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Selective Oxidation of the Side Chain at C-3 of Indoles

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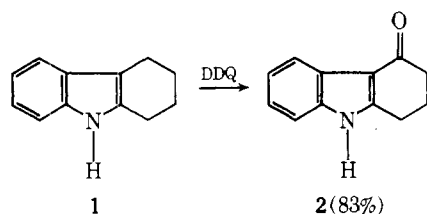
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Treatment of 1,2,3,4-tetrahydrocarbazole (**1**) with dichlorodicyanobenzoquinone (DDQ) in aqueous tetrahydrofuran at 0 °C readily gave 1,2,3,4-tetrahydrocarbazol-4-one (**2**) in a high yield. This selective oxidation of C-3 side chains of indoles was extended to cycloalkan[b]indoles (**8**–**11**) to afford the corresponding ketones (**12**–**15**). The oxidation of *N*-methyl (**17**) and *N*-benzyl (**18**) derivatives also proceeded smoothly. 2,3-Dimethylindoles (**23**) gave 2-formylindole (**25**) as well as the expected 3-formylindole (**24**), but the yield of **25** was lower in tetrahydrofuran containing acetic acid. Oxidation of 3-ethyl-2-methylindole (**26**) gave again only a 3-acyl product (**27**). 3-Monosubstituted indoles (**35**–**40**) under similar conditions gave the corresponding 3-acylindoles including a β -keto derivative of tryptophan (**46**). Oxidation of methyl 1-benzylindole-3-propionate (**49**) in anhydrous tetrahydrofuran gave methyl 1-benzylindole-3-acrylate (**50**) in a high yield.

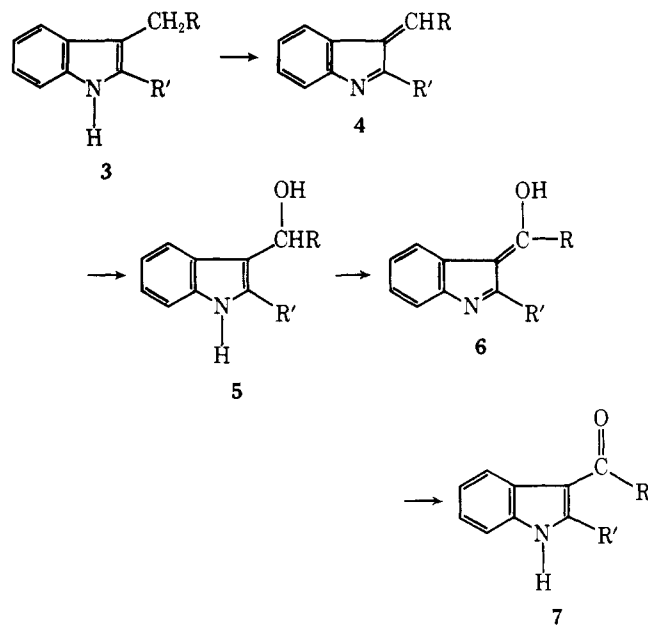
Despite numerous reports on the oxidation of indole derivatives,¹ no general method for the selective oxidation of side chains at C-3 is so far available. Thus, oxidation of 3-substituted and 2,3-disubstituted indoles usually occurs on the pyrrole ring and at the 2 substituent, not at the 3 substituent. This is because most oxidizing agents act as electrophiles and first attack C-3 of the indole ring leading to the oxidation of the pyrrole portion and to the formation of 2-acylindoles. Among many oxidative reactions of phenols with dichlorodicyanobenzoquinone (DDQ), Becker² showed that the selective benzylic oxidation of suitable phenols proceeded smoothly in methanol. This reaction was successfully extended to an alternative synthesis of tetralones from tetralins.³ In the present paper, we describe an application of the DDQ oxidation to indoles for a convenient and selective oxidation of C-3 side chains in indoles.

Treatment of tetrahydrocarbazole (**1**) with 2 equiv of DDQ in methanol at 20 °C under nitrogen or argon led to a blue-colored solution, but the color rapidly changed to pale yellow. Tetrahydrocarbazol-4-one (**2**) was isolated from the reaction



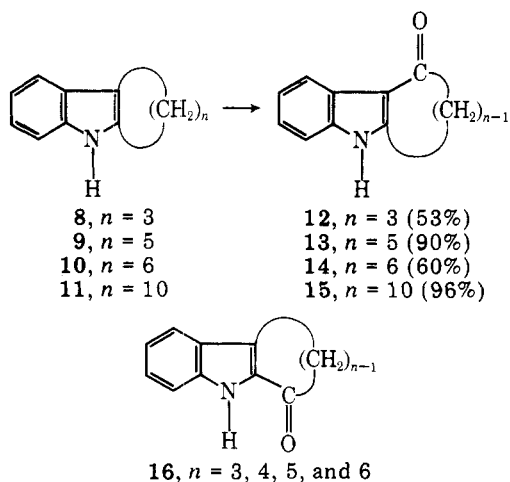
mixture as a single oxidation product, but only in 22% yield. The yield improved slightly at 0 °C (27%). However, in aqueous tetrahydrofuran the oxidation proceeded quite rapidly and **2** was isolated in 70% yield when reacted at 20 °C and in 83% yield at 0 °C.

No detectable formation of 1,2,3,4-tetrahydrocarbazol-1-one, which was synthesized selectively from **1** with several oxidizing agents,⁴ was observed in these conditions. This selective oxidation can be explained by four consecutive reactions (from **3** to **7**), dehydrogenation, addition of water, an-

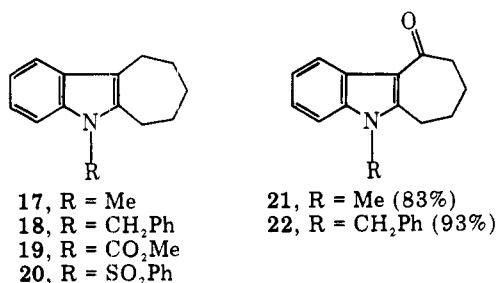


other dehydrogenation, and isomerization as shown in the following scheme. Since DDQ is known to be a strong electron acceptor, the initial step in the oxidation of electron-donative indoles by DDQ must be the formation of charge-transfer complexes, which readily change to **4** and 2,3-dichloro-5,6-dicyanohydroquinone (DDH).^{2,3}

Several cycloalkan[b]indoles (**8**–**11**) were oxidized under similar conditions to afford the corresponding ketones (**12**–**15**) as the sole products,⁵ and their structural establishment rested on spectral data. In particular, the distinction between the ketones (**12**–**15**) and **16** was provided by UV spectra. Shioiri⁸ reported that a series of **16** and 2-acylindoles have two characteristic strong bands at about 240 and 310 nm, whereas the DDQ oxidation products have three strong bands at 240–250, 260–270, and 290–300 nm, which are characteristic of 3-acylindoles.

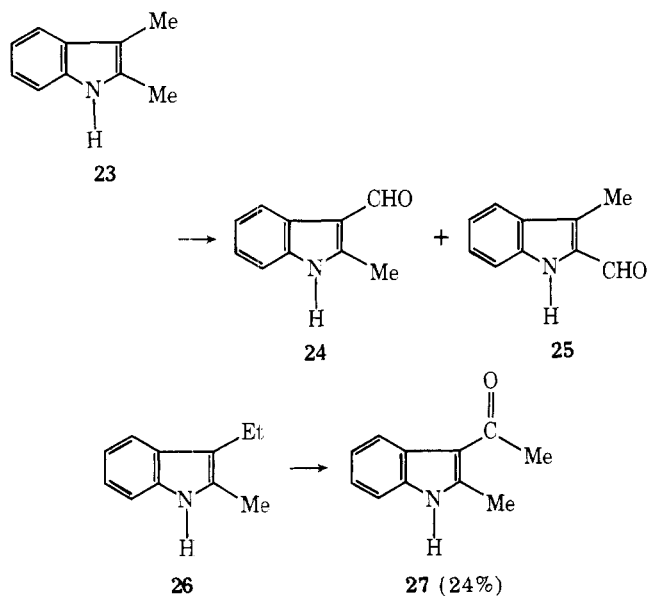


N-Methyl (**17**) and *N*-benzyl (**18**) derivatives also gave **21** and **22**, respectively, in a high yield, but **19** and **20** substituted



with electron-withdrawing groups were recovered unchanged, because **19** and **20** could not form charge-transfer complexes.

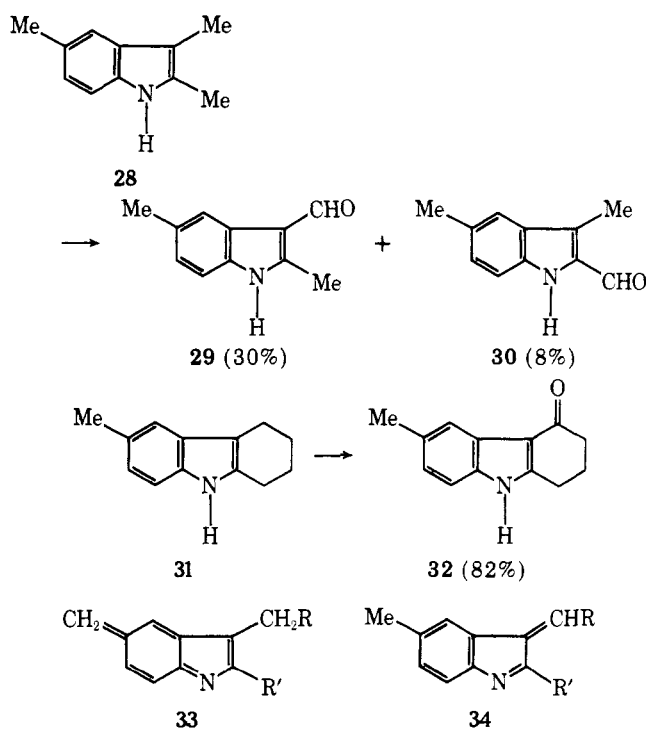
When 2,3-dimethylindole (**23**) was oxidized, 2-formyl compound (**24**) as well as the expected 3-formyl product (**25**) was isolated, though yields of both products were unsatisfactory. The yield of **25** was nearly doubled when reacted at



a higher temperature (42 °C), but when tetrahydrofuran containing acetic acid instead of water was used as a less nucleophilic solvent, the formation of **25** was clearly depressed (Table I). Oxidation of 3-ethyl-2-methylindole (**26**) gave again only a 3-keto product (**27**), though in a moderate yield.

In order to learn more about the selectivity of the DDQ oxidation, **28** and **31** having a C-5 side chain para to the NH group were next oxidized to give **29**, **30**, and **32**. No formation

of 5-formyl products indicates that an intermediate (**33**) is less favorable than **34**.



Finally, oxidation of 3-monosubstituted indoles was examined. Skatole (**35**), ethyl indoleacetate (**36**), and ethyl indolepropionate (**37**) readily gave the corresponding carbonyl

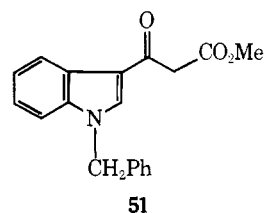
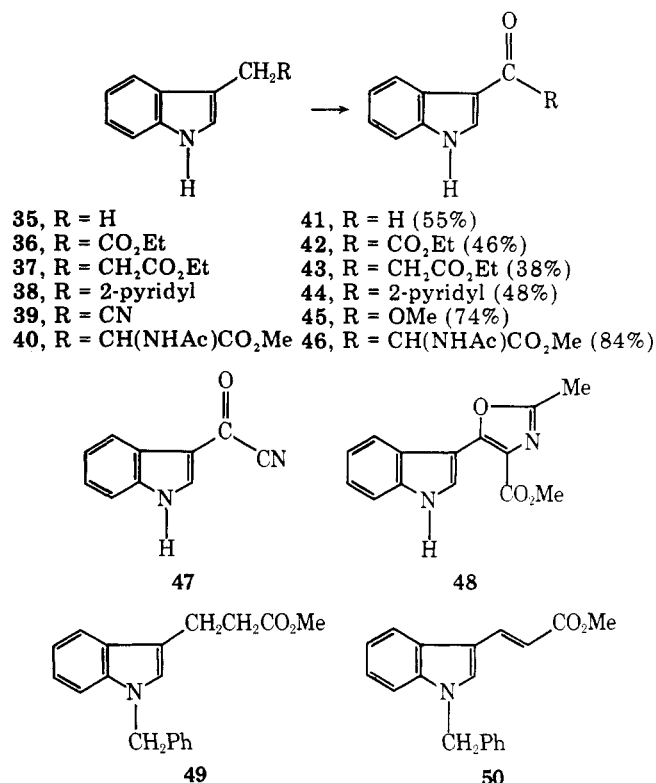


Table I. Oxidation of 2,3-Dimethylindole (23)

Solvent	Temp, °C	Yield, %	
		24	25
THF-H ₂ O (10:1)	0	14	9
	22	14	14
	42	13	25
THF-AcOH (45:1)	20	16	4

compounds (41–43). Indolylpyridylmethane (38) also gave the expected ketone (44). Indoleacetonitrile (39), when oxidized in methanol, gave methyl indolecarboxylate (45), which must have been formed by methanolysis of the initially formed ketonitrile (47). Oxidation of *N*-acetyltryptophan methyl ester (40) in aqueous tetrahydrofuran gave smoothly a new type of oxidation product of tryptophan (46) in a high yield, while in anhydrous tetrahydrofuran the main product changed to an oxazole derivative (48) though only in 33% yield. Oxidation of methyl *N*-benzylindolepropionate (49) in methanol gave a mixture of a 3-keto product (51) and a dehydrogenation product (50), while in anhydrous tetrahydrofuran with 1.3 equiv of DDQ 50 formed selectively in 80% yield.

Experimental Section

General Procedure for DDQ Oxidation of Cycloalkan[b]indoles. To an ice-cooled solution of 0.5 mmol of cycloalkan[b]indoles (1, 8, 9, 10, 11, 17, 18, 31) in 5.5 ml of 90% aqueous THF, 227 mg (1 mmol) of DDQ in 2 ml of THF was added dropwise with stirring in argon or nitrogen atmosphere. The reaction mixture first turned blue, then after a few minutes light yellow. The stirring was continued for 1 h and then the solvent was evaporated to dryness. The residue was extracted with EtOAc and the extract was purified by passing through an alumina column to give almost pure ketones (2, 12, 13, 14, 15, 21, 22, 32).

1,2,3,9-Tetrahydro-4*H*-carbazol-4-one⁶ (2). Yield 83%; mp 219–221 °C (EtOH); *m/e* (rel intensity) 185 (M⁺, 75), 157 (100); λ (EtOH) 242.5, 265, 295.5 nm; ν (Nujol) 3050, 1608 cm⁻¹.

3,4-Dihydrocyclopent[b]indol-1(2*H*)-one (12). Yield 53%; mp 252–253 °C (EtOH); *m/e* (rel intensity) 171 (M⁺, 100), 143 (76); λ (EtOH) 237, 260, 283, 290 nm; ν (Nujol) 3200, 1655 cm⁻¹.

Anal. Calcd for C₁₁H₉NO: C, 77.17; H, 5.30; N, 8.18. Found: C, 76.94; H, 5.39; N, 8.18.

6,7,8,9-Tetrahydrocyclohept[b]indol-10(5*H*)-one⁷ (13). Yield 90%; mp 220–221 °C (EtOH); *m/e* (rel intensity) 199 (M⁺, 100), 170 (97); λ (EtOH) 243.5, 266.5, 296 nm; ν (Nujol) 3155, 1600 cm⁻¹.

5,6,7,8,9,10-Hexahydro-11*H*-cyclooct[b]indol-11-one (14). Yield 60%; mp 235–237 °C (EtOH); *m/e* (rel intensity) 213 (M⁺, 57), 170 (100); λ (EtOH) 245, 266.5, 302 nm; ν (Nujol) 3150, 1608 cm⁻¹.

Anal. Calcd for C₁₄H₁₅NO: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.97; H, 7.16; N, 6.51.

6,7,8,9,10,11,12,13-Octahydrocycloundec[b]indol-14(5*H*)-one (15). Yield 96%; mp 197–199 °C (EtOH); *m/e* (rel intensity) 269 (M⁺, 100), 226 (35), 212 (35); λ (EtOH) 250, 277.5, 304 nm; ν (Nujol) 3150, 1610 cm⁻¹.

Anal. Calcd for C₁₈H₂₃NO: C, 80.25; H, 8.61; N, 5.20. Found: C, 80.10; H, 8.51; N, 5.11.

5-Methyl-6,7,8,9-tetrahydrocyclohept[b]indol-10(5*H*)-one⁷ (21). Yield 83%; mp 132–134 °C (EtOH); *m/e* (rel intensity) 213 (M⁺, 100), 184 (63), 144 (66); λ (EtOH) 251, 267, 308 nm; ν (Nujol) 1635, 1615, 1605 cm⁻¹.

Anal. Calcd for C₁₄H₁₅NO: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.92; H, 7.20; N, 6.57.

5-Benzyl-6,7,8,9-tetrahydrocyclohept[b]indol-10(5*H*)-one (22). Yield 93%; mp 87–89 °C (MeOH); *m/e* (rel intensity) 289 (M⁺, 100); λ (EtOH) 250, 267, 307 nm; ν (Nujol) 1635, 1615, 1605 cm⁻¹.

Anal. Calcd for C₂₀H₁₉NO: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.12; H, 6.62; N, 4.90.

6-Methyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-one (32). Yield 82%; mp 280–282 °C (EtOH); *m/e* (rel intensity) 199 (M⁺, 74), 171 (100), 143 (79); λ (EtOH) 246.5, 268.5, 295 nm; ν (Nujol) 3175, 1620 cm⁻¹.

Anal. Calcd for C₁₃H₁₃NO: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.60; H, 6.56; N, 6.94.

Oxidation of 2,3-Dimethylindole (23). **A. In Aqueous THF.** To a solution of 227 mg (1 mmol) of DDQ in 5.5 ml of 90% aqueous THF,

72 mg (0.5 mmol) of 23 in 3 ml of THF was added dropwise with stirring under argon or nitrogen at 0, 22, or 42 °C. The stirring was continued for 4 h at 0 °C, 3.5 h at 22 °C, or 1 h at 42 °C, and then the solvent was evaporated to dryness. The residue was extracted with Et₂O and the extract was chromatographed over an alumina column. Elution with Et₂O gave two fractions. Yields are given in Table I. The first fraction was 2-formyl-3-methylindole^{4,9} (25); mp 138–141 °C (hexane); *m/e* (rel intensity) 159 (M⁺, 100), 158 (58), 130 (72); λ (EtOH) 237.5, 313 nm; ν (Nujol) 3275, 1640 cm⁻¹. The second fraction was 3-formyl-2-methylindole¹¹ (24); mp 199–201 °C [sublimation at 120 °C (1 Torr)]; *m/e* (rel intensity) 159 (M⁺, 80), 158 (100), 130 (40); λ (EtOH) 245, 267, 303 nm; ν (Nujol) 3150, 1620 cm⁻¹.

B. In THF Containing AcOH. Compound 23 (0.5 mmol) was treated with DDQ (1 mmol) in 5 ml of THF containing 0.1 g of AcOH at 20 °C for 2 h under argon. Workup as described above gave 24 and 25 (Table I).

3-Acetyl-2-methylindole (27). To a solution of 159 mg (1 mmol) of 3-ethyl-2-methylindole (26) in 11 ml of 90% aqueous THF, 454 mg (2 mmol) of DDQ in 3 ml of THF was added at 20 °C under argon. After being stirred for 1.5 h, the reaction mixture was concentrated in vacuo and extracted with Et₂O. The extract was purified by passing through an alumina column to give 41 mg (24%) of 27; mp 195–196 °C (50% aqueous EtOH);¹⁰ *m/e* (rel intensity) 173 (M⁺, 42), 158 (100); λ (EtOH) 242.5, 267, 300 nm; ν (Nujol) 3150, 1610 cm⁻¹.

Oxidation of 2,3,5-Trimethylindole (28). Compound 28 (0.5 mmol) was oxidized at 20 °C, and workup as described above gave a mixture of 29 (30%) and 30 (8%).

3-Formyl-2,5-dimethylindole (29). Mp 221–222 °C (benzene); *m/e* (rel intensity) 173 (M⁺, 85), 172 (100), 144 (42); λ (EtOH) 250, 271.5, 304.5 nm; ν (Nujol) 3175, 1630, 1620 cm⁻¹.

Anal. Calcd for C₁₁H₁₁NO: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.28; H, 6.49; N, 8.09.

2-Formyl-3,5-dimethylindole¹¹ (30). Mp 181–183 °C [sublimation at 80 °C (1 Torr)]; *m/e* (rel intensity) 173 (M⁺, 100), 172 (58), 144 (60); λ (EtOH) 237, 316.5 nm; ν (Nujol) 3250, 1640 cm⁻¹.

General Procedure for DDQ Oxidation of 3-Monosubstituted Indoles. To a stirring solution of DDQ (1 mmol) in 5.5 ml of 90% aqueous THF, 0.5 mmol of 3-monosubstituted indole (35, 36, 37, 38, 40) in 3 ml of THF was added dropwise at 25 °C under argon or nitrogen. The solution first turned blue, then brown, and finally yellow. The stirring was continued for 1–2 h. The reaction mixture was concentrated and purified by passing in Et₂O (in the case of 35, 38), EtOAc (36), EtOAc-EtOH (50:1) (40), or CH₂Cl₂ (37) through alumina (35, 36, 38, 40) or silica gel (37) to give 3-acylindoles (41, 42, 43, 44, 46).

3-Formylindole¹² (41). Yield 55%; mp 193–195 °C (Et₂O); *m/e* (rel intensity) 145 (M⁺, 99), 144 (100), 116 (48); λ (EtOH) 243.5, 260, 296.5 nm; ν (Nujol) 3150, 1640, 1615 cm⁻¹.

Ethyl Indole-3-glyoxylate¹³ (42). Yield 46%; mp 184–185 °C (EtOH); *m/e* (rel intensity) 217 (M⁺, 14), 144 (100); λ (EtOH) 256, 268.5, 274.5 (sh), 321 nm; ν (Nujol) 3150, 1728, 1620 cm⁻¹.

Ethyl 3-(Indol-3-yl)-3-oxopropionate¹⁴ (43). Yield 38%; mp 120–121 °C (Et₂O); *m/e* (rel intensity) 231 (M⁺, 23), 144 (100); λ (EtOH) 243, 260, 300 nm; ν (Nujol) 3225, 1740, 1630, 1615 cm⁻¹.

1*H*-Indol-3-yl-2-pyridinylmethane (44). Yield 48%; mp 189–190 °C (EtOH); *m/e* (rel intensity) 222 (M⁺, 60), 221 (37), 194 (18), 144 (100); ν (Nujol) 3150, 1595 cm⁻¹; λ (EtOH) 240, 258, 270, 275 (sh), 330 nm.

Anal. Calcd for C₁₄H₁₀N₂O: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.54; H, 4.50; N, 12.47.

DL-*N*-Acetyl-β-oxotryptophan Methyl Ester (46). Yield 84%; mp 202–205 °C (EtOH); *m/e* (rel intensity) 274 (M⁺, 1), 144 (100); λ (EtOH) 245, 263, 306 nm; ν (Nujol) 3375, 1740, 1665, 1650 cm⁻¹.

Anal. Calcd for C₁₄H₁₄N₂O₄: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.28; H, 5.13; N, 10.21.

Methyl Indole-3-carboxylate (45). To a stirring solution of 0.5 mmol of indole-3-acetonitrile (39) in 5 ml of MeOH, 1 mmol of DDQ in 2 ml of MeOH was added at 20 °C. The stirring was continued for 3 h and then for 1 h at 40 °C. The solution was concentrated and extracted with CH₂Cl₂. The extract was chromatographed on a silica gel column eluting with CH₂Cl₂ to give 64 mg (74%) of 45; mp 146–148 °C (50% aqueous MeOH);¹⁵ *m/e* (rel intensity) 175 (M⁺, 53), 144 (100).

5-(Indol-3-yl)-4-methoxycarbonyl-2-methylloxazole (48). A solution of 137 mg (0.5 mmol) of 40 and 1 mmol of DDQ in 5 ml of THF was heated under reflux for 2 h. The reaction mixture was concentrated and extracted with EtOAc. The extract was passed through an alumina column to give 45 mg (33%) of 48; mp 239–240 °C (EtOH); *m/e* (rel intensity) 256 (M⁺, 100); λ (EtOH) 223.5, 250 (sh), 274, 288.5 (sh), 331.5 nm; ν (Nujol) 3150, 3100, 1710 cm⁻¹.

Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.76; H, 4.65; N, 10.89.

Oxidation of Methyl (1-Benzylindol-3-yl)-3-propionate (49). **A. In MeOH.** To a solution of 146 mg (0.5 mmol) of 49 in 5 ml of MeOH, 227 mg (1 mmol) of DDQ in 2 ml of MeOH was added dropwise with stirring under argon at 20 °C. The stirring was continued for 1 h, and then the solvent was evaporated to dryness. The residue was extracted with CH_2Cl_2 and the extract was chromatographed on a silica gel column. Elution with CH_2Cl_2 gave two fractions.

The first fraction was 50 mg (34%) of **methyl 1-benzylindole-3-acrylate (50)**: mp 106–108 °C (MeOH); ν (Nujol) 1700, 1620 cm^{-1} ; λ (EtOH) 226, 274, 333 nm; *m/e* (rel intensity) 291 (M^+ , 32), 91 (100).

Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.52; H, 5.77; N, 4.81.

The second fraction was 56 mg (36%) of **methyl 3-(1-benzylindol-3-yl)-3-oxopropionate (51)**: mp 131–132 °C (MeOH); ν (Nujol) 1735, 1640 cm^{-1} ; λ (EtOH) 245, 260 (sh), 304 nm; *m/e* (rel intensity) 307 (M^+ , 25), 234 (46), 91 (100).

Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.17; H, 5.45; N, 4.28.

B. In Anhydrous THF. To a solution of 146 mg (0.5 mmol) of 49 in 6 ml of anhydrous THF, 148 mg (0.65 mmol) of DDQ in 2 ml of anhydrous THF was added dropwise with stirring under argon at 20 °C. After being stirred for 45 min, the solvent was evaporated to dryness. The residue was purified by passing in Et_2O -hexane (1:1) through an alumina column to give 117 mg (80%) of 50.

Registry No.—1, 942-01-8; 2, 15128-52-6; 8, 2047-91-8; 9, 2047-89-4; 10, 22793-63-1; 11, 13357-61-4; 12, 61364-20-3; 13, 14961-03-6; 14, 61364-21-4; 15, 61364-22-5; 17, 52751-32-3; 18, 61364-23-6; 21,

52850-96-1; 22, 61364-24-7; 23, 91-55-4; 24, 5416-80-8; 25, 5257-24-9; 26, 35246-18-5; 27, 22582-52-1; 28, 21296-92-4; 29, 61364-25-8; 30, 1463-67-8; 31, 17177-17-2; 32, 51626-88-1; 35, 83-34-1; 36, 778-82-5; 37, 40641-03-0; 38, 5580-44-9; 39, 771-51-7; 40, 16108-06-8; 41, 487-89-8; 42, 51079-10-8; 43, 52816-02-1; 44, 61364-26-9; 45, 942-24-5; 46, 61364-27-0; 48, 61364-28-1; 49, 57901-09-4; 50, 61364-29-2; 51, 61364-30-5.

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A Mild Process for the Oxidation of Partially Protected Carbohydrates¹

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A new process for selective hydroxyl to carbonyl oxidation in carbohydrate systems is described. This process consists of esterification of the alcohol to be oxidized using the acid chloride of pyruvic acid and subsequent photochemical reaction of the resulting pyruvate ester. Eight partially protected monosaccharides (1–5 and 11–13) were oxidized and found to give good yields of the corresponding carbonyl compounds. Of these eight the oxidation of three tetraacetates of D-glucopyranose (11–13) was of particular interest because of the sensitivity of the oxidation products to thermal and base-catalyzed elimination of the elements of acetic acid. The process described here is currently the only one known to allow oxidation of compounds 11–13 without causing further reaction.

Among the chemical transformations of carbohydrates, selective oxidation of hydroxyl groups to carbonyls is certainly one of the most useful.² For example, selective oxidation of a hydroxyl group to a carbonyl is often the first step in epimerization of a chiral center. When oxidation is followed by reaction with Grignard, Wittig, or other addition reagents, branched-chain carbohydrates result. If oxidation is combined with oximation and reduction, amino sugars are produced. Each of these three transformations is an essential process in carbohydrate chemistry, particularly in the synthesis of antibiotics, nucleosides, and nucleotides.

Considerable progress has been made in the past decade in the area of mild oxidation reactions of carbohydrates. The Pfizner–Moffatt³ and related, methyl sulfoxide based reagents have been shown to be extremely versatile.^{4,5} Ruthenium tetroxide also has been found to be widely applicable to oxidation of carbohydrate systems.^{6,7} Chromium trioxide in pyridine is another, mild oxidizing agent of considerable value.⁸ Interest is increasing in indirect oxidation via formation and photochemical decomposition of azides.⁹ A variety of additional methods and reagents (e.g., platinum and oxy-

gen, electrochemical, and enzymic) have been used, although typically in somewhat specialized situations.

It is clear that considerable versatility currently exists in the chemist's ability to oxidize carbohydrates under relatively mild conditions; however, equally clear are the advantages of an even more versatile and mild oxidation process, that is, one which would oxidize primary and secondary hydroxyl groups with equal effectiveness and would not catalyze further reactions such as elimination of substituents adjacent to the newly formed carbonyl. In addition, this new process would be conducted at or below room temperature in a neutral, nonreactive solvent in the absence of catalytic or reactive materials (hydrogen or metal ions, powerful dehydrating agents, etc.). The research reported here describes an oxidation sequence which possesses all the characteristics mentioned above as desirable in a new oxidation process.

Results and Discussion

Initially selected for study were five alcohols whose oxidation to the corresponding carbonyl compounds by widely used oxidizing agents was well known. Oxidation of each of these