absorption at 13.85 μ. Moreover, these effects afford additional proof that deuterium is bonded to carbon. The intense N–D band in N-deuterioindole appeared at 3.95 μ, but no other significant change in the spectrum was observed.

Experimental

3-Deuterioindole.—A mixture of 10 g. of indole and 5 ml. of 0.005 *N* sulfuric acid in D_2O was refluxed under nitrogen for 12 hr., the minimum time required for complete exchange. The solution was cooled and then was extracted with dry benzene. The extract was washed twice with D_2O and once with a saturated solution of sodium chloride in D_2O, then was dried over anhydrous calcium sulfate and evaporated. The residual white solid contained about 60% 1,3-dideuterioindole; as indicated by the intensities of the NH and ND peaks in the infrared, the balance was 3-deuterioindole. The mixture was refluxed with 50 ml. of water under nitrogen for a minimum of 3 hr. The mixture was cooled and extracted with benzene. The benzene extract was washed with a saturated salt solution, dried over calcium sulfate, and evaporated. The residual solid was recrystallized twice from a benzene–hexane mixture and then was dissolved in warm hexane. The clear solution, which was decanted from the oil that formed upon standing, was concentrated and cooled. White crystals (0.70 g.) of 87% pure 3-deuterioindole were obtained, m.p. 50.5–51.5°. The purity of the product was determined from the integrated n.m.r. spectrum in carbon tetrachloride by comparison of the areas of the β- and α-H peaks.

The principal peaks of the infrared spectra of indole and 3-deuterioindole, determined in KBr, are given below. Italic values are those which do not appear in the other spectrum. The presence of deuterium on nitrogen made little difference in the spectrum, except for the NH and ND peaks.

Indole.—*2.92* (*vs*), 3.18 (vw), 3.23 (w), 5.15 (w), 5.25 (w), 5.33 (w), 5.47 (w), 5.58 (w), *5.82* (*w*), 5.89 (w), 6.16 (m), 6.30 (w), *6.61* (*w*), 6.68 (w), 6.83 (s), 7.03 (s), *7.35* (*s*), 7.45 (s), 7.80 (m), 8.00 (s), *8.27* (*w*), 8.69 (w), 8.82 (m), 9.15 (s), *9.40* (*s*), 9.87 (w), 9.93 (w), 10.70 (m), *11.13* (*m*), 11.45 (m), *11.60* (*m*), *13.05* (*s*), 13.43 (vs), 13.85 (vs).

Additional Peaks in 3-Deuterioindole.—*6.05* (*w*), *8.49* (*w*), *12.05* (*m*), *12.40* (*s*), *13.72* (*s*).

Acknowledgment.—The authors are indebted to Dr. Charles Angell for advice in the interpretation of the infrared spectra.

Reduction of Some Oxindolylidene Derivatives to 3-Substituted Oxindoles by Sodium Borohydride[1]

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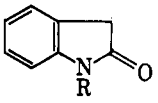
Received February 7, 1964

The 3-position of oxindole possesses distinct anionoid character. In 1909, Wahl and Bagard[2a] reported that base- or acid-catalyzed condensation of oxindole (**1**, R = H) with carbonyl compounds led to the formation of oxindolylidene derivatives (**2**). The trivial name "isoindogenides" has been given to the class of compounds with structure **2**. The isoindogenide 3-α-picolylideneoxindole (**2a**) first attracted our attention as a synthetic intermediate for spirooxindole derivatives (**3**).[3] Compounds with the proposed structure **2a** were previously reported by Abramovitch and Hey[4] and by Akkerman and Veldstra.[5] In both cases **2a** was prepared by condensation of isatin with α-picoline, but the two groups gave different melting points for their products.

A reaction between oxindole and 2-pyridinecarboxaldehyde, catalyzed by piperidine, gave a compound whose elemental analysis and spectra accord with constitution **2a**, and the melting point of this compound agrees with the value given by Akkerman and Veldstra. More recently 3-α-picolylideneoxindole (**2a**), which is described as exhibiting strong cholinergic effects, was included in a hydrogenation study of pyridine derivatives, but the method for preparing **2a** was not given.[6] When oxindole and the pyridinealdehyde were condensed in methanol, or when diethylamine was used as the basic catalyst in an open container, the major product was the carbinol (**4**).

Some additions to the class of isoindogenides are reported in Table I and in the Experimental section. In some cases, both oxindole and N-methyloxindole were used. The carbonyl compounds employed (and the products formed) were 2-pyridinecarboxaldehyde (**2a** and **b**), 2-pyrrolecarboxaldehyde (**2c** and **d**), furfural (**2e**), and cyclohexanone.[7]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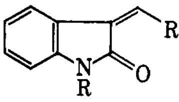
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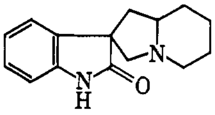
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The scope of sodium borohydride reductions has been greatly expanded beyond the original conception that this reagent was limited to the reduction of carbonyl or imine groups. In particular, there are several reports in which carbon–carbon double bonds of enamines and α,β-unsaturated esters are reduced.[8,9] We found adventitiously that sodium borohydride reduces the 3-*exo* double bond in several isoindogenides.[10] The reaction occurs with a wide variation of substituents. For example, α-picolylideneoxindole (**2a**) is reduced to α-picolyloxindole (**5**)[11] by sodium borohydride, and 3-benzylideneoxindole (**2**, R′ = phenyl) is converted to 3-benzyloxindole (**6**). The proof of structure in the latter case was accomplished by comparing the product of the borohydride reduction with a sample of 3-benzyloxindole prepared by catalytic hydrogenation of benzylideneoxindole.[12] Even with an aliphatic

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[1] We gratefully acknowledge a grant in support of this research from the Tennessee Heart Association.

[2] (a) A. Wahl and P. Bagard, *Compt. rend.*, **148**, 716 (1909); (b) W. B. Wright and K. H. Collins, *J. Am. Chem. Soc.*, **78**, 221 (1956); (c) P. L. Julian, E. W. Meyer, and H. C. Printy, "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 185; (d) W. C. Sumpter and F. M. Miller, "Heterocyclic Compounds," Vol. 8, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1954, p. 142.

(3) R. G. Mason, M. A. Thesis, Fisk University, 1962.

(4) R. A. Abramovitch and D. H. Hey, *J. Chem. Soc.*, 1697 (1954).

(5) A. M. Akkerman and H. Veldstra, *Rec. trav. chim.*, **73**, 629 (1954).

(6) G. N. Walker, *J. Org. Chem.*, **27**, 2967 (1962).

(7) 3-Furfurylideneoxindole has already been described: J. Staněk and D. Rybář, *Chem. Listy*, **40**, 173 (1946).

(8) I. W. Elliott and J. O. LeFlore, *J. Org. Chem.*, **25**, 3181 (1963); J. Szmuszkovicz, "Advances in Organic Chemistry," Vol. 4, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 82.

(9) J. A. Meschino and C. H. Bond, *J. Org. Chem.*, **28**, 3129 (1963); M. S. Brown and H. Rapoport, *ibid.*, **28**, 3261 (1963); H. LeMoal, R. Carrié, and M. Bargain, *Compt. rend.*, **251**, 2541 (1960).

(10) These reductions were initiated with the hydrochloride salt of **2a** to establish the structure. The chemistry of these salts will be the subject of a separate communication.

(11) α-Picolyloxindole (**5**) has also been prepared by Walker (ref. 6).

(12) E. Kircher, *Nachr. kgl. Ges. Wiss. Gottingen Math.-Physik. Kl.*, 154 (1921); *Chem. Abstr.*, **17**, 1012 (1923).

Table I

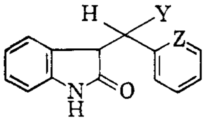
Isoindogenides[a]

Compound	R	R′	M.p., °C.	Yield, %	Formula	Carbon, %		Hydrogen, %		Nitrogen,	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
2a	H	2-Pyridyl	205–206	94	$C_{14}H_{10}N_2O$	75.66	75.88	4.51	4.73		
2b	CH_3	2-Pyridyl	159–160	87	$C_{15}H_{12}N_2O$	76.25	76.31	5.12	5.12	11.86	11.74
2c	H	2-Pyrryl	221–222	88	$C_{13}H_{10}N_2O$	74.67	74.35	4.80	4.71	13.33	13.05
2d	CH_3	2-Pyrryl	141–142	83	$C_{14}H_{12}N_2O$	74.98	74.82	5.39	6.65	12.49	12.67
2e	CH_3	2-Furyl	134–135	82	$C_{14}H_{11}NO_2$	74.65	74.40	4.92	4.94	6.22	6.51
2f	H	Styryl	205–206	71	$C_{17}H_{13}NO$	82.57	82.57	5.30	5.59	5.66	5.65
2g	H	2,6-Dimethyl 1,5-Heptadienyl	137–138	64	$C_{18}H_{21}NO$	80.85	80.82	7.92	7.86	5.24	5.50

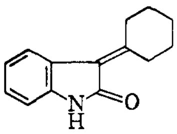
[a] A typical preparation is described for **2a** in the Experimental. Compounds **2f** and **2g** were prepared by azetropic distillation of a benzene solvent rather than in isopropyl alcohol by condensation of oxindole with cinnamaldehyde and citral, respectively.

substituent the reduction is successful under mild conditions. 3-Cyclohexylideneoxindole (**7**) is reduced to 3-cyclohexyloxindole (**8**) in 94% yield. Leucoisoindigo (**10**)[13] can be prepared quantitatively from isoindigo (**9**) on treatment with sodium borohydride in aqueous isopropyl alcohol.

Earlier Lindwall and MacLennan demonstrated that sodium dithionite was capable of reducing 3-phenacylideneoxindole to 3-phenacyloxindole.[14] This reagent is also effective in converting 3-α-picolylideneoxindole (**2a**) to 3-α-picolyloxindole (**5**), but dithionite in hot aqueous methanol did not completely reduce 3-benzylideneoxindole to 3-benzyloxindole under the same conditions.



4, Y = OH; Z = N
5, Y = H; Z = N
6, Y = H; Z = CH



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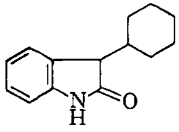

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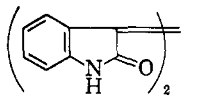

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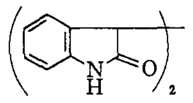

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Experimental

3-α-Picolylideneoxindole.—To oxindole (10 g.) dissolved in isopropyl alcohol (100 ml.) was added all at once 2-pyridinecarboxaldehyde (10 ml.) and piperidine (2 ml.). The orange solution was boiled 20 min. and cooled. On scratching, there separated orange crystals (15.7 g.), m.p. 203–205°. For analysis a sample, m.p. 205–206°, was recrystallized from aqueous isopropyl alcohol.

3-α-Picolylideneoxindole methiodide was obtained after the base was suspended in dichloromethane and methyl iodide for 5 days. The salt, m.p. 232–233°, crystallized as red needles; infrared spectrum was at 5.88 and 6.22 μ.

Anal. Calcd. for $C_{15}H_{13}IN_2O$: C, 49.47; H, 4.29; N, 7.69. Found: C, 49.57; H, 4.07; N, 7.95.

3-Oxindolyl-2-pyridylcarbinol.—A methanolic solution (30 ml.) of oxindole (2.0 g.) and 2-pyridinecarboxaldehyde (2 ml.) was treated with diethylamine (1 ml.) and boiled 20 min., during which time a precipitate (3.2 g.) formed. The solid, m.p. 180–185°, was recrystallized several times from ethanol to afford pale yellow crystals, m.p. 184–185°.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 70.25; H, 5.06; N, 11.65. Found: C, 70.31; H, 5.06; N, 11.75.

3-α-Picolyloxindole.—To a warm solution of α-picolylideneoxindole (0.5 g.) in 50% aqueous ethanol (20 ml.) was added sodium borohydride (0.25 g.). On further heating for 15 min., the color faded from orange to pale yellow. More water (30 ml.) was added, and the solution was boiled vigorously in an open flask for 5 min. On cooling, a brown oil separated. The aqueous solution was decanted from oil and cooled overnight, whereupon a colorless solid (0.25 g., m.p. 129–131°) precipitated. The brown oil crystallized from aqueous ethanol as prismatic needles (0.20 g.) that proved identical by melting point and infrared spectra with the reaction product from the aqueous layer. The analytical sample (m.p. 130–131°) was obtained after several recrystallizations from aqueous alcohol or from benzene–ligroin (lit.[6] m.p. 130–132°).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.40; N, 12.50. Found: C, 74.88; H, 5.42; N, 12.11.

The same reduction product was obtained in 67% yield when α-picolylideneoxindole was reduced by sodium dithionite[14] or when the hydrochloride was treated with sodium borohydride.

3-Benzyloxindole. A. By Sodium Borohydride Reduction.—Treatment of 3-benzylideneoxindole (1.0 g.) with sodium borohydride (0.5 g.) in aqueous ethanol gave on dilution with water and chilling 0.9 g. of 3-benzyloxindole, m.p. 129–131°, in two crops. This product proved identical by mixture melting point and infrared spectra with 3-benzyloxindole prepared by catalytic hydrogenation of 3-benzylideneoxindole.

B. By Sodium Dithionite.—To a solution of 3-benzylideneoxindole (0.2 g.) in warm methanol (15 ml.) was added sodium dithionite (0.4 g.) and water (10 ml.). The mixture was shaken and heated to boiling for 15 min. Some of the methanol was boiled off, but the yellow color remained. The cooled solution deposited yellow needles that were identified as starting benzylideneoxindole (0.12 g., 60%). Concentration of the filtrate afforded colorless needles, 0.05 g., m.p. 125–128, that proved to be 3-benzyloxindole by mixture melting point and infrared spectral comparison with an authentic sample.

Cyclohexylideneoxindole.—Oxindole (5 g.) was heated in dry benzene (100 ml.) under reflux conditions together with cyclohexanone (6 ml.) and piperidine (1.5 ml.). The mixture was allowed to reflux 8 hr., and the benzene was distilled. The residual oil was dissolved in hot methanol (20 ml.), filtered, and cooled. An orange solid (4.6 g.) was deposited, m.p. 182–183°. Recrystallization from methanol raised the melting point to 192–193°.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.14; N, 6.57. Found: C, 78.97; H, 6.78; N, 6.81.

3-Cyclohexyloxindole. A. Catalytic Reduction.—A solution of cyclohexylideneoxindole (1.0 g.) in 80% aqueous ethanol (100 ml.) was exhaustively hydrogenated in the presence of 10% palladium on charcoal at 3 atm. After 3 hr., the mixture was filtered, and the filtrate was concentrated to afford colorless needles (0.5 g.), m.p. 167–168°. An analytical sample (m.p. 168–169°) was recrystallized from aqueous methanol.

Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.21; H, 8.31; N, 6.16.

B. Borohydride Reduction.—A sample of cyclohexylidene oxindole (0.75 g.) was dissolved in hot methanol (40 ml.), and 5 ml. of water was added. Sodium borohydride (0.3 g.) was added to the hot solution, and the solution was boiled 15 min. in an open flask; water was added in small portions to replace the methanol. The colored mixture deposited a light yellow crystalline product (0.71 g.), m.p. 165–167°. Recrystallization from methanol gave colorless crystals, m.p. 168–169°. This product

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[13] C. W. Hansen, *Ann. chim.* (Paris), [10]**1**, 94 (1924).

[14] H. G. Lindwall and J. S. MacLennan, *J. Am. Chem. Soc.*, **54**, 4739 (1932).

proved to be identical with cyclohexyloxindole from the catalytic reduction (part A) by mixture melting point and infrared spectral comparison.

Reduction of Isoindigo.—A hot suspension of isoindigo (0.5 g.) in 2-propanol (40 ml.) and water (5 ml.) was treated with sodium borohydride (0.12 g.). Within 10 min. all of the solid had dissolved, and the boiling solution was colorless. More water (20 ml.) was added, and the mixture was kept hot 20 min. longer. The solution was concentrated under reduced pressure to one-third of the original volume, and a solid began to separate. The suspension was reheated and the solid was dissolved by addition of alcohol. On standing, the hot filtered solution deposited colorless crystals, 0.5 g., m.p. 258°. Recrystallization from alcohol raised the melting point to 272–274°. Mixture melting point and infrared spectra showed the product was identical with a sample of leucoisoindigo prepared by zinc–acetic acid reduction of isoindigo.[13]

Long-Range Deshielding by Chlorine

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Edward C. Taylor

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Princeton, New Jersey

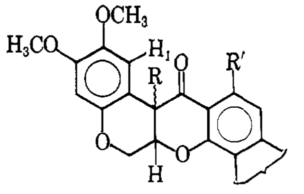
Received December 5, 1963

Long-range shielding and deshielding effects have been known to n.m.r. spectroscopists for some time.[2] Most of the clearly defined examples involve the anisotropy of unsaturated functions. We report herein the observation of an unusually large chemical shift produced by a chlorine atom five bonds distant from the shifted proton.

Compounds **2–5**, Table I, having R_3 = Cl, all show an absorption in the range τ 0.97–1.20, integrated intensity of one proton. This peak has been assigned to H_4 on the aromatic ring. It appears as the X portion of an ABX system: an intense quartet and two weak combination bands.[3,4] The AB portion of the spectrum, H_2 and H_3, is complicated by overlap and/or coupling to H_1, so that the values for J_{AX} and J_{BX} cannot be obtained. However, the sum $|J_{AX} + J_{BX}|$ = 10.0 c.p.s. can be measured.

Upon reductive removal of the chlorine atom (compound **1**) the H_4 peak merges with the $H_2 + H_3$ resonance at *ca.* τ 2.0.

A long-range deshielding effect, produced by the anisotropy of the carbon–oxygen double bond, previously has been noted for the carbonyl group in formally similar structures. For example, Crombie and Lown[5] have used the shielding of the 1-hydrogen by the 12-carbonyl to assign the geometry of the B/C ring fusion in a series of rotenoids (I). Anet[6] has found that restricted rotation of the N-acetyl group in strychnospermine (II) produces a downfield shift of the aromatic proton at C-12. At room temperature, rotation of the acetyl group is sufficiently rapid that the two possible environments for C-12 are averaged out. At lower temperatures, that conformation having the carbonyl adjacent in space to C-12 displays the unusual shift. The geometry of this frozen conformation closely resembles that of compounds **1–5**.



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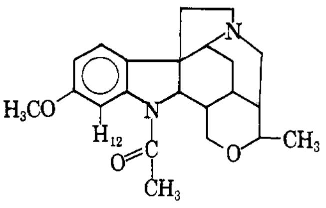
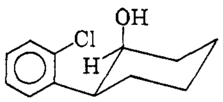


II

A few reports of such deshielding by chlorine are scattered through the literature. Huitric[7] recently has suggested that, in *cis*-2-(*o*-chlorophenyl)cyclohexanols (III), the *o*-chlorine causes a downfield shift of the 1-hydrogen resonance. However, the shift is smaller by an order of magnitude than that observed in this work (0.1 p.p.m. *vs.* 0.8–1.0 p.p.m.).

The spectrum of 5,7-dichloroquinoline[8] (IV) shows a downfield shift of 0.48 p.p.m. for H_4 when compared to 5,7-dimethylquinoline. In this instance, the chlorine and the shifted proton are *four* bonds apart in a *conjugated* system; a part of the effect may be transmitted through the π-system. Similarly, the indicated aromatic protons of V[9] show a downfield shift of 0.52 p.p.m. when compared to the aromatic protons of 9,10-dihydroanthracene.

Finally, Osawa and Neeman[10] report chemical shifts for H_4 in the estrones (VIa and b) of τ 2.82 and 3.14, respectively, a difference of 0.32 p.p.m.



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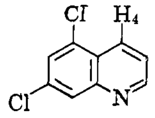

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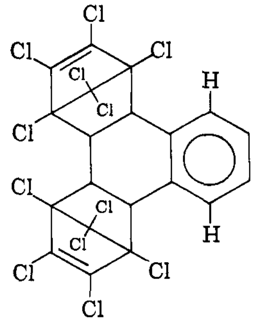
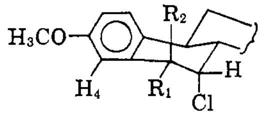


V



VIa, R_1 = Cl; R_2 = H
b, R_1 = H; R_2 = Cl

It is possible that the great magnitude of the shift observed in our pyrrolo[1,2-*a*]quinoxalines results from both electrostatic electron withdrawal (a field effect) *and* the anisotropy[11] of the carbon–chlorine bond,[12] rather than the latter alone. Either effect should be enhanced by the close approach of the two atoms;

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[1] Allied Chemical Corp. Fellow, 1962–1963; National Science Foundation Predoctoral Fellow, 1963–1964.

[2] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 112 ff.

[3] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 137.

[4] Strictly speaking, H_4 is the X part of an ABCX system; however, since H_4 does not appear to be coupled to H_1, ABX is a reasonable description.

[5] L. Crombie and J. W. Lown, *Proc. Chem. Soc.* (London), 299 (1961).

[6] F. A. L. Anet, *Can. J. Chem.*, **41**, 883 (1963).

[7] A. C. Huitric, *J. Org. Chem.*, **27**, 715 (1962).

[8] F. A. L. Anet, *J. Chem. Phys.*, **32**, 1274 (1960).

[9] Varian Associates, "High Resolution NMR Spectra Catalog," Spectrum No. 338.

[10] Y. Osawa and M. Neeman, *J. Am. Chem. Soc.*, **85**, 2856 (1963).

[11] Ref. 2, p. 115.

[12] G. S. Reddy and J. H. Goldstein, *J. Chem. Phys.*, **38**, 2736 (1963).