17. Nucleophilic Substitution in the Allylic System of Codeine and Pseudocodeine: Reactions with Lithium Cyano(methyl)- and (Aryl)cyanocuprates. Crystal and Molecular Structure of 8α-Phenyl-6,7-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan and 6α-Phenyl-7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan

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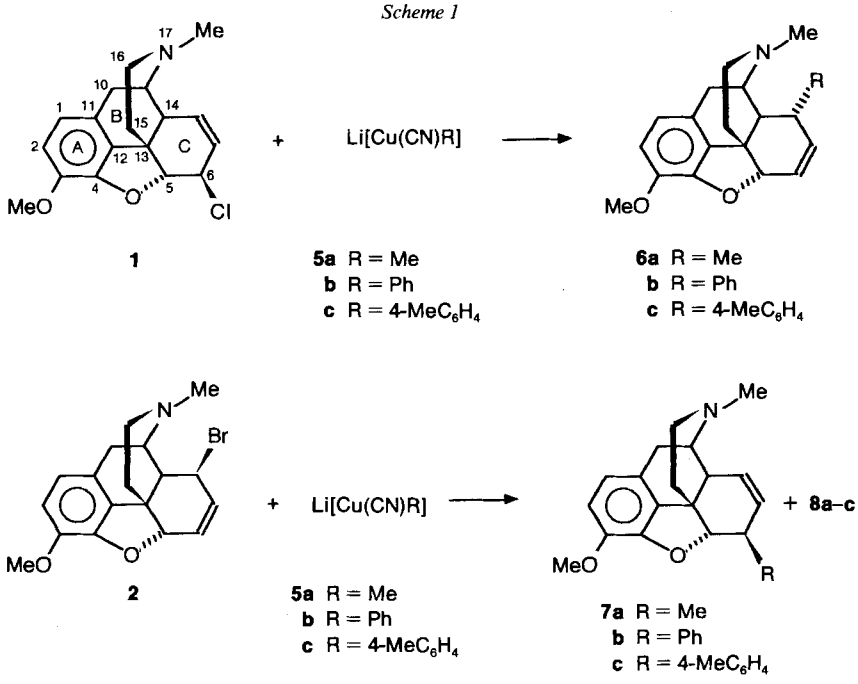
Nucleophilic substitution of 6β-chloro-7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan (**1**) and 8α-bromo-6,7-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan (**2**) with lithium cyano(methyl)- and (aryl)cyanocuprates(I) (**5a–c**) was accompanied by allylic rearrangement with both change and retention of orientation of the substituting group (*Scheme 1, Table 1*). Nucleophilic substitution in 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-yl methanesulfonate (**3**) and 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6β-yl methanesulfonate (**4**) proceeded without allylic rearrangement with both change and retention of the orientation of the substituting group (*Scheme 2, Table 1*). X-Ray diffraction studies of the products 6,7-didehydro-4,5α-epoxy-3-methoxy-17-methyl-8α-phenylmorphinan (**6b**) and 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methyl-6β-phenylmorphinan (**7b**) were carried out (*Figs. 1* and *2*).

Introduction. – Nucleophilic substitution in cyclic as well as acyclic allylic systems is widely used in preparative organic chemistry [1]. Reactions of this kind involving the alkaloids of the morphine series were studied in cases of substitution of halogenide atoms, mesyloxy, and tosyloxy groups upon reaction with halogenide, azide, and hydride ions, secondary amines, and stabilized carbanions [2–9]. The use of organic derivatives of Li, Mg, and Zn as nucleophiles resulted in the formation of product mixtures [10]. The type of nucleophilic substitution depends on the structure of the allylic system of ring C of codeine derivatives [11]. In those cases where the nucleophilic attack of the back side of the leaving group is not hindered, substitution proceeds normally by S_N2 mechanism to give α-oriented substituents in the allylic system of codeine. If this direction of nucleophilic attack is hindered, the nucleophilic substitution with allylic rearrangement takes place by an S_N2' mechanism to give β-oriented substituents.

Results. – We found that nucleophilic substitution in 6β-chloro-7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan (= 6β-chloro-6-deoxycodeine; **1**) and 8β-bromo-6,7-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan (= 8β-bromo-8-de-

Scheme 1



1

5a R = Me
b R = Ph
c R = 4-MeC_6H_4

6a R = Me
b R = Ph
c R = 4-MeC_6H_4

2

5a R = Me
b R = Ph
c R = 4-MeC_6H_4

7a R = Me
b R = Ph
c R = 4-MeC_6H_4

Table 1. *Yields and Product Distributions of the Reactions of* **1–4** *with* **5**

	1/5a	**1/5b**	**1/5c**	**2/5a**	**2/5b**	**2/5c**	**3/5a**	**3/5c**	**4/5a**	**4/5b**
Main product	**6a**	**6b**	**6c**	**7a**	**7b**	**7c**	**7a**	**8c**	**8a**	**8b**[a])
Yield [%]	42	35	32	40	37	33	45	34	40	–
M.p. [°C]	133–133.5	132–133.5	85–87	133–135	115–117	53–54	133–135	52–54	114–115	–
Isomer ratio: 8α	100	100	100	–	–	–	–	–	–	–
6β	–	–	–	82	98	52	60	32	2	
6α	–	–	–	18	2	48	40	68	98	

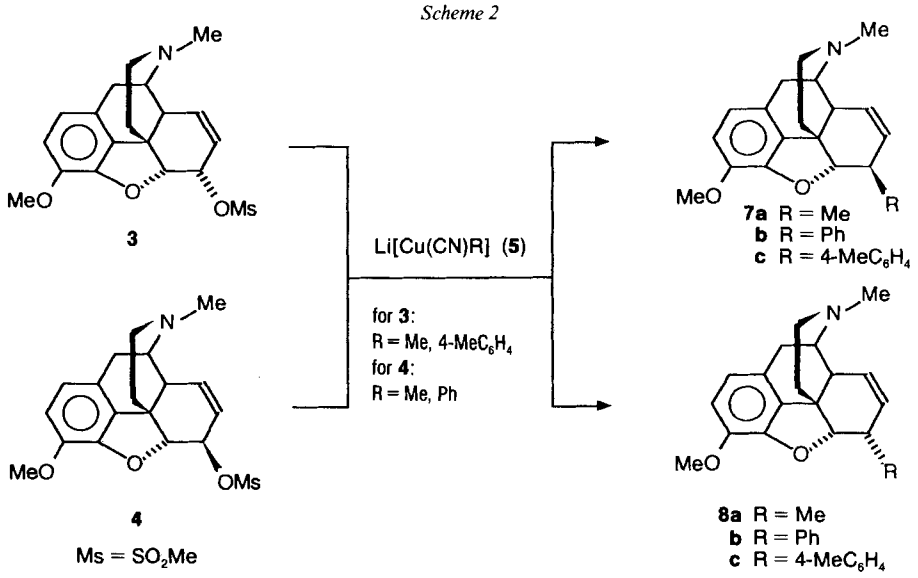
[a]) The product was not isolated in pure form.

oxypseudocodeine; **2**) upon reaction with lithium cyano(methyl)-, cyano(phenyl)-, and cyano(tol-4-yl)cuprates(I) (**5a–c**) proceeds with the substitution of the halogen atom by the hydrocarbon group. In these reactions, **1** yields exclusively 8α-substituted derivatives **6a–c** of 8-deoxypseudocodeine, whereas **2** gives 6β-substituted derivatives **7a–c** of 6-deoxycodeine as major products (*Scheme 1, Table 1*).

Thus, nucleophilic substitution of the β-oriented halogen atom in the allylic system of 6-deoxycodeine and 8-deoxypseudocodeine upon reaction with lithium cyano(methyl)- and (aryl)cyanocuprate involves allylic rearrangement accompanied by inversion of substituent orientation in the case of **1** and partial retention of substituent orientation in the case of **2**. In contrast, nucleophilic substitution in halogen derivatives of 6-deoxycodeines and 6-deoxypseudocodeines upon reaction with stabilized carbanions always proceeds with allylic rearrangement and retention of the substituent orientation [8] [9].

We also found that 6α-*O*-mesylcodeine (**3**) and 6β-*O*-mesylcodeine (**4**) react with **5** to give a mixture of 6β- and 6α-substituted derivatives **7** and **8**, respectively (*Scheme 2*). The relation of isomers depends on the structure of the precursor, **3** or **4**, and on the nature of the cuprate, **5a–c** (*Table 1*).

Scheme 2



We obtained 6β-*O*-mesylcodeine (**4**) for the first time by the reaction of 6-isocodeine (= 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6β-ol) [12] with methanesulfonyl (mesyl) chloride in the presence of Et_3N.

The elemental analyses (*Table 2*) as well as the ^{1}H-NMR spectra (*Table 3*) are in good agreement with the proposed structures **6a–c**, **7a–c**, and **8a–c**. The molecular structure of phenyl-substituted derivatives **6b** (*Fig. 1*) and **7b** (*Fig. 2*) were confirmed by X-ray diffraction studies.

Table 2. *Elemental Analyses of Compounds* **4**, **6a–c**, **7a–c**, **8a**, *and* **8c**

Compound	Formula	Calc. [%]			Found [%]		
		C	H	N	C	H	N
4[a])	$C_{19}H_{23}NO_5S$	60.48	6.10	3.70	60.35	6.34	3.63
6a	$C_{19}H_{23}NO_2$	76.74	7.80	4.71	76.45	7.77	4.42
b	$C_{24}H_{25}NO_2$	80.19	7.01	3.90	80.10	6.99	3.85
c	$C_{25}H_{27}NO_2$	80.33	7.23	3.75	80.18	7.25	3.54
7a	$C_{19}H_{23}NO_2$	76.74	7.80	4.71	76.26	7.82	4.57
b	$C_{24}H_{25}NO_2$	80.19	7.01	3.90	80.08	7.03	3.91
c	$C_{25}H_{27}NO_2$	80.33	7.23	3.75	79.95	7.15	3.42
8a	$C_{19}H_{23}NO_2$	76.74	7.80	4.71	76.50	7.96	4.63
c	$C_{25}H_{27}NO_2$	80.33	7.23	3.75	80.35	7.47	3.55

[a]) Calc.: S 8.50; found: S 8.74.

Table 3. *^{1}H-NMR Data of Compounds* **4**, **6a–c**, **7a–c**, *and* **8a–c**[a])

4	6.71, 6.64 (*2d, J* = 8.2, 8.2, 2 arom. H); 5.85 (*m*, 2 olef. H); 4.96 (*m*, H–C(6)); 4.67 (*m*, H–C(5)); 3.82 (*s*, MeO); 3.01 (*s*, $MeSO_2$); 2.45 (*s*, MeN)
6a	6.66, 6.53 (*2d, J* = 8.2, 8.2, 2 arom. H); 5.66 (*dd, J* = 10.4, 4.5, H–C(7)); 5.53 (*m*, H–C(6)); 4.78 (*m*, H–C(5)); 3.71 (*s*, MeO); 2.37 (*m*, H–C(8)); 2.27 (*s*, MeN); 0.39 (*d, J* = 7.4, Me–C(8))
6b	7.06 (*m*, 5 arom. H); 6.68, 6.61 (*2d, J* = 8.2, 8.2, 2 arom. H); 5.83 (*dd, J* = 10.5, 4.5, H–C(7)); 5.75 (*m*, H–C(6)); 4.97 (*m*, H–C(5)); 3.88 (*s*, MeO); 2.37 (*m*, H–C(8)); 2.29 (*s*, MeN)
6c	7.03 (*m*, 4 arom. H); 6.62, 6.48 (*2d, J* = 8.2, 8.2, 2 arom. H); 6.05 (*dd, J* = 10.4, 4.3, H–C(7)); 5.88 (*m*, H–C(6)); 4.96 (*m*, H–C(5)); 3.88 (*s*, MeO); 2.39 (*m*, H–C(8)); 2.32 (*s*, MeN); 2.21 (*s*, MeC_6H_4)
7a	6.60, 6.48 (*2d, J* = 8.2, 8.2, 2 arom. H); 5.71 (*m*, H–C(7)); 5.27 (*dd, J* = 3.1, 9.9, H–C(8)); 4.47 (*m*, H–C(5)); 3.76 (*s*, MeO); 2.39 (*s*, MeN); 2.36 (*m*, H–C(6)); 1.03 (*d, J* = 7.6, Me–C(6))
7b	7.30 (*m*, 5 arom. H); 6.70, 6.58 (*2d, J* = 8.2, 8.2, 2 arom. H); 5.88 (*m*, H–C(7)); 5.59 (*m*, H–C(8)); 4.84 (*m*, H–C(5)); 3.88 (*s*, MeO); 3.00 (*m*, H–C(6)); 2.44 (*s*, MeN)
7c	7.04 (*m*, 4 arom. H); 6.64, 6.45 (*2d, J* = 8.2, 8.2, 2 arom. H); 5.58 (*m*, H–C(7)); 4.86 (*m*, H–C(5)); 3.89 (*s*, MeO); 3.00 (*m*, H–C(6)); 2.46 (*s*, MeN); 2.29 (*s*, MeC_6H_4)
8a	6.58, 6.44 (*2d, J* = 8.2, 8.2, 2 arom. H); 5.43 (*m*, H–C(7)); 5.27 (*dd, J* = 2.2, 9.6, H–C(8)); 4.68 (*d, J* = 5.2, H–C(5)); 3.76 (*s*, MeO); 2.39 (*s*, MeN); 1.17 (*d, J* = 7.4, Me–C(6))
8b	7.15 (*m*, 5 arom. H); 6.72, 6.62 (*2d, J* = 8.2, 8.2, 2 arom. H); 5.80 (*m*, 2 olef. H); 5.09 (*d, J* = 3.1, H–C(5)); 3.88 (*s*, MeO); 3.00 (*m*, H–C(6)); 2.44 (*s*, MeN)
8c	7.20 (*m*, 4 arom. H); 6.78, 6.71 (*2d, J* = 8.2, 8.2, 2 arom. H); 5.78 (*m*, 2 olef. H); 5.09 (*d, J* = 2.7, H–C(5)); 3.87 (*s*, MeO); 2.95 (*m*, H–C(6)); 2.40 (*s*, MeN); 2.34 (*s*, MeC_6H_4)

[a]) Solvent $CDCl_3$; δ in ppm relative to Me_4Si as internal reference, *J* (apparent coupling constant) in Hz.

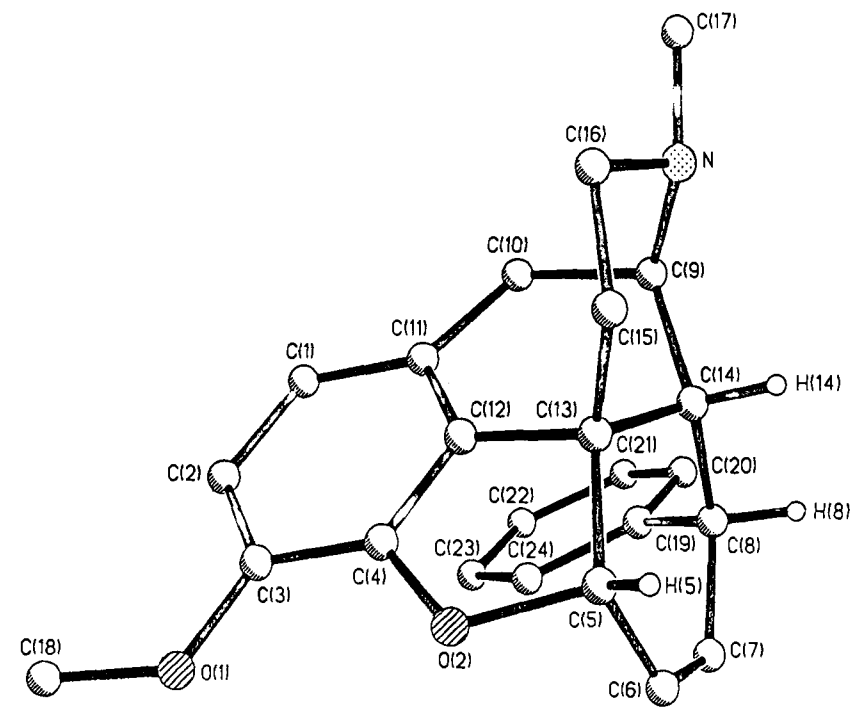


Fig. 1. *Molecular structure of 6,7-didehydro-4,5α-epoxy-3-methoxy-17-methyl-8α-phenylmorphinan* (**6b**). No H-atoms shown, except H(5), H(8), and H(14).

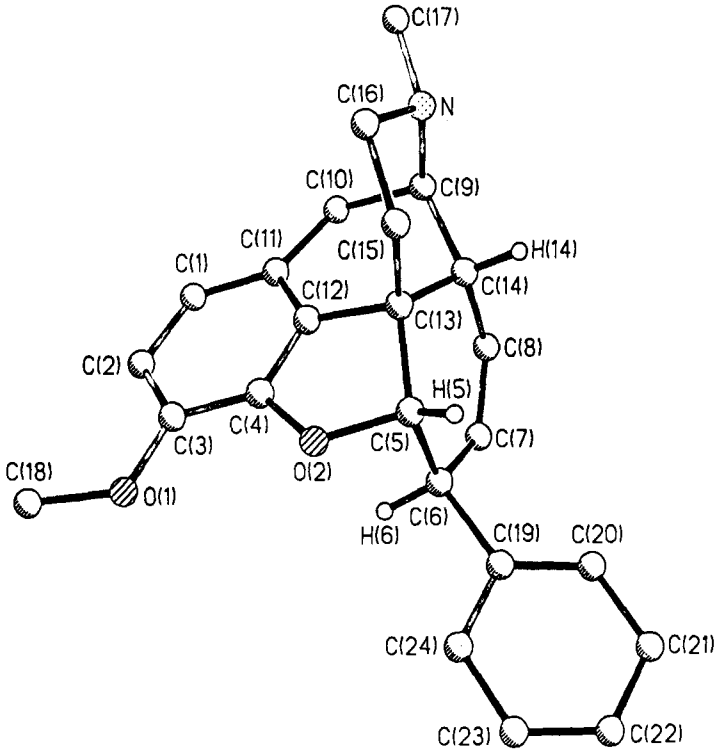


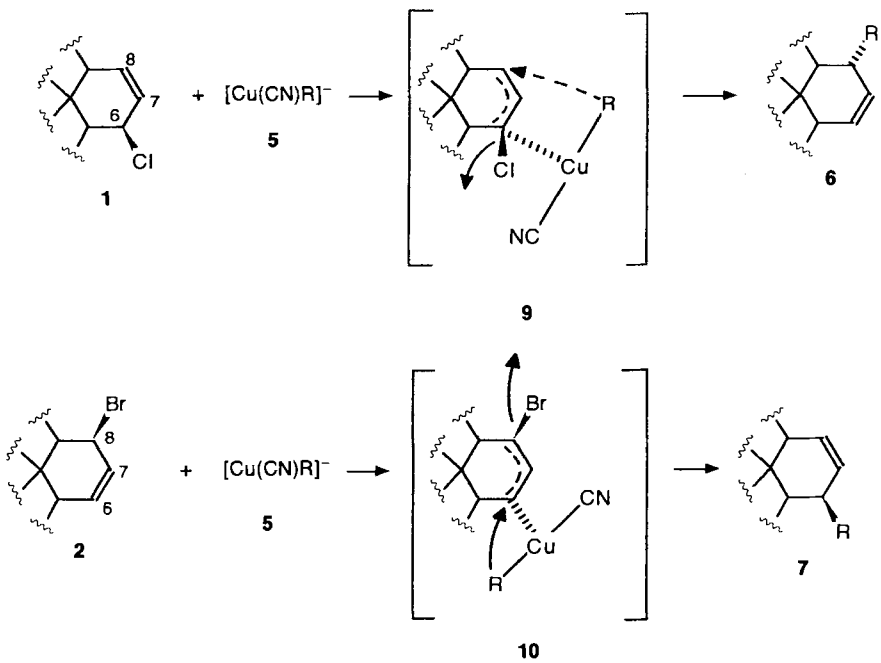
Fig. 2. *Molecular structure of 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methyl-6β-phenylmorphinan* (**7b**). No H-atoms shown, except H(5), H(6), and H(14).

The basic geometric parameters in the molecules **6b** and **7b** are quite usual for codeine derivatives. They were described in detail for 8β-bromo-6,7-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan (**2**) [13] and 8β-[bis(methoxycarbonyl)methyl]-8-deoxypseudocodeine [9]. In both **6b** and **7b**, the B/C ring fusion is *cis* and ring B may be described as a sofa with C(14) being distant from the plane C(9)–C(10)–C(11)–C(12)–C(13) by 0.703 and 0.704 Å in **6b** and **7b**, respectively. The dihydrofuran ring, *cis*-fused with ring C, has the form of an envelope, in which the C(5) atom is deviated from the plane O(2)–C(4)–C(12)–C(13) by 0.380 and 0.573 Å for **6b** and **7b**, respectively. The piperidine ring, N–C(9)–C(14)–C(13)–C(15)–C(16), *trans*-fused with ring C, is in the conformation of an arm-chair, and the Me group at the N-atom is in equatorial orientation.

The most essential geometric differences of molecules **6b** and **7b** concern the conformation of ring C. Ring C of **6b** (C(6)=C(7) 1.322(8) Å) has the conformation of a sofa with the deviation of atom C(14) by 0.446 Å from the plane C(13)–C(5)–C(6)–C(7)–C(8), whereas deviation of atom C(13) from the plane C(5)–C(6)–C(7)–C(8)–C(14) in **7b** (C(7)=C(8) 1.329(8) Å) is 0.426 Å. The plane of the phenyl ring C(19)–C(20)–C(21)–C(22)–C(23)–C(24) formes the dihedral angle 83.4 and 65.2°, respectively, with the plane of the ethylene bond, *i.e.* with C(5)–C(6)–C(7)–C(8) in **6b** and C(6)–C(7)–C(8)–C(14) in **7b**.

Discussion. – The results of our studies of nucleophilic substitution in the allylic system of codeine and pseudocodeine with the formation of a new C–C bond reported in the present paper and earlier [8] [9] [14] are in reasonable agreement with the literature data on nucleophilic substitution in alicyclic allylic systems on reaction with stabilized carbanions and lithium dimethylcuprates [1] [10] [15]. The '*syn*'-attack at the C(γ) atom is most typical for stabilized carbanions, whereas the reactions with organocopper reagents taking place with the same mechanism may also proceed *via* intermediate σ-allyl-type copper complexes. One may suppose that in the reaction involving 6β-chloro-6-deoxycodeine (**1**), the σ-allyl-copper complex **9**, with α-orientation of the Cu-atom, is formed. Simultaneously, intramolecular attack at C(8) to yield α-substituted products **6** takes place (*Scheme 3*).

Scheme 3



The reaction of 8β-bromo-8-deoxypseudocodeine (**2**) evidently involves '*syn*'-attack at C(6) with the formation of intermediate complexes **10** and β-substituted products **7**, according to the mechanism reported for reactions with stabilized carbanions [1] [8] [9] [14] (*Scheme 3*).

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Experimental Part

General. Reactions were monitored by TLC: silica gel (*Silufol*), $CHCl_3$/MeOH/25% NH_3 9.5:0.5:0.05. Column chromatography: silica gel (100/160 µ), from *Chemapol*, Czechoslovakia. ^{1}H-NMR Spectra: *Bruker-WP-200-SY* spectrometer at 200 MHz in $CDCl_3$.

Crystal Data for **6b** *and* **7b**. $C_{24}H_{25}NO_2$, $M = 359.5$, orthorhombic, space group $P2_12_12_1$; $a = 9.460(2)$ and 8.421(4), $b = 9.576(2)$ and 10.609(6), $c = 20.552(4)$ and 21.01(1) Å, $V = 1862.4(3)$ and 1876.8(5) Å^3, $D_c = 1.282$ and 1.272 g·cm^{-3}, resp.; $Z = 4$, $F(000) = 768$, $\mu(\lambda MoK_\alpha) = 0.8$ cm^{-1}. Unit-cell parameters were determined, and intensities of 1197 and 1310 independent reflections, resp., with $F^2 \geq 3\sigma(F^2)$ were collected on a *Siemens-P-3/PC* 4-circle automatic diffractometer at +20° up to $\theta_{max} = 27$ and 29° ($\lambda = 0.71073$ Å (MoK_α), graphite monochromator, $\theta/2\theta$ scan); no absorption correction was applied. Both structures were solved and refined by means of the PC version of the SHELXTL programme package [16] using an *IBM* PC computer. All H-atoms were located in the difference *Fourier* synthesis and in the least-squares refinement in the 'riding'-model approximation with isotropic temperature factors. Final discrepancy factors are 0.0468 and 0.0578, weighted R-factors $R_w = 0.0477$ and 0.0613, resp. Absolute configurations of both molecules were assigned on the basis of the known configurations of the codeine fragment. Atomic coordinates, thermal parameters, bond lengths, and bond angles were deposited at the *Cambridge Crystallographic Data Centre*.

6β-O-Mesylcodeine (*= 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6β-yl Methanesulfonate*; **4**). In a *Dean-Stark* apparatus, a soln. of 6-isocodeine·H_2O (31.7 g, 100 mmol) in 350 ml of CH_2Cl_2 was refluxed. Every 45 min, 15 ml of the azeotropic mixture was trapped and removed (total 45 ml). The soln. was cooled in an ice-bath, mesyl chloride (17 ml, 220 mmol) added, and the resulting mixture stirred for 1 h. Et_3N (10 ml, 75 mmol) was then added and the mixture stirred for 0.5 h at r.t. (TLC: almost 100% conversion). After addition of 2N KOH, the product was extracted with CH_2Cl_2. Workup in the usual way afforded 30 g of crude solid **4** which was crystallized from AcOEt: 25 g (66%) of pure **4**. M.p. 142–144°.

Nucleophilic Substitution of Codeine and Pseudocodeine Derivatives, General Procedure. One equiv. of CuCN in anh. THF (cooled to −5°) was added to a stirred soln. of 1 equiv. of the corresponding organolithium derivative in anh. Et_2O at −5° under Ar. After stirring for 20 min at −5°, 0.32 equiv. of **1–4** were added, and the mixture was kept for 20 min at −5°. Then the mixture was treated with aq. sat. NH_4Cl soln., concentrated *in vacuo*, alkalinized with 2N NH_4OH (pH 9.5), and extracted with $CHCl_3$. The org. layer was dried (Na_2SO_4) and evaporated and the residue chromatographed (silica gel, $CHCl_3$). The resulting solid was recrystallized from a mixture of AcOEt/heptane 1:4: pure products as colorless crystals, yields 20–40%.

6,7-Didehydro-4,5α-epoxy-3-methoxy-17-methyl-8α-phenylmorphinan (**6b**). According to the *General Procedure*, with CuCN (2.68 g, 30 mmol), THF (20 ml), PhLi (2.52 g, 30 mmol), and **1** (3.18 g, 10 mmol). Workup: 10 ml of aq. sat. NH_4Cl soln., concentration to *ca.* 5 ml, extraction with $CHCl_3$ (3 × 30 ml), and chromatography on silica gel, deactivated with 30% (by weight) of H_2O: 1.26 g (35%) of **6b**.

7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methyl-6β-phenylmorphinan (**7b**). According to the *General Procedure* and as described for **6b**, using **2** (3.62 g, 10 mmol) instead of **1**: 1.33 g (37%) of **7b**.

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