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. 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 μg/kg when administered subcutaneously to mice in the usual battery of analgesic assays (tail flick, tail pinch, HCl writhing). In our hands, this potency represents an increment of at least 10^6 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^{-9} M in the [3H]naloxone binding assay. This is 30 times greater than the potency of morphine (IC_{50} = 2.4 × 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 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 cyclohexanedicarboxylic acid 7 to its α-amimonitrite 3, mp 79–81
Articles

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

William F. Michne,* Thomas R. Lewis, Stephen J. Michalec, Anne K. Pierson, and Franklin J. Rosenberg

Sterling-Winthrop Research Institute, Rensselaer, New York 12144. Received April 27, 1979

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 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; 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. 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. In order to evaluate the subjective effects of candidate compounds, a method was developed 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, nalorphine and other analgesics with high antagonist potency, such as levallorphan and...