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A FACILE SYNTHESIS OF 1,4-DIHYDRO-1-ALKYL-2H-3,1-BENZOXAZINES AND RELATED COMPOUNDS

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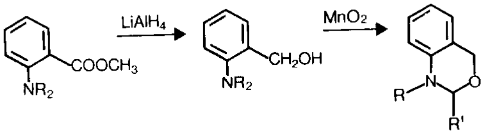
Abstract: o-Dialkylaminobenzyl alcohols are easily oxidized by MnO_2 to 1,4-dihydro-1-alkyl-2H-3,1-benzoxazines and related compounds.

The oxidation of benzylic alcohols to the corresponding aldehydes by active MnO_2 is well established[1]. Ready oxidation of dialkyl anilines to a variety of products by the same reagent is also well known[2]. We have now found that when both structural features are present in a benzene ring in ortho position to one another the predominant product of a MnO_2 oxidation may be a 1,4-dihydro-1-alkyl-2H-3,1-benzoxazine.



Thus, when 2-(dimethylamino)-3-methylbenzyl alcohol 4 is stirred in CH_2Cl_2 solution with a ten-fold amount (by weight) of active MnO_2 (Merck) 1,4-dihydro-1,8-dimethyl-2H-3,1-benzoxazine 5 is formed in an exothermic reaction within 10-15 minutes. 5 may be isolated after filtration and evaporation of the CH_2Cl_2 solution simply by distillation of the residue. Representative examples of this oxidation are listed in Table 1. Yields are generally in the range of 80%. The ratio of benzoxazine to aldehyde was determined by GC. None of these N-alkylated 1,4-dihydro-2H-3,1-benzoxazines has been mentioned before in the literature. The two tricyclic compounds, 1,2,3,3a-tetrahydro-5H-pyrrolo[1,2-a][3,1]benzoxazine 20 and 2,3,4,4a-tetrahydro-1H,6H-pyrido[1,2-a][3,1]benzoxazine 23 are also new. An interesting case is the oxidation of the homologous phenethyl alcohol 31 to 1,2,4,5-tetrahydro-6-nitro-1-methyl-3,1-benzoxazepine 32 which takes place in excellent yield.

The respective starting benzylic alcohols were obtained by reduction of the correspondingly substituted N-dialkyl anthranilates. These in turn are easily prepared from the corresponding methyl anthranilates by the usual methods of N-alkylation. The phenethyl alcohol 31 was prepared by alkali catalysed condensation of 6-nitro-2-dimethylaminotoluene with formaldehyde. All the products were isolated either by distillation or by preparative column chromatography. The structures were ascertained by ^{1}H-NMR- and MS-spectrometry. All compounds showed correct elemental analyses.

The aldehydes may be prepared as major products by oxidation of the benzylic alcohols with $CrO_3 \cdot pyr \cdot HCl$. Thus 4 is oxidized with that reagent to give 5 and 6 in a ratio of 1:10.

These benzoxazines are rather stable compounds. Thus 2 could be nitrated with acetyl nitrate in glacial acetic acid to give 1,4-dihydro-6,8-dinitro-1-methyl-2H-3,1-benzoxazine, mp.140°, in good yield.

From what is known about MnO_2-oxidations (ref. 1-4) it is likely that the first step in this reaction is the formation of a carbinolamine. From there three routes may lead to a 1,4-dihydro-2H-3,1-benzoxazine. At present we have no particular preference. Steric factors may play a role in influencing the course of the reaction. Thus, 4, 25, 27 and 29 are converted nearly exclusively to benzoxazines while in the oxidation of 1, 7 and 10 considerable amounts of aldehydes are formed, too. Interestingly, the chloro compound 13 is oxidized exclusively to the aldehyde.

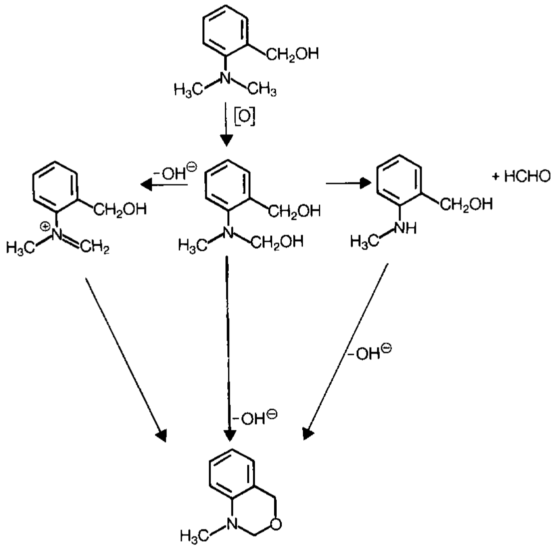
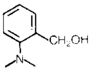
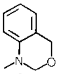
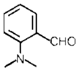
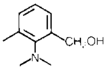
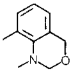
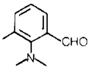
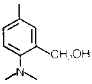
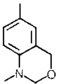
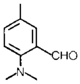
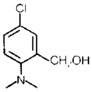
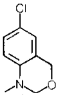
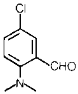
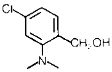
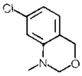
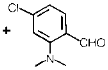
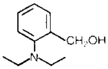
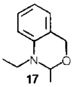
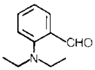
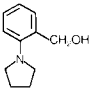
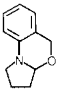
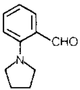
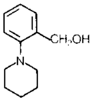
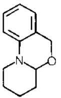
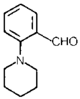
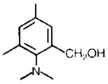
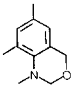
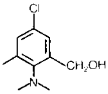
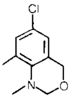
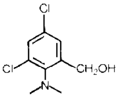
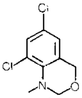
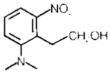
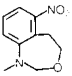
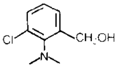
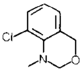
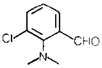


Table 1.

Starting[5] Material	Products[6]	Ratio Oxazine/aldehyde
 1	 2 +  3	2/3
 4	 5 +  6	84/1
 7	 8 +  9	3/2
 10	 11 +  12	4/3
 13	 14 +  15	–/1
 16	 17 +  18	5/2
 19	 20 +  21	12/1
 22	 23 +  24	9/1
 25	 26	1/–
 27	 28	1/–
 29	 30	1/–
 31	 32	1 –
 33	 34 +  35	24 1

References and Footnotes

1. A.J. Fatiadi, Synthesis 7, 65 (1976).
2. A.J. Fatiadi, Synthesis 7, 133 (1976).
3. H.B. Henbest and A. Thomas, J.Chem.Soc. 1977, 3032.
4. E.F. Bratt and Van de Castle, J.Org.Chem. 26, 2973 (1961).
5. mp of hydrochlorides: 1, 112-113°; 4, 103-104°; 7, 97-99°; 10, 140°; 13, 135°; 19, 116-119°; 22, 142-144°; 27, 126°; 29, 143°; 31, 88-89° (free base); 33, 151°.
6. Physical constants of those products obtained in larger amounts. Compounds not spezifically mentioned were oils showing the expected spectral data. bp. of 2, 60° (0.15 mm); of 5, 55-56° (0.1 mm); of 6, 55° (0.1 mm); of 20, 92-94° (0.1 mm); 23, 101-105° (0.1 mm); of 26, 104° (0.15 mm); 28, 107-109° (0.15 mm); 30, 116-118° (0.15 mm); of 34, 108-111° (0.15 mm); mp of 32, 60°.

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