SYNTHETIC STUDIES OF CROWNED MORPHINES: SYNTHESIS AND CHEMICAL TRANSFORMATIONS OF CROWNED THEBAINE

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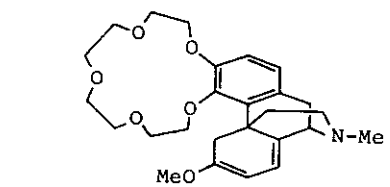
Recently, it has been suggested that the transmission of pain and the mechanism of action of opiates, e.g. morphine, closely relate to sodium ion transport processes in opioid receptor membranes. Therefore, it is interesting to introduce the ion transport function into biologically active opiate molecules by intramolecular incorporation of crown ether ring. We now describe the first synthesis of crowned thebaine (1) as the synthetic potential precursor of crowned morphine (2) and related compounds. The synthesis started with thebaine (3) which is now regarded as a new raw material for analgesic agents after the discovery of the opium-free popy *Papaver bracteatum*. Although thebaine is labile against strong acid or base treatments which are needed for the construction of crown ether ring, tricarbonyliron complex (4) nicely solves these problems. After demethylation of 4 by BBr_3, the protected polyether function was introduced to C3 position of 4 by nucleophilic substitution. Deprotection, tosylation, reductive C4-C5 ether ring cleavage, and the intramolecular cyclization by high-dilution method afforded the tricarbonyliron complex of crowned thebaine in satisfactory yields. Decomplexation by trimethylamine oxide gave crowned thebaine (1), whose structure was confirmed by spectroscopic data. The reaction of 1 with dimethyl acetylenedicarboxylate gave a new type of 1:1 adduct (5) instead of the Diels-Alder adduct. Chemical transformation of 1 to biologically more important derivatives will be also presented.



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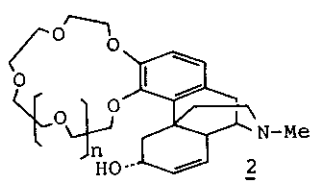

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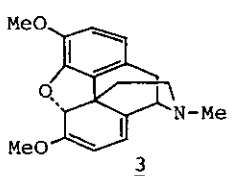

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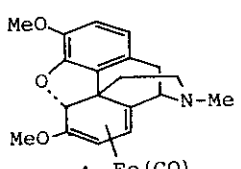

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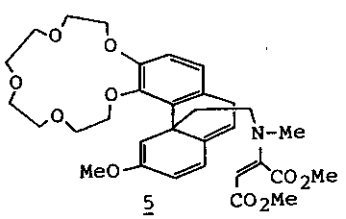

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