JOC Notes

Decoration of the Aromatic Ring of Dihydrocodeinone (Hydrocodone) and 14-Hydroxydihydrocodeinone (Oxycodone)

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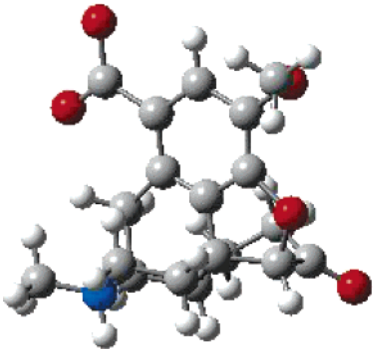

Improved protocols for the preparation of 1-bromodihydrocodeinone (1-bromohydrocodone) and 1-bromo-14-hydroxydihydrocodeinone (1-bromooxycodone) and synthesis of the corresponding 1-chloro and 1-iodo derivatives have been achieved using the corresponding *N*-halosuccinimides in acidic milieu. The corresponding 1-carboethoxy derivative of 14-hydroxydihydrocodeinone (1-carboethoxyoxycodone) has been prepared by Pd-catalyzed reaction with carbon monoxide in ethanol. The ester was hydrolyzed to the corresponding zwitterionic amino acid.

Well before the proof of the structure of morphine, **1**, through total synthesis,[1] and even before the proposal defining its (nearly) correct structure,[2] it was clear that an aromatic ring was present in the alkaloids isolated from *Papaver* spp.,[3] and significant efforts to elucidate the products of electrophilic aromatic substitution[4] were undertaken.

Thus, 1-chloro, 1-bromo, and 1-nitrocodeine had been prepared and characterized as early as 1851.[5a−c] Shortly thereafter, the 1-sulfonic acids of both morphine **1** and codeine **2** were in hand, and 1-nitrocodeine was reduced to the 1-amino derivative, which was then diazotized and converted to the corresponding phenol.[6]

More recently, modified methods for bromination and chlorination of these and related bases have appeared,[7] and reports of chloromethylation,[8] formylation,[9] and aminomethylation,[10] all at C-1 and diazocoupling[11] at C-2 have been published. Further, in this vein, initial use of palladium catalysis[12] has been effected to convert 6-OH silyl-protected 1-bromocodeine to C-1 derivatives and the similarly protected trifluoromethanesulfonate derivative of morphine to C-3 derivatives.[13]

Recognizing that the vagaries of Pd-catalyzed aryl alkylation and acylation processes are often a function of halide (as well as specific catalyst), we report here an improved process for the bromination of dihydrocodeinone (hydrocodone) **3** and 14-hydroxydihydrocodeinone (oxycodone) **4** to produce the corresponding 1-bromo derivatives as well as the production of the corresponding iodides[14] and the chloride of 14-hydroxydihydrocodeinone (oxycodone) **4**, using the appropriate *N*-halosuccinimides. We also report the palladium chloride ($PdCl_2$)-catalyzed coupling of these aryl halides to carbon monoxide in the presence of ethanol to produce the 1-carboethoxy derivatives **5**. The latter, in the case of the 1-carboethoxy ethyl ester of 14-hydroxydihydrocodeinone (oxycodone) **4**, has been hydrolyzed to the corresponding zwitterion **6**.

The general methods[5,15] for the bromination of the aromatic ring of codeine **2**, such as using Br_2 or combinations of NaBr and oxidants, proved unsatisfactory for 14-hydroxydihydrocodeinone (oxycodone) **4** and dihydrocodeinone (hydrocodonone) **3**. However, encouraged by reports[16,17] of successful aryl halogenation with *N*-halo-

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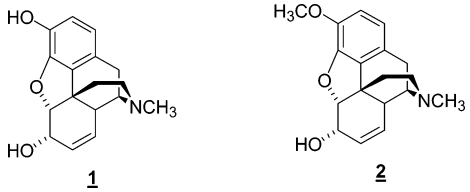
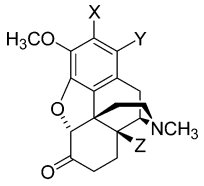
TABLE 1. Results of Bromination of 14-Hydroxydihydrocodeinone (Oxycodone), 4 (R = OH, X = H), with NBS in Dilute Aqueous Acid[a,b]

ratio of NBS to oxycodone (**4**)[c]	% conv of **4** to **7** and **8** at room temp/12 h[d]	% 1,2-di-dibromide, **7** at 12 h[e]
0.5	42	0
1.0	100	0
1.5	100	34
2.0	100	50
2.5	100	83
3.0	100	100

[a] The results shown are for the reaction carried out in 0.1 N TFA. [b] Similar results can also be obtained in, among others, 0.1 N H_2SO_4, HBr, HCl, HNO_3, and $HClO_4$. [c] The reactions were carried out on a millimolar scale. [d] Calculated by measurement of the integrated signals at $\delta = 6.87$ ppm (s) for the product and the aromatic AB quartet centered around $\delta = 6.65$ ppm (q) for the starting material in the ^{1}H NMR spectrum of the reaction mixture. The monobromide **8** and the dibromide **7** are the only detected products. Subtraction of the reported yield of dibromide provides the yield of monobromide. [e] Calculated by measurement of the integrated signals for the methoxy (CH_3O-) protons $\delta = 3.84$ ppm (s) for the monobromide and $\delta = 4.11$ ppm (s) for the dibromide in the ^{1}H NMR spectrum of the reaction mixture.

succinimides under acidic conditions, we found that the reported method could be developed (Table 1) for these compounds. Interestingly, as shown in the table the previously unknown 1,2-dibromide **7** was readily obtained, and indeed, production of monobromide **8** to the exclusion of the dibromo isomer **7** was attained by careful adjustment of equivalents of *N*-bromosuccinimide (NBS). The same was true for the corresponding 1-bromodihydrocodeinone **9** (data not shown). Interestingly, and





3 - **12**

in contrast to other bromination methods,[5,15] the reactions with NBS clearly avoided halogenation at nonaromatic positions. As shown in Table 2, conditions could also be optimized for the formation of the corresponding iodo derivative, 1-iodo-14-hydroxydihydrocodeinone (1-iodooxycodone) **10**, by using *N*-iodosuccinimide[18] (NIS) in place of NBS. The reaction with NIS was much more easily selective for monohalogenation, and it could routinely be effected so as to produce the iodide **10** in purified (recrystallized) yields of greater than 85%. Further, although not examined in detail, it appears that the extent of ionization of the acid utilized in the reaction is important. That is, for example, trifluoroacetic acid (TFA) is superior to acetic acid. Indeed, the same procedure could also be utilized for the formation of 1-iododihydrocodeinone (1-iodohydrocodone) **11** from dihydrocodeinone (hydrocodone) **3**.

Interestingly, reaction of 14-hydroxydihydrocodeinone (oxycodone) **4** with *N*-chlorosuccinimide (NCS) could also be effected, but only at elevated temperature. The ^{1}H NMR spectrum of crude reaction products using 3 or more equivalents of NCS had peaks consistent with some dichlorination of the aromatic ring, that is, singlets at $\delta = 4.13$ and 4.72 ppm as well as peaks for the monochloro product (see Experimental Section). There is also a suggestion (an appearance in the crude material of a doublet of doublets at approximately $\delta = 5.23$ ppm) that a trace of a 7-chloro product may be present.

TABLE 2. Results of Iodination of 14-Hydroxydihydrocodeinone (Oxycodone), 4, with NIS in Dilute Aqueous Acid[a,b]

ratio of NIS to oxycodone[c]	% reaction of **4**at room temp at 1 h[d–f]
0.24	12
0.36	21
0.56	37
0.84	63
1.08	96
1.57	ca. 100
2.24	ca. 100
2.71	ca. 100
3.22	ca. 100
4.01	ca. 100

[a] The results shown are for the reaction carried out in 0.1 N TFA. [b] Similar results can also be obtained in, among others, 0.1 N H_2SO_4, HNO_3, and $HClO_4$. Neither HBr nor HCl gave complete conversion after 60 min, with the former yielding only 7% *of the corresponding 1-bromo-derivative* and the latter only 50% of the iodide conversion under the standard conditions used. [c] The reactions were carried out on a millimolar scale. [d] The reaction time of 1 h was chosen based upon a separate study using 5% molar excess NIS in 0.1 N H_2SO_4 and measuring conversion as a function of time. The amount of product formed did not increase after 60 min. [e] Calculated by measurement of the integrated signals of the ^{1}H NMR spectrum of the reaction mixture at $\delta = 7.10$ ppm (s) for the reaction product and the aromatic AB quartet centered around $\delta = 6.65$ ppm (q) for the starting material. [f] In contrast to the results found for NBS bromination (Table 1), no evidence for dihalogenation could be adduced.

TABLE 3. Morphinone Compounds in This Study

compound * = new compound	X	Y	Z
3	H	H	H
4	H	H	OH
5 *	H	CO_2Et	OH
6 *	H	CO_2H	OH
7 *	Br	Br	OH
8	H	Br	OH
9	H	Br	H
10 *	H	I	OH
11 *	H	I	H
12 *	H	Cl	OH

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Both 1-bromo-14-hydroxydihydrocodeinone (1-bromooxycodone), **8**, and 1-iodo-14-hydroxydihydrocodeinone (1-iodooxycodone), **10**, could be converted to the corresponding carboethoxy derivative with carbon monoxide (CO) in ethanol in the presence of palladium(II) chloride and triphenylphosphine.[13] However, under the same experimental conditions, the iodide **10** produced higher yields of the 1-carboethoxy-14-hydroxydihydrocodeinone (1-carboethoxyoxycodone) **5** than did the bromide **8**, as the latter failed to react completely under conditions satisfactory for the former.

Hydrolysis of the 1-carboethoxy derivative **5** in aqueous methanolic potassium hydroxide followed by back-titration to a pH ca. 6.3 with dilute (0.1 N) HCl and removal of the solvent mixture at reduced pressure resulted in crystallization of the zwitterion, **6**.[18]

The structures proposed for the carbonylated products were confirmed by determination of the X-ray structure of these readily crystallized materials. While there were no unusual structural features found, we were able to determine that **6** is a dihydrate and that the substitution patterns of **5** and **6** are correctly presented, without resorting to, in this case, the negative inference of nOe experiments.

In part because of the paucity of methods for their production, aromatic ring-substituted morphinans have not been extensively tested for opiate activity. We show here that they are accessible, and we conclude that their preparation with palladium catalysis can be affected despite electron-donating substituents on that ring. The morphinones that were prepared in this study are found in Table 3.

Experimental Section

1-Iodo-14-hydroxydihydrocodeinone (1-Iodooxycodone) 10. With stirring, at room temperature, 14-hydroxydihydrocodeinone (oxycodone) **2** (R = OH, X = H), 300 mg (0.95 mmol), was dissolved in H_2SO_4 (0.1 N, 50 mL), and *N*-iodosuccinimide[19] (250 mg, 1.11 mmol) was added in one portion. The reaction mixture was stirred until TLC indicated the starting material (R_f = 0.45) had been consumed, and the mixture was then poured into a separatory funnel containing dichloromethane (50 mL). Sufficient aqueous sodium hydroxide (10%) solution was added to raise the pH of the aqueous layer to ca. 10, the organic layer was separated, and the aqueous layer was extracted further with three portions of 90:10 dichloromethane−methanol (25 mL). The organic extracts were combined and dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure. The residue was taken up in 10:90 methanol−dichloromethane and filtered through a plug of silica gel, after which the solvent was removed at reduced pressure and the residue crystallized from a 20% solution in hot methanol to give 1-iodo-14-hydroxydihydro-codeinone (1-idooxycodone) **10** (380 mg, 86% of theory, mp 158−162 °C). ^{1}H NMR δ 7.10 (s, 1H), 4.66 (s, 1H), 3.87 (s, 3H), 2.41(s, 3H), 1.50−3.05 (m, 12H); ^{13}C NMR δ 208.2, 146.0, 144.4, 130.4, 128.7, 123.8, 90.7, 86.4, 70.4, 65.1, 57.1, 50.8, 45.3, 43.0, 36.6, 30.8, 31.6, 28.0; IR (KBr) C=O, 1730.5 cm^{-1}; calcd for $C_{18}H_{20}NO_4I$: C, 48.99; H, 4.57; N, 3.174. Found: C, 48.90; H, 4.70; N, 3.21.

1-Iododihydrocodeinone (1-Iodohydrocodone). 11 was obtained from dihydrocodeinone (hydrocodone) **3** following the procedure for 1-iodo-14-hydroxydihydrocodeinone (1-iodooxycodone) **10** given above in 97% yield, mp 209−214 °C. ^{1}H NMR δ 7.11 (s, 1H), 4.66 (s, 1H), 3.87 (s, 3H), 2.42 (s,3H), 1.17−3.3 (m, 13H, alphatic); ^{13}C NMR δ 207.6, 146.3, 144.3, 129.9, 128.7, 123.4, 91.7, 87.1, 59.9, 57.1, 48.0, 46.8, 43.2, 42.7, 40.4, 35.7, 26.0, 25.7; IR (KBr) C=O, 1722.1 cm^{-1}; exact mass (M + Na$^+$) calcd for $C_{18}H_{20}N0_3I$ (Na): 448.0386; found: 448.0374.

1-Bromo-14-hydroxydihydrocodeinone (1-Bromoxycodone) 8. The procedure for preparation of 1-iodo-14-hydroxydihydrocodeinone (1-iodooxycodone) **10** described above was followed with the substitution of NBS for the NIS used there. mp 179−181 °C (lit.[5b] 181−185 °C). IR (KBr) C=O 1728.0 cm^{-1}; exact mass (M + Na$^+$) calcd for $C_{18}H_{20}NO_4Br$ (^{79}Br): 416.0474; found: 416.0476 and (^{81}Br) 418.0453, found: 418.0465; C, 54.84; H, 5.11; N, 3.55. Found: C, 54.82; H, 5.26; N, 3.58.

1-Bromodihydrocodeinone (1-Bromohydrocodone). 9 was obtained from dihydrocodeinone (hydrocodone) **3** following the procedure for 1-iodo-14-hydroxydihydrocodeinone (1-iodooxycodone) **10** described above and monitoring the reaction by TLC (silica gel, 95:5 methanol−dichloromethane and a trace of concentrated ammonium hydroxide, R_f = 0.37) with the substitution of NBS for the NIS used there. mp 204−205 (lit.[15] 204−207 °C).

1,2-Dibromo-14-hydroxydihydrocodeinone (1,2-Dibromooxycodone) 7. The procedure for the preparation of 1-bromo-14-hydroxydihydrocodeinone (1-bromoxycodone) **8**, noted above, was followed. Thus, 14-hydroxydihydrocodeinone (oxycodone) **4**, 530 mg (1.59 mmol), was treated in 0.1 N TFA as above with 3 equiv of NBS for 24 h. The crude product was worked up as usual and purified from the monobromide by thick layer chromotography on silica gel eluted with CH_2Cl_2−MeOH (95:5) containing a trace of concd NH_4OH (R_f = 0.39) to give the 1,2-bromo-14-hydroxydihydrocodeinone (1,2-dibromooxycodone) **7**, 120 mg, 16%, mp 175−178 °C. Attempts to drive the reaction to completion failed. IR (KBr) C=O 1730.1 cm^{-1}; ^{1}H NMR δ 4.70 (s, 1H), 4.10s (3H), 2.42 (s, 3H) 3.4−1.5 (m 12H); ^{13}C δ 207.6, 146.2, 141.7, 130.4, 127.6, 118.6, 116.5, 90.9, 70.0, 64.5, 60.5, 50.4, 44.9, 42.8, 36.1, 31.3, 30.4, 25.0; exact mass calcd for $C_{18}H_{19}NO_4Br_2$ + Na: 495.9558 (Br 81), 493.9578 (Br79); found: 495.9558, 493.9561

1-Chloro-14-hydroxydihydrocodeinone (1-Chlorooxycodone) 12. With stirring, at room temperature, 14-hydroxydihydrocodeinone (oxycodone) **4**, 1.00 g (3.2 mmol), and *N*-chlorosuccinimide (854 mg, 6.4 mmol) were added to 0.1 N HCl (50 mL), and the mixture was heated at 90 °C for 6 h. After cooling to room temperature, the workup was as indicated above, to give 950 mg of product **12**, 85%, mp 193−195 °C. IR (KBr) C=O 1730 cm^{-1}; ^{1}H NMR δ 6.74 (s, 1H), 4.68 (s, 1H), 3.88 (s, 3H), 2.42 (s, 3H), 3.17−1.50 (m, 11H), 5.5 (s, 1H); ^{13}C NMR δ 208.3, 144.2, 143.9, 130.8, 124.0, 123.0, 114.9, 90.9, 64.4, 57.1, 50.8, 45.2, 43.0, 36.3, 31.60, 31.59, 30.7, 21.4; exact mass calcd for $C_{18}H_{20}NO_4Cl$ (M + Na$^+$) (^{35}Cl): 372.0986; found: 372.098; (^{37}Cl) 374.0949; found: 374.0965.

1-Carboethoxy-14-hydroxydihydrocodeinone (1-Carboethoxyoxycodone) 5. With stirring, in a 10 cm × 50 cm cylindrical glass pressure vessel with a threaded sealing cap and at 80 °C, a mixture of 1-iodo-14-hydroxydihydrocodeinone (1-iodooxycodone) **10** (2.56 g 5.80 mmol), palladium(II) chloride (29 mg, 0.16 mmol), and triphenylphosphine (170 mg, 0.65 mmol) were dissolved in ethanol (10 mL) and triethylamine (2.5 mL, 2.45 g, 26.9 mmol). The vessel was purged with argon, which was then replaced with CO, and the vessel was pressurized to 45 psi with carbon monoxide. Stirring and heating were continued for 24 h, after which the solvent was removed from the dark reaction mixture at reduced pressure. The residue was chromatographed on silica gel, and the product was eluted with 95:5 dichloromethane−methanol containing a trace of concentrated ammonium hydroxide to yield 1.42 g of **5** (63%) mp 139−140 °C (methanol). IR (KBr) C=O 1696.4 and 1728.6 cm^{-1}; ^{1}H NMR δ 7.52 (s, 1H), 5.2 (s, 1H), 4.75 (s, 1H), 4.34 (q, 2H, J = 7), 3.93 (s, 3H), 2.42 (s, 3H), 1.39 (t, 3H, J = 7), 3.65−1.63 (m, 11H); ^{13}C NMR δ 208.1, 166.6, 149.1, 142.9, 130.5, 129.2, 121.1, 117.6, 91.2, 69.9, 64.3, 60.9, 56.9, 50.6, 45.1,43.0, 36.3, 31.6, 31.0, 23.4, 14.7; exact mass calcd for $C_{21}H_{25}NO_6$ (M + Na$^+$): 410.1580; found: 410.1581.

1-Carboxy-14-hydroxydihydrocodeinone (1-Carboxyoxycodone) 6. The carboxylic acid ester **5** (100 mg, 0.26 mmol) was suspended in a 1:1 mixture of water and absolute ethanol

(20 mL), and with stirring, KOH (330 mg, 6.0 mmol) was added as solid. The aqueous mixture was stirred until dissolution was complete, and the reaction mixture was allowed to stand at room temperature overnight. After the probe of a pH meter was inserted, 0.10 N HCl was added slowly from a buret until the pH was in the range 6.65−6.72, at which time the solvent was removed at reduced pressure and during which time crystallization began (89.3 mg, 93%, 2 crops). The product was recrystallized from a 15% solution in hot water to give crystals for crystallography. The zwitterion was recrystallized from water, mp 194−197 °C. IR (KBr) C=O 1729.2, 1563.3; ^{1}H NMR δ 7.51 (s, 1H); 3.3 (s, 3H), 2.83 (s, 3H) 3.69−1.0.60 (m 14 H); ^{13}C NMR δ 211.1, 169.6, 148.9, 143.3, 128.7, 126.7, 122.5, 118.8, 90.5, 70.6, 66.4, 57.1, 49.2, 47.1, 41.5, 35.0, 31.0, 27.8, 24.9; exact mass calcd for $C_{19}H_{22}NO_6$ ($M + H^+$): 360.1447; found: 360.1447.

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Supporting Information Available: Spectra, including IR, ^{1}H NMR, and ^{13}C NMR, of all new compounds and X-ray crystallographic CIF files for **5** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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