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.

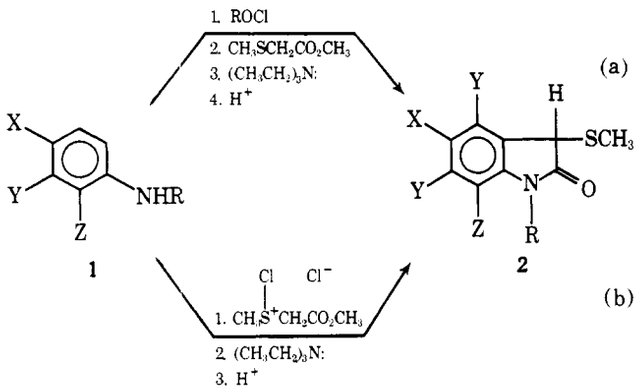
Isatins have long been considered as valuable synthetic intermediates in the preparation of both pharmaceuticals and dyes. Thus, considerable effort has been devoted to developing useful synthetic approaches to this class of compounds. Unfortunately, the most widely utilized procedures required catalysis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

Table I. Yields of Isatins from 3-Methylthiooxindoles (2)

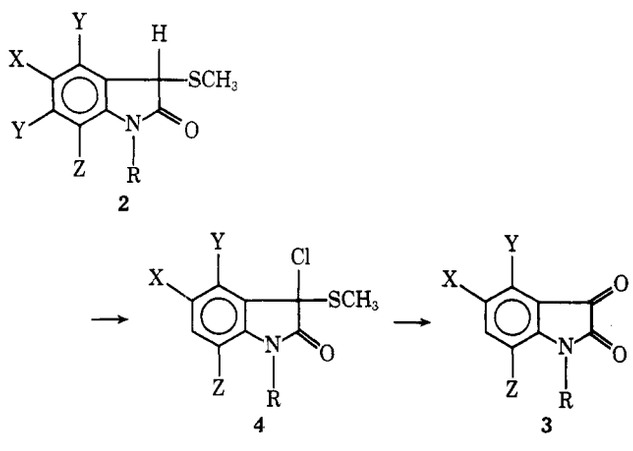
Registry no.	Oxindole X	Y	Z	R	% yield of isatin (3)	Mp, °C	Lit. mp, °C
40800-64-4	H	H	H	H	78	200–202	200–201[12]
40800-66-6	CH_3	H	H	H	74	185–187	187[13]
50461-38-6	OCH_3	H	H	H	81	202–204	201–202[14]
61394-53-4	Cl	H	H	H	75	249–252	247 dec[15]
61394-56-7	$CO_2C_2H_5$	H	H	H	56	206–207	
61394-58-9	CN	H	H	H	65	270–272 dec	
40800-69-9	NO_2	H	H	H	78	252–254 dec	254–255 dec[16]
61394-91-0	CF_3	H	H	H	73	191–193	246[17]
40800-70-2	H	NO_2	H	H	40	248–250 dec	
40800-67-7	H	H	CH_3	H	71	270–272	267[18]
40800-68-8	H	H	H	CH_3	61	132–134	134[19]

severe limitations on the breadth of the method. We now wish to report a new general method for the synthesis of isatins which can tolerate a broad spectrum of electron-withdrawing and electron-donating substituents.

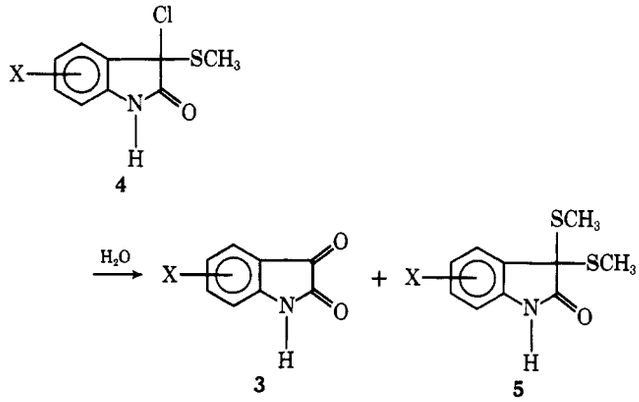
Recently, we reported two general methods for the conversion of anilines into 3-methylthiooxindoles.[3,4] As shown below in eq a and b, both of these processes permit a one-pot sequence of reactions for the conversion of 1 into 2.[5] In principle, 2 should serve as an excellent isatin precursor if suitably mild conditions could be developed for the oxidation of the 3 position. Previously, we had utilized the directive effect of a neighboring thio function for the conversion of a thiomethyl group into an aldehyde precursor via *N*-chlorosuccinimide oxidation.[6] We reasoned that *N*-chlorosuccinimide might be equally as efficient in replacing the methine hydrogen at the 3 position of 2 with chloride. Hydrolysis of the chloro sulfide would then provide the desired isatins.



In order to establish whether isatins of general formula 3 could be prepared from 2 via the chlorination of 2 to 4 and subsequent hydrolysis of 4, we subjected a series of 3-methylthiooxindoles[7] to the appropriate reaction conditions. A solution of 2 in carbon tetrachloride or methylene chloride[8] was treated with 1.1–1.3 equiv of *N*-chlorosuccinimide at room temperature for 1–12 h. Since they were relatively unstable, the resulting 3-chloro-3-methylthiooxindoles were dissolved in a minimum amount of tetrahydrofuran without purification and the solutions were added to a vigorously stirred slurry of 1 equiv of red mercuric oxide and 1 equiv of boron trifluoride etherate in 4:1 v/v water–tetrahydrofuran.[9,10] Workup involved extraction with chloroform and chromatography on silica gel to give the pure isatins. As shown in Table I, the yield varied from 40 to 81% for the 11 isatins listed. Substituents could be varied from strongly electron donating (methoxyl) to strongly electron withdrawing (ethoxycarbonyl, cyano, nitro). Substituents in the 4, 5, and 7 positions of 2 provided no complications. Even the N-substituted isatins were available through this process.



In an attempt to simplify the hydrolysis step, the conversion of 4 into 3 was attempted without the aid of the sulfur scavenging red mercuric oxide and the boron trifluoride etherate catalyst. When 4 was refluxed in 20% aqueous tetrahydrofuran for 4–18 h, it completely converted into a mixture of two products. The major product was the desired isatin, 3. Spectroscopic analysis (IR, NMR) combined with mass spectrometric and elemental analysis identified the minor product as the 3,3-dithioketal 5. The formation of this dithioketal



presumably resulted from the reaction of 3 or 4 with the methanethiol generated in the hydrolysis of 4. When X was hydrogen, we obtained a 68% yield of isatin and a 24% yield of its 3,3-dithioketal. For X equal to 5-methoxyl, 5-methyl, and 5-chloro the yields of isatins were 62, 63, and 68%, respectively, while the yields of the 3,3-dithioketals were 24, 14, and 12%, respectively. Unfortunately, column chromatography was necessary for the efficient separation of the isatin from the 3,3-dithioketal.

^{13}C Chemical Shifts of Isatins. Our detailed study of the ^{13}C chemical shifts of oxindoles and our determination of

Table II. ^{13}C Chemical Shifts for Substituted Isatins

Registry no.	Compd		2	3	3a	4	5	6	7	7a	Substituent
91-56-5	Isatin	Obsd	159.5	184.6	117.9	138.5	124.8	122.9	112.4	150.9	
608-05-9	5-CH_3	Obsd	159.5	184.6	117.8	138.8	132.0	124.8	112.1	148.5	20.1
		Calcd			117.8	139.2	133.9	123.6	112.1	148.4	
39755-95-8	5-OCH_3	Obsd	159.6	184.1	118.1	124.9	155.4	108.8	113.3	144.7	55.8
		Calcd			118.3	123.8	157.2	108.2	113.6	144.1	
17630-76-1	5-Cl	Obsd	159.1	183.4	119.1	137.3	126.9	124.2	113.9	149.2	
		Calcd			119.2	138.5	129.5	122.9	113.7	149.8	
25128-38-5	5-$CO_2C_2H_5$	Obsd	159.4	183.4	117.8	139.0	124.6	125.0	112.3	154.1	164.6, 60.9, 14.2
		Calcd			118.0	139.8	126.5	124.2	112.3	155.2	
345-32-4	5-CF_3	Obsd	159.9	183.2	118.2	134.8[a]	123.3[b]	121.3[c]	112.9	153.6	124.0[d]
		Calcd			118.2	136.3	115.8	120.7	112.7	154.1	
61394-92-1	5-CN	Obsd	159.4	182.6	118.6[e]	141.7	104.9	128.5	113.1	153.7	118.3[e]
		Calcd			119.0	142.5	107.2	126.9	113.5	155.4	
611-09-6	5-NO_2	Obsd	159.9	182.4	118.2	133.2	142.7	119.6	112.6	155.3	
		Calcd			118.7	135.0	145.1	119.4	113.2	157.0	
1127-59-9	7-CH_3	Obsd	159.6	184.3	117.3	139.2	122.3[e]	121.6[e]	121.1	149.0	15.9
		Calcd			117.8	136.0	124.7	123.8	121.8	151.8	

[a] J_{CCCF} = 3.4 Hz. [b] J_{CCF} = 33 Hz. [c] J_{CCCF} = 3.6 Hz. [d] J_{CF} = 272 Hz. [e] Values may be interchanged.

chemical shift substituent constants for such systems[20] prompted us to provide similar data for the isatins prepared as part of this study. Table II lists the isatins prepared and the positions of their carbon resonances. In arriving at the calculated values, we used the shift parameters which we had established for oxindoles. In the case of the 5-trifluoromethylisatin, we used the literature value for the trifluoromethyl group.[21,22] In general, the values calculated on the basis of these shift parameters agreed very well with the observed values.

In summary, we have developed a relatively simple, good yield method for the preparation of isatins from anilines via oxindoles. Since our published methods for the conversion of anilines into oxindoles give high yields, the overall yields of the isatins listed in Table I from the appropriate ortho, meta, or para-substituted anilines vary from 25 to 66%.

Experimental Section[23]

3-Methylthiooxindoles. 3-Methylthiooxindole, 5-methyl-3-methylthiooxindole, 5-methoxy-3-methylthiooxindole, 5-nitro-3-methylthiooxindole, 4-nitro-3-methylthiooxindole, 7-methyl-3-methylthiooxindole, and 1-methyl-3-methylthiooxindole were prepared according to the published procedures.[3,4] In all cases the physical constants and spectroscopic properties agreed well with those described in the literature.

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 pure product (9.10 g, 77.5%): mp 171–173 °C (recrystallized from methanol); IR (KBr) 3100 (NH) and 1705 cm^{-1} (C=O); NMR (Me_2SO-d_6) τ −1.40 (bs, 1 H, NH), 2.70 (m, 2 H, H_4 and H_6), 3.20 (d, 1 H, $J_{6,7}$ = 8 Hz, H_7), 5.50 (s, 1 H, H_3), and 8.05 (s, 3 H, 3-SCH_3).

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.

3-Methylthio-5-trifluoromethyloxindole. Utilizing the general procedure described in the literature,[3] *p*-trifluoromethylaniline was converted to 3-methylthio-5-trifluoromethyloxindole on a 0.0124-mol scale. Recrystallization of the product from cyclohexane gave pure 3-methylthio-5-trifluoromethyloxindole (2.32 g, 76%): mp 139.0–140.5 °C (recrystallized from cyclohexane); IR (KBr) 3200 (NH) and 1730 cm^{-1} (C=O); NMR ($CDCl_3$) τ 0.57 (bs, 1 H, NH), 2.37 (d, 1 H, $J_{4,6}$ = 1 Hz, H_4), 2.47 (d of d, $J_{4,6}$ = 1, $J_{6,7}$ = 8 Hz, H_6), 3.00 (d, 1 H, $J_{6,7}$ = 8 Hz), 5.67 (s, 1 H, H_3), and 7.90 (s, 3 H, 3-SCH_3).

Anal. Calcd for $C_{10}H_8F_3NOS$: C, 48.58; H, 3.26; N, 5.67. Found: C, 48.48; H, 3.29; N, 5.58.

5-Ethoxycarbonyl-3-methylthiooxindole. On a 0.05-mol scale ethyl *p*-aminobenzoate was converted to 5-ethoxycarbonyl-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 benzene); IR (KBr) 3240 (NH), 1735 (C=O), and 1695 cm^{-1} (C=O); NMR ($CDCl_3$) τ 0.20 (1 H, bs, NH), 2.00 (d, 1 H, $J_{4,6}$ < 1 Hz, H_4), 2.10 (d of d, 1 H, $J_{4,6}$ < 1, $J_{6,7}$ = 8 Hz, H_6), 3.05 (d, 1 H, $J_{6,7}$ = 8 Hz, H_7), 5.50 (q, 2 H, $CO_2CH_2CH_3$), 5.70 (s, 1 H, H_3), 8.00 (s, 3 H, SCH_3), 8.60 (t, 3 H, $CO_2CH_2CH_3$).

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 0.0466-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) τ −1.00 (bs, 1 H, NH), 2.27 (d of d, 1 H, $J_{4,6}$ = 2, $J_{6,7}$ = 9 Hz, H_6), 2.31 (d, 1 H, $J_{4,6}$ = 2 Hz, H_4), 3.00 (d, 1 H, $J_{6,7}$ = 9 Hz, H_7), 5.34 (s, 1 H, H_3), 7.97 (s, 3 H, SCH_3).

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.

Isatin. A solution of 3-methylthiooxindole (1.70 g, 0.0095 mol) and *N*-chlorosuccinimide (1.34 g, 0.01 mol) in 100 mL of carbon tetrachloride was stirred at room temperature for 1 h, the precipitate of succinimide was removed by filtration, and the filtrate was evaporated. The residue, which was obtained, was dissolved in a minimum of tetrahydrofuran and added to a vigorously stirred slurry of red mercuric oxide powder (2.17 g, 0.01 mol) and boron trifluoride etherate (1.43 g, 0.01 mol) in 20% aqueous tetrahydrofuran (70 mL). After stirring at room temperature for 1 h, 200 mL of ether was added, the reaction mixture was filtered through a pad of Celite, the organic phase of the filtrate was separated, dried over anhydrous magnesium sulfate, and filtered, and this filtrate was evaporated to give isatin (1.07 g, 78%), mp 200–202 °C (lit.[12] mp 200–201 °C), after recrystallization from benzene.

5-Methylisatin. A solution of 5-methyl-3-methylthiooxindole (1.00 g, 0.0052 mol) and *N*-chlorosuccinimide (700 mg, 0.0053 mol) in carbon tetrachloride (100 mL) was stirred at room temperature for 1 h. The precipitate was removed by filtration and the filtrate was evaporated to give the crude 3-chloro-5-methyl-3-methylthiooxindole, which was dissolved in tetrahydrofuran (20 mL) and added to a vigorously stirred slurry of red mercuric oxide (1.13 g, 0.0052 mol) and boron trifluoride etherate (745 mg, 0.0052 mol) in 70 mL of 20% aqueous tetrahydrofuran. After stirring at room temperature for 2 h, the reaction mixture was filtered through a Celite pad, and the filtrate was extracted with two 100-mL portions of chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and filtered, and the filtrate was evaporated. The residue was chromatographed on silica gel. Elution with chloroform gave 5-methylisatin (610 mg, 0.0038 mol, 74%), mp 185–187 °C (recrystallized from ethanol), as red needles (lit.[13] mp 187 °C).

5-Methoxyisatin. A solution of 5-methoxy-3-methylthiooxindole (420 mg, 2 mmol) and *N*-chlorosuccinimide (270 mg, 2 mmol) in carbon tetrachloride (75 mL) was stirred at room temperature for 1 h. The precipitate was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in tetrahydrofuran (10 mL) and added to a vigorously stirred slurry of red mercuric oxide (435 mg, 2 mmol) and boron trifluoride etherate (290 mg, 2 mmol) in

aqueous 20% tetrahydrofuran (40 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was filtered through a pad of Celite and the filtrate was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel to give 5-methoxyisatin (287 mg, 81%), mp 202–204 °C (recrystallized from benzene) (lit.[14] mp 201–203 °C).

5-Chloroisatin. A solution of 5-chloro-3-methylthiooxindole (1.35 g, 6.3 mmol) and *N*-chlorosuccinimide (950 mg, 7 mmol) in carbon tetrachloride (100 mL) was refluxed for 1 h and cooled, and the precipitate was removed by filtration. The filtrate was concentrated to dryness. The residue was dissolved in 25 mL of tetrahydrofuran and added rapidly to a vigorously stirred slurry of red mercuric oxide (1.37 g, 6.3 mmol) and boron trifluoride etherate (900 mg, 6.3 mmol) in 100 mL of 20% aqueous tetrahydrofuran. After stirring for 3 h, the solution was filtered through a pad of Celite and the filtrate was extracted with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and filtered and the filtrates were concentrated to give a red solid which was chromatographed on silica gel with chloroform as the eluent. There was obtained 5-chloroisatin (850 mg, 75%), mp 248–251 °C (recrystallized from ethanol) (lit.[15] mp 247 °C).

5-Ethoxycarbonylisatin. A solution of 5-ethoxycarbonyl-3-methylthiooxindole (1.50 g, 7 mmol) and *N*-chlorosuccinimide (1.25 g, 9.3 mmol) in methylene chloride (150 mL) was stirred at room temperature for 24 h. The solvent was removed in vacuo and the residue was dissolved in tetrahydrofuran and added to a vigorously stirred slurry of red mercuric oxide (1.53 g, 7 mmol) and boron trifluoride etherate (1.00 g, 7 mmol) in 100 mL of 50% aqueous tetrahydrofuran. After stirring at room temperature for 1 h, the red solution was extracted with chloroform. The organic extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated and the residue was chromatographed on silica gel. Elution with chloroform gave 5-ethoxycarbonylisatin (860 mg, 56%) as a yellow solid: mp 205–207 °C (recrystallized from ether); IR (KBr) 3265 (NH), 1765 (ester C=O), 1750 (C=O), and 1700 cm^{-1} (amide C=O); NMR (Me_2SO-d_6) τ −1.00 (1 H, bs, NH), 1.80 (d of d, 1 H, $J_{4,6}$ = 2, $J_{6,7}$ = 9 Hz, H_6), 1.90 (d, 1 H, $J_{4,6}$ = 2 Hz, H_4), 3.20 (d, 1 H, $J_{6,7}$ = 9 Hz, H_7), 5.65 (q, 2 H, $CO_2C\mathbf{H}_2CH_3$), and 8.60 (t, 3 H, $CO_2CH_2C\mathbf{H}_3$); mass spectrum *m/e* obsd 219.0534 (calcd, 219.0531).

Anal. Calcd for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.23; H, 4.18; N, 6.51.

5-Cyanoisatin. A solution of 5-cyano-3-methylthiooxindole (950 mg, 4.66 mmol) and *N*-chlorosuccinimide (800 mg, 5.95 mmol) in 100 mL of methylene chloride was stirred at room temperature for 24 h. The solvent was removed in vacuo and the residue, which was dissolved in a minimum of tetrahydrofuran, was added to a vigorously stirred slurry of red mercuric oxide (1.00 g, 4.7 mmol) and boron trifluoride etherate (670 mg, 4.7 mmol) in 100 mL of 50% aqueous tetrahydrofuran. After 2 h, the reaction mixture was filtered through a pad of Celite. The pad was washed with three 100-mL portions of chloroform. The organic layer was separated, dried over anhydrous magnesium sulfate, and filtered, and the filtrate was evaporated. The residue was chromatographed on silica gel. Elution with chloroform–ethanol (9:1 v/v) gave 5-cyanoisatin as an orange solid (525 mg, 65%): mp 270–272 °C dec; IR (KBr) 3100 (NH), 2220 (C≡N), 1730 (C=O), and 1710 cm^{-1} (C=O); NMR (Me_2SO-d_6) τ −1.30 (1 H, bs, NH), 2.00 (d of d, 1 H, $J_{4,6}$ = 2, $J_{6,7}$ = 8.5 Hz, H_6), 2.10 (d, 1 H, $J_{4,6}$ = 2 Hz, H_4), and 2.90 (d, 1 H, $J_{6,7}$ = 8.5 Hz, H_7); mass spectrum *m/e* obsd 172.0238 (calcd, 172.0272).

Anal. Calcd for $C_9H_4N_2O_2$: C, 62.80; H, 2.34; N, 16.28. Found: C, 62.37; H, 2.41; N, 16.07.

5-Nitroisatin. A solution of 3-methylthio-5-nitrooxindole (900 mg, 4 mmol) and *N*-chlorosuccinimide (600 mg, 4.5 mmol) in 50 mL of chloroform was stirred at room temperature for 1 h and then evaporated to dryness in vacuo. The residue was dissolved in 15 mL of tetrahydrofuran and added to vigorously stirred slurry of red mercuric oxide powder (900 mg, 4.3 mmol) and boron trifluoride etherate (600 mg, 4.3 mmol) in 100 mL of 20% aqueous tetrahydrofuran. After stirring at room temperature for 2 h, the reaction mixture was extracted with three 100-mL portions of chloroform. The chloroform layer was dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was recrystallized from 95% ethanol to give 5-nitroisatin (600 mg, 78%), mp 252–254 °C (lit.[16] mp 254–256 °C).

5-Trifluoromethylisatin. A solution of 3-methylthio-5-trifluoromethyloxindole (1.40 g, 0.0057 mol) and *N*-chlorosuccinimide (800 mg, 0.006 mol) in 100 mL of carbon tetrachloride was stirred at room temperature for 1 h. The precipitated succinimide was removed by filtration, and the filtrate was evaporated to give a yellow solid which was dissolved in 30 ml of tetrahydrofuran and added to a vigorously stirred slurry of red mercuric oxide (1.30 g, 5.8 mmol) and boron trifluoride etherate (860 mg, 5.8 mmol) in 100 ml of 20% aqueous tetrahydrofuran. The resulting mixture was stirred for 2 h at room temperature and filtered through a pad of Celite, and the filtrate was extracted with four 100-mL portions of methylene chloride. The methylene chloride extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to give a residue which was chromatographed on silica gel. Elution with methylene chloride gave 5-trifluoromethylisatin as yellow needles (860 mg, 73%): mp 191–193 °C (recrystallized from benzene) (lit.[17] mp 246 °C); IR (KBr) 3200 (NH), 1750 (C=O), 1710 cm^{-1} (C=O); NMR (Me_2SO-d_6), τ −1.20 (bs, 1 H, NH), 2.15 (d, 1 H, H_6), 2.30 (s, 1 H, H_4), 2.90 (d, 1 H, $J_{6,7}$ = 8 Hz, H_7); mass spectrum *m/e* obsd 215.0196 (calcd, 215.0194).

Anal. Calcd for $C_9H_4F_3NO_2$: C, 50.24; H, 1.87; N, 6.51. Found: C, 50.12; H, 1.92; N, 6.43.

A phenylhydrazone derivative of 5-trifluoromethylisatin was prepared: mp 263–265 °C; mass spectrum *m/e* obsd 305.0767 (calcd for $C_{15}H_{10}F_3N_3O$, 305.0776).

4-Nitroisatin. A solution of 3-methylthio-4-nitrooxindole (1.58 g, 7 mmol) and *N*-chlorosuccinimide (1.20 g, 9 mmol) in 100 mL of methylene chloride was stirred at room temperature for 48 h. The solvent was removed in vacuo. The residue was dissolved in 25 mL of tetrahydrofuran and added rapidly to a vigorously stirred slurry of red mercuric oxide (1.52 g, 7 mmol) and boron trifluoride etherate (1.00 g, 7 mmol) in 100 mL of 50% aqueous tetrahydrofuran. After stirring for 3 h, the solution was filtered through a Celite pad which was then washed with copious amounts of chloroform. The organic layer was separated, dried over anhydrous magnesium sulfate, and filtered and the filtrate was evaporated. The residue was chromatographed on silica gel. Elution with chloroform–ethanol (9:1) gave 4-nitroisatin (535 mg, 40%): mp 248–250 °C dec (recrystallized from ethanol); IR (KBr) 3200 (NH), 1750 (C=O), 1710 (C=O), 1520 (NO_2), and 1350 cm^{-1} (NO_2); NMR (Me_2SO-d_6) τ −1.30 (1 H, bs, NH), 2.20–2.80 (m, 3 H, aryl H).

Anal. Calcd for $C_8H_4N_2O_4$: C, 50.00; H, 2.10; N, 14.58. Found: C, 49.93; H, 2.27; N, 14.46.

7-Methylisatin. A solution of 7-methyl-3-methylthiooxindole (1 g, 0.0052 mol) and *N*-chlorosuccinimide (0.7 g, 0.0052 mol) in chloroform (100 mL) was stirred at room temperature for 1 h. The solution was evaporated and the residue was dissolved in a minimum amount of tetrahydrofuran (ca. 10 mL) and added to a vigorously stirred slurry of red mercuric oxide (1.13 g, 0.0052 mol) and boron trifluoride etherate (0.75 g, 0.0054 mol) in 50 mL of 20% aqueous tetrahydrofuran. After stirring at room temperature for 1 h, 150 mL of ether was added, the reaction mixture was filtered through a pad of Celite, the organic phase of the filtrate was separated, dried over anhydrous magnesium sulfate, and filtered, and the solvent was evaporated. The red residue was recrystallized from methanol to give 0.6 g (71%) of 7-methylisatin, mp 267–269 °C (lit.[18] mp 267 °C).

1-Methylisatin. A solution of 1-methyl-3-methylthiooxindole (1.07 g, 5.56 mmol) and *N*-chlorosuccinimide (800 mg, 6.0 mmol) in 75 ml of carbon tetrachloride was stirred at room temperature for 1 h and filtered, and the filtrate was evaporated to give a residue. The residue was dissolved in 20 mL of tetrahydrofuran and rapidly added to a vigorously stirred slurry of red mercuric oxide (1.20 g, 5.56 mmol) and boron trifluoride etherate (790 mg, 5.56 mmol) in 75 mL of 20% aqueous tetrahydrofuran. After stirring at room temperature for 1 h, the reaction mixture was filtered through a Celite pad, and the filtrate was extracted with ether. Evaporation of the ether layer gave a residue which was purified by chromatography on silica gel. Elution with methylene chloride gave 1-methylisatin (550 mg, 61%): mp 131–133 °C (lit.[17] mp 130–133 °C); NMR ($CDCl_3$) τ 2.23–2.60 (m, 2 H, aromatic H), 2.71–2.90 (m, 2 H, aromatic H), and 6.70 (s, 3 H, NCH_3).

Isatin and 3,3-Dimethylthiooxindole. A solution of 3-methylthiooxindole (1.79 g, 0.01 mol) and *N*-chlorosuccinimide (1.45 g, 0.011 mol) in 100 mL of carbon tetrachloride was stirred at room temperature for 1 h. The precipitated succinimide was removed by filtration and the filtrate was evaporated to dryness on a rotary evaporator. The residue was boiled in 100 mL of 20% aqueous tetrahydrofuran for 6 h and cooled, and the solution was extracted with chloroform. The chloroform extract was dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel. Elution with chloroform gave 3,3-dimethylthiooxindole (560 mg, 24%): mp 163–164 °C (recrystallized from benzene); IR (KBr) 3180 (NH) and 1700 cm^{-1} (C=O); NMR ($CDCl_3$) τ 0.98 (bs, 1 H, NH), 2.87 (m, 4 H, aryl H), and 7.83 (s, 6 H, SCH_3).

Anal. Calcd for $C_{10}H_{11}NOS_2$: C, 53.30; H, 4.92; N, 6.22. Found: C, 53.00; H, 5.01; N, 6.12.

Further elution with chloroform gave isatin (1.00 g, 68%), mp 200–202 °C (recrystallized from benzene) (lit.[12] mp 200–201 °C).

5-Methoxyisatin and 3,3-Dimethylthio-5-methoxyoxindole. A suspension of 5-methoxy-3-methylthiooxindole (1.00 g, 4.8 mmol) and *N*-chlorosuccinimide (650 mg, 4.8 mmol) was refluxed for 1 h in 100 mL of carbon tetrachloride. The cooled solution was filtered and the filtrate was evaporated to give a residue which was refluxed in 100 mL of 20% aqueous tetrahydrofuran for 18 h. After cooling, the dark solution was extracted with chloroform. The chloroform layer was separated, dried over anhydrous magnesium sulfate, and filtered and the filtrate was evaporated. The residue was chromatographed on silica gel. Elution with chloroform gave 3,3-dimethylthio-5-methoxyoxindole (300 mg, 24%): mp 167–169 °C (recrystallized from benzene); IR (KBr) 3200 (NH) and 1705 cm^{-1} (C=O); NMR ($CDCl_3$) τ 0.65 (bs, 1 H, NH), 3.10 (m, 2 H, H_6 and H_7), 3.16 (d, 1 H, $J_{4,6}$ = 2 Hz, H_4), 6.20 (s, 3 H, OCH_3) and 7.80 (s, 6 H, SCH_3); mass spectrum *m/e* obsd 255.0382 (calcd, 255.0387).

Anal. Calcd for $C_{11}H_{13}NO_2S_2$: C, 51.74; H, 5.13; N, 5.49. Found: C, 51.88; H, 5.19; N, 5.42.

Further elution with chloroform gave 5-methoxyisatin (525 mg, 62%), mp 202–204 °C (lit.[14] mp 201–202 °C).

5-Methylisatin and 3,3-Dimethylthio-5-methyloxindole. A solution of 5-methyl-3-methylthiooxindole (1.00 g, 5.2 mmol) and *N*-chlorosuccinimide (700 mg, 5.5 mmol) in 100 mL of carbon tetrachloride was stirred at room temperature for 1 h and filtered to remove the succinimide, and the solvent was removed in vacuo. The residue was dissolved in 100 mL of 20% aqueous tetrahydrofuran and refluxed for 5 h. After cooling, the reaction mixture was extracted with three 100-mL portions of chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and filtered, and the filtrate was evaporated to give a residue which was chromatographed on silica gel. Elution with chloroform gave 3,3-dimethylthio-5-methyloxindole (172 mg, 14%): mp 188–189 °C (recrystallized from methanol); IR (KBr) 3170 (NH) and 1705 cm^{-1} (C=O); NMR ($CDCl_3$) τ 0.60 (1 H, bs, NH), 2.80–3.20 (3 H, m, aryl H), 7.75 (3 H, s, 5-CH_3), and 8.00 (6 H, s, SCH_3); mass spectrum *m/e* obsd 239.0460 (calcd, 239.0438).

Further elution with chloroform gave 5-methylisatin (525 mg, 63%), mp 185–187 °C (recrystallized from 95% ethanol) (lit.[13] mp 187°C).

5-Chloro-3,3-dimethylthiooxindole and 5-Chloroisatin. A solution of 5-chloro-3-methylthiooxindole (1.35 g, 6.3 mmol) and *N*-chlorosuccinimide (935 mg, 7.0 mmol) in 100 mL of carbon tetrachloride was refluxed for 1 h and cooled, and the precipitated succinimide was removed by filtration. The filtrate was evaporated and the residue was dissolved in 100 mL of 20% aqueous tetrahydrofuran and refluxed for 18 h. After cooling, the reaction mixture was extracted with two 100-mL portions of chloroform. The organic solution was dried over anhydrous magnesium sulfate and filtered, and the filtrate was evaporated. The residual solid was chromatographed on silica gel. Elution with methylene chloride gave 5-chloro-3,3-dimethylthiooxindole (200 mg, 12%): mp 222–224 °C (recrystallized from ethanol); IR (KBr) 3150 (NH) and 1700 cm^{-1} (C=O); NMR ($CDCl_3$) τ −0.25 (1 H, bs, NH), 2.75 (1 H, d, $J_{6,7}$ = 8 Hz, H_7), 2.80 (1 H, m, H_6), 3.10 (m, 1 H, H_4), 7.83 (s, 6 H, SCH_3); mass spectrum *m/e* obsd 258.9897 (calcd, 258.9892).

Anal. Calcd for $C_{10}H_{10}NOClS_2$: C, 46.23; H, 3.88; N, 5.39. Found: C, 46.44; H, 4.02; N, 5.28.

Further elution with methylene chloride gave 5-chloroisatin (770 mg, 68%), mp 249–252 °C (recrystallized from ethanol) (lit.[15] mp 247 °C).

^{13}C NMR Spectra. The ^{13}C NMR spectral measurements were made on a Varian CFT-20 nuclear magnetic resonance spectrometer with dimethyl sulfoxide-d_6 as solvent. Chemical shifts are listed in parts per million downfield from tetramethylsilane. Spectra were noise decoupled. In those instances where additional information was needed for specific assignments, off-resonance or gated decoupling was utilized.

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Registry No.—*p*-Chloroaniline, 106-47-8; *p*-trifluoromethylaniline, 455-14-1; ethyl *p*-aminobenzoate, 94-09-7; *p*-cyanoaniline, 873-74-5; *N*-chlorosuccinimide, 128-09-6; 5-trifluoromethylisatin phenylhydrazone derivative, 61446-52-4; 4-nitroisatin, 61394-93-2; 1-methylisatin, 2058-74-4; 3,3-dimethylthiooxindole, 35524-65-3; 3,3-dimethylthio-5-methoxyoxindole, 61394-94-3; 3,3-dimethylthio-5-methyloxindole, 61394-95-4; 5-chloro-3,3-dimethylthiooxindole, 61394-96-5.

References and Notes

(1) National Institutes of Health Postdoctoral Fellow, 1974–1975.
(2) The most commonly quoted methods for the preparation of isatins are those of Sandmeyer [T. Sandmeyer, *Helv. Chim. Acta*, **2**, 234 (1919)] and of Stollé [R. Stollé, *J. Prakt. Chem.*, **105**, 137 (1922)]. The Sandmeyer approach involves treatment of an aniline with trichloroacetaldehyde and then with hydroxylamine in base. The resulting isonitrosoacetanilide is then heated in sulfuric acid. The Stollé method involves initial treatment of an aniline with oxalyl chloride followed by Friedel–Crafts type acylation in the presence of a strong Lewis acid. Since both methods require electrophilic attack on the aromatic ring, the presence of strong electron-withdrawing groups tends to inhibit the reaction. For a recent review of isatin chemistry see F. D. Popp, *Adv. Heterocycl. Chem.*, **18**, 1 (1975).
(3) P. G. Gassman and T. J. van Bergen, *J. Am. Chem. Soc.*, **96**, 5508 (1974).
(4) P. G. Gassman, G. Gruetzmacher, and T. J. van Bergen, *J. Am. Chem. Soc.*, **96**, 5512 (1974).
(5) In the case of meta substituents (1, Y ≠ H), a mixture of 4- and 6-substituted oxindoles is often formed. In general, the 4:6 ratio of the products is a function of the electronic nature of the substituents. Electron-withdrawing substituents tend to direct the site of attack so that 4-substituted oxindoles predominate. Electron-donating substituents tend to reside primarily on the 6 position of the resulting oxindoles (P. G. Gassman, B. W. Cue, Jr., and T.-Y. Luh, unpublished studies).
(6) P. G. Gassman and H. R. Drewes, *J. Am. Chem. Soc.*, **96**, 3002 (1974); P. G. Gassman and D. R. Amick, *Tetrahedron Lett.*, 3463 (1974).
(7) Some of the 3-methylthiooxindoles utilized in this study are previously unreported. These new oxindoles were prepared via the previously mentioned literature procedures.[3,4]
(8) The choice of solvent was determined by the relative solubilities of the appropriate oxindole.
(9) Hydrolysis could be accomplished without the aid of mercuric oxide and boron trifluoride etherate. However, yields were lower under simple aqueous conditions owing to the competitive formation of the dithioketal of the isatin (see below).
(10) The hydrolysis procedure described is a modification of the Vedejs–Fuchs[11] procedure as previously described by us.[6]
(11) E. Vedejs and P. L. Fuchs, *J. Org. Chem.*, **36**, 366 (1971).
(12) T. Sandmeyer, *Helv. Chim. Acta*, **2**, 234 (1919).
(13) P. J. Meyer, *Chem. Ber.*, **16**, 2261 (1883).
(14) E. Giovannini and P. Portmann, *Helv. Chim. Acta*, **31**, 1381 (1948).
(15) G. Heller, *Chem. Ber.*, **43**, 2892 (1910).
(16) W. C. Sumpter and W. F. Jones, *J. Am. Chem. Soc.*, **65**, 1802 (1943).
(17) P. M. Maginnity and C. A. Gaulin, *J. Am. Chem. Soc.*, **73**, 3579 (1951). The discrepancy between our melting point and that reported in the literature is of concern. All spectroscopic data were consistent with our assigned structure. In an attempt to resolve this inconsistency, we attempted to repeat the preparation described in the literature. However, we were unable to reproduce the results described by Maginnity and Gaulin for the preparation of 5-trifluoromethylisatin. Since our sample had been purified by recrystallization from benzene, while that described in the literature had been recrystallized from acetic acid, we thought that the different melting points might be associated with different crystalline forms. However, recrystallization of our sample from acetic acid failed to change the melting point.
(18) R. Bauer, *Chem. Ber.*, **42**, 2111 (1909).
(19) W. Borsche and R. Meyer, *Chem. Ber.*, **54**, 2844 (1921).
(20) P. G. Gassman, D. P. Gilbert, and T.-Y. Luh, *J. Org. Chem.*, preceding paper in this issue.
(21) 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", Verlag 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.
(22) 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).
(23) Melting points and boiling points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 137 infrared spectrophotometer. NMR spectra were obtained on a Varian associates T-60 or A-60-D nuclear magnetic resonance spectrometer. Microanalyses were performed by the Scandinavian Microanalytical Laboratories, Herlev, Denmark.