Hagaman, F. M. Schell, and P. M. Wovkulich, "Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances", in G. C. Levy, "Topics in Carbon-13 NMR Spectroscopy", Vol. 2, Wiley-Interscience, New York, N.Y., 1976.
(9) C.-j. Chang, H. G. Floss, and G. E. Peck, *J. Med. Chem.*, **18**, 505 (1975).
(10) C.-j. Chang and G. E. Peck, *J. Pharm. Sci.*, **64**, 1019 (1976).
(11) C.-j. Chang, *J. Org. Chem.*, **41**, 1881 (1976).
(12) C.-j. Chang, unpublished results.
(13) N. J. Cussans and J. N. Huckerby, *Tetrahedron*, **31**, 2587, 2591, 2719 (1975).
(14) J. L. Marshall, D. E. Miiller, S. A. Conn, R. Seiwell, and A. M. Ihrig, *Acc. Chem. Res.*, **7**, 333 (1974), and references cited therein.
(15) (a) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972; (b) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972; E. Breitmaier and W. Voelter, "^{13}C NMR Spectroscopy", Verlag Chemie, Weinheim/Bergstr., Germany, 1974.
(16) J. L. Marshall and R. Seiwell, *J. Magn. Reson.*, **15**, 150 (1974).
(17) ^{13}C NMR spectral data of catechol in Me_2SO-d_6: C_1, 146.0 ppm, $^3J(C_1-H_5)$ = 8.6, $^3J(C_1-H_3)$ = 5.8, $^2J(C_1-H_6)$ = 1.5 Hz; C_3, 117.0 ppm, $^1J(C_1-H_5)$ = 157.4, $^3J(C_3-H_5)$ = 6.4, $^2J(C_3-H_4)$ = 3.1 Hz; C_4, 121.1 ppm, $^1J(C_4-H_4)$ = 160.7, $^3J(C_4-H_6)$ = 8.4 Hz, $^3J(C_1-H_5) > {}^3J(C_1-H_3)$.
(18) D. E. Dorman, M. Jautelat, and J. D. Roberts, *J. Org. Chem.*, **36**, 2757 (1971).
(19) (a) R. Freeman, *J. Chem. Phys.*, **53**, 457, 1970; (b) O. A. Gansow and W. Schittenhelm, *J. Am. Chem. Soc.*, **93**, 4294 (1971).

Substituent Effects on the Carbon-13 Spectra of Oxindoles

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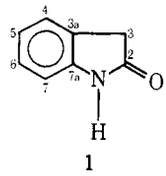
A detailed study of the ^{13}C NMR spectra of oxindoles has been made. A series of 40 oxindoles with varying substitution in the 3, 4, 5, 6, and 7 positions was investigated. Substituents on the 3 position were hydrogen, methyl, and thiomethoxyl. Substituents on the 4, 5, 6, or 7 positions were methoxyl, methyl, hydrogen, chloro, carboethoxy, cyano, and nitro. A set of shift parameters were established for each of these substituents. These were closely related to (but not identical with) previously published shift effects reported for substituents on simple derivatives of benzene. Certain long-range effects were correlated with σ inductive parameters.

Recently, we described a simple process for the preparation of oxindoles in high overall yield from readily available, inexpensive starting materials.[1-4] This has made oxindoles attractive precursors for a wide variety of synthetic schemes designed for the preparation of indole type alkaloids. Since our process for the preparation of oxindoles permitted the presence of both electron-withdrawing and electron-donating substituents on the aromatic nucleus, it also provided the potential for a wide variation in the substitution patterns of the desired indole derivatives. Since ^{13}C NMR is an extremely powerful tool in the elucidation of structure in the alkaloid field,[5] it became of interest to know the exact effect of substituents on the ^{13}C chemical shifts in indole and oxindole type systems. We report here a detailed study of substituent effects on the ^{13}C chemical shifts in oxindoles.

Relatively little is known about the ^{13}C NMR spectral properties of oxindoles. Wenkert and his co-workers have studied the ^{13}C NMR spectrum of oxindole (1) and of a few



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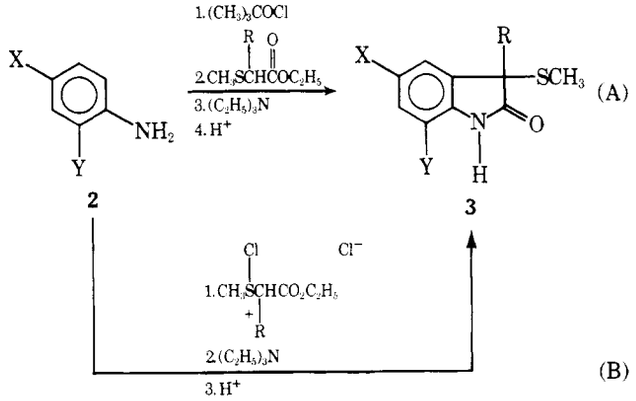
oxindole derived alkaloids.[6] In the case of 1, the chemical shifts were based on analogy with aniline.[6] Our current study concurs with the literature assignments and adds considerable supporting evidence for the assignments.

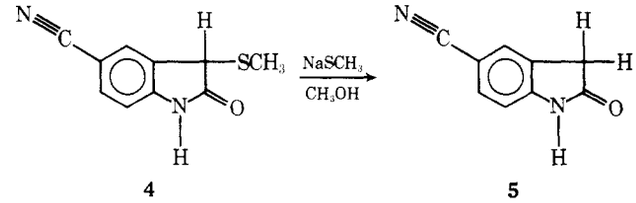
Synthesis of Oxindoles. With the exception of 5-nitrooxindole, which was prepared by the direct nitration of oxindole,[7] all of the oxindoles investigated as part of this study were prepared through either procedure A[1,3] or B.[2,4] In general, method A was used for the preparation of oxindoles bearing electron-withdrawing substituents and process B was used to prepare those oxindoles with electron-donating substituents. Table I lists the yields of oxindoles prepared specifically for this study. All of the other oxindoles investigated were prepared either as previously reported,[1-4] as part of a



(A)

(B)

study of isatin synthesis,[8] or as part of a detailed study of substituent effects on [2,3]-sigmatropic rearrangements of ylides derived from azasulfonium salts.[9] The desulfurization was accomplished in most cases through Raney-nickel reduction. However, in the case of nitro and cyano substituted oxindoles, where side reactions could be noted on Raney-nickel reduction, the thiomethoxyl group was removed via reaction with sodium thiomethoxide in methanol. For example, 4 could be converted into 5 in 62% yield by this method.



4 5

NMR Spectral Studies and Discussion. The ^{13}C NMR spectra of all of the oxindoles studied were obtained in dimethyl sulfoxide-d_6 as solvent with all shifts listed in parts per million relative to tetramethylsilane. Since the values obtained for oxindole (1) were slightly different from those reported by Wenkert and co-workers in chloroform-d, we also

Table I. Conversion of Anilines (2) into 3-Methylthiooxindoles (3)

Registry no.	2			Method	% yield of 3
	X	Y	R		
106-47-8	Cl	H	H	A	77
873-74-5	CN	H	H	A	80
94-09-7	$CO_2C_2H_5$	H	H	A	73
	Cl	H	CH_3	A	81
	CN	H	CH_3	A	67
	$CO_2C_2H_5$	H	CH_3	A	78
106-49-0	CH_3	H	CH_3	B	47
104-94-9	CH_3O	H	CH_3	B	46
88-74-4	H	NO_2	H	A	31
95-53-4	H	CH_3	CH_3	B	43

Table II. ^{13}C Chemical Shifts of Aryl Unsubstituted Oxindoles[a]

Registry no.	Compd (substituents)	Position									
		2	3	3a	4	5	6	7	7a	CH_3	SCH_3
59-48-3	1 (3-H,3-H)[b]	178.6	36.3	125.4	124.4	122.2	127.9	110.0	142.9		
	1 (3-H, 3-H)	176.6	35.9	125.9	124.4	121.3	127.5	109.3	143.8		
1504-06-9	6 (3-H,3-CH_3)	179.7	40.2	131.4	123.7	121.3	127.6	109.1	142.4	15.1	
40800-64-4	7 (3-H,3-SCH_3)	176.2	45.4	126.7	124.8	121.8	128.7	109.3	142.6		11.9
40800-77-9	8 (3-CH_3,3-SCH_3)	178.0	49.3	131.4	123.6	121.9	128.7	109.6	141.1	20.9	11.2

[a] All spectra were measured in dimethyl sulfoxide-d_6 vs. Me_4Si with values listed in parts per million downfield from tetramethylsilane unless otherwise specified. [b] Spectrum measured in chloroform-d for comparison.

Table III. ^{13}C Substituent Parameters for Oxindoles in Dimethyl Sulfoxide-d_6

Substituent	^{13}C shift, ppm			
	C_1	Ortho	Meta	Para
OCH_3	32.8 ± 0.7	−14.8 ± 0.5	1.4 ± 0.4	−7.0 ± 0.6
CH_3	9.4 ± 0.5	0.9 ± 0.7	−0.1 ± 0.2	−2.5 ± 0.2
Cl	5.1 ± 1.3	0.1 ± 0.5	1.6 ± 0.3	−1.1 ± 0.1
$CO_2C_2H_5$	1.7 ± 0.6	1.3 ± 0.7	0.2 ± 0.4	4.5 ± 0.5
CN	−17.4 ± 0.7	4.3 ± 1.1	1.1 ± 0.3	4.5 ± 0.2
NO_2	20.1 ± 0.6	−4.3 ± 1.0	0.9 ± 0.7	6.3 ± 0.6

ran 1 in the same solvent and reproduced the reported values within ±0.1 ppm. Thus, the differences noted in dimethyl sulfoxide-d_6 could be attributed to solvent effects. Table II lists the spectral data for a series of oxindoles differing only in the substitution at the 3 position. As can be seen from this table, substitution at the 3 position by a thiomethoxy group had little effect on the chemical shifts of carbons other than C-3. Comparison of **7** with **1** and of **8** with **6** indicated a shift of +9.3 ± 0.2 ppm as a result of this substitution. Interestingly, comparison of **1**, **6**, **7**, and **8** showed that placement of a methyl group at the 3 position shifted C-3a more than it did C-3 (+5.1 ± 0.4 vs. +4.1 ± 0.2 ppm). A significant shift of +2.4 ± 0.7 ppm due to the C-3 methyl was also noted at C-2.

Utilizing the spectral data determined for **1**, **7**, and **8** as standards, we could determine the effect of aryl ring substituents on the chemical shifts of the carbons of the oxindole nucleus. In each case a noise decoupled spectrum was obtained. Since the structures of all of the compounds under study were well established, the only problem involved the assignment of the individual resonance signals to the appropriate carbon atoms. The literature contains several empirical methods for the assignment of carbon resonances.[10] For simple benzene derivatives a series of substituent parameters has been developed.[10,11] Utilizing these established parameters and, when necessary, either off-resonance or gated decoupling we were able to assign almost all of the resonance signals. Having assigned the resonance signals to specific carbons, we were able to do a statistical refinement[11] of the shift substituent parameters as applied to oxindoles in dimethyl sulfoxide-d_6. These values and their standard deviations are listed in Table III. The parameters listed in Table III differ by as much as 2 ppm from those described for monosubstituted benzenes in carbon tetrachloride. It was not established whether these small deviations from the literature values were a function of the change in solvent system, the change in the structure of the nucleus, or of both. It should be noted that the chemical shift of the para position correlated reasonably well in a Hammett type correlation with $\sigma+$ as had been previously noted for monosubstituted benzenes.[10,11]

Utilizing the statistical parameters listed in Table III, we were able to calculate "predicted" spectra for the oxindoles studied. Tables IV–VI list these calculated values along with the experimentally determined values. More than 85% of the calculated chemical shifts agree with the experimental value by 1 ppm or less. Of the 222 comparisons which were made, only seven calculated values differed from the experimental values by more than 2 ppm.[12] Interestingly, six of the seven values which varied were the two bridgehead positions and in each of these six examples the substituent was on the adjacent carbon. In each of these cases, the resonance occurred upfield from what had been predicted on the basis of substituent group shift parameters. Whether these variations have their origin in steric interactions between the 4 and 3 substituents and between the 7 and 1 substituents has not been established. However, it should be noted that no major discrepancies occur when the 3 position bears only hydrogens.

Of passing interest as part of this study was the observation

Table IV. ^{13}C Chemical Shifts of Substituted Oxindoles

Registry no.	Substituent		Position, ppm downfield from Me_4Si								
			2	3	3a	4	5	6	7	7a	Substituent
7699-18-5	5-OCH_3	Exptl	176.3	36.3	127.2	109.4	154.7	112.3	111.6	137.1	55.5
		Calcd			127.3	109.6	154.1	112.7	110.7	136.8	
3484-35-3	5-CH_3	Exptl	176.5	35.9	125.9	125.2	130.1	127.7	109.0	141.4	20.8
		Calcd			125.8	125.3	130.7	128.4	109.2	141.3	
17630-75-0	5-Cl	Exptl	176.3	36.0	125.5	124.6	128.1	127.4	110.5	142.7	
		Calcd			127.5	124.5	126.4	127.6	110.9	142.7	
61394-49-8	5-$CO_2C_2H_5$	Exptl	176.7	35.5	126.1	125.2	122.7	129.3	108.9	148.3	165.7, 60.3, 14.2
		Calcd			126.1	125.9	123.0	128.8	109.5	148.3	
61394-50-1	5-CN	Exptl	176.3	35.4	127.2	127.8	103.1	132.9	110.2	148.3	119.7
		Calcd			127.0	128.7	103.9	131.8	110.4	148.3	
20870-79-5	5-NO_2	Exptl	176.7	35.6	127.0	119.9	141.8	124.9	109.0	150.3	
		Calcd			126.8	120.1	141.4	123.2	110.2	150.1	
61394-51-2	4-NO_2	Exptl	175.4	37.2	122.5	143.9	115.7	129.1	114.9	146.0	
		Calcd			121.6	144.5	117.0	128.4	115.6	144.7	

Table V. ^{13}Chemical Shifts of Substituted 3-Methylthiooxindoles

Registry no.	Substituent		Position, ppm downfield from Me_4Si									
			2	3	3a	4	5	6	7	7a	SCH_3	Substituent
50461-38-6	5-OCH_3	Exptl	176.0	45.9	128.0	109.9	155.0	113.7	111.5	135.9	11.8	55.5
		Calcd			128.1	110.0	154.6	113.9	110.7	135.6		
40800-66-6	5-CH_3	Exptl	176.1	45.4	126.7	125.4	130.7	129.0	109.2	140.1	11.8	20.6
		Calcd			126.6	125.7	131.2	129.6	109.2	140.1		
40800-67-7	7-CH_3	Exptl	176.5	45.5	126.2	122.0	121.6	129.8	118.8	141.1	11.8	16.3
		Calcd			126.6	122.3	121.7	129.6	118.7	143.5[a]		
61394-52-3	4-CH_3	Exptl	176.2	44.7	124.0	135.3	123.3	128.6	107.0	142.6	11.6	17.9
		Calcd			127.6[a]	134.2	122.7	128.6	106.8	142.5		
61394-53-4	5-Cl	Exptl	175.7	45.5	125.9	124.8	129.0	128.6	110.9	141.5	11.8	
		Calcd			128.3	124.9	126.9	128.8	110.9	141.5		
61394-54-5	4-Cl	Exptl	175.1	45.3	123.7	130.5	122.2	130.5	108.3	144.4	11.7	
		Calcd			126.8[a]	129.9	121.9	130.3	108.2	144.2		
61394-55-6	6-Cl	Exptl	176.1	44.9	125.7	126.3	121.5	132.9	109.5	144.1	11.8	
		Calcd			125.6	126.4	121.9	133.8	109.4	144.2		
61394-56-7	5-$CO_2C_2H_5$	Exptl	176.4	45.2	127.1	125.6	123.5	131.0	109.4	147.1	11.8	165.5, 60.5, 14.2
		Calcd			126.9	126.1	123.5	130.0	109.5	147.1		
61394-57-8	4-$CO_2C_2H_5$	Exptl	175.6	45.9	127.7[b]	127.4[b]	122.6	129.0	113.3	143.6	11.9	165.4, 60.9, 14.0
		Calcd			128.0	126.5	123.1	128.9	113.8	142.8		
61394-58-9	5-CN	Exptl	176.0	44.9	128.3	128.3	104.0	134.1	110.4	146.9	11.9	119.3
		Calcd			127.8	129.1	104.4	133.0	110.4	147.1		
61394-59-0	4-CN	Exptl	174.9	45.0	129.9	108.3	125.6	129.9	113.9	143.7	11.7	116.2
		Calcd			131.0	107.4	126.1	129.8	113.8	143.7		
40800-69-9	5-NO_2	Exptl	176.4	45.3	128.0	120.3	142.3	125.9	109.6	149.0	11.9	
		Calcd			127.6	120.5	141.9	124.4	110.2	148.9		
40800-70-2	4-NO_2	Exptl	174.8	45.8	122.5	144.9	116.8	130.4	115.2	144.5	11.9	
		Calcd			122.4	144.9	117.5	129.6	115.6	143.5		
61394-60-3	7-NO_2	Exptl	176.3	44.2	[c]	131.0	122.0	123.6	130.6	138.9	11.9	
		Calcd			127.6	131.1	122.7	124.4	129.4	138.3		

[a] Value not used in the calculation of substituent shift constants. [b] Values indicated may be reversed. [c] Resonance signal not discernible.

that substituents at C-6 promoted a systematic change in the position of the carbon resonance for C-2 as shown by a correlation of the chemical shift of C-2 with the σ value of the substituent (slope = -1.08, $r = 0.980$). However, substituents in the 4, 5, or 7 positions resulted in relatively random shifts of the C-2 resonance.[13]

In summary, we have demonstrated that the shift parameters established for monosubstituted benzenes can be extrapolated to much more complex systems with only minor modifications. Furthermore, we have firmly established the ^{13}C spectral properties for oxindoles as a class of compounds.

Experimental Section[14]

^{13}C NMR Spectra. ^{13}C NMR spectra were determined at 20 MHz on a Varian CFT-20 NMR spectrometer. Spectra were obtained in dimethyl sulfoxide-d_6 (Me_2SO-d_6) in 8-mm tubes. The spectra were recorded at ambient temperature by using the deuterium resonance of Me_2SO-d_6 as the internal lock signal. Typical pulse widths were 10 μs. Chemical shifts were measured at 4000-Hz sweep width spectra and referred to the center peak of Me_2SO-d_6 which was set at 39.6 ppm downfield from tetramethylsilane. The accuracy is within ± 0.05 ppm.

3-Methylthiooxindoles. 3-Methylthiooxindole, 3-methyl-3-methylthiooxindole, 5-methyl-3-methylthiooxindole, 7-methyl-3-methylthiooxindole, 5-methoxy-3-methylthiooxindole, 5-nitro-3-methylthiooxindole, and 4-nitro-3-methylthiooxindole were prepared according to the published procedures.[1-4] In all cases the physical constants and spectroscopic properties agreed well with those described in the literature. The 4- or 6-substituted 3-methylthiooxindoles and 3-methyl-3-methylthiooxindoles were prepared as part of another study.[8]

5-Chloro-3-methylthiooxindole. On a 0.055-mol scale, *p*-chloroaniline was converted to 5-chloro-3-methylthiooxindole according to the general procedure of Gassman and van Bergen.[3] Recrystallization of the crude oxindole from methanol gave 9.1 g (78%) of pure product: mp 171–173 °C; IR (KBr) 3100 (NH) and 1705 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 1.95 (3 H, s, 3-SCH_3), 4.50 (1 H, s, H_3), 6.80 (1 H, d, J = 8 Hz, H_7), 7.30 (2 H, m, H_4 and H_6), and 11.40 (1 H, bs, NH).

Table VI. ^{13}C Chemical Shifts of Substituted 3-Methyl-3-methylthiooxindoles

Registry no.	Substituent		Position, ppm downfield from Me_4Si										
			2	3	3a	4	5	6	7	7a	SCH_3	CH_3	Substituent
61394-61-4	5-OCH_3	Exptl	178.1	50.1	132.8	110.2	155.3	113.8	110.5	134.4	11.4	21.1	55.6
		Calcd			132.8	108.8	154.7	113.9	111.0	134.1			
61394-62-5	4-OCH_3	Exptl	177.9	49.4	116.2	156.2	105.6	130.2	102.9	142.3	11.2	18.8	55.6
		Calcd			116.6	156.4	107.1	130.1	102.6	142.5			
61394-63-6	6-OCH_3	Exptl	178.5	49.0	123.2	124.4	106.9	160.0	96.4	142.4	11.3	21.1	55.3
		Calcd			124.4	125.0	107.1	161.5	94.8	142.5			
61394-64-7	5-CH_3	Exptl	178.0	49.4	131.5	124.2	130.8	129.0	109.3	138.7	11.3	21.0[b]	20.7[b]
		Calcd			131.3	125.5	131.3	129.6	109.5	138.6			
61394-65-8	4-CH_3	Exptl	177.8	50.1	127.9	135.1	124.2	128.6	107.3	141.4	11.1	19.5	17.4
		Calcd			132.3[a]	133.0[a]	122.8	128.6	107.1	141.0			
61394-66-9	6-CH_3	Exptl	178.3	49.2	128.5	123.4	122.5	138.4	110.3	141.2	11.2	21.0[b]	21.3[b]
		Calcd			128.9	123.5	122.8	138.1	110.5	141.0			
61394-67-0	7-CH_3	Exptl	178.6	49.6	131.2	121.0	122.0	131.0	119.1	139.8	11.3	21.1	16.5
		Calcd			131.3	121.1	121.8	129.6	119.0	142.0[a]			
61394-68-1	5-Cl	Exptl	177.6	49.7	133.6	123.8	126.1	128.6	111.1	140.0	11.3	20.7	
		Calcd			133.0	123.7	127.0	128.8	111.2	140.0			
61394-69-2	4-Cl	Exptl	176.9	50.7	130.1	126.9	122.9	130.5	108.6	143.3	11.3	18.6	
		Calcd			131.5	128.7	122.0	130.3	108.5	142.7			
61436-90-6	6-Cl	Exptl	177.9	49.1	130.4	125.1	121.7	133.0	109.8	142.6	11.3	20.7	
		Calcd			130.3	125.2	122.0	133.8	109.7	142.7			
61394-70-5	5-$CO_2C_2H_5$	Exptl	178.2	49.2	131.7	124.4	123.7	131.0	109.6	145.7	11.3	20.7	165.5, 60.5,
		Calcd			131.6	124.9	123.6	130.0	109.8	145.6			14.2
61436-91-7	6-CO_2CH_3	Exptl	177.6	49.5	136.8	123.8	123.4	130.0	109.7	141.6	11.3	20.6	165.8, 52.2
		Calcd			135.9	123.8	123.2	130.4	110.9	141.3			
61394-71-6	5-CN	Exptl	177.8	49.2	132.7	127.4	104.1	134.1	110.5	145.5	11.3	20.4	119.3
		Calcd			132.5	127.9	104.5	133.0	110.7	145.6			
61394-72-7	4-CN	Exptl	176.8	49.7	133.5	107.2	126.1	130.0	114.3	142.5	11.4	19.0	116.0
		Calcd			135.7[a]	106.2	126.2	129.8	114.1	142.2			
61394-73-8	6-CN	Exptl	177.3	49.4	137.0	124.7	126.6	111.2	112.2	141.9	11.4	20.4	118.7
		Calcd			135.9	124.7	126.2	111.3	113.9	142.2			
61394-74-9	6-NO_2	Exptl	177.4	49.5	138.9	124.4	117.5	147.8	104.1	142.3	11.3	20.4	
		Calcd			137.7	124.5	117.6	148.8	105.3	142.0			

[a] Value not used in the calculation of substituent shift constant. [b] Values indicated may be reversed within any horizontal line.

Anal. Calcd for C_9H_8ClNOS: C, 50.58; H, 3.73; N, 6.56. Found: C, 50.59; H, 3.83; N, 6.51.

5-Carboethoxy-3-methylthiooxindole. On a 0.05-mol scale, ethyl *p*-aminobenzoate was converted to 5-carboethoxy-3-methylthiooxindole according to the procedure of Gassman and van Bergen.[3] The reaction gave 9.20 g (73%) of the desired oxindole: mp 151–153 °C (recrystallized from C_6H_6); IR (KBr) 3240 (NH), 1735 (C=O), 1695 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.40 (3 H, t, $CH_3CH_2O_2C$), 2.00 (3 H, s, SCH_3), 4.30 (1 H, s, H_3), 4.50 (2 H, q, OCH_2CH_3), 6.95 (1 H, d, J = 8 Hz, H_7), 7.90 (1 H, dd, J_1 = 8, J_2 < 1 Hz, H_6), 8.00 (1 H, J < 1 Hz, H_4), and 9.80 (1 H, bs, NH).

Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found: C, 57.36; H, 5.19; N; 5.49.

5-Cyano-3-methylthiooxindole. Utilizing the general procedure for the synthesis of oxindoles, as described by Gassman and van Bergen,[3] *p*-cyanoaniline was converted into 5-cyano-3-methylthiooxindole on a 0.046-mol scale. Recrystallization from methanol gave the pure oxindole (7.30 g, 80% yield): mp 182–183 °C; IR (KBr) 3100 (NH), 2220 (C≡N), and 1720 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 2.03 (3 H, s, SCH_3), 4.66 (1 H, s, H_3), 7.00 (1 H, d, J = 9 Hz, H_7) 7.69 (1 H, d, J = 2 Hz, H_4), 7.73 (1 H, dd, J_1 = 9, J_2 = 2 Hz, H_6), and 11.00 (1 H, bs, NH).

Anal. Calcd for $C_{10}H_8N_2OS$: C, 58.80; H, 3.95; N, 13.72. Found: C, 58.65; H, 4.06; N, 13.40.

5-Chloro-3-methyl-3-methylthiooxindole. The product was obtained from *p*-chloroaniline and ethyl methylthiopropionate by the general procedure of Gassman and van Bergen[3] on a 0.04-mol scale. Recrystallization of the crude product from cyclohexane gave 7.3 g (81%) of pure oxindole: mp 158.0–159.5 °C; IR (KBr) 3100 (NH) and 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.66 (3 H, s, CH_3), 1.89 (3 H, s, SCH_3), 6.87 (1 H, dd, J_1 = 8, J_2 = 1 Hz, H_7), 7.20 (1 H, dd, J_1 = 8, J_2 = 2 Hz, H_6), 7.27 (1 H, bs, H_4), 9.57 (1 H, bs, NH); mass spectrum *m/e* obsd 227.0716 (calcd, 227.0712).

Anal. Calcd for $C_{10}H_{10}ClNOS$: C, 52.75; H, 4.43; N, 6.15. Found: C, 52.78; H, 4.62; N, 6.33.

5-Carboethoxy-3-methyl-3-methylthiooxindole. The oxindole was prepared by the general procedure.[3] *p*-Carboethoxyaniline (4.95 g, 0.03 mol) was transformed into the oxindole (5.3 g, 67%): mp 219–221 °C (recrystallized from ethanol); IR (KBr) 3250 (NH), 1715 (C=O), 1685 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 1.32 (3 H, t, J = 6.7 Hz, CH_3CH_2–), 1.58 (3 H, s, CH_3), 1.90 (3 H, s, SCH_3), 4.30 (2 H, q, J = 6.7 Hz, CH_3CH_2O), 6.96 (1 H, d, J = 9 Hz, H_7), 7.80 (1 H, bs, H_4), 7.88 (1 H, d, J = 9 Hz, H_6), 10.97 (1 H, bs, NH); mass spectrum *m/e* obsd 265.0784 (calcd, 265.0772).

Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.86; H 5.79; N, 5.29.

5-Cyano-3-methyl-3-methylthiooxindole. *p*-Aminobenzonitrile (2.36 g, 0.02 mol) was converted to the corresponding oxindole (3.4 g, 78%) by the general method of Gassman and van Bergen.[3] The product was recrystallized from etaanol: mp 171–173 °C; IR (KBr) 3100 (NH), 2210 (CN), 1705 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 1.57 (3 H, s, CH_3), 1.90 (3 H, s, SCH_3), 6.92 (1 H, d, J = 8 Hz, H_7), 7.57 (1 H, d, J = 8 Hz, H_6), 7.63 (1 H, bs, H_4), 11.08 (1 H, bs, NH); mass spectrum *m/e* obsd 218.0495 (calcd, 218.0514).

Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83. Found: C, 60.59; H, 4.71; N, 12.86.

3,7-Dimethyl-3-methylthiooxindole. *o*-Toluidine (4.70 g, 0.044 mol) was transformed into the corresponding oxindole by the method of Gassman, Gruetzmacher, and van Bergen.[4] The crude product was recrystallized from ethanol to give pure oxindole (3.9 g, 43%): mp 175–177 °C; IR (KBr) 3150 (NH), 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.65 (3 H, s, CH_3), 1.92 (3 H, s, SCH_3), 2.29 (3 H, s, $ArCH_3$), 6.96 (3 H, m, aromatic protons), 10.55 (1 H, bs, NH); mass spectrum *m/e* obsd 207.0715 (calcd, 207.0717).

Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.73; H, 6.32; N, 6.76. Found: C, 63.80; H, 6.32; N, 6.79.

3,5-Dimethyl-3-methylthiooxindole. Using the same method as described in the literature,[4] *p*-toluidine (4.70 g, 0.044 mol) was converted into the corresponding oxindole (4.3 g, 47%): mp 165–167 °C (recrystallized from EtOH); IR (KBr) 3100 (NH), 1705 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.63 (3 H, s, CH_3), 1.85 (3 H, s, SCH_3), 2.30 (3 H, s, $ArCH_3$), 6.68–7.00 (3 H, m, aromatic protons), 9.83 (1 H, bs, NH); mass spectrum *m/e* obsd 207.0711 (calcd, 207.0717).

Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.73; H, 6.32; N, 6.76. Found: C, 63.68; H, 6.30; N, 6.85.

5-Methoxy-3-methyl-3-methylthiooxindole. *p*-Anisidine (5.4

g, 0.044 mol) was converted to the oxindole according to the literature method.[4] The crude material was recrystallized from ethanol to give 4.5 g (46%) of the desired product: mp 182–183 °C; IR (KBr) 3200 (NH), 1700 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 1.50 (3 H, s, CH_3), 1.85 (3 H, s, SCH_3), 3.67 (3 H, s, OCH_3), 6.63–6.93 (3 H, m, aromatic protons), and 10.30 (1 H, bs, NH); mass spectrum *m/e* obsd 223.0668 (calcd, 223.0667).

Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.19; H, 5.83; N, 6.31.

7-Nitro-3-methylthiooxindole. *o*-Nitroaniline (12.14 g, 0.088 mol) was transformed into the corresponding oxindole according to the literature procedure.[3] Recrystallization from methanol gave 3.05 g (31%) of yellow crystals: mp 205–207 °C dec; IR (KBr) 3200 (NH), 1705 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 2.07 (3 H, s, SCH_3), 4.75 (1 H, s, H_3), 7.20 (1 H, dd, J_1 = 7, J_2 = 8 Hz, H_5), 7.70 (1 H, dd, J_1 = 7, J_3 = 2 Hz, H_4), 8.10 (1 H, dd, J_2 = 8, J_3 = 2 Hz, H_6), 11.60 (1 H, bs, NH); mass spectrum *m/e* obsd 224.0258 (calcd, 224.0255).

Anal. Calcd for $C_9H_8N_2O_3S$: C, 48.21; H, 3.60; N, 12.49. Found: C, 48.03; H, 3.68; N, 12.48.

5-Chlorooxindole. 5-Chloro-3-methylthiooxindole (2.0 g, 9.4 mmol) was converted to 5-chlorooxindole by Raney-nickel reduction in the same manner as described in the literature.[3] After crystallization from benzene–cyclohexane, the pure product was obtained (1.0 g, 63%), mp 195–197 °C (lit.[15] mp 198.0–198.5 °C).

5-Methoxyoxindole. The product was obtained by treatment of 5-methoxy-3-methylthiooxindole (1 g, 5.8 mmol) with Raney nickel as described previously[3] to give 0.61 g (64%) of the pure product, mp 268 °C dec (lit.[7] mp 270 °C dec).

5-Carboethoxyoxindole. 5-Carboethoxy-3-methylthiooxindole (2.0 g, 7.97 mmol) was treated in the same manner as described in the literature[3] to give 0.91 g (56%) of the desired product: mp 190–192 °C (recrystallized from ethanol); IR (KBr) 3200 (NH), 1715, 1700 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 1.30 (3 H, t, J = 7 Hz, CH_3CH_2), 1.85 (2 H, s, $-CH_2$), 4.25 (2 H, q, J = 7 Hz, CH_3CH_2O), 6.87 (1 H, d, J = 8 Hz, H_7), 7.72 (1 H, bs, H_4), 7.78 (1 H, d, J = 8 Hz, H_6), 10.70 (1 H, bs, NH); mass spectrum *m/e* obsd 205.0753 (calcd, 205.0739).

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40. Found: C, 64.23; H, 5.42.

5-Nitrooxindole. This compound was prepared by nitration of oxindole as described in the literature,[7] mp 234–236 °C (lit.[7] mp 236 °C).

5-Cyanooxindole. 5-Cyano-3-methylthiooxindole (1.02 g, 5.0 mmol) in methanol (30 mL) was added dropwise to a cooled (0 °C) methanolic solution of sodium methyl mercaptide prepared from 2 g (0.87 g-atom) of sodium and an excess of methyl mercaptan (ca. 15 mL) in methanol (200 mL). The mixture was stirred overnight at room temperature. Part of the solvent was removed in vacuo and the rest was poured onto cold water and extracted with ether. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was crystallized from ethanol to give pure 5-cyanooxindole (0.49 g, 62%): mp 249–251 °C; IR (KBr) 3200 (NH), 2200 (CN), 1705 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 3.58 (2 H, s, CH_2), 6.95 (1 H, d, J = 8 Hz, H_7), 7.97 (1 H, bs, H_4) 8.00 (1 H, d, J = 8 Hz, H_6), and 10.87 (1 H, bs, NH); mass spectrum *m/e* obsd 158.0491 (calcd, 158.0480).

Anal. Calcd for $C_9H_6N_2O$: C, 68.34; H, 3.82. Found: C, 68.04; H, 4.00.

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References and Notes

(1) P. G. Gassman and T. J. van Bergen, *J. Am. Chem. Soc.*, **95**, 2718 (1973).
(2) P. G. Gassman, T. J. van Bergen, and G. D. Gruetzmacher, *J. Am. Chem. Soc.*, **95**, 6508 (1973).
(3) P. G. Gassman and T. J. van Bergen, *J. Am. Chem. Soc.*, **96**, 5508 (1974).
(4) P. G. Gassman, G. D. Gruetzmacher, and T. J. van Bergen, *J. Am. Chem. Soc.*, **96**, 5512 (1974).
(5) For some recent leading references see E. Wenkert, J. S. Bindra, C.-J. Chang, D. W. Cochran, and F. M. Schell, *Acc. Chem. Res.*, **7**, 46 (1974), and references cited therein; L. Zelta and G. Gatti, *Tetrahedron*, **31**, 1403 (1975); W. Grahn and C. Reichardt, *ibid.*, **32**, 125 (1976); S. S. Tafurs, J. L. Occolowitz, T. K. Elzey, J. W. Paschal, and D. E. Dorman, *J. Org. Chem.*, **41**, 1001 (1976); A. Ahond, A.-M. Bui, and P. Potier, *ibid.*, **41**, 1878 (1976); G. W. Gribble, R. B. Nelson, J. L. Johnson, and G. C. Levy, *ibid.*, **40**, 3720 (1975).
(6) E. Wenkert, C.-J. Chang, A. O. Clouse, and D. W. Cochran, *Chem. Commun.*, 961 (1970).
(7) E. Giovannini and P. Portmann, *Helv. Chim. Acta*, **31**, 1375 (1948).
(8) P. G. Gassman, B. W. Cue, Jr., and T.-Y. Luh, *J. Org. Chem.*, following paper in this issue.
(9) All 4- and 6-substituted oxindoles fall into the latter category; P. G. Gassman, B. W. Cue, Jr., and T.-Y. Luh, manuscript in preparation.
(10) For general references see G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972; J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972; E. Breitmaier and W. Voelter, "^{13}C NMR Spectroscopy", Verlage Chemie, Weinheim/Bergstr., Germany, 1974; L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley-Interscience, New York, N.Y. 1972; G. E. Maciel, "Topics in Carbon-13 NMR Spectroscopy", G. Levy, Ed., Wiley-Interscience, New York, N.Y., 1974.
(11) G. L. Nelson, G. C. Levy, and J. D. Cargiolic, *J. Am. Chem. Soc.*, **94**, 3089 (1972); D. K. Dalling, D. M. Grant, and E. G. Paul, *ibid.*, **95**, 3718 (1973); H. Eggert and C. Djerassi, *ibid.*, **95**, 3710 (1973); D. E. Dorman, M. Jautelat, and J. D. Roberts, *J. Org. Chem.*, **36**, 2757 (1971); D. R. Paulson, F. Y. N. Tang, G. F. Moran, A. S. Murray, B. P. Pelka, and E. M. Vesquez, *ibid.*, **40**, 184 (1975).
(12) Because of the size of these deviations, these seven experimental values were not incorporated into the statistical analysis used to establish the parameters listed in Table III. These values are marked by an "*a*" in Tables V and VI.
(13) Similarly, little correlation existed between the inductive effect parameters for the substituents and the position of the C-3 resonance. However, the C-3 methyl group was systematically shifted by substituents in both the 5 and 6 positions. A plot of σ vs. chemical shift gave a slope of −0.74 (r = 0.977).
(14) All melting points and boiling points are uncorrected. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. ^1H NMR spectra were obtained on Varian A-60-D, T-60, or HA-100 nuclear magnetic resonance spectrometers.
(15) T. A. Foglia and D. Swern, *J. Org. Chem.*, **33**, 4440 (1968).

A General Method for the Synthesis of Isatins

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A new method has been developed for the conversion of anilines into isatins. The general process utilizes our efficient method for the conversion of anilines into 3-methylthiooxindoles, which in turn serve as key intermediates. Oxidation of the methine carbon in the 3 position of the 3-methylthiooxindoles with *N*-chlorosuccinimide, followed by hydrolysis of the chlorinated intermediate, provides a simple route to isatins. This method is compatible with the presence of either strongly electron-withdrawing or strongly electron-donating substituents on the starting aniline. Yields range from good to excellent. An analysis of the ^{13}C NMR spectral properties of isatins is included.

Isatins have long been considered as valuable synthetic intermediates in the preparation of both pharmaceuticals and dyes. Thus, considerable effort has been devoted to developing useful synthetic approaches to this class of compounds. Unfortunately, the most widely utilized procedures required catalysis by strong acid,[2] a condition which imposed rather