EFFECT OF 2-Me SUBSTITUENT ON THE CONFORMATION OF 1-(2-PHENETYL) PHARMACOPHORE IN 4-PROPANOYL(PHENYL)AMINOPIPERIDINES

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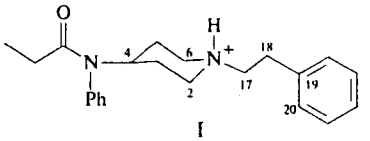
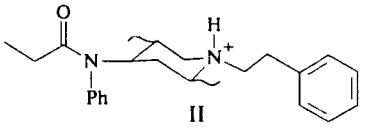
Previously [1 – 6], we used the experimental and calculated crystal-structural data for fentanyl and stereoisomers of its 3-methyl, 3,5- and 2,5-dimethyl derivatives to establish that the conformation characteristics of 4-propionylaniline pharmacophore are strongly dependent on the presence and orientation of the Me substituent in positions 3 and/or 5 of the piperidine ring [1 – 6]. This result allowed us to suggest a hypothesis of "productive" (with respect to the morphine-like properties) conformation of the 4-propionylaniline pharmacophore.

At the same time, pharmacological investigations of 4-anilinopiperidine representatives unambiguously indicated that a 2-phenethyl group in position 1 of the piperidine ring significantly increases the analgesic activity [7, 8]. Therefore, the 1-(2-phenethyl) substituent can be considered, from the standpoint of the analgesic properties, as a pharmacophore group. Moreover, the results reported in [9, 10] are indicative of a significant influence of the conformation characteristics of this pharmacophore on the analgesic properties of 4-anilinopiperidines. This can be judged from the fact that 2,5-dimethylfentanyl produces a lower narcotizing action as compared to that of 3-methylfentanyl [11, 12], which can be explained by the effect of methyl group in position 2 on the conformation characteristics of the 1-(2-phenethyl) pharmacophore.

In order to study the conformation characteristics of the 1-phenethyl pharmacophore and elucidate the role of the 2-methyl group and its orientation, we have calculated the conformations of the fentanyl (I) cation and of three actually isolated stereoisomers of phenaridine (II), namely, the 2e,5e, 2e,5a, and 2a,5a isomers (IIa, IIb, and IIc, respectively) [11].



I



II

I – fentanyl;
II – phenaridine;
IIa – 2e,5e isomer;
IIb – 2e,5a isomer;
IIc – 2a,5a isomer; ("a" and "e" indicate the axial and equatorial positions, respectively).

METHOD

The method used for the conformation calculations was similar to that described previously [3, 4]. The conformational energies were calculated on an IBM PC / AT-386 computer using the MM2 program package [13] with complete calculation of the molecular geometry. In the general case, the calculations were made using the standard parameters of potential for the given program version. The potentials of bond lengths and bond and torsion angles involving amide and tertiary nitrogen atoms were taken (as in [3, 4]) from [14]. For the missing parameter describing the N(amide) – C(arom) bond, we used the constant values $l_0 = 1.446$ Å (mean crystal-structural value) and $K_s = 5.0$ mdyn / Å.

The starting coordinates were taken equal to the corresponding crystal-structural values [2, 5, 6, 15].

The conformational energy maps of $E_{conf} = f(\tau_3, \tau_4)$ were obtained by variation of the torsion angles τ_3 = C(2)N(1) – C(17)C(18) and τ_4 = N(1)C(17) – C(18)C(19) with complete calculation of the geometry of cations. For both angles, the scan step was $|\Delta\tau| = 10°$.

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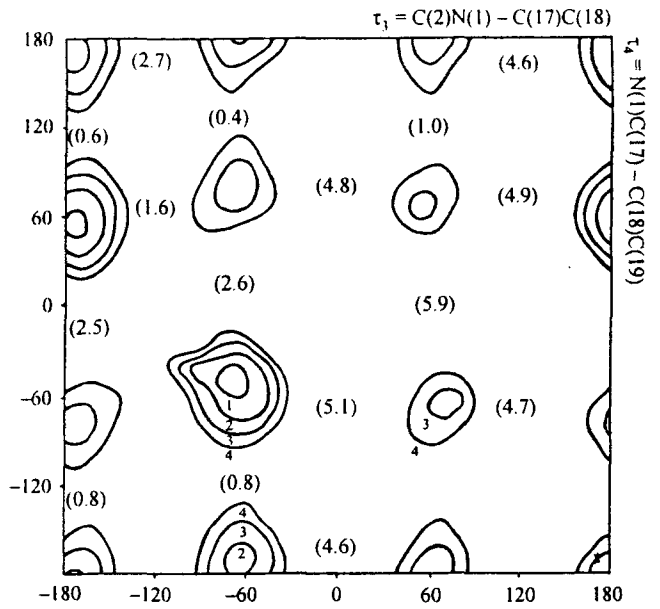

Fig. 1. Conformational energy map $E_{conf} = f(\tau_3, \tau_4)$ for compound I. Cross symbol indicates the conformation in the crystal [9].

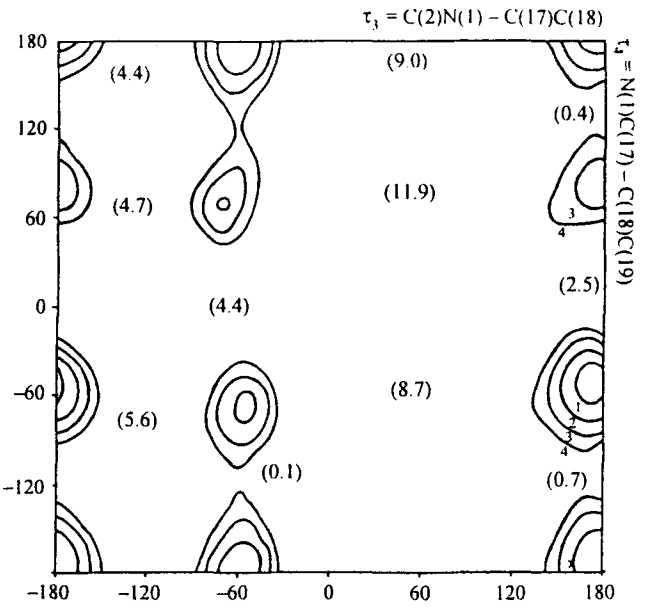

Fig. 2. Conformational energy map $E_{conf} = f(\tau_3, \tau_4)$ for compound IIa. Cross symbol indicates the conformation in the crystal [5].

The E_{conf} values in Figs. 1 – 4, expressed in kcal / mole and measured from the global minimum, are indicated at the corresponding isolines. In this work we consider potential minima differing from the global minimum by not more than 4 kcal / mole. Data in parentheses between the neighboring potential wells give the minimum potential barriers (kcal / mole) measured from the outer isolines of the wells.

RESULTS AND DISCUSSION

An analysis of the conformational energy maps (relative depths of the potential wells) allowed us to select the most favorable systems to be compared with the other, less favorable but still possible conformations.

The calculations showed nine energy minima for compound I in the region of $-180° < \tau_3 < 180°$ and $-180° < \tau_4 < 180°$ (Fig. 1), which correspond to retarded conformations: there are three potential wells along τ_3 and three wells along τ_4 situated near the angles 60, – 60, and – 180°. The energies of these minima are markedly different. The most stable, nearly coinciding energies ($\Delta E \sim 0.1$ kcal / mole) are obtained for the conformations corresponding to $\tau_3 \sim -70°$, $\tau_4 \sim -50°$ and $\tau_3 \sim -170°$, $\tau_4 \sim 60°$. The next stable conformations with virtually coinciding energies ($\Delta E \sim 0.0$ kcal / mole), observed at $\tau_3 \sim -60°$, $\tau_4 \sim -170°$ and $\tau_3 \sim -170°$, $\tau_4 \sim 170°$, lose $\Delta E \sim 0.9$ kcal / mole to the previous pair. The other five minima, which are markedly less favorable as compared to the first two couples, are situated at $\tau_3 \sim -170°$, $\tau_4 \sim -80°$; $\tau_3 \sim -70°$, $\tau_4 \sim 80°$, $\tau_3 \sim 60°$, $\tau_4 \sim 180°$; $\tau_3 \sim 55°$, $\tau_4 \sim 65°$; and $\tau_3 \sim 70°$, $\tau_4 \sim -70°$.

Figures 2 – 4 show the conformational energy maps for the actually isolated stereoisomers of phenaridine. The calcu-

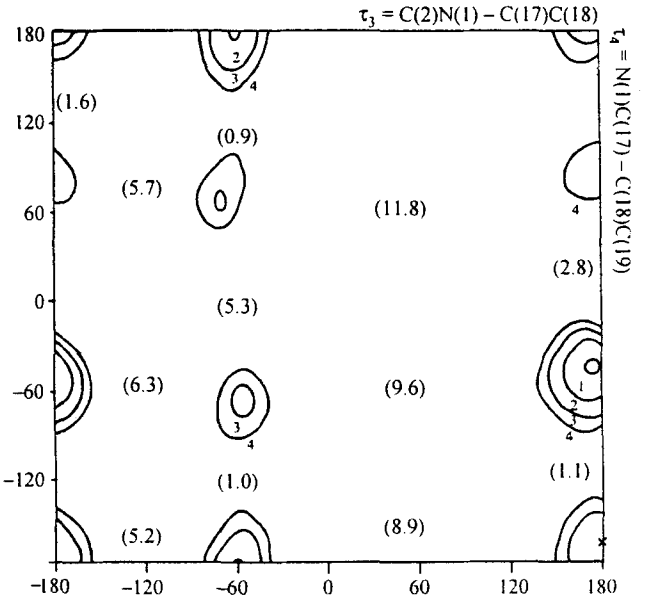

Fig. 3. Conformational energy map $E_{conf} = f(\tau_3, \tau_4)$ for compound IIb. Cross symbol indicates the conformation in the crystal [6].

lations showed that there are six minima for the known isomers of compound II in the region of $-180° < \tau_3 < 180°$ and $-180° < \tau_4 < 180°$. The minima are observed for the τ_3, τ_4 values corresponding to crossed conformations. The potential wells are situated near the values $\tau_3 = -60°$ and 180°and $\tau_4 = -180$, – 60, and 60°. As expected, the calculation also showed that the conformational characteristics of the 1-phenethyl pharmacophore are almost the same for IIa and IIb conformations (cf. Figs. 2 and 3), differing only slightly

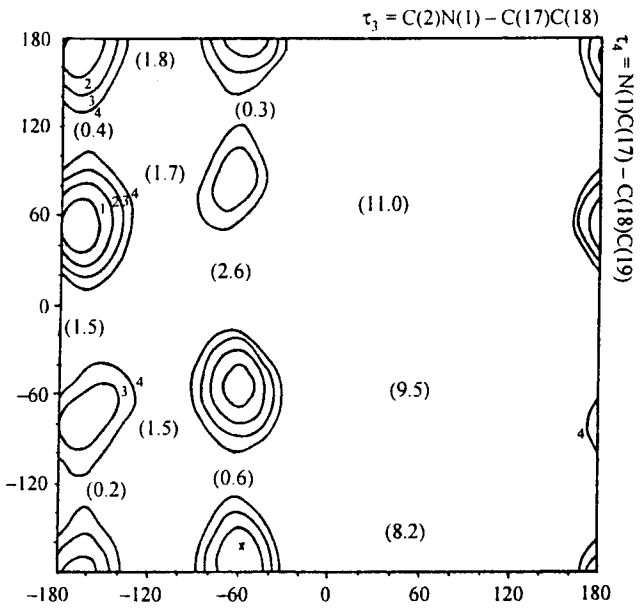

Fig. 4. Conformational energy map $E_{conf} = f(\tau_3, \tau_4)$ for compound IIc. Cross symbol indicates the conformation in the crystal [2].

by the depths of minima. The deepest minima ($\tau_3 \sim 170°$, $\tau_4 \sim -50°$) have virtually equal parameters.

In the case of compound IIa, the second level of stability is achieved in a group of four minima with slightly differing energies. The most favorable conformation in this group ($\tau_3 \sim -60°$, $\tau_4 \sim -180°$) loses only $\Delta E = 0.5$ kcal/mole to the lowest minimum of the system. The next stable conformation ($\tau_3 \sim 180°$, $\tau_4 \sim -170°$) is less favorable by $\Delta E = 0.6$ kcal/mole and $\Delta E = 0.1$ kcal/mole relative to the first and second minima. The fourth minimum ($\tau_3 \sim -55°$, $\tau_4 \sim -70°$) is superior by $\Delta E = 0.2$ kcal/mole as compared to the fifth ($\tau_3 \sim -70°$, $\tau_4 \sim 70°$), while losing $\Delta E = 1.2$ kcal/mole to the lowest energy minimum. The least favorable conformation, which is observed at ($\tau_3 \sim 170°$, $\tau_4 \sim 80°$), differs from the most favorable one by $\Delta E = 1.7$ kcal/mole.

As noted above, the most stable conformation of compound IIb corresponds to $\tau_3 \sim 170°$, $\tau_4 \sim -50°$. In contrast to the structure of IIa, the second stability level of IIb is observed at $\tau_3 \sim -60°$, $\tau_4 \sim 180°$ and loses $\Delta E = 0.9$ kcal/mole to the most favorable conformation. The third stability level of IIb is represented by three conformations. The most favorable in this group occurs at $\tau_3 \sim 180°$, $\tau_4 \sim -170°$, losing $\Delta E = 1.1$ kcal/mole and 0.2 kcal/mole to the global and second stable minima, respectively. This conformation is more stable than the other two in the group ($\tau_3 \sim -50°$, $\tau_4 \sim -70°$ and $\tau_3 \sim -70°$, $\tau_4 \sim 70°$) with an energy gain of $\Delta E = 0.6$ kcal/mole and 0.8 kcal/mole, respectively. The least stable conformation of IIb is that observed at $\tau_3 \sim 180°$, $\tau_4 \sim 80°$.

Figure 4 shows the E_{conf} pattern for compound IIc. This structure also exhibits six potential minima, of which the lowest does not exceed 4 kcal/mole as measured from the global minimum. The energy minima of IIc correspond, like those of the above structures, to the crossed conformations and can be subdivided into three levels with respect to stability, each level comprising two minima. The most stable conformations are observed at $\tau_3 \sim -170°$, $\tau_4 \sim 70°$ and $\tau_3 \sim -60°$, $\tau_4 \sim -60°$, the first being more favorable by $\Delta E = 0.3$ kcal/mole. The second stable pair is observed at $\tau_3 \sim -60°$, $\tau_4 \sim -170°$ and $\tau_3 \sim -170°$, $\tau_4 \sim 170°$ and differ in the energy by $\Delta E = 0.4$ kcal/mole, the former conformation being more favorable (albeit losing $\Delta E = 0.7$ kcal/mole to the most stable conformation of IIc). The third pair of minima, having virtually the same energies ($\Delta E = 0.0$ kcal/mole), are situated at $\tau_3 \sim -60°$, $\tau_4 \sim 80°$ and $\tau_3 \sim -160°$, $\tau_4 \sim -80°$ and less favorable by 2.0 kcal/mole as compared to the most stable conformation of IIc.

The results of our calculations indicate that the conformation characteristics of the 1-(2-phenethyl) pharmacophore of 4-anilinopiperidines depend on whether a Me substituent is present in position 2 of the piperidine ring. Apparently, the presence of the 2-Me group gives rise to additional steric constraints. This results in the fact that the energy minima at $\tau_3 \sim 60°$ for the phenaridine isomers are situated 4 kcal/mole above the global minimum.

The conformation characteristics of the 1-(2-phenethyl) pharmacophore are also affected by the orientation of the 2-Me group relative to the piperidine ring. For example, the conformation with an axial arrangement of the 2-Me group (isomer IIc, Fig. 4) has virtually the same characteristics as those of fentanyl I (Fig. 1). In contrast to the case of IIc, the conformation characteristics of the 1-(2-phenethyl) pharmacophore in isomers IIa and IIb (with the 2-Me group occupying the equatorial position with respect to the piperidine ring) markedly differ from those observed in conformation I.

Taking into account that the analgesic activity of 3-methylfentanyl is considerably (by a factor of about 30) higher as compared to that of fentanyl [12], while the activity of phenaridine is only three times that of fentanyl [11], we may suggest that the presence of the 2-Me group produces a general negative effect on the analgesic activity of 4-anilinopiperidines. The fact that the individual analgesic activity of isomer IIc is considerably higher than that of isomer IIb [11] is explained by the fact that the negative effect due to the presence of the 2-Me group is less pronounced for the axial arrangement of this group in the structure.

On the basis of the calculation results, we may also suggest that the productive, biologically active conformation of the 1-(2-phenethyl) pharmacophore corresponds to one of the conformations corresponding to $\tau_3 \sim -60°$, $\tau_4 \sim -60°$ or $\tau_3 \sim -170°$, $\tau_4 \sim 60°$, rather than to an elongated configuration observed in the crystal (see the points indicated by cross symbols in Figs. 1 – 4).

It must be also noted that the crystal-structural conformations of the 1-(2-phenethyl) pharmacophore observed for both fentanyl I [15] and the isomers of II [2, 5, 6] do not correspond to the most stable conformations obtained theoreti-

cally. This discrepancy is apparently related to the effect of crystal packing and the fact that the energy barriers between the calculated and experimental crystallographic conformations are not very high.

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