SYNTHESIS OF NOVEL SULFUR-CONTAINING STRONG ANALGESIC (S-ETORPHINE)

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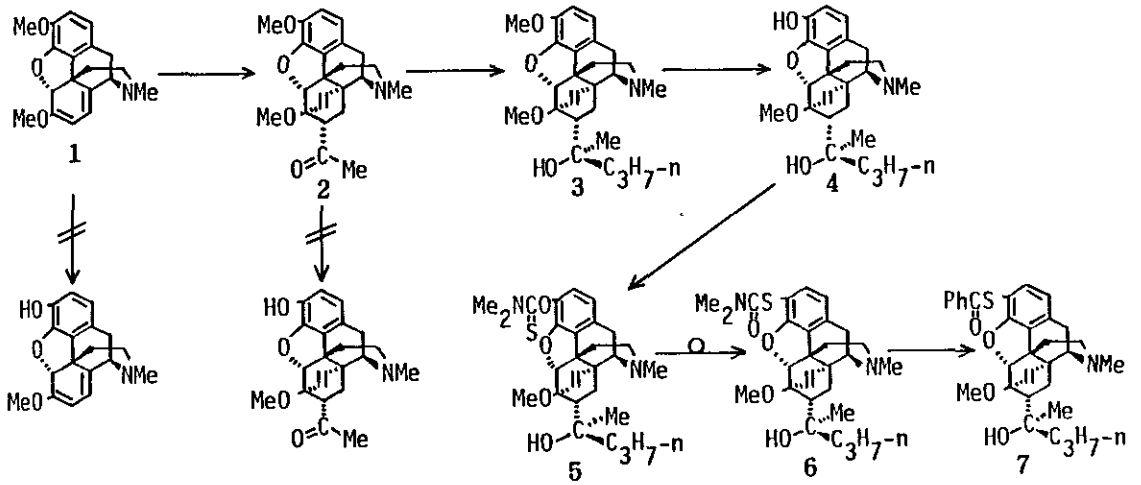
Much efforts have been made to produce a non-narcotic strong analgesic without side effects. Recently, a novel sulfur-containing benzomorphan, 8-benzoylthio-1,2,3,4,5,6-hexahydro-2,6-methano-3,6,11-trimethyl-3-benzazocine (S-metazocine) was exploited as a candidate for non-narcotic strong analgesics[1].

In this report we introduced sulfur group into etorphine (4) and its related compounds. The Newman-Kwart rearrangement was employed for the regioselective introduction of sulfur groups. Since demethylation of 1 or 2 with BBr_3 in CH_2Cl_2 or with EtSNa in DMF was unsuccessful, a synthetic approach through 4 was investigated. 3-(N,N-Dimethylthiocarbamoyl)etorphine (5, mp.239-240°) was obtained from 4 in 80% yield. Thermal rearrangement of 5 was examined under several conditions. The product 6 (mp.198-200° as fumarate) was afforded in 60% yield at 300° for 5min. Reduction of 6 with $LiAlH_4$ and successive benzoylation gave benzoylthio-etorphine (S-etorphine, 7, mp.179-182°(dec.) as fumarate) in 78% yield.

S-Etorphine (7) was 2~3 times more active analgesic than morphine in spite of low opioid receptor interaction.



1) E. Imai, M. Ban, M. Hori, M. Niwa, M. Nozaki, and H. Fujimura, "Advances in Endogenous and Exogenous Opioids", ed. by H. Takagi and E.J. Simon, Kodansha, Tokyo, pp.396 .