SYNTHESIS OF DIHYDROMORPHINONES FROM DIHYDROCODEINONES

V. N. Kalinin, N. I. Kobel'kova, and D. E. Bodrov

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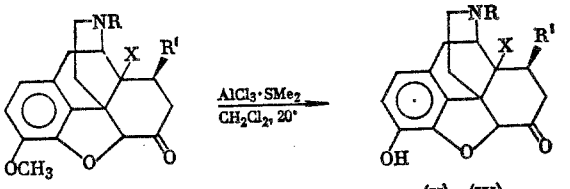
O-Demethylation in morphine alkaloids is an important reaction for the preparation of agonists and antagonists of opiates. BBr_3 [1-3], pyridine hydrochloride [4], and alkali metal mercaptides [5, 6] are used for this purpose. The AlX_3—alkyl sulfide system is an effective O-dealkylating agent for aryl methyl ethers [7].

We have found that morphines containing a ketone function in the C ring may be readily obtained from the corresponding codeine derivatives upon O-demethylation by the $AlCl_3 \cdot SMe_2$ complex. The reaction is carried out in CH_2Cl_2 at 20°C with an alkaloid/complex ratio of 1/10. The dihydromorphine yields are 70-85%. This method is applicable for the O-demethylation of dihydrocodeinone (I), 14-hydroxydihydrocodeinone (II), and their N-(cyclopropylmethyl)nor derivatives (III) and (IV).



(I)-(V) (V)-(IX)

R = Me, R′ = X = H (I), (V); R = Me, R′ = H, X = HO (II), (VI);

R = CH_2—⟨|, R′ = X = H (III), (VII); R = CH_2—⟨|, R′ = H, X = HO (IV), (VIII);

R = Me, R′ = Ph, X = H (V), (IX).

8β-Phenyldihydromorphinone (IX) is obtained in good yield from 8β-phenyldihydrocodeinone. Special interest is found in the preparation of 14-hydroxyldihydromorphinone (VI) and naltrexone (VIII).

We should note that the use of $AlCl_3$ or $AlBr_3$ in absence of sulfide gives low yields of the O-demethylation products, which is apparently related to the lability of the oxygen bridge in morphine alkaloids and the formation of a complex of AlX_3 at the oxygen or nitrogen atoms of (I)-(V).

EXPERIMENTAL

Analytical thin-layer chromatography was carried out on Silufol silica gel plates.

General O-Demethylation Reaction Procedure. A sample of 40 g (0.3 mole) $AlCl_3$ was added with stirring at 20°C to 100 ml (1.9 moles) Me_2S in 250 ml CH_2Cl_2 and then a solution of the corresponding dihydrocodeinone (0.03 mole) in CH_2Cl_2 was added dropwise. The reaction was monitored by thin-layer chromatography. At the end of the reaction in ~30 min, 2 N hydrochloric acid was added dropwise. The aqueous layer was separated, made basic by the addition of aqueous ammonia to pH 8-9, extracted with chloroform, and dried over Na_2SO_4. The solvent was distilled off in vacuum and the residue was recrystallized. Dihydromorphinone (V) was obtained by 80% yield, mp 265-267°C (from ethyl acetate—heptane) [8]. 14-Hydroxydihydromorphinone (VI) was obtained in 85% yield, mp 245-247°C (from ethanol) [4]. N-(Cyclopropylmethyl)nordihydromorphinone (VII) was obtained in 78% yield, mp of the monohydrate 114-115°C (from ethanol) [9]. Naltrexone (VIII) was obtained in 75% yield, mp 167-169°C (from acetone) [10]. 8β-Phenyldihydromorphinone (IX) was obtained in 78% yield, mp 160-162°C (from heptane—ethyl acetate). IR spectrum (cm^{-1}): 3450 (OH).

A. N. Nesmeyanov Institute of Heteroorganic Compounds, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 2, pp. 488-489, February, 1988. Original article submitted June 29, 1987.

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CONCLUSIONS

A preparative method was proposed for obtaining dihydromorphinones based on the O-demethylation of dihydrocodeinones using the $AlCl_3 \cdot Me_2S$ complex in CH_2Cl_2.

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