[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Solid Manganese Dioxide as an Oxidizing Agent

BY R. J. HIGHET AND W. C. WILDMAN

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Solid manganese dioxide has been shown capable of oxidizing two benzyl alcohols to benzaldehydes, three amines to the corresponding Schiff bases, an aldehyde–ammonia to a lactam and two hemiacetals to lactones. The method provides a convenient route to codeinone. The spectrum of the oxidation product of lycorenine shows it to be a six-membered lactone

Recent investigations have shown manganese dioxide to be a reliable selective oxidizing agent for allylic alcohols.[1] This paper describes experiments further exploring its oxidizing power.

Although several secondary benzylic alcohols have been oxidized by manganese dioxide,[2,3] two workers have reported primary benzylic alcohols to be unaffected.[2,4] While the present work was in progress, a method was described for the preparation of benzaldehydes by the use of larger proportions of the manganese oxide.[5] Similar results have been obtained in these laboratories. However, with the Attenburrow oxide, the effect of the solvent upon the yield noted by the previous authors,[5] is not significant. It would appear that a higher ratio of manganese dioxide to alcohol results in a higher yield of aldehyde with a shorter reaction period. Benzil and benzyl methyl ether are unaffected by such treatment. Adipoin, easily oxidized by bismuth oxide,[6] is likewise unaffected.[7]

TABLE I

THE EFFECT OF TREATMENT OF TWO BENZYL ALCOHOLS WITH MANGANESE DIOXIDE

Compound	Time, hr.	Solvent	Yield,[a] %
Benzyl alcohol	1	Chloroform	61
	23	Chloroform	89
	1	Ether	70
	24	Ether	78
	1	Hexane	61
	24	Hexane	78
Veratryl alcohol	3	Chloroform	58

[a] Calculated from weight of 2,4-dinitrophenylhydrazone derivative.

The oxidation of amines by manganese dioxide apparently has not been investigated.[1] As shown in Table II, primary and secondary amines are oxidized slowly and in low yield. Infrared spectra of the reaction mixtures from which the solid oxide has been separated show the development of a very strong C–N double bond at 6.08 μ. Although it was impossible to isolate the proposed imine intermediates, the infrared spectrum of the benzylamine oxidation product and that of hydrobenzamide were almost identical. The extent of the oxidation was determined in each case by hydrolysis of the base to the corresponding aldehyde and conversion to the 2,4-dinitrophenylhydrazone. As anticipated, a tertiary amine is not affected. After a chloroform solution of hydrohydrastinine had been stirred for 168 hours over manganese dioxide, its infrared spectrum was identical with that of the starting material.

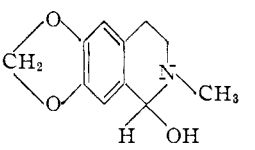
TABLE II

THE EFFECT OF TREATMENT OF VARIOUS AMINES WITH MANGANESE DIOXIDE

Compound	Time, hr.	Yield,[a] %
Benzylamine	24	34
N-Methylpiperonylamine	40	21
N-Methylbenzylamine	44	24
Hydrohydrastinine	168	0

[a] See text.

Quite a different type of product was obtained from the oxidation of several aldehyde derivatives. Hydrastinine (I) was converted quickly to the corresponding lactam, oxyhydrastinine (II), in 76% yield. Apparently the benzyl activation is not essential to this type of reaction, for 2-hydroxytetrahydropyran (III) was converted to the lactone (IV) after 21 hours; the infrared spectrum of the chloroform reaction mixture showed a strong peak at 5.78 μ and a greatly diminished hydroxyl peak. The product still gave a positive Schiff test. The presence of IV is assured, since its silver salt was identical with that of an authentic specimen.



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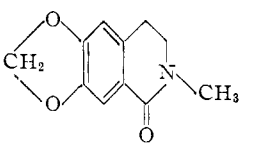

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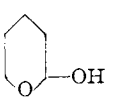

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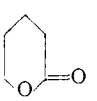


IV

Because of the success of the previously mentioned work, lycorenine was subjected to a similar oxidation. Lycorenine, a minor alkaloid of the *Amaryllidaceae*, has been assigned the formula V by Wenkert.[8] The lactone obtained by the manganese dioxide oxidation of lycorenine shows a carbonyl band at 5.84 μ. Therefore, the lactone may

(1) (a) *Cf.* B. C. L. Weedon, *Ann. Repts.*, **49**, 142 (1952); **50**, 169 (1953); (b) see also F. Sondheimer, E. Amendolla and G. Rosenkranz, THIS JOURNAL, **75**, 5932 (1953), and references cited therein.

(2) D. L. Turner, *ibid.*, **76**, 5175 (1954).

(3) H. Rapoport and S. Masamune, *ibid.*, **77**, 4330 (1955).

(4) S. Ball, T. W. Goodwin and R. A. Morton, *Biochem. J.*, **42**, 516 (1948).

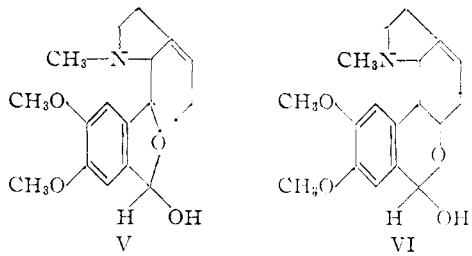
(5) M. Harfenist, A. Bavley and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

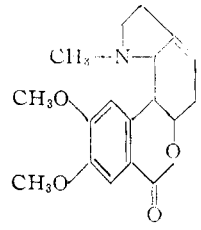
(6) W. Rigby, *J. Chem. Soc.*, 793 (1951).

(7) Sondheimer, *et al.* (ref. 1b), have reported that 17α,21-diol-20-keto steroids are cleaved by manganese dioxide to 17-keto steroids; unfortunately, the experimental details of this reaction are not available.

(8) E. Wenkert, *Chemistry and Industry*, 1262 (1954).

be formulated as VII and lycorenine probably possesses the structure VI.[9]



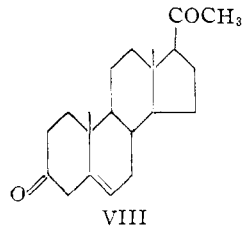


VII

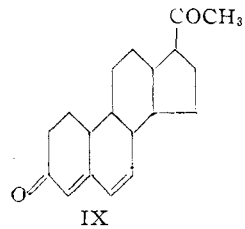
The oxidation product of V would be expected to show absorption similar to that of *m*-meconine (5.68 μ) or phthalide (5.65 μ). The carbonyl absorption of VII should be close to that of ethyl benzoate (5.84 μ).

To provide further experience with the treatment of complex alkaloids, the oxidation of codeine to codeinone was studied. Stirring a chloroform solution of the alcohol over manganese dioxide for 20 minutes produced a 96% conversion to the ketone; longer periods failed to increase the conversion and rendered the purification of the product more difficult. Since earlier workers have emphasized the importance of adsorption in these reactions,[4,10] the effect of adding 5% pyridine was investigated and found to reduce the conversion to 84%.

The observation by Sondheimer, *et al.*,[1b] that the unconjugated ketone VIII was readily dehydrogenated by manganese dioxide to the conjugated dienone IX prompted an investigation into the effect of manganese dioxide upon a hydroaromatic compound. However, 9,10-dihydroanthracene, which has been shown by Linstead, *et al.*, to be one of the more readily dehydrogenated hydroaromatic compounds,[11] was dehydrogenated only very slowly; the ultraviolet spectrum of a sample which had been stirred with manganese dioxide for 138 hours showed a conversion of 1%.



VIII



IX

(9) In a private communication Prof. S. Uyeo has disclosed that chromic acid oxidation of lycorenine leads to VII and that this lactone is identical with homolycorine.

(10) G. Wald, *J. Gen. Physiology*, **31**, 489 (1948).

(11) E. A. Braude, L. M. Jackman and R. P. Linstead, *J. Chem. Soc.*, 3564 (1954).

Experimental[12]

Codeinone.—Codeine (201 mg., 0.67 mmole) was dissolved in 25 ml. of chloroform and stirred over 600 mg. of manganese dioxide[13] for 10 minutes. The solution was filtered through a sintered glass funnel, the manganese dioxide washed twice with chloroform, and the filtrates concentrated at reduced pressure to provide 196 mg. of light brown crystalline material, $E_{232\ m\mu}$ 11,400 (70% conversion; codeine, $E_{232\ m\mu}$ 6,300; codeinone, $E_{232\ m\mu}$ 13,300). A portion of the precipitate (183 mg.) was dissolved in 2 ml. of chloroform and extracted with 1.5 ml. of 0.5 *N* sulfuric acid. On cooling, the solution deposited white needles which were washed repeatedly with water and dried to give 77 mg. (36%) of the hydrosulfate, m.p. 176° (reported[14] 176°). When this procedure was carried out by stirring 206 mg. of codeine over 2.0 g. of manganese dioxide for 20 minutes, the crude product obtained by concentration of the chloroform solution had the m.p. 176–177° (reported[14] 185–186°); $E_{232\ m\mu}$ 13,000 (96% codeinone). The infrared spectrum was essentially identical with that of pure codeinone. However, the yield of isolated hydrosulfate was not improved.

Benzyl Alcohol.—A solution of 0.109 g. (1 mmole) of benzyl alcohol in 40 ml. of solvent was stirred at room temperature with 1.0 g. of manganese dioxide. After the given period of time, the solution was filtered. The solid was washed with chloroform and ethanol and the washings were added to the original filtrate. The combined solutions were treated with 9 ml. of 2,4-dinitrophenylhydrazine reagent[15] and allowed to stand 1 hour. Approximately half of the solvent was removed in an air jet and the solid was removed by filtration. The solid was washed once with ethanol, once with ethanol containing a trace of pyridine and finally with ethanol. In each case the dried solid showed a m.p. of 240–241 ± 1° (reported[16] 237°). A blank determination using benzyl alcohol gave no solid derivative under these conditions.

Veratryl Alcohol.—By the same procedure as for benzyl alcohol, 1 mmole of veratryl alcohol gave a 58% yield of the 2,4-dinitrophenylhydrazone of veratraldehyde, m.p. 265–266° (reported[17] 265°), after treatment with manganese dioxide for 3 hours.

When the same technique was employed, adipoin, benzil, benzyl methyl ether and hydrohydrastinine were unchanged after reaction periods of 5, 94, 47 and 168 hours, respectively, as determined by infrared spectra.

The oxidation of benzylamine, N-methylbenzylamine and N-methylpiperonylamine followed the procedure given for benzyl alcohol except that 30 ml. of chloroform was used as the reaction solvent. To ensure hydrolysis of the imine, the conversion to the 2,4-dinitrophenylhydrazone was carried out with 2,4-dinitrophenylhydrazine sulfate in aqueous ethanol. The reaction times and yields of the aldehyde derivatives are listed in Table II. The 2,4-dinitrophenylhydrazone of benzaldehyde melted at 236–237°. The 2,4-dinitrophenylhydrazone derived from N-methylpiperonylamine, m.p. 271–272°, showed no depression in melting point when mixed with an authentic sample of the 2,4-dinitrophenylhydrazone of piperonal, m.p. 269–270°. Benzylamine gave no derivative under similar conditions.

Hydrastinine.—A solution of 1 mmole of hydrastinine in 40 ml. of chloroform was stirred with 1 g. of manganese dioxide for 24 hours. One-milliliter samples of the chloroform solution were withdrawn at 0, 10, 20, 30, 40, 60, 90, 120, 300, 420 and 1440 minutes. The chloroform was removed by evaporation and the residue was dissolved in 0.1 ml. of chloroform; the progress of the reaction was followed

(12) All melting points were observed on a Kofler microscope hot-stage and are corrected. Infrared and ultraviolet spectra were determined by Mrs. Iris J. Siewers and Miss Fleur C. Bateman. Infrared spectra were recorded with a Perkin-Elmer Model 21 double-beam spectrophotometer.

(13) J. Attenburrow, *et al.*, *J. Chem. Soc.*, 1094 (1952).

(14) S. P. Findlay and L. F. Small, THIS JOURNAL, **72**, 3247 (1950). Dr. Findlay, to whom we are indebted for a description of this procedure for isolating codeinone hydrosulfate, has reported obtaining a 59% yield of the salt by conducting this procedure on a larger scale.

(15) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

(16) N. R. Campbell, *Analyst*, **61**, 392 (1936).

(17) H. H. Strain, THIS JOURNAL, **57**, 760 (1935).

by the infrared spectra of these samples. A perceptible amide band was present after 10 minutes, and the spectra indicated that the reaction essentially was complete at the end of 3 hours. After 24 hours, the spectrum was identical with that of an authentic specimen of oxyhydrastinine.[18] At that time the manganese dioxide was removed by filtration and washed twice with chloroform. The chloroform solution was washed three times with dilute hydrochloric acid and concentrated to give a solid which was recrystallized from cyclohexane, 86 mg., m.p. 96–98° (reported[18] for oxyhydrastinine 97–98°). A mixed melting point with an authentic sample, m.p. 97–98°, showed no depression. The acid solution gave 37 mg. of crude unreacted hydrastinine, m.p. 87–96°, identical in its infrared spectrum with the starting hydrastinine. The yield of oxyhydrastinine was 76% based on the starting material consumed and the removal of 11 aliquots.

2-Hydroxypyran.—A solution of 1 mmole of 2-hydroxytetrahydropyran[19] in 20 ml. of chloroform was stirred with 1.0 g. of manganese dioxide at room temperature for 24 hours. Samples of 1-milliliter volume were withdrawn at 0, 75 and 1275 minutes. A moderately strong lactone band at 5.78 μ was found after the reaction had run 75 minutes. At the end of 1275 minutes the band at 5.78 μ was very strong. The hydroxyl band at 2.95 μ showed a concurrent decrease in intensity but still was present at the end of the reaction. The reaction product gave a positive fuchsin test. The reaction product was converted to its silver salt which was identical in its infrared spectrum with that of an authentic specimen.[20]

Lycorenine.—The alkaloid was obtained in trace amounts from *Lycoris radiata* Herb. by a conventional procedure[21] and recrystallized from methanol–acetone for analysis; m.p. 198–200°; $[\alpha]^{24}D$ +144° (*c* 1.03, methanol); $[\alpha]^{25}D$ +180° (*c* 1.12, chloroform). The material was identical with an authentic specimen kindly furnished by Prof. S. Uyeo.

Anal. Calcd. for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.21; H, 7.33; N, 4.34.

A solution of 94 mg. of lycorenine in 31 ml. of chloroform was oxidized by the above method with 0.5 g. of manganese dioxide. After 1.75 hours, the reaction mixture was filtered and the manganese dioxide was washed with ethanol. The combined organic solutions were concentrated to a brown oil that was triturated with ethyl acetate. Fractional crystallization from ethyl acetate gave 14 mg. of impure lycorenine, m.p. 182–188° and 30 mg. of a lactone, m.p. 174–176°, a portion of which was sublimed for analysis, m.p. 175–176°, $[\alpha]^{25}D$ +93.6° (*c* 0.84, chloroform). The compound showed strong lactone absorption in chloroform at 5.84 μ.

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.46; H, 6.61; N, 4.66.

(18) M. Freund and W. Will, *Ber.*, **20**, 2401 (1887).

(19) G. F. Woods, *Org. Syntheses*, **27**, 43 (1947).

(20) W. W. Westerfield, *J. Biol. Chem.*, **143**, 177 (1942).

(21) W. C. Wildman and C. J. Kaufman, THIS JOURNAL, **76**, 5815 (1954).

BETHESDA 14, MARYLAND

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF CORNELL UNIVERSITY AND MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Elimination Reactions of Bicyclic Quaternary Salts. I. The Base Degradation of Tropinone Methiodide[1]

BY J. MEINWALD, S. L. EMERMAN, N. C. YANG AND G. BÜCHI

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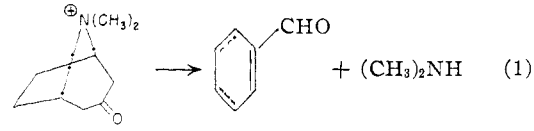
The base degradation product of tropinone methiodide (I), hitherto considered to be a dihydrobenzaldehyde (II), is shown to be a mixture of cycloheptadienones. One component of the mixture, cycloheptadien-3,5-one (VI), has been isolated and characterized. Evidence for the formation of cycloheptadien-2,4-one (V) was also obtained. The Diels–Alder reactions of these dienones as well as of tropone and tropilidene are discussed.

The structure of tropinone is firmly established on the basis of sound degradative evidence supplemented by independent syntheses.[2] The report that tropinone methiodide (I) is converted under a variety of basic conditions into dimethylamine and a *dihydrobenzaldehyde* (II) according to equation 1 is, therefore, rather surprising.[3] Such a transformation would necessitate the contraction of the seven-membered ring to a cyclohexane derivative. Several different base-catalyzed ring contractions of carbonyl compounds are well known, which provide some formal analogy for the reported



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skeletal rearrangement of tropinone. One of these is the benzilic acid rearrangement of cyclic α-diketones,[4] a second is the Faworskii rearrangement of α-haloketones[5] and a third is the conversion of tropolone and its derivatives into benzenoid compounds.[6] It does not seem possible, however, to construct mechanisms directly related to any of the mechanisms of the above-mentioned rearrangements, which would be capable of accommodating the tropinone ring contraction. Since the formation of a dihydrobenzaldehyde seemed intrinsically unlikely, and since the structural evidence available

(1) A preliminary Communication of some of the results reported in this paper has appeared in *Chemistry and Industry*, 1063 (1953).

(2) For convenient reviews of the chemistry of tropinone see T. A. Henry, "The Plant Alkaloids," Churchill, Ltd., London, 1949, 4th Edn., or R. H. F. Manske and H. L. Holmes, "The Alkaloids," Academic Press, Inc., New York, N. Y., 1950, Vol. 1.

(3) (a) The fact that this transformation could be carried out under relatively gentle conditions was initially considered to provide evidence for the presence of a bridged cyclohexane nucleus in tropinone. When later developments disproved this hypothesis, the transformation seems to have been ignored or forgotten. The reaction was discovered almost simultaneously by R. Willstätter, *Ber.*, **29**, 393 (1896); and G. Ciamician and P. Silber, *ibid.*, **29**, 490 (1896). The second double bond in II was postulated to be in either of the two dotted positions. (b) The same "dihydrobenzaldehyde" had been obtained earlier from anhydroecgonine dibromide: see A. Einhorn, *ibid.*, **26**, 451 (1893); A. Eichengrün and A. Einhorn, *ibid.*, **23**, 2870 (1893).

(4) Two examples of this type of contraction are cited by R. C. Fuson, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 360. For a discussion of the reaction mechanism see C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 480.

(5) R. B. Loftfield, THIS JOURNAL, **73**, 4707 (1951).

(6) See, for example, W. von E. Doering and L. H. Knox, *ibid.*, **74**, 5683 (1952).