THE PREFERRED CONFORMATION IN BRONCHODILATORY AGENTS. THE CRYSTAL STRUCTURE OF ISOPROTERENOL SULFATE DIHYDRATE.

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SUMMARY

The crystal and molecular structure of isoproterenol sulfate dihydrate has been determined by single crystal X-ray diffraction methods. A comparison of the conformations in ephedrine, noradrenalin and isoproterenol suggests a preferred conformation for bronchodilatory drugs.

The relationship between conformation and biological activity is intriguing. However, the possibility of different conformations in the crystalline state and in vivo complicates the problem. We are investigating molecules of biological interest in the solid state to establish possible correlations between conformation and biological activity and to provide models for additional studies. Our results from the crystal structure study of isoproterenol sulfate dihydrate have suggested a possible relationship between conformation and bronchodilatory action.

Isoproterenol sulfate dihydrate, $[3,4\text{-}(OH)_2C_6H_3CH(OH)CH_2NH_2\text{-}CH(CH_3)_2]_2SO_4\cdot 2H_2O$, can be obtained as clear, plate-like crystals from water. There are eight molecules in an orthorhombic unit cell (space group Pbca) with dimensions of a = 26.065 ± 0.007 Å, b = 15.263 ± 0.005 Å and c = 13.690 ± 0.004 Å. All the reflections with $2\theta \leq 135°$ for Cu-Kα radiation were measured, of which the 2872 reflections greater than 1.2 times the background count were used in the analysis.

The structure was solved by locating the SO_4 group using the symbolic addition method[1] and the remaining atoms in successive Fourier syntheses. The structure was refined by least-squares methods with anisotropic thermal parameters to an R, the usual residual, of 9.1%. A full report of our study will be forthcoming.

Since there are two isoproterenol cations per asymmetric unit, we have two independent measurements of the molecular dimensions. Except for the C-C bond in the ethyl side chain, none of the bond lengths in the two cations are significantly different. One C-C bond length in the side chain is 1.446 Å, which is shorter than expected and significantly different from the usual value of 1.507 Å found in the other cation. No satisfactory explanation for this difference is possible at present.

The strong bronchodilatory action of isoproterenol is similar to that of epinephrine (noradrenalin), norepinephrine (noradrenalin) and ephedrine. The conformation of ephedrine in the crystalline state was given by Phillips[2] and is reproduced in Figure 1. The crystal structure of noradrenalin is known[3] and the conformation is also given in Figure 1. The conformation in both isoproterenol cations is identical and is illustrated in Figure 1 for comparison with ephedrine and noradrenalin. In all three cations the hydroxy group is cis to the amino nitrogen. The N···O distances vary from 2.65 to 2.98 Å but are reasonably constant considering the differences in the groups on the amino nitrogens.

Since the conformations of the three different molecules are identical, this conformation may be required for bronchodilatory action. The question of whether the conformation is retained in vivo is of prime importance. Recent studies of similar compounds in solution[4] were interpreted in terms of a similar conformation. Therefore, it appears likely that the conformation found in the solid for isopro-

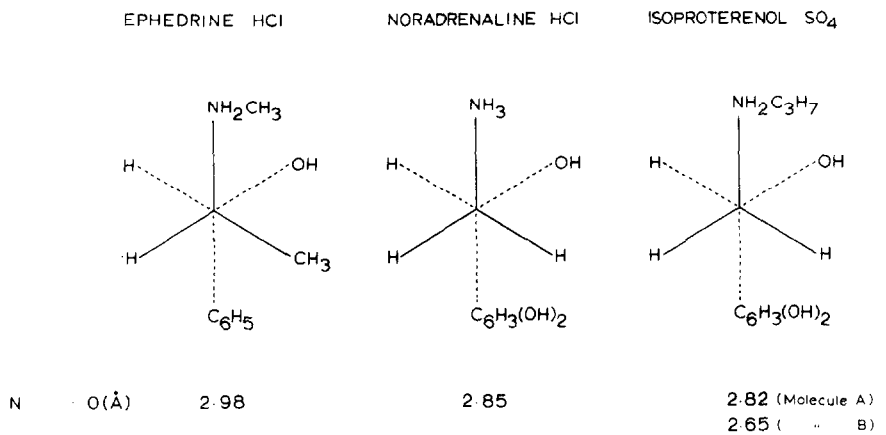

Figure 1. The conformations about the C-C bond of the ethyl side chain in ephedrine, noradrenalin and the two isoproterenol cations. The N···O nonbonded distance is given for each of the cations.

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terenol is retained in solution and is a prerequisite for broncho-dilatory action.

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