

159. *Syntheses of Heterocyclic Compounds. Part IX.¹ Action of Manganese Dioxide on Heterocycles.*

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Manganese dioxide oxidises active methyl groups in pyridine, quinoline, and isoquinoline to a carboxyl group. The effect of this reagent on indole and tetrahydrocarbazole and its peroxide has also been studied.

MANGANESE DIOXIDE has been used as a specific reagent for oxidising allylic alcohols,² but it has also been employed as a non-specific agent as in the oxidation of *N*-alkyl groups.³ For instance methylamines are converted into *N*-formyl amines and other *N*-alkyl amines yield the parent amine and the aldehyde derived from the alkyl group. We, therefore, expected this reagent also to affect active methyl groups in heterocyclic systems such as quinoline, pyridine, or isoquinoline.

When a benzene or light petroleum solution of quinaldine was refluxed for several hours with a tenfold excess of manganese dioxide, hydrated manganese quinaldinate was obtained by extracting the oxide with hot water. The free acid was isolated by way of its copper salt. Lepidine, α - and γ -picoline, and 1-methylisoquinoline also gave the corresponding acid in *ca.* 20% yield, whereas β -picoline did not react and 3-methyl-quinoline and -isoquinoline were little affected (below 5%). None of the picoline *N*-oxides could be oxidised. Yields were almost the same when water was used as solvent and unchanged material accounted in every case for the deficit of the product. In the reaction with quinaldine, even when redistilled, a little 2-quinolylacetanilide was invariably produced. Its formation was traced to the presence of a small quantity of *N*-methylaniline as impurity which is converted into formanilide during the reaction. The latter combines with quinaldine to give probably 1-hydroxy-2-quinolyethyl-anilide which is oxidised to the above amide. The result of a test experiment in which a mixture of quinaldine, *N*-methylaniline, and manganese dioxide was heated supported this view. Purification of quinaldine by reflux over manganese dioxide followed by distillation was in fact found to be most efficient

¹ Part VIII, Meth-Cohn and Suschitzky, *J.*, 1964, 2609.

² Gritter and Wallace, *J. Org. Chem.*, 1959, **24**, 1051.

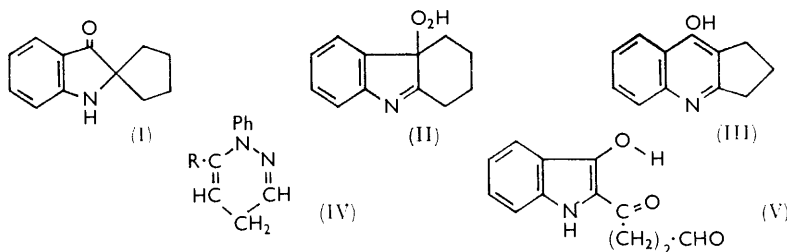
³ Henbest and Thomas, *J.*, 1957, 3032.

since this procedure completely removed *N*-alkylanilines which are common impurities from the usual manufacturing process.

We also treated indole and tetrahydrocarbazole and its peroxide with manganese dioxide. The reaction with indole was carried out in hot benzene and the manganese dioxide extracted with hot water. Evaporation of the aqueous extract gave a manganese-containing solid which, on treatment with hot dilute sulphuric acid, evolved carbon monoxide and left anthranilic acid. Careful neutralisation of the extract furnished *N*-formylanthranilic acid in good yield. This result is comparable with that of other oxidising agents such as peracids and ozone which open the nitrogen-containing ring in indole at the 2,3 position⁴ to give 2-formamidobenzaldehyde.

Tetrahydrocarbazole gave several products, depending on reaction conditions, when refluxed with benzene or toluene over manganese dioxide. Under nitrogen, carbazole and 1-oxotetrahydrocarbazole were produced as the result of aromatisation of a cyclohexene ring and oxidation of an allylic methylene group, respectively. A small quantity of benzaldehyde was noticed with toluene as the solvent. Xylene, a higher boiling solvent, favoured carbazole formation at the expense of the ketone. Oxidation of an allylic methylene group to a ketone⁵ as well as dehydrogenation of rings by manganese dioxide has been observed.⁶ It is of interest that 9,10-dihydroanthracene was dehydrogenated only to the extent of 1%,⁷ and 1,2,3,4-tetrahydroquinoline and 2,3-dihydroindole gave the corresponding aromatic compounds, but yields are not stated.⁸

Oxidation under the same conditions in air produced a complex mixture which included the previous products. Chromatography of the reaction mixture over alumina gave a highly fluorescent fraction from which the spiro-compound (I) and the quinoline (III) were obtained. Since these have previously been described by Robertson⁹ as base-catalysed rearrangement products of tetrahydrocarbazole hydroperoxide (II), it was thought that the peroxide might be adventitiously formed in our reaction, and in fact be responsible for some of the products. To confirm this view pure hydroperoxide (II) was treated with manganese dioxide and indeed yielded, apart from an unknown substance (cf. below), the two compounds (I) and (III) that were also obtained from tetrahydrocarbazole with manganese dioxide in air. Thus the hydroperoxide (II) rearranges by catalytic decomposition with manganese dioxide in the same way as with sodium hydroxide.⁹



The unknown substance had the empirical formula $C_{12}H_{11}NO_3$ and was soluble in dilute sodium hydroxide, but insoluble in acid. It could not be diazotised, unlike the parent hydroperoxide (II) and other hydrogenated carbazolenines which behave as aromatic, primary amines in mineral acid because the $-N=C<$ group suffers hydrolysis. That the nitrogen atom had lost its basicity was further indicated by a sharp spectral

⁴ Witkop, *Annalen*, 1944, **556**, 103; Witkop and Fiedler, *ibid.*, 1947, **558**, 91.

⁵ Henbest, Jones, and Owen, *J.*, 1957, 4909.

⁶ Fales, *J. Amer. Chem. Soc.*, 1955, **77**, 5118.

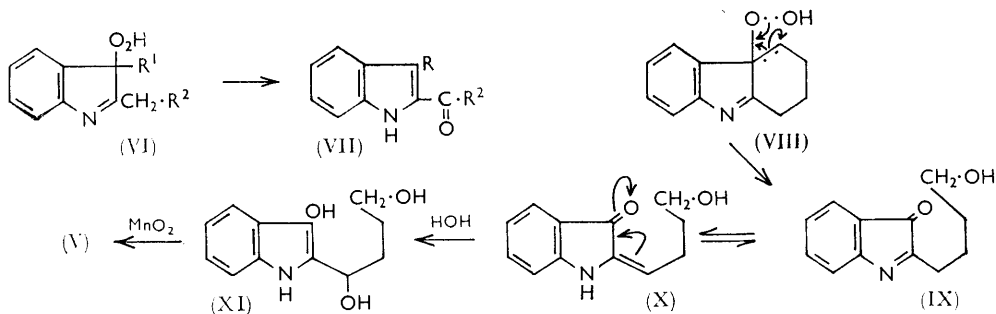
⁷ Highnet and Wildman, *J. Amer. Chem. Soc.*, 1955, **77**, 4399.

⁸ McGovern, *Diss. Abs.*, 1963, **23**, 2700.

⁹ Beer, McGrath, and Robertson, *J.*, 1950, 2118, 3283.

band at 3488 cm^{-1} characteristic of an $>\text{NH}$ group in indole.^{10a} The substance was strongly reducing (positive Fehling's and Tollen's test) and gave a derivative with phenylhydrazine or 2,4-dinitrophenylhydrazine with loss of two molecules of water. Spectral bands at 1740 and 1690 cm^{-1} (in CHCl_3) indicated two carbonyl groups. The first was not affected by change of solvent and the second shifted to 1660 cm^{-1} when the substance was examined as solid (KBr disc). Consideration of spectral and chemical evidence pointed to the presence of a hydrogen-bonded aryl ketone and an aliphatic aldehyde.^{10b} The condensation result with phenylhydrazine can be explained if the two carbonyl groups are in a 1:4 relation leading to the formation of a pyridazine. This is analogous to the reaction of levulic or β -benzoylpropionaldehyde with phenylhydrazine which yields the dihydropyridazine¹¹ (IV; R = Me or Ph). The reason for the chelation and also for the acidity of the substance was ascribed to the presence of a hydroxyl group which absorbed at 3260 cm^{-1} and was possibly derived from the hydroperoxide group in compound (II). As expected it did not react with diazomethane. Distillation with zinc dust furnished indole. On the basis of the foregoing evidence the enolic indoxyl structure (V) was assigned to the substance since it accounts satisfactorily for the observed reactions and properties. It is noteworthy that the hydroxy-form also predominates in the related 2-acetylindoxyl.¹² Additional confirmation for the structure was derived from its n.m.r. spectrum (cf. Experimental section). The product from phenylhydrazine is, therefore, the pyridazine (IV; R = 2-indoxyl).

Since neither the spiran (I) nor the quinoline (III) is transformed into the indoxyl (V) under the reaction conditions they are precluded as intermediates. The recently discussed decomposition of 2,3-disubstituted indolenin-3-yl hydroperoxides (VI; R¹ and R² = alkyl) to give 2-acylindoles (VII; R¹ and R² as in VI) for which several mechanistic explanations have been put forward¹³ bears some formal resemblance to our reaction (cf. II \rightarrow V). However, we do not consider that the general mechanism underlying these transformations is applicable to our case, since indoxyl formation is not usually observed in these reactions. Moreover, tetrahydro-1-oxocarbazole, which should logically be an intermediate if the reaction path corresponded to that postulated for indoles (cf. (VI) \rightarrow (VII) with (II) \rightarrow tetrahydro-1-oxocarbazole), is unaffected by manganese dioxide. We favour



the reaction sequence set out below (VIII) \rightarrow (V) for the oxidative decomposition of the hydroperoxide (VIII). The ring-opening (VIII) \rightarrow (IX) has its parallel in the thermal and catalytic fission of cycloalkyl and cycloalkenyl hydroperoxides,¹⁴ and the required oxidations to give the keto-aldehyde (V) are feasibly due to the action of manganese dioxide which is known to produce carbonyl compounds even from non-activated primary and

¹⁰ Bellamy, "Infra-red Spectra of Complex Molecules," Methuen and Co. Ltd., London, 1958 (a) p. 252, (b) pp. 137, 155.

¹¹ Harries, *Ber.*, 1898, **31**, 37.

¹² Su and Tsou, *J. Amer. Chem. Soc.*, 1960, **82**, 1187.

¹³ Leete, *J. Amer. Chem. Soc.*, 1961, **83**, 3645; Taylor, *Proc. Chem. Soc.*, 1962, 247; Wasserman and Floyd, *Tetrahedron Letters*, 1963, **29**, 2009; Chen and Leete, *ibid.*, p. 2013.

¹⁴ Hawkins, "Organic Peroxides," Spon Ltd., London, 1961, pp. 46, 58.

secondary alcohols.¹⁵ It was thought that manganese dioxide might concurrently act as a hydrogen transfer agent to the reactive C=N bond and thereby convert the indolenine form (IX) into that of the indole (V). However, the reagent did not cause reduction of benzylideneaniline or benzophenone in presence of boiling propan-2-ol, though the latter was smoothly oxidised to acetone. An alternative route involving rearrangement to the exocyclic enamine (X) and addition of water from the hydrated manganese dioxide is, therefore, suggested for this change (IX) \longrightarrow (XI).

EXPERIMENTAL

Manganese Dioxide.—This was prepared by heating manganese oxalate dihydrate in a thin layer (1—2 cm.) at 250° for 2 hr. in an oven and then allowing the oxide to cool in air.

Oxidation of Methyl-heterocycles.—A solution of the methyl heterocycle (5 g.) in benzene, petrol (b. p. 80—100°), or water (200 ml. in each case) was refluxed over manganese dioxide (50 g.) for 10 hr. The oxide was filtered off, then extracted with water in a Soxhlet and the aqueous extract evaporated to dryness leaving the manganese salt of the corresponding acid (cf. Table). With water as solvent the filtrate was extracted with chloroform to remove starting material and then evaporated to dryness yielding some of the manganese salt. The free acid was obtained by removing manganese from an acidified aqueous solution of the salt with aqueous sodium hydroxide followed by filtration and precipitation of the organic copper salt in the filtrate (copper sulphate). A suspension of the copper salt in water was then decomposed by hydrogen sulphide and the organic acid obtained on evaporation of the filtrate. Yields appeared to be independent of the solvent.

Quinaldine was purified by reflux over manganese dioxide for 2 hr. followed by fractionation.

2-Quinolylacetanilide.—After oxidation of redistilled quinaldine (10 g.) with manganese dioxide in light petroleum as above, steam distillation of the reaction mixture from which manganese dioxide had been removed left an oil which on crystallisation from light petroleum (b. p. 80—100°) gave white needles of *2-quinolylacetanilide*, m. p. 138° (0.05 g.) (Found: C, 77.5; H, 5.0. C₁₇H₁₄N₂O requires C, 77.8; H, 5.4%). The amide was also obtained in 50% yield by refluxing pure quinaldine (2 g.), *N*-methylaniline (0.5 ml.), and manganese dioxide (15 g.) in petrol (b. p. 80—100°) for 2 hr.

Oxidation of Indole.—A benzene solution (100 ml.) of indole (1 g.) was stirred and refluxed over manganese dioxide (10 g.) for 20 hr. The oxide was filtered off and the filtrate on evaporation gave starting material (0.5 g.). Extraction (Soxhlet) of the manganese dioxide with boiling water followed by evaporation gave a manganese-containing solid. With warm, aqueous sulphuric acid it evolved carbon monoxide, and anthranilic acid was obtained from the solution. With cold, aqueous sulphuric acid *N*-formylanthranilic acid, m. p. and mixed m. p.¹⁶ 165°, was obtained. The yield was 0.53 g., *i.e.*, 75.7% based on indole consumed.

Oxidation of Tetrahydrocarbazole.—(a) *Under nitrogen.* A benzene solution (150 ml.) of tetrahydrocarbazole (4 g.) under nitrogen was kept boiling and stirred in presence of manganese dioxide (20 g.) for 12 hr. Manganese dioxide was removed by filtration and the filtrate chromatographed over alumina. The first fractions yielded carbazole (15%), m. p. 241° (sublimation *in vacuo*). Subsequent fractions deposited more starting material and finally 1-oxotetrahydrocarbazole (20%), m. p. 166°, identical with the compound prepared by Kent's method¹⁷ from phenylhydrazine and cyclohexane-1,2-dione in acetic acid. With toluene as solvent a small quantity of benzaldehyde was isolated by steam distillation.

When the reaction was carried out in xylene under nitrogen for 10 hr. the yield of carbazole was 45% and that of ketone 15%.

(b) *In air.* Reaction as in (a) was carried out in air and treated as above. The initial fractions contained starting material (40%) and carbazole (3%), separable by sublimation. Later fractions were highly fluorescent and deposited the spiroindoxyl (I) (10%). Final elution of the column was with ethanol, yielding the cyclopentenoquinoline (III) (10%) on part evaporation and tetrahydro-1-oxocarbazole (25%) on complete removal of the solvent.

¹⁵ Barakat, Abdel-Wahab, and El-Sadr, *J.*, 1956, 4685; Harrison, *Proc. Chem. Soc.*, 1964, 110.

¹⁶ Anschütz and Schmidt, *Ber.*, 1902, **35**, 3475.

¹⁷ Kent and McNeil, *J.*, 1938, 8.

Oxidation of methyl-heterocycles (RMe) (1 part) with manganese dioxide (10 parts) in hot petrol (b. p. 80—100°) for 10 hr.

R	Yield * of Mn salt (%)	Found (%)		Formula	Reqd. (%)	
		C	H		C	H
2-Pyridyl	17	43.4	4.1	$C_{12}H_8N_2O_4Mn, 2H_2O$	43.0	3.6
	0	—	—	—	—	—
4-Pyridyl	24	48.3	2.4	$C_{12}H_8N_2O_4Mn$	48.2	2.7
2-Quinolyl	26	55.4	3.5	$C_{20}H_{12}N_2O_4Mn, 2H_2O$	55.2	3.7
3-Quinolyl	2	60.0	3.3	$C_{20}H_{12}N_2O_4Mn$	60.2	3.0
4-Quinolyl	22	60.2	3.5	"	"	"
1-Isoquinolyl	28	59.9	3.1	$C_{20}H_{12}N_2O_4Mn$	"	"
3-Isoquinolyl	4	60.0	3.0	"	"	"

* Starting material accounted for the rest of the products.

Oxidation of Tetrahydrocarbazoleninyl Hydroperoxide.—The peroxide (II) was prepared by dissolving tetrahydrocarbazole in a large excess of hot petrol (b. p. 60—80°) and irradiating the filtered solution with ultraviolet light at room temperature for 12 hr. Crystals of the peroxide (85%), m. p. 121° (lit.,⁹ 122°), were filtered off.

In a typical experiment the peroxide (4 g.) dissolved in diethyl ether (200 ml.) was agitated for 4 hr. with manganese dioxide (20 g.). The fluorescent mixture was filtered and the residue extracted with hot chloroform which on evaporation left 4-hydroxy-2,3-cyclopentenoquinoline (0.5 g.). The m. p. of this compound and the m. p.s of its benzoyl and methyl derivatives were undepressed on admixture with the corresponding authentic substances prepared by Robertson's method.⁹ The benzoyl compound had m. p. 130° (lit.,⁹ 134°) (Found: C, 79.1; H, 5.2; N, 5.1. Calc. for $C_{19}H_{15}NO_2$: C, 78.9; H, 5.2; N, 4.8%); the methyl derivative, m. p. 219° (lit.,⁹ 219—220°) (Found: C, 71.8; H, 6.7; N, 6.9. Calc. for $C_{13}H_{13}NO \cdot H_2O$: C, 71.9; H, 7.0; N, 6.5%); and the *acetyl* compound, m. p. 85° (Found: C, 73.9; H, 6.0; N, 6.3. $C_{14}H_{13}NO_2$ requires C, 74.0; H, 5.8; N, 6.2%).

The ethereal filtrate from the manganese dioxide had a strong, green fluorescence and left a yellow solid (0.9 g.) on evaporation. Extraction of the residue with light petroleum (b. p. 60—80°) gave the spiroindoxyl (I) (0.7 g.) m. p. 77—78° (lit.,⁹ 78—79°). It was identical (mixed m. p. and infrared spectrum) with an authentic specimen.⁹

The petrol-insoluble residue from above (0.2 g.) gave on recrystallisation from dioxan—water (20 : 80) the *indoxyl* (V), m. p. 189°, as fine needles (Found: C, 66.1; H, 5.1; N, 6.7. $C_{12}H_{11}NO_3$ requires C, 66.2; H, 5.1; N, 6.4%). The n.m.r. spectrum (in trifluoroacetic acid) showed chemical shifts in accord with the suggested structure; τ 7.1 and 7.2 ($CH_2 \cdot CH_2$) adjacent to an aromatic C=O and aliphatic $-C(H) \cdot O$ group, respectively, $CO \cdot CH_2 \cdot CH_2 \cdot C(H) \cdot O$ integrated for 4 protons only since the aldehydic proton must be "buried" in the aromatic region.

When treated with phenylhydrazine in acidified, hot ethanolic solution 2-(2,5-dihydro-2-phenylpyridazin-3-yl)-2-indoxyl (IV; R = 2-indoxyl) separated as needles, m. p. 147—148° (Found: C, 74.6; H, 5.1; N, 14.7. $C_{18}H_{15}N_3O$ requires C, 74.8; H, 5.2; N, 14.5%). With 2,4-dinitrophenylhydrazine the *pyridazinylindoxyl* [(IV; Ph = 2,4- $C_6H_3(NO_2)_2$)] was obtained as red needles, m. p. 290° (Found: C, 56.5; H, 3.2; N, 18.6. $C_{18}H_{13}N_5O_5$ requires C, 57.0; H, 3.45; N, 18.5%).

Attempted Hydrogen-transfer Reactions.—(a) A solution of benzophenone (5 g.) in propan-2-ol (100 ml.) was refluxed over manganese dioxide (25 g.). Apart from acetone (5.6 g.), which was continuously removed by fractionation, no product was detected (thin layer chromatography).

(b) A mixture of benzylideneaniline and propan-2-ol gave similar results.

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