A Facile Synthesis of *anti*-Benzaldoxime

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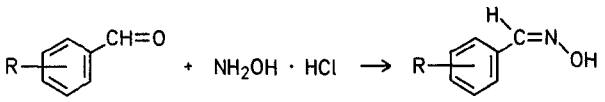
In connection with our synthetic work on N-hydroxypeptides[1] it was necessary to develop a procedure for the preparation of *anti*-benzaldoxime and some of its derivatives. These are in turn converted to nitrones which by hydrolysis yield N-hydroxyamino acids[2]. The usual procedures[3,4,5] for *anti*-benzaldoxime have not been successfully carried out on a large scale, rapid reversion of the *anti*-oxime to the low-melting *syn*-oxime occuring during work-up and handling[2]. A recent improved procedure[6] is suitable for large-scale preparations and affords better yields; however, it is tedious and consists of several reaction steps.

We here report a convenient and very simple procedure for the preparation of *anti*-benzaldoxime in which benzaldehyde is refluxed with hydroxylamine hydrochloride in methanol and the resultant oxime hydrochloride is converted into free *anti*-benzaldoxime by treatment with cold water and recrystallization from ether/petroleum ether. The yield is 35%.



In the same manner, *anti*-4-methoxybenzaldoxime and *anti*-2,4-dimethoxybenzaldoxime were obtained in 70 and 80% yields, respectively.

The hydrochlorides of benzaldoximes which exhibit a low basicity dissociate in methanol. In these cases, the yields of *anti*-benzaldoxime could occasionally be increased by carrying out the reaction in methanolic hydrogen chloride[7]. Thus, from 4-chlorobenzaldehyde and hydroxylamine hydrochloride in methanol there was only obtained a 10% yield of *anti*-4-chlorobenzaldoxime whereas the *syn*-isomer was formed in 80% yield. However, when the reaction was carried out in 10% methanolic hydrogen chloride the yield of *anti*-4-chlorobenzaldoxime was 70%.

anti-Benzaldoxime:

Benzaldehyde (106 g, 1 mol) and hydroxylamine hydrochloride (69.5 g, 1 mol) were refluxed for 3 hr in methanol (300 ml). The methanol was removed in vacuo and the residue was shaken vigorously with dry ether. The hydrochloride which crystallized was collected by filtration and washed with ether. The salt was shaken for 1 min in ice-cold water (500 ml), filtered, and immediately redissolved in ether. The solution was dried with sodium sulfate, filtered, and cooled. Upon the gradual addition of petroleum ether (b.p. 40–60°), *anti*-benzaldoxime precipitated in the form of colorless needles; yield: 42.5 g (35%); m.p. 130° (Ref.[6], m.p. 129.5–130°).

anti-4-Methoxybenzaldoxime:

Analogous procedure; yield: 70%; m.p. 130° (Ref.[3], m.p. 130–130.5°).

anti-3,4-Dimethoxybenzaldoxime:

Analogous procedure; yield: 80%; m.p. 142° (Ref.[8], 135°).

anti-4-Chlorobenzaldoxime[7]:

4-Chlorobenzaldehyde (139.5 g, 1 mol) and hydroxylamine hydrochloride (69.5 g, 1 mol) were refluxed for 3 hr in 10% meth-

anolic hydrogen chloride (300 ml). The reaction mixture was then treated as described above; yield: 109 g (70%); m.p. 148° (Ref.[9], m.p. 147°).

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