Nucleophilic Substitution in the Allyl System of Codeine and Pseudocodeine in their Reactions with Lithium Methyl- and Aryl-cyanocuprates. Crystal and Molecular Structure of 8α-Phenyl-6,7-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan and 6β-Phenyl-7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan

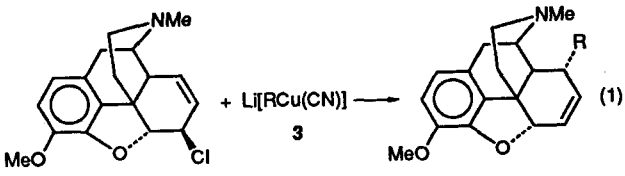
Valery N. Kalinin,* Irina L. Belyakova, Vladimir V. Kobak, Pavel V. Petrovskii, Aleksandr I. Yanovsky and Yurii T. Struchkov

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 117813 Moscow, Russian Federation. Fax: +7 095 135 5085

It has been shown that nucleophilic substitution in 6β-chloro-7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan and 8β-bromo-6,7-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan is accompanied by allylic rearrangement with both a change in and retention of the orientation of the substituting group. X-Ray diffraction studies of 8α-phenyl-6,7-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan and 6β-phenyl-7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan have been carried out.

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 have been studied in the cases of substitution of halogenide atoms, mesyl- and tosyl-oxy groups upon action of halogenide, azide and hydride ions, secondary amines and stabilized carbanions.[2–9] The use of organic derivatives of lithium, magnesium and zinc as nucleophiles results in the formation of product mixtures.[10]

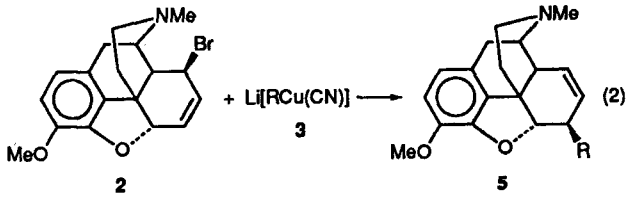
We have found that nucleophilic substitution in 6β-chloro-7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan (6β-chloro-6-desoxycodeine) **1** and 8β-bromo-6,7-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan (8β-bromo-8-desoxypseudocodeine) **2** upon action of lithium methyl-, phenyl- and *p*-tolyl-cyanocuprates **3a–c** proceeds with the substitution of the halogen atom by the hydrocarbon group. In these reactions compound **1** yields exclusively 8α-substituted derivatives of 8-desoxypseudocodeines **4a–c** [eqn. (1)]:



1 **4**

a R = Me
b R = Ph
c R = C_6H_4-Me-*p*

whereas compound **2** gives 6β-substituted derivatives of 6-desoxycodeines **5a–c** [eqn. (2)] as major products.



2 **5**

a R = Me
b R = Ph
c R = C_6H_4-Me-*p*

Reactions were carried out in a mixture of diethyl ether and THF at −5°C.† The elemental analysis data as well as the results of IR, NMR and mass spectroscopic studies are in good agreement with the proposed structure of compounds **4a–c** and **5a–c**. Molecular structures of phenyl-substituted derivatives **4b** (Fig. 1) and **5b** (Fig. 2) have been elucidated with the help of X-ray diffraction studies.‡

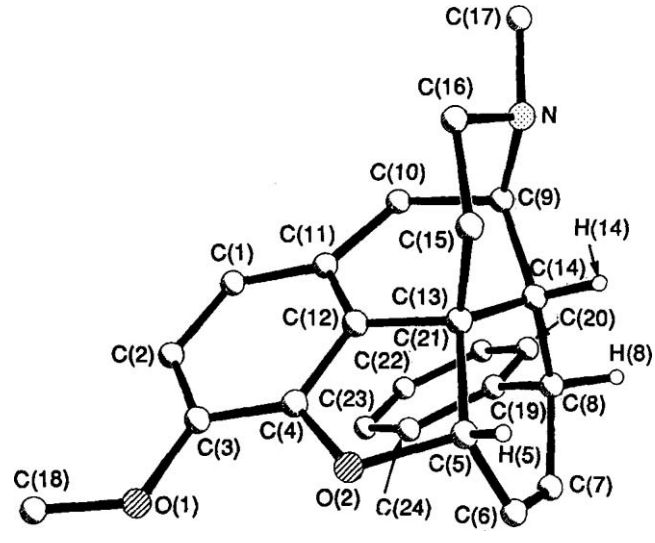


Fig. 1 Molecular structure of 8α-phenyl-6,7-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan **4b**. The H atoms [with the exception of H(5), H(8) and H(14)] are not shown

Thus, the nucleophilic substitution of the β-oriented halogen atom in the allylic system of codeine and pseudocodeine upon action of lithium methyl- and aryl-cyanocuprate involves allylic rearrangement accompanied by inversion of substituent orientation in the case of 6β-chloro-6-desoxypseudocodeine **1** and retention of substituent orientation in the case of 8β-bromo-8-desoxypseudocodeine **2**.

† *Typical procedure*: 1 equiv. of CuCN in anhydrous, freshly-distilled THF at −5°C in an atmosphere of dry argon was added with stirring to 0.95 equiv. of the corresponding organolithium compound in anhydrous diethyl ether. After being stirred for 20 min at −5°C, 0.32 equiv. of compound **1** or **2** were added and the mixture was left to stand for 20 min at the same temperature. When the reaction was complete (TLC monitoring) the mixture was treated with 3 ml of aqueous, saturated NH_4Cl. The product was extracted with $CHCl_3$, chromatographed on a silica gel column, deactivated by 30% (by weight) of H_2O (eluent: $CHCl_3$) and recrystallized from ethyl acetate–heptane (1:4). The yields of final products in the form of colourless crystals were 20–40%, m.p. 133–133.5, 123–133.5, 85–87, 133–135, 115–117 and 53–54°C for **4a–c** and **5a–c**, respectively.

‡ Crystal data for **4b** and **5b**, respectively: $C_{24}H_{25}NO_2$, $M = 359.5$, orthorhombic, space group $P2_12_12_1$, $a = 9.460(2)$ and $8.241(4)$, $b = 9.576(2)$ 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 Mg m^{-3}, $Z = 4$, $F(000) = 768$, $\mu(\lambda MoK\alpha) = 0.8$ cm^{-1}, 1197 and 1310 reflections with $F^2 \geq 3\sigma(F^2)$ were collected at +20°C up to $\theta_{max} = 27$ and 29° [$\lambda = 0.71073$ Å (MoKα), 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[11] 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. Absolute configurations of both molecules have been assigned on the basis of the known configurations of the codeine fragment. Atomic coordinates, bond lengths and bond angles have been deposited at the Cambridge Crystallographic Data Centre (see Notice to Authors, *Mendeleev Commun.*, 1993, Issue 1).

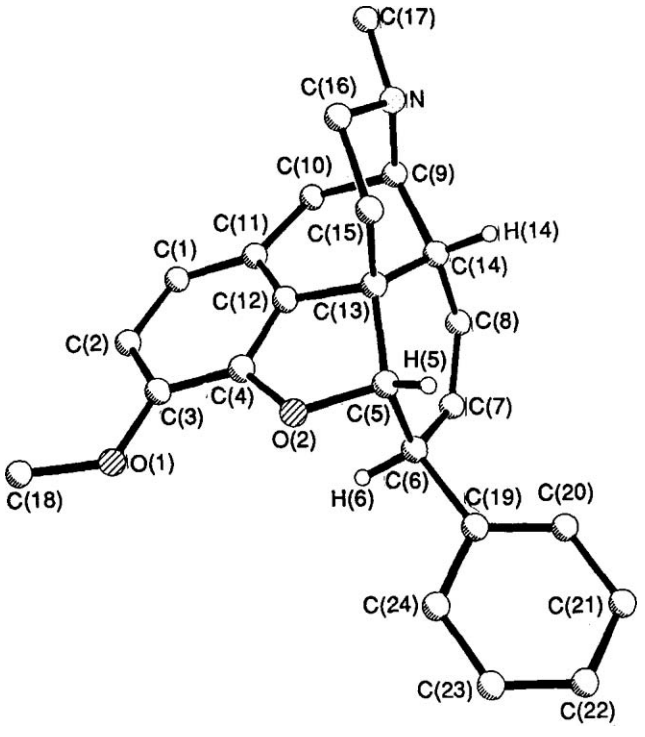
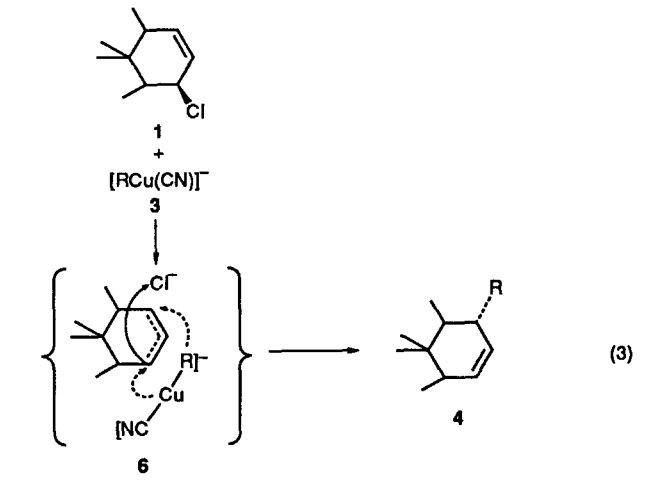


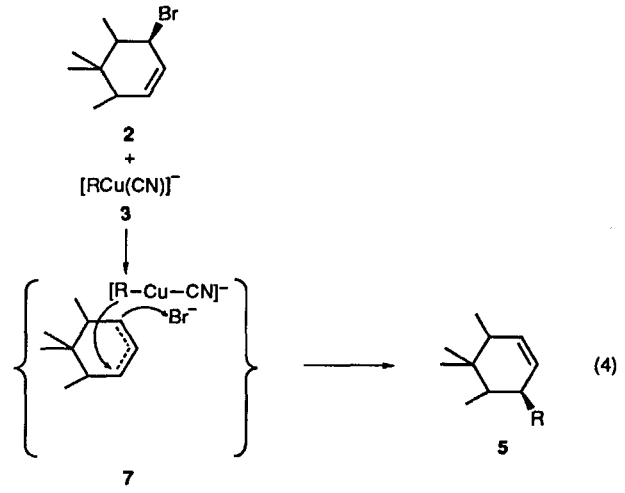
Fig. 2 Molecular structure of 6β-phenyl-7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan **5b**. The H atoms [with the exception of H(5), H(6) and H(14)] are not shown

In contrast, nucleophilic substitution in halogen derivatives of desoxycodeines and desoxypseudocodeines upon action of stabilized carbanions always proceeds with allylic rearrangement and retention of the substituent orientation.[8,9] The results of our studies of nucleophilic substitution in the allylic system of codeine and pseudocodeine with the formation of a new carbon–carbon bond reported in the present paper and earlier[8,9] are in reasonable agreement with the literature data on nucleophilic substitution in alicyclic allylic systems on action of stabilized carbanions and lithium dimethylcuprates.[1,11,12] The *syn*-attack at the γ-carbon atom is most typical for stabilized carbanions, whereas the reactions with organocopper reagent 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-desoxycodeine **1** the σ-allyl copper complex **6**, with α-orientation of the metal atom, is formed. Simultaneously, intramolecular attack at C-8 to yield α-substituted products **4** [eqn. (3)] takes place.

The reaction of 8β-bromo-8-desoxypseudocodeine **2** evidently involves *syn*-attack at C-6 with the formation of intermediate complexes **7** and β-substituted products **5**, according to the mechanism reported for reactions with stabilized carbanions[1,8,9] [eqn. (4)].



(3)



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