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STUDIES IN THE (+)-MORPHINAN SERIES I. AN ALTERNATE CONVERSION OF (+)-DIHYDROCODEINONE INTO (+)-CODEINE.

Ikuo Iijima and Kenner C. Rice*

Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, Bethesda, Maryland 20014, USA

J. V. Silverton

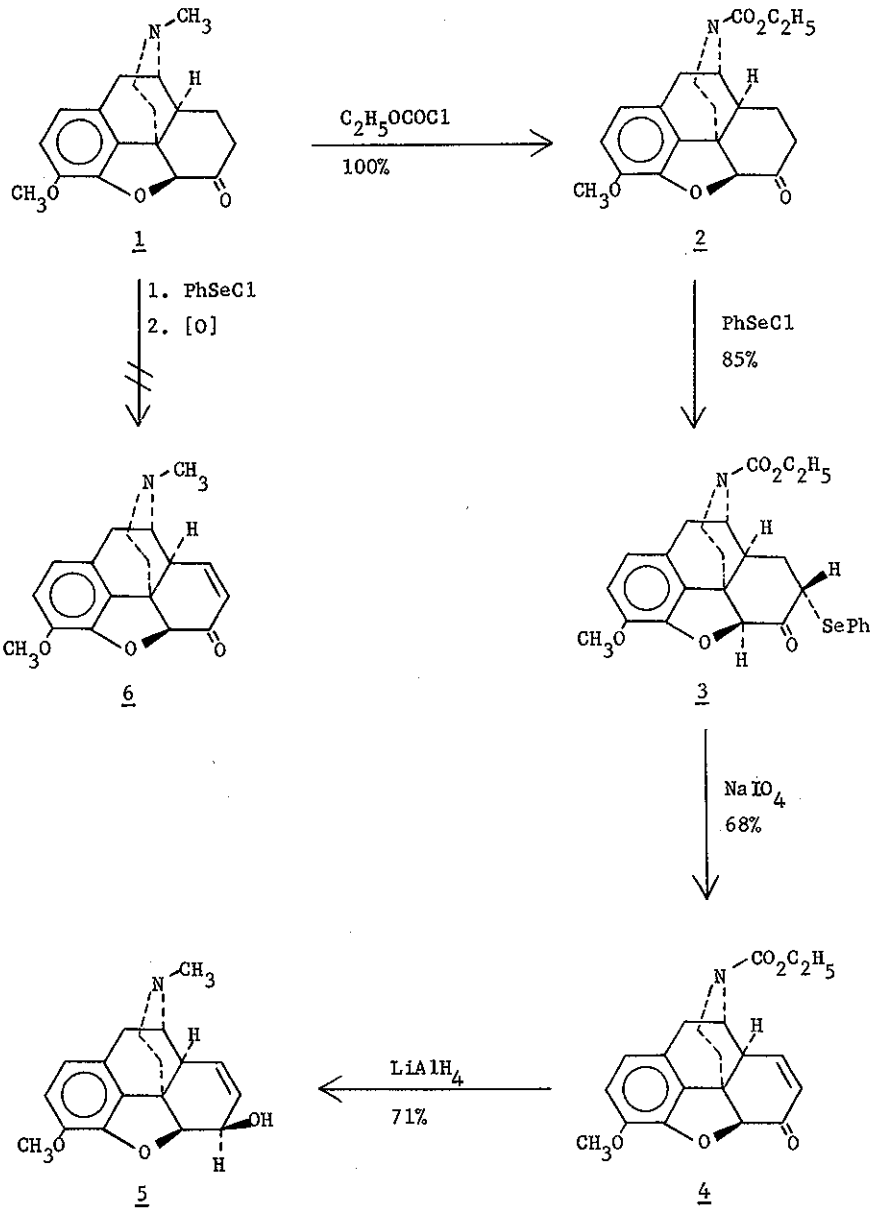
Laboratory of Chemistry, National Heart, Lung and Blood Institute, Bethesda, Maryland 20014, USA

A novel four-step transformation of (+)-dihydrocodeinone (1) to unnatural (+)-codeine (5) via N-carbethoxy-7-phenylselenonordihydrocodeinone (3) (40% overall yield) is described. The structure and absolute configuration of 3 were confirmed by single crystal X-ray analysis.

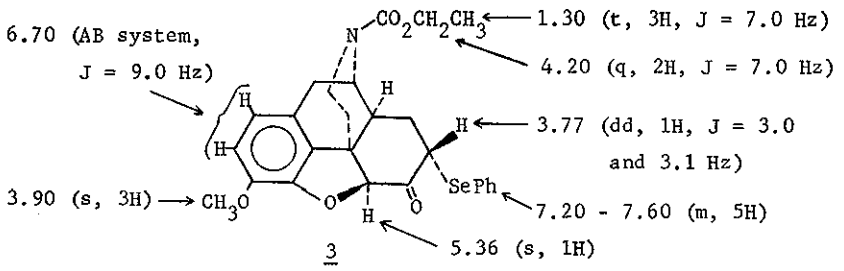
An elegant conversion of (-)-dihydrocodeinone (1)[1] into (-)-codeinone (6)[1], a key intermediate for preparation of natural (-)-codeine (5)[1] and related compounds has recently been described[2]. In the following report, we would like to present an alternate route, which was used earlier in our laboratory to prepare the corresponding enantiomers in the (+)-series.

(+)-Dihydrocodeinone (1), obtained from the alkaloid sinomenine in one step by the original method by Goto[3], could not be converted into (+)-codeinone (6) via the 7-phenylseleno derivative, in agreement with results previously[2] reported. However, when interference of the basic amine function present in 1 was eliminated by conversion of 1 to the neutral carbamate 2, introduction of the required 7,8-double bond was readily accomplished by reaction with phenylselenenyl chloride to give 3, followed by the usual oxidation-elimination sequence[4]. Reduction of the resulting N-carbethoxynorcodeinone (4), with lithium aluminum hydride then provided (+)-codeine (5). Thus, treatment of (+)-dihydrocodeinone (1) with excess ethyl chloroformate in refluxing benzene (16 hrs) quantitatively afforded the carbamate 2 as a foam: ir ($CHCl_3$), 1720 (>C=O) and 1680 (N-C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.0 Hz, $-CH_2\underline{CH_3}$), 3.93 (s, 3H, OCH_3), 4.20 (q, 2H, J = 7.0 Hz, $-\underline{CH_2}-CH_3$), 4.68 (s, 1H, C_5-H), mass spectrum m/e (rel %) 357 (78, M^+), 284 (20), 241 (100).

Reaction of 2 with phenylselenenyl chloride in ethyl acetate containing a catalytic amount of 37% HCl (25°, 4.5 hrs) provided 3 (85%) as colorless prisms from Et_2O: mp 129°; ir ($CHCl_3$) 1720 (C=O) and 1680 (N-C=O) cm^{-1}; mass spectrum, m/e (rel %) 513 (100, M^+), 355 (65); $[\alpha]_D^{23}$+251.1° (c 0.538, ethanol). Anal. ($C_{26}H_{27}NO_5Se$) C,H,N. Assignment of the axial configuration for the 7-phenylseleno substituent was made after examination of the NMR spectrum of 3 in deuteriochloroform which showed a doublet of doublets at δ 3.77


C_2H_5OCOCl
100%
1. PhSeCl
2. [O]
PhSeCl
85%
$NaIO_4$
68%
$LiAlH_4$
71%

(C-7 H, J = 3.0 and 3.1 Hz) and a singlet at δ 5.36 (C-5 H). The magnitude of the coupling constants for the C-7 proton was indicative of the equatorial configuration for this proton. This conclusion was supported by the observed low field shift (δ 0.48) of the C-5 proton relative to that of the unsubstituted carbamate 2 which can be attributed to 1,3-diaxial interaction of this proton with the 7-phenylseleno group; similar low field shifts have previously been observed for 1,3-diaxial interactions of this type[4]. The nmr absorptions in deuteriochloroform (δ units) of 3 which were readily assignable are shown below.



3

Final confirmation of the structure of 3, including its absolute configuration, was obtained by a single crystal X-ray analysis using techniques which have been described previously[5].

Crystal Data MW 512.46, habit: orthorhombic prismatic, space group $P2_12_12_1$ (No. 19), cell dimensions (from least squares refinement of $\pm\theta$ data): a = 7.975(1), b = 15.738(1), c = 18.323(1)Å, V = 2299.7Å^3, Z = 4, Dx = 1.480 g cm^{-3}, Dm = 1.47(1) g/cm^{-3}, μ = 25.57 cm^{-1}.

For data collection an approximately spherical sample, radius ~0.11 mm, was obtained by stirring a crystal in ethanol. Data were collected to a maximum sin θ/λ of 0.61 A^{o-1} and 2156 observed reflections and 344 unobserved reflections (1σ) resulted. Programs used were from the XRAY72[6] system except for local programs used in data processing. A spherical absorption correction, $\mu R = 0.28$, Lorentz and polarization corrections were applied to the data. Given the presence of the selenium atom, structure solution was routine and all atoms, including hydrogen, were found and included in the least squares refinement. Hydrogen atom thermal parameters were set to the isotropic parameters of the atoms to which they were attached but all other atoms were refined with anisotropic thermal parameters. The final R-factor was 0.031 (Rw = 0.039). The corresponding values for a molecule with the opposite absolute configuration were R = 0.041 (Rw = 0.050) and the R-factor ratio is sufficiently large to confirm that the absolute configuration used is correct at any practical level of probability and is as expected for the unnatural (+)-series. The molecular conformation and numbering used in the crystallographic work are given in Figure 1. The thermal parameters for C(3") and C(4")[7], in the side chain, are rather large and there may possibly be some disorder. Intermolecular contacts generally correspond to Van der Waals interactions except for the side chain where there are few close contacts.

Discussion of structure The bond lengths are given in Table 1 and the bond angles in Table 2. The esd.s in this structure, despite the presence of the heavy selenium atom, are as good as those in the most directly comparable structure, that of morphine hydrate[8], which had no atoms heavier than oxygen. In general, apart from the differences caused by the different chemical structure, comparable bond lengths are very similar. The similarity extends to

Table 1 . Bond lengths in Angstroms. Esd.s are 0.003Å for bonds involving the Selenium atom and otherwise range from 0.004Å to to 0.006Å, except for the C(3")-C(4") bond which has an esd. of of 0.01Å.

Se	C(1')	1.925	Se	C(6)	1.997	C(1')	C(2')	1.384
C(1')	C(6')	1.372	C(2')	C(3')	1.380	C(3')	C(4')	1.381
C(4')	C(5')	1.372	C(5')	C(6')	1.387	C(1)	C(2)	1.383
C(2)	C(3)	1.396	C(3)	C(3a)	1.378	C(3)	O(3)	1.384
C(3)	C(3m)	1.425	C(3a)	O(4)	1.367	C(3a)	C(9b)	1.386
O(4)	C(4a)	1.460	C(4a)	C(5)	1.534	C(4a)	C(9c)	1.545
C(5)	O(5)	1.216	C(5)	C(6)	1.500	C(6)	C(7)	1.527
C(7)	C(7a)	1.516	C(7a)	C(8)	1.545	C(7a)	C(9c)	1.525
C(8)	C(9)	1.538	C(8)	N(12)	1.475	C(9)	C(9a)	1.510
C(9a)	C(9b)	1.374	C(9b)	C(9c)	1.516	C(9c)	C(10)	1.549
C(10)	C(11)	1.522	C(11)	N(12)	1.464	N(12)	C(1")	1.349
C(1")	O(1")	1.202	C(1")	O(2")	1.361	O(2")	C(3")	1.451
C(3")	C(4")	1.467						

Table 2 . Bond angles in degrees. Esd.s are less than or equal to 0.3°.

C(1')	Se	C(6)	98.9	C(2')	C(1')	Se	118.6
C(6')	C(1')	Se	120.7	C(2')	C(1')	C(6')	120.7
C(1')	C(2')	C(3')	119.6	C(2')	C(3')	C(4')	120.1
C(3')	C(4')	C(5')	119.7	C(4')	C(5')	C(6')	120.8
C(1')	C(6')	C(5')	119.1	C(2)	C(1)	C(9a)	121.4
C(1)	C(2)	C(3)	122.0	C(2)	C(3)	C(3a)	116.9
C(2)	C(3)	O(3)	121.0	C(3a)	C(3)	O(3)	122.1
C(3)	C(3a)	O(4)	127.7	C(3)	C(3a)	C(9b)	119.8
O(4)	C(3a)	C(9b)	112.5	C(3)	O(3)	C(3m)	113.7
C(3a)	O(4)	C(4a)	105.5	O(4)	C(4a)	C(5)	107.9
O(4)	C(4a)	C(9c)	105.5	C(5)	C(4a)	C(9c)	112.4
C(4a)	C(5)	O(5)	120.6	C(4a)	C(5)	C(6)	117.4
O(5)	C(5)	C(6)	122.0	C(5)	C(6)	Se	107.6
C(7)	C(6)	Se	108.6	C(5)	C(6)	C(7)	111.6
C(6)	C(7)	C(7a)	111.6	C(7)	C(7a)	C(8)	114.8
C(7)	C(7a)	C(9c)	112.2	C(8)	C(7a)	C(9c)	106.9
C(7a)	C(8)	C(9)	114.5	C(7a)	C(8)	N(12)	107.4
C(9)	C(8)	N(12)	111.2	C(8)	C(9)	C(9a)	114.6
C(1)	C(9a)	C(9)	127.3	C(1)	C(9a)	C(9b)	115.1
C(9)	C(9a)	C(9b)	117.4	C(3a)	C(9b)	C(9a)	124.5
C(3a)	C(9b)	C(9c)	108.2	C(9a)	C(9b)	C(9c)	127.2
C(4a)	C(9c)	C(7a)	119.6	C(4a)	C(9c)	C(9b)	98.5
C(4a)	C(9c)	C(10)	111.4	C(7a)	C(9c)	C(9b)	108.8
C(7a)	C(9c)	C(10)	108.3	C(9b)	C(9c)	C(10)	109.5
C(9c)	C(10)	C(11)	111.6	C(10)	C(11)	N(12)	111.2
C(8)	N(12)	C(11)	116.8	C(8)	N(12)	C(1")	117.4
C(11)	N(12)	C(1")	124.0	N(12)	C(1")	O(1")	125.7
N(12)	C(1")	O(2")	111.0	O(1")	C(1")	O(2")	123.2
C(1")	O(2")	C(3")	117.5	O(2")	C(3")	C(4")	108.6

the different C-O bond lengths in the five-membered ring. The aliphatic six-membered rings adopt chair conformations with some distortion caused by the presence of the aromatic ring which is itself not quite planar. The benzene ring of the phenylseleno substituent is planar. The configuration of the carbon atom bearing the phenylseleno substituent can be deduced from the torsion angles O(5)-C(5)-C(6)-Se: 112° and O(5)-C(5)-C(6)-H(6): 0°[7] and agrees with the deductions from spectroscopic data. In the Cahn-Prelog notation C(6)[7] is S.

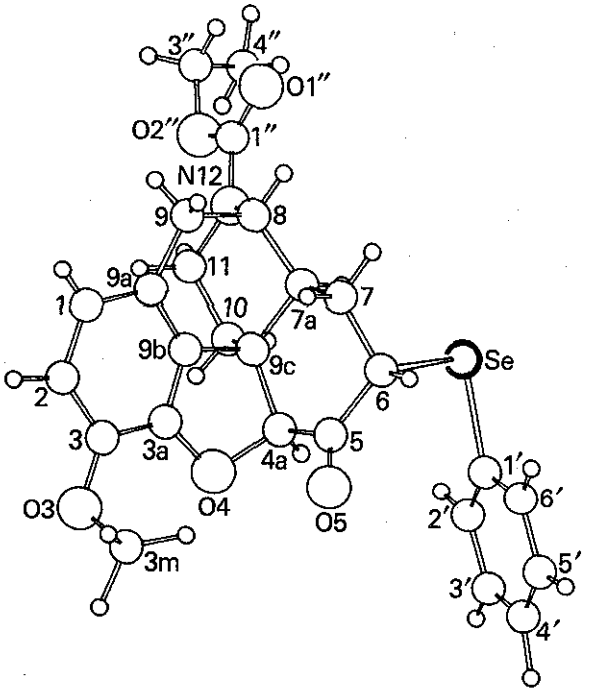


Figure 1

Oxidation of 3 with $NaIO_4$ (8.0 mols) in EtOAc-H_2O (20 hr) gave N-carbethoxy-norcodeinone (4) directly (68%) as a colorless foam: ir ($CHCl_3$) 1690 cm^{-1} (both C=O); NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.0 Hz, $CH_2\underline{CH_3}$), 3.86 (s, 3H, $O\underline{CH_3}$), 4.21 (q, 2H, J = 7.0 Hz, $\underline{CH_2}CH_3$), 4.70 (s, 1H, C_5-H), 6.11 (dd, 1H, J = 10.1 Hz, 3 Hz, C_7-H), 6.70 (dd, 1H, J = 10.1, 1.7 Hz, C_8-H)[9], mass spectrum m/e (rel %) 355 (93, M^+) 240 (100). Reduction of 4 with excess lithium aluminum hydride in refluxing tetrahydrofuran gave 71% of (+)-codeine (5). Recrystallization from water gave the monohydrate of 5; mp 154-156°, $[\alpha]_D^{23}$ +136.1°, (c 0.693 ethanol) [lit.[10] mp 147°, $[\alpha]_D^{25}$ +137.4°, (c 0.743 ethanol); (-)-enantiomer, lit.[11] mp 154-156°, $[\alpha]_D^{15}$ -136° (c 2, ethanol)]; chromatographically and spectroscopically indistinguishable from an authentic sample of the natural levoratatory enantiomer except for the opposite sign of optical rotation. Using the reactions discussed here, we have reproducibly (40-42% overall yield) converted 1 to (+)-codeine (5), from which we have readily[12] prepared (+)-morphine. In light of recent developments[2] however, we have now revised our route to (+)-codeine (5) and other important congeners of the (+)-series. Details concerning these transformations and reports on the biological activity of the various (+)-compounds will be published elsewhere.

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