

The Periodate Oxidation of Heterocycles. II. 2-Methylindole and 2,3-Diphenylindole^{1,2}

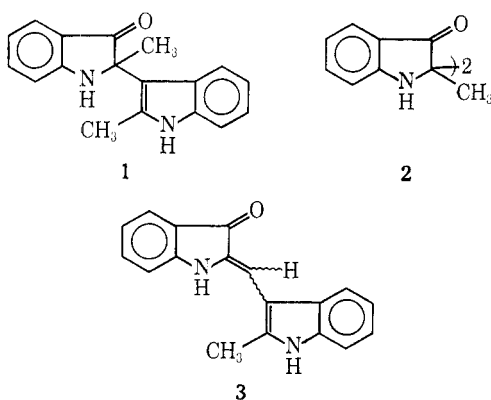
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The oxidations of 2-methylindole and 2,3-diphenylindole with sodium periodate in aqueous methanol have been examined. Only the indoxyl dimers 2-methyl-2,3'-(2'-methylindolyl)indoxyl (**1**), 2,2'-dimethyl-3,3'-dioxodiindolyl-2,2' (**2**), and 2-[3'-(2'-methylindolyl)methylene]indoxyl (**3**) are isolated from the treatment of 2-methylindole. The products from the oxidation of 2,3-diphenylindole include 2,2-diphenylindoxyl, *o*-benzamidobenzophenone, and the reaction intermediate 3-hydroxy-2,3-diphenylindolenine.

In an earlier study of the oxidation of indoles by periodate species, it was found that 2,3-disubstituted indoles suffered cleavage of the 2,3 double bond or conversion into 2-acylindoles.² This work has been extended to new examples. The action of sodium periodate on 2-methylindole has been examined to determine the course of the reaction with indoles unsubstituted in the 3 position. It was found that the reaction mixture contained at least four products by tlc. However, one of these materials was consumed during isolation and a new compound was formed. Three crystalline compounds (**1**–**3**) were isolated and identified.



Compound **1**, obtained in 39% yield, was identified as 2-methyl-2,3'-(2'-methylindolyl)indoxyl⁵ by comparison with an authentic sample. This compound is the major product isolated from the treatment of 2-methylindole with a variety of oxidizing agents, including oxygen,⁶ hydrogen peroxide,⁵ and peracetic acid.⁷

When **1** was exposed to the reaction conditions, **2** was obtained in 62% yield. However, **1** is not necessarily an intermediate in the formation of **2**, since **1** fragments under a variety of conditions to 2-methylindole and 2-methylindolone.⁸

Compound **2**, obtained in 33% yield, shows absorption maxima in its infrared (1700 and 1623 cm^{-1}) and ultraviolet-visible (387 $\text{m}\mu$) spectra which have been described⁹ as typical for indoxyls. The nuclear magnetic resonance spectrum indicated the presence of two equivalent methyl groups. On this basis, **2** was assigned the structure of 2,2'-dimethyl-3,3'-dioxodiindolyl-2,2'.¹⁰ This assignment was confirmed by synthesis.

Compound **3**, corresponding to the product appearing in the reaction mixture after work-up, was isolated in 4% yield. This material gave spectra consistent with the following structural elements: normal indole (271, 281, and 288 $\text{m}\mu$), isatin-like chromophore (392 and 492 $\text{m}\mu$), α,β -unsaturated carbonyl (1655 cm^{-1}), and conjugated double bond (1625 cm^{-1}). The nmr spectrum (dimethyl sulfoxide- d_6) indicated a singlet methyl group at δ 2.57. In comparison, the methyl group of 2-methylindole appears at δ 2.18 and the 2' methyl group in compound **1** is found at δ 2.51. The mass spectrum indicated a molecular weight of 274 and molecular formula of $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}$. These data suggested structure **3**, 2-[3'-(2'-methylindolyl)methylene]indoxyl. The structural assignment for compound **3** was verified by an independent synthesis¹¹ from indoxyl¹² and 2-methylindole-3-aldehyde.¹³

It is possible for the indogenide **3** to occur as two geometric isomers. However, we found only one isomer, whose geometry was not established.

The second indole chosen for study was 2,3-diphenylindole. Three products were obtained from 2,3-diphenylindole by oxidation with sodium periodate. Two of the three compounds were shown by melting point and spectral comparisons to be 2,2-diphenylindoxyl¹⁴ and *o*-benzamidobenzophenone.¹⁵ These compounds were obtained in yields of 8 and 42%, respectively. The third product was identified as 3-hydroxy-2,3-diphenylindolenine (**4**). Combustion analysis of **4** indicates the formula $\text{C}_{20}\text{H}_{15}\text{NO}$. The infrared spectrum shows no carbonyl absorption but peaks at 3600 and 1540 cm^{-1} . Catalytic hydrogenation of **4** gives a quantitative yield of 2,3-diphenylindole. That **4** is not an N-hydroxyindole was shown by a negative ferric

(1) This work was supported by the National Institutes of Health (Grant HE 09521) and a Public Health Service career program award 1-K3-NB-28,105 from the National Institute of Neurological Diseases and Blindness.

(2) Part I: Lloyd J. Dolby and David L. Booth, *J. Amer. Chem. Soc.*, **88**, 1049 (1966).

(3) Alfred P. Sloan Research Fellow, 1965–1967.

(4) National Defense Education Act Predoctoral Fellow, 1964–1967.

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(11) (a) A. Baeyer, *Chem. Ber.*, **16**, 2188 (1883); (b) for a general discussion of this topic, see R. C. Elderfield, "Heterocyclic Compounds," Vol. 3, John Wiley & Sons, Inc., New York, N. Y., 1952, p 200.

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(13) G. Plancher and U. Ponti, *Atti accad. Naz. Lincei, Rend., Cl. Sci. Fis. Mat. Nat.*, **16**, 130 (1908); *Chem. Abstr.*, **2**, 1147 (1908).

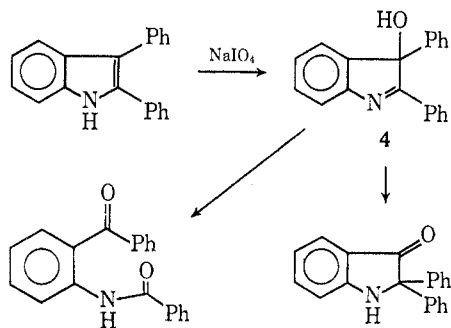
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(15) P. Grammaticakus, *Bull. Soc. Chim. Fr.*, 86 (1953).

chloride test and the lack of a bathochromic shift in the ultraviolet spectrum in alkaline solution.¹⁶

Compound **4** was readily reduced with sodium borohydride to compound **5**, which was transformed by a trace of acid or merely on standing to 2,3-diphenylindole. The infrared spectrum for compound **5** showed NH absorption at 3450 cm⁻¹, an OH band at 3650 cm⁻¹, the loss of N=CR₂ absorption at 1540 cm⁻¹, and the appearance of the typical C₆H₅NCR₂ band at 1620 cm⁻¹. The ultraviolet spectrum showed no absorption above 260 mμ. The nmr spectrum consisted of an aromatic multiplet centered at δ 7.02, a singlet for the tertiary benzylic proton at δ 4.92, and a broad peak consisting of the NH and OH protons at δ 3.17. All of the above data is consistent with formulation of **5** as 3-hydroxy-2,3-diphenylindoline. Previously, Witkop and Patrick obtained 11-hydroxy-1,2,3,4,10,11-hexahydrocarbazole by sodium borohydride reduction of the corresponding indolenine.¹⁷ These authors also noted that the hydrated indole was stable only in the absence of any trace of acid. The facile dehydration of **5** is another example of this sensitivity toward acid.

It was of interest to determine if **4** could act as an intermediate in the periodate oxidation of 2,3-diphenylindole. Indeed, treatment of **4** with sodium periodate yielded *o*-benzamidobenzophenone and 2,2-diphenylindoxyl. This transformation was complete in much less time (12 hr vs. 48 hr) than the corresponding partial conversion of 2,3-diphenylindole into the same products. We suggest the following reaction sequence for the periodate oxidation of 2,3-diphenylindole.



This suggestion is in accord with the previous results on indole oxidation.¹⁸⁻²⁰ All of the products which have been obtained from the oxidation of indoles by sodium periodate are readily rationalized on the basis of a β-hydroxyindolenine intermediate. However, the oxidation of 2,3-disubstituted indoles by methanolic periodic acid gives 2-acylindoles,² and we find that β-hydroxyindolenines are not converted into 2-acylindoles by methanolic periodic acid. It appears that the corresponding β-methoxyindolenine is the intermediate in this case, since the oxidation of tetrahydrocarbazole by methanolic periodic acid yields 11-methoxytetrahydrocarbazolenine, which is further converted into 1-oxotetrahydrocarbazole under the reaction conditions.²¹

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(18) B. Witkop and J. B. Patrick, *ibid.*, **73**, 2196 (1951).

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(21) Unpublished results of S. R. Twedt, deceased.

Experimental Section²²

2-Methylindole was prepared by modification of the procedure of Allen and Van Allen.²³ Acetyl-*o*-toluidine^{24,25} (100 g) and sodium amide²⁶ (64 g) were mixed in a 1-l., three-necked, round-bottom flask equipped with a nitrogen atmosphere and a syringe cap through which passed a spatula. Dry ether (50 ml) was added to the mixture and with a steady current of nitrogen passing above it, and the mixture was heated rapidly to 240–260° (external measurement) and held there for 10 min by means of a silicone oil heating bath. The spatula was used to press the tan crust into the molten mass during the heating period.

Ethanol (50 ml) followed by warm water (250 ml) was added to the cooled reaction mixture. The flask was heated until any remaining ethanol had been driven off, all solid had dissolved, and two distinct layers had formed. While still hot the two layers were separated, and upon cooling the upper layer completely solidified. The solidified material and a small amount of material, extracted from the water layer, were subjected to molecular distillation at 80° (0.03 mm) in a large sublimation apparatus to give 2-methylindole, yield 71.2 g (81%), mp 57–58° (lit.²⁷ mp 50°).

Treatment of 2-Methylindole with Sodium Periodate.—A sample of 2-methylindole (0.23 g, 0.00175 mol) was dissolved in methanol (15 ml) and water (5 ml). To this, under nitrogen, was added dropwise 0.488 *M* sodium periodate (7 ml), methanol (8 ml), and water (5 ml). After 1 hr the yellow solution containing solid sodium iodate showed on tlc (8:1 chloroform-ethyl acetate) four substances in addition to starting material.

After 3 hr the dark orange mixture was filtered and extracted with dichloromethane, the extract was dried, and the solvent was removed to give a dark brown, tarry mass. Thin layer chromatography of this mass indicated the presence of a new material, red-orange in color, near the origin and the loss of one of the materials noted prior to the work-up.

The brown material was dissolved in dichloromethane, placed on a column of silica gel (50 g), and eluted with 4:1 chloroform-hexane to give three crystalline materials.

A. 2,2'-Dimethyl-3,3'-dioxodiindolyl-2,2' (2).—The first material eluted was crystallized from methanol to give 0.10 g (39%) of 2,2'-dimethyl-3,3'-dioxodiindolyl-2,2' (**2**), mp 174–176° dec (lit.¹⁰ mp 174° dec). This material was shown to be identical (uv, ir, nmr, and mixture melting point) with authentic material prepared as described below.

B. 2-Methyl-2,3'-(2'-methylindolyl)indoxyl (1).—The second product, yield 0.082 g (33%), mp 209–211° dec (lit.²⁸ mp 212° dec), which was obtained as yellow to pale orange crystals (from methanol), was identified as 2-methyl-2,3'-(2'-methylindolyl)indoxyl (**1**). The structural assignment was based on comparison (uv, ir, nmr, tlc, and mixture melting point) with authentic material prepared as described below.

C. 2-[3'-(2'-Methylindolyl)methylene]indoxyl (3).—The third product, yield 0.010 g (4%), was identified as 2-[3'-(2'-methylindolyl)methylene]indoxyl (**3**). It was identical in all respects (uv, ir, nmr, tlc, and mixture melting point) with authentic indogenide prepared as described below, from indoxyl and 2-methylindole-3-aldehyde.

(22) Melting points and boiling points are uncorrected. Anhydrous magnesium sulfate was used to dry solutions unless otherwise noted. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill., Berkeley Analytical Laboratories, Berkeley, Calif., or Alfred Bernhardt Mikroanalytisches Laboratorium, Mulheim (Ruhr), West Germany. Infrared spectra were determined with a Beckman IR-5 or IR-7 infrared spectrophotometer using chloroform as solvent. Ultraviolet-visible spectra were determined on a Cary Model 15 spectrophotometer. A Varian Associates A-60 instrument was used to record the nmr spectra. Unless otherwise noted, deuteriochloroform was used as solvent and tetramethylsilane was the internal standard. The mass spectrum was determined by the Morgan-Schaffer Corp., Quebec, Canada. Baker silica gel was used for column chromatography and the column was continuously eluted with the indicated solvent. Silica gel G (according to Stahl) was used for thin layer chromatography and 8:2 chloroform-ethyl acetate was used as eluent. The spots were visualized using iodine or a 3% ceric sulfate–10% sulfuric acid solution.

(23) C. F. H. Allen and J. Van Allen, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 597.

(24) F. Beilstein and A. Kuhlberg, *Justus Liebig's Ann. Chem.*, **156**, 72 (1870).

(25) Prepared in 85% yield by the method of I. S. Ioffe, *J. Gen. Chem. USSR*, **14**, 812 (1944); *Chem. Abstr.*, **39**, 3786^c (1945).

(26) The amide was used as received without additional grinding.

(27) H. Fischer, *Justus Liebig's Ann. Chem.*, **236**, 116 (1886).

(28) B. Witkop, *ibid.*, **558**, 98 (1947).

A mass spectrum of this compound showed the parent peak at m/e 274 and a peak at m/e 257 which was ascribed to the loss of hydroxyl. Calculations using the percentages of the M, M + 1, and M + 2 peaks gave the molecular formula $C_{13}H_{14}N_2O$.

N,O-Diacetyl-2-methylindoxyl was prepared in 24% yield from 1-(2'-carboxyphenyl)aminopropionic acid²⁹ following the procedure of Van Alphen.¹⁰ It had the following properties: mp 132–133° (lit.¹⁰ mp 134°); ir max (CHCl₃) 1768 and 1770 cm⁻¹; nmr δ 2.33, 2.41, and 2.58 (s, CH₃-2) and 1- and 3-acetyl CH₃), 7.32 (m, 4-6-Ar H), and 8.08 (m, 7-Ar H).

2,2'-Dimethyl-3,3'-dioxodiindolyl-2,2' (2).—A mixture of N,O-diacetyl-2-methylindoxyl (0.351 g, 0.0015 mol), dioxane (10 ml), and 2 N aqueous sodium hydroxide (40 ml) was allowed to stir uncovered for a period of 72 hr. The product did not precipitate as described by Van Alphen.¹⁰ The mixture was acidified with glacial acetic acid to pH 5.5 and extracted first with dichloromethane and then with ether. The solvent was partially removed and the extract was chromatographed to give 0.406 g (16%) of the 2,2'-diindoxyl 2: mp 173–174° dec (from methanol) [lit.¹⁰ mp 174° dec (from benzene)]; $\lambda_{\max}^{\text{CHCl}_3}$ 245 m μ (ϵ 35,600), 255 (s, 15,000), and 387 (6600); nmr δ 1.14 (s, CH₃-2 and -2'), 6.13 (br s, NH-1 and -1'), and 6.87 and 7.50 (m, 10-Ar H).

2-Methyl-2,3'-(2'-methylindolyl)indoxyl (1) was prepared in 45–52% yield as yellow to orange crystals (from methanol), mp 210–211° (lit.²⁸ mp 212°), by treating 2-methylindole with 40% hydrogen peroxide in glacial acetic acid according to the method of Witkop.²⁸ The hydrogen peroxide must be added dropwise with stirring and the temperature kept below 80°, or only a dark red, tarry material results.

In one experiment the residue, after removal of the 2,3'-indolylindoxyl, was column chromatographed to give an additional amount of the dimer and a small amount of red-orange solid, which was shown (tlc, uv) to be identical with the indogenide 3 isolated from the sodium periodate oxidation of 2-methylindole.

2-Methyl-2,3'-(2'-methylindolyl)indoxyl (1) possessed the following spectra properties:³⁰ nmr (acetone-*d*₆) δ 1.88 and 2.51 (s, CH₃-2 and -2') and 6.98 and 7.58 (m, 9-Ar H and NH-1).

N,O-Diacetylindoxyl was prepared in 6% yield from phenylglycine-*o*-carboxylic acid³¹ by the method of Friedlander and Kunz.³² When the phenylglycine-*o*-carboxylic acid was added in small portions to the boiling solution of acetic anhydride and sodium acetate, there was considerable foaming. The acid could be added without difficulty to the cool solution. After complete addition of the acid and boiling for 10 min, the product was isolated by extraction with dichloromethane and crystallization from very dilute alcohol.

In another experiment, a mixture of the acid, sodium acetate, and acetic anhydride was boiled for 10 min. In this case, although there was no foaming, the yield of N,O-diacetylindoxyl, after isolation as described above, was only 3%.

The product had the following spectral properties: ir max (CHCl₃) 1755 and 1780 cm⁻¹ (C=O); nmr δ 2.32 and 2.53 (s, 1- and 3-acetyl CH₃), 7.35 (m, 4-6-Ar H), 7.67 (s, 2-Ar H), and 8.44 (m, 7-Ar H).

2-Methylindole-3-aldehyde.—When 2-methylindole (11.14 g, 0.085 mol) was treated with phosphorus oxychloride and dimethylformamide according to the procedure of James and Snyder,³³ there resulted 13.0 g (96%) of 2-methylindole-3-aldehyde: mp 197–200° (from water) (lit.¹³ mp 198°); ir max (CHCl₃) 3480 (NH) and 1650 cm⁻¹ (C=O); $\lambda_{\max}^{\text{EtOH}}$ 246 m μ (ϵ 13,300), 367 (10,100) and 303 (11,500); nmr (acetone-*d*₆) δ 2.74 (s, CH₃-2), 3.01 (br m, NH), 7.20 (m, 4-6-Ar H), 8.14 (m, 7-Ar H), and 12.18 (s, 3-aldehyde H).

2-[3'-(2'-Methylindolyl)methylene]indoxyl (3).—To a stirring mixture of N,O-diacetylindoxyl (0.956 g, 0.0044 mol) in methanol (40 ml), under nitrogen, was added a solution of potassium hydroxide (2.5 g) in water (10 ml). The mixture became cherry red in color and after 3 hr, concentrated hydrochloric acid (3 ml) was added to give a green-red solution of indoxyl. A sample of 2-methylindole-3-aldehyde (0.676 g, 0.0043 mol) dissolved in methanol (30 ml) was added to the acidified solution over a period of 6 hr.

(29) Prepared in 66% yield by the method cited in A. I. Vogel, "Practical Organic Chemistry," Vol. 3, John Wiley & Sons, Inc., New York, N. Y., 1962, p 980.

(30) For infrared and ultraviolet spectra, see ref 9.

(31) Prepared in 62% yield by the method cited in ref 29.

(32) P. Friedlander and J. Kunz, *Chem. Ber.*, **55**, 1600 (1922).

(33) P. N. James and H. R. Snyder in "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 539.

Water (ca. 40 ml) was added to dissolve the precipitated potassium chloride and to cause precipitation of the indogenide 3 as it formed.

After the solution had been stirred for 18 hr, 3 (0.366 g crude) was filtered off and crystallized from acetone-hexane to give 0.263 g of red-orange microcrystals. Extraction of the mother liquor provided 0.143 g of aldehyde and a small amount of indigo. The yield of 3 was 29% based upon unrecovered aldehyde. The product had the following characteristics: mp 263–264° dec; ir max (KBr) 1650 (C=O) and 1617 cm⁻¹ (C=C); $\lambda_{\max}^{\text{EtOH}}$ 231 m μ (ϵ 22,000), 271 (15,500), 279 (s, 14,900), 288 (s, 10,900), 392 (8930), and 492 (20,500); nmr (dimethyl sulfoxide-*d*₆) δ 2.57 (s, CH₃-2), 7.5 (br m, 8-Ar H and 1-vinyl H), and 9.12 and 11.83 (br s, NH-2).

Anal. Calcd for C₁₃H₁₄N₂O: C, 78.81; H, 5.15; N, 10.21. Found: C, 79.07; H, 5.30; N, 10.51.

Treatment of 2-Methyl-2,3'-(2'-methylindolyl)indoxyl (1) with Sodium Periodate.—A sample of 2-methyl-2,3'-(2'-methylindolyl)indoxyl (1, 0.029 g, 1.05 × 10⁻⁴ mol) was dissolved in a mixture of methanol (3 ml), water (1 ml), and 0.488 M sodium periodate (1.5 ml) and stirred for 4 hr. After filtration and treatment in the usual way, the residue was column chromatographed to give 2,2'-dimethyl-3,3'-dioxodiindolyl-2,2' (2, 0.019 g, 62%) and a small amount of green oil.

2,3-Diphenylindole.—A mixture of benzoic acid (64 g, 0.3 mol), aniline (96 g, 1.0 mol), and aniline hydrochloride (40 g, 0.3 mol) were refluxed and then treated according to the procedure of Fennel³⁴ to give 64 g (79%) of the title compound: mp 226–227° (lit.³⁴ mp 227–228°); $\lambda_{\max}^{\text{EtOH}}$ 205 m μ (ϵ 35,100), 225 (24,600), 247 (21,600), and 307 (16,800); nmr δ 7.12 (br m, 13-Ar H and NH) and 7.67 (m, 7-Ar H).

Treatment of 2,3-Diphenylindole with Sodium Periodate.—A sample of 2,3-diphenylindole (0.47 g, 1.75 × 10⁻³ mol) was stirred for 36 hr and then refluxed for 48 hr in 0.488 M sodium periodate (7 ml), methanol (23 ml), and water (10 ml). Although tlc (8:1 chloroform-ethyl acetate on silica gel) showed the presence of starting material, the reaction mixture was treated in the usual way and chromatographed over silica gel (50 g) using 4:1 chloroform-hexane as an eluent to give 0.050 g of starting material plus three other compounds.

A. 2,2-Diphenylindoxyl.—The first compound (0.042 g, 8%), which crystallized as yellow-green needles from methanol, mp 184–186° (lit.¹⁴ mp 185–186°), was shown to be 2,2-diphenylindoxyl by comparison of ir, uv, and nmr spectra with those reported¹⁴ for this compound.

B. *o*-Benzamidobenzophenone.—The second compound, initially obtained as a pale yellow oil, crystallized upon standing. This material (0.220 g, 42%), mp 90–91° (lit.¹⁵ mp 91°), was *o*-benzamidobenzophenone. The ultraviolet spectrum and melting point were consistent with those reported for this compound.¹⁵ The compound had the following infrared spectral characteristics: ir max (CHCl₃) 3330 (NH), 1675 (ketone C=O), and 1625 cm⁻¹ (amide C=O).

C. 3-Hydroxy-2,3-diphenylindolenine.—The last material from the column was crystallized from petroleum ether (bp 30–60°) to give 0.060 g (12%) of the title compound as white needles: mp 191–193°; ir max (CHCl₃) 3600 (OH) and 1540 cm⁻¹ (C=N); $\lambda_{\max}^{\text{EtOH}}$ 245 m μ (ϵ 14,100) and 317 (12,200) and the same spectrum with base, but with acid λ_{\max} 248 m μ (ϵ 8900) and 338 (12,600); nmr (DMSO-*d*₆) δ 6.94 (s, 3-hydroxyl H), 7.27 (br m, 13-Ar H), and 8.14 (m, 7-Ar H).

Anal. Calcd for C₂₀H₁₅NO: C, 84.19; H, 5.30; N, 4.91. Found: C, 84.07; H, 5.27; N, 5.08.

Reduction of 2-Hydroxy-2,3-diphenylindolenine. A. By Catalytic Hydrogenation.—A mixture of 3-hydroxy-2,3-diphenylindolenine (0.03 g, 1 × 10⁻⁴ mol), 10% palladium on carbon (0.03 g), and absolute ethanol (15 ml) containing triethylamine (3 drops) was stirred at 25° for 8 hr in the presence of hydrogen (1 atm). The mixture was filtered and the filtrate was concentrated to dryness. Comparison (ir, uv, nmr, and tlc) with authentic material showed it to be 2,3-diphenylindole.

B. By Sodium Borohydride.—A stirring mixture of 3-hydroxy-2,3-diphenylindolenine (0.029 g, 1 × 10⁻⁴ mol) in methanol (10 ml) was treated with excess sodium borohydride for 1 hr. Water (10 ml) and then saturated sodium carbonate solution (5 ml) were added to the mixture, and then it was extracted with dichloromethane. The extract was dried over sodium sulfate and

the solvent was removed to give 0.025 g (87%) of 3-hydroxy-2,3-diphenylindoline: ν_{max} (CHCl₃) 3650 (OH), 3450 (NH), and 1620 cm⁻¹ (PhNCR₃); $\lambda_{\text{max}}^{\text{EtOH}}$ 242 and 305 m μ ; nmr δ 3.17 (br s, NH-1 OH-1), 4.92 (s, 2-benzylic H), and 7.02 (br m, 14-Ar H).

This compound dehydrated very rapidly upon standing or during attempted crystallization from ethanol-water. Treatment with warm acetic acid caused complete dehydration, giving 2,3-diphenylindole. The ultraviolet spectrum and tlc of the dehydrated product were identical with those of authentic material.

Treatment of 3-Hydroxy-2,3-diphenylindolenine with Sodium Periodate.—A sample of 3-hydroxy-2,3-diphenylindolenine (0.005 g, 1.75×10^{-5} mol) was dissolved in methanol (4.5 ml), water (1.5 ml), and 0.488 M sodium periodate (0.5 ml) and refluxed for

12 hr. After cooling the mixture was treated in the usual manner to provide nearly white solid (0.005 g, 95%).

Comparison (ir, tlc) with authentic material demonstrated that this material was *o*-benzamido benzophenone containing a little 2,2-diphenylindoxyl.

Registry No.—1, 23740-95-6; 2, 23740-96-7; 3, 23740-97-8; 4, 23740-98-9; 2-methylindole, 95-20-5; N,O-diacetyl-2-methylindoxyl, 23741-00-6; N,O-diacetylindoxyl, 16800-67-2; 2-methylindole-3-aldehyde, 5416-80-8; 2,3-diphenylindole, 3469-20-3; 3-hydroxy-2,3-diphenylindolenine, 23829-47-2.

Stereochemistry at Trivalent Nitrogen. VIII. Steric and Solvent Effects on Slow Nitrogen Inversion in an Isoxazolidine^{1a}

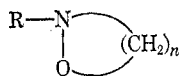
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Chemical-shift nonequivalence arising from slow nitrogen inversion in *cis*-1,8-dimethyl-2-oxa-1-azabicyclo[3.3.0]octane (**2**) was observed. An assignment of the configurations at nitrogen in the two diastereomers observed in low-temperature nmr spectra can be made on the basis of steric and solvent effects on the equilibrium constant, and on the effect of the orientation of the lone pair of electrons on chemical shifts. The nitrogen inversion barrier was determined using complete line-shape methods, and its dependence on solvent and steric factors is discussed.

Numerous reports have appeared in recent years describing temperature dependence in the nmr spectra of amine derivatives which have a heteroatom (especially nitrogen, oxygen, or sulfur) directly bonded to the nitrogen atom. This behavior results from conformational interchange which is slow on the nmr time scale. Two classes of compounds which have received considerable attention in this respect are the cyclic and acyclic trialkylhydroxylamines. Although earlier papers^{2,3} postulated a substantial barrier to inversion of the nitrogen pyramid as the origin of chemical-shift nonequivalence of diastereotopic nuclei in acyclic trialkylhydroxylamines, more recent work has indicated that the results observed more probably reflect the existence of a substantial barrier to torsion about the N-O bond.⁴ By contrast to the acyclic compounds, chemical-shift nonequivalence in the cyclic systems **1** can be unequivocally ascribed to slow nitrogen inversion when the size of the heterocyclic ring is small enough to eliminate ring inversion as a possible process. When this work was begun, reports of

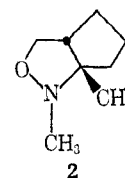


1, $n = 1, 2, 3, 4$

slow nitrogen inversion had appeared for oxaziridines⁵⁻⁷ (**1**, $n = 1$) and a substituted 1,2-oxazeti-

dine⁸ (a derivative of **1**, $n = 2$) in which the heteroatoms are part of strained rings. However, a dihydro-1,2-oxazine (an unsaturated derivative of **1**, $n = 4$) was reported to exhibit chemical-shift equivalence resulting from more rapid nitrogen inversion.⁸ Hence, it was of interest to determine whether the presence of a strained ring was a requirement for the observation of slow nitrogen inversion or whether the presence of the oxygen atom would slow nitrogen inversion in isoxazolidines (**1**, $n = 3$) so that chemical-shift nonequivalence could be observed. Most recently, chemical-shift nonequivalence in isoxazolidines (**1**, $n = 3$) and tetrahydro-1,2-oxazines (**1**, $n = 4$) has been described^{9,10} indicating that a strained ring is not a prerequisite for a measurable nitrogen inversion barrier.

The bicyclic isoxazolidine **2** represents an additional example of a molecule which exhibits chemical-shift



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nonequivalence due to hindered stereomutation at nitrogen. Comparison of the barrier to nitrogen inversion in **2** with those in other examples of the isoxazolidine system indicates that a significant steric effect on the inversion rate obtains.

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