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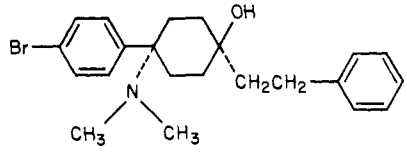
Communications to the Editor

4-(*p*-Bromophenyl)-4-(dimethylamino)-1-phenethylcyclohexanol, an Extremely Potent Representative of a New Analgesic Series

Sir:

The search for effective centrally acting analgesic agents devoid of addicting properties has led to an unusually rich selection of compounds on which to base the structural requirements for opioid activity. Most structures exhibiting this activity, in fact, fit a common pattern in possessing an aromatic ring attached to a quaternary center, or its equivalent, and a basic nitrogen atom at a remove of the equivalent of an ethylene unit.[1-3] We report a compound which shows extremely potent opioid analgesic activity in which the basic nitrogen atom *is attached directly to the quaternary center.*

The trans amino alcohol 1 exhibits ED_{50} values of 0.1



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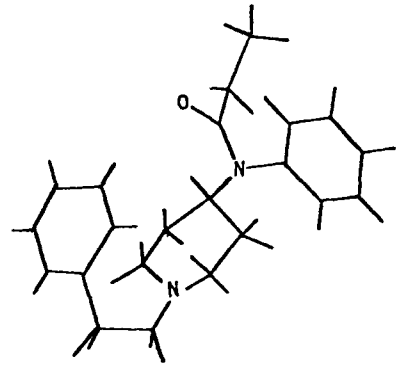
μg/kg when administered subcutaneously to mice in the usual battery of analgesic assays (tail flick, tail pinch, HCl writhing).[4] In our hands, this potency represents an increment of at least 10^4 over the milligram potency of morphine sulfate in the same assays (ED_{50} values of 1.5, 1.6, and 0.6 mg/kg). That this is indeed a manifestation of opioid activity is suggested by the finding that the analgesic effects are blocked by naloxone and that 1 exhibits an IC_{50} of 8×10^{-10} M in the [^{3}H]naloxone binding assay.[5] This is 30 times greater than the potency of morphine ($IC_{50} = 2.4 \times 10^{-8}$). Thus, the rank order of the two agents is in the same direction both in vivo and in vitro. We interpret this as a reflection of the greater potency of 1 and its enhanced ability to penetrate the central nervous system relative to morphine. The cis amino alcohol **6**, by contrast, is far less effective than 1, showing ED_{50} values in the mouse analgesic assay of 7.9, 7.9, and 7.0 mg/kg on tail flick, tail pinch, and HCl writhing, respectively.

The extreme in vivo potency and high binding affinity of 1 indicate that this compound is capable of conforming very precisely to the steric and bonding requirements of the analgesic opioid receptor. Thus, conformations of 1 which closely superimpose over those of other synthetic opioids and endorphins may specify the active conformations of the compounds. For example, comparisons of Dreiding models of 1 and fentanyl (Figure 1) reveal that the molecules can be arranged as to give point for point



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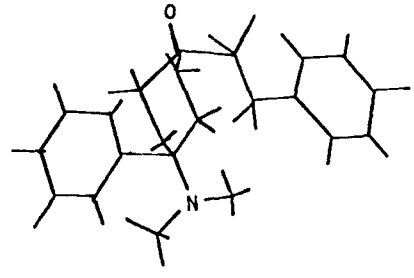

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Figure 1. Dreiding models of 1 and fentanyl.

coincidence for all salient structural features. Thus, starting at the left, the two benzene rings can be directly superimposed (though the link to the rest of the molecule is rotated by 60°). The basic nitrogen atoms of the two molecules similarly fall in the exact same spot in space as do the extreme right-hand benzene rings. The hydroxyl group in 1 falls in the middle of the amide function of fentanyl. Though the conformations required to achieve this superposition give rise to nonbonding interaction, energy gained in forming putative agonist–receptor complexes is probably sufficient to outweigh such interactions. Similarly, 1, but not **6**, can be shown to superimpose over the endogenous peptide, enkephalin. This coincidence includes the two phenyl rings of either compound, the nitrogen 1 and the nitrogen of Tyr, and the hydroxyl of 1 and the Met carboxyl. Thus, the potent opioid activity of 1 correlates with its conformational similarities with other opioids. More rigorous examination of these common conformations may lead to a better understanding of the analgesic opioid receptor. The reliability of such projections depends strictly upon the precision of fit of the model agonist and the receptor. The title compound, 1, is thus ideally suited for such studies.

Preparation of 1 starts by conversion of the monoketal of cyclohexanedione **2**[7] to its α-aminonitrile **3**, mp 79–81

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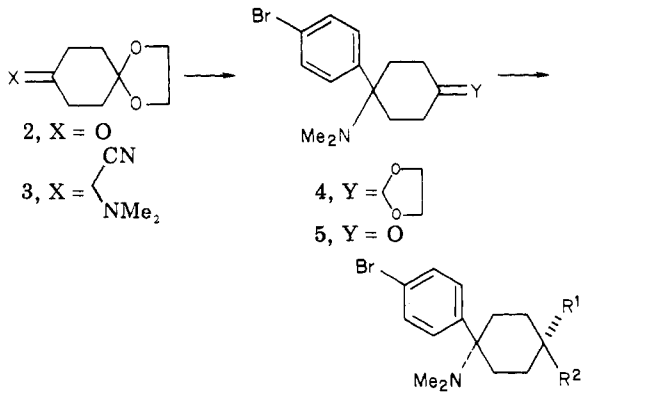
Scheme I



°C (78% yield),[6] by means of KCN and Me_2NH·HCl (Scheme I). Displacement of the cyano group[8] by means of a Grignard reagent obtained from *p*-dibromobenzene and a single equivalent of Mg gave amino ketal **4**, mp 254–255.5 °C (HCl salt, 30%); this was then hydrolyzed to the corresponding ketone **5**, mp 115–118 °C (69%). Condensation of **5** with the Grignard reagent from β-phenethyl bromide led to a 1:1 mixture of the amino alcohols **1** and **6**. These proved readily separable on silica gel: elution with 5% MeOH in CH_2Cl_2 gave the trans isomer **1** (HCl salt), mp 242–243 °C. Elution with 20% MeOH in CH_2Cl_2 gave the cis isomer (HCl salt, 1.5 H_2O), mp 208–210 °C.[9]

References and Notes

(1) O. Schaumaun, *Pharmazie*, **4**, 364 (1949).
(2) A. H. Beckett and A. F. Casey, *J. Pharm. Pharmacol.*, **6**, 986 (1954).
(3) P. S. Portoghese, *J. Pharm. Sci.*, **55**, 865 (1966).
(4) The test compound was administered subcutaneously to male CF-1 mice (18–22 g) as a suspension or solution in 0.25% aqueous methylcellulose. Fifteen minutes later they were subjected to the tail-flick, tail-pinch and HCl-writhing measurements of analgesia. Briefly, a high-intensity light was directed at the middle third of the animal's tail simultaneously with the start of a photoelectric timer. The number of seconds required for the animal to flick its tail out of the light path was recorded. Animals with response latencies greater than $\bar{X}$ + 2 SD of control were scored as analgesic. Then a bulldog arterial clamp was applied to the base of the tail. A lack of turning in response to that stimulus was scored as analgesia. Finally, the mice received 0.2 mL of 0.08 N HCl intraperitoneally and they were observed for 15 min for writhing. The absence of writhing response was scored as analgesia. Six mice were used at each dose level, and doses at 0.3 log intervals were tested. ED_{50} and 95% confidence intervals were calculated by the method of Spearman and Karber. The upper and lower confidence intervals were never more than 2 and 0.5 times the ED_{50}, respectively.
(5) C. B. Pert and S. H. Snyder, *Science*, **179**, 1011 (1973).
(6) All new compounds gave satisfactory analyses for C, H, and N.
(7) Prepared by a modification of the procedure of M. Haslanger and R. G. Lawton, *Tetrahedron Lett.*, 155 (1974).
(8) C. R. Hauser and D. Lednicer, *J. Org. Chem.*, **24**, 46 (1954).
(9) The stereochemistry assignment was based upon X-ray crystallography, performed graciously by D. J. Duchamp.

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Articles

(2,6-Methano-3-benzazocin-11β-yl)alkanones. 1. Alkylalkanones: A New Series of *N*-Methyl Derivatives with Novel Opiate Activity Profiles

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A general stereospecific synthesis of (*N*-methyl-2,6-methano-3-benzazocin-11β-yl)alkanones is described and applied to the preparation of a series of alkyl ketones wherein the alkyl group is a straight or terminally branched chain containing from one to six carbon atoms. Several compounds with methoxy groups in the aromatic ring are in the morphine range of potency; they are uniformly inactive as phenazocine antagonists. Phenolic analogues range up to 100 times as potent as morphine. Those containing five or six carbon atoms in the alkyl group exhibit phenazocine antagonist activity, in one case equivalent to naloxone. This compound (**3e**) is selective for phenazocine in its antagonist action.

Several years ago it was demonstrated that the potent narcotic antagonist nalorphine is an analgesic in man[2,3] but that its use is attended by psychic effects which preclude its clinical acceptance. Initially the compound was found to possess no morphine-like addiction liability;[4] later it was found that physical dependence could develop after chronic administration but that the abstinence syndrome occurring after drug withdrawal is qualitatively and quantitatively different from that produced by the narcotic analgesics.[5] These observations have encouraged the search for new clinically acceptable analgesics to focus attention on compounds which show narcotic antagonism as one aspect of their pharmacological action profiles.[6] In order to evaluate the subjective effects of candidate compounds, a method was developed[7] whereby scores on a questionnaire are compared with scores obtained when using reference drugs. The LSD scale, for example, measures psychotomimetic changes. In contrast to morphine and codeine,[8] nalorphine[9,10] and other analgesics with high antagonist potency, such as levallorphan[10] and

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