322; calc'd. for $C_{17}H_{18}NO_3Cl$, 319 and 321; the ratio of the observed peak heights is close to the one expected from the known relative abundances of the chlorine isotopes. The identification is confirmed by elemental analysis and by the nmr spectrum, which closely resembles that of (1) except for the changes in the aromatic region showing that the chlorine is located in this part of the molecule. Compound (2) is remarkably insoluble in the common organic solvents including even pyridine. It is, however, soluble enough in DMSO for an acceptable spectrum to be obtained, but detailed nmr studies were carried out on the chloroform-soluble methyl ether of (2).

Methylation of (2) with diazomethane gave a methyl ether identical in every respect with a sample of the known[2] monochlorocodeine (3), prepared according to the method of Speyer and Rosenfeld[2b] by treatment of codeine (4) hydrochloride in 30% aqueous formic acid with H_2O_2. Mp and mixed mp 175-176°C (lit.[2] 175-176°); ir and nmr spectra identical. The nmr spectrum resembles that of (4) except for the replacement of the AB quartet (2H), δ 6.55 and 6.66, caused by the aromatic protons of (4),[3,4] by a singlet (1H), δ 6.68. In addition, the doublet (1H) produced[3] by the 10ß-proton of (4) is significantly shifted upfield in the spectrum of (3), a shift, undoubtedly ascribable to the influence of the chlorine upon this benzylic proton, which will be discussed later. In all other respects, the spectra of (3) and (4) are almost identical (see Figure 1), proving that no change other than replacement of one of the aromatic protons by chlorine has taken place in the formation of (2) and (3) from (1).

The new compound (2) and its previously known methyl ether (3) clearly must be the 1- or 2-chloro derivatives of (1) and (4), respectively. Speyer and Rosenfeld[2b] left the question of the location of the chlorine atom open, and we are not aware of any subsequent research bearing on this point. However, the analogous bromination of (1)[5] and (4)[2] by action of H_2O_2 on their hydrobromides has been unequivocally shown to produce the 1-bromo compounds (5) and (6), respectively. Compound (6) can also be made by direct bromination of (4).[2a,7] The proof of the constitution of (6) was furnished by Small and Turnbull,[6] who converted this compound through standard degradative reactions into 1-bromo-3,4-dimethoxyphenanthrene (1-bromodimethylmorphol) (7), which was identical with a sample prepared by straightforward synthesis and different from the synthetic isomer with the bromine in position 2.

On bromination of (1) hydrobromide by action of H_2O_2, Morel et al.[5] had obtained a crystalline hydrobromide of a monobromomorphine, but had not made the corresponding base or commented



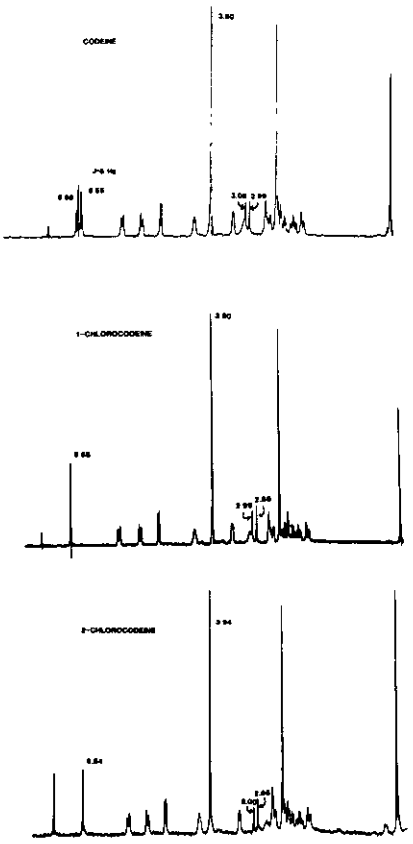
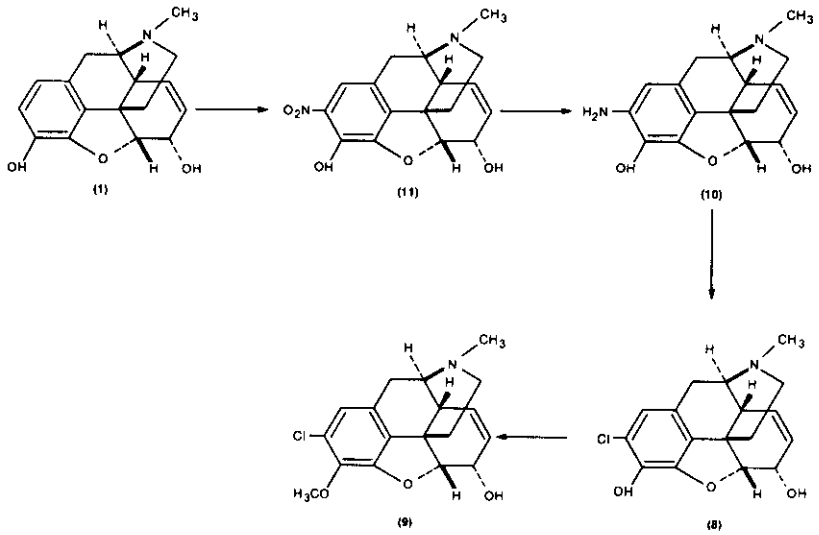


Figure 1. 220 kHz Spectra of Codeine and the Two Chlorocodeines in $CDCl_3$.

upon the structure of their salt. This salt was subsequently shown by Ochiai and Nakamura[8] to be the hydrobromide of 1-bromomorphine (5) through conversion into (6), identical with authentic material.

During the bromination of (1) in HBr by H_2O_2, the bromine is thus directed to position 1, meta to the free phenolic hydroxyl, rather than to the available ortho-position 2, as would have been anticipated. It seemed probable that our chlorination of morphine in aqueous HCl by KIO_3 could take an analogous course. This expectation was shown to be correct by preparation of the hitherto unknown authentic 2-chloromorphine (8) and 2-chlorocodeine (9) from 2-aminomorphine (10) of known structure, and proof that these two compounds are different from (2) and (3), respectively.



2-Aminomorphine (10) has been prepared from the 2-nitromorphine (11) of Wieland and Kappelmeier[9] by reduction with Sn/HCl,[9] electrolytically[8] or, recently, with formamidine sulfinic acid.[10] Compound (11) is formed on action of nitrous fumes on (1); it had initially been interpreted[9] as the 2-nitroso derivative of (1), but was later shown[8,11] to be 2-nitromorphine. Its structure, crucial for the identification of (2) as 1-chloromorphine, is established by the following facts:

(A) 2-Nitrocodeine (12), from (11) and diazomethane,[8] is different from the 1-nitrocodeine (13) obtained on direct nitration of (4).[2a,12] This nitrocodeine (13) has been converted to 1-bromocodeine, (6), through reduction to 1-aminocodeine (14) and subsequent Sandmeyer reaction.[8] The structure of this series is thus securely established on the basis of Small and Turnbull's

proof[6] of the constitution of (6). The 2-aminocodeine (15) prepared by reduction of (12) differs[8] from the above 1-aminocodeine (14); the bromocodeine (16) obtained from it is similarly different from (6). The two nitrocodeines, (12) and (13), are thus different and form different series of transformation products, of which the one derived from 1-nitrocodeine (13) is identified as the 1-substituted series by the identity of its brominated member with (6). These interrelationships are shown in Scheme I.

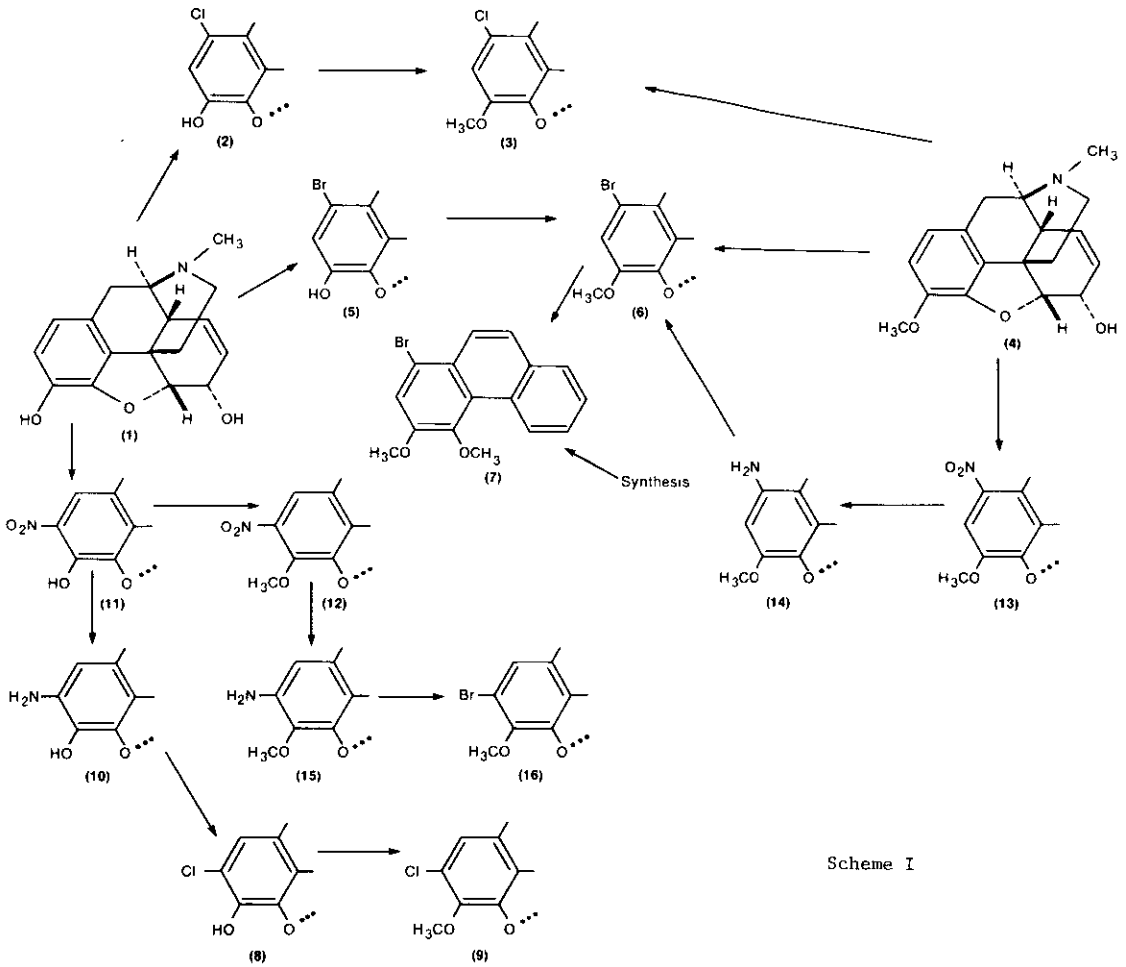
(B) The aminomorphine (10) of Wieland and Kappelmeier, on diazotization in alcoholic solution with ethyl nitrite, followed by addition of alcoholic HCl, produces[9] a yellow hydrochloride interpreted as the salt of an "o-diazophenol anhydride." Compounds of this type (also referred to as diazooxides or quinone diazides) can form only from ortho- and para-, but not from meta-aminophenols.[13]

(C) The infrared spectrum of (11) suggests[11b] the presence of intramolecular hydrogen bonding between the phenolic hydroxyl and the nitro group.

For the purpose of our preparation of 2-chloromorphine (8), a sample of 2-aminomorphine (10) was made by reduction of (11) with formamidine sulfinic acid.[10] The compound was converted into (8) by a novel technique of diazotization in ice-cold concentrated HCl and subsequent uv irradiation.[14] The resulting (8), mp 175-182°C, with diazomethane gave 2-chlorocodeine (9), mp 145-146°C; the mixed mp with authentic 1-chlorocodeine (3) of mp 174-176°C was depressed to ∿122-133°C. The two isomeric chlorocodeines, (3) and (9), were cleanly separated by TLC on silica gel, 5% methanol in chloroform as solvent; (3), R_f 0.26; (9), R_f 0.22.

The fact that these transformations of (10) have indeed achieved the desired goal of replacement of the amino group by chlorine, without changes elsewhere in the molecule, is established by the 220 kHz nmr spectrum of (9), which is very similar to those of (3) and (4), as expected; see Fig. 1. Again, a singlet (1H) replaces the AB quartet of the aromatic protons of (4). In addition, the signal from the methoxyl protons of (9) is significantly shifted downfield from its position in both (3) and (4): δ 3.94 vs 3.83 (lit.[3] 3.84 $\pm$ 1). This shift, undoubtedly caused by the neighboring chlorine atom, constitutes further evidence for the fact that (9) is indeed 2-chlorocodeine, and hence (3) the 1-isomer.

Supporting evidence for this structural assignment was obtained from an investigation of the effect of the chlorine on the spectrophotometrically measured acidities of the phenolic hydroxyls in (2) and (8). The observed pK_a values of 8.1, 7.4 and 9.1 for (2), (8) and (1), respectively, clearly show the greater effect on the acidity produced by the chlorine in the ortho-position in (8); cf. phenol, pK_a 9.99, ortho-chlorophenol, pK_a 8.56, meta-chlorophenol, pK_a 9.12.[15] The spectrophotometric values are based on the absorption spectra of the samples in the completely protonated form (pH 4.68), as the anions in 0.2 N NaOH, and at intermediate pH values;


Cl
HO
O
(2)
Cl
H3CO
O
(3)
CH3
N
H
H
HO
O
H
OH
(1)
Br
HO
O
(5)
Br
H3CO
O
(6)
Br
H3CO
OCH3
(7)
Synthesis
CH3
N
H
H
H3CO
O
H
OH
(4)
O2N
HO
O
(11)
O2N
H3CO
O
(12)
H2N
H3CO
O
(14)
O2N
H3CO
O
(13)
H2N
HO
O
(10)
H2N
H3CO
O
(15)
Br
H3CO
O
(16)
Cl
HO
O
(8)
Cl
H3CO
O
(9)

Scheme I

see Experimental. No attempts were made to correct for the influence of the protonated amine on the acidity of the phenol.

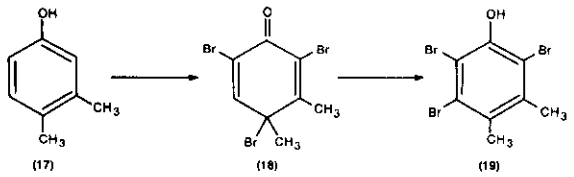
From the foregoing, it is clear that halogenation of (1) and (4) by treatment of their solutions in aqueous HCl or HBr with oxidizing agents (KIO_3, $KClO_3$, H_2O_2), as well as straightforward bromination of (4) with bromine water, invariably produce compounds carrying the halogen in position 1 rather than 2. This orientation is unexceptional in the case of (4), where the location of the halogen would be determined by competition of the directing influences of the two ether oxygens in positions 3 and 4. However, in the case of morphine, the free phenol, this halogenation represents a violation of the classical rules for electrophilic aromatic substitution, since it involves attachment of the substituent para to the ether oxygen, and hence in meta to the phenolic hydroxyl, which should of course have the vastly superior ortho-para directing power; substitution in position 2 should thus be the normal course of the reaction. It is of interest to note the contrast between these anomalous halogenations and the perfectly normal formation of (11) on nitration of (1).

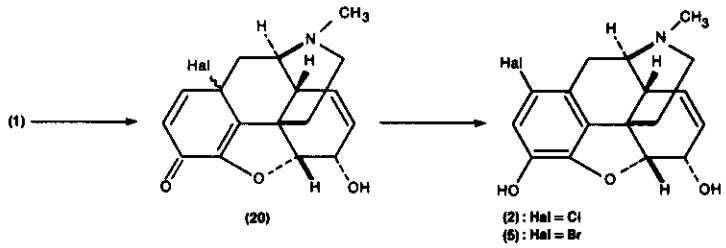
Surprisingly, this unusual contravention of well-proved rules, although long known in the case of the bromination of morphine,[5,6] has, to the best of our knowledge, not produced any published comment, except for a brief discussion[8] which attempts to interpret the anomaly on the basis of a Mills-Nixon effect. Any satisfactory mechanism should explain the anomalous meta-halogenations and, if possible, the difference in orientation of the substitution by the halogens and the nitro group.[16]

Electrophilic halogenations meta to a free phenolic hydroxyl have been observed in a number of cases (see ref. 17 and literature quoted there), but the mechanisms of such reactions seem to have been studied little until quite recently. Among possible interpretations of the formation of (2) and (5), the sequence shown in Scheme II is the one most closely supported by mechanistic studies[17,18] of the halogenation of simple phenols. For instance, the introduction of bromine into position 5 of 3,4-dimethylphenol, (17), has been shown by de la Mare and coworkers[17] to proceed by way of the 2,5-dienone (18), which can be isolated, and which re-aromatizes to (19) by an acid-catalyzed 1,2-shift of the bromine on carbon 4 into the position meta to the phenolic hydroxyl. It has been established[17] that in the formation of (18), normal ortho-bromination in positions 2 and 6 occurs fast, the ipso-bromination at C-4 taking place more slowly. For the halogenation of morphine in acidic solution, a similar sequence via the dienone (20), with subsequent H^+-catalyzed re-aromatization to (2) or (5), respectively, can easily be written (Scheme II), but analogy to the case of (17) would suggest that, also in (1), normal ortho-halogenation should precede the ipso-halogenation to the dienone (20); if so, formation of 1,2-dihalo compounds, rather than of (2) or (5), would be expected. However, a recent study of the chlorination of

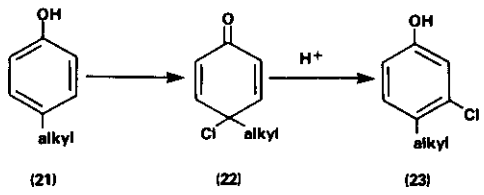
p-alkylphenols (21) (alkyl = methyl, ethyl, isopropyl, t-butyl) by Fischer and Henderson[18a] has shown that substantial yields of 4-alkyl-4-chloro-2,5-cyclohexadienones (22) can be obtained, and that "attack at a substituted para-position is competitive with attack at unsubstituted ortho-position."[18a] Furthermore, the dienones so obtained are rearranged[18b] to the corresponding 4-alkyl-3-chlorophenols (23) in almost quantitative yield by trichloromethanesulfonic acid at 35°C.

These observations nicely explain the formation of (2) and (5) by the sequence shown in Scheme II. In addition, this interpretation also seems capable of accounting for the different results of halogenation and nitration of (1). Aromatic nitration by ipso-attack is well known.[19] In the case of 4-alkyl-4-nitro-2,5-cyclohexadienones, however, the very ready aromatization, even under non-acidic conditions, does not proceed by 1,2-migration and does not yield any 3-nitrophenols, but produces 2-nitrophenols by other mechanisms (see ref. 18b, and literature quoted there).





Scheme II



In this connection, it is also of interest to note that the reaction of Wieland and Kappelmeier[9] generates, in addition to a yield of ∿60-65% of the nitrate salt of 11, the nitrate (∿20%) of another, very unstable base, "morphine quinitrol," interpreted by the authors as a 2,4-cyclohexadienone arising through ipso-attack at position 4 of the morphine skeleton; however, the published evidence does not seem to exclude the alternative structure of a 2,5-dienone arising through ipso-attack para to the phenolic hydroxyl.

Additional experiments are in progress which are designed to determine the structural parameters and reaction conditions that are significant in directing the halogenation of (1) into the meta-position.

EXPERIMENTAL

1-Chloromorphine (2). In a typical experiment, a solution of morphine (1) (3.56 g, 0.0125 mol) in concentrated hydrochloric acid (28 ml) was mixed with an aqueous solution of potassium iodate (2.67 g, 0.0125 mol) in water (22 ml). The mixture was diluted with acetone (150 ml) and heated with stirring at 70-75° for 20 hrs. After this time, the acetone was distilled off and the remaining aqueous solution was extracted with chloroform (2 x 40 ml). The chloroform extract was discarded. The aqueous layer on cooling deposited the hydrochloride of (2). For conversion to the free base, an aqueous solution of this salt was adjusted to pH 7-8 with ammonia. This resulting precipitate was filtered off and dried. Recrystallization from pyridine gave 1.8 g of (2), mp 240°C (decomp.), whose TLC indicated that no detectable amount of the isomeric 2-chloromorphine (8) is present in the reaction mixture. Calcd. for $C_{17}H_{18}NO_3Cl \cdot 1/2\ H_2O$: C, 62.10; H, 5.83; N, 4.26; Cl, 10.78%. Found: C, 61.90; H, 6.21; N, 4.30; Cl, 10.32%.

1-Chlorocodeine (3). This compound was prepared by methylation of (1) with diazomethane in methanol - ether (1:1) in the usual manner. It proved to be identical with authentic (3)[2b] in every respect: mp and mixed mp 175-176°C, ir and nmr spectra identical. The nmr spectrum of (3) is shown in Figure 1.

2-Chloromorphine (8). A solution of 600 mg (2 mmol) of 2-aminomorphine (10)[9,10] in conc. hydrochloric acid (2 ml) was stirred and cooled to 0°. To this was added in portions, below the surface of the liquid, a solution of 160 mg (2.3 mmol) of sodium nitrite in water (2 ml). The solution was kept at 4° overnight; it was next irradiated in a quartz tube held next to a quartz immersion well (Hanovia 450 watt mercury lamp, Corex filter) for 3 hr, after which time the original diazonium chromophore (λ_{max} 312 nm, ε 4840) had completely disappeared. The solution was chilled in a dry ice - acetone bath and adjusted to pH 7 (pH indicator paper) with concentrated sodium hydroxide. The water was evaporated and the residual salts were extracted three times with hot ethanol. The combined extracts were evaporated to give a dark residue which was chromatographed

on silica gel using 10% methanol/chloroform (1 L), followed by 15% methanol/chloroform (1 L). On evaporation of the solvent, 2-chloromorphine (8) was obtained as off-white crystals. Yield, 450 mg (68%). The base was recrystallized from methanol, yielding white crystals of mp 175-182° after darkening from 165°. Calcd. for $C_{17}H_{18}NO_3Cl \cdot 1/4\ H_2O$: C, 62.96, H, 5.75; N, 4.32; Cl, 10.93%. Found: C, 62.62; H, 5.81; N, 4.56; Cl, 10.86%.

2-Chlorocodeine (9). 2-Chloromorphine (8) (200 mg, 0.63 mmol) in methanol (20 ml) was treated dropwise with ethereal diazomethane (generated from N-methyl-N'-nitro-N-nitrosoguanidine) until TLC (silica gel, 10% methanol in chloroform) showed the complete disappearance of the starting material. Evaporation of the solvent left a residue (217 mg) of chromatographically homogeneous, crystalline (9); yield, 100%. Recrystallization from water gave 125 mg as off-white crystals of mp 140-142°C. A second crystallization produced white crystals of mp 145-146°C. The nmr spectrum of (9) is shown in Fig. 1. Calcd. for $C_{18}H_{20}NO_3Cl$: C, 64,76; H, 6.04; N, 4.20; Cl, 10.63%. Found: C, 65.03; H, 5.98; N, 4.25; Cl, 10.48%.

Determination of pK_a. The uv spectra of the chloromorphines, (2) and (8), as the free phenols and phenolate anions are given in Table I. Aliquots of the stock solutions of (1) (40 µl), (2) (40 µl) and (8) (100 µl) were added to 0.05 M phosphate buffer (3.0 ml), and the degree of ionization as a function of pH was determined from the optical density at 301 nm. Three or more determinations at intermediate pH values were made. The pK_a values obtained agreed within ± 0.1 pH unit.

Table I

Compound	Solvent	λ_{max}, nm	ε
(1)	acetate buffer, pH 4.7	285	1541
(1)	0.2 N NaOH	298	2825
(2)	acetate buffer, pH 4.7	280	2300
(2)	0.2 N NaOH	302	3600
(8)	acetate buffer, pH 4.7	288	1500
(8)	0.2 N NaOH	301	3600

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