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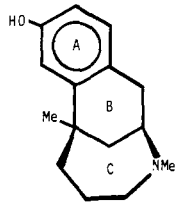
Communications to the Editor

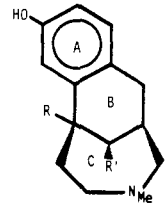
X-Ray Analytical Reexamination of Correlation of Nitrogen Lone-Pair Orientation with Analgetic Activity

Sir:

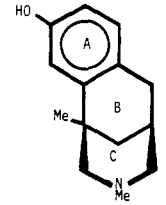
Although the exact nature of forces controlling the binding affinity of analgesics and their antagonists at the opiate receptor site is still poorly understood, recently developed stereochemical studies of analgesics and related compounds appear to be important for the model of opiate–receptor function and the stereochemical structure–activity relationships at this receptor site.[1-12] Among these, Belleau et al. proposed the importance of the relative spatial orientation of the N lone-electron pair in morphinans for interaction with the opiate receptor from comparison of the x-ray structure of *N*-methyl-*D*-normorphinan hydrobromide (which is neither an analgesic nor an antagonist) with that of the morphinan and benzomorphan ring systems.[6] The lone pair of the former projects toward the benzene ring; those of the latter two ring systems project away from the benzene ring. Cochran stated that the interatomic distance between the benzene ring and the hydrogen atom on the cationic nitrogen is important for the interaction of an analgesic with the receptor.[7] On the other hand, Opheim et al.[9] and Schiller et al.[10] suggested that the cationic (protonated) form of the opiate drug is the active species and interacts with the receptor via ionic association and that the distance of the cationic nitrogen atom relative to the benzene ring is critical for the interaction.



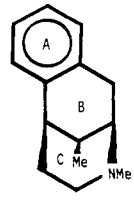
9-hydroxy-3,7-dimethyl-2,3,4,5,6,7-hexahydro-2,7-methano-1H-3-benzazonine (I)



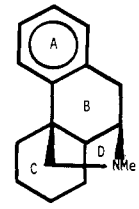
10-hydroxy-4-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine (IIa, R = R' = H)
10-hydroxy-1,4,12β-trimethyl-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine (IIb, R = R' = Me)



9-hydroxy-1,3-dimethyl-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine (III)



2,9β-dimethyl-6,7-benzomorphan



N-methyl-D-normorphinan

Table I. Amino Hydrogen to Phenyl (H-Ph) Distances, Nitrogen to Phenyl (N-Ph) Distances, and Angles of *N*-Methyl Bond to the Best Plane of Nitrogen-Containing Ring (N-C Bond Angle) Calculated from Atomic Coordinates from Crystal Structure Data

Compd	H-Ph distance,[a,b] Å	N-Ph distance,[c] Å	N-C bond angle,[d] deg
I[e]	3.99	4.45	21
IIa	5.46	4.86	5
IIb	5.47	4.87	−2
III	3.63	4.11	26
2,9β-Dimethyl-6,7-benzomorphan[f]	5.37	4.69	−2.5
N-Methyl-*D*-normorphinan[g]	4.27	4.17	−53

[a] Average H-C distance to the six atoms of the benzene ring. [b] Hydrogen atom on the cationic nitrogen. [c] Average N-C distance to the six atoms of the benzene ring. [d] Angles toward the benzene ring are designated as minus. [e] Sample was prepared by the method of Takeda. See ref 13. [f] See ref 18. [g] See ref 19.

These interesting postulations prompted us to examine the x-ray structure of the seven-membered C-ring homologue (I, IIa, and IIb) and an N-position isomer (III) of 6,7-benzomorphans, since we have been investigating the structural features needed for analgesic activity. Compounds I,[13] IIa, and IIb[14] have been shown to be analgetically as potent as morphine and III[15] as potent as codeine.

The single-crystal x-ray analyses were carried out with hydrobromide salts of racemic I, IIa, IIb, and III.[16] The detailed results of x-ray work will be published separately.[17] The established stereostructures revealed that the C ring of compounds I, IIa, and IIb is a zigzag conformation with the same orientation of the atoms and that the C ring of III is a chair conformation, as shown in Figure 1.

More importantly, whereas the axial-like, N lone-electron pairs of IIa and IIb project away from the benzene ring, the corresponding electron pairs of I and III orient toward the benzene ring. Although these results draw attention to the possibility that compounds I and III invert themselves, at the receptor site, to take a conformation in which the N lone pair projects away from the benzene ring, we may conclude that the orientation of the N lone-electron pair or the distance between the benzene ring and

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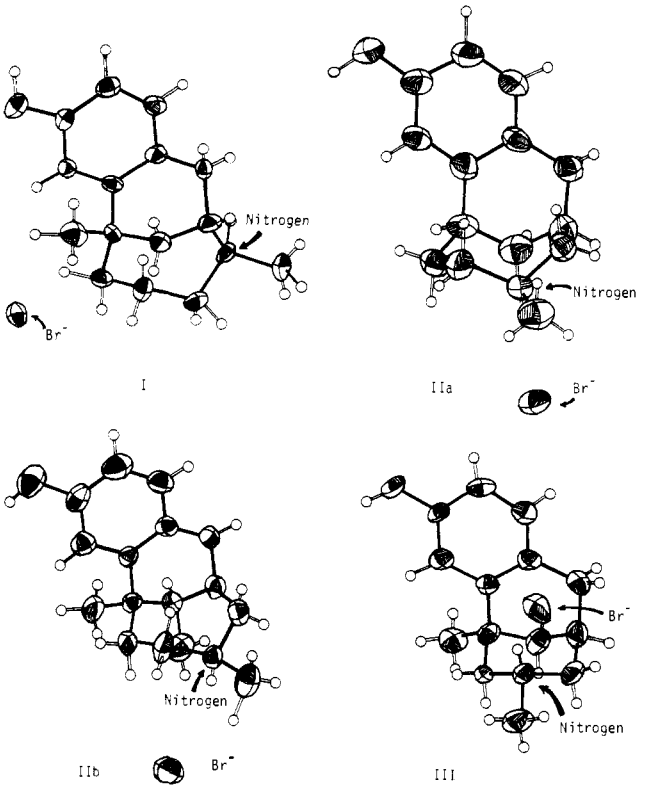

Figure 1. Perspective drawing of racemic hydrobromide salts of I, IIa, IIb, and III. The thermal vibrational ellipsoids of the nonhydrogen atoms are scaled to 50% probability. The hydrogen atoms are shown as spheres of an arbitrary size.

hydrogen on cationic nitrogen (Table I) of benzomorphan and morphinan analogues (deduced from the structure in crystalline state) does not account for structurally induced variations in their pharmacological properties.

Table I also shows the results of calculations of the distance between the cationic nitrogen and the benzene ring (N–Ph distance) and the angle between the *N*-methyl bond and the best plane of the nitrogen-containing ring (N–C bond angle) using atomic coordinates from crystal-structure data of I, IIa, IIb, III, 2,9β-dimethyl-6,7-benzomorphan[18] and *N*-methyl-*D*-normorphinan.[19] It can be seen that the N–Ph distances of *N*-methyl-*D*-normorphinan and III are shorter than those of I, IIa, IIb, and 6,7-benzomorphan. In light of the suggestion of Opheim et al.[9] and Schiller et al.,[10] it may be conceivable that, in the case of molecules having an axial relationship between the benzene ring and the nitrogen-containing ring (analogues of benzomorphan and morphinan),[20] the N–Ph distance is important for stereochemically controlled binding of analgesics at the receptor site. Though the possibility exists for the N–C bond angle to correlate with the activity, definitive conclusions regarding the role of the N–C bond angle in analgetic activity must await further experimental results. Work is progress investigating stereostructural features in analgesics.

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(16) It is conceivable that the x-ray data obtained from salts are relevant to the free base.
(17) Y. Iitaka and A. Itai, unpublished results.
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(20) Molecules having either an axially or equatorially oriented phenylpiperidine moiety can have substantial analgesic activity. From this and other facts it was suggested that there may be some different modes of opiate–receptor interaction.[4,8,11] Therefore, our conclusion on the opiate–receptor interaction may be restricted to the molecules having an axial relationship between the benzene ring and the nitrogen-containing ring.

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