The Periodate Oxidation of Indoles[1]

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Abstract: The action of sodium periodate cleaves the indolic double bond of several 2,3-disubstituted indoles to give the corresponding ketoamides in good yields. In contrast, periodic acid oxidation of tetrahydrocarbazole, N-methyltetrahydrocarbazole, and 2,3-dimethylindole affords the corresponding 2-acylindoles.

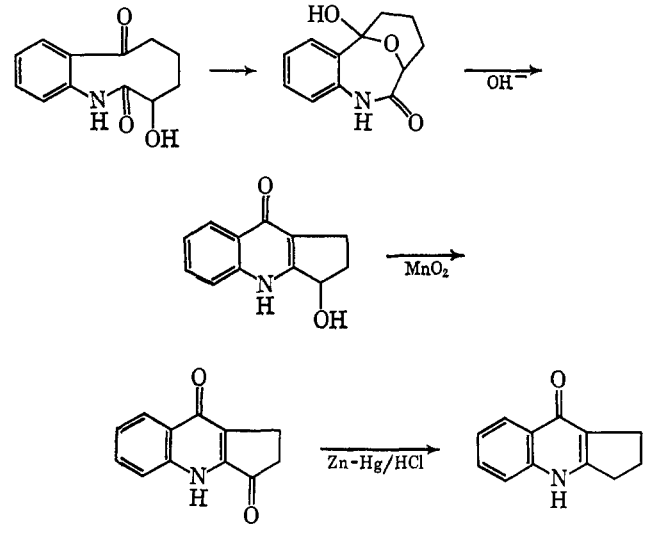
Although sodium periodate has been used to cleave 1,2-diols in molecules bearing an indole nucleus without apparent oxidation of the indole ring,[4] we find that both sodium periodate and periodic acid readily oxidize a variety of indole derivatives. Sodium periodate cleaves the indolic double bond whereas periodic acid oxidation affords 2-acyindole derivatives. The disappearance of the tryptophan absorption in proteins upon treatment with periodate was first observed by Maekawa[5a] and the cleavage of ethyl indole-3-propionylglycinate by periodate has been examined.[5b] We find that the cleavage of the indolic double bond by periodate is quite general. However, the reaction does seem to require a substituent in the 3 position since we were not able to characterize the products from the sodium periodate oxidation of 2-phenylindole, and the parent compound, indole, gives a black, resinous material. The results of the sodium periodate oxidations are summarized in Table I.

Table I. Products from the Sodium Periodate Cleavage of Indole Derivatives

Compound	Product	Yield, %
3-Methylindole	*o*-Formaminoacetophenone	82
2,3-Dimethylindole	*o*-Acetaminoacetophenone	85
Tetrahydrocarbazole	1-Aza-8,9-benzcyclononenedi-2,7-one	99
N-Methyltetrahydrocarbazole	N-Methyl-1-aza-8,9-benzcyclononenedi-2,7-one	77
1-Hydroxytetrahydrocarbazole	Hemiketal of 3-hydroxy-1-aza-8,9-benzcyclononenedi-2,7-one	45

Except for the cleavage products from N-methyltetrahydrocarbazole and 1-hydroxytetrahydrocarbazole, the products were identified by comparison of their properties with those recorded in the literature. The cleavage product from N-methyltetrahydrocarbazole was identified from its spectral properties and subsequent cyclization to N-methyl-2,3-cyclopenteno-4-quinolone which was prepared as previously described by methylation of 2,3-cyclopenteno-4-quinolone.[6] This transformation also establishes that the methylation of 2,3-cyclopentanto-4-quinolone occurs on nitrogen.

The product from the sodium periodate cleavage of 1-hydroxytetrahydrocarbazole was confusing at first since the ultraviolet spectrum resembled an oxindole rather than those of the previously obtained ketolactams. In addition, the infrared spectrum showed only a single carbonyl peak. However, the action of dilute base afforded a hydroxy-γ-quinolone which was oxidized to a ketone by manganese dioxide. Clemmensen reduction of the keto-γ-quinolone yielded the known 2,3-cyclopenteno-4-quinolone. These observations suggest that the cleavage product from 1-hydroxytetrahydrocarbazole is the expected 3-hydroxy-1-aza-8,9-benzcyclononenedi-2,7-one which exists as the hemiketal.



The oxidation of indoles has been studied quite extensively especially by Witkop and co-workers.[7] These studies have yielded a variety of methods for cleaving the indolic double bond. These include ozonolysis,[7,8] oxidation by peracids,[9] and autoxidation.[10,11] However, the sodium periodate oxidation is easy to carry out and gives very good yields.

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(2) Alfred P. Sloan Research Fellow, 1965–1967.
(3) U. S. Public Health Service Predoctoral Fellow, 1962–1965.
(4) E. E. van Tamelen, M. Shamma, A. W. Burgstahler, J. Wolinsky, R. Tamms, and P. E. Aldrich, *J. Am. Chem. Soc.*, 80, 5006 (1958); E. E. van Tamelen, L. J. Dolby, and R. G. Lawton, *Tetrahedron Letters*, **No. 19**, 30 (1960); J. Barton and J. Harley-Mason, *Chem. Comm.* (London), 298 (1965).
(5) (a) K. Maekawa, *Bull Agr. Chem. Soc. Japan*, **19**, 28 (1955); (b) B. Witkop, *Advan. Protein Chem.*, **16**, 252 (1961).
(6) R. Beer, L. McGrath, and A. Robertson, *J. Chem. Soc.*, 3283 (1950).
(7) See B. Witkop and S. Goodwin, *J. Am. Chem. Soc.*, **75**, 337 (1953), and previous papers in the series.
(8) B. Witkop and J. Patrick, *ibid.*, **74**, 3855 (1952).
(9) B. Witkop and H. Fiedker, *Ann.*, **558**, 91 (1947); B. Witkop, *ibid.*, **558**, 98 (1947); *J. Am. Chem. Soc.*, **72**, 1428 (1950).
(10) B. Witkop and J. Patrick, *ibid.*, **73**, 2196 (1951).
(11) H. Wasserman and M. Floyd, *Tetrahedron Letters*, **No. 29**, 2009 (1963).

Surprisingly, the action of periodic acid on several indoles derivatives was found to give 2-acylindoles. These results are summarized in Table II. No special effort was made to obtain maximum yields from N-methyltetrahydrocarbazole and 2,3-dimethylindole and the yields recorded in Table II could undoubtedly be improved. If a limited amount of periodic acid is used, the reaction mixture liberates iodine and in earlier experiments an iodinated 1-ketotetrahydrocarbazole was isolated. To minimize iodine formation the reaction is carried out by adding the indole to excess periodic acid. The product 2-acylindoles are very stable to the action of sodium periodate or periodic acid.

Table II. Products from the Periodic Acid Oxidation of Indole Derivatives

Compound	Product	Yield, %
Tetrahydrocarbazole	1-Ketotetrahydrocarbazole	62
N-Methyltetrahydrocarbazole	N-Methyl-1-ketotetrahydrocarbazole	25
2,3-Dimethylindole	2-Formyl-3-methylindole	10

Two other methods are available for oxidizing 2,3-disubstituted indole to the corresponding 2-acylindoles. Autoxidation sometimes effects this transformation although the reaction fails entirely in the case of tetrahydrocarbazole.[11-15] The other method is lead tetraacetate oxidation which converts 2,3-dimethylindole to 2-diacetoxymethyl-3-methylindole.[16] However, periodic acid oxidation appears to be superior to either of these methods.

It does not seem worthwhile at this point to speculate on the mechanism of oxidation of indoles by periodate species, but it is worth noting that 1-hydroxytetrahydrocarbazole cleaves normally with sodium periodate and the action of periodic acid gives no 1-ketotetrahydrocarbazole although we were not able to characterize the products from this reaction.

Experimental Section[17]

1-Aza-8,9-benzcyclononenedi-2,7-one. A solution of tetrahydrocarbazole (2.518 g, 0.0147 mole) in 75 ml of methanol was added to a solution of sodium metaperiodate (6.921 g, 0.0323 mole) in 35 ml of water. The solution became warm and sodium iodate appeared as white needles. After 2.5 hr the aqueous solution was extracted with methylene chloride. The methylene chloride was dried over sodium sulfate and removed to give 2.951 g (99%) of crystalline 1-aza-8,9-benzcyclononenedi-2,7-one. Recrystallization from ethyl acetate gave pure material, mp 156–157° (lit.[10] mp 156–157°). The infrared spectrum showed peaks at 3390, 1670, and 1645 cm^{-1}; the ultraviolet spectrum showed λ_{max}^{EtOH} 233 mμ and 280 mμ.

Stoichiometry of the Sodium Metaperiodate Cleavage of Tetrahydrocarbazole. A 9.00-ml aliquot of 0.0938 *M* tetrahydrocarbazole solution in methanol and a 25.00-ml aliquot of 0.0961 *M* sodium metaperiodate solution in water were stirred for 24 hr in a sealed system. Initially there was a precipitate of tetrahydrocarbazole which dissolved in 6 hr to give a slightly yellow solution. Three 3.00-ml aliquots were removed and analyzed by diluting with 5-ml of water, and adding 0.5 g of sodium bicarbonate, 1 ml of 20% potassium iodide, and a 10.00-ml aliquot of 0.104 *M* sodium arsenite solution. After allowing the solution to stand for 15 min, 3 drops of starch indicator was added and the excess arsenite was titrated with 0.091 *M* iodine requiring 10.60, 10.58, and 10.58 ml. By this method, it was shown that 1.94 moles of sodium metaperiodate was required per mole of tetrahydrocarbazole.

***o*-Acetaminoacetophenone.** A solution of sodium metaperiodate (5.676 g, 0.0265 mole) in water (50 ml) was added to a solution of 2,3-dimethylindole (1.725 g, 0.0119 mole) in methanol (50 ml). The solution was stirred at room temperature for 8 hr. The oil obtained, after extraction with methylene chloride and removal of the solvent, was filtered through 50 g of Florisil with ether. The yield of *o*-acetaminoacetophenone was 1.785 g (85%). Recrystallization from petroleum ether (bp 30–60°) gave pure *o*-acetaminoacetophenone, mp 74–75° (lit.[18] mp 74–75°). The nmr spectrum showed NH (broad) τ 1.5, aromatic protons 1.2–3.2, CCH_3 (singlets) 7.40 and 7.83.

***o*-Formaminoacetophenone.** A solution of skatole (3.961 g, 0.032 mole) in methanol (60 ml) was added to a solution of sodium metaperiodate (13.401 g, 0.0626 mole) in water (70 ml). After 24 hr at room temperature, the sodium iodate was filtered off and the crystals were washed with methanol. The methanol was removed *in vacuo* and the aqueous layer was extracted with methylene chloride. The methylene chloride was dried over sodium sulfate and removed. The crude crystalline material obtained was dissolved in a minimum amount of benzene and chromatographed over 90 g of Florisil. Elution with 200 ml of benzene removed a small amount of material. Elution with 400 ml of ether gave 4.022 g (82%) of crystalline *o*-formaminoacetophenone. Recrystallization from petroleum ether (bp 30–60°) gave pure material, mp 78–79° (lit[9] mp 77°). The nmr showed NH (broad) τ 1.4, aromatic protons 1.3–2.2, and CHO (broad) 1.3–1.8.

N-Methyl-1-aza-8,9-benzcyclononenedi-2,7-one. A solution of sodium metaperiodate (4.404 g, 0.0206 mole) in 20 ml of water was added to a solution of N-methyltetrahydrocarbazole (1.663 g, 0.0090 mole) in 60 ml of methanol. After 24 hr at room temperature, the reaction mixture was processed as previously described to give 1.914 g of crude product. The crude product was dissolved in benzene and chromatographed over 60 g of activity II alumina with benzene. The first 150 ml of benzene gave 0.341 g of an orange oil; continued elution with 500 ml of benzene gave 1.502 g (77%) of crystalline N-methyl-1-aza-8,9-benzcyclononenedi-2,7-one, mp 82–83° after recrystallization from petroleum ether (bp 60–68°). The ultraviolet spectrum showed, λ_{max}^{EtOH} 277 mμ (ε 9000) and 275 mμ (ε 200); the infrared spectrum showed peaks at 1700 and 1650 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 72.04; H, 6.86; N, 6.32.

N-Methyl-2,3-cyclopenteno-4-quinolone. A. By Methylation of 2,3-Cyclopenteno-4-quinolone. The 2,3-cyclopenteno-4-quinolone was prepared by the method of Witkop[12] from 1-aza-8,9-benzcyclononenedi-2,7-one (2.900 g, 0.0142 mole) in 100 ml of 2 *N* sodium hydroxide. The quinolone was not purified but was submitted directly to the methylating conditions of Beer, McGrath, and Robertson.[6]

The crude crystalline material (1.751 g, 62% over-all) was recrystallized from benzene to give pure material, mp 217–218° (lit.[6] mp 219–220°).

B. From Cyclization of N-Methyl-1-aza-8,9-benzcyclononenedi-2,7-one. The procedure of Witkop[12] was used. A sample of N-methyl-1-aza-8,9-benzcyclononenedi-2,7-one (1.500 g, 0.00691 mole) was dissolved in 100 ml of 3 *N* sodium hydroxide and heated on a steam bath for 1 hr. The solution was extracted with methylene chloride, which was dried over sodium sulfate and removed to give 1.113 g (81%) of crystalline product. Recrystallization from benzene gave mp 217–218°. There was no depression of the

(12) B. Witkop, J. Patrick, and M. Rosenblum, *J. Am. Chem. Soc.*, 73, 2641 (1951).
(13) E. Leete, *ibid.*, 83, 3645 (1961).
(14) W. I. Taylor, *Proc. Chem. Soc.*, 247 (1962).
(15) F. Chen and E. Leete, *Tetrahedron Letters*, No. 29, 2013 (1963).
(16) W. I. Taylor, lecture presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 4, 1963.
(17) All melting points are uncorrected. Infrared spectra were determined with a Beckman IR-5 infrared spectrophotometer and ultraviolet spectra were measured with a Cary Model 11 spectrophotometer. Proton magnetic resonance spectra were determined in deuteriochloroform solution, unless otherwise stated, using tetramethylsilane as an internal standard with a Varian A-60 spectrometer. Woelm alumina was employed in column chromatography. Microanalyses were determined by Micro-Tech Laboratories of Skokie, Ill., Pascher and Pascher Laboratories of Bonn, Germany, and Berkeley Analytical Laboratories of Berkeley, Calif.
(18) N. J. Leonard and S. N. Boyd, *J. Org. Chem.*, 11, 405 (1946).

melting point of this compound when mixed with the compound obtained from the methylation of the known 2,3-cyclopenteno-4-quinolone. The infrared spectra of these compounds were superimposable.

The Hemiketal of 3-Hydroxy-1-aza-8,9-benzcyclononenedi-2,7-one. A solution of sodium metaperiodate (4.861 g, 0.02271 mole) in 25 ml of water was added portionwise to a solution of 1-hydroxytetrahydrocarbazole (2.132 g, 0.0113 mole) in 40 ml of methanol. A precipitate of sodium iodate formed immediately. The solution was allowed to stand at room temperature for 24 hr with occasional swirling. The crystalline sodium iodate was filtered off and most of the methanol was removed *in vacuo*. The aqueous solution was extracted with methylene chloride and the methylene chloride gave an oil which crystallized when a small amount of methylene chloride was added. The aqueous layer was extracted continuously with methylene chloride and the two portions were combined to give 1.123 g (45%) of white crystalline hemiketal. Recrystallization from water gave pure hemiketal, mp 195–196°. The infrared spectrum (Nujol) showed peaks at 3450, 3250, 3120, and 1650 cm^{-1}; the ultraviolet spectrum showed λ_{max}^{EtOH} 250 mμ (ϵ 10,800), 281 (2200), and 288 (1600); the nmr (pyridine) showed OH (singlet) τ 0.70, CH (multiplet) 4.80, CH_2 (multiplets) 7.80 and 8.35; (dimethyl sulfoxide) OH (singlet) τ 0.02, aromatics and NH centered at 2.71.

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.66; H, 6.15; N, 6.24.

3-Hydroxy-2,3-dihydro-1H-cyclopenta[*b*]quinolone. A sample of the hemiketal of 3-hydroxy-1-aza-8,9-benzcyclononenedi-2,7-one (0.543 g, 0.00248 mole) was dissolved in 25 ml of 1 *N* sodium hydroxide. The solution was stirred at room temperature for 30 min and then heated on a steam bath for 30 min. During this time the solution turned from yellow to colorless. On neutralization with acetic acid, the 3-hydroxy-2,3-dihydro-1H-cyclopenta[*b*]-quinolone (0.470 g, 94%) crystallized from the aqueous solution and was filtered off. Recrystallization from water gave pure 3-hydroxy-2,3-dihydro-1H-cyclopenta[*b*]quinolone, mp 275° dec. The infrared spectrum (KBr) showed peaks at 1600 and 1550 cm^{-1}; the ultraviolet spectrum showed λ_{max}^{EtOH} 215 mμ (ϵ 10,800), 238 (35,400), 242 (32,800), 321 (5700), and 334 (6500).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.77; H, 5.73; N, 7.12.

3-Keto-2,3-dihydro-1H-cyclopenta[*b*]quinolone. A 1.041-g (0.00518 mole) sample of 3-hydroxy-2,3-dihydro-1H-cyclopenta[*b*]-quinolone was dissolved in 300 ml of dioxane and 5 g of active manganese dioxide was added portionwise during 20 min with stirring. After 24 hr, the manganese dioxide was filtered off and the dioxane was removed to give 0.734 g (71%) of crystalline 3-keto-2,3-dihydro-1H-cyclopenta[*b*]quinolone. Recrystallization from ethanol, using Norit to decolorize, gave colorless crystals which did not melt below 350° but became progressively darker from 220°. The infrared spectrum (KBr) had peaks at 1700, 1610, and 1560 cm^{-1}; the ultraviolet spectrum showed λ_{max}^{EtOH} 215 mμ (ϵ 10,300), 247 (17,600), 258 (24,600), 359 (5300), and 375 (4700).

Anal. Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 71.85; H, 4.76; N, 7.43.

Clemmensen Reduction of 3-Keto-2,3-dihydro-1H-cyclopenta-[*b*]quinolone. A solution of 3-keto-2,3-dihydro-1H-cyclopenta-[*b*]quinolone (0.250 g, 0.00126 mole) in 5 ml of water and 10 ml of concentrated hydrochloric acid was added to 2 g of freshly prepared amalgamated zinc.[19] The solution was refluxed for 10 hr after which it was neutralized to pH 7 with 5 *N* sodium hydroxide. The zinc hydroxide was filtered off and placed in Soxhlet extractor and extracted with methylene chloride giving 0.100 g (43%) of 2,3-cyclopenteno-4-quinolone, mp 326–327° dec (lit.[12] mp 325–327°) after recrystallization from benzene–ethanol. The ultraviolet spectrum showed λ_{max}^{EtOH} 237, 315, and 327 mμ. This material was identical in all respects with an authentic sample of 2,3-cyclopenteno-4-quinolone prepared by the method of Witkop and coworkers[12] from 1-aza-8,9-benzcyclononendi-2,7-one.

Attempted Sodium Metaperiodate Cleavage of 1-Ketotetrahydrocarbazole. Solutions of 1-ketotetrahydrocarbazole (0.716 g, 0.00387 mole) in methanol (50 ml) and sodium metaperiodate (1.711 g, 0.00799 mole) in water (50 ml) were mixed and heated on a steam bath for 24 hr, followed by stirring at room temperature for 36 hr. Extraction of the water–methanol solution with methylene chloride gave only starting material in near quantitative yield.

1-Ketotetrahydrocarbazole. A solution of tetrahydrocarbazole (2.123 g, 0.0124 mole) in 50 ml of methanol was added dropwise to a solution of paraperiodic acid in 10 ml of water and 25 ml of methanol. The paraperiodic acid solution was stirred at 0–5°. After the addition of the tetrahydrocarbazole (approximately 30 min), the solution was stirred at room temperature for an additional 30 min. Water was added, followed by extraction with ether. The ether layer was washed with a dilute solution of sodium thiosulfate, then water, and finally dried over sodium sulfate. After removal of the ether, the crystalline material was chromatographed over 75 g of activity II alumina with benzene. The column was eluted with 100 ml of benzene giving a small amount of dark red material. Continued elution with 300 ml of ether gave 1.423 g (62%) of 1-ketotetrahydrocarbazole. Ultraviolet, infrared, and nmr spectra were identical with authentic 1-ketotetrahydrocarbazole.

2-Formyl-3-methylindole. A solution of 2,3-dimethylindole (1.000 g, 0.0069 mole) in methanol (30 ml) was added dropwise to a solution of paraperiodic acid (5.100 g, 0.0224 mole) in 1:1 water–methanol (40 ml) which was cooled in an ice–salt bath. The addition took 30 min, after which the solution immediately was extracted with ether. The ether layer was washed with a dilute solution of sodium thiosulfate, then water, and finally dried over sodium sulfate. The material remaining after the removal of the ether was chromatographed over 30 g of activity II alumina. This produced 0.112 g (10%) of 2-formyl-3-methylindole when the column was eluted with 10% ether–benzene. After recrystallization from benzene, the pure material showed mp 136–139° (lit.[20] mp 139–140°). The infrared spectrum showed peaks at 3450, 3310, and 1640 cm^{-1}; the ultraviolet spectrum showed λ_{max}^{EtOH} 237 and 313 mμ.

N-Methyl-1-ketotetrahydrocarbazole. A solution of N-methyltetrahydrocarbazole[21] (0.509 g, 0.00275 mole) in methanol (30 ml) was added dropwise to a cooled solution of paraperiodic acid (0.633 g, 0.00279 mole) in 1:1 methanol–water (30 ml). After the addition (20 min), the solution was stirred for 3.5 hr, after which it was extracted with ether. The ether layer was washed with dilute sodium thiosulfate and then dried over sodium sulfate. After removal of the ether, the residue was chromatographed over 15 g of activity II alumina. The column was eluted first with 100 ml of petroleum ether (bp 60–68°) which removed some oily material. Continued elution with 100 ml of benzene gave 0.136 g (25%) of crystalline N-methyl-1-ketotetrahydrocarbazole, identical in all respects with authentic material prepared previously.[22]

(19) E. L. Martin, *J. Am. Chem. Soc.*, **58**, 1438 (1936).

(20) W. I. Taylor, *Helv. Chim. Acta*, **33**, 164 (1950).

(21) Prepared by the method of T. S. Stevens and S. H. Tucker, *J. Chem. Soc.*, 2140 (1923).

(22) L. J. Dolby and D. L. Booth, *J. Org. Chem.*, **30**, 1550 (1965).