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Aporphines. 27. Mechanistic Aspects of the Rearrangement of Thebaine and Codeine Analogues in Methanesulfonic Acid. Improved Method for Synthesis of N-Alkylated Aporphines

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The rearrangement of thebaine (**1a**), northebaine (**1b**), and *N*-(2-hydroxyethyl)northebaine (**1c**) in methanesulfonic acid leading to the formation of novel N-alkylated-2-O-methylated normorphothebaine derivatives **4a–c** was investigated. We have observed that a stable methoxonium intermediate **3** is formed under such conditions, which on further treatment with acid leads to the aporphines **4a–c**. The codeine derivatives **5a–e** are described and are similarly converted to the apocodeine analogues **6a–c** by rearrangement in methanesulfonic acid. This method in certain instances results in improved yields over those previously reported. The synthesis of the antitumor aporphine mustard **6c** is described.

The need for CNS penetrating antitumor agents led to the choice of aporphine alkaloids as carrier bases bearing a nitrogen mustard moiety. Conventional routes to this tetracyclic ring system usually entail either a multistep scheme[1a–c] or the rearrangement of opium alkaloids to the corresponding aporphines.[2,3] The selection of the latter method was prompted by several advantages, namely, the preservation of the chiral center at the 6a carbon atom, readily available starting materials, and synthetic ease.

In a previous communication,[4] we described the preparation of normorphothebaine (**2b**) from northebaine (**1b**) using concentrated HCl at 95–100 °C in a sealed pressure bottle. This procedure was adopted from earlier publications[5a–d] describing the conversion of thebaine (**1a**) to morphothebaine (**2a**).

In an effort to improve conditions and yields for the synthesis of normorphothebaine and its nitrogen-substituted derivatives required for the synthesis of such aporphine mustards, we investigated this rearrangement using CH_3SO_3H. If the hydrochloric acid solution in the rearrangement of **1a** is diluted with water and heated at 50–60 °C, a more complicated rearrangement occurs, resulting in the formation of thebenine.[6,7] The common intermediate for both **2a** and thebenine appears to be the dienone IIa[8] which under strongly acidic conditions prevents participation of the nitrogen electrons in the rearrangement process making IIb favorable for conversion to **2a**. Under weakly acidic conditions, unprotonated IIa, through its enol IIb, can produce scission of ring B to give thebenine.[7] Quaternary salts of IIa, namely, the methoperchlorate[7] and the methotrifluoroacetate,[9] were prepared and isolated in over 75% yield from the corresponding salts of thebaine (**1a**). Channon et al.[9] have shown that quaternary salts of **1a** in CF_3COOH containing concentrated H_2SO_4 formed a stable quaternary salt of the methoxonium ion **3a**. We have observed that solutions of thebaine (**1a**), northebaine (**1b**), and *N*-(2-hydroxyethyl)northebaine (**1c**) in CH_3SO_3H also formed the red methoxonium intermediates **3a–c** (δ 4.7, $=O^+CH_3$; UV_{max} 420 nm, log ϵ 4.05) which remained stable for periods of over 16 h at room temperature. Heating the solution at 90–100 °C for 30 min led to the

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(2) J. H. Hensiak, J. G. Cannon, and A. M. Burkman, *J. Med. Chem.*, 8, 557 (1965).

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(5) (a) W. C. Howard, *Ber.*, **17**, 527 (1884); (b) C. Knorr and R. Pschorr, *ibid.*, **38**, 3153 (1905); (c) C. Schopf and F. Borkowsky, *Justus Liebigs Ann. Chem.*, **458**, 148 (1927); (d) H. L. Holmes, *Alkaloids*, **2**, 112 (1952).

(6) The formation of thebenine via the dienone IIa (Scheme I) was rationalized by Fleischacker et al.[7]

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(8) Attempts to isolate the dienone IIa have not been successful. However, the existence of this transient intermediate was indirectly demonstrated by its reduction to metathebainone whose structure was unambiguously confirmed (K. W. Bentley, S. F. Dyke, and A. R. Marshall, *Tetrahedron*, **21**, 2553 (1965)).

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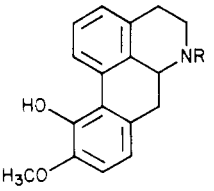
Table I. Apocodeine, Norapocodeine, and *N*-(2-Hydroxyethyl)norapocodeine by Rearrangement of Codeine Analogues in CH_3SO_3H[a]



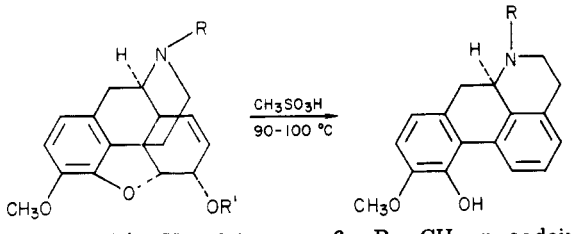
compd	R	mp, °C	% yield
6a[b]	CH_3	125-127[c]	32
6a·HCl[d]		257-260 dec[e]	56
6b·HCl[f]	H	277-280 dec[g]	23
6b·HCl[h]	H	274-276 dec	26
6c	CH_2CH_2OH	68-72	42

[a] The conditions for the rearrangement are described in the Experimental Section for **6c**. [b] Workup of the reaction mixture with aqueous $KHCO_3$ produces the free base which is further purified chromatographically or converted to the hydrochloride salt with ethereal hydrogen chloride. [c] Lit.[15] mp 124 °C. Purification was carried out by preparative-plate silica gel chromatography using 15% MeOH in EtOAc. [d] The highest yield of apocodeine (**6a**) was obtained in this experiment from codeine-6-(2-phenyltetrazole) ether (**5d**). [e] Lit.[15] 260-263 °C dec. [f] From norcodeine (**5b**). [g] Lit.[14] mp 270 °C. [h] From norcodeine-6-(2-phenyltetrazole) ether (**5e**).

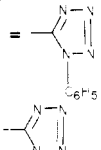
disappearance of the methoxonium absorption in the NMR and the appearance of two methoxy peaks as a doublet centered at δ 3.75. Further heating in the presence of H_2O (16% v/v in CH_3SO_3H) did not affect the course of the reaction.

The identification of the methoxonium intermediate **3** under these conditions (methanesulfonic acid) further supports the mechanism proposed for the rearrangement of **1** to **4** (Scheme I). However, under more strongly acidic conditions, formation of the dienone IIa is favored, leading to the formation of **2**. This method thus provides a convenient route for the preparation of N-alkylated-2-O-methylated morphothebaine derivatives **4a-c** in 60–79% crude yield.

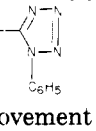
As a logical extension of this work, this procedure was applied to the rearrangement of codeine derivatives **5a-e**



5a, R = CH_3; R^1 = H codeine
b, R = H; R^1 = H norcodeine
c, R = CH_2CH_2OH; R^1 = H
d, R = CH_3; R^1 =



e, R = H; R^1 =



6a, R = CH_3, apocodeine
b, R = H
c, R = CH_2CH_2OH
d, R = CH_2CH_2Cl

with some improvement in the yields of the corresponding *R*-(−)-apocodeine (**6a-c**) over those reported previously.[10] Methanesulfonic acid had previously been employed for the rearrangement of morphine to apomorphine in yields of 9–23%.[3] Results of such rearrangements are summarized in Table I, and a representative example of the procedure is described for 6-(2-hydroxyethyl)norapocodeine (**6c**) in the Experimental Section.

Rearrangement of the 6-(2-phenyltetrazole) ether of codeine (**5d**) gave a surprisingly high yield (56%) of apocodeine (**6a**), while rearrangement of the analogous norcodeine ether derivative (**5e**) to norapocodeine (**6b**) occurred in only 26% yield. Conversion of **6c** to the cytotoxic[11] single arm mustard 6-(2-chloroethyl)norapocodeine (**6d**) was accomplished in the usual manner with $SOCl_2$.

Northebaine (**1b**) was prepared from thebaine by the method developed by Pohland[12] et al., while norcodeine (**5b**) was obtained by N-demethylation of codeine using methyl chloroformate followed by treatment of the intermediate carbamate with 80% hydrazine.[13] Alkylation of northebaine (**1b**) or norcodeine **5b** with 2-bromoethanol in absolute alcohol in the presence of sodium carbonate gave the 2-hydroxyethyl derivatives of northebaine (**1c**) and norcodeine (**5c**), respectively. The 6-(2-phenyltetrazole) ether derivatives of codeine (**5d**) and norcodeine (**5e**) were prepared by a procedure described by Barber and Rapoport[14] for the preparation of the 6-methyl ether of codeine. Sodium hydride was used to generate the allylic alkoxide which reacted instantaneously with 5-chloro-1-phenyl-1*H*-tetrazole. Alkylation of the nitrogen in norcodeine (**5b**) was not observed under these conditions.

Experimental Section

General Methods. Evaporations were carried out in a Buchi rotary evaporator in vacuo at a bath temperature below 50 °C. Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Analyses were performed by Galbraith Laboratories, Knoxville, TN. Samples for analyses were dried at 10^{-2} mm over silica gel at 55 °C. Preparative TLC was carried out on silica gel (Analteck, 20 × 20 cm, 2000 microns). Column chromatography was performed on silica gel (Baker, 5-3405, 60–200 mesh). Detection was done in UV light (MINERALLIGHT) or with iodine vapors. The IR spectra were measured in $CHCl_3$ or KBr with a Perkin-Elmer Model 700 spectrometer. NMR spectra were obtained with a Varian T-60 spectrometer in $CDCl_3$ or CD_3SOCD_3; $(CH_3)_4Si$ was used as an internal standard. UV spectra were carried out in EtOH with a Beckman DB-G grating spectrophotometer. Mass spectra were determined on a 12-90-G Nuclide mass spectrometer. Optical rotations were obtained on a Perkin-Elmer polarimeter Model 141.

Tetrahydrofuran (THF), acetonitrile (CH_3CN), and hexamethylphosphoramide (HMPA) were distilled and dried over Linde molecular sieves.

2,10-Dimethoxy-11-hydroxyaporphine (4a). A solution of 2 g (6.4 mmol) of thebaine alkaloid (**1a**) (Mallinckrodt) in 10 mL of CH_3SO_3H was heated at 90–95 °C for 30 min and cooled to room temperature, and 2 mL of H_2O was added. The solution was reheated at 90–95 °C for 1 h, cooled, and poured into cold concentrated HCl (20 mL). After 15 min, the mixture was filtered and the colorless solid dissolved in 20 mL of EtOH. The alcohol solution was neutralized with aqueous $KHCO_3$ and filtered, and the colorless solid was washed with H_2O and dried to give 1.2 g (60%) of **4a**, mp 141–144 °C. Recrystallization from 25 mL of CH_3CN gave 0.5 g of (**4a**) as colorless needles: mp 159–160 °C; NMR ($CDCl_3$) δ 7.9 (d, 1 H, C_1-H), 6.7 (s, 2 H, C_8-H, C_9-H), 6.6 (d, 1 H, C_3-H), 3.9 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 2.5 (s, 3

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(11) The antitumor activity of this compound designated as NSC 291102, together with the antitumor activity of related aporphine mustards, will be reported in *J. Med. Chem.*, **23**, (1980).

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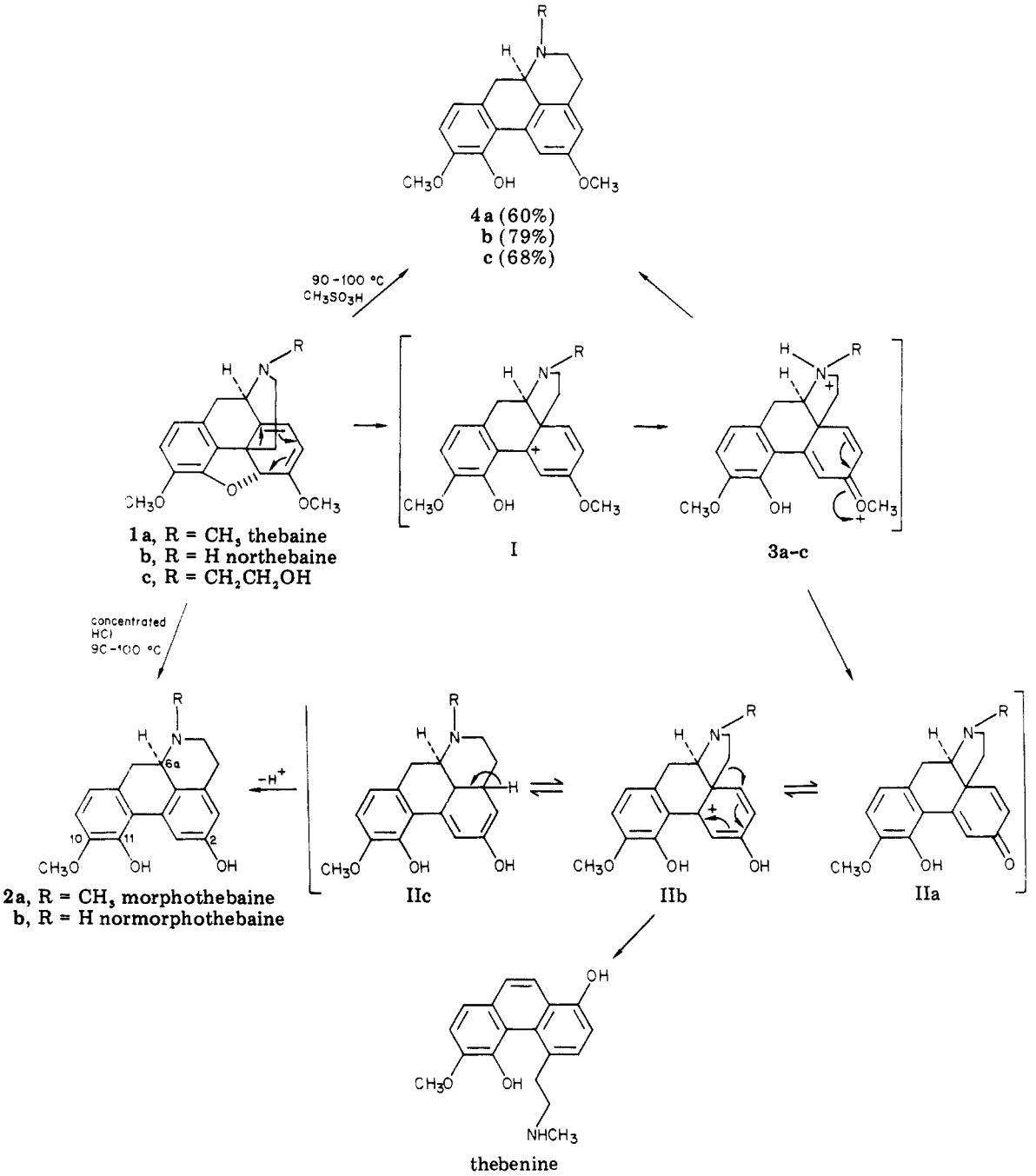
(13) G. A. Brine, K. G. Boldt, C. K. Hart, and F. I. Carroll, *Org. Prep. Proced. Int.*, **8**, 103-106 (1976); K. Rice and E. L. May, *J. Heterocycl. Chem.*, **14**, 665 (1977).

(14) R. B. Barber and H. Rapoport, *J. Med. Chem.*, 18, 1074 (1977).

(15) K. Folkers, *J. Am. Chem. Soc.*, 58, 1814 (1936).

Scheme I



H, NCH_3); UV_{max} (EtOH) 300 (log ϵ 3.91), 278 (4.18), 268 nm (4.17); mass spectrum, m/e 312 (M^+), 311 ($M^+ - 1$); $[\alpha]^{23}_D$ -127.8° (c 0.50, EtOH).

Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.79; N, 4.49. Found: C, 73.62; H, 6.34; N, 4.54.

2,10-Dimethoxy-11-hydroxynoraporphine (4b). A solution of northebaine (**1b**) (2 g, 6.7 mmol) in 10 mL of CH_3SO_3H was treated similarly as described for **1a** to give, after the same workup, 1.4 g (79%) of crude **4b**. Recrystallization of a small sample from CH_3CN with charcoal treatment gave a pure sample of **4b**: mp 205–206 °C; NMR ($CDCl_3$ + Me_2SO-d_6) δ 8.2 (s, 1 H, NH), 7.9 (d, 1 H, C_1-H), 6.6 (d, 2 H, C_8-H, C_9-H), 6.6 (d, 1 H, C_3-H), 3.9 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 2.6–3.2 (m, 7 H); UV_{max} (EtOH) 300 (log ϵ 3.90), 279 (4.15), 269 nm (414); mass spectrum, m/e 297 (M^+), 296 ($M^+ - 1$); $[\alpha]^{28}_D$ -88.7° (c 0.46, EtOH).

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.63; H, 6.59; N, 4.74.

6-(2-Hydroxyethyl)northebaine (1c). A mixture of 1.85 g (6.2 mmol) of northebaine (**1b**), 0.88 g (7.0 mmol) of $NaHCO_3$, and 0.82 g (6.5 mmol) of 2-bromoethanol in 25 mL of absolute EtOH was refluxed with stirring for 16 h. The mixture was cooled and filtered, and the solid was washed with 20 mL of alcohol. The product was washed with H_2O to remove inorganic salts and dried, giving 1.1 g of **1c**, mp 187–190 °C. The filtrate was concentrated to give a second crop weighing 0.4 g, mp 188–190 °C (total yield of **1c** was 71%). An analytical sample of **1c** was obtained by recrystallization from 95% EtOH: mp 192–194 °C; NMR ($CDCl_3$) δ 6.6 (s, 2 H), 5.3 (s, 2 H), 5.3 (s, 1 H), 3.83 (s, 3 H), 3.6 (s, 3 H), 2.6–3.4 (m, 7 H), 3.6–4.0 (m, 4 H).

Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.50; H, 6.95; N, 3.99.

2,10-Dimethoxy-6-(2-hydroxyethyl)-11-hydroxynoraporphine (4c). A solution of 0.36 g (1.1 mmol) of **1c** in 5 mL of CH_3SO_3H was heated at 90 °C for 0.5 h. The solution was cooled, poured into 50 mL of saturated aqueous $KHCO_3$, and filtered. The light tan crystalline product was washed with H_2O and dried to give 0.25 g (68%) of analytically pure **4c** as a hydrate: mp 102–106 °C (resolidified and remelted at 145–148 °C); NMR ($CDCl_3$ + Me_2SO-d_6) δ 7.9 (d, 1 H, C_1-H), 6.65 (s, 2 H, C_8-H, C_9-H), 6.55 (d, 1 H, C_3-H), 3.9 (s, 3 H, OCH_3), 3.8 (s, 3 H, OCH_3); UV_{max} (EtOH) 300 (log ϵ 3.92), 279 (4.17), 269 nm (4.15); mass spectrum, m/e 341 (M^+); $[\alpha]^{23}_D$ -29.5° (c 0.22, EtOH).

Anal. Calcd for $C_{20}H_{23}O_4 \cdot 0.75H_2O$: C, 67.69; H, 6.95; N, 4.10. Found: C, 67.64; H, 6.79; N, 4.02; H_2O (Karl Fisher), 3.74.

***N*-(2-Hydroxyethyl)norcodeine (5c).** A mixture of 13.8 g (48 mmol) of norcodeine,[13] 5.8 g (69 mmol) of $NaHCO_3$, 145 mL of absolute alcohol, and 6.16 g (49 mmol) of 2-bromoethanol was allowed to reflux with stirring under N_2 for 27 h. The solution was filtered hot, giving a mixture of product and inorganic material weighing 7.6 g, mp 189–195 °C. The filtrate was concentrated to 100 mL under vacuum and cooled to give an additional 7.2 g of product, mp 185–195 °C. Recrystallization of 3 g of the crude product from 35 mL of ethanol gave 1.1 g of near colorless crystals: mp 190–192 °C; NMR ($CDCl_3$ + Me_2SO-d_6) δ 6.5 (dd, 2 H), 5.6 (d, 1 H), 5.22 (d, 1 H), 4.75 (d, 1 H), 4.2 (br, 1 H), 3.78 (s, 3 H), 3.7–3.2 (m, 8 H), 2.9–2.4 (m, 4 H); mass spectrum, *m/e* 329 (M^+).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 14.01. Found: C, 69.11; H, 7.19; N, 4.20.

Codeine-6-(2-phenyltetrazole) Ether (5d). A solution of 1 g (3.3 mmol) of codeine in 50 mL of dry THF (distilled from CaH_2) was added to a suspension of 0.34 g (6.9 mmol) of NaH (50% dispersion in mineral oil, previously washed with 2 × 15 mL of dry THF). After being stirred for 1 h at room temperature under N_2, the mixture was treated with a solution of 1.2 g (6.7 mmol) of 5-chloro-1-phenyl-1*H*-tetrazole (Aldrich) in 50 mL of dry THF. The mixture was stirred for 15 min at room temperature and quenched with 20 mL of 1 N alcoholic $NaOC_2H_5$. The solution was diluted with 50 mL of H_2O and evaporated to remove solvents. The aqueous solution was extracted with $CHCl_3$, and the combined extracts were washed with H_2O, dried (Na_2SO_4), and evaporated to give a crude solid which was recrystallized from 25 mL of CH_3CN, yielding 0.78 g (53%) of **5d** as colorless crystals: mp 207–208 °C; NMR ($CDCl_3$) δ 8.0–7.8 (m, 2 H), 7.65–7.4 (m, 3 H), 6.65 (d, 2 H), 5.95–5.4 (m, 4 H), 3.75 (s, 3 H), 3.5–3.2 (m, 2 H), 3.0–2.75 (m, 2 H), 2.5 (s, 3 H), 2.5–1.9 (m, 4 H); IR ($CHCl_3$) 2900, 1600, 1500, 1450 cm^{-1}; mass spectrum, *m/e* 443 (M^+).

Anal. Calcd for $C_{25}H_{25}N_5O_3$: C, 67.71; H, 5.68; N, 15.79. Found: C, 67.73; H, 5.72; N, 15.84.

Norcodeine-6-(2-phenyltetrazole) Ether (5e). A solution of 2.65 g (9.7 mmol) of norcodeine[10] (**5b**) in a mixture of 50 mL of dry THF and 7 mL of dry hexamethylphosphoramide (HMPA) was added to a suspension of 0.50 g (10.4 mmol) of NaH. (50% dispersion in mineral oil, washed with 2 × 20 mL of dry THF). After being stirred for 1.5 h at room temperature under N_2, the mixture was added to a solution of 1.84 g (10.2 mmol) of 5-chloro-1-phenyl-1*H*-tetrazole in 50 mL of dry THF and 2 mL of dry HMPA. The cloudy solution was stirred for 15 min at room temperature and quenched with 35 mL of 1 N alcoholic $NaOC_2H_5$. The solution was diluted with 50 mL of H_2O and evaporated under vacuum to remove THF. The aqueous solution was diluted to 100 mL with H_2O and extracted with 5 × 50 mL of $CHCl_3$. The extract was washed with 3 × 50 mL of H_2O, dried, filtered, and evaporated to give an oily residue, from which a light yellow solid precipitated after cooling for 17 h. The product was filtered, washed with H_2O to remove all solvents, and dried to give 2.7 g (64%), mp 186–188 °C. A 500-mg sample of the product recrystallized from 5 mL of CH_3CN in long light yellow needles to give 250 mg of **5e**, mp 191–192 °C. Mixture melting point with norcodeine was depressed (157–172 °C): NMR ($CDCl_3$) δ 7.95–7.8 (m, 2 H), 7.6–7.4 (m, 3 H), 6.65 (s, 2 H), 5.95–5.3 (m, 4, H), 3.75 (s, 3 H), 3.1–2.6 (m, 5 H), 2.2–2.7 (m, 3 H); IR (KBr) 2875, 1580, 1490, 1440 cm^{-1}; mass spectrum, *m/e* 429 (M^+).

Anal. Calcd for $C_{24}H_{23}N_5O_3$: C, 67.12; H, 5.39; N, 16.31. Found: C, 67.24; H, 5.50; N, 16.22.

6-(2-Hydroxyethyl)norapocodeine (6c). A solution of 1 g (3 mmol) of **5c** in 5 mL of methanesulfonic acid was heated at 95 °C for 45 min. The solution was cooled to about 50 °C and poured slowly into a solution of 14 g of $KHCO_3$ in 75 mL of H_2O with stirring. After 1 h the mixture was filtered and the near colorless solid washed with H_2O and dried, giving 0.79 g (84%) of **6c**. A 200-mg sample of the product was purified by preparative-plate chromatography with 5% MeOH in EtOAc, recovering a band at R_f 0.35–0.60. The yield of pure product as a hydrate was 100 mg (42%): mp 68–72 °C; NMR ($CDCl_3$) δ 8.3 (dd, 1 H, J = 7.0 and 0.75 Hz), 7.2 (q, 1 H), 7.0 (dd, 1 H), 6.75 (s, 2 H), 3.82 (s, 3 H), 3.7–2.2 (m, 11 H); mass spectrum, *m/e* 311 (M^+); UV_{max} (EtOH) 274 nm (log ϵ 3.62); $[\alpha]^{23}_{Hg546}$ -55.5°.

Anal. Calcd for $C_{19}H_{21}NO_3 \cdot {}^1/_3H_2O$: C, 71.90; H, 6.87; N, 4.41; H_2O, 1.89. Found: C, 71.66; H, 7.03; N, 4.36, H_2O (Karl Fisher) 1.22.

6-(2-Chloroethyl)norapocodeine (6d). A mixture of 3 g (9.63 mmol) of 6-(2-hydroxyethyl)norapocodeine (**6c**), 100 mL of dry CH_3CN, and 2.5 mL of $SOCl_2$ was stirred at room temperature for 3 h. The solution was evaporated to dryness, and the residue was stirred for 72 h with a mixture of Et_2O (75 mL) and saturated aqueous $KHCO_3$ (30 mL). The mixture was then filtered, and the Et_2O layer was separated, dried (Na_2SO_4), and evaporated to give 739 mg (23%) of **6d**, mp 79–83 °C. No further purification of this material was required: ^1H NMR ($CDCl_3$, 60 MHZ) δ 8.2 (dd, 1 H, J = 7.0 and 0.75 Hz), 7.1 (q, 1 H), 7.0 (dd, 1 H), 6.8 (s, 2 H), 3.95 (s, 3 H), 3.7–2.5 (m, 11 H); IR ($CHCl_3$) 3450, 3000, 2900 cm^{-1}; UV (EtOH) 274 nm (log ϵ 3.99).

Anal. Calcd for $C_{19}H_{20}ClNO_2$: C, 69.19; H, 6.11; Cl, 10.75; N, 4.25. Found: C, 68.96; H, 6.34; Cl, 10.53; N, 4.13.

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Registry No. **1a**, 115-37-7; **1b**, 2579-67-1; **1c**, 73378-04-8; **4a**, 73378-05-9; **4b**, 70521-87-8; **4c**, 73384-20-0; **5a**, 76-57-3; **5b**, 467-15-2; **5c**, 73378-06-0; **5d**, 73378-07-1; **5e**, 73378-08-2; **6a**, 641-36-1; **6a**·HCl, 6377-14-6; **6b**·HCl, 73378-09-3; **6c**, 73378-10-6; **6d**, 73378-11-7; 2-bromoethanol, 540-51-2; 5-chloro-1-phenyl-1*H*-tetrazole, 14210-25-4.

Prostaglandins and Congeners. 27.[1] Synthesis of Biologically Active 16-Halomethyl Derivatives of 15-Deoxy-16-hydroxyprostaglandin E_2

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The 16-CF_3, -CHF_2, -CH_2F, and -CH_2Cl derivatives of DL-15-deoxy-16-hydroxyprostaglandin E_2 (**8a**, **8b**, **8c**, and **8d**, respectively) were prepared by conjugate addition of the lithiocuprates derived from the appropriately functionalized vinylstannanes **4** to cyclopentenone **6**. Hydrolysis of the rather stable O–Si linkage at C-16 of the prostaglandin is discussed. The ^{13}C NMR chemical shifts of the prostaglandin analogues and intermediates are noted.

Recent reports from these laboratories and elsewhere have described the 15-deoxy-16-hydroxy-16-methyl-prostaglandins (**8e**) as potent bronchodilators[2] and gastric antisecretory agents.[3] It is well-known that introduction

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