coupling constants $J_{4,4a}$ and $J_{4a,5}$ are the same for the three solvents studied.

The signal for the C-5 proton in oxytetracycline appears rather far downfield at about 5 p.p.m. Acylation of the C-5 hydroxyl causes a large shift of over 1 p.p.m. downfield. Paramagnetic shifts are also caused, predictably, by aromatization of the C ring.

The splitting pattern is not always clear. Sometimes a multiplet with a half-width of 5–11 c.p.s. is seen; sometimes a doublet can be discerned (3–4 c.p.s.) that is also found in the signals for C-4a or C-5a protons, depending upon the particular molecule under study. In no case does the splitting pattern imply a *trans*-diaxial relationship of the C-5 proton to its adjacent protons; rather a pseudo-equatorial conformation is suggested.

The signal for the C-5a proton appears generally at about 3 p.p.m., unless it becomes allylic, in which case a paramagnetic shift is observed. The coupling constant with the C-5 proton is never greater than 4 c.p.s., sometimes much less, when only a somewhat broadened singlet is seen.

The β-6-deoxy derivatives **4** and **6** show the signal for the C-6 methyl group farther upfield than the α analog **5**. This finding is consistent with the assigned stereochemistry[2] since it implies a pseudo-axial position for the C-methyl group in the β isomer and a pseudo-equatorial position for the α epimer. In corraboration, the C-methyl signal for **4** and **6** appears as a doublet (J = 6–8 c.p.s.), while the corresponding peak for **5** is a broadened singlet.

The signals for the aromatic protons show the expected chemical shift. Sometimes the splitting pattern is simple; *i.e.*, for **3** (DMSO) a triplet appears at 7.6 and two doublets at 7 and 7.2 p.p.m., respectively. The signal for the C-8 proton appears at 6.8 p.p.m. when C-7 is substituted by chlorine and C-9 by a *t*-butyl group[4] ($CHCl_3$). Without the *t*-butyl group but with a C-7 chlorine,[4] two doublets appear at 7.0 and 7.6 p.p.m. ($CHCl_3$). Interesting data on the relation of chemical shift and degree of ionization have been published recently.[6]

The signals for the easily exchangeable protons,[9] comprising the O–H and N–H, can be found between 4 and 16 p.p.m. and are greatly solvent dependent. In several instances these labile protons were exchanged for deuterium ions to make definite assignments of peaks possible.

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Oxidations with Manganese Dioxide

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Manganese dioxide has proved a valuable oxidizing agent for certain functional groups. In addition to α,β-unsaturated primary and secondary alcohols, which are converted to the corresponding aldehydes and ketones, many other compounds are oxidized smoothly by this reagent.[1]

More recently, manganese dioxide has been used in effecting a variety of transformations: methylpyridinemethanols to methylpyridinecarboxaldehydes[2]; 2-indolemethanol to 2-indolecarboxaldehyde[3]; diarylmethanes to tetraarylethanes or diaryl ketones[4]; phenylhydrazides to carboxylic acids[5,6]; primary aromatic amines and hydrazobenzenes to azobenzenes[7,8]; N-benzylanilines to benzalanilines[8]; 1,2,3,4-tetrahydroquinoline, 2,3-dihydroindole, and acridane to quinoline, indole, and acridine, respectively[8]; simple and tricyclic indolines to indoles[9]; and quinaldine, lepidine, α- and γ-picoline, and 1-methylisoquinoline to the corresponding carboxylic acids.[10] It has also been reported that primary and secondary saturated alcohols are oxidized to the carbonyl compounds in good yields when sufficient quantities of the oxidant and pure solvents are used.[11]

In this laboratory we have used manganese dioxide to oxidize in good yields pyridinemethanols to the corresponding aldehydes, mercaptans to disulfides,[12] aliphatic α-hydroxy ketones to 1,2-diketones, and N-phenylhydroxylamine to nitrosobenzene. The general experimental procedure is as follows. A suspension of manganese dioxide in a solution of the substance to be oxidized was stirred vigorously for 5–6 hr and the oxide was removed by filtration and washed with ether. The filtrate and washings were concentrated under reduced pressure, and the product was isolated by distillation or recrystallization. The results are summarized in Table I.

Some of the oxidations described in this paper may be effected in comparable yields by other reagents: lead tetraacetate (pyridinemethanols to pyridinecarboxaldehydes,[13] thiols to disulfides[14]); selenium dioxide (methylpyridines[15] and pyridinemethanols[16] to pyridinecarboxaldehydes); concentrated nitric acid [imidazole-4- (or 5-) methanol to the aldehyde[17]]; dimethyl sulfoxide (thiols to disulfides[18]); and cupric acetate, ferric chloride,[19] or bismuth oxide[20] (acyloins to diketones). The present method deserves consideration as a synthetic route by virtue of its simplicity, selectivity, and ease of product isolation.

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TABLE I
OXIDATION CONDITIONS AND YIELDS

Substance oxidized	Solvent (ml/g of oxidant)	Product	Bp (mm) or mp, °C Obsd	Bp (mm) or mp, °C Lit	Yield, %
2-Pyridinemethanol[a]	Chloroform (10)	2-Pyridinecarboxaldehyde	68–70 (13–14)	70–73 (13)[b]	68
2-Pyridinemethanol[a]	Benzene (10)	2-Pyridinecarboxaldehyde	68–70 (13–14)		54
3-Pyridinemethanol[a]	Chloroform (10)	3-Pyridinecarboxaldehyde	78–80 (10–11)	86–89 (13)[b]	67
3-Pyridinemethanol[a]	Benzene (10)	3-Pyridinecarboxaldehyde	78–80 (10–11)		78
4-Pyridinemethanol[a]	Chloroform (10)	4-Pyridinecarboxaldehyde[c]	77–78 (11–12)	77–78 (12)[d]	73
4-Pyridinemethanol[a]	Benzene (10)	4-Pyridinecarboxaldehyde[c]	77–78 (11–12)		68
6-Methyl-2-pyridinemethanol[a]	Chloroform (8)	6-Methyl-2-pyridinecarboxaldehyde[e]	71 (11)	70–72 (9)[u]	67
2-Pyridinemethanol 1-oxide[a]	Chloroform (12)	2-Pyridinecarboxaldehyde 1-oxide hydrate	75–77[f]	78–80[g]	62
3-Pyridinemethanol 1-oxide[a]	Chloroform (10)	3-Pyridinecarboxaldehyde 1-oxide[h]	131–133[i]		51
4-Pyridinemethanol 1-oxide[a]	Chloroform (10)	4-Pyridinecarboxaldehyde 1-oxide[j]	149–150	148–150[k]	69
2,6-Pyridinedimethanol[l]	Chloroform (8)	2,6-Pyridinedicarboxaldehyde[m]	122–123	124[n]	54
Imidazole-4-(or 5)-methanol[o,p]	Dioxane (10)	Imidazole-4- (or 5-) carboxaldehyde	174	173–174[p]	59
Benzenethiol	Chloroform (10)	Phenyl disulfide	60	61[q]	92
2-Propene-1-thiol	Chloroform (10)	Allyl disulfide	74–76 (15)	78–80 (16)[q]	66
α-Toluenethiol	Chloroform (10)	Benzyl disulfide	69–70	71–72, 69–70[q]	82
5-Hydroxy-4-octanone	Chloroform (10)	4,5-Octanedione[r]	56–58 (12)	60 (12)[q]	58
4-Hydroxy-3-hexanone	Ethyl ether (10)	3,4-Hexanedione[s]	34–36 (12)	32 (10)[q]	52
N-Phenylhydroxylamine	Water (10)	Nitrosobenzene	64–66	67.5–68[q]	40[t]

[a] From F. Raschig Gmbh., Ludwigshafen. a. Rhein, Germany. [b] See ref 13. [c] Semicarbazone mp 215°; N. Campbell ("Chemistry of Carbon Compounds," Vol IV, Part A, E. H. Rodd, Ed., Elsevier Publishing Co., New York, N. Y., 1957, p 553) reported mp 216°. [d] J. P. Wibaut, E. C. Kooyman, and H. Boer, *Rec. Trav. Chim.*, **64**, 30 (1945). [e] Semicarbazone mp 218°, lit.[2] mp 216°. [f] Recrystallization from benzene raised the melting point to 80°. [g] See ref. 15. [h] *Anal.* Calcd for $C_6H_5NO_2$: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.18; H, 3.94; N, 11.34. Oxime mp 230–231° (recrystallized from 50% ethyl alcohol). *Anal.* Calcd for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.40; H, 4.47; N, 20.46. [i] Recrystallized from benzene. [j] Semicarbazone mp 248–250° dec, lit.[k] mp 246–248° dec. [k] S. Furukawa, *Yakugaku Zasshi*, **78**, 957 (1958); *Chem. Abstr.*, **53**, 3219*g* (1959). [l] By reduction of di-*n*-butyl 2,6-pyridinedicarboxylate, purchased from F. Raschig Gmbh. [m] Phenylhydrazone mp 198–199°, lit.[24] mp 199.5°; dioxime mp 212° dec, lit.[24] mp 211.5°. *Anal.* Calcd for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.44. Found: C, 50.79; H, 4.12; N, 25.58. [n] See ref 24. [o] J. R. Totter and W. J. Darby, "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p 460. [p] R. A. Turner, C. F. Huebner, and C. R. Scholz, *J. Am. Chem. Soc.*, **71**, 2801 (1949). [q] See ref 26. [r] Dioxime mp 183°, lit.[26] mp 186–187°. [s] Dioxime mp 190°, lit.[26] mp 185°; semicarbazone mp 271° dec, lit.[26] mp 270° dec. [t] On nitrobenzene. [u] See ref 2.

Experimental Section

All oxidations were carried out at reflux, except for imidazole-4- (or 5-) methanol (dioxane at 80°) and N-phenylhydroxylamine (water at 0°).

The oxidant:substance weight ratio was 5:1 in all but two cases [2,6-pyridinedimethanol and imidazole-4- (or 5-) methanol] where best results were obtained with a 10:1 ratio.

The following two examples illustrate the general experimental procedure.

Oxidation of 2,6-Pyridinedimethanol to 2,6-Pyridinedicarboxaldehyde.—2,6-Pyridinedimethanol was prepared in 58% yield (mp 118°, lit.[21] mp 114–118°) by reduction of di-*n*-butyl 2,6-pyridinedicarboxylate with lithium aluminum hydride following essentially the method described by Jones and Kornfeld[22] and by Mićović and Mihailović.[13]

A suspension of 60 g of freshly prepared manganese dioxide[23] in a solution of 5.7 g of 2,6-pyridinedimethanol in 500 ml of chloroform was stirred at reflux for 5 hr. The mixture was filtered, and the oxide was washed with five 100-ml portions of ether. The combined filtrate and washings were evaporated to dryness under reduced pressure, and the residue was recrystallized from petroleum ether (bp 55–75°) yielding 3 g (54%) of 2,6-pyridinedicarboxaldehyde: mp 122–123°, lit.[24] mp 124°; phenylhydrazone mp 198–199°, lit.[24] mp 199.5°; dioxime mp 212° dec, lit.[24] mp 211.5°.

Anal. (dioxime). Calcd for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.44. Found: C, 50.79; H, 4.12; N, 25.58.

Oxidation of N-Phenylhydroxylamine to Nitrosobenzene.—A cold (0°), aqueous solution of N-phenylhydroxylamine was prepared from 30 g (0.244 mole) of nitrobenzene, 15 g of ammonium chloride, 37.2 g of zinc dust, and 850 ml of water.[25] A mixture of this solution with 85 g of manganese dioxide was stirred vigorously at 0° for 3 hr. Steam distillation yielded 10.5 g (40%) of nitrosobenzene, mp 64–66°. One recrystallization from ethyl alcohol raised the melting point to 67–68° (lit.[26] mp 67.5–68°). The infrared spectrum of the product was identical with that of an authentic sample of nitrosobenzene.[25]

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A Convenient Preparation of γ-Keto Acids

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In connection with the studies of γ-lactone derivatives,[1] it has now been found that 3,4-dibromo-3-carboxyalkanoic acids (II)[2] obtained by bromination

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