STRUCTURE-ACTIVITY RELATIONSHIPS OF OXYGENATED MORPHINANS. II. SYNTHESIS AND BIOLOGICAL PROPERTIES OF 4-METHOXYMORPHINAN-6-ONES WITH NARCOTIC ANTAGONIST SIDE-CHAINS ON NITROGEN.

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ABSTRACT - The synthesis of narcotic antagonists from the 4-methoxymorphinan-6-one series is described. The synthesis started from optically active 4-hydroxy-6-keto-N-formylmorphinan prepared from morphine, by employing conventional procedures. The compounds have pentazocine-like agonist activity and N-cyclopropylmethyl-4-methoxymorphinan-6-one is somewhat more potent than nalorphine as a narcotic antagonist.

The interesting antinociceptive properties of 4-methoxy-N-methylmorphinan-6-one 4, which was found to be 3-4 times more active than morphine,[1] suggested the preparation of analogs with N-substituents known to convert agonists to agonist-antagonists or narcotic antagonists in normal opioids.[2] For their synthesis a scheme elaborated in connection with another program,[3] proved workable.

The optically active N-formyl ketone 1, prepared in several steps from natural morphine,[3] was first treated with methyl p-toluenesufonate in DMF in the presence of sodium hydride to afford the enol ether 2 in 68% yield: mp 169-172°; $[\alpha]_D^{26}$ -215.5° (0.97, $CHCl_3$); ir (cm^{-1}, KBr) 1650 (CHO); nmr (δ, $CDCl_3$) 8.00 (1H, s, CHO), 7.08 (1H, dd, ArH, J = 8, 8 Hz), 6.68 (2H, d, ArH, J = 8 Hz), 5.52 (1H, s, C_5-H), 3.82 and 3.58 (6H, 2s, 2 OCH_3); m/e 313 (M^+). Hydrolysis of 2 with aqueous methanolic HCl afforded the norketone 3 in 87% yield: mp 136-138°; $[\alpha]_D^{25}$ -75.7° (0.88, $CHCl_3$); ir (cm^{-1}, KBr) 3330 (NH), 1705 (C = O); nmr (δ, $CDCl_3$) 7.07 (1H, dd, ArH, J = 8, 8 Hz), 6.68 (2H, d, ArH, J = 8 Hz), 4.04 (1H, d, C_5-H, J = 13 Hz), 3.82 (3H, s, OCH_3);

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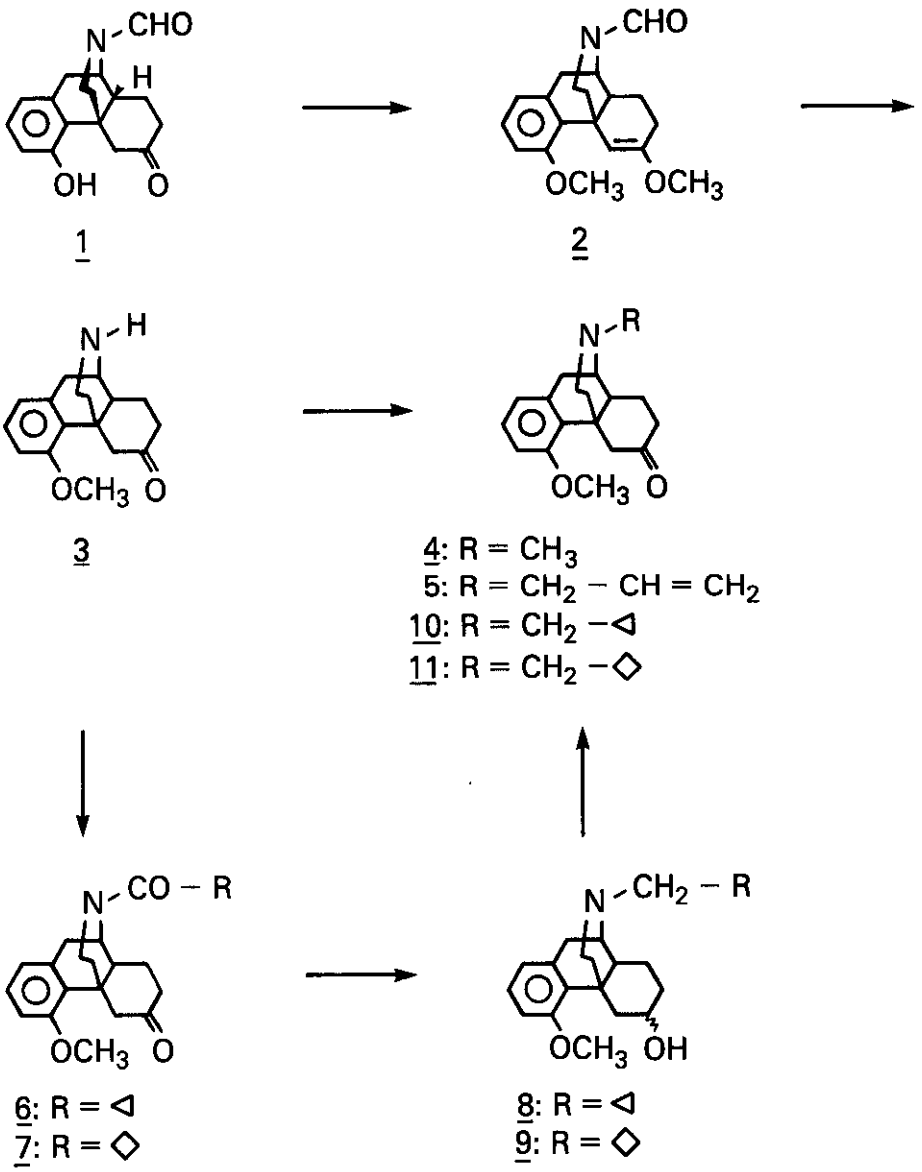

Since compound 1 is derived from natural morphine, all the morphinans shown above, have the same absolute configuration at the centers of chirality.

m/e 271 (M^+). Norketone 3 could reductively be N-methylated to afford 4, identical with material prepared differently. N-Allylation of 3 with allyl bromide in DMF in the presence of potassium carbonate afforded the N-allylmorphinan ketone 5 (yield 93%): mp 84-86°; $[\alpha]_D^{26}$ -114.6° (0.79, $CHCl_3$); ir (cm^{-1}, KBr) 1710 (C = O); nmr (δ, $CDCl_3$) 7.03 (1H, dd, ArH, J = 8, 8 Hz), 6.65 (2H, d, ArH, J = 8 Hz), 5.82 (1H, m, CH=), 5.12 (2H, m, $=CH_2$), 4.03 (1H, d, C_5-H, J = 13 Hz), 3.75 (3H, s, OCH_3); m/e 311 (M^+).

For the introduction of the N-cyclopropylmethyl- and N-cyclobutylmethyl groups to afford 10 and 11, procedures already elaborated with other morphinans were utilized.[4]

Thus, acylation of 3 with cyclopropylcarbonyl chloride afforded the amide 6 in 85% yield: mp 144-147°; $[\alpha]_D^{26}$ - 210.0° (1.04, $CHCl_3$); ir (cm^{-1}, KBr) 1710 (C = O), 1625 (amide); nmr (δ, $CDCl_3$) 7.14 (1H, dd, ArH, J = 8, 8 Hz), 6.70 (2H, d, ArH, J = 8 Hz), 4.08 (1H, d, C_5-H, J = 13 Hz), 3.82 (3H, s, OCH_3); m/e 339 (M^+). With cyclobutylcarbonyl chloride the amide 7 was similarly obtained (yield 96%): mp 125-126°; $[\alpha]_D^{26}$ -204.5° (0.76, $CHCl_3$); ir (cm^{-1}, KBr) 1710 (C = O), 1630 (amide); nmr (δ, $CDCl_3$) 7.14 (1H, dd, ArH, J = 8, 8 Hz), 6.70 (2H, d, ArH, J = 8 Hz), 4.06 (1H, d, C_5-H, J = 13 Hz), 3.82 (3H, s, OCH_3); m/e 353 (M^+). Reduction of 6 and 7 with LAH afforded mixtures of carbinols 8 and 9 which were directly oxidized by Oppenauer oxidation to the desired ketones 10 (77% yield) and 11 (70% yield). 10.HCl: mp 284-286° (dec.); $[\alpha]_D^{26}$ -57.6° (1.1, $CHCl_3$); ir (cm^{-1}, KBr) 1710 (C = O); nmr (δ, $CDCl_3$) 12.30 (1H, s, broad, $\overset{+}{N}H$), 7.14 (1H, dd, ArH, J = 8, 8 Hz), 6.72 (1H, d, ArH, J = 8 Hz), 6.68 (1H, d, ArH, J = 8 Hz), 4.06 (1H, d, C_5-H, J = 13 Hz), 3.80 (3H, s, OCH_3); m/e 325 (M^+). 11.HCl: mp 248-251° (dec.); $[\alpha]_D^{26}$ -49.3° (0.97, $CHCl_3$); ir (cm^{-1}, KBr) 1710 (C = O); nmr (δ, $CDCl_3$) 12.32 (1H, s, broad, $\overset{+}{N}H$), 7.10(1H, dd, ArH, J = 8, 8 Hz), 6.66 (2H, d, ArH, J = 8 Hz), 4.00 (1H, d, C_5-H, J = 13 Hz), 3.78 (3H, s, OCH_3); m/e 339 (M^+).

Each of the N-substituted 4-methoxymorphinan-6-ones (5, 10 and 11) had at least pentazocine-like antinociceptive activity in one or more assays in mice, and N-cyclopropyl-4-methoxymorphinan-6-one (10) had narcotic antagonist activity. The antagonist potency of 10 appeared to fall between nalorphine and naloxone in the mouse tail-flick antagonism assay.

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