MORPHINANS AND 6-KETOMORPHINANS UNSUBSTITUTED IN THE AROMATIC RING. HIGH ANALGESIC ACTIVITY OF (-)-6-KETO-N-METHYLMORPHINAN, IV.[1]

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Abstract — Elimination of the phenolic hydroxy group from (-)-4-hydroxy-6-keto-N-methylmorphinan (1) afforded the morphinan ketone 3 which was several times more potent as an analgesic than morphine. Removal of the carbonyl group in 3 by a Wolff-Kishner reduction gave the unsubstituted morphinan 7 which was only half as potent as morphine.

For a systematic study regarding the structure-activity-relationship of 6-ketomorphinans and their corresponding methylene analogs we needed a sample of optically pure (-)-N-methylmorphinan (7). This compound has been prepared by several investigators in racemic form[2] and resolved by Henecka into optical isomers.[3] Since the reports regarding its analgesic activity gave conflicting results,[2] we decided to prepare 7 by an unambiguous route and to compare its activity with that of ketomorphinan 3. The 4-hydroxy ketone 1, prepared from dihydromorphine in four steps,[4] has the required stereochemistry and was chosen as a starting material. The chemistry applied for converting 1 into 7 is illustrated in Scheme 1, affording (-)-6-keto-N-methylmorphinan (3) as an intermediate. This compound exhibited unusually high analgesic activity in the hot plate assay (Table 1), suggesting the preparation of its N-allyl analog 6 as a possible narcotic antagonist.

The details of the preparation of 3,5,6 and 7 can be summarized as follows: The phenyltetrazolyl ether 2 was prepared from 1 in the usual way[5] and afforded crystalline material in 75% yield: mp 172-174°; $[\alpha]_D^{26} = -37.4°$ (1.35, $CHCl_3$). Catalytic hydrogenation of 2 in acetic acid over equal amounts of Pd/C at room temperature afforded the ketone 3 in 77% yield: mp 164-166°; $[\alpha]_D^{26} = -137.8°$ (0.92, $CHCl_3$); ir (cm^{-1}, KBr) 1710 (C=O); m/e 255 (M^+). Reaction of 3 with 2,2,2-trichloroethyl chloroformate in chloroform in the presence of potassium hydrogen carbonate[6] afforded the carbamate 4 as glass in 94% yield: ir (cm^{-1}, KBr) 1755 (ester), 1710 (C=O);

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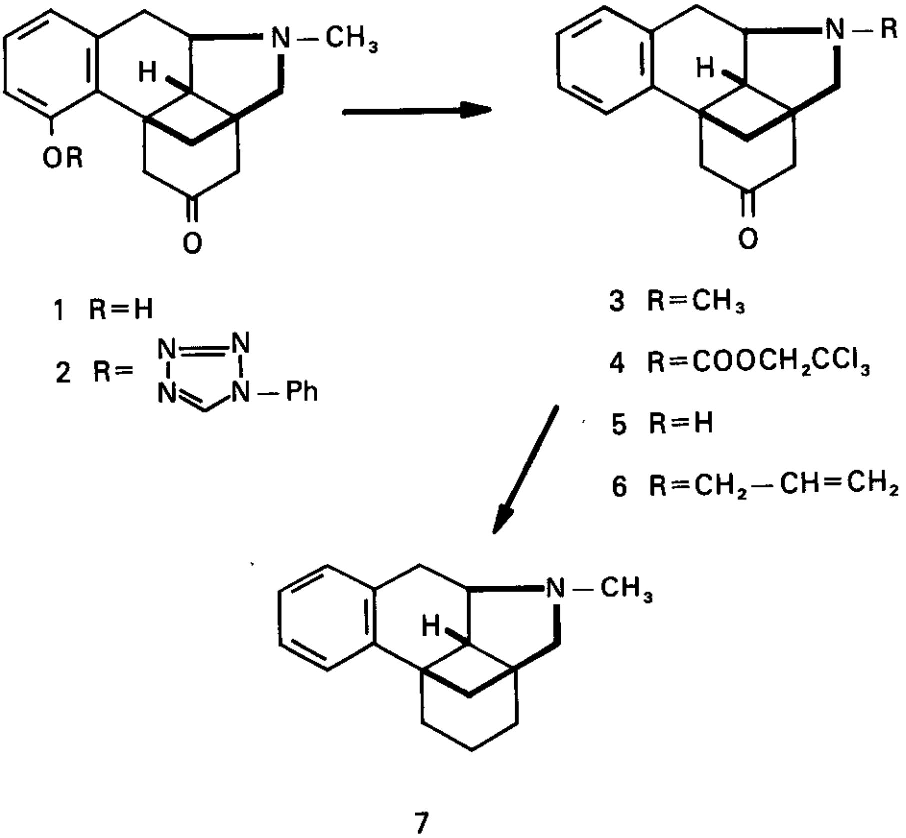
*Dedicated to Professor Kyosuke Tsuda on the occasion of his 75th birthday.



Scheme 1

m/e 415(M$^+$), 417 (M$^+$ +2), 419 (M$^+$ +4). Treatment of 4 with zinc and ammonium chloride in refluxing ethanol afforded the norbase 5 in 51% yield. 5.HCl: mp 268-271° (dec.); $[\alpha]_D^{24}$ -89.6° (0.94, EtOH); m/e 241 (M$^+$). N-Allylation of 5 by conventional procedures[7] afforded the (-)-6-keto-N-allylmorphinan 6 in 71% yield. 6.HCl: mp 206-210°; $[\alpha]_D^{25}$ -108.8° (0.98, EtOH); m/e 281 (M$^+$).[8] Wolff-Kishner reduction of ketone 3 with 64% hydrazine hydrate in triethylene glycol afforded the oily morphinan 7 in 95% yield: m/e 241 (M$^+$). The d-tartrate of 7 was prepared in the usual way: mp 116-117° (lit.[3] 115-117°); $[\alpha]_D^{26}$ = -13.2° (1.02, H_2O).[9]

TABLE 1

ANALGESIC ACTIVITY OF MORPHINANS BY THE HOT PLATE ASSAY

Compound	ED_{50}[a)]
1 as HBr	1.6 (1.2-2.1)
3 as base	0.3 (0.27-0.4)
7 as tartrate	2.3 (1.7-3.2)
Morphine as sulfate	1.0 (0.8-1.2)
Levorphanol as tartrate	0.2 (0.1-0.3)

[a)] Determined in mice by sc injection.[10-12] The ED_{50}, the effective dose at which half the animals are effected, values are in mg/kg. The parenthesis numbers are 95% standard error limits determined by computerized probit analysis. The salts were introduced in aqueous solution; the base in Emulphor EL 620 mixture.

It has long been known that morphinans substituted in the 3-position with a hydroxy group are potent antinociceptive agents.[2] Recent findings have shown that 4-methoxy-substituted 6-ketomorphinans are equally potent antinociceptive agents.[13] This would suggest that the aromatic ring of morphinans could be substituted with a hydroxy group at C-3 or by methoxy groups at C-4 or C-3,4 in order to obtain compounds with potent analgesic activity. We have now shown that ketone 3, unsubstituted in the aromatic ring, is about three times as potent as morphine and eight times as potent as the comparable methylene compound 7 (Table 1). These observations indicate that structure-activity relationships derived from work on the C-3 oxygenated opiates are too simplistic; predictions are becoming increasingly more difficult to make in the design of potent analgesics in this class of compounds.

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