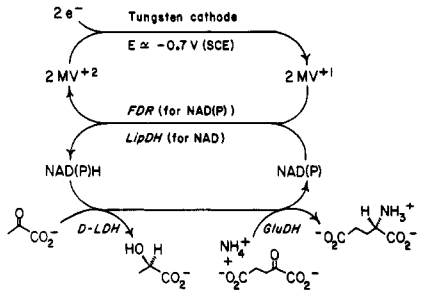
Scheme I. Electrochemical Regernation of NAD(P)H[a]



[a] Abbreviations: MV, methyl viologen; FDR, ferredoxin-NADP reductase; LipDH, lipoamide dehydrogenase; D-LDH, D-lactate dehydrogenase; GluDH, glutamic dehydrogenase.

(total volume 600 mL) containing sodium α-ketoglutarate (20 g, 120 mmol, neutralized with ~13 mL of 10 N NH_4OH), NADP (0.12 mmol, 0.2 mM), MV^{2+} (0.31 g, 1.2 mmol), β-mercaptoethanol (0.94 g, 1.2 mmol), Na_2SO_4 (4.2 g, 30 mmol), and glutamic dehydrogenase (GluDH, EC 1.4.1.3, 40 U, 1 mL of gel). The pH was controlled at 8.0 by adding deoxygenated 1 N H_2SO_4 with a peristaltic pump. The reaction was complete in 7 days. The decanted solution was concentrated to ~100 mL and the pH adjusted to 6.5, followed by addition of ethanol (60 mL). Crystalline monosodium L-glutamate (17.8 g) was obtained after cooling. This material contained 96% of monosodium L-glutamate (101 mmol),[14] corresponding to a 84% isolated yield. The turnover numbers (and residual activities) for cofactor and enzymes were as follows: NADP, 1000 (68%); GluDH, 1.1×10^7 (92%); FDR, 7.5×10^5 (80%). The current efficiency was 105 ± 10%.

The relative activities of flavoenzymes for NADH regeneration under the conditions employed in these reactions were LipDH (yeast)/LipDH (pig heart)/FDR = 1:4:7 [ca. 3 μmol of NAD reduced min^{-1} (mg of FDR)$^{-1}$]. FDR-catalyzed NADPH regeneration is 5 times as fast as the reaction using FDR-catalyzed NADH regeneration, while LipDH-catalyzed NADPH regeneration is 10% as fast as that for NADH regeneration. Under the reaction conditions studied, FDR is more stable ($\tau_{1/2}$ = 16 days) than LipDH ($\tau_{1/2}$ = 7 days).

The electrochemical method for NAD(P)H regeneration summarized in Scheme I is more convenient than that based on hydrogenase,[5] since hydrogenase is not commercially available and requires a nonroutine fermentation for its preparation. In both schemes, LipDH has relatively low stability and catalytic activity (~1 U/mg, 2 mM MV^{2+}, pH 7.8, −0.72 V vs. SCE); FDR is more expensive but more stable and active (~3 U/mg under the same conditions). The overall reaction rate in systems using FDR or LipDH is limited by the reduction of NAD(P) by MV^{1+} under FDR or LipDH catalysis.[15] Increasing the concentration of MV^{1+} increases this rate but may lead to increased side reactions.

Acknowledgment. This research was supported by grants from the NIH (GM 26543) and NSF (80-12722 CHE). R.D. held a Chevron Fellowship.

(14) Bergmeyer, H. U. "Methods of Enzymatic Analysis"; Verlag Chemie, Academic Press: New York, 1974.

(15) The reduction of NADP by MV^{1+} catalyzed by FDR has been reported to be first order in FDR (ref 7), which is consistent with our result. Since LDH was in excess in the reaction system, and the rate of production of lactate was proportional to the concentration of FDR, LipDH or MV^{2+} (but not LDH), we concluded that the rate-limiting step was the reduction of NAD(P) catalyzed by flavoenzymes.

Registry No. NAD(P)H, 53-57-6; NAD(P), 53-59-8; MV^{2+}, 1910-42-5; MV^{1+}, 79028-21-0.

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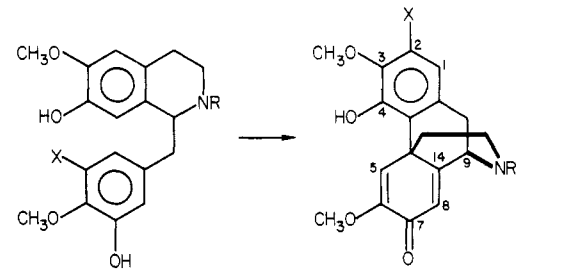
Biomimetic Approaches to Morphine Alkaloids. Total Synthesis of (±)-2-Hydroxycodeine and (±)-Noroxycodone[1]

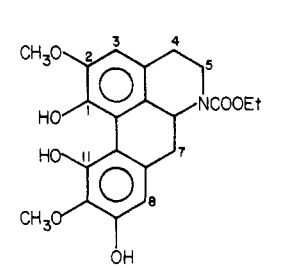
Summary: Oxidative coupling of a triphenolic hydroxynorreticuline substrate with $VOCl_3$ affords the corresponding 2-hydroxynorsalutaridine derivative in good yield; the latter is readily converted to the title compounds via (±)-*N*-(ethoxycarbonyl)-2-hydroxynorthebaine.

Sir: The key step in the biosynthesis of the morphine alkaloids is the regioselective para–ortho oxidative cyclization of reticuline (1) to salutaridine (2).[2] The discovery in our laboratory that oxidative coupling of the reticuline derivative 3 with thallium(III) trifluoroacetate gave the salutaridine 4 as the major product resulted in the first biomimetic synthetic route to these alkaloids[3] and was latter extended to yield some morphine alkaloid analogues.[4] Szántay and co-workers very recently reported remarkable success in achieving the same regioselectivity with a variety of oxidants in the presence of certain organic acids.[5]



1, R = CH_3; X = H
3, R = COOEt; X = H
5, R = COOEt; X = OH

2, R = CH_3; X = H
4, R = COOEt; X = H
6, R = COOEt; X = OH



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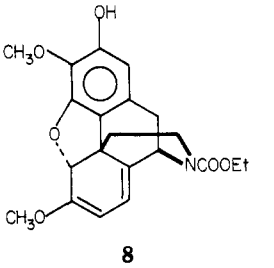

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(1) Taken in part from Zoda, M. F. Ph.D. Dissertation, The Florida State University, 1981.

(2) For a succinct review, see: Herbert, R. B. In "Comprehensive Organic Chemistry"; Barton, D., Ollis, W. D., Ed.; Pergamon: Oxford, 1979; Vol 5, p 1076.

(3) (a) Schwartz, M. A.; Mami, I. S. *J. Am. Chem. Soc.* **1975**, *97*, 1239. (b) Schwartz, M. A. U.S. Patent 4 003 903, 1977; *Chem. Abstr.* **1977**, *86*, 155848g.

(4) Schwartz, M. A.; Wallace, R. A. *Tetrahedron Lett.* **1979**, 3257.

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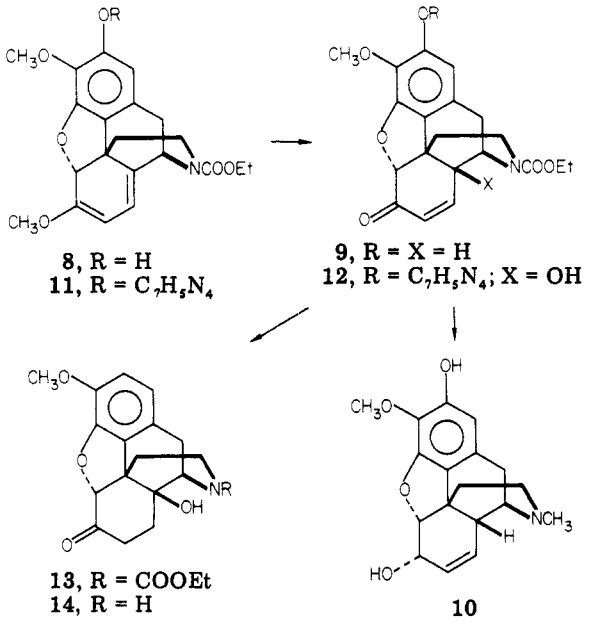
An alternate approach to this key step can be envisioned, in which the functionalization of the benzyltetrahydroisoquinoline substrate is modified in such a way as to limit the number of possible direct coupling products. For example, oxidative cyclization of the triphenolic *N*-(ethoxycarbonyl)-5′-hydroxynorreticuline (**5**) should afford the morphinandienone **6** and aporphine **7** as the only primary coupling products because of the symmetrical disposition of the phenolic hydroxyl groups;[6] furthermore, formation of **7** by direct coupling of **5** might be disfavored due to the unavoidable peri interaction between the C-1 and C-11 hydroxyl groups. We now report application of this approach to efficient total syntheses of (±)-2-hydroxycodeine and (±)-7,8-dihydro-14-hydroxynorcodeinone (noroxycodone), the latter of which is a precursor to the pharmacologically important 14-hydroxymorphinan derivatives.[7]

The hydroxynorreticuline **5** was prepared[1] in six steps and 50% overall yield via the Bischler–Napieralski route[8] from (3,5-bis(benzyloxy)-4-methoxyphenyl)acetic acid[9] and (4-hydroxy-3-methoxyphenethyl)amine.[10] A solution of triphenol **5** in anhydrous ether (7×10^{-4} M) was oxidized with 2.5 mol equiv of $VOCl_3$[11] by stirring under nitrogen at −78 °C for 5 h and at 25 °C for 3 h. Preparative TLC separation of the crude product afforded a 16% recovery of unreacted starting material **5** and a 64% yield of (±)-*N*-(ethoxycarbonyl)-2-hydroxynorsalutaridine (**6**), which crystallized upon standing in ether: mp 208–210 °C; IR ($CHCl_3$) 1672, 1667, 1618 cm^{-1}; NMR ($CDCl_3$) δ 7.47 (s, H-5), 6.34 (s, H-1), 6.27 and 6.23 (each s, H-8, two signals due to carbamate rotamers), 5.11 and 5.01 (each br s, H-9, two signals due to carbamate rotamers), 3.92 (s, OMe), 3.75 (s, OMe).[12a]

None of the aporphine **7** could be detected from the oxidative cyclization of **5** with $VOCl_3$ in ether. However, treatment of **5** with $VOCl_3$ in anhydrous CH_2Cl_2, under otherwise identical conditions, resulted in isolation of unreacted starting material (13%), dienone **6** (37%), and aporphine **7** (24%), which crystallized from $CHCl_3$/ether: mp 243–248 °C dec; NMR ($CDCl_3$) δ 6.68 (s, H-8), 6.57 (s, H-3), 4.00 (s, OMe), 3.95 (s, OMe); mass spectrum (70 eV), *m/e* 401 (M^+), 299 (base peak).[12b] This interesting change in product distribution with change in solvent may be the result of a change in the mechanism of $VOCl_3$ oxidation of phenols in these two solvents, as has been previously suggested.[11]

Dienone **6** was reduced with $NaBH_4$ (MeOH, 0 °C, 0.5 h) and the crude dienol was cyclized by sequential treatment[13] with $SOCl_2$ in cold pyridine (−10 °C, 2.5 h) and hot aqueous NaOH to afford (±)-*N*-(ethoxycarbonyl)-2-hydroxynorthebaine (**8**) in 47% overall yield: mp 199–200 °C (from ether); NMR ($CDCl_3$) δ 6.27 (s, H-1), 5.59 (br m, H-8), 5.17 (s, H-5), 5.07 (d, *J* = 7 Hz, H-7), 4.02 (s, OMe), 3.64 (s, OMe).[12a] Hydrolysis of the enol ether moiety of **8** was effected by the method developed[14] for thebaine itself; addition of **8** in dichloromethane to anhydrous HBr in *n*-butyl ether (−20 to 0 °C, 20 min) followed by quenching with cold saturated aqueous $NaHCO_3$ gave the codeinone analogue **9** as a colorless oil in 85% yield: IR ($CHCl_3$) 1685 cm^{-1} (br); NMR δ 6.65 (d, *J* = 8 Hz, H-8), 6.29 (s, H-1), 6.13 (dd, *J* = 3 and 8 Hz, H-7), 4.68 (s, H-5), 4.03 (OMe). Completion of the synthesis of (±)-2-hydroxycodeine (**10**) was achieved by concurrent reduction of the ketone and carbamate functions in **9** with $LiAlH_4$ (THF, reflux, 19 h) to give **10** in 55% yield: mp 235–240 °C dec; NMR ($CDCl_3$/Me_2SO-d_6) δ 6.18 (s, H-1), 5.66 (d, *J* = 10 Hz, H-7), 5.28 (dd, *J* = 1.5 and 10 Hz, H-8), 4.83 (d, *J* = 7 Hz, H-5), 4.17 (m, H-6), 3.93 (s, OMe), 2.43 (s, NMe).[12b] The only significant differences in the NMR spectra of **10** and authentic (−)-codeine obtained under the same conditions were that the latter showed H-2 at δ 6.66 (d, *J* = 8.5 Hz), H-1 at 6.56 (d, *J* = 8.5 Hz) and the OMe at 3.83 (s).



In order to provide entry into the 14-hydroxymorphinan series, we converted[6b] the 2-hydroxynorthebaine **8** to the 1-phenyltetrazol-5-yl ether **11** (5-chloro-1-phenyltetrazole, K_2CO_3, DMF, 85 °C, 2.5 h, 96% yield). The latter was subjected without purification to photochemically generated singlet oxygen[4,7] (rose bengal sensitization, CH_2Cl_2/10% MeOH, 5 °C, 0.5 h) followed by quenching with thiourea (25 °C, 12 h) to afford the 14-hydroxynorcodeinone derivative **12** as an oil in 63% yield: IR ($CHCl_3$) 1685 cm^{-1}; NMR ($CDCl_3$) δ 6.83 (d, *J* = 10 Hz, H-8), 6.75 (s, H-1), 6.17 (d, *J* = 10 Hz, H-7), 4.78 (s, H-5), 3.89 (s, OMe). Hydrogenolysis[6b] of the tetrazolyl ether moiety of **12** (10% Pd/C, EtOAc/95% EtOH 1:1; 80 h) was accompanied by double-bond reduction to give (±)-*N*-(ethoxycarbonyl)-7,8-dihydro-14-hydroxynorcodeinone (**13**) in 51% yield as an oil:[12a,b] IR ($CHCl_3$) 1727, 1685 cm^{-1}. Hydrolysis of **13** in refluxing 5 N H_2SO_4 (18 h) afforded (±)-noroxycodone (**14**) in 93% yield: mp 198–202 °C; IR ($CHCl_3$) 1724 cm^{-1}; NMR ($CDCl_3$) 6.71 (d, *J* = 8.5 Hz, H-2), 6.63

(5) Szántay, C.; Blaskó, G.; Bárczai-Beke, M.; Péchy, P.; Dörnyei, G. *Tetrahedron Lett.* **1980**, *21*, 3509.

(6) This strategy has been applied with some success to generation of the morphinan system by Grewe-type[6a] acid-catalyzed cyclization of an olefinic diphenol[6b] and by electrooxidative cyclization of alkoxylaudanosine derivatives:[6c,d] (a) Rice, K. C. *J. Org. Chem.* **1980**, *45*, 3135 and references cited therein. (b) Beyerman, H. C.; Lie, T. S.; Maat, L.; Bosmann, H. H.; Buurman, E.; Bijsterveld, E. J. M.; Sinnige, H. J. M. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 24. (c) Falck, J. R.; Miller, L. L.; Stermitz, F. R. *Tetrahedron* **1974**, *30*, 931. (d) Miller, L. L., University of Minnesota, personal communication, 1981.

(7) See, for example: Schwartz, M. A.; Wallace, R. A. *J. Med. Chem.* **1981**, in press, and references therein.

(8) See, for example: Rice, K. C.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 592.

(9) Schöpf, C.; Winterhalder, L. *Justus Liebigs Ann. Chem.* **1940**, *544*, 73.

(10) Schwartz, M. A.; Zoda, M.; Vishnuvajjala, B.; Mami, I. *J. Org. Chem.* **1976**, *41*, 2502.

(11) Schwartz, M. A.; Rose, B. F.; Holton, R. A.; Scott, S. W.; Vishnuvajjala, B. *J. Am. Chem. Soc.* **1977**, *99*, 2571.

(12) The compound gave satisfactory: (a) combustion analytical data or (b) high-resolution mass spectral data.

(13) Sohar, P.; Schoenewaldt, E. F. U.S. Patent 3 894 026, 1975; *Chem. Abstr.* **1976**, *84*, 5226x.

(14) Gavard, J.-P.; Krausz, F.; Rull, T. *Bull. Soc. Chim. Fr.* **1965**, 486.

(d, J = 8.5 Hz, H-1), 4.65 (s, H-5), 3.90 (s, OMe).[12b] The IR, NMR, and mass spectra of **14** were indistinguishable from those of authentic (−)-noroxycodone.

Intramolecular oxidative coupling of the triphenolic benzyltetrahydroisoquinoline **5** with $VOCl_3$ thus provides biomimetic access to the morphinandienone system in significantly improved yields[3,5] and leads to short synthetic pathways to the 2-hydroxy- and 14-hydroxymorphinans (five steps and seven steps from **5**, respectively). We are currently investigating the conversion of **5** to codeine itself, the successful completion of which would represent one of the more efficient total syntheses of codeine and morphine on record.

Acknowledgment. This work was supported by Public Health Service Grant DA 01962 from the National Institute on Drug Abuse. We thank Mallinckrodt, Inc. for providing us with generous samples of authentic codeine and noroxycodone, and Ms. Ingeborga Holak for preparing and carrying out the initial oxidation experiments with triphenol **5**.

Registry No. (±)-**5**, 79043-20-2; (±)-**6**, 79043-21-3; (±)-**7**, 79043-22-4; (±)-**8**, 79043-23-5; (±)-**9**, 79043-24-6; (±)-**10**, 79043-25-7; (±)-**11**, 79043-26-8; (±)-**12**, 79057-55-9; (±)-**13**, 79057-56-0; (±)-**14**, 79043-27-9; 3,5-bis(benzyloxy)-4-methoxybenzeneacetic acid, 54186-42-4; 4-hydroxy-3-methoxyphenethylamine, 554-52-9; 5-chloro-1-phenyltetrazole, 14210-25-4.

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Carbonylation of Aryllithium Reagents in the Presence of Alkyl Halides: One-Pot Synthesis of Diarylalkylcarbinols and Derivatives[1]

Summary: The carbonylation of ArLi (Ar = Ph, *o*-anisyl) in the presence of alkyl bromides affords diarylalkylcarbinols in good yields. The reaction may be used to obtain alcohols functionalized in the alkyl chain; it can also be adapted to afford substituted tetrahydrofurans.

Sir: Although several mechanistic studies and synthetic applications of alkali aromatic ketyls[2] have been recently published, no further research on the mechanism of the reaction of phenyllithium with carbon monoxide have been reported since the work of one of us with Whitesides et al.[3] At that time, an unattractive feature of the reaction was the formation of several products. Nevertheless, reaction conditions have recently been developed for the preparation of α,α-diphenylacetophenone (94% yield).[4] We now report the high-yield production of diarylalkylcarbinols by this reaction. Besides their synthetic interest, these experiments are mechanistically relevant since they provide experimental evidence for the intermediacy of benzoyllithium: "the most important mechanistic question still unresolved"[3] in 1973.

Table I. Preparation of Diphenylalkylcarbinols[a]

RBr	% yield 3	4	others
n-C_4H_9Br	80	15	
n-C_3H_7Br	74	21	
n-$C_{12}H_{25}Br$	65	17	
i-C_3H_7Br	28	42	15[b]
t-C_4H_9Br	20	38	22[c]

[a] The yields represent the percent conversion. In all cases the compounds were identified by spectroscopic methods and confirmed by independent synthesis. [b] 1,1-Diphenyl-2-methyl-*n*-propyl isopropyl ether. [c] 1,1-Diphenyl-2-methyl-*n*-propyl *tert*-butyl ether and benzhydryl *tert*-butyl ether.

Diphenylalkylcarbinols are easily formed by adding the appropriate alkyl bromide to a solution of phenyllithium (prepared as previously described)[4] in THF at −78 °C and exposing the mixture to carbon monoxide (1 atm pressure). Fast gas absorption occurs, which ceases within 10 min. The reaction mixture is quenched with a saturated solution of ammonium chloride. Extraction with ligroin yield a mixture of products **3** and **4** (eq 1).

$$\underset{\mathbf{1}}{PhLi} + \underset{\mathbf{2}}{RBr} + CO \rightarrow \underset{\mathbf{3}}{Ph_2RCOH} + \underset{\mathbf{4}}{PhC(O)C(OH)HPh} \quad (1)$$

The results obtained for different alkyl bromides are shown in Table I. As can be observed, better yields are given by primary alkyl bromides. The lower yield of R = n-$C_{12}H_{25}$ is probably due to its smaller solubility in THF.[5] The products from secondary and tertiary alkyl bromides contain mixed-ether byproducts. Some of these ethers are difficult to prepare by other methods, and further efforts will be made to find suitable conditions for their formation in higher yields. The reaction described in eq 1 is highly dependent on the ratio of reagents. If the ratio, r = [1]/[2], is bigger than 1/3, more **4** is produced, and, therefore, the yield of **3** diminishes [58% (r = 1), 69% (r = 0.5)]. If the ratio is smaller, the yield of **3** also decreases [48% (r = 0.2)], due to the competing formation of alkylbenzene (Wurtz coupling). More reactive halides such as benzyl, vinyl, or allyl and alkyl iodides react with **1** at −78 °C.

An additional interesting feature of this reaction is the nonreactivity of alkyl chlorides. When alkyl chlorides are used instead of bromides, the same several products are formed as in the reaction of phenyllithium with CO *in the absence* of alkyl chlorides. The mechanistic reason for such differential reactivity of these halides is not clear to us, but it offers an useful way of preparing carbinols functionalized in the alkyl chain. Thus, if the reaction is carried out with R = $CH_2CH_2CH_2Cl$, 4-chloro-1,1-diphenyl-*n*-butanol (**6**) is produced in 48% yield[6] (eq 2). The product may be isolated by column chromatography or distillation at reduced pressure.

$$\underset{\mathbf{1}}{PhLi} + \underset{\mathbf{5}}{BrCH_2CH_2CH_2Cl} + CO \rightarrow \underset{\mathbf{6}}{Ph_2C(OH)(CH_2)_3Cl} + \mathbf{4} \quad (2)$$

The described one-pot preparation of **6** gives better yields than the previously reported several-step synthesis.[7]

(1) Presented in part at the XV Argentine Chemical Symposium, Tucumán, 1980.
(2) (a) C. G. Screttas and M. M. Screttas, *J. Org. Chem.*, **46**, 993 (1981); (b) S. M. Rosenfeld, *Tetrahedron Lett.*, 2655 (1978); (c) J. G. Smith and D. J. Mitchell, *J. Am. Chem. Soc.*, **99**, 5045 (1977); (d) H. W. Wang, G. Levin, and M. Szwarc, *ibid.*, **99**, 5056 (1977); (e) J. F. Garst and C. D. Smith, **ibid.**, **98**, 1520 (1976).
(3) L. S. Trzupek, T. L. Newirth, E. G. Kelly, N. S. Nudelman, and G. M. Whitesides, *J. Am. Chem. Soc.*, **95**, 8118 (1973).
(4) N. S. Nudelman and A. A. Vitale, *Org. Prep. Proced.* **13**, 144 (1981).
(5) In fact, if a 0.5 M solution of PhLi is used, a 50% yield of **3** and 29% yield of **4** are produced. When [PhLi] = 0.3 M (keeping the reagent ratio at 1:3), the yields reported in Table I are obtained.
(6) In this case the best yield is obtained by using a 0.1 M solution of phenyllithium and keeping r = $^1/_3$.

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