2,3,6,6-tetramethyl-2-methoxy-4-heptanone, 51392-33-7; *tert*-butyl neopentyl ketone, 868-91-7; *tert*-butyllithium, 594-19-4; *tert*-butylacetyl chloride, 7065-46-5; *tert*-butylneopentylacetic acid, 51392-34-8.

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References and Notes

(1) Financial support from the National Science Foundation is gratefully acknowledged.
(2) (a) N. J. Turro, *Accounts Chem. Res.*, **2**, 25 (1969); (b) N. J. Turro, R. B. Gagosian, S. S. Edelson, T. R. Darling, and W. B. Hammond, *Trans. N. Y. Acad. Sci.*, **33**, 396 (1971); (c) see H. H. Wasserman, H. W. Adickes, and O. E. de Ochoa, *J. Amer. Chem. Soc.*, **93**, 5586 (1971), and earlier papers in the series; (d) see B. H. Bakker, G. J. A. Schilder, T. R. Bok, H. Steinberg, and T. J. de Boer, *Tetrahedron*, **29**, 93 (1973), and earlier papers in the series.
(3) See R. Breslow and M. Oda, *J. Amer. Chem. Soc.*, **94**, 4787 (1972), for the preparation of cyclopropanones by cycloaddition of cyclopropenone with dienes.
(4) (a) J. F. Pazos and F. D. Greene, *J. Amer. Chem. Soc.*, **89**, 1030 (1967); (b) D. B. Sclove, J. F. Pazos, R. L. Camp, and F. D. Greene, *ibid.*, **92**, 7488 (1970); (c) F. D. Greene, R. L. Camp, L. Kim, J. F. Pazos, D. B. Sclove, and C. J. Wilkerson, *Proc. Int. Congr. Pure Appl. Chem., 23rd*, **2**, 325 (1971).
(5) F. D. Greene, *et al.*, *J. Org. Chem.*, forthcoming publications.
(6) A. S. Kende, *Org. React.*, **11**, 261 (1960).
(7) (a) Landolt-Bornstein, "Zahlenwerte and Funktionen," Vol. I, Part 3, Springer-Verlag, West Berlin, 1951, p 252. (b) P. Ramart-Lucas, *Bull. Soc. Chim. Fr.*, (5) **10**, 13 (1943). (c) We wish to thank Professor K. Williamson, Mount Holyoke College, for the ^{13}C nmr for cyclopropanone **1**.
(8) R. C. Benson, W. H. Flygare, M. Oda, and R. Breslow, *J. Amer. Chem. Soc.*, **95**, 2772 (1973).
(9) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, N. Y., 1972, p 289.
(10) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969). See also G. R. Sullivan, J. A. Dale, and H. S. Mosher, *ibid.*, **38**, 2143 (1973).
(11) G. M. Whitesides and D. W. Lewis, *J. Amer. Chem. Soc.*, **92**, 6979 (1970).
(12) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Amer. Chem. Soc.*, **86**, 397 (1964).
(13) For summaries of optical parameters, see P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965.
(14) These medium changes pose uncertainties in analysis of the data for n, $k_{forward}$, and $k_{reverse}$ in $k_{obsd} = k_f[H_2O]^n + k_r[H_2O]^{n-1}$. At 80° over the range of $[H_2O] = 1.46$–2.76 M in aqueous dioxane, the data correspond approximately to $n = 2.5$, $k_f = 1.3 \times 10^{-5}$ M^{-n} sec^{-1}, and $k_r = 0.6 \times 10^{-5}$ $M^{-(n-1)}$ sec^{-1}.
(15) For example, see C. Rappe, L. Knutsson, N. J. Turro, and R. B. Gagosian, *J. Amer. Chem. Soc.*, **92**, 2032 (1970).
(16) P. S. Wharton and A. R. Fritzberg, *J. Org. Chem.*, **37**, 1899 (1972).
(17) For a study of alkoxy ketone formation from chloro ketone under Favorskii conditions, see F. G. Bordwell and M. W. Carlson, *J. Amer. Chem. Soc.* **92**, 3370, 3377 (1970).
(18) The question of ring opening to oxyallyl is taken up in detail in a forthcoming publication (ref 5).
(19) It is not possible from these results to determine whether reprotonation of the enolate anion affords *cis*- or *trans*-cyclopropanone. Generation of the *cis*-cyclopropanone might be expected to lead to rapid attack at the greatly deshielded carbonyl, but by the same token the hydrogens are also more exposed. In a somewhat related case, reprotonation of the enolate from *trans*-di-*tert*-butylcyclobutanedione (ref 5) affords only the trans compound. On this basis, one might expect the di-*tert*-butylcyclopropanone enolate to be reprotonated with regeneration of the *trans*-cyclopropanone.
(20) Reaction of tetramethylcyclopropanone with oxygen is mentioned in ref 2a. Dependence on water content is not described.
(21) F. D. Greene, W. Adam, and G. A. Knudsen, Jr., *J. Org. Chem.*, **31**, 2087 (1966); W. Adam and Y. M. Cheng, *J. Amer. Chem. Soc.*, **91**, 2109 (1969).
(22) D. H. Gibson and C. H. DePuy, *Tetrahedron Lett.*, 2203 (1969).
(23) R. Davis, C. Granito, and H. P. Schultz, *Org. Syn.*, **47**, 75 (1967).
(24) K. Bott, *Chem. Ber.*, **100**, 978 (1967).
(25) J. Ciabattoni and E. C. Nathan, III, *J. Amer. Chem. Soc.*, **91**, 4766 (1969).

Reactions of 2,3-Dibromoindole Derivatives with Bromine and Other Oxidizing Agents. 2,3-Dibromoindole → 3,3-Dibromooxindole Transformation

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When an excess of bromine was allowed to react with 2,3-dibrominated polybromoindoles in acetic acid, the corresponding 3,3-dibrominated oxindoles were isolated. Only in one case, both oxidation and substitution took place. 2,3-Dibrominated polybromoindoles were the main reaction products when the bromination was carried out in anhydrous carbon tetrachloride. Present results confirm a previously proposed pathway according to which a 3,3-dibrominated indolenine (6) is the possible intermediate in the formation of 3,3-dibrominated oxindoles by reaction of some indoles with excess bromine. When 2,3-dibrominated polybromoindoles were treated with chromic anhydride or with peracetic acid the corresponding 3,3-dibrominated oxindoles were isolated in fairly good yields. This method could be used as a diagnostic tool in the structure determination of 2,3-dibromoindoles.

Halogenation of the indole nucleus has been extensively studied. Several halogenating agents, in aqueous and nonaqueous media, have been employed, and beside substitution products oxindole derivatives were almost always found.[1,2] It is known that an aqueous medium favors oxidation and an anhydrous one bromination, and that the two reactions are always competitive, neither one being completely excluded. However, more than one pathway has been proposed to explain the formation of 3-halooxindoles from indoles.[1b,2a,b,d] We have now investigated the behavior of some 2,3-dibrominated polybromoindoles with bromine in aqueous (acetic acid) and in nonaqueous media (carbon tetrachloride).

When excess bromine was added to an acetic acid suspension of 2,3,5,6-tetrabromoindole (**1a**),[1a] 3,3,5,6-tetrabromooxindole (**2a**, 67% yield) was formed. Compound **2a** was hydrolyzed with alkali to 5,6-dibromoisatin (**3a**)[1a] and led, with phenylhydrazine, to a β-phenylhydrazone identical with an authentic sample prepared from **3a**; these facts indicate that two bromine atoms in compound **2a** are in the 3 position.[1b] The infrared spectrum of **2a** shows strong N–H and C=O peaks at 3200 and 1730 cm^{-1}, respectively, in good agreement with those found for other 3,3-dibrominated oxindoles.[1b,3]

The main product of the reaction of **1a**[1a] with excess bromine in anhydrous CCl_4 was a nonoxindolic material

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Experimental Section[12]

(12) Melting points are uncorrected. Ir spectra were obtained on a Perkin-Elmer Infracord 137, in Nujol mulls. Comparison between compounds were made on the basis of their infrared spectra. $MgSO_4$, was used as drying agent, unless stated otherwise.

Isatin-β-phenylhydrazones.—All β-phenylhydrazones were obtained according to the general procedure described by Da Settimo and Nannipieri for the preparation of 5,6-dibromo-1-methylisatin-β-phenylhydrazone.[13]

Reactions with Bromine in Acetic Acid.—These reactions were all carried out in an open erlenmeyer flask at room temperature, unless stated otherwise. Commercial acetic acid (ca. 98%) was not previously dried.

Reactions with Bromine in Carbon Tetrachloride.—These reactions were all performed in anhydrous conditions; Carbon tetrachloride was previously dried with $CaCl_2$.

1,1,5,6-Tetrabromooxindole (2a). A. By Treatment of 2,3,5,6-Tetrabromoindole (1a) with Bromine in Acetic Acid.— To a well-stirred suspension of 0.1 g (0.23 mmol) of 1a[14] in 2 ml of acetic acid 0.62 g (3.90 mmol) of bromine was added. The resulting solution was stored at room temperature for 15 hr; a precipitate formed which was collected by filtration, washed with acetic acid and water, and dried to yield 0.07 g (67.5%) of practically pure 2a. An analytical sample, pale yellow prisms darkening above 210° without melting, was crystallized from acetic acid. The ir spectrum showed bands at ca. 3200 (N-H) and 1730 cm^{-1} (C=O).

Anal. Calcd for $C_8H_3Br_4NO$: C, 21.40; H, 0.67; Br, 71.22. Found: C, 21.67; H, 0.75; Br, 71.31.

The hydrolysis of 2a, carried out according to Stolé,[2a] with a mixture of ethanol and 2N aqueous sodium hydroxide, gave 5,6-dibromoisatin (3a)(65% yield), mp 266–290° (lit.[14] mp 288–290°).

The β-phenylhydrazone obtained from 2a was identical with that obtained from 3a; an analytical sample, orange needles, mp 266–268°, was obtained after crystallization from ethanol.

Anal. Calcd for $C_{14}H_9Br_2N_3O$: C, 42.53; H, 2.28; Br, 40.55. Found: C, 42.69; H, 2.30; Br, 40.61.

B. By Oxidation of 1a with Chromic Anhydride.—A suspension of 0.2 g of 1a in a mixture of 3 ml of acetic acid and 1 ml of water was treated, with stirring, with small portions (0.4 g total) of chromic anhydride. The suspension was heated slightly, stored at room temperature for 24 hr, and then poured into water. A precipitate formed which was collected by filtration, washed with water, and dried to give 0.15 g (72%) of practically pure 2a.

C. By Oxidation of 1a with Peracetic Acid.—To a suspension of 0.2 g of 1a in 6 ml of acetic acid, 1 ml of 36% hydrogen peroxide was added. After storage at room temperature for 5 days, the resulting solution was concentrated under reduced pressure; a precipitate formed which was collected by filtration, washed with acetic acid and water, and dried to yield 0.075 g (15%) of practically pure 2a. The acetic mother liquor was evaporated in vacuo to give an additional 0.05 g (60% total yield) of crude 2a.

Bromination of 1a in Carbon Tetrachloride. 2,3,5,6,7-Pentabromoindole (2b), and 1,1,3,5,6-Pentabromooxindole (2d).—A suspension of 1.0 g (2.30 mmol) of 1a[14] in 30 ml of anhydrous SCl_2 was treated with 2.8 g (19.6 mmol) of bromine. After 72 hr at room temperature with occasional stirring 0.115 g (11%) of 2a was collected by filtration. The filtrate was concentrated on a steam-bath to about 8 ml to give 0.6 g of practically pure 1b. The mother liquor was evaporated and the residue was dissolved in benzene and passed through a column of neutral alumina (grade I); elution with benzene gave additional 0.06 g (47% total yield) of pure 1b. An analytical sample, white crystals, mp 206–207.5°, was crystallized from benzene; the ir spectrum showed a band at ca. 3500 cm^{-1} (N-H).

Anal. Calcd for $C_8H_3Br_5N$: C, 18.79; H, 0.39; Br, 78.2. Found: C, 19.00; H, 0.32; Br, 77.8.

1,1,3,5,6,7-Pentabromooxindole (2b). A. By Treatment of 2,3,5,6,7-Pentabromoindole (1b) with Bromine in Acetic Acid.—To a suspension of 0.1 g (0.195 mmol) of 1b in 2.5 ml of acetic acid 0.39 g (2.44 mmol) of bromine was added with stirring. Stirring was continued at room temperature for 24 hr. The mixture was then poured into 40 ml of water to give a precipitate which was collected by filtration, washed, and suspended in a 3% solution of sodium thiosulfate; the resulting compound was again collected, washed with water, and dried to give 0.08 g (78%) of practically pure 2b. A sample crystallized from acetic acid gave yellow needles darkening above 220° with decomposition without melting. The ir spectrum showed bands at ca. 3100 (N-H) and 1745 cm^{-1} (C=O).

Anal. Calcd for C_8HBr_6NO: C, 18.20; H, 0.38; Br, 75.80. Found: C, 18.49; H, 0.45; Br, 76.01.

The β-phenylhydrazone obtained from 2b was crystallized from dimethylformamide to give orange needles melting at 312–314° with decomposition.

Anal. Calcd for $C_{14}H_8Br_5N_3O$: C, 25.42; H, 1.69; Br, 50.60. Found: C, 25.60; H, 1.71; Br, 50.89.

B. By Treatment of 7-Bromoindole (4) with Bromine in Acetic Acid.—To an ice-cold solution of 4.65 g (29.0 mmol) of bromine in 6 ml of acetic acid, 3 ml of acetic acid containing 0.3 g (1.53 mmol) of 4[15] was added dropwise with stirring. The mixture was allowed to warm to 25° and stand for 3 hr, while being stirred. It was then poured into water; a precipitate formed which was collected by filtration, and suspended in a 3% solution of sodium thiosulfate; the resulting compound was again collected, washed with water, and dried to give 0.035 g (67.5%) of practically pure 2b. It was crystallized twice from acetic acid to give colourless needles darkening above 210° without melting. The ir spectrum showed a band at ca. 1740 cm^{-1} (C=O).

Anal. Calcd for $C_8H_2Br_6NO$: C, 20.00; H, 0.42; Br, 74.00. Found: C, 20.16; H, 0.70; Br, 74.01.

The β-phenylhydrazone obtained from 2b was crystallized twice from acetic acid to give orange crystals, mp 192–193°.

Anal. Calcd for $C_{14}H_7Br_5N_3O$: C, 26.90; H, 2.04; Br, 49.10. Found: C, 26.79; H, 1.98; Br, 49.40.

B. By Oxidation of 1a with Chromic Anhydride.—A suspension of 0.15 g of 1a in a mixture of 4 ml of acetic acid and 1 ml of water was treated with 0.3 g of chromic anhydride. The mixture was stored at room temperature for 48 hr, and then poured into water. A precipitate formed which was collected by filtration, washed with water, and dried to yield 0.160 g (52%) of practically pure 2c.

C. By Oxidation of 1a with Peracetic Acid.—To a suspension of 0.2 g of 1a in 1.5 ml of acetic acid, 0.5 ml of 36% hydrogen peroxide was added. After storage at room temperature for 30 days, a precipitate was collected by filtration, washed with water, and dried to give 0.08 g (77.5%) of 2c.

Reaction of 2,3,5,6-Tetrabromo-1-methylindole (1c) with Bromine. A. In Acetic Acid. Constant-Melting Mixture of 1,3,5,6-Tetrabromo-1-methyloxindole (2e) and 3,3,5,6-Pentabromo-1-methyloxindole (2f).—To a suspension of 0.5 g (1.12 mmol) of 1c[16] in 15 ml of acetic acid 0.5 g (3.12 mmol) of bromine was added. After 48 hr at room temperature with occasional stirring, a precipitate was collected by filtration, washed with acetic acid and water, and dried to yield 0.190 g of a mixture of 2e[16] and 2f. The acetic mother liquor was concentrated under reduced pressure to give an additional 0.18 g of the same mixture. All attempts to separate the components of such mixture both by column chromatography and by fractional crystallization were unsuccessful. When the mixture was crystallized twice from acetic acid, crystals were obtained softening at 210–213° with darkening (the melting range remained unchanged through several crystallizations); the ir spectrum showed a band at ca. 1735 cm^{-1} (C=O). Both the melting range and the ir spectrum of the mixture were identical with those of an artificial mixture containing 2e and 2f in 7:3 ratio. Compounds 2e and 2f were contained in 54 and 19.5% yield respectively [yields were based on 7:3 ratio (w/w) of 2e to 2f].

B. In Carbon Tetrachloride. 2,3,5,6-Tetrabromo-1-methylindole (1c) and Constant-Melting Mixture of 2e and 2f.—To a well-stirred suspension of 2.0 g (4.47 mmol) of 1a[14] in 50 ml of anhydrous SCl_2, 3.12 g (19.5 mmol) of bromine was added. Stirring was continued for 48 hr at room temperature. A precipitate was collected by filtration and suspended in a 3% solution of sodium thiosulfate; the resulting compound was again collected, washed with water, and dried to give 0.8 g of practically pure 1d. The mother liquor was concentrated under reduced pressure to about 25 ml, and treated with additional 1.87 g (11.7 mmol) of bromine. After 48 hr at room temperature a precipitate was collected by filtration, and worked up as described above to yield an additional 1.0 g (76% total yield) of practically pure 1d. It was crystallized twice from benzene to give white needles, mp 214–216°.

Anal. Calcd for $C_9H_5Br_4N$: C, 20.60; H, 0.76; Br, 76.00. Found: C, 20.78; H, 1.02; Br, 76.02.

The mother liquor (from which compound 1d was collected) was allowed to evaporate slowly at room temperature; the residue consisted of 0.4 g of the constant-melting mixture of 2e and 2f described in A.

1,3,4,5,6-Pentabromo-1-methyloxindole (2e). A. By Treatment of 2,3,4,5,6-Pentabromo-1-methylindole (1d) with Bromine in Acetic Acid.—To a well-stirred suspension of 0.8 g (1.52 mmol) of 1d in 15 ml of acetic acid 0.64 g (4 mmol) of bromine was added. After 72 hr at room temperature with stirring a precipitate was collected by filtration, and worked-up as described for the treatment of 2b with bromine in acetic acid to yield 0.65 g (79%) of practically pure 2e. An analytical sample, yellow crystals darkening above 240° with decomposition and without melting, was crystallized from acetic acid; the ir spectrum showed a band at ca. 1745 cm^{-1} (C=O).

Anal. Calcd for $C_9H_4Br_5NO$: C, 20.00; H, 0.74; Br, 74.00. Found: C, 19.92; H, 0.80; Br, 73.65.

The β-phenylhydrazone obtained from 2e was crystallized from acetic acid to give orange needles, mp 215–217°.

Anal. Calcd for $C_{15}H_9Br_5N_3O$: C, 26.50; H, 2.04; Br, 49.10. Found: C, 27.01; H, 1.98; Br, 48.95.

B. By Oxidation of 1d with Chromic Anhydride.—A suspension of 0.8 g od 1d in 13 ml of acetic acid was treated, with stirring, with small portions (0.6 g total) of chromic anhydride. The suspension was heated slightly for 1 hr and then poured into 100 ml of water. After storage at room temperature overnight, a precipitate was collected by filtration, washed with water, and dried to give 0.253 g (49%) of practically pure 2e.

C. By Oxidation of 1d with Peracetic Acid.—A suspension of 0.2 g of 1d in 3 ml of acetic acid was treated with 2 ml of 36% hydrogen peroxide. After storage at room temperature for 7 days, a precipitate was collected by filtration, washed with acetic acid and water, and dried to yield 0.2 g (97%) of practically pure 2e.

1,3,4,5,6-Pentabromooxindole (2f).—To an ice-cold solution of 9.4 g (58.8 mmol) of bromine in 10 ml of acetic acid, 10 ml of acetic acid containing 1.22 g (6.21 mmol) of 4-bromoindole (4)[17] was added dropwise with stirring. The mixture was allowed to warm to 25° and stored for 40 hr, while being stirred. It was then poured into water; a precipitate formed which was collected by filtration, suspended in a 3% solution of sodium thiosulfate, again collected, washed with water, dried, dissolved in benzene and passed through a column of silica gel (1.6 × 42 cm); elution with benzene gave 1.04 g (31.5%) of practically pure 2f. A sample crystallized from acetic acid gave yellow brown crystals darkening above 230° without melting; the ir spectrum showed bands at ca. 3200 (N-H) and 1730 cm^{-1} (C=O).

Anal. Calcd for $C_8H_2Br_6NO$: C, 18.20; H, 0.38; Br, 75.80. Found: C, 18.36; H, 0.35; Br, 75.43.

Several attempts to brominate 3 by adding bromine to a solution of the compound in acetic acid gave only brown amorphous products.

The β-phenylhydrazone obtained from 2f was crystallized twice from dimethylformamide to give orange crystals, mp 293–295°.

Anal. Calcd for $C_{14}H_8Br_5N_3O$: C, 25.42; H, 1.69; Br, 50.60. Found: C, 25.54; H, 1.74; Br, 50.81.

4,5,6-Tribromo-1-methylisatin (3b). A. From 1,3,4,5,6-Pentabromo-1-methyloxindole (2d).—The hydrolysis of 2d was carried out according to Stolé,[2a] with a mixture of ethanol and 2N sodium hydroxide. The pure isatin 3b, obtained in 27% yield as red needles after sublimation at 220°/3 mm and crystallization from benzene, melted at 253–255°. The ir spectrum showed band at ca. 1750 cm^{-1} (C=O).

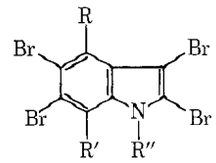
Anal. Calcd for $C_9H_4Br_3NO_2$: C, 27.16; H, 1.01; Br, 60.26. Found: C, 27.61; H, 1.10; Br, 60.44.

The β-phenylhydrazone obtained from 3b was identical with a sample prepared from 2d.

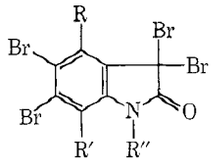
B. From 1,1,3,4,5,6-Pentabromooxindole (2f).—When 0.5 g of 2f was treated as described for the methylation of 2,3,5,6,7-pentabromoindole (1b), except that the mixture was stirred for 24 hr, a solution formed which was diluted with water, and acidified with sulfuric acid; a red precipitate formed which after sublimation at 240°/3 mm and crystallization from benzene gave 0.03 g (8%) of pure 3b.

Oxidation of 2,3,5,6-Tetrabromo-1-methylindole (1e). A. With Chromic Anhydride.—A suspension of 0.5 g of 1e[16] in a mixture of 15 ml of acetic acid and 2 ml of water was treated with 0.5 g of chromic anhydride. The mixture was heated slightly in order to dissolve the solid, then allowed to cool to 25°, and poured in 100 ml of water. After storage at room temperature overnight a precipitate was collected by filtration, washed with water, and dried to yield 0.28 g of a mixture of 5,6-dibromo-1-methylisatin (3c) and 3,3,5,6-tetrabromo-1-methyloxindole (2g). Fractional crystallization of the mixture from methanol yielded first 0.15 g (29%) of compound 2g, darkening above 220° with slow decomposition (lit.[16] darkening above 220° with slow decomposition), and then 0.12 g (33.3%) of compound 3c, mp 255–256° (lit.[16] 255–256°).

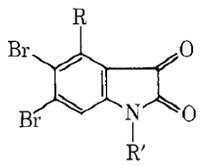
B. With Peracetic Acid.—Compound 2g was obtained in 83% yield from 0.3 g of 1e as described for the oxidation of 1a with peracetic acid, except that the mixture was stirred at room temperature for 3 days.



1a, R = R′ = R″ = H
b, R = R″ = H; R′ = Br
c, R = H; R′ = Br; R″ = CH_3
d, R = Br; R′ = H; R″ = CH_3
e, R = R′ = H; R″ = CH_3



2a, R = R′ = R″ = H
b, R = R″ = H; R′ = Br
c, R = H; R′ = Br; R″ = CH_3
d, R = Br; R′ = H; R″ = CH_3
e, R = R′ = H; R″ = CH_3
f, R = Br; R′ = R″ = H



3a, R = R′ = H
b, R = Br; R′ = CH_3
c, R = H; R′ = CH_3

(47% yield) (no C=O peak, N-H stretching at 3600 cm^{-1}) to which structure **1b** was assigned. Although the reaction was carried out under dry conditions, a small amount (11% yield) of the oxindole **2a** was isolated.[4] Structure **1b** was assigned to the nonoxindolic material, because it gave, with excess bromine in acetic acid suspension, the pentabromooxindole **2b**, which was also obtained by adding 7-bromoindole (**4**)[5] to an excess of bromine in acetic acid solution. Compound **2b** gave with phenylhydrazine 5,6,7-tribromoisatin β-phenylhydrazone.

When an acetic acid suspension of 2,3,5,6,7-pentabromo-1-methylindole (**1c**), obtained by methylation of **1b**, was treated with an excess of bromine, 3,3,5,6,7-pentabromo-1-methyloxindole (**2c**) (C=O peak at 1740 cm^{-1}, 67% yield) was isolated. Two bromine atoms are in the 3 position because compound **2c** gave, with phenylhydrazine, 5,6,7-tribromo-1-methylisatin β-phenylhydrazone.

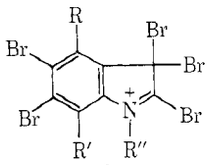
The reaction of 2,3,5,6-tetrabromo-1-methylindole (**1e**)[1b] with excess bromine was also solvent dependent. When the reaction was carried out in acetic acid, an oxindolic material (C=O band at 1735 cm^{-1}), whose melting range remained unchanged through several crystallizations, was isolated. This material was identified as a mixture of 3,3,5,6-tetrabromo-1-methyloxindole (**2e**)[1b] and 3,3,4,5,6-pentabromo-1-methyloxindole (**2d**). Its infrared spectrum and melting range were identical with those of an artificial mixture containing **2e** and **2d** in 7:3 ratio (w/w). Similar constant-melting mixtures of isomeric and nonisomeric bromoindoles have been already described.[1,5]

Structure **2d**[6] (C=O peak at 1745 cm^{-1}) was assigned to the minor product of the reaction of **1e** with bromine on the basis of its elemental composition and of the fact that it was different from **2c**; **2d** was hydrolyzed with alkali to isatin **3b**, which gave the same β-phenylhydrazone as **2d**. Structure **3b** was proved as follows: 4-bromoindole (**5**)[7] was added to an excess of bromine in acetic acid solution to yield 3,3,4,5,6-pentabromooxindole (**2f**) (N-H band at 3200 cm^{-1}, C=O band at 1730 cm^{-1}); compounds **2f** and **2b** are isomers; compound **2f** gave a β-phenylhydrazone with phenylhydrazine, and isatin **3b** by methylation with dimethyl sulfate in alkaline medium (hydrolysis of **2d** to **3b** accompanies the methylation).

When the reaction of **1e** with excess bromine was carried out in anhydrous CCl_4, 2,3,4,5,6-pentabromo-1-methylindole (**1d**, 76% yield) and the same mixture (from the mother liquor) of **2e**[1b] (13.5% yield) and **2d** (5% yield) were formed. Structure **1d** was assigned, because **1d** and **1c** are isomers, and **1d** led, with excess bromine in acetic acid, to the oxindole **2d** (79% yield).

When the results of the reactions of 2,3,5,6-tetrabromo-1-methylindole (**1e**) with bromine and of the unmethylated analog **1a** are compared, it can be seen that the bromination of the aromatic ring occurs at the 7 position in the nonmethylated and at the 4 position in the N-methylated compound. These results can be explained with the assumption that there is a preference for electrophilic attack on position 7 but that the *N*-methyl group exerts a sufficiently strong steric hindrance to prevent substitution at the 7 position, making attack at carbon 4 competitive.

In a previous paper we found that, when 1-methylindole was treated with excess bromine, 3,3,5,6-tetrabromo-1-methyloxindole (**2e**) was obtained; in one case also 2,3,5,6-tetrabromo-1-methylindole (**1e**) was isolated from the reaction mixture.[1b] The mode of conversion of 1-methylindole to the oxindole **2e** is an interesting problem. Using a 5:1 molar ratio of reagent to substrate, bromination of the benzene ring took place;[1b] when bromine atoms substitute on the benzene ring they have a very marked stabilizing effect, so that hydrolysis of 2,3-dibrominated polybromoindoles requires very drastic conditions.[1b] Therefore it was excluded that oxindole **2e** was formed by bromination of the 3 position of 3,5,6-tribromo-1-methyloxindole; in fact, the latter compound should be formed by hydrolysis of 2,3,5,6-tetrabromo-1-methylindole (**1e**); it was excluded also that oxindole **2e** was formed by bromination of a simple intermediate nonbrominated oxindole,[8] because, when simple oxindoles are brominated, bromine attacks only positions 3, 5, and 7.[1b,9] The formation of oxindole **2e** was believed to involve electrophilic attack on position 3 of indole **1e** to give an intermediate 3,3-dibrominated indolenine 6 (R = R′ = H; R″ = CH_3), followed by rapid attack of a nucleophile (H_2O or BrO^-). The same hypothetical intermediate 6 satisfactorily ra-



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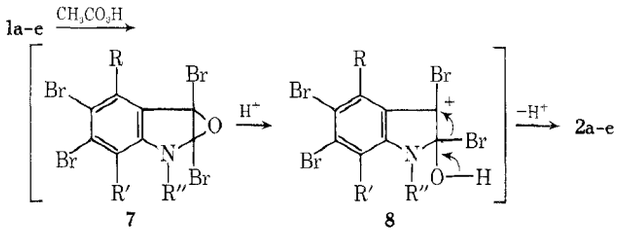
tionalizes the formation of oxindoles **2a–e** from the corresponding indoles **1a–e**. Then the present results seem to confirm the previously proposed pathway, whereas the mechanisms proposed by other authors[8] appear to be not effective in this case.

A matter of particular interest is the action of two oxidizing agents, chromic anhydride and peracetic acid, on 2,3-dibrominated indoles **1a–e**. Although in these compounds bromine atoms (electron-attracting substituents) substitute on the benzene ring, position 2 is substituted, and compounds **1c–e** are N-substituted also (such factors promote generally oxidation of some indole derivatives to *o*-acylamino ketones or to anthranilic acids);[1a,2a,10] nevertheless the reaction of **1a–e** with chromic anhydride and with peracetic acid did not yield usual products of oxidation.

When products **1a–d** were treated with chromic anhydride or with peracetic acid the corresponding 3,3-dibromooxindoles **2a–d** were isolated in yields ranging from 49 to 90%. Compound **1e** gave 3,3,5,6-tetrabromo-1-methyloxindole (**2e**, 83% yield) when the reaction was carried out with peracetic acid, whereas compound **2e** (29% yield) and 5,6-dibromo-1-methylisatin (**3c**, 33% yield) were isolated by reaction with chromic anhydride.

Since all 2,3-dibromoindoles were converted to 3,3-dibromooxindoles, this method could be used as a diagnostic tool in the structure determination of 2,3-dibromoindoles.

One possible explanation of the unusual oxidative reaction could involve the formation of an epoxide intermediate **7**, followed by opening of the epoxide ring to give a carbonium ion **8**, a 1,2 shift, and expulsion of the proton



to yield the observed 3,3-dibromooxindole. Similar molecular rearrangements have been already observed in the peracid epoxidation of several haloalkenes.[11]

Acknowledgment. This work was supported by a grant from the Consiglio Nazionale delle Ricerche.

Registry No.—**1a**, 17826-06-1; **1b**, 51417-37-9; **1c**, 51417-38-0; **1d**, 51417-39-1; **1e**, 25055-55-4; **2a**, 51417-40-4; **2a** β-phenylhydrazone, 51417-41-5; **2b**, 51417-42-6; **2b** β-phenylhydrazone, 51417-43-7; **2c**, 51417-44-8; **2c** β-phenylhydrazone, 51417-45-9; **2d**, 51417-46-0; **2d** β-phenylhydrazone, 51417-47-1; **2e**, 25055-56-5; **2f**, 51417-48-2; **2f** β-phenylhydrazone, 51417-49-3; **3b**, 51417-50-6; **4**, 51417-51-7.

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References and Notes

(1) (a) A. Da Settimo, M. F. Saettone, E. Nannipieri, and P. L. Barili, *Gazz. Chim. Ital.*, **97**, 1304 (1967); (b) A. Da Settimo and E. Nannipieri, *J. Org. Chem.*, **35**, 2546 (1970).
(2) (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); (c) J. C. Powers, *ibid.*, **31**, 2627 (1966); (d) R. J. Bass, *Tetrahedron*, **27**, 3263 (1971).
(3) R. L. Hinman and C. P. Bauman, *J. Org. Chem.*, **29**, 2431 (1964).
(4) It is not unlikely that atmospheric moisture present in the reaction vessel might have supplied the oxygen for oxindole formation. Indeed, only a trace amount of water (4.6 mg) is required for the formation of the observed 115 mg of **2a** (see Experimental Section), and the ir spectrum of the crude reaction product was identical with that of the pure oxindole. Other authors (see ref 2b) have reported a similar formation of oxindoles when working in anhydrous conditions.
(5) B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **38**, 1467 (1960).
(6) Compound **2d** was obtained, as pure compound, from **1d** (see below).
(7) G. Pappalardo and T. Vitali, *Gazz. Chim. Ital.*, **88**, 1147 (1958).
(8) *E.g.*, under Witkop's[2a] or Hinman's[2b] conditions simple oxindoles are intermediates in the formation of 3-bromooxindoles.
(9) (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).
(10) See, *e.g.*, (a) R. J. S. Beer, T. Donavanik, and A. Robertson, *J. Chem. Soc.*, 4139 (1954); (b) K. Schofield and R. S. Theobald, *ibid.*, 1505 (1950); (c) A. Da Settimo and M. F. Saettone, *Tetrahedron*, **21**, 1923 (1965).
(11) See, *e.g.*, (a) R. N. McDonald and P. A. Schwab, *J. Amer. Chem. Soc.*, **85**, 4004 (1963); (b) R. N. McDonald and T. T. Tabor, *ibid.*, **89**, 6573 (1967); (c) R. N. McDonald and R. N. Steppel, *ibid.*, **92**, 5664 (1970); (d) W. A. Denny, V. Kumar, G. D. Meakins, J. Pragnell, and J. Wicha, *J. Chem. Soc., Perkin Trans. 1*, 486 (1972).

Stereochemistry and Mechanism of the Thermal [1,3] Alkyl Shift of Stable 1,4-Dialkyl-1,4-dihydropyrazines[1a,b]

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Stable 8-π-electron 1,4-dialkyl-1,4-dihydropyrazines are readily prepared by reaction of *N*-benzyldiphenacylamine hydrobromide with primary aliphatic amines provided care is taken to avoid the subsequent rearrangement. The previously postulated intermediacy of 1,4-dibenzyl-1,4-dihydro-2,6-diphenylpyrazine (**1a**) in the rearrangement to 1,2-dihydropyrazine **2a** is demonstrated and the reaction proceeds in 95 ± 2% yield with first-order kinetics. Crossover recombination experiments show 12 ± 6% intermolecular contribution from a radical dissociation–recombination process which is prevented with butanethiol scavenger. Chiral **24** rearranges in the presence of the scavenger with ≥95% stereospecificity and with inversion of the migrating group indicating an 88 ± 6% component of a concerted [1,3] sigmatropic shift with suprafacial allylic utilization.

We wish to report the general synthesis and chemistry of novel 1,4-dialkyl-2,6-diphenyl-1,4-dihydropyrazines[1] **1** and a study of the stereochemistry and mechanism of their thermally induced rearrangement to the isomeric 1,2-dialkyl-3,5-diphenyl-1,2-dihydropyrazines **2**. Compounds of structure **1** are of interest in possessing an 8π available electron system which is potentially antiaromatic[2] or homoaromatic.[3] In addition, the structural similarity between the 1,4-dihydro-1,4-dialkylpyrazines and the reactive ring of the isoalloxazine portion of the reduced flavin coenzymes **3**[4] and the marked propensity of both to undergo redox reactions (which see) renders **1** of interest as model compounds for the latter. The structurally related 5,10-dihydrophenazines **4** have been employed as analogs of riboflavin.[4,5] The recent discovery of the importance of the 1,4-dihydropyrazine moiety in the biolumi-