followed by acidification at 0°. At higher temperature, the acid is readily cyclodehydrated. Recrystallization from cold acetone–hexane yielded white needles: mp 273°; ν_{max}^{KBr} 2650 (bonded OH), 1690 (COOH) cm^{-1}.

Anal. Calcd for $C_{12}H_8O_4$: C, 66.64; H, 3.72. Found: C, 66.42; H, 3.86.

Oxidation of Acenaphthene. By Potassium Ferricyanide.—Acenaphthene (308 mg, 2 mmol) was oxidized with 30 g of potassium ferricyanide and 10 g of potassium hydroxide in 160 ml of water in the same manner as described previously. After 5 days, the unreacted acenaphthene was removed by filtration and the filtrate acidified. Extraction with ether followed by evaporation yielded 46 mg (23%) of 1,8-naphthalic acid anhydride, mp 274–276°, mass spectrum *m/e* 198. The low yield of the oxidation product was probably due to the insolubility of acenaphthene in water.

Registry No.—**2**, 25055-69-0; **3**, 25055-70-3; **4**, 25055-71-4; **5**, 25055-72-5; **6**, 81-84-5; **7**, 518-05-8.

Reaction of Indole Derivatives with Bromine. Substitution, Oxidation, and Dimerization

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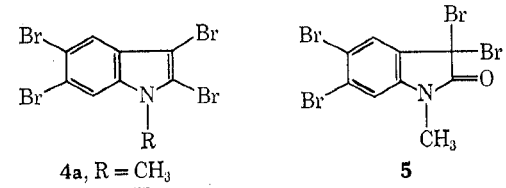
Bromination of 1-methylindole (**1**), 1-methylindole-3-carboxaldehyde (**2**), and ethyl 1-methylindole-3-glyoxylate (**3**), in some solvents and with different mole ratios of bromine to indole, was investigated. Bromination of **1** in acetic acid, when 5:1 mol ratio of reactants was used, gave 2,3,5,6-tetrabromo-1-methylindole (**4a**) and, under somewhat different conditions, 2′,3,5,5′,6,6′-hexabromo-1,1′-dimethyl-2,3′-diindolyl (**6a**); in both cases 3,3,5,6-tetrabromo-1-methyloxindole (**5**) was also isolated. 5-Bromo-1-methylindole-3-carboxaldehyde (**12a**), compound **4a**, and 3,3,5-tribromo-1-methyloxindole (**10a**) were obtained by bromination of **2** (3:1 mol ratio) in acetic acid. Bromination of **3** in acetic anhydride gave mixture of 5- and 6-bromo derivatives (**14a** and **14b**) when a 2.5:1 mol ratio was used, whereas with a 4:1 mol ratio the 5,6-dibromo derivative (**14c**) was isolated in excellent yield. The structure of the compounds was proven on the basis of ir spectra and chemical evidence.

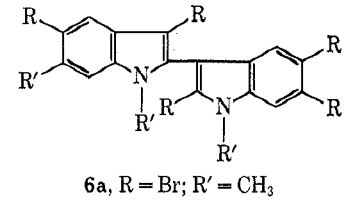
In the course of our work on the chemistry of indoles we have extensively investigated the nitration[1] and, more recently, the bromination[2] of indole derivatives. Although the action of brominating agents upon indoles in different media has been investigated to some extent,[3] comparatively little attention has been devoted to the reaction of indoles with bromine. In a previous paper on this subject we examined the reactions of indole-3-carboxaldehyde, 2-methylindole-3-carboxaldehyde, and ethyl indole-3-glyoxylate with bromine in acetic acid; it was seen that 5 and 6 positions are the normal sites of electrophilic substitution when electron-attracting substituents are present in the β position.[2] In order to extend our knowledge on this topic we have now investigated the bromination of 1-methylindole (**1**), 1-methylindole-3-carboxaldehyde (**2**), and ethyl 1-methylindole-3-glyoxylate (**3**) with bromine.

The bromination of **1**, when carried out in acetic acid with an equimolar amount of bromine, did not afford definite products; with a 5:1 mol ratio of reagent to substrate the course of the reaction was dependent on the temperature, and it was possible to isolate satisfactory amounts of solid compounds. When bromine was added to an ice-cold acetic solution of **1**, 1-methyl-2,3,5,6-tetrabromoindole (**4a**) (53% yield) and 1-methyl-3,3,5,6-tetrabromooxindole (**5**) (from the acetic mother liquor; 8.5% yield) were formed. When the reaction was carried out at room temperature, a product was isolated (42.8% yield) for which, on the basis of analytical data, molecular weight determination, and evidence outlined below, we suggest the dimeric structure **6a**; also in this case, **5** was produced (8.5% yield). The proposed structure **6a** was confirmed by its preparation, in 78% yield, through bromination of the dimer **6b**; the latter was prepared both by treating 1-methylindole (**1**) with dioxane–bromine complex in THF solution according to Kunori,[4] and by methylation of 2,3′-diindolyl (**6c**).[5] The latter synthesis of **6b**

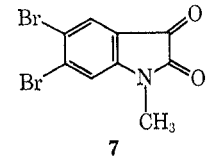


4a, R = CH_3
b, R = H

5



6a, R = Br; R′ = CH_3
b, R = H; R′ = CH_3
c, R = R′ = H



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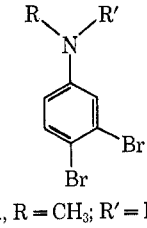
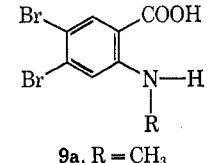


8a, R = CH_3; R′ = H
b, R = CH_3; R′ = tosyl
c, R = H; R′ = tosyl



9a, R = CH_3
b, R = H

(1) (a) G. Berti, A. Da Settimo, and O. Livi, *Tetrahedron*, **20**, 1397 (1964); (b) A. Da Settimo and M. F. Saettone, *ibid.*, **21**, 823 (1965); (c) A. Da Settimo and M. F. Saettone, *ibid.*, **21**, 1923 (1965).

(2) A. Da Settimo, M. F. Saettone, E. Nannipieri, and P. L. Barili, *Gazz. Chim. Ital.*, **97**, 1304 (1967).

(3) See, *e.g.*, (a) W. B. Lawson, A. Patchornik, and B. Witkop, *J. Amer. Chem. Soc.*, **82**, 5918 (1960); (b) R. L. Hinman and C. P. Bauman, *J. Org. Chem.*, **29**, 1206 (1964).

(4) M. Kunori, *Nippon Kagaku Zasshi*, **83**, 836 (1962); *Chem. Abstr*, **59**, 1573c (1963).

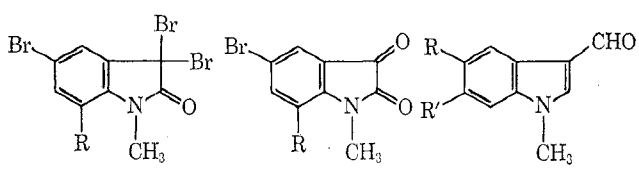
(5) T. E. Young, *J. Org. Chem.*, **27**, 507 (1962).

had the purpose to confirm the previously suggested structure.[4] Compound **6a** gave a negative Ehrlich reaction (both the 2 positions are substituted) and its chromic oxidation gave as the only solid compound, 5,6-dibromo-1-methylisatin (**7**). Unfortunately **7** was isolated in too low yield (less than 50%) to make sure that in both benzene rings the bromine atoms are in the 5,6 positions. On the other hand, as previously shown[2] and corroborated by the present work, positions 5 and 6, at least under our experimental conditions, are substituted more readily than the other positions of the aromatic ring. 5,6-Dibromo-1-methylisatin (**7**) was prepared by reaction of 3,4-dibromo-N-methylaniline (**8a**) with oxalyl chloride in the presence of anhydrous aluminum chloride. The oxidation of **7** with hydrogen peroxide gave 4,5-dibromo-N-methylanthranilic acid (**9a**) which was also obtained by methylation of 4,5-dibromoanthranilic acid (**9b**).[2]

Structure **4a** has been demonstrated by comparison with the compound obtained by methylation of 2,3,5,6-tetrabromoindole (**4b**).[2]

To the minor product of the bromination of **1** has been assigned the structure **5**, because it was hydrolyzed with alkali to 5,6-dibromo-1-methylisatin (**7**) and it gave 4,5-dibromo-N-methylanthranilic acid (**9a**) on oxidation. The reaction of **5** with phenylhydrazine led to a β-phenylhydrazone identical with an authentic sample prepared from **7**. The infrared spectrum of **5** shows a strong C=O peak at 1735 cm^{-1} in good agreement with those found for 3,3,5-tribromo-1-methyloxindole (**10a**) and 3,3,5,7-tetrabromo-1-methyloxindole (**10b**) (1730 and 1725 cm^{-1}, respectively), prepared for comparison through bromination of 1-methyloxindole.

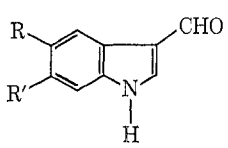
Bromooxindole **10a** can be hydrolyzed to 5-bromo-1-methylisatin (**11a**);[6] analogously **10b** can be hydrolyzed to 5,7-dibromo-1-methylisatin (**11b**).[7] The β-phenylhydrazones obtained from **10a** and **10b** are identical with those obtained from **11a**[8] and **11b**, respectively.



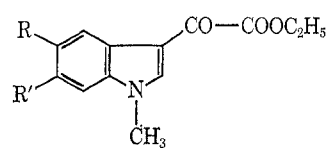
10a, R = H
b, R = Br

11a, R = H
b, R = Br

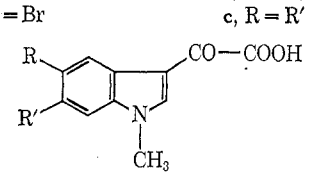
12a, R = Br; R′ = H
b, R = H; R′ = Br
c, R = R′ = Br



13a, R = Br; R′ = H
b, R = H; R′ = Br
c, R = R′ = Br



14a, R = Br; R′ = H
b, R = H; R′ = Br
c, R = R′ = Br



15a, R = Br; R′ = H
b, R = H; R′ = Br
c, R = R′ = Br

Several attempts to brominate 1-methylindole-3-carboxaldehyde (**2**) in acetic anhydride, or in carbon tetrachloride with different mole ratios of indole to bromine, were unsuccessful. When the reaction was carried out in acetic acid with a 1:1.5 mol ratio of substrate to bromine, the unreacted aldehyde was partly recovered together with a mixture of mono- and polybrominated products, whereas with excess bromine (1:3 mol) 5-bromo-1-methylindole-3-carboxaldehyde (**12a**)[9] (16.7% yield, also obtained by methylation of **13a**[2]), 2,3,5,6-tetrabromo-1-methylindole (**4a**) (26.7% yield), and a small amount (6.2%) of 3,3,5-tribromo-1-methyloxindole (**10a**) were isolated.

Displacements of formyl, acetyl, or carboxylic groups, similar to the one giving **4a** from **2**, have been already reported in indole chemistry.[1a,2,10]

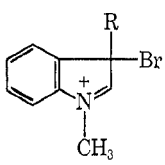
An attempt to brominate ethyl 1-methylindole-3-glyoxylate (**3**) with bromine in acetic acid did not give satisfactory results, because mostly amorphous material was obtained. On the other hand, when the reaction with bromine was carried out in acetic anhydride, substitution products were isolated in fairly good yields. Reaction of **3** with an about equimolar amount of bromine gave, in 94% yield, a product whose melting point remained unchanged through several crystallizations. This material was identified as a constant-melting mixture of 5- and 6-bromo-1-methylindole-3-glyoxylate (**14a** and **14b**). Similar constant-melting mixtures of isomeric bromoindoles have been already described[2] and, in one case, were erroneously considered as a single compound.[11,12] Saponification of the mixture of **14a** and **14b** led to an analogous mixture of the corresponding acids **15a** and **15b**; subsequent decarboxylation with copper chromite in quinoline gave a mixture of 5- and 6-bromo-1-methylindole-3-carboxaldehyde (**12a**[9] and **12b**) in an about 7:3 ratio; fractional crystallization of this mixture from benzene–petroleum ether (bp 60–80°) gave in low yield the two pure compounds **12a** and **12b**. Therefore, 5-bromo derivative **14a** is the main product of the reaction of **3** with bromine in acetic anhydride. Several attempts to separate the components **14a** and **14b** and **15a** and **15b** of the two constant-melting mixtures both by column chromatography and by fractional crystallization were unsuccessful. 6-Bromo-1-methylindole-3-carboxaldehyde (**12b**) was also obtained by methylation of **13b**.[2]

Bromination of ethyl 1-methylindole-3-glyoxylate (**3**) with bromine (1:2.5 mol) in acetic anhydride led to a mixture of **14a**, **14b**, and ethyl 5,6-dibromo-1-methylindole-3-glyoxylate (**14c**); when a larger excess of bromine (1:4 mol) was used, practically pure **14c** (95% yield) was isolated. Compound **14c** was also obtained, in 96% yield, by bromination of the mixture of **14a** and **14b**. Structure **14c** has been proved by hydrolysis to the acid **15c** and decarboxylation of the latter to 5,6-dibromo-1-methylindole-3-carboxaldehyde (**12c**), a compound also obtained by methylation of 5,6-dibromoindole-3-carboxaldehyde (**13c**).[2]

(6) W. Borsche and W. Jacobs, *Ber.*, **47**, 363 (1914).
(7) R. Pummerer and F. Meininger, *Justus Liebigs Ann. Chem.*, **590**, 189 (1954).
(8) J. Martinet, *Ann. Chim.* (Paris), **11**, 85 (1919); *Chem. Zentralbl.*, **III**, 569, (1919).
(9) W. E. Noland and C. Reich, *J. Org. Chem.*, **32**, 828 (1967).
(10) W. E. Noland and K. R. Rush, *ibid.*, **31**, 70 (1966).
(11) R. Majima and M. Kotake, *Ber.*, **63**, 2237 (1930).
(12) B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **38**, 1467 (1960).

When the results of the bromination of 1-methylindole-3-carboxaldehyde and ethyl 1-methylindole-3-glyoxylate are compared with the results of the bromination of the unmethylated analogs,[2] it can be seen that N-methylindoles give better yields of bromo derivatives. In fact, indole-3-carboxaldehyde gives the 5-, 6-, and 5,6-dibromo derivatives in only very low yields (6, 3, and 5%, respectively), and ethyl indole-3-glyoxylate gives the 5,6-dibromo derivative in 82% yield.[2] Evidently, the nitrogen methylation stabilizes the indole ring and reduces the formation of tarry materials.

An interesting aspect of these reactions is the formation of dimer **6a** and of oxindoles together with simple substitution products. It is known that, in the reactions of indoles with halogenating agents, oxidation and substitution are competitive reactions.[3,13] In fact, according to Hinman and Bauman,[3b] although aqueous acetic acid favors oxidation and anhydrous acetic acid bromination, neither one is completely excluded; either of these reactions takes place *via* the same ionic intermediate **16**, which can be converted both into a 2- or 3-bromoindole derivative and into an oxindole **17**; as the second step, further bromination of



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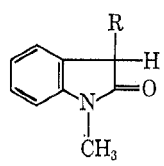

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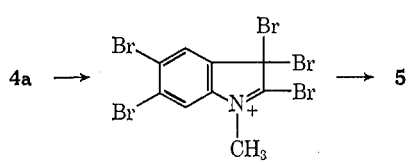
the previously formed oxindole would take place. Furthermore, and the present paper supports it (see the synthesis of compound **10b** described in the Experimental Section), it has been shown that, when oxindoles are brominated, bromine attacks only positions 3, 5, and 7.[14]

If oxindoles are intermediates in the formation of bromooxindoles, we cannot therefore explain the formation of oxindole **5** (brominated in position 6) from the corresponding oxindole **17** (R = H). On the other hand, the formation of bromooxindoles by hydrolysis of previously formed α-brominated tri- or tetrabromoindoles is very unlikely, because, when a bromine atom substitutes the benzene ring, hydrolysis of α-bromoindoles requires very drastic conditions.[3b] An attempt at hydrolysis of 2,3,5,6-tetrabromo-1-methylindole (**4a**) both by refluxing it for 5 hr with a 1:1 mixture of 3 *N* sulfuric acid and dioxane, and by storing it at room temperature for 2 days with a 1:3 mixture of concentrated hydrogen bromide and acetic acid, resulted in the complete recovery of the starting material. A possible, even if purely hypothetical, route to explain the formation of oxindole **5** could be the following one.



The hypothetical intermediate **16** rationalizes very well the formation of the dimer **6a**; probably the dimer **6b** is formed by attack of **16** on a molecule of 1-methylindole (**1**), according to the mechanism proposed by Kunori;[4] successively **6b** is brominated. This dimerization is similar to the formation of indole and skatole dimers under acidic conditions, where a proton rather than a bromonium ion initiates the process.[15] We hope that work now in progress will shed more light on these problems.

Experimental Section[16]

Brominations of 1-Methylindole (1). A. 2,3,5,6-Tetrabromo-1-methylindole (4a) and 3,3,5,6-Tetrabromo-1-methyloxindole (5).—To an ice-cold solution of 1 g (7.63 mmol) of **1** in 6 ml of acetic acid was added dropwise with stirring a solution of 6.1 g (38.0 mmol) of bromine in 6 ml of acetic acid. Stirring was continued for 2 hr at room temperature. The precipitate was collected, suspended in a 3% solution of sodium thiosulfate, again collected, and washed with water to give 2.5 g of crude **4a**. Compound **4a** was purified by dissolving it in 500–600 ml of benzene and passing the resulting solution through a column of neutral alumina (grade I, 1.5 × 25 cm). Elution with benzene gave 1.8 g (53%) of practically pure **4a**. An analytical sample, colorless crystals, mp 168–170°, was obtained by crystallization from petroleum ether (bp 60–80°).

Anal. Calcd for $C_9H_5Br_4N$: C, 24.16; H, 1.12; Br, 71.59. Found: C, 24.46; H, 1.42; Br, 71.41.

The acetic mother liquor was diluted with water; after storage for 12 hr at room temperature, the precipitate was collected, washed with water, and dried to give 0.6 g of a product that was dissolved in benzene and passed through a column of silica gel (1.5 × 25 cm). Elution with 1:1 benzene–petroleum ether (bp 60–80°) mixture gave some fractions containing a product that, after crystallization from acetic acid, yielded 0.3 g (8.5%) of **5** as light yellow plates, darkening above 220° with slow decomposition; the ir spectrum showed a strong band at *ca.* 1735 cm^{-1} (C=O).

Anal. Calcd for $C_9H_5Br_4NO$: C, 23.40; H, 1.08; Br, 69.20. Found: C, 23.60; H, 1.10; Br, 69.40.

B. 2′,3,5,5′,6,6′-Hexabromo-1,1′dimethyl-2,3′-diindolyl (6a) and 3,3,5,6-Tetrabromo-1-methyloxindole (5).—The bromination of **1** (0.5 g, 3.82 mmol) was carried out as described in A above, except that bromine (3.05 g, 19.0 mmol) was added at room temperature. Benzene eluted 0.6 g (42.8%) of practically pure **6a** as the only solid compound. The pure compound, white crystals darkening above 260° without melting, was obtained after crystallization from DMSO, mol wt 733.7 (calcd for $C_{18}H_{10}Br_6N_2$, 750; Rast method).

Anal. Calcd for $C_{18}H_{10}Br_6N_2$: C, 29.42; H, 1.36; Br, 65.30. Found: C, 29.20; H, 1.38; Br, 64.90.

Also in this case, from the acetic mother liquor, 0.15 g (8.5%) of **5** was obtained.

2,3,5,6-Tetrabromo-1-methylindole (4a) by Methylation of 2,3,5,6-Tetrabromoindole (4b).—To a suspension of 0.04 g of **4b**[2] in 2 ml of 2 *N* aqueous sodium hydroxide, 0.1 ml of dimethyl sulfate was added with stirring. Stirring was continued for 10 hr while small amounts of 2 *N* aqueous sodium hydroxide and of dimethyl sulfate were again added at intervals. The precipitate was collected, washed with water, and dried to yield 0.04 g (96.8%) of practically pure **4a**.

3,4-Dibromo-N-methyl-N-tosylaniline (8b).—To a well-stirred suspension of 8.1 g (32.2 mmol) of 3,4-dibromoaniline in 160 ml of 2 *N* aqueous sodium hydroxide was added in small portions 9.6 g (50.3 mmol) of *p*-toluenesulfonyl chloride. Stirring was continued for 4 hr at room temperature. The precipitate was collected, suspended in concentrated hydrochloric acid, again collected, and washed with water to yield 10.7 g (82%) of the tosyl derivative **8c**, mp 120–125°. To a solution of 5.0 g of **8c**

(13) J. C. Powers, *J. Org. Chem.*, **31**, 2627 (1966).

(14) (a) R. Stollé, R. Bergdoll, M. Luther, A. Auerhahn, and W. Wacker, *J. Prakt. Chem.*, **128**, 1 (1930); (b) W. C. Sumpter, M. Miller, and L. N. Hendrick, *J. Amer. Chem. Soc.*, **67**, 1656 (1945).

(15) R. L. Hinman and E. R. Shull, *J. Org. Chem.*, **26**, 2339 (1961); G. F. Smith and A. E. Walters, *J. Chem. Soc.*, 940 (1961); B. Berti, A. Da Settimo, and D. Segnini, *Ann. Chim.* (Rome), **52**, 535 (1962).

(16) Melting points are uncorrected. Ir spectra were obtained on a Perkin-Elmer Infracord 137, in Nujol mulls. Commercial acetic acid (*ca.* 98%) used in the brominations was not previously dried; acetic anhydride was freshly distilled. Comparisons between compounds were made on the basis of their infrared spectra. $MgSO_4$ was used as the drying agent, unless stated otherwise.

in a mixture of 25 ml of ethanol and 25 ml of 2 *N* aqueous sodium hydroxide was added dropwise with stirring an excess of dimethyl sulfate. Compound **8b** started to precipitate and was filtered off at intervals, while stirring was continued and small amounts of 2 *N* aqueous sodium hydroxide and of dimethyl sulfate were again added over a period of 6 hr. The collected precipitates were washed with water and dried to give 3.0 g (58%) of the pure compound **8b**, mp 78–80°. An analytical sample was obtained by crystallization from ethanol.

Anal. Calcd for $C_{14}H_{13}Br_2NO_2S$: C, 40.11; H, 3.12; Br, 38.13; S, 7.65. Found: C, 40.23; H, 3.04; Br, 37.87; S, 7.96.

5,6-Dibromo-1-methylisatin (7). A. By Synthesis.—A mixture of 6.32 g of 3,4-dibromo-N-methyl-N-tosylaniline (**8b**) and 65 ml of 75% sulfuric acid was heated at 100° for 1 hr. After cooling, the mixture was poured into crushed ice, made alkaline with 20% aqueous sodium hydroxide, and extracted with ether; the extract was washed with water, dried, and evaporated. The residual brown oil consisted of 3.0 g (75%) of **3,4-dibromo-N-methylaniline** (**8a**) and was directly used for the synthesis of **7**.

To an ice-cold suspension of 3.0 g (11.3 mmol) of **8a** in 150 ml of anhydrous carbon disulfide was added with stirring 2.87 g (22.6 mmol) of oxalyl chloride. Stirring was continued for 30 min and then the mixture was treated with 5 g of anhydrous aluminum chloride, while being stirred and refluxed for 3 hr. After cooling, the mixture was treated with crushed ice to give 1.45 g (40%) of a red precipitate, which consisted of a mixture of **7** and, probably, of 4,5-dibromo-1-methylisatin. The organic layer was separated, and the aqueous layer was extracted with ether; the combined organic extracts were washed with water, dried, and evaporated to yield 0.1 g of the same mixture of isomeric dibromoisatins (total yield 43%). Fractional crystallization from methanol of the combined mixtures yielded, as the first fraction, 0.52 g (14.4%) of **7**. An analytical sample, red crystals, mp 255–256°, was obtained by crystallization from benzene; the ir spectrum of **7** showed two strong bands at *ca.* 1735 (C=O) and 1600 cm^{-1} (C=O) and lacked the band at *ca.* 824 cm^{-1}, observed in the spectrum of the mixture of the two dibromoisatins.

Anal. Calcd for $C_9H_5Br_2NO_2$: C, 33.88; H, 1.58; N, 4.39; Br, 50.10. Found: C, 33.79; H, 1.80; N, 4.39; Br, 49.92.

B. From 3,3,5,6-Tetrabromo-1-methyloxindole (5).—A mixture of 0.1 g of **5**, 2 ml of 2 *N* aqueous sodium hydroxide, 4 ml of water, and 5 ml of ethanol was refluxed for 1 hr. Ethanol was evaporated and the residual aqueous solution was acidified with concentrated hydrochloric acid; a precipitate formed that consisted of 0.025 g (36.2%) of practically pure **7**.

C. By Oxidation of 6a.—A suspension of 0.2 g of **6a** in a mixture of 4 ml of acetic acid and 1 ml of water was treated with 0.3 g of chromic anhydride and heated at 100° for 30 min; 0.25 g of chromic anhydride was again added; and the suspension was heated at 100° for an additional 30 min. After cooling, the mixture was poured into 200 ml of water and extracted with three 100-ml portions of benzene. The combined extracts were washed with water, dried, and concentrated to give 0.050 g (28.7%) of practically pure **7**.

5,6-Dibromo-1-methylisatin-β-phenylhydrazone. A. From 5,6-Dibromo-1-methylisatin (7).—A mixture of 0.04 g of **7**, 5 ml of ethanol, and three drops of acetic acid was treated with phenylhydrazine in slight excess and refluxed for 1 hr. Upon cooling, a precipitate formed, which was collected and washed with ethanol to give 0.045 g (88%) of the β-phenylhydrazone; an analytical sample, orange needles, mp 220–222°, was obtained after crystallization from acetic acid.

Anal. Calcd for $C_{15}H_{11}Br_2N_3O$: N, 10.3; Br, 39.1. Found: N, 10.5; Br, 39.3.

B. From 3,3,5,6-Tetrabromo-1-methyloxindole (5).—When 0.1 g of **5** was treated exactly as described in A, 0.06 g (67.7%) of the same β-phenylhydrazone was obtained.

4,5-Dibromo-N-methylanthranilic acid (9a). A. By Methylation of 4,5-Dibromoanthranilic acid (9b).—When 0.2 g of **9b**[2] was treated as described for 2,3,5,6-tetrabromoindole (**4b**), except that the mixture was stirred for 24 hr, a precipitate formed, which dissolved almost completely when the reaction mixture was heated on a steam bath; a small amount of undissolved amorphous material was eliminated by filtration. The filtrate was cautiously acidified with 2 *N* hydrochloric acid; a precipitate formed which was collected, washed with water, and dried to yield 0.08 g (38%) of **9a**. An analytical sample was obtained after two sublimations at 220° (3 mm). The pure compound, light yellow needles, melted at 258–260° (fast heating); on slow heating, the compound volatilized without melting. The ir spectrum showed bands at *ca.* 3360 (NH) and *ca.* 1670 cm^{-1} (C=O).

Anal. Calcd for $C_9H_7Br_2NO_2$: C, 31.06; H, 2.27; Br, 51.80. Found: C, 31.00; H, 2.39; Br, 51.50.

B. By Oxidation of 5,6-Dibromo-1-methylisatin (7).—A suspension of 0.1 g of **7** in a mixture of 5 ml of 2 *N* aqueous sodium hydroxide and 3 ml of water was treated with 3 ml of 36% hydrogen peroxide, heated at 100° for 1 hr, and stored at room temperature for 2 days. The mixture was cautiously acidified with 2 *N* hydrochloric acid; a precipitate formed which was collected, washed with water, and dried to yield 0.025 g (25.8%) of **9a**.

C. By Oxidation of 3,3,5,6-Tetrabromo-1-methyloxindole (5).—A suspension of 0.3 g of **5** in a mixture of 8 ml of 2 *N* aqueous sodium hydroxide and 5 ml of water, was treated with 3 ml of 36% hydrogen peroxide and heated at 100° for 2 hr. After cooling, the undissolved material was collected and washed with water; 0.13 g of the starting material was recovered. The combined filtrates were acidified with 2 *N* hydrochloric acid to give 0.05 g (44.2%, based on unrecovered starting material) of **9a**.

1,1′-Dimethyl-2,3′-diindolyl (6b).—To an ice-cold, stirred solution of 0.464 g (2.0 mmol) of 2,3′-diindolyl[5] in 20 ml of dry DMF, was added, under nitrogen, 0.2 g (41.6 mmol) of a 50% suspension of sodium hydride in mineral oil. The mixture was allowed to warm to 25° and stand for 2 hr, while being stirred. It was then cooled in an ice bath and treated with a solution of 0.68 g (48.0 mmol) of methyl iodide in 12 ml of dry ether. The resulting solution was left for 18 hr under nitrogen at 25°, concentrated under reduced pressure to about 10 ml, and poured into water. A precipitate formed which was collected, washed with water, and dried to give 0.52 g (100%) of **6b**, mp 133–135° (lit.[4] mp 134–135°), identical with an authentic sample prepared according to Kunori by treating 1-methylindole (**1**) with dioxane–bromine complex in THF solution.[4]

The compound gave a positive Ehrlich test, and its chromic oxidation, carried out as described for the conversion of **6a** into **7**, gave, as a single compound, 1-methylisatin, mp 134° (lit.[17] mp 134°).

Compound 6a by Bromination of 6b.—To a well-stirred suspension of 0.5 g (1.92 mmol) of **6b** in 5 ml of acetic acid, 2 ml of acetic acid containing 2.49 g (15.5 mmol) of bromine was added dropwise at room temperature. Stirring was continued for 5 hr at room temperature. The precipitate was collected, washed with acetic acid, dried, and crystallized from DMSO to give 1.1 g (78%) of practically pure **6a**.

3,3,5-Tribromo-1-methyloxindole (10a). A. By Bromination of 1-Methyloxindole.—A solution of 0.3 g (2.04 mmol) of 1-methyloxindole in 25 ml of dry carbon tetrachloride was treated with 2.0 g (12.5 mmol) of bromine and refluxed until the evolution of hydrogen bromide ceased (*ca.* 6 hr). The resulting solution was concentrated to about 6 ml; on cooling, a precipitate formed which was collected and washed with carbon tetrachloride to give 0.55 g (70%) of practically pure **10a**. An analytical sample, pale yellow prisms, mp 171–173°, was obtained after crystallization from acetic acid; the ir spectrum showed a strong band at *ca.* 1730 cm^{-1} (C=O).

Anal. Calcd for $C_9H_6Br_3NO$: C, 28.20; H, 1.56; Br, 62.50. Found: C, 28.48; H, 1.68; Br, 62.20.

The hydrolysis of **10a**, carried out according to Stollé,[14a] with a mixture of ethanol and 2 *N* aqueous sodium hydroxide, gave 5-bromo-1-methylisatin (**11a**), mp 172–173° (lit.[6] mp 172–173°).

The β-phenylhydrazone obtained from **10a** was identical with an authentic sample prepared from **11a** and melted at 170–172° (lit.[8] mp 164°).

B. By Bromination of 5-Bromo-1-methyloxindole.—Practically pure **10a** was also obtained in 95% yield, when 5-bromo-1-methyloxindole[14a] was brominated exactly as described in A.

3,3,5,7-Tetrabromo-1-methyloxindole (10b). A. By Bromination of 1-Methyloxindole.—A solution of 10 g (62.5 mmol) of bromine in 30 ml of water containing 15 g of potassium bromide was added to a boiling solution of 2.0 g (13.6 mmol) of 1-methyloxindole in 200 ml of water. The mixture was allowed to cool at room temperature and stand for 1 night. The precipitate was collected, washed with water, dried, dissolved in 250 ml of carbon tetrachloride, and treated with excess bromine. The resulting solution was refluxed until the evolution of hydrogen bromide ceased (*ca.* 15 hr), and then was concentrated; 5.5 g (87.4%) of practically pure **10b** crystallized on cooling. An analytical sample, pale yellow needles, mp 227–230°, was crys-

(17) E. Fischer and O. Hess, *Ber.*, **17**, 565 (1884).

tallized from acetic acid; the ir spectrum showed a strong band at *ca.* 1725 cm^{-1} (C=O).

Anal. Calcd for $C_9H_5Br_4NO$: C, 23.40; H, 1.08; Br, 69.20. Found: C, 23.70; H, 1.20; Br, 68.90.

The hydrolysis of **10b**, carried out according to Stollé[14a] with a mixture of ethanol and 2 *N* aqueous sodium hydroxide, gave 5,7-dibromo-1-methylisatin (**11b**), mp 182–183° (lit.[7] mp 182–183°).

B. By Bromination of 3,3,5-Tribromo-1-methyloxindole (10a).—A solution of 1.67 g (10.4 mmol) of bromine in 10 ml of water containing 3 g of potassium bromide was added to a boiling solution of 1.0 g (2.60 mmol) of **10a** in 300 ml of 10% aqueous acetic acid. After storage at room temperature for 1 night, a precipitate was collected, washed with water, and crystallized from acetic acid to give 1.0 g (83%) of pure **10b**.

5,7-Dibromo-1-methylisatin-β-phenylhydrazone.—A mixture of 0.2 g of **10b**, 10 ml of ethanol, and 0.2 ml of acetic acid was treated with excess phenylhydrazine and refluxed for 2 hr. Ethanol was evaporated; the phenylhydrazone, orange needles, crystallized on cooling (80% yield). An analytical sample, mp 200–201.5°, was crystallized from acetic acid.

Anal. Calcd for $C_{15}H_{11}Br_2N_3O$: C, 44.03; H, 2.69; Br, 39.10. Found: C, 44.39; H, 2.68; Br, 38.86.

The same phenylhydrazone was obtained by a similar treatment of 5,7-dibromo-1-methylisatin (**11b**).

Bromination of 1-Methylindole-3-carboxaldehyde (2). 5-Bromo-1-methylindole-3-carboxaldehyde (12a), 2,3,5,6-Tetrabromo-1-methylindole (4a), and 3,3,5-Tribromo-1-methyloxindole (10a).—To a solution of 0.2 g (1.26 mmol) of **2** in 2.5 ml of acetic acid, 2 ml of acetic acid containing 0.605 g (3.78 mmol) of bromine was added dropwise with stirring. Stirring was continued for 1 hr at room temperature. A precipitate formed which was collected, washed with acetic acid, and suspended in a 3% solution of sodium thiosulfate; the resulting compound was again collected, washed with water, and dried to give 0.05 g (16.7%) of practically pure **12a**. An analytical sample, colorless needles, mp 137–138° (lit.[9] mp 138°), was crystallized from methanol; the ir spectrum showed a band at *ca.* 1650 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_8BrNO$: C, 50.44; H, 3.39; Br, 33.60. Found: C, 50.74; H, 3.28; Br, 33.38.

The acetic mother liquor separated, after storage at room temperature for one night, 0.15 g (26.7%) of **4a**, and then was diluted with water; a precipitate was collected and crystallized from acetic acid (charcoal) to give 0.03 g (6.2%) of **10a**.

5-Bromo-1-methylindole-3-carboxaldehyde (12a) by Methylation of 5-Bromoindole-3-carboxaldehyde (13a).—Compound **12a** was obtained in 91.7% yield from 0.2 g of **13a**[2] as described for the methylation of 2,3,5,6-tetrabromoindole (**4b**), except that the mixture was stirred for 20 hr.

Ethyl 1-Methylindole-3-glyoxylate (3).—A solution of 6.0 g (45.8 mmol) of 1-methylindole (**1**) in 100 ml of dry ether was treated dropwise at 0°, while being stirred, with 11.2 g (88.2 mmol) of oxalyl chloride. 1-Methylindole-3-glyoxalyl chloride was rapidly formed as orange crystals. Stirring was continued for 45 min at room temperature; the chloride was then collected, washed with ether (8.8 g, mp 116–117°), and treated with 20 ml of dry ethanol. After 15 hr of storage at room temperature, 8.0 g (75.7%) of **3** was collected. An analytical sample was obtained after two crystallizations from ethanol, mp 90–91°; the ir spectrum showed bands at *ca.* 1720 (C=O) and *ca.* 1630 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.81; H, 5.78; N, 5.94.

Brominations of Ethyl 1-Methylindole-3-glyoxylate (3). A. Constant-Melting Mixture of 5- and 6-Bromo-1-methylindole-3-glyoxylate (14a and 14b).—To a solution of 0.5 g (2.16 mmol) of **3** in 2 ml of acetic anhydride was added dropwise with stirring a solution of 0.416 g (2.60 mmol) of bromine in 1 ml of acetic anhydride. The mixture was left at room temperature for 5 hr and then poured into crushed ice; the precipitate which formed was collected and washed with water to give 0.63 g (94%) of a mixture of **14a** and **14b**, which was crystallized twice from ethanol to yield colorless needles, mp 114–116° (the melting point remained unchanged through several crystallizations); the ir spectrum showed bands at *ca.* 1740 (C=O) and *ca.* 1640 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{12}BrNO_3$: C, 50.32; H, 3.87; Br, 25.80. Found: C, 50.09; H, 3.86; Br, 25.97.

All attempts to separate the components of such mixture both by column chromatography and by fractional crystallization were unsuccessful.

B. Ethyl 5,6-Dibromo-1-methylindole-3-glyoxylate (14c).—When 1.0 g (4.32 mmol) of **3** was treated with 2.77 g (17.3 mmol) of bromine exactly as described in A, 1.6 g (95%) of **14c** was obtained. Purification by crystallization from ethanol gave an analytical sample, colorless needles, mp 129–130°. The ir spectrum showed bands at *ca.* 1725 (C=O) and *ca.* 1630 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{11}Br_2NO_3$: C, 40.10; H, 2.83; Br, 41.13. Found: C, 40.29; H, 2.81; Br, 41.05.

When the constant melting mixture of **14a** and **14b** was treated with bromine (1:2 mol ratio) in acetic anhydride and worked up exactly as described above, compound **14c** was obtained in 96% yield.

Constant-Melting Mixture of 5- and 6-Bromo-1-methylindole-3-carboxylic Acid (15a and 15b).—A suspension of 0.37 g of the mixture of **14a** and **14b** in 10 ml of 2 *N* aqueous sodium hydroxide was heated at 100° for 2 hr. Acidification of the alkaline solution with concentrated hydrochloric acid gave 0.3 g (89%) of a mixture of **15a** and **15b**, which, after crystallization from methanol, melted at 238–240° (the melting point remained unchanged through several crystallizations); the ir spectrum showed bands at *ca.* 3300 (OH), *ca.* 1755 (C=O), and *ca.* 1625 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_8BrNO_3$: Br, 28.40. Found: Br, 28.63.

All attempts to separate the components of such mixture both by column chromatography and by fractional crystallization were unsuccessful.

Decarboxylation of the Constant-Melting Mixture of 15a and 15b. 5- and 6-Bromo-1-methylindole-3-carboxaldehyde (12a and 12b).—Two grams of the mixture of **15a** and **15b**, 6 ml of quinoline, and a catalytic amount of copper chromite were heated at 235–240° until the evolution of carbon dioxide ceased. After cooling the mixture was poured in 2 *N* hydrochloric acid; a precipitate formed which was collected, washed, dried, and extracted repeatedly with hot benzene; the combined extracts (charcoal) were washed with 2 *N* aqueous sodium carbonate, dried, and concentrated on steam bath. Acidification of the alkaline extract with 2 *N* hydrochloric acid gave 0.5 g of the starting mixture of the acids **15a** and **15b**. Fractional dilution of the benzene solution with petroleum ether (bp 60–80°) yielded first compound **12a**[9] (0.03 g after crystallization from methanol, 2.36% based on unrecovered starting material) and then 0.22 g (17.3% based on unrecovered starting material) of a mixture of **12a** and **12b** (its ir spectrum was identical with the spectrum of an artificial mixture containing **12a** and **12b** in 7:3 ratio); the last fractions contained 0.013 g (1.05% based on unrecovered starting material) of practically pure **12b**. An analytical sample of **12b**, white crystals, mp 150–151°, was obtained by crystallization from benzene; the ir spectrum showed a strong band at *ca.* 1650 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_8BrNO$: C, 50.44; H, 3.39; Br, 33.60. Found: C, 50.80; H, 3.45; Br, 33.41.

6-Bromo-1-methylindole-3-carboxaldehyde (12b) by Methylation of 6-Bromoindole-3-carboxaldehyde (13b).—Compound **12b** was obtained in 88% yield from 0.07 g of **13b**[2] as described for the methylation of 5-bromoindole-3-carboxaldehyde (**13a**) except that the mixture was stirred for 40 hr.

5,6-Dibromo-1-methylindole-3-glyoxylic Acid (15c).—A suspension of 0.32 g of **14c** in 10 ml of 2 *N* aqueous sodium hydroxide was heated at 100° for 2 hr. Acidification of the alkaline solution with concentrated hydrochloric acid gave 0.28 g (94.5%) of **15c**. An analytical sample was crystallized from an acetone–methanol mixture to give light yellow plates, mp 251–253° dec. The ir spectrum showed bands at *ca.* 3300 (OH), *ca.* 1770 (C=O), and *ca.* 1630 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_7Br_2NO_3$: C, 36.60; H, 1.93; Br, 44.30. Found: C, 36.85; H, 1.87; Br, 44.05.

5,6-Dibromo-1-methylindole-3-carboxaldehyde (12c). A. By Decarboxylation of Acid 15c.—The decarboxylation of 0.2 g of **15c** was carried out as described for the mixture of **14a** and **14b**. The washed and dried benzene extract (charcoal) was concentrated and diluted with petroleum ether (bp 30–50°); the solution slowly separated 0.04 g (22.8%) of **12c**. The compound was crystallized from benzene to give light yellow prisms, mp 209–211°; the ir spectrum showed a strong band at *ca.* 1650 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_7Br_2NO$: C, 37.89; H, 2.21; Br, 50.45. Found: C, 38.16; H, 2.26; Br, 50.20.

B. By Methylation of 5,6-Dibromoindole-3-carboxaldehyde

(13c).—The methylation of 0.2 g of 13c,[2] carried out as described for 5-bromoindole-3-carboxaldehyde (13a), gave 0.185 g (88.5%) of 12c.

Registry No.—Bromine, 7726-95-6; **3**, 25055-54-3; **4a**, 25055-55-4; **5**, 25055-56-5; **6a**, 25055-57-6; **7**, 25055-58-7; **7** (phenylhydrazone), 25055-59-8; **8b**, 25055-60-1; **9a**, 25055-61-2; **10a**, 25055-62-3; **10b**, 25055-63-4; **10b** (phenylhydrazone), 25055-64-5; **12b**, 25055-65-6; **12c**, 25055-66-7; **14a**, 25055-67-8; **14b**, 25055-68-9; **14c**, 25055-50-9; **15a**, 25055-51-0; **15b**, 25055-52-1; **15c**, 25055-53-2.

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Alkyl Nitrate Nitration of Active Methylene Compounds. VIII. Synthesis of α-Nitrosulfonate Esters

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The alkyl nitrate nitration of neopentyl sulfonate esters gives the corresponding neopentyl α-nitrosulfonate esters in good yield. On the other hand, the nitration of ethyl sulfonate esters such as ethyl 1-butanesulfonate (**1a**) leads not only to ethyl 1-nitro-1-butanesulfonate (**2a**) but also to potassium 1-nitro-1-butanesulfonate (**3**). Compound **3** arises from a β-elimination reaction on the ester portion of the molecule which occurs during the nitration step and not during anion formation or during the acidification step.

In continuation of our studies of the alkyl nitrate nitration,[1] we are now reporting on its application to the preparation of α-nitrosulfonate esters which constitute a new class of compounds.

In preliminary experiments it was established that nitration of ethyl 1-butanesulfonate (**1a**) gave best results in the potassium amide–liquid ammonia system, affording a 54.8% yield of ethyl 1-nitro-1-butanesulfonate (**2a**). The yield of **2a** was only 35.5 and 37.0%, respectively, when nitrations were performed in sodium amide–liquid ammonia and potassium *t*-butoxide–THF. In addition to **2a**, potassium 1-nitro-1-butanesulfonate (**3**) was also obtained in each of the base-solvent systems employed (eq 1). However, only neopentyl α-nitrobutanesulfonate (**2b**) was obtained from the nitration of neopentyl butanesulfonate (**1b**).

$$\underset{\mathbf{1}}{H_3C(CH_2)_3SO_3R} \xrightarrow[2.\ H^+]{1.\ KNH_2\text{–liquid } NH_3\text{–}R^1ONO_2}$$

$$\underset{\mathbf{2}}{H_3C(CH_2)_2CH(NO_2)SO_3R} + \underset{\mathbf{3}}{H_3C(CH_2)_2CH(NO_2)SO_3^-K^+} + \underset{\mathbf{12}}{CH_2{=}CH(CH_2)_5CH_3} \quad (1)$$

a, R = CH_2CH_3; b, R = $CH_2C(CH_3)_3$; c, R = $(CH_2)_7CH_3$; $R^1 = C_2H_5$ or n-C_3H_7

The acid salt rather than the nitronate structure was assigned to compound **3** on the basis of its nmr spectrum which showed the characteristic methine proton absorption at 5.48–5.72 ppm.

The results of the nitration of various neopentyl sulfonate estera are summarized in Table I. It is noteworthy that in order to obtain optimum yields of α-nitrosulfonate esters containing 8–12 carbons in the side chain, more concentrated reaction mixtures had to be employed, (instead of 250 ml, only 100 ml of liquid ammonia was used). In the case of neopentyl 1-hexadecanesulfonate (**4**), no nitrated product was obtained. Even though anion formation was carried out with potassium amide in THF at 65°, 95% of the ester **4** was recovered. The failure of **4** to undergo nitration was due to the fact that it was not converted to its anion. This was ascertained from a deuterium-exchange experiment, for nmr and mass spectral data showed that no deuterium was incorporated into **4** after treatment with potassium amide in liquid ammonia and subsequent acidification with deuterium oxide in anhydrous ether.[2] Under similar reaction conditions, deuterium was incorporated into **1b** and neopentyl 1-dodecanesulfonate to the extent of 100 and 75%, respectively.

The nitration was also successful with a disulfonate ester.

The nitration was also successful with a disulfonate ester. Thus dineopentyl 1,4-butanedisulfonate was converted into dineopentyl 1,4-dinitro-1,4-butanedisulfonate in 68.9% yield.

The neopentyl α-nitrosulfonate esters were identified by infrared and nmr spectra and by conversion to the corresponding bromo derivatives (eq 2).

$$\underset{\mathrm{NO_2}}{\mathrm{RCHSO_3R^1}} \xrightarrow[2.\ Br_2;\ CCl_4]{1.\ KOH\text{–}C_2H_5OH} \underset{\mathrm{NO_2}}{\overset{\mathrm{Br}}{\mathrm{RCSO_3R^1}}} \quad (2)$$

In contrast to the results in the nitration of *t*-butyl α-methylbutyrate which led with decarboxylation to 2-nitrobutane,[1a] neopentyl 2-butanesulfonate was converted to neopentyl 2-nitro-2-butanesulfonate (**5**) in 34.7% yield. The lower yield of **5** as compared with **2b** could be caused by the methyl group in the α position, which lowers the acidity of the α hydrogen[3] and hinders the approach of base in forming the carbanion.

The nitration of ethyl 2-butanesulfonate (**6**) led in 53.1% yield to potassium 2-nitro-2-butanesulfonate (**7**) instead of the expected α-nitrosulfonate ester. In addition to **7**, 35.1% ethyl 3-methyl-3-pentanesulfonate (**8**) was also isolated (eq 3).

(1) For previous publications, see (a) H. Feuer and R. P. Monter, *J. Org. Chem.*, **34**, 991 (1969); (b) H. Feuer and J. P. Lawrence, *J. Amer. Chem. Soc.*, **91**, 1856 (1969); (c) W. E. Truce, T. C. Klinger, J. E. Paar, and by H. Feuer, and D. K. Wu, *J. Org. Chem.*, **34**, 3104 (1969).

(2) A steric factor might be responsible for preventing conversion of compound **4** to its anion. Models indicate that coiling back of the alkyl chain could hinder approach to the α hydrogen.

(3) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, New York, N. Y., 1959.