

Manganese Dioxide Oxidation of 3,4,4a,5-Tetrahydro[1,2,4]triazino[6,1-c][1,4]benzoxazines

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Since we developed [1] a synthetic entry to 3,4,4a,5-tetrahydro[1,2,4]triazino[6,1-c][1,4]benzoxazines **1**, we decided to explore the chemistry of this novel ring system. Its behaviour towards manganese dioxide is here described.

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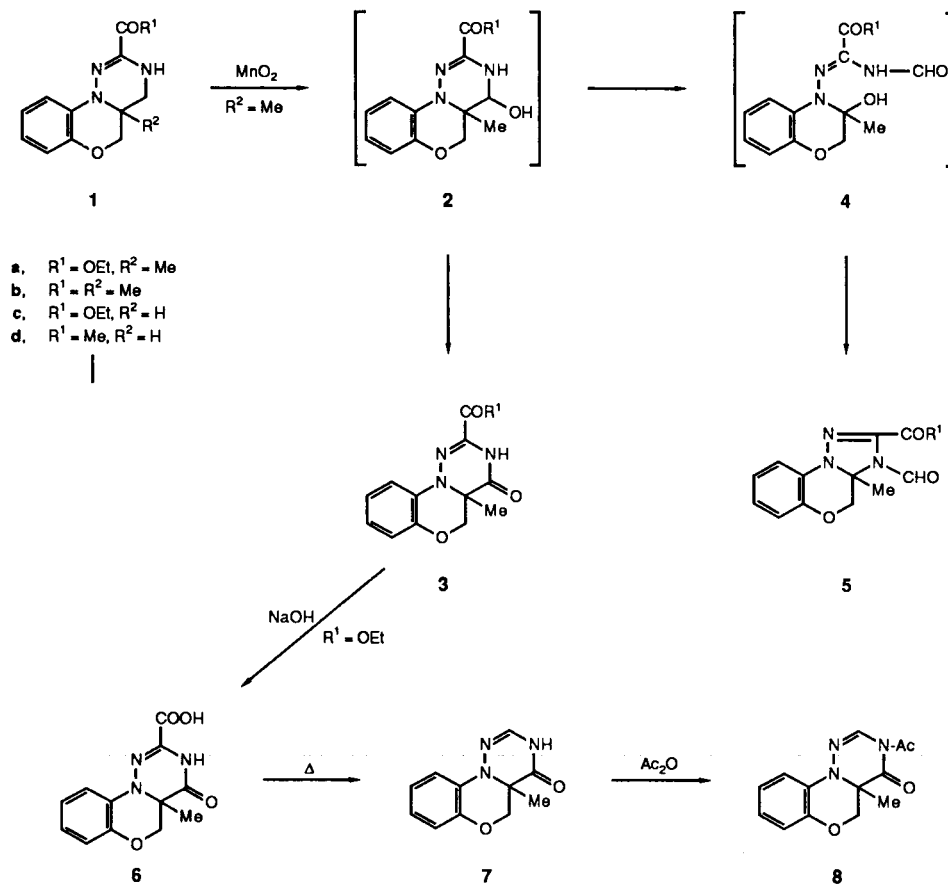
Upon treatment with active manganese dioxide [2] in chloroform, all substrates **1a-d** underwent change at room temperature. Compounds **1c,d** led to very complex mixtures which were not further considered as having no synthetic utility. In contrast, a rather clean reaction took place in the case of **1a,b** to give **3** as the main product along with a minor amount of **5**.

The structures of the products came from analytical and spectral data. While the ir spectrum of **3b** presented two bands in the carbonyl region (1685 and 1720 cm^{-1}), only one carbonyl absorption at 1720 cm^{-1} was apparent in the ir spectrum of **3a**. The latter structure however was con-

firmed by the ^{13}C nmr spectrum (δ 159.6 and 163.4) [3] as well as by chemical transformations. In fact, alkaline hydrolysis of **3a** followed by thermal decarboxylation of the corresponding acid **6** gave the 2-unsubstituted compound **7**, whose ir spectrum showed just one carbonyl band at 1715 cm^{-1} . Furthermore, treatment of **7** with acetic anhydride led to the *N*-acetyl derivative **8**, which exhibited two ir absorptions at 1725 and 1690 cm^{-1} .

Diagnostic spectral features for compounds **5a,b** were (i) the ^1H nmr signal at δ ca. 9.5 (not exchangeable), (ii) the ir band at 1680-1690 cm^{-1} , and (iii) the intense peak at ($M^+ - 29$) in the mass spectrum.

Scheme



The formation of **3**, which implies the conversion of a methylene group into a carbonyl, has some precedent in the manganese dioxide oxidation of cyclocompounds [4-6]. However, the obtainment of **5** is unprecedented at all. It may be that **5** derives from the transient hydroxy-derivative **2** via the ring-opened species **4**, the formation of which may somehow resemble the oxidative α,β -fragmentation of amines in the presence of manganese dioxide [7]. It remains to be noted that dehydrogenation of the CH_2NH grouping to an azomethine moiety [7] was not observed in the present case.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 298 spectrophotometer. The nmr spectra were recorded on Varian EM-390 (^1H) and Bruker WP80SY (^{13}C) instruments; chemical shifts are given in δ from tetramethylsilane as the internal standard (J in Hz). Mass spectra were obtained on a VG-70EQ apparatus. Silica gel used for chromatography was Merck Kieselgel 60 (70-230 mesh ASTM). Active manganese dioxide was purchased from Fluka AG Company.

Reaction of Compound **1a** with Manganese Dioxide.

A solution of **1a** (0.80 g) in chloroform (200 ml) was treated with active manganese dioxide (8.0 g) and stirred at room temperature for 90 hours. The undissolved material was filtered off, the solution was evaporated, and the residue was chromatographed on a silica gel column with benzene-ethyl acetate (9:1) as eluant. First fractions gave 2-ethoxycarbonyl-3-formyl-3a-methyl-3a,4-dihydro-3H-[1,2,4]triazolo[5,1-c][1,4]benzoxazine **5a** (0.13 g), mp 100° (from *n*-pentane); ir (Nujol): 1720, 1680 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.40 (t, 3H, J = 7), 1.78 (s, 3H), 3.60 (d, 1H, J = 10), 4.41 (q, 2H, J = 7), 4.96 (d, 1H, J = 10), 6.8-7.6 (m, 4H), 9.40 (s, 1H); ms: m/e 200 (100), 214 (70), 246 (42), 260 (67), 289 (67) M^+ .

Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_4$: C, 58.12; H, 5.23; N, 14.53. Found: C, 58.16; H, 5.11; N, 14.62.

Subsequent fractions gave 2-ethoxycarbonyl-4a-methyl-4-oxo-3,4,4a,5-tetrahydro[1,2,4]triazino[6,1-c][1,4]benzoxazine **3a** (0.52 g), mp 183° (from diisopropyl ether); ir (Nujol): 3270, 1720 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.21 (s, 3H), 1.42 (t, 3H, J = 7), 4.22 (d, 1H, J = 10.5), 4.42 (q, 2H, J = 7), 4.64 (d, 1H, J = 10.5), 6.8-7.1 (m, 3H), 7.5-7.8 (m, 1H), 9.2 (br s, 1H); ^{13}C nmr (deuteriochloroform): δ 14.2 (q), 14.9 (q), 55.4 (s), 62.8 (t), 68.2 (t), 115.7 (d), 116.8 (d), 122.4 (d), 122.7 (d), 126.7 (s), 129.3 (s), 143.0 (s), 159.6 (s), 163.4 (s); ms: m/e 200 (24), 246 (44), 274 (100), 289 (80) M^+ .

Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_4$: C, 58.12; H, 5.23; N, 14.53. Found: C, 58.25; H, 5.17; N, 14.62.

Alkaline Hydrolysis of Compound **3a**.

Compound **3a** (0.38 g) was treated with 0.3 M sodium hydroxide in ethanol (50 ml) and stirred at room temperature for 1.5 hours. The resulting solution was acidified with aqueous hydrochloric acid, the solvent was removed under reduced pressure, and the residue was taken up with water and extracted with chloroform. The organic solution was dried (sodium sulfate) and evaporated to give the acid **6** in the crude state (0.25 g), mp $172-175^\circ$ dec. This material was suspended in benzene (50 ml) and refluxed for 12 hours. After removal of the solvent, the

residue was treated with diisopropyl ether and filtered to afford 4a-methyl-4-oxo-3,4,4a,5-tetrahydro[1,2,4]triazino[6,1-c][1,4]benzoxazine **7** (0.12 g), mp 205° (from benzene); ir (Nujol): 3240, 1715 cm^{-1} ; ^1H nmr (acetone- d_6): δ 1.19 (s, 3H), 4.18 (d, 1H, J = 10.5), 4.52 (d, 1H, J = 10.5), 6.8-7.0 (m, 3H), 7.16 (d, 1H, J = 2), 7.4-7.6 (m, 1H), 9.7 (br s, 1H).

Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_2$: C, 60.81; H, 5.11; N, 19.34. Found: C, 60.92; H, 5.18; N, 19.25.

Reaction of Compound **7** with Acetic Anhydride.

A solution of compound **7** (90 mg) in acetic anhydride (20 ml) was refluxed for 2 hours. The solvent was removed *in vacuo* and the residue was taken up with ether and washed with aqueous sodium hydrogen carbonate. The organic solution was dried (sodium sulfate) and evaporated. Addition of *n*-pentane followed by filtration gave 3-acetyl-4a-methyl-4-oxo-3,4,4a,5-tetrahydro[1,2,4]triazino[6,1-c][1,4]benzoxazine **8** (55 mg), mp 100° (from cyclohexane); ir (Nujol): 1725, 1690 cm^{-1} ; ^1H nmr (acetone- d_6): δ 1.29 (s, 3H), 2.60 (s, 3H), 4.24 (d, 1H, J = 10.5), 4.60 (d, 1H, J = 10.5), 6.7-7.3 (m, 3H), 7.4-7.6 (m, 1H), 7.86 (s, 1H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.08; H, 4.96; N, 16.27.

Reaction of Compound **1b** with Manganese Dioxide.

A solution of **1b** (0.36 g) in chloroform (100 ml) was treated with active manganese dioxide (3.6 g) and stirred at room temperature for 72 hours. The undissolved material was filtered off, the solution was evaporated, and the residue was chromatographed on a silica gel column with benzene-ethyl acetate (9:1) as eluant. First fractions contained 2-acetyl-3-formyl-3a-methyl-3a,4-dihydro-3H-[1,2,4]triazolo[5,1-c][1,4]benzoxazine **5b** (46 mg), mp 104° (from diisopropyl ether); ir (Nujol) 1680-1690 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.78 (s, 3H), 2.57 (s, 3H), 3.65 (d, 1H, J = 10), 5.06 (d, 1H, J = 10), 6.9-7.6 (m, 4H), 9.60 (s, 1H); ms: m/e 230 (100), 259 (65) M^+ .

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.35; H, 4.96; N, 16.33.

Subsequent fractions contained 2-acetyl-4a-methyl-4-oxo-3,4,4a,5-tetrahydro[1,2,4]triazino[6,1-c][1,4]benzoxazine **3b** (0.25 g), mp 154° (from diisopropyl ether); ir (Nujol): 3260, 1720, 1685 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.34 (s, 3H), 2.57 (s, 3H), 4.22 (d, 1H, J = 10.5), 4.66 (d, 1H, J = 10.5), 6.8-7.2 (m, 3H), 7.5-7.8 (m, 1H), 8.8 (br s, 1H); ms: m/e 244 (100), 259 (95) M^+ .

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.08; H, 4.98; N, 16.11.

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