mers of 2-fluoro-3-bromosuccinic acid esters takes place at higher temperatures. Such interconversion must involve the scission of a chemical bond and its regeneration in a different steric fashion.

Fluorine has been found to be an activating group. Bergmann[18] has shown that, on treatment with a base, fluoroacetic esters readily produce carbanions which can be alkylated. In view of this it appeared plausible that carbanion IX might be instrumental in the interconversion of the *threo* and *erythro* isomers. To test this possibility a sample of the dimethyl fumarate derivative and deuterated methanol (CH_3OD) was heated to 150–155° for 2 hr. The n.m.r. spectrum indicated the usual conversion of the *erythro* to the *threo* isomer, but no deuterium incorporation. It is evident, therefore, that a carbanion is not involved in the isomer interconversion. We have observed that hydrogen fluoride failed to add to bromomaleate and bromofumarate.

No etching of the n.m.r. tubes was observed during the heating experiments. Reversible elimination and addition of hydrogen fluoride is, therefore, unlikely to be involved in the interconversion of these esters.

A free-radical mechanism does not appear to be involved because e.p.r. spectra studies on the heated sample of the dimethyl maleate derivative failed to indicate any unpaired electrons. Moreover, if free radicals are formed, the n.m.r. spectrum at high temperature should have shown broadening of the peaks.[19] The proton n.m.r. peaks, however, were found to be sharp at all the temperatures studied. If, however, free radicals have very short life or are produced in small concentrations, our methods for the detection of free radicals may have been inadequate.

The mediation of a carbonium ion in the interconversion of the *threo* and the *erythro* epimers is possible. Further work will be necessary to get definitive evidence about the mechanism of interconversion of the isomeric fluorobromo esters.

Acknowledgment.—We wish to thank Dr. E. R. Malinowski and Professors P. Allen and J. van der Veen for helpful discussions, and R. Spanier for determining some of the n.m.r. spectra. This work was supported in part by a grant (CA-05079) from the National Cancer Institute of the U. S. Public Health Service.

(19) S. I. Weisman, C. R. Bruce, and R. E. Norberg, *J. Chem. Phys.*, **24**, 473 (1958).

Reactions of N-Bromosuccinimide and Indoles. A Simple Synthesis of 3-Bromooxindoles[1]

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N-Bromosuccinimide (NBS) in *t*-butyl alcohol converts 3-alkylindoles such as skatole, indole-3-acetic acid, and other indole-3-alkanoic acids to the corresponding oxindoles when a 1:1 mole ratio of NBS to indole is used. 3-Bromooxindoles are obtained with a 2:1 ratio of reactants. Oxindoles are intermediates in the formation of 3-bromooxindoles, but NBS does not attack oxindoles in dry alcohol. The hydrogen bromide evolved in oxindole formation in the first step must catalyze the formation of 3-bromooxindoles, probably by way of the enol form of the oxindole. Basic catalysis of 3-bromination of oxindoles by NBS can be effected also, but in neutral aqueous *t*-butyl alcohol 5-bromooxindoles are formed. In glacial acetic acid NBS effects bromination of the indole hetero ring. The reaction of indoles and NBS is the method of choice for the synthesis of oxindole-3-acetic acid and related compounds, as well as oxindole analogs of tryptamine and tryptophan. The reaction also provides the first simple and general route to 3-alkyl-3-bromooxindoles, stable intermediates which undergo facile replacement of the halogen by alcohols, water, and other nucleophiles. The mechanisms of oxindole formation and bromination are discussed. The ultraviolet and infrared absorption spectra of the bromoindoles are tabulated.

Interest in the products of chemical and enzymatic oxidations of indoles[2] prompted us to seek new methods for the synthesis of oxindoles and dioxindoles related to indole-3-acetic acid (IAA). Lawson and Witkop have shown that N-bromosuccinimide (NBS) can be used to convert indoles to oxindoles[3,4] and have drawn attention to the importance of the solvent in determining the nature of the products—nonaqueous media favoring bromine substitution of the hetero ring, aqueous media supporting oxindole formation.[5]

In the course of further studies on the effects of solvents, we have found that NBS in *t*-butyl alcohol is an excellent system for converting a variety of 3-alkylindoles to the corresponding oxindoles in one operation. Depending on the NBS–indole ratio, either simple oxindoles or 3-bromooxindoles can be obtained (eq. 1). The latter compounds are stable but reactive intermediates accessible for the first time by a simple and convenient procedure. Some of their reactions will be described in a forthcoming publication.[6] We have also studied the reactions of NBS and a variety of indoles in glacial acetic acid, in which substitution predominates.

Reactions in *t*-Butyl Alcohol.—The reactions of NBS and indoles in *t*-butyl alcohol are summarized in Table I.

(1) Presented before the Organic Division of the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

(2) (a) R. L. Hinman and P. Frost, "Plant Growth Regulation," R. Klein, Ed., Iowa State University Press, Ames, Iowa, 1961, p. 205; (b) R. L. Hinman, C. Bauman, and J. Lang, *Biochem. Biophys. Res. Commun.*, **5**, 250 (1961).

(3) W. B. Lawson and B. Witkop, *J. Org. Chem.*, **26**, 263 (1961).

(4) *t*-Butyl hypochlorite has been used to transform members of the indole alkaloids to oxindoles by pathways analogous to those described here, but generally involving migration of an alkyl group from the 2-position [N. Finch and W. E. Taylor, *J. Am. Chem. Soc.*, **84**, 3871 (1962); J. Shavel and H. Zinnes, *ibid.*, **84**, 1320 (1962)].

(5) W. B. Lawson, A. Patchornik, and B. Witkop, *ibid.*, **82**, 5918 (1960).

(6) R. L. Hinman and C. P. Bauman, *J. Org. Chem.*, in press.

TABLE I

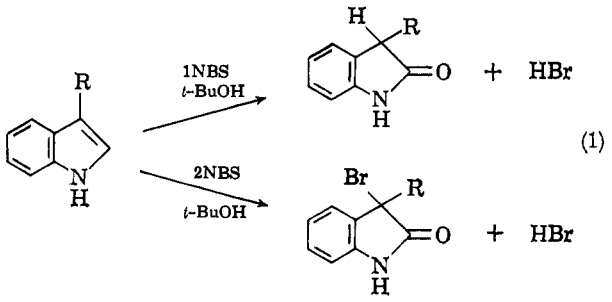
REACTIONS OF INDOLES WITH N-BROMOSUCCINIMIDE IN *t*-BUTYL ALCOHOL

Indole	Mole ratio of NBS–indole	Solvent[a]	Product	% yield	Recrystn. solvent[b]	M.p., °C.	Reported m.p., °C.	Empirical formula	Anal., % Calcd. C	H	N	Br	Found C	H	N	Br
Skatole	1	B[c]	3-Methyloxindole	26	W, A–H	124–125	123–124[d]	C_9H_9NO	73.43	6.17	9.52		73.21	6.27	9.56	
Indole-3-acetic acid	1	A[c]	Oxindole-3-acetic acid	42	A–B	145–146	147[e]	$C_{10}H_9NO_3$								
Indole-3-propionic acid	1	B[f]	Oxindole-3-propionic acid	52	A, W	169–170	169–170[g]	$C_{11}H_{11}NO_3$	64.38	5.40	6.82		64.62	5.57	6.92	
Indole-3-butyric acid	1	B[c]	Oxindole-3-butyric acid	50	A, B, M	170–171		$C_{12}H_{13}NO_3$	65.74	5.98	6.39	(219)[h]	65.58	5.93	6.38	(218)[h]
Indole-3-caproic acid	1.1	A[c]	Oxindole-3-caproic acid	4[i]	A	159.5–160.0		$C_{14}H_{17}NO_3$	67.97	6.93	5.67		68.02	7.30	5.43	
3-(β-Benzamidoethyl)-indole	1	B[f]	3-(β-Benzamidoethyl)-oxindole	35	A	195–197	194[j]	$C_{17}H_{16}N_2O_2$	72.83	5.75	10.00		72.56	5.78	10.16	
Tryptamine·HBr	1	B[k]	3-(β-Aminoethyl)oxindole hydrobromide	31	A–E, E	266–268 dec.		$C_{10}H_{13}BrN_2O$	46.70	5.09	10.90	31.08	46.55	5.22	10.68	31.20
N^{α}-Acetyltryptophan	1	C[c]	α-Acetamido(oxindole-3)-propionic acid	14	A–M	214.0–214.5	209–210[l]	$C_{13}H_{14}N_2O_4$	59.53	5.38	10.68		59.87	5.37	11.21	
			α-Acetamido(dioxindole-3)-propionic acid lactone	8	M–W	290–293 dec.	284 dec.[m]	$C_{13}H_2N_2O_4$	59.99	4.65	10.77		60.07	4.72	10.88	
Skatole	2	A[f]	3-Bromo-3-methyloxindole	42	A–B	143 dec.		C_9H_8BrNO	47.81	3.57	6.20	35.35	47.61	3.54	6.36	35.29
Indole-3-acetic acid	2	A[f]	3-Bromooxindole-3-acetic acid	75	A–B	151–152 dec.		$C_{10}H_8BrNO_3$	44.46	2.98	5.19	29.59	44.59	3.20	5.05	29.80
Indole-3-propionic acid	2	A[f]	3-Bronooxindole-3-propionic acid	44[n]												
Indole-3-butyric acid	2	A[f]	3-Bromooxindole-3-butyric acid	63	T–B	140–141 dec.		$C_{12}H_{12}BrNO_3$	48.34	4.06	4.70	26.80	48.54	4.04	4.63	26.60

[a] A, *t*-butyl alcohol; B, 95% *t*-butyl alcohol; C, 81% *t*-butyl alcohol. [b] A = acetone; B = benzene; E = absolute ethanol; H = hexane; M = methanol; T = tetrahydrofuran; W = water. [c] *t*-Butyl alcohol not purified before use. [d] Ref. 28. [e] Ref. 8. [f] *t*-Butyl alcohol dried over sodium sulfate and treated once with Darco G. [g] P. L. Julian and H. C. Printy, *J. Am. Chem. Soc.*, **75**, 5301 (1953). [h] Neut. equiv. [i] Result of one experiment; low yield probably a result of not purifying solvent. [j] Ref. 11b. [k] Treated twice with Darco before use. [l] Ref. 10b. [m] Ref. 10a. [n] Bromooxindole could not be crystallized; converted to dioxindole with dilute sulfuric acid; yield given is of dioxindole.

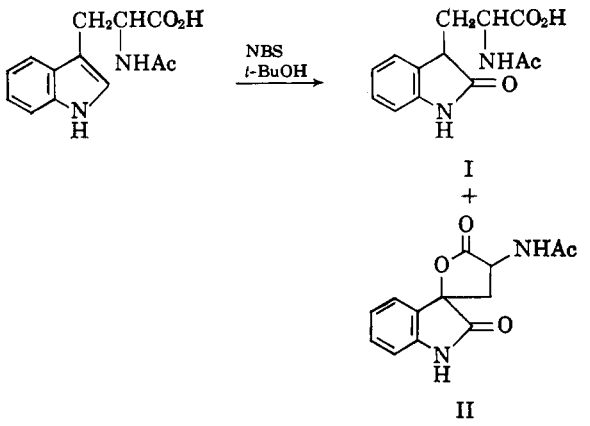
The synthesis of an oxindole by use of a 1:1 mole ratio of NBS and indole could be carried out in an open erlenmeyer flask at room temperature, and the course of the reaction was readily followed by the changes in the ultraviolet spectrum.[7] Reactions were usually complete as soon as all the NBS had dissolved. Although oxindoles were obtained when anhydrous *t*-butyl alcohol was used, the yields were improved considerably when 5% of water was added to the solvent, presumably because water is the source of the oxygen introduced at the 2-position. The addition of still more water tends to promote 5-bromination of the oxindole already formed. Moreover, for the synthesis of oxindole-3-acetic acid (OAA), dry conditions are preferable since rearrangement of oxindole-3-acetic acid to 3,4-dihydroquinolone-4-carboxylic acid is facilitated by a more polar medium.[8] When water was not added, however, purification of the solvent was usually required to remove an impurity which exerts a powerful effect on the product distribution between oxindoles and α-bromoindoles (see Experimental).

Although the yields are modest, the simplicity of the method recommends it over those reported previously for the conversion of indoles to oxindoles.[3,9] An attractive application of the procedure was the synthesis of α-acetamidooxindole-3-propionic acid (I) from N^{α}-acetyltryptophan. The oxindolealanine, previously accessible only by multistep procedures,[10] was obtained in 14% yield (based on unrecovered starting material) along with the lactone of α-acetamidodioxindole-3-propionic acid (II), the latter apparently arising from the presence of the sodium bicarbonate added to increase the solubility of the starting material in the reaction medium (see col. 2).



(1)

The oxindole analog of tryptamine[11] was also synthesized by this method. Attack on the primary amino group was avoided by the addition of hydrogen bromide prior to the reaction with NBS. Attempts to apply this technique to the synthesis of oxindole-3-alanine were unsuccessful.



II

The reaction of 2 moles of NBS with a 3-alkylindole *in aqueous media* leads to a 5-bromooxindole.[5] The oxindole, a modified acetanilide, is apparently brominated *para* to the acylamino group as rapidly as the latter is formed in the polar medium. In *t*-butyl alcohol, as used in the present work, the reaction follows a different path and 3-alkyl-3-bromooxindoles are formed (Table I). This procedure, which affords the first simple general route to 3-alkyl-3-bromooxindoles, is also simple to carry out. Reaction of the second mole of NBS is slower than the first, but the reaction is usually complete within 1–2 hr. after the NBS has been added. Since water promotes 5-bromination of oxindoles, the *t*-butyl alcohol was usually dried before use, in contrast to the practice of adding water when only 1 mole of NBS was used. Removal of impurities from the solvent was necessary for optimum results.

The 3-bromooxindoles were characterized by their elemental analyses, labile halogen (precipitate with alcoholic silver nitrate within 3 sec. at room temperature), typical oxindolic carbonyl and NH peaks in the infrared, and conversion to dioxindoles and 3-methoxyoxindoles by treatment with water and methanol, respectively (reactions which will be described in detail in a subsequent publication).[6]

In several experiments with indole-3-acetic acid both 3-bromooxindole-3-acetic acid and its *t*-butyl ester were obtained. The hydrogen bromide evolved during the reaction was probably responsible for the esterification, but we have been unable to effect direct esterification of the isolated acid under comparable conditions. Indole-3-propionic acid (IPA) was converted to the 3-bromooxindole, as indicated by the characteristic ultraviolet spectrum of the class,[7] but the product could not be obtained in solid form. It was characterized by hydrolysis under acidic conditions to a mixture of crystalline β-dioxindole-3-propionic acid and its lactone. By carrying out the reaction of indole-3-propionic acid and NBS in the presence of sodium bicarbonate, the lactone could be obtained directly.

t-Butyl hypochlorite and bromine in *t*-butyl alcohol were also examined as reagents for oxindole formation. From the reaction of a 2:1 mole ratio of *t*-butyl hypochlorite to skatole, no 3-chlorooxindole could be isolated. Only a very small amount of what was presumably 5-chloro-3-methyloxindole was obtained. Bromine and indole-3-butyric acid (IBA) (1:1 mole ratio)

(7) The marked differences between the ultraviolet spectra of alkylindoles [λ_{max} ~ 288 mμ (ε ~ 7000), see Table V] and the derived oxindoles [λ_{max} ~ 250 mμ (ε ~ 8000)] are well-known. The spectra of 3-bromooxindoles, which have not previously been recorded, show an unexpected difference from the parent oxindoles by having a double peak in the 220–230-mμ region and no observable maximum in the normal oxindolic region near 250 mμ. Thus, in 95% ethanol, 3-methyloxindole absorbs at λ_{max} 207, 249, and 278 (sh) mμ (ε 27,400, 8720, 1440), whereas 3-bromo-3-methyloxindole absorbs at λ_{max} 217, 229 (sh), and 310 mμ (ε 16,900, 13,400, and 940).

(8) P. L. Julian, H. C. Printy, R. Ketcham, and R. Doone, *J. Am. Chem. Soc.*, **75**, 5309 (1953).

(9) (a) W. E. Sumpter and F. M. Miller, "Heterocyclic Compounds with Indole and Carbazole Systems," Interscience Publishers, Inc., New York, N. Y., 1954, p. 134; (b) C. E. Dalgliesh and W. Kelly, *J. Chem. Soc.*, 3723 (1958).

(10) (a) P. L. Julian, E. E. Dailey, H. C. Printy, H. L. Cohen, and S. Hamashige, *J. Am. Chem. Soc.*, **78**, 3503 (1956); (b) J. W. Cornforth, R. H. Cornforth, C. E. Dalgliesh, and A. Neuberger, *Biochem. J.*, **48**, 591 (1951); (c) T. Wieland, O. Weiberg, and W. Dilger, *Ann.*, **592**, 69 (1955).

(11) (a) J. Harley-Mason and R. F. J. Ingleby, *J. Chem. Soc.*, 3639 (1958); (b) K. Freter, M. Weissbach, B. Redfield, S. Udenfriend, and B. Witkop, *J. Am. Chem. Soc.*, **80**, 983 (1958).

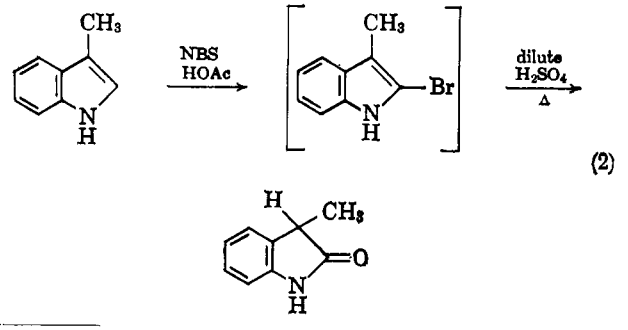
gave a low yield of oxindole-3-butyric acid. Bromine has been used more successfuly in aqueous acetic acid.[3]

Reactions in Acetic Acid.—To gain further insight into the effect of solvent on the reactions of indoles with NBS, a number of reactions were carried out in glacial acetic acid. As shown in Table II, NBS in this solvent at room temperature rapidly brominates indoles at an available position in the hetero ring. Indole itself gave a mixture of products which could not be identified.[12]

Although brominodoles were the main products, oxindolic materials were invariably found also and recognized by their ultraviolet and infrared spectra. In view of the marked instability of the bromoindoles in the presence of acids, it seemed likely that the oxindolic material was formed by the action of hydrogen bromide evolved during the reaction. However, scrupulous drying of the acetic acid and work-up of the product by first pouring the reaction mixture into base did not eliminate the oxindoles. Since some 2,6-dibromoindole-3-butyric acid was isolated from the reaction of NBS with indole-3-butyric acid in *t*-butyl alcohol from which the main product (63%) was the 3-bromooxindole-3-butyric acid (Table I), it is apparent that substitution and oxidation are competitive reactions, and that the balance is shifted by the solvent, but that neither reaction is completely excluded.[13]

The simple bromoindoles were not very stable, undergoing gradual decomposition on standing, a process accelerated by acid or light.[12] When heated with acidic silver nitrate solution, a precipitate of silver bromide formed rapidly, but in the absence of acid, no precipitate formed, even on prolonged heating. The resistance of a presumed 2-bromolysergic acid diethylamide to reaction with silver oxide has been noted previously.[14] 2-Bromoskatole was recovered unchanged after 24 hr. in refluxing ethanolic potassium hydroxide solution.

The instability under acidic conditions of indoles substituted at the α-position by bromine and other related leaving groups has been used previously to obtain oxindoles.[5,11b,14] We have found that by simply adding sulfuric acid to the reaction mixture of NBS and a 3-alkylindole and refluxing, the 3-alkyloxindole can be obtained in one over-all operation, without isolation of the intermediate (eq. 2). Thus, oxindole-3-butyric



(2)

TABLE II

SUBSTITUTION REACTIONS OF N-BROMOSUCCINIMIDE WITH INDOLES[a]

Starting indole	Mole ratio of NBS-indole	Product indole	% yield	M.p., °C.	Recrystn. solvent[b]	Empirical formula	Anal., % Calcd. C	H	N	Br	Found C	H	N	Br
3-Methyl	1	2-Bromo-3-methyl	45	88–90 dec.	A–W	C_9H_8BrN	51.48	3.84	6.67	38.06	51.54	4.00	6.71	37.89
2-Methyl	1[c]	3-Bromo-2-methyl	50	90–91 dec.[d]	B–H	C_9H_8BrN	51.48	3.84	6.67	38.06	51.55	3.79	6.77	37.98
1,2-Dimethyl	1[e]	3-Bromo-1,2-dimethyl	64	73–74 dec.	M	$C_{10}H_{10}BrN$	53.59	4.51	6.25	35.65	53.33	4.58	6.46	35.23
3-*n*-Propyl	1	2-Bromo-3-*n*-propyl	25[f] (crude)											
3-*n*-Propyl	2	2,6-Dibromo-3-*n*-propyl	*f*											
2-Bromo-3-methyl	1	2,6-Dibromo-3-methyl	48	99–101 dec.[g]	E–W									
Indole-3-butyric acid	1	2-Bromoindole-3-butyric acid	19	99–100	W	$C_{12}H_{12}BrNO_2$	51.08	4.28	4.96 (282)[h]	28.32	51.29	4.52	4.94	28.28 (280[h])
Indole-3-butyric acid	2	2,6-Dibromoindole-3-butyric acid	*i*	165–166 dec.	M–W	$C_{12}H_{11}Br_2NO_2$	39.92	3.07	3.88	44.27	39.99	3.21	4.20	44.32

[a] Solvent was glacial acetic acid, dried before use with triacetyl borate, except where noted otherwise. [b] A = acetic acid; B = benzene; E = ethanol; H = hexane; M = methanol; W = water. [c] Acetic acid not dried. [d] Terent'ev, Belenkii, and Yanovskaya [*Zh. Obshch. Khim.*, **24**, 1265 (1954)] report m.p. 86–87°. [e] Solvent *t*-butyl alcohol. [f] Product was an oil which could not be purified; identified by ultraviolet and infrared spectra and by hydrolysis to the corresponding oxindole. [g] Lit.[5] m.p. 100° dec. [h] Neut. equiv. [i] Isolated as a by-product from reactions in *t*-butyl alcohol.

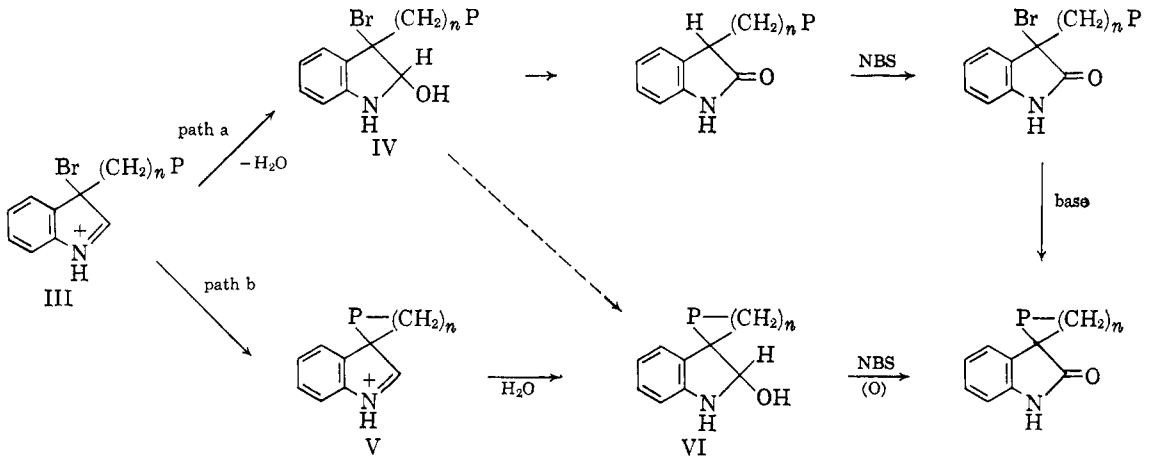
(12) Conversion of indole to 3-bromoindole by use of dioxane dibromide or pyridinium bromide perbromide has been reported [K. Piers, C. Meimaroglow, R. V. Jardine, and R. K. Brown, *Can. J. Chem.*, **41**, 2399 (1963)]. This method was particularly effective with pyridine as the solvent. From attempts to brominate skatole with NBS in 2,6-lutidine we were unable to obtain any pure product.

(13) Although the formation of 5-bromo-3-methyloxindole from skatole in aqueous acetic acid may be a result of hydrolysis of the α-bromoindole, it seems more likely that it arises by a change in reaction mechanism (see below).

(14) K. Freter, J. Axelrod, and B. Witkop, *J. Am. Chem. Soc.*, **79**, 3191 (1957).

CHART I

POSSIBLE PATHWAYS OF OXINDOLE FORMATION



acid was obtained in 41% over-all yield from indole-3-butyric acid and 3-methyloxindole was obtained in 26% yield from skatole. For simple conversion of an indole to an oxindole, however, the reaction with NBS in *t*-butyl alcohol is more convenient.

Although hydrolysis of α-bromoindoles takes place quite readily, introduction of a bromine into the aromatic ring has a very marked retarding effect. 2,6-Dibromoskatole underwent no perceptible hydrolysis during 2 hr. in a refluxing ethanolic solution, which was 1.1 *M* in sulfuric acid. With refluxing dioxane as solvent, as used by Witkop,[5] hydrolysis to the oxindole took place. With 2,6-dibromo-3-*n*-propylindole, only partial hydrolysis was effected during 19 hr. even in refluxing dioxane in which the sulfuric acid concentration was 4.5 *M*.

2,6-Dibromoindole-3-butyric acid behaved similarly. The decreased reactivity is probably the result of a decrease in the basicity of the ring system since 3-protonation[15] is undoubtedly the first step in hydrolysis.

Mechanisms of the Reactions.—Witkop has proposed[5] two pathways for the reaction of NBS and indoles in aqueous media which account for both the formation of oxindole derivatives from simple indoles such as skatole, and the formation of spirolactones of oxindoles which bear a polar group (P) on the side chain at the 3-position. The general form of this scheme is shown, with minor simplifying changes, in Chart I with the 3-bromoindolenine (III), the first species formed in the interaction of NBS and an indole, as an intermediate common to both.[16] When group P is a polar species in a polar medium, ring closure to the spirolactone must occur prior to formation of the amide function of the oxindole because the aqueous conditions employed would facilitate bromination of the benzene ring, rather than the 3-bromination required for lactone formation.[17]

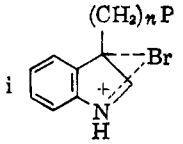
In *t*-butyl alcohol only pathway a appears to be applicable, since oxindoles are obtained from the reaction of 1 mole of NBS with 1 mole of indole even if the side chain at the 3-position bears a cyclizable carboxyl group. That ring closure by path b does not occur is understandable in view of the high acidity (from evolved hydrogen bromide) and low polarity of the medium which would repress ionization to the nucleophilic carboxylate ion. (In aqueous systems the carboxylate ion must be the active species rather than the undissociated carboxyl group, as formulated previously.[5])

By this scheme bromination rather than oxidation occurs in acetic acid because this solvent is not sufficiently nucleophilic to react with intermediate III. The pathway can be shifted by addition of more reactive nucleophiles. When skatole and NBS reacted in dry glacial acetic acid containing dry sodium acetate, 3-methyloxindole and other oxindolic or dioxindolic materials were obtained in 73% yield.[18] We have also observed a change over to oxindole formation when water was added to the acetic acid, as reported previously.[5,13]

Formation of a 3-bromooxindole from an indole must occur *via* bromination of an intermediate oxindole, a stepwise transformation which can be observed directly in the ultraviolet spectra[7] as each mole of NBS is added. The mode of conversion of oxindole to 3-bromooxindole is an interesting problem, however, since NBS in dry *t*-butyl alcohol did not attack 3-methyloxindole or oxindole-3-butyric acid over a period of a few hours, and, when 10% of water was added, only 5-bromooxindoles were formed.[19] The paradox was resolved when it was found that under dry conditions the addition of either hy-

(15) R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, **84**, 2534 (1962).

(16) In the previously proposed reaction pathway[5] a bromonium ion (i) was proposed as the common intermediate. Hydration would then yield IV, but intramolecular displacement of bromine requires the formation



of a 2-bromoindoline which would, in turn or simultaneously, lose hydrogen bromide yielding V. In the absence of any data on the nature of the intermediates, it is more economical to consider III as the first-formed intermediate, common to both pathways.

(17) None of these pathways is completely specific. Under Witkop's conditions for synthesis of 5-bromodioxindole-3-propionic acid lactone in an acetonitrile–water system, buffered by acetate at pH 4,[5] we have found that some 3-bromination of oxindoles may occur, although 5-bromination is expected and preferred. A particularly sensitive test is provided by oxindole-3-acetic acid. Any 3-bromooxindole-3-acetic acid which is formed is rapidly converted in the aqueous medium to 3-methyleneoxindole,[2b,6] which is readily detected by its intense ultraviolet absorption. Only 5–10% of 3-bromination was observed by this method.

(18) 3-Methyloxindole made up only 12% of this mixture. Since the bromine in intermediates such as III would be easily displaced by reactive nucleophiles, the formation of dioxindoles would not be surprising.

(19) For a general review of the halogenation of oxindoles see ref. 9a, p. 140.

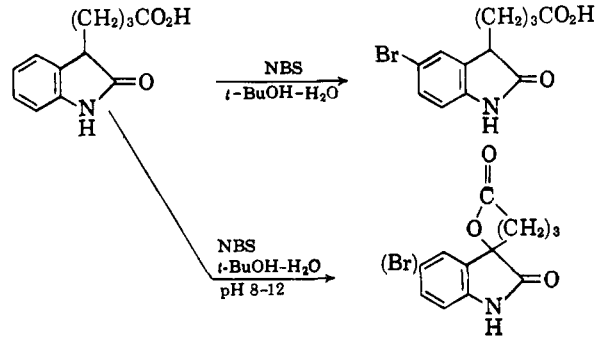
TABLE III

SPECTRAL CHARACTERISTICS OF BROMOINDOLES

No.	Compound	Ultraviolet: λ_{max}, mμ (ε) in 95% ethanol			Infrared, μ (KBr): NH region	Infrared, μ (KBr): C=O region
1	2-Bromoskatole	223 (35,800)	277 sh	(7480)	2.98	
			282	(7780)		
			291	(6570)		
2	Skatole	223 (34,800)	276 sh	(5450)		
			282	(5860)		
			291	(4930)		
3	3-Bromo-2-methylindole	223 (33,700)	275 sh	(6980)	2.99	
			281	(7500)		
			289	(6670)		
4	2-Methylindole	220 (33,600)	272	(7140)		
			277	(7040)		
			288	(5360)		
5	3-Bromo-1,2-dimethylindole	227 (34,800)	277 sh	(6640)		
			283	(7440)		
			291 sh	(7080)		
6	1,2-Dimethylindole	223 (34,400)	276	(7200)		
			282	(7650)		
			291	(6420)		
7	2-Bromoindole-3-butyric acid	224 (35,700)	275–277 sh	(7750)	2.91	5.82
			283	(8200)		
			291	(6950)		
8	2,6-Dibromoskatole	230 (38,000)	286	(8370)	2.95 sh	5.89
			297 sh	(7300)	2.97	
9	2,6-Dibromoindole-3-butyric acid	229 (41,600)	286	(8780)	2.95	5.84
					3.00	5.96

drogen bromide or sulfuric acid promoted bromination of the 3-position. Moreover, molecular bromine substituted the 3-position without addition of acid under dry conditions (with water present, 5-bromooxindoles were formed). The 3-bromination of an oxindole is thus clearly analogous to α-bromination of a ketone, with acid required to produce the reactive enol form. In the reactions of NBS with indoles, the formation of hydrogen bromide in the first step provides the catalyst to make NBS an active brominating agent for the 3-position. Bromine would also be present because of the reaction: NBS + HBr ⇌ succinimide + Br_2.[20]

The analogy between oxindoles and ketones in halogenations also accounts for a number of reported instances of 3-halogenations of oxindoles which occur in aqueous media. Thus, simple indoles and N-alkyloxindoles react with hypohalites to yield 3,3-dihalooxindoles,[19] lysergic acid derivatives yield dioxindoles when treated with calcium hypochlorite,[21] and 3-alkyloxindoles have been converted to dioxindoles by alkaline hypoiodite.[10a,22] In these cases 3-halogenation of the oxindole takes place *via* the enolate ion formed under the basic conditions of the hypohalite reactions.[23] A good demonstration of the latter pathway was provided by the reaction of NBS with oxindole-3-butyric acid. Whereas 5-bromooxindole-3-butyric acid was obtained in 73% yield in 90% *t*-butyl alcohol containing no acidic or basic catalyst, in 80% *t*-butyl alcohol, brought to pH 8 or 12 by the addition of sodium hydroxide, a mixture of dioxindole-3-butyric acid lactone and 5-bromodioxindole-3-butyric acid lactone was obtained, along with oxindole-3-butyric acid. The lactones could only have been formed by prior bromination of the 3-position.[24] Halogenation of the benzene



ring can apparently compete successfully with 3-halogenation only in relatively polar media under acidic or near neutral conditions. 3-Halogenation of oxindoles by bromine in carbon tetrachloride[19] or chlorobenzene[25] are simply additional examples of the acid-catalyzed behavior observed in *t*-butyl alcohol.

(20) These results provide additional evidence in support of path b under Witkop's conditions. Moreover, in the use of bromoamides for cleavage of C-tryptophyl peptide bonds it has been pointed out that cleavage of C-oxindolealanine peptides occurs to a much smaller extent than does cleavage of the corresponding indole derivatives. The conditions used (aqueous acetate–formate buffer at pH 4) are those most likely to promote bromination of the oxindole's benzene ring. Even after deactivation of that ring by bromination, substitution of bromine at the 3-position would be slow because of the acid catalysis required. It is particularly interesting that, in 10 *M* lithium acetate at pH 4, N-bromoacetamide is as effective in cleaving an oxindolealanine peptide bond as the corresponding one containing a tryptophan residue. Apparently 3-bromination occurs in this case, but it is not clear why these conditions favor it (*cf.* ref. 17).

(21) F. Troxler and A. Hofmann, *Helv. Chim. Acta*, **42**, 793 (1959).

(22) P. L. Julian, H. C. Printy, and E. E. Dailey, *J. Am. Chem. Soc.*, **78**, 3501 (1956).

(23) In the conversion of lysergic acid derivatives to dioxindoles,[21] an alternate though less attractive route would involve displacement by hydroxyl of the halogen of a reactive intermediate such as III prior to oxindole formation. Moreover, under basic conditions, oxindoles can be oxidized by air to dioxindoles (P. L. Julian, F. W. Meyer, and H. C. Printy, "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 241). What part this pathway plays in the media used for hypohalite oxidations is not known.

(24) The formation of dioxindole-3-propionic acid lactone from indole-3-propionic acid and NBS in the presence of bicarbonate may have occurred by this pathway or by path b of Chart I or both.

(25) E. Giovannini and P. Portmann, *Helv. Chim. Acta*, **31**, 1375 (1948).

Experimental[26]

Ultraviolet and infrared absorption spectra of the bromoindoles are listed in Table III, from which it is apparent that bromination effects little change in the ultraviolet spectrum of a methylindole. The spectra of all the oxindolic products have been determined and will be summarized and discussed with additional examples in a subsequent paper.[6]

Reactions in *t*-Butyl Alcohol.—These reactions were all performed in the same general manner, differing slightly only in the work-up procedure. The examples given below are illustrative of the method or are important because of the particular product or an unusual variation in method. The *t*-butyl alcohol was purified by the following general method (see further discussion below). A mixture of 7 g. of Darco G in 500 ml. of *t*-butyl alcohol, previously dried over sodium sulfate, was stirred for 10 min. at 50°. The mixture was filtered by gravity through a heated funnel. When water was added, purification was unnecessary (Table IV).

TABLE IV

EFFECT OF TREATMENT OF *t*-BUTYL ALCOHOL ON THE INDOLE–OXINDOLE TRANSFORMATION

Treatment of *t*-butyl alcohol[a]	*R* value[b]
None (used as supplied)	0.60
Darco (1X)[c]	1.84
Darco (2X)	3.06
Alumina (IX)[d]	1.98
1% water added	3.24
5% water added	3.10
Darco (1X), then 5% water added	3.22
Anhydrous Na_2SO_4[e]	1.40
Anhydrous Na_2SO_4, then Darco (1X)	2.14
Anhydrous Na_2SO_4, then 5% water added	3.15
$Na_2SO_4 \cdot 10H_2O$[e]	3.13

[a] All experiments were carried out with one batch of *t*-butyl alcohol (Matheson Coleman and Bell Cat. No. BX 1800). [b] *R* value = absorbance at 248 mμ/absorbance at 282 mμ for the reaction of 0.0025 mole each of IBA and NBS in 16.3 ml. of solvent. Spectra were obtained by diluting portions of the reaction mixture with *t*-butyl alcohol which had been dried and treated with Darco. [c] Darco G (1.5 g.)/100 ml. of solvent. [d] Alumina (1.5 g.)/100 ml. of solvent. [e] Sodium sulfate (15 g.)/100 ml. of solvent.

Oxindole-3-acetic Acid.—To a solution of 3.50 g. (0.02 mole) of indole-3-acetic acid in 130 ml. of *t*-butyl alcohol was added in small portions with stirring 3.56 g. (0.02 mole) of N-bromosuccinimide at 21–23°. After 2 hr. the solution was concentrated to a thick sirup under reduced pressure at room temperature, 30 ml. of water was added, and the mixture was extracted with three 40-ml. portions of ethyl acetate. The extract was washed with saturated salt solution, dried over sodium sulfate, and evaporated at room temperature. Residual ethyl acetate was entrained by repeated evaporation with acetone *in vacuo*. The residue was then taken up in 1.5 ml. of acetone and 25 ml. of benzene. Upon standing at −20° for several days, a cream-colored solid formed, which after recrystallization from an acetone–benzene mixture gave 1.61 g. (42%) of oxindole-3-acetic acid, m.p. 141–143°, which was obtained only by drying *in vacuo* for 1 hr. at 55°. The melting point could be raised to 145–146° by recrystallization from a mixture of acetone and benzene (lit.[8] m.p. 147°). The product was identified by its undepressed mixture melting point with an authentic specimen.[27]

3-Methyloxindole.—To a solution of 3.28 g. (0.025 mole) of skatole in 163 ml. of 95% *t*-butyl alcohol was added 4.45 g. (0.025 mole) of N-bromosuccinimide with stirring over a period of 19 min. The reaction mixture was kept under nitrogen and at a temperature of 20 ± 2°. After 2.5 hr. the solution was concentrated under reduced pressure at room temperature to a volume of a few milliliters, 30 ml. of water was added, and the mixture was extracted with three 25-ml. portions of ethyl acetate. The extract was washed with saturated salt solution, dried over sodium sulfate, and evaporated. The residue was crystallized from water and then from an acetone–hexane mixture. Less pure crops were recrystallized from a benzene–hexane mixture before recrystallization from an acetone–benzene mixture. Several crops of 3-methyloxindole were obtained from the last solvent mixture, totaling 0.94 g. (26%), m.p. 119–123° (lit.[28] m.p. 123–124°). An analytical sample melted at 124–125°.

3-(β-Benzamidoethyl)oxindole.—The procedure described for the preparation of 3-methyloxindole was followed with the exception that the residue from the ethyl acetate extract was crystallized from acetone. From 2.64 g. (0.01 mole) of 3-(β-benzamidoethyl)indole in 65 ml. of 95% *t*-butyl alcohol was obtained 0.97 g. (35%) of 3-(β-benzamidoethyl)oxindole, m.p. 194–197°. An analytical sample, m.p. 195–197°, was obtained by recrystallization from acetone.

3-(β-Aminoethyl)oxindole Hydrobromide.—To a solution of 3.20 g. (0.02 mole) of tryptamine in 130 ml. of 95% *t*-butyl alcohol was added 2.3 ml. (0.02 mole) of 48% hydrobromic acid followed by 3.56 g. (0.02 mole) of N-bromosuccinimide, which was added with stirring over a period of 16 min. The reaction mixture was kept under nitrogen and at a temperature of 21–23°. After 1 hr. the solution was concentrated under reduced pressure at room temperature to a thick sirup. The residual solvent was entrained by repeated evaporation with benzene. To the residue was added 50 ml. of benzene and 100 ml. of acetone. Pale pink crystals (1.45 g., m.p. 262–264° dec.) of 3-(β-aminoethyl)oxindole hydrobromide were filtered and washed with acetone. A semi-solid material, which also formed in the benzene–acetone mixture, was mixed with 10 ml. of absolute ethanol and 50 ml. of acetone yielding an additional 0.13 g. of product, m.p. 262–264° dec., giving a total yield of 1.58 g. (31%). An analytical sample, m.p. 266–268° dec., was obtained by recrystallization from absolute ethanol.

α-Acetamidodioxindole-3-propionic Acid and α-Acetamidooxindole-3-propionic Acid Lactone.—To a solution of 4.92 g. (0.02 mole) of N^{α}-acetyltryptophan and 1.68 g. (0.02 mole) of sodium bicarbonate in a mixture of 35 ml. of water and 150 ml. of *t*-butyl alcohol was added, with stirring at 25°, 3.56 g. (0.02 mole) of NBS. After 3 hr. the mixture was concentrated at room temperature, and to the sirupy residue was added a mixture of water and methanol. The white crystals which formed upon standing were filtered and recrystallized from a methanol–water mixture, yielding 0.41 g. of α-acetaminodioxindole-3-propionic acid lactone, m.p. 277–282° dec. (8%). An analytical sample, m.p. 290–293° dec., was obtained by recrystallization from a methanol–water mixture.

Concentration of the filtrate followed by the addition of a few milliliters of water gave two crops of N-acetyltryptophan (20%) and three crops of material which contained both indolic and oxindolic substances as indicated by the ultraviolet spectra. The filtrate was concentrated to a sirup, diluted with 25 ml. of water, and extracted with three 30-ml. portions of ethyl acetate. The ethyl acetate extract was evaporated at room temperature, and the residue was mixed with ether and a few milliliters of methanol. Two crops of oxindolic material (0.31 g., m.p. 192–202°) were obtained, followed by a crop of material melting at at 115–117°. The addition of acetone to the filtrate followed by cooling gave 0.38 g. of white crystals of α-acetaminooxindole-3-propionic acid, m.p. 209–210° dec. (9.2% based on unrecovered starting material). Recrystallization of the oxindolic material melting at 192–202° from methanol–ether gave four crops of the oxindole totaling 0.20 g., m.p. 202–212° (4.6% based on unrecovered starting material).

An analytical sample of α-acetamidooxindole-3-propionic acid, m.p. 214.0–214.5°, was obtained by recrystallization from an acetone–methanol mixture and then from acetone alone.

3-Bromo-3-methyloxindole.—To a solution of 5.2 g. (0.04 mole) of skatole in 260 ml. of *t*-butyl alcohol was added over a period of 1 hr. in small portions 14.2 g. (0.08 mole) of N-bromosuccinimide with stirring at 22–23°. After an additional 2 hr. the mixture was evaporated under reduced pressure at room temperature. After the addition of 50 ml. of anhydrous ether to the sirupy residue, the crystals of succinimide that formed were filtered and washed with 50 ml. of ether. A second crop of succinimide was removed by filtration. The filtrate was concentrated to about 50 ml. and cooled. A cream-colored solid

(26) Melting points and boiling points are uncorrected. Ultraviolet absorption spectra were determined with a Beckman DK-2 recording spectrophotometer, using quartz cells of 1-cm. light path. Infrared spectra were obtained with a Perkin-Elmer 21 recording spectrophotometer equipped with sodium chloride optics.

(27) The authors are indebted to Dr. Percy Julian for the sample of oxindole-3-acetic acid.

(28) L. Horner, *Ann.*, **548**, 117 (1941).

formed, which when recrystallized from ether, gave 2.1 g. of pale yellow crystals of 3-bromo-3-methyloxindole, m.p. 142–143° dec. Additional crops of product obtained from the mother liquor and from the recrystallization of the first crop afforded, after recrystallization from an acetone–benzene mixture, an additional 1.7 g. of product, m.p. 140–142° dec., giving a total yield of 3.8 g. (42%). Recrystallization from a chloroform–carbon tetrachloride mixture gave an analytical sample as pale yellow crystals, m.p. 142° dec. (decomposition gradual). The infrared spectrum (KBr) showed typical oxindolic features: NH band at 3.12 μ and double carbonyl band at 5.76 and 5.91 μ.

3-Bromooxindole-3-butyric Acid.—To a solution of 10.2 g. (0.05 mole) of indole-3-butyric acid in 325 ml. of anhydrous *t*-butyl alcohol, which had previously been treated with Darco G, was added in small portions 17.8 g. (0.10 mole) of N-bromosuccinimide with stirring over a period of 80 min. The reaction mixture was kept under nitrogen and at a temperature of 22–24°. After 5 hr. the mixture was evaporated under reduced pressure at room temperature. To the residue was added 125 ml. of anhydrous ether. The white crystals of succinimide that formed were filtered and washed with 125 ml. of ether. The filtrate was evaporated, and the residual ether was entrained by repeated evaporation with benzene until crystallization began. The cream-colored crystals (8.66 g., m.p. 137–138° dec.) of 3-bromooxindole-3-butyric acid were filtered and washed with benzene. Additional crops of the bromooxindole were obtained from the filtrate by the addition of peroxide-free tetrahydrofuran and benzene followed by concentration and cooling. Purification by recrystallization from a tetrahydrofuran–benzene mixture gave a total yield of 9.40 g. (63%), m.p. 138–142° dec. An analytical sample melted at 140–142° dec.

3-Bromooxindole-3-acetic Acid.—To a solution of 13.1 g. (0.075 mole) of indole-3-acetic acid in 490 ml. of anhydrous *t*-butyl alcohol, which had previously been treated with Darco G, was added in small portions 26.7 g. (0.15 mole) of N-bromosuccinimide with stirring under nitrogen over a period of 1 hr. at 21–23°. After an hour the mixture was concentrated at room temperature to a thick sirup which was then mixed with 200 ml. of anhydrous ether. White crystals of succinimide were removed by filtration and washed with 125 ml. of ether. After concentration of the filtrate to approximately 100 ml. and cooling, a second crop of succinimide was removed by filtration. The filtrate was evaporated at room temperature, and residual solvent was entrained by repeated evaporation with benzene *in vacuo* until the sirupy residue began to crystallize. The residue was then mixed with 150 ml. of benzene and 11.0 g. of pale chartreuse crystals of 3-bromooxindole-3-acetic acid, m.p. 152–153° dec. (melting point taken slowly), was obtained. Two additional crops of product totaling 2.22 g. (total yield 65%), m.p. 150–153° dec., were obtained. In another experiment, exhaustive work-up of the mother liquor, including recrystallizations from an acetone–benzene mixture, gave an additional 10% of product.

In some experiments a more soluble product was obtained by concentration of the mother liquors from the crystallizations of 3-bromooxindole-3-acetic acid. This white solid proved to be **t-butyl 3-bromooxindole-3-acetate**, which melted at 134–135° dec. after crystallization from a mixture of acetone and benzene.

Anal. Calcd. for $C_{14}H_{16}BrNO_3$: C, 51.55; H, 4.94; Br, 24.50; N, 4.29. Found: C, 51.97; H, 5.09; Br, 25.05; N, 4.46.

The ester was distinguished from the free acid in various stages of the work-up by the fact that in 95% ethanol the ultraviolet spectra of those samples containing primarily 3-bromooxindole-3-acetic acid changed rapidly toward that of 3-methyleneoxindole,[2b,6] while the spectra of those containing the ester did not change. Although ester formation occurred frequently, it did not seem to be reproducible. Moreover, attempts to prepare the *t*-butyl ester by reaction of the free acid and isobutylene[29] were completely unsuccessful. Evidence for ester formation was found in the ultraviolet spectra of the reaction mixtures, but in every case either unchanged acid was recovered or decomposition of the acid occurred forming insoluble material, apparently derived from 3-methyleneoxindole, the usual decomposition product of the acid.[2b,6]

Dioxindole-3-propionic Acid Lactone.—To a solution of 9.46 g. (0.05 mole) of indole-3-propionic acid and 4.20 g. (0.05 mole) of sodium bicarbonate in a mixture of 125 ml. of water and 325 ml. of *t*-butyl alcohol was added, with stirring at 21–23°, 17.8 g. (0.10 mole) of NBS in small portions over a period of 90 min. After 4 hr. 8.40 g. (0.10 mole) of sodium bicarbonate and 25 ml. of water were added, and the mixture was stirred for 16 hr. The mixture was concentrated to 200 ml., 200 ml. of water was added, and the mixture was extracted with three 150-ml. portions of ethyl acetate. The extract was washed with saturated salt solution, dried over sodium sulfate, and evaporated at room temperature. Residual ethyl acetate was entrained by repeated evaporation with benzene *in vacuo*. The sirupy residue was taken up in a mixture of benzene and methanol. White crystals which formed upon cooling were filtered and recrystallized from benzene and then from water, yielding 2.20 g. (22%) of dioxindole-3-propionic acid lactone, m.p. 132.5–133°. An analytical sample recrystallized from benzene melted at 134°.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.90. Found: C, 64.98; H, 4.76; N, 6.82.

2-Bromoskatole.—To a solution of 3.28 g. (0.025 mole) of skatole in 40 ml. of anhydrous glacial acetic acid (previously dried with triacetyl borate) was added slowly with stirring a solution of 4.45 g. (0.025 mole) of N-bromosuccinimide in 170 ml. of glacial acetic acid. The reaction mixture, which was kept under nitrogen at 19–21°, was stirred for 2.5 hr. and then was neutralized to pH 7 with a solution of 136 g. of sodium hydroxide in 250 ml. of water with cooling in an ice bath under nitrogen. The cream-colored precipitate that formed was filtered by suction, washed with water several times, and then dried *in vacuo* over potassium hydroxide. The solid was sublimed by heating in a water bath at approximately 0.025 mm. The sublimate was 2.36 g. (45%) of a white solid, 2-bromoskatole, m.p. 88–90° dec. An analytical sample was prepared by crystallization from aqueous acetic acid. Crystallization without decomposition was successful only after sublimation.

The product underwent slow decomposition to a black solid at room temperature but could be preserved when stored under nitrogen in the dark at −20°.

2,6-Dibromoskatole.—To a solution of 2.10 g. (0.01 mole) of 2-bromoskatole in 30 ml. of anhydrous glacial acetic acid (previously dried with triacetyl borate) was added dropwise with stirring under nitrogen a solution of 1.78 g. (0.01 mole) of NBS in 70 ml. of anhydrous acetic acid. The mixture was stirred for 3 hr. at 18–20° and then was poured slowly with stirring and cooling into a mixture of 75 g. of sodium hydroxide and 50 g. of ice in 125 ml. of water. The cream-colored precipitate that formed was filtered by suction, washed with ice water until free of base, and dried *in vacuo* over potassium hydroxide. The solid was dissolved in 75 ml. of warm 95% ethanol, and water was added to the saturation point. Upon cooling, 1.09 g. of tan crystals of 2,6-dibromoskatole, m.p. 96–98° dec. (lit.[5] m.p. 100° dec.), was obtained. Concentration of the filtrate gave an additional 0.31 g., m.p. 99–101° dec.; total yield was 1.40 g. (48%).

3-Methyloxindole by Hydrolysis *in situ* of 2-Bromoskatole.—To a solution of 26.2 g. (0.20 mole) of skatole in 400 ml. of glacial acetic acid was added 35.6 g. (0.2 mole) of NBS over a period of 20 min. in an atmosphere of nitrogen. The solution was stirred for 1 hr. at 15–18°. Then 300 ml. of 5% sulfuric acid and 150 ml. of ethanol were added, and the mixture was refluxed under nitrogen for 2.25 hr. The mixture was concentrated *in vacuo* to 500 ml., diluted with 1 l. of water, and extracted with three 400-ml. portions of ether. The extract was neutralized by washing with dilute sodium hydroxide, washed with saturated salt solution, dried over sodium sulfate, and concentrated under reduced pressure. The residual oil was distilled *in vacuo*. The distillate (16.7 g., b.p. 127–150° at 0.55-mm. pressure) was recrystallized from benzene yielding 8.0 g. (28%) of 3-methyloxindole, m.p. 121–122° (lit.[28] m.p. 123–124°).

3-*n*-Propyloxindole by Hydrolysis of 2-Bromo-3-*n*-propylindole.—To a solution of 3.18 g. (0.02 mole) of 3-*n*-propylindole in 32 ml. of glacial acetic acid (previously dried with triacetyl borate) was added dropwise with stirring at 16–20° under nitrogen a solution of 3.56 g. (0.02 mole) of N-bromosuccinimide in 136 ml. of anhydrous glacial acetic acid. After 2 hr. the solution was poured slowly with stirring and cooling into a mixture of 120 g. of sodium hydroxide and 100 g. of ice in 200 ml. of water. The temperature of the mixture was not allowed to exceed 25°, and the mixture was kept under nitrogen during these operations. The solution was decanted from a brown tar that formed and then was extracted with 3 100-ml. portions of ethyl acetate. The extract, after drying over sodium sulfate, was evaporated at room

(29) A. L. McCloskey, G. S. Fonken, R. W. Kluiber, and W. S. Johnson, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p. 261.

temperature. A portion of the oily residue was placed in a sublimation apparatus, and at 90° and 0.025-mm. pressure 0.30 g. of a colorless sirup was collected on the Dry Ice-cooled condenser. The sirup, crude 2-bromo-3-*n*-propylindole, gave a negative test with alcoholic silver nitrate but gave a positive test when nitric acid was added followed by heating for 30 sec. The ultraviolet spectrum of the product showed λ_{max}^{EtOH} 224, 275 sh, 283, and 291 mμ. The infrared spectrum showed a strong band at 2.97 μ (indolic N–H). The presence of a medium strong band at 5.84 μ (C=O) indicated that the sirup was contaminated.

The remainder of the residual oil was distilled in a short-path distillation apparatus at about 90° and 0.04-mm. pressure. A total of 0.91 g. of oil was collected, but the product was contaminated by spattering of the residue. The total yield of crude 2-bromo-3-*n*-propylindole was 1.17 g. (25%). The product decomposed when an attempt was made to distil it by the conventional method.

The residue from the short-path distillation was mixed with 1.1 ml. of concentrated sulfuric acid, 2 ml. of water, and 20 ml. of 95% ethanol and was refluxed under nitrogen for 25 hr. The mixture was concentrated to a volume of 10 ml., water was added to the saturation point, and the mixture was extracted with ether. The ether layer, after washing with 1 *N* sodium bicarbonate and drying over sodium sulfate, was treated with Norit A and evaporated. The residue was extracted with two 50-ml. portions of hot water and then with 200 ml. of boiling water. A total of 0.18 g. of white crystals of 3-*n*-propyloxindole, m.p. 78.0–79.5°, was obtained from the combined aqueous extracts. An analytical sample, m.p. 81–82°, was obtained by recrystallization, first from hexane and then from water.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 8.00. Found: C, 75.12; H, 7.43; N, 8.26.

2,6-Dibromo-3-*n*-propylindole.—To a solution of 4.0 g. (0.025 mole) of 3-*n*-propylindole in 40 ml. of anhydrous glacial acetic acid (previously dried with triacetyl borate) was added dropwise with stirring under nitrogen at 16–20° a solution of 8.9 g. (0.05 mole) of N-bromosuccinimide in 340 ml. of anhydrous glacial acetic acid over a period of 110 min. After 2 hr. the mixture was neutralized to pH 5 by pouring it under nitrogen into a liter of a solution containing an equivalent amount of sodium hydroxide cooled in a Dry Ice bath so that the temperature did not exceed 25°. The mixture was extracted with ethyl acetate and the extract, after drying, was concentrated to a thick sirup. Attempts to isolate the product by crystallization and by distillation failed. The ultraviolet spectrum of the reaction mixture showed absorption at 229 and 286 mμ, which suggested that a 2,6-bromoindole was present. An attempt to hydrolyze the dibromoindole by refluxing for 19 hr. with 30 ml. of 4.5 *M* sulfuric acid and 60 ml. of dioxane resulted in only partial hydrolysis, as indicated by the ultraviolet spectrum of the mixture. Only 8 mg. of a solid, m.p. 195–198°, was isolated. The ultraviolet spectrum, λ_{max}^{EtOH} 215, 251–257, and 289 mμ, and infrared spectrum, λ_{max}^{KBr} 3.02, 5.82, 5.95 μ, indicated that the product was impure 6-bromo-3-*n*-propyloxindole.

5-Chloro-3-methyloxindole from Reaction of *t*-Butyl Hypochlorite and Skatole.—To a solution of 5.28 g. (0.025 mole) of skatole in 165 ml. of *t*-butyl alcohol, which had been dried over sodium sulfate and treated with Darco, was added with stirring under nitrogen at 25–25° a solution of 5.44 g. (0.050 mole) of *t*-butyl hypochlorite in 25 ml. of purified *t*-butyl alcohol over a period of 40 min. After 4.33 hr. the solution was concentrated with mild warming to an oily residue, which was taken up in benzene and a small amount of acetone, and hexane was added to the saturation point. After a brown tarry material had been removed, two crops of a white solid were obtained, totaling 0.49 g., m.p. 182–198° (cloudy until approx. 225°). The solid was recrystallized from an acetone–benzene mixture, then from benzene, and then from a methanol–water mixture yielding 0.13 g. (2.8%) of product, presumably 5-chloro-3-methyloxindole, m.p. 201–203°. An analytical sample, m.p. 201–203°, was obtained by an additional recrystallization from a methanol–water mixture.

Anal. Calcd. for C_9H_8ClNO: C, 59.51; H, 4.44; N, 7.71; Cl, 19.52. Found: C, 59.29; H, 4.66; N, 7.61; Cl, 19.30.

Oxindole-3-butyric Acid (by Reaction of Indole-3-butyric Acid and Bromine).—To a solution of 4.06 g. (0.02 mole) of indole-3-butyric acid in 130 ml. of *t*-butyl alcohol which had been dried over calcium sulfate was added with stirring at 22–24° a solution of 3.20 g. (0.02 mole) of bromine in 30 ml. of anhydrous *t*-butyl alcohol over a period of 35 min. After 4 hr. the solution was concentrated at room temperature to an oily residue which was taken up in a mixture of benzene and ethyl acetate. The solution was washed with water three times and dried over calcium sulfate; then hexane was added to the saturation point. Upon standing, 0.12 g. of oxindole-3-butyric acid, m.p. 165–167°, was obtained. The addition of hexane to the filtrate caused a brown oil to form, which when separated and mixed with acetone gave three additional crops of product, totaling 0.16 g., m.p. 163–168° (total yield 6.4%).

5-Bromooxindole-3-butyric Acid.—A solution of 1.0 g. (4.6 mmoles) of oxindole-3-butyric acid and 0.81 g. (4.6 mmoles) of N-bromosuccinimide in 130 ml. of 90% *t*-butyl alcohol was stirred at room temperature for 2 days. The solution was concentrated *in vacuo* at room temperature to a thick sirup. After the addition of 15 ml. of water, the mixture was extracted with three 20-ml. portions of ethyl acetate. The extract was dried over sodium sulfate and evaporated; the residual oil was crystallized from a mixture of acetone and benzene. Two crops of crystals were obtained, which upon recrystallization from a benzene–ethyl acetate mixture gave several crops of crystals of 5-bromooxindole-3-butyric acid, m.p. 156–159°, totaling 1.0 g. (73%).

An analytical sample, m.p. 158°, was obtained by recrystallization twice from an ethyl acetate–benzene mixture and then twice from water.

Anal. Calcd. for $C_{12}H_{12}BrNO_3$: C, 48.34; H, 4.06; N, 4.70; Br, 26.80. Found: C, 48.45; H, 4.24; N, 4.91; Br, 26.67.

Oxindole-3-butyric Acid and N-Bromosuccinimide at pH 11–12.—To a solution of 1.1 g. (5.0 mmoles) of oxindole-3-butyric acid in a mixture of 5.3 ml. of 1 *N* sodium hydroxide and 20 ml. of *t*-butyl alcohol was added slowly with stirring 0.89 g. (5.0 mmoles) of N-bromosuccinimide. The pH of the solution dropped from 11–12 to 7–8 during the reaction time. After 2.5 hr., 30 ml. of water was added, and the solution was concentrated *in vacuo* at room temperature to about 60 ml. An oil formed which, after the addition of a few milliliters of ether followed by cooling and scratching, crystallized to give 0.57 g. of white crystals, m.p. 164–175°, the ultraviolet spectrum of which (λ_{max}^{EtOH} 259, 300 mμ) indicated it was probably a mixture of 5-bromodioxindole-3-butyric acid lactone and dioxindole-3-butyric acid lactone. Oxindole-3-butyric acid was recovered (24% crude) from the reaction mixture.

Reproducibility of Reactions in *t*-Butyl Alcohol. Effect of Impurities.—A thorough study of the reaction variables, prompted by difficulties in reproducing yields of oxindoles, revealed that the presence of an impurity in the *t*-butyl alcohol was responsible for increased yields of α-bromoindoles sufficient to make the product mixture exceedingly difficult to separate. The effectiveness of various methods of treating the solvent to promote oxindole formation alone are shown in Table IV.[30] It is evident that two treatments with Darco are sufficient to prepare the solvent for use in oxindole syntheses, although generally only one treatment was employed in preparative work. Alumina is also effective. The beneficial effects of either adding water or drying with sodium sulfate appear contradictory but may be accounted for by the promotion of addition of water[31] to the 3-bromoindolenine (III) in the former case, and by removal of some of the undesirable impurity by adsorption in the latter. Hydrated sodium sulfate may perform both functions.

The practical consequences of the results shown in Table IV are twofold. If the indole-to-oxindole transformation is desired, addition of water to the solvent will give satisfactory results without further purification. On the other hand, when the reaction of an indole with 2 moles of NBS is to be carried out for the synthesis of a 3-bromooxindole, treatment with Darco is the preferred method, since water facilitates bromination of the benzene ring and other reactions. Even the addition of 1% of water to the medium has a deleterious effect which is shown by the failure of the ultraviolet spectrum to take on the complete charac-

(30) The values of the ratio in Table IV vary from 0.6 to 3.2. The highest ratios observed have been about 3.5. The residual indolic absorption may have been due to starting material, unreacted because of wastage of NBS, or to α-bromoindoles. The isolation of 2,6-dibromoindole-3-butyric acid from almost all reactions of IBA with 2 moles of NBS indicates that the latter is the case and that the reaction in *t*-butyl alcohol never gives a completely clean-cut conversion to oxindole.

(31) Analysis of reaction mixtures by v.p.c. showed that enough water is formed from the *t*-butyl alcohol to account for oxindole formation. The water was not determined directly but was estimated from the amounts of *t*-butyl bromide and isobutylene which are readily separated on a polypropylene glycol column.

teristics of the 3-bromooxindole. [For oxindole formation alone, 1% of water appears to be as useful as 5% (Table IV), but no experiments on a preparative scale have been performed in the former.]

When a sample of *t*-butyl alcohol was distilled and the collected fractions were used as the reaction medium, the value of R decreased as the fraction number increased. Moreover, many commercial samples of the alcohol showed an anomalous absorption maximum at 236 mμ, and the peak became more intense in the later fractions. The presence of benzene obscures this peak, but, as the benzene is removed in the first fractions, the new absorption peak becomes visible. Treatment with Darco reduced the peak to a slight shoulder, and NBS had a similar effect. However, a second treatment with Darco had no further effect on the absorption spectrum even though the value of R increased further (Table IV), and treatment of *t*-butyl alcohol with NBS followed by distillation yielded solvent with the same R value as that observed before the NBS treatment. Moreover, many samples of *t*-butyl alcohol do not show this anomalous absorption but do give low R values. Whether the impurity absorbing at 236 mμ is responsible for the low R values is, therefore, a moot point at this time.

All attempts to concentrate the impurity by careful fractionation or to identify it by v.p.c. analysis have been unsuccessful. Samples of *t*-butyl alcohol rich in the impurity discharged the color of potassium permanganate and gave negative Beilstein tests for halogen and negative tests for thiophene. A number of substances suggested by the position of the absorption maximum or by the likelihood of their presence as contaminants of commercial *t*-butyl alcohol have been added to reaction mixtures of NBS and indole-3-butyric acid in small quantities, but without effect on the value of R. These included 2,5-dimethyl-2,4-hexadiene, diisobutylene, mesityl oxide, thiophene, and *n*-butyraldehyde.

The impurity is present in many, but not all, commercial samples of *t*-butyl alcohol, even those of the specially purified grade used in the analysis of corticosteroids (Matheson Coleman and Bell, Catalog No. BX 1800). From the lot analysis of the best samples, the impurity must be present in very small amounts (<0.1%). If this is the case, its effect on the product distribution is of a remarkable catalytic nature.

Preparation of Cyclic Siloxazanes

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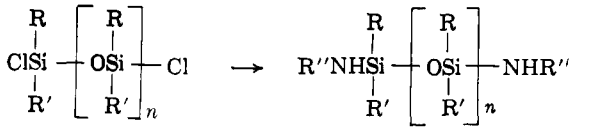
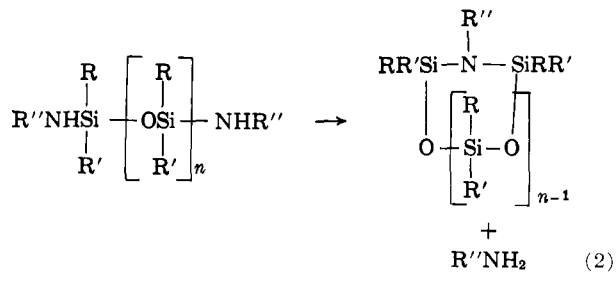
The preparation and characterization of a number of mixed cyclic siloxane–silazane compounds (*i.e.*, cyclic siloxazanes) is described.

This report describes the preparation and some properties of mixed cyclic silicon compounds having both siloxane and silazane bonds (*i.e.*, cyclic siloxazanes), which were of interest to us as intermediates for polymerization and condensation reactions. At the outset of this work, this class of compounds had not been isolated and characterized. Since then, Kruger and Rochow[1] have described the preparation and isolation of several of the compounds reported in this paper. The compounds prepared in this work are listed in Fig. 1 and their properties in Table I.

The general reactions for the preparation of the cyclic siloxazanes are indicated in eq. 1 and 2. Most of the



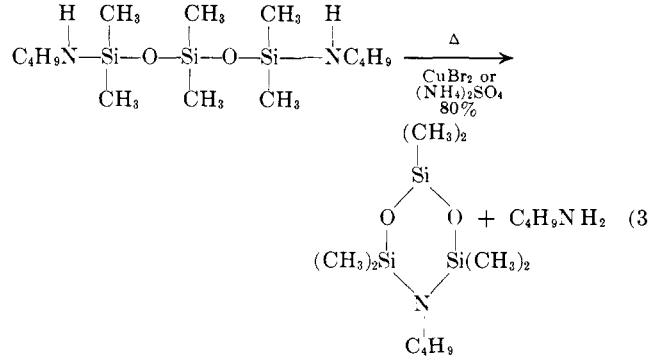
(1)



(2)

dichlorosiloxanes used in reaction 1 were prepared by the partial hydrolysis of the dialkyldichlorosilane followed by distillation to separate the individual members of the homologous series of materials formed. These products have been described previously.[2,3] The intermediate for the preparation of IX (1,5-dichloro-1,1,5,5-tetramethyl-3,3-diphenyltrisiloxane) was prepared by the condensation of diphenylsilanediol and dimethyldichlorosilane in pyridine–benzene solution.

The products of reaction 1 were not isolated when R″ was H, but the presence of these diaminosiloxanes in the crude reaction products was indicated in some cases by the NH_2 band splitting (near 3390 cm.$^{-1}$) in the infrared spectra. On heating, this splitting disappeared. When R″ was butyl, only the diaminosiloxane was formed, with no cyclization occurring even during the distillation of the product. In the presence of an acidic catalyst, however, cyclization and elimination of butylamine took place readily, as indicated in eq. 3 for the preparation of VII.



(3)

The yield of the low cyclic isolated varied from 21–81%. No attempt was made to optimize yields. Most of the reactions were run by passing ammonia into a moderately concentrated solution of the dichloropolysiloxane; this procedure might be expected to favor the formation of the larger cyclics and linear polymers at the

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(2) W. I. Patnode and D. F. Wilcock, *J. Am. Chem. Soc.*, **68**, 358 (1946).

(3) W. H. Daudt and J. F. Hyde, *ibid.*, **74**, 386 (1952).