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Communications to the Editor

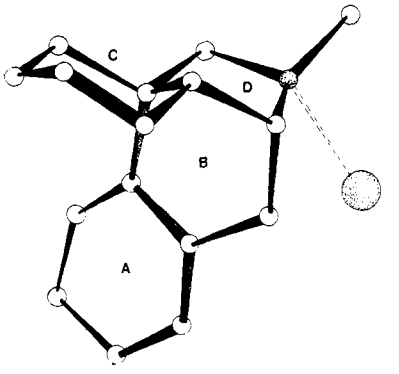
Importance of the Nitrogen Lone Electron Pair Orientation in Stereospecific Opiates

Sir:

In recent years, important new information has accumulated concerning the stereochemical basis of structure-activity relationships at the analgesic receptor level.[1] Elegant methods now appear to be available for the localization and isolation of the receptor through the work of Snyder and coworkers.[2] However, the actual nature of the forces controlling agonist and antagonist binding at this level is still poorly understood. Absolute optical specificity of the receptor is displayed toward conformationally rigid agonists and antagonists of the morphinan series[1] but rarely toward flexible structures which may exhibit bimodal[3] and perhaps polymodal binding.[4] The unimodal binding of the morphinans may thus allow a study of conformational effects at the specific active site proper in the absence of possible complications from exo binding,[5] bimodal binding,[3] or binding on peripheral control sites[4] (polymodal binding). One aspect of conformation-activity relationships which appears to have escaped attention until now concerns stereoelectronic effects about the basic nitrogen of morphinans as opposed to stereoisomerism about chiral carbons. We now wish to present concrete evidence that the relative spatial orientation of the N lone electron pair (with or without an attached proton) in morphinans is of critical importance for productive interaction with the opiate receptor.

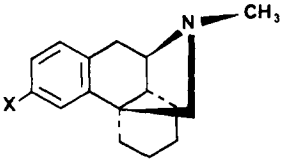
Our recently developed total synthesis of 14-substituted (hydroxyl) morphinans and isomorphinans[6] as based on earlier explorations[7] has allowed after appropriate modification the synthesis of the five-membered ring D analogs Ia and Ib of *N*-methylmorphinan and 3-hydroxyl-*N*-methylmorphinan (racemorphan), respectively.† The pure racemates Ia and Ib proved completely inactive as analgesics in the usual laboratory mouse tests. They were also totally devoid of antagonist activity and none of the common side effects characteristic of narcotics were observed. Only general CNS stimulation preceded by ataxia was produced in mice and rats at 5-20 mg/kg.

The complete inability of Ia and Ib to interact with the morphine receptor led us to an X-ray analysis of the three-dimensional structure of Ia whose crystal habit as the hydrobromide salt proved ideal for this purpose. The detailed X-ray work will be published separately when refinement of the atomic parameters is completed.‡ The



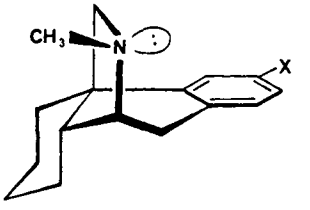
IIa

Figure 1. Stereoview of the crystal structure of *N*-methyl-D-normorphinan hydrobromide. The shaded atoms are nitrogen and bromine, respectively.

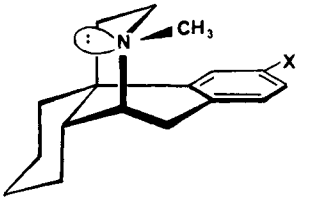


Ia, X=H

Ib, X=OH



IIb



III

†B. Belleau, T. Conway, and T. Doyle, unpublished results.

‡F. R. Ahmed and A. D. Hardy, unpublished results.

available data conclusively establish stereostructure IIa and Ia·HBr (Figure 1). Comparison of this structure with the X-ray structure of the morphinan and benzomorphan ring systems[8-11] reveals that whereas the protonated, axial N lone electron pairs of the latter project *away* from the benzene ring (III), the corresponding lone pair of Ia projects *toward* the phenyl ring (IIb). Since the lack of analgesic activity of Ia and Ib cannot be related to anomalous dissociation behavior (*N*-methylpyrrolidine being somewhat more basic than *N*-methylpiperidine by 0.38 pK_a unit[12]) or to any significant distortions about rings A, B, and C, we conclude that the orientation of the N lone electron pair is a key determinant of productive interactions with the morphine receptor.§ Even if the stereochemistry of IIa were to be inverted about the nitrogen atom in solution or in the free base form at the receptor level (thus causing the *N*-methyl to assume a seemingly more hindered position), it remains that the lone pair would be conformationally twisted outward by some 20–25° relative to the morphinan lone pair (III). It appears probable then that conformational transmission of subtle distortion effects in the lone pair *orientation* of morphinans and related analogs[14,&] may account at least in part for structurally induced variations in their pharmacological properties. It seems likely that this lone pair orientation effect on receptor binding may be equally important for high antagonistic potencies.[6,15,16] The stereochemically controlled mechanism of the lone pair interaction with the analgesic receptor is examined in the following communication.[17]

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B. Belleau*

Department of Chemistry, McGill University Montreal, Quebec, Canada H3C 3G1

T. Conway

Bristol Laboratories of Canada Candiac, Quebec, Canada

F. R. Ahmed, A. D. Hardy

Division of Biological Sciences, National Research Council of Canada, Ottawa, Ontario, Canada

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§According to a Referee, this conclusion is in contradiction with literature reports[13a] that the quaternary salt *N*-methylmorphine, in which the N lone pair of morphine is unavailable, possesses significant analgesic activity when administered intracerebrally and intraventricularly (hot-plate and licking tests, respectively). However, a detailed perusal of these reports reveals that the effects of *N*-methylmorphine (a blocker of neuromuscular transmission) differ significantly from those induced by morphine. For instance, morphine caused a greater and consistent fall in body temperature; acute tolerance did not develop with *N*-methylmorphine and no cross tolerance developed between morphine and its quaternary analog. The latter did not prevent the development of tolerance to morphine and, most significantly, nalorphine did not prevent the fall in body temperature after application of *N*-methylmorphine but blocked the morphine-induced fall in temperature. Finally, shortly after intraventricular injection of *N*-methylmorphine, a toxic state developed which was characterized by convulsive behavior similar to that induced by other types of quaternary drugs. We conclude on the basis of these observations that *N*-methylmorphine appears not to interact directly with the opiate receptor. It appears firmly established[13b] that morphine antagonists interact directly with the morphine receptors (see ref 2).

& In a personal communication, Dr. Walker has kindly informed us that the five-membered ring C analogs of the benzomorphans reported in that paper are also devoid of analgesic activity.

Clastic Binding on the Opiate Receptor

Sir:

In the preceding communication[1] we have shown that the orientation of the N lone electron pair of morphinans is a key determinant of stereospecific productive binding on the opiate receptor. That the N-protonated form of opiates is the active species[2] is unproved. Electrostatic forces between charges with or without the mediation of a proton bridge[1] can hardly be sensitive to geometrical effects about the charges. Since a regiospecific orientation of the N lone pair of morphinans appears essential for analgesic activity,[1] the protonated form may be tentatively ruled out as the active species. On that basis, the heuristic hypothesis offers itself that the N lone pair of the free base may interact with an electrophilic site whereupon a stereospecific electron transfer leading to oxidation of the *N*-methyl substituent may be operative. We are here tentatively viewing this possible electron injection at the opiate receptor level as forming part of the overall receptor response and not as an extrinsic preliminary step as required by the N-demethylation hypothesis of Beckett, Casy, and Harper[2] (which has since been held invalid[3,4]). Such electronic phenomena at the receptor or enzyme levels shall be conveniently referred to as clastic binding. Earlier, we have demonstrated by the method of deuterium isotope effects that clastic binding is characteristic of