Structure Proof of II and III.—If the β-chloroketone II was obtained pure, it was dehydrohalogenated to the corresponding III by refluxing with 25% aqueous sodium bicarbonate for 2 hr. The resulting III, or III obtained by dehydrohalogenation of the crude mixture (*vide supra*), was derivatized, hydrogenated over Raney nickel at room temperature and three atmospheres pressure to the corresponding isopropyl ketone and the latter also derivatized. Yields of III from II were 60–85%; hydrogenations were essentially quantitative. The results are given in Table IV.

Miscellaneous.—In one experiment with ferric chloride in place of aluminum chloride, propionyl chloride gave only the rearranged chloroketone IIb (Table I). With nitromethane as solvent, the propionyl chloride–aluminum chloride complex did not form a homogeneous solution, and even after a 10-hr. reaction period, only 9 g. of product, b.p. 52–67° at 5 mm., was obtained. It was obviously a mixture of chloroketones and was not investigated further. The reaction between phosgene, aluminum chloride and cyclopropane gave a complex mixture which requires further examination.

EAST LANSING, MICHIGAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

The Fischer Indole Synthesis. IV. Halogen Interchange during the Zinc Halide Induced Fischer Reactions of Acetophenone 2,6-Dihalophenylhydrazones[1]

BY ROBERT B. CARLIN AND GERALD W. LARSON[2]

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Acetophenone 2,6-dibromophenylhydrazone, when heated with zinc chloride, yields a mixture containing about equimolar amounts of 2-phenyl-5,7-dibromoindole (II) and of 2-phenyl-5-chloro-7-bromoindole (III) plus a trace of 2-phenyl-7-bromoindole (I). Acetophenone 2,6-dichlorophenylhydrazone, when heated with zinc bromide, behaves similarly; the products are 2-phenyl-5,7-dichloroindole (IV) and 2-phenyl-5-bromo-7-chloroindole (V) in about 1:3 molar ratio. The four 2-phenyl-5,7-dihaloindoles II-V all have closely similar melting points, and mixtures show slight or no melting point depressions. Separation of mixtures is not practicable by any of the methods tried. The four pure indoles II-V were synthesized from the corresponding acetophenone 2,4-dihalophenylhydrazones and their infrared spectra measured. Characteristic differences in the spectra, particularly in the 13–14 μ region, were used as the means of identification of the components of the mixtures obtained from the 2,6-dihalophenylhydrazones. A mechanism featuring an intermediate (*e.g.*, VI) having an allylic halide structural sequence is proposed to account for the observed halogen interchange; the "positive halogen" hypothesis seems inadequate to account for the interchange. Cyclohexanone 2,6-dibromophenylhydrazone, heated with zinc chloride, yields, after chloranil dehydrogenation of the product, an unknown monobromocarbazole.

Investigations of the Fischer indole transformations of 2,6-dichlorophenylhydrazones have disclosed that 5,7-dichloroindoles are formed in the presence of zinc chloride but that 7-monochloroindoles are the products when stannous chloride is the promoter.[3] A mechanism was proposed[3b] to account for the behavior of these 2,6-dichlorophenylhydrazones in the Fischer reaction which included as an essential feature the migration or reductive removal of "positive" chlorine. To provide evidence bearing on the general validity of this proposed mechanism, a study of 2,6-dibromophenylhydrazones in the Fischer reaction was undertaken, and this paper reports the reactions of acetophenone 2,6-dibromophenylhydrazone with zinc chloride and with zinc bromide. Since the reaction of acetophenone 2,6-dichlorophenylhydrazone with zinc chloride already was known,[3a] the series could be completed by carrying out the reaction of this dichlorophenylhydrazone with zinc bromide. The latter reaction also is reported in this paper.

In a preliminary investigation, Fisher[4] found that acetophenone 2,6-dibromophenylhydrazone, when heated with zinc chloride in nitrobenzene, was converted to a crystalline product, m.p. 139°, that gave a positive Ehrlich test. The product was shown to be related to 2-phenylindole, for it afforded this compound on catalytic reductive dehalogenation. That it was not 2-phenyl-5,7-dibromoindole was shown by preparation of the latter, m.p. 149°, from acetophenone 2,4-dibromophenylhydrazone. Elementary analysis of the material of m.p. 139° suggested that it might be a mixture of 2-phenyl-5,7-dibromoindole and 2-phenyl-7-bromoindole. There was reason to suppose that mixtures of halogen-substituted 2-phenylindoles showed little or no melting point depression and that they often melted sharply. Fisher's investigations were abandoned when efforts to effect separations of the material of m.p. 139° into its components by fractional crystallization, by high vacuum sublimation, by liquid–liquid extraction and by chromatography on alumina all failed.

Inasmuch as the yield of the material of m.p. 139° from acetophenone 2,6-dibromophenylhydrazone was only about 5%, quite large amounts of the dibromo phenylhydrazone had to be prepared if a detailed study of the product was to be carried out. The first problem encountered, then, was the preparation of substantial amounts of 2,6-dibromoaniline, the precursor of the corresponding phenylhydrazine. In our hands the preparative method for this compound described in "Organic Syntheses"[5] led to erratic results; all too often the procedure afforded quite low yields of a product containing too much tribromoaniline to be useful in our work. More consistent yields of a superior product were realized when 2,6-dibromoaniline was prepared from sulfanilic acid through the barium dibromosulfanilate, following the general procedure given

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[1] Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Carnegie Institute of Technology.

[2] Allied Chemical and Dye Corp. Fellow, 1952–1953.

[3] (a) R. B. Carlin and E. E. Fisher, THIS JOURNAL, **70**, 3421 (1948); (b) R. B. Carlin, J. G. Wallace and E. E. Fisher, *ibid.*, **74**, 990 (1952).

[4] E. E. Fisher, Ph.D. Thesis, Carnegie Institute of Technology, 1948.

[5] M. K. Seikel, "Org. Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 261.

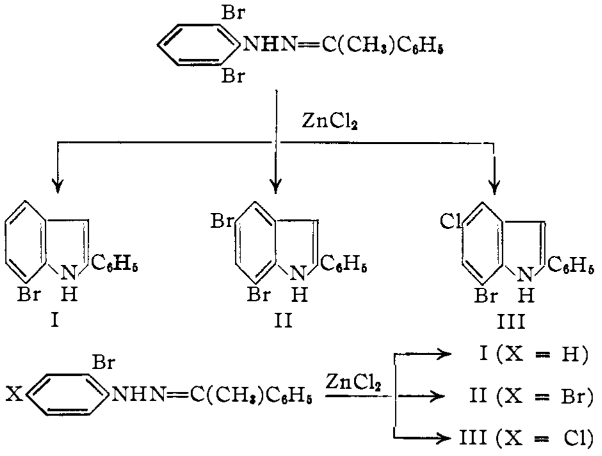
by Orton and Pearson.[6] Compared to the "Organic Syntheses" procedure, the method of Orton and Pearson involves a more convenient bromination, a more readily purified intermediate (the barium salt), and a faster desulfonation to a purer product. However, both methods suffer from the disadvantage that they are restricted in practice to comparatively small runs; about a 75-g. run is optimum in our adaptation of the Orton and Pearson procedure. This limitation prompted an investigation of two alternative schemes, the first of which involved the steps: 2,6-dibromo-4-nitroacetanilide → 2,6-dibromo-4-aminoacetanilide → 2,6-dibromoacetanilide → 2,6-dibromoaniline. This route failed when satisfactory conditions for effecting the second (deamination) step in good yield could not be found. The second alternative route involved the bromination of *p*-iodoaniline to 2,6-dibromo-4-iodoaniline, from which selective reductive removal of the iodine atom should lead to the required 2,6-dibromoaniline. This synthesis was abandoned when the bromination reaction was shown not to lead to the dibromoiodoaniline as the chief product.

The conversion of 2,6-dibromoaniline to the corresponding phenylhydrazine and of the latter to acetophenone 2,6-dibromophenylhydrazone followed established[3] procedures. When a nitrobenzene solution of the phenylhydrazone was heated for ten minutes at 170–180° with excess zinc chloride, a product was formed from which two crystalline fractions were separated. One, formed in only trace amounts, was 2-phenyl-7-bromoindole (I), identical with a specimen prepared from acetophenone *o*-bromophenylhydrazone. The major crystalline product was the material of m.p. 139° first isolated by Fisher. Catalytic reductive dehalogenation of this product again afforded 2-phenylindole; but, in addition, qualitative examination of the halide ions produced by the hydrogenation disclosed the presence not only of bromide but also of chloride ions. Analytical results and molecular weight determinations proved to be in accord with the postulate that the material of m.p. 139° was about an equimolar mixture of 2-phenyl-5,7-dibromoindole (II) and 2-phenyl-5-chloro-7-bromoindole (III). Accordingly, the two pure dihaloindoles were prepared from acetophenone 2,4-dibromophenylhydrazone and from the corresponding 2-bromo-4-chlorophenylhydrazone, respectively, in order that the properties of mixtures of these two indoles could be observed and compared with that of the material of m.p. 139°. A crude melting point diagram was constructed from the melting points of the two pure dihaloindoles II and III and of eight mixtures of varying compositions: III melted at 143°, and II at 149°; however, the minimum m.p. of the mixtures examined was 139°, that of a mixture containing about 60% by weight of the dibromoindole, and all mixtures melted sharply. These observations were therefore also in accord with the postulate that the material of m.p. 139° was about an equimolar mixture of II and III. The ultraviolet absorption spectra of II and III, of mixtures of the two, and of the material of m.p. 139° all were too closely similar to permit of valid conclusions.

Definitive evidence proving the identity of the material of m.p. 139° with an equimolar mixture of II and III came from an examination of the infrared spectra. Although small but significant differences between the spectra of II and III occur in the 8–9 μ and in the 10–11 μ regions, truly striking differences may be found in the 13–14 μ region. Both II and III have sharp and intense bands at about 13.18μ and about 13.66μ. In addition to these, however, III has an intense band at 13.36 and II an intense band at 13.82 μ, neither of which is present in the spectrum of the other compound. The spectrum of the material of m.p. 139° shows every unique band of both II and III, including those at 13.36 and 13.82 μ. Furthermore, the spectrum of an equimolar mixture of II and III is superimposable over that of the material of m.p. 139°. Figure 1 shows the relationships among the infrared spectra.

After the nature of the material of m.p. 139° had been established beyond doubt, a new attempt was made to separate it into its components by chromatography over alumina. After much labor, this procedure yielded a fraction, m.p. 142°, whose infrared spectrum showed it to be a mixture considerably enriched in III. Apparently, then, a separation can theoretically be achieved by this means, but it is not a practicable method.

Thus, three indoles were produced by the action of zinc chloride on acetophenone 2,6-dibromophenylhydrazone: a trace of I and about equimolar amounts of II and III.



The formation of I involved substitution of a bromine atom by hydrogen during the course of the Fischer reaction; II appears to require for its formation simply a bromine migration. But a bromine of the initial phenylhydrazone must be exchanged for chlorine from the zinc chloride at some time during the formation of III.

It then became important to an understanding of the mechanism of Fischer reactions of 2,6-dihalophenylhydrazones to know whether analogous exchange of halogen occurs when 2,6-dichlorophenylhydrazones are treated with zinc bromide. Accordingly, a solution of acetophenone 2,6-dichlorophenylhydrazone in nitrobenzene was heated with excess zinc bromide at 150–175° for ten minutes. A crystalline product, m.p. 139°, was formed to the extent of about 12% of the weight

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(6) K. J. P. Orton and C. Pearson, *J. Chem. Soc.*, **113**, 735 (1908).

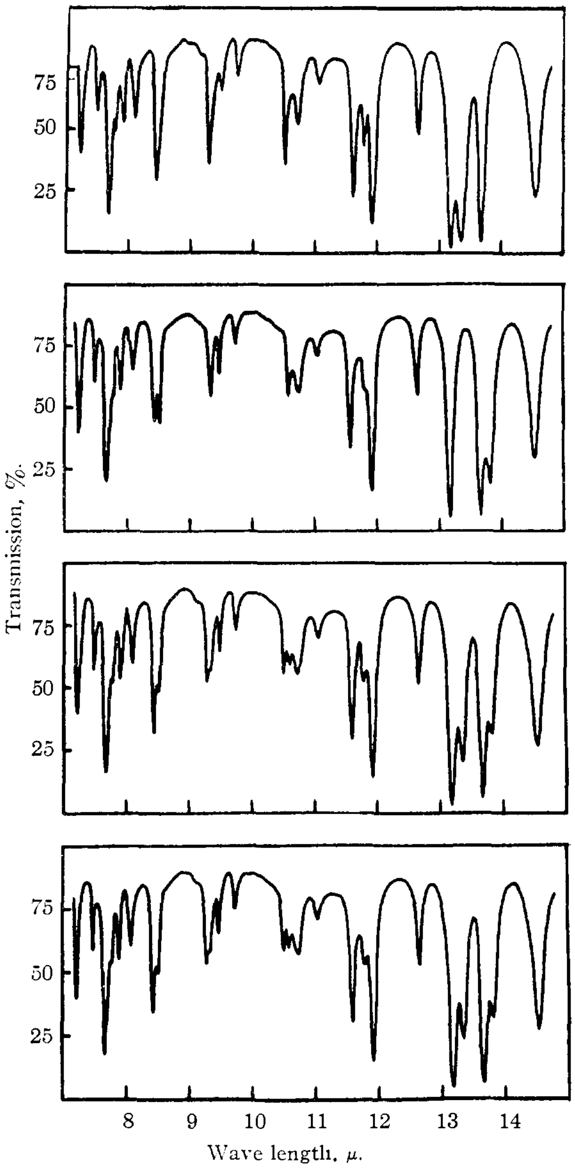
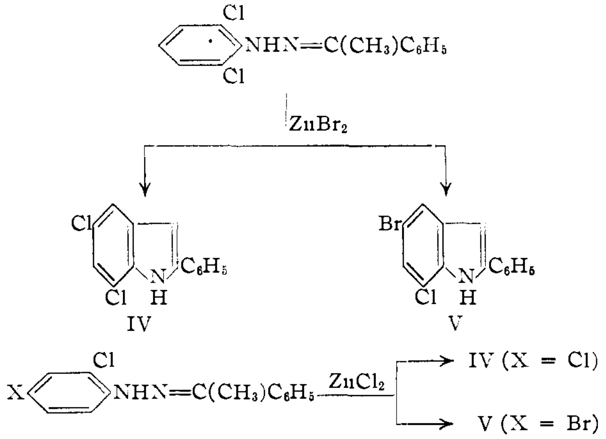


Fig. 1.—The infrared absorption spectra from 7–15 μ of: top, 2-phenyl-5-chloro-7-bromoindole (III); second, 2-phenyl-5,7-dibromoindole (II); third, the 139° product (mixture A) from acetophenone 2,6-dibromophenylhydrazone and zinc chloride; bottom, an equimolar mixture of II and III.

of the initial phenylhydrazone. Mixtures of this product with the material of m.p. 139° obtained from acetophenone 2,6-dibromophenylhydrazone and zinc chloride and with pure 2-phenyl-5-bromo-7-chloroindole, m.p. 139°, showed no depressions. This behavior, of course, constitutes no proof of identity; rather it is a demonstration of the degree to which the 2-phenyl-5,7-dihaloindoles form isomorphous systems. Isomorphism among structurally similar aromatic halogen compounds is not an unfamiliar occurrence.[7]

Sodium fusion of the new product of m.p. 139° disclosed the presence in it of bromine. Analogy with the preceding case led to the hypothesis that it might be a mixture of 2-phenyl-5,7-dichloroindole (IV) and 2-phenyl-5-bromo-7-chloroindole (V). These two indoles were therefore prepared from the corresponding acetophenone 2,4-dihalophenylhydrazones and their infrared spectra were measured. Like their analogs, II and III, the indoles IV and V possessed strikingly characteristic bands in the 13–14 μ region, in addition to the two bands at about 13.18 μ and at about 13.66 μ that are shown by all four of these compounds. The indole IV showed an intense band at 13.03 μ and V an intense band at 13.50 μ that were found in none of the other 2-phenyl-5,7-dihaloindoles. The spectrum of the product of m.p. 139° showed both of these unique bands, but the relative intensities suggested that in this mixture V predominated over IV in amount. A calculation based on the intensities of the 13.50 μ band resulted in the estimate that the mixture of m.p. 139° consisted of V to the extent of 77% by weight. A calculation based on the carbon content of the mixture of m.p. 139° gave 75% as its weight content in V (about 70 mole %). Thus, it appears justifiable to conclude that the molar ratio of V to IV in this mixture was about 3:1. No evidence could be found



that even a trace amount of 2-phenyl-7-chloroindole or any other monohaloindole had been formed in the reaction of acetophenone 2,6-dichlorophenylhydrazone with zinc bromide.

To complete the series of reactions between acetophenone 2,6-dihalophenylhydrazones and zinc halides, the 2,6-dibromophenylhydrazone was heated to 165° in nitrobenzene solution with zinc bromide for ten minutes. In accordance with expectations, the only product detected, isolated in about 8% yield, was 2-phenyl-5,7-dibromoindole (II), identical with a synthetic specimen prepared in the manner previously formulated. Again, no monohaloindole was identified in the crude product.

Preliminary experiments were carried out with the intention of discovering whether 2,6-dibromophenylhydrazones of other ketones behave like that of acetophenone when heated with zinc chloride. Ethyl levulinate 2,6-dibromophenylhydrazone and excess zinc chloride were diluted with sand and heated to 130–140° for 20 minutes. Saponification of the product with methanolic potassium hydroxide produced only an impure acid in amounts so small that characterization was not attempted.

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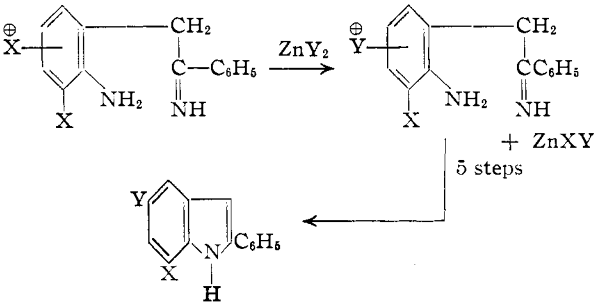
(7) *Cf.* G. Owen, *J. Chem. Soc.*, **123**, 3392 (1923); C. W. Gibby and W. A. Waters, *ibid.*, 2151 (1931); J. J. Sudborough and J. V. Lakhumalani, *ibid.*, **111**, 41 (1917).

Cyclohexanone 2,6-dibromophenylhydrazone, sand and zinc chloride were heated to 110° for 0.5 hour. The crude product, boiled in xylene solution with chloranil, yielded a crystalline compound, m.p. 124–125°, whose composition corresponded to that of a monobromocarbazole and which yielded carbazole on catalytic reductive debromination. However, its melting point did not correspond to any of those reported for the four monobromocarbazoles by Barclay and Campbell.[8] Evidently a reinvestigation of the properties of these four compounds must be carried out before a structure can be assigned to the product isolated in the present work. In any case, it appears likely that the major product from cyclohexanone 2,6-dibromophenylhydrazone and zinc chloride was a monobromotetrahydrocarbazole. If this is true, then the 2,6-dibromophenylhydrazones of acetophenone and of cyclohexanone do not behave similarly when treated with zinc chloride, and it remains to be established whether either type of behavior is typical and general. Investigations directed toward this end are in progress.

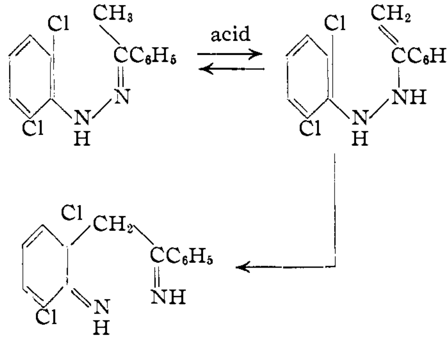
Discussion

The observations just described show that when acetophenone 2,6-dibromophenylhydrazone is heated with zinc chloride, or when the analogous 2,6-dichlorophenylhydrazone is heated with zinc bromide, in either case a mixture of two 5,7-dihalogenindoles is formed. In one of the two indoles, both of the halogens are of the type present in the original phenylhydrazone; in the other indole, the halogen present in the 5-position comes from the zinc halide. The mode of formation of the indoles containing two different halogens almost certainly does not involve a halogen exchange step prior to the initiation of the indole reaction, for if such an exchange occurred from either initial dihalophenylhydrazone, the product would be acetophenone 2-bromo-6-chlorophenylhydrazone, which is now known[9] to yield three, rather than just two, 2-phenyl-5,7-dihaloindoles when treated with either zinc halide. Furthermore, the stability of halogen in 5,7-dihaloindoles under the comparatively drastic conditions employed in these reactions has been established[3b] already; therefore the exchange of halogen in the present work could not have occurred subsequent to indole formation. For example, 2-phenyl-5-bromo-7-chloroindole (V) could not have been formed first by transformation of the hydrazone to the dichloroindole IV, followed by partial conversion of the latter to V, an unlikely process for additional reasons that are obvious.

It follows that the halogen exchange reactions that led to the formation of III and of V must have occurred during the course of the indole reaction itself. A mechanism previously advanced[3b] to explain the formation of 5,7-dichloroindoles from 2,6-dichlorophenylhydrazones was based on the migration of chlorine in an electron-poor or "positive" condition during the indole reaction. The formation of III and of V, products of halogen interchange with the zinc halides, can be accommodated by this mechanism only by assuming that the positive halogen ion, first formed from the reacting phenylhydrazone, interacts with the zinc halide to form a new positive halogen, which then substitutes into the aromatic ring at what is ultimately to become the 5-position of the indole. Such an assumption does not appear unreasonable when X = Cl and Y = Br, so that the formation of V might be rationalized this way. However, the formation of III by a parallel sequence (X = Br, Y = Cl) demands in effect the oxidation of chloride ion to positive chlorine by the agent positive bromine, an unattractive postulate in view of the well known relative oxidation–reduction potentials of the two halogen–halide ion systems. Also difficult to reconcile with the hypothesis that *ortho* halogen is displaced in a positive condition in the Fischer reaction is the observation recorded by Milne and Tomlinson[10] that cyclohexanone *o*-chlorophenylhydrazone in aqueous sulfuric acid yields as one of its products 6-hydroxy-1,2,3,4-tetrahydrocarbazole (and not a "hydroxyisocarbazole," as had been reported earlier[11]).



The evidence now at hand therefore suggests that at least those Fischer reactions of *o*-halophenylhydrazones which lead to substitution of a new atom or group into the 5-position of the indole probably involve the displacement of the *ortho* halogen as halide ion. A displacement of this sort can be treated as a nucleophilic substitution reaction if an intermediate (as distinguished from a transition state) such as VI is postulated. This intermediate is formally similar to the dienone intermediate in the *para* Claisen rearrangement, for which an imposing body of evidence has been gathered.[12] The suggestion has been made pre-



VI

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[8] B. M. Barclay and N. Campbell, *J. Chem. Soc.*, 530 (1945).

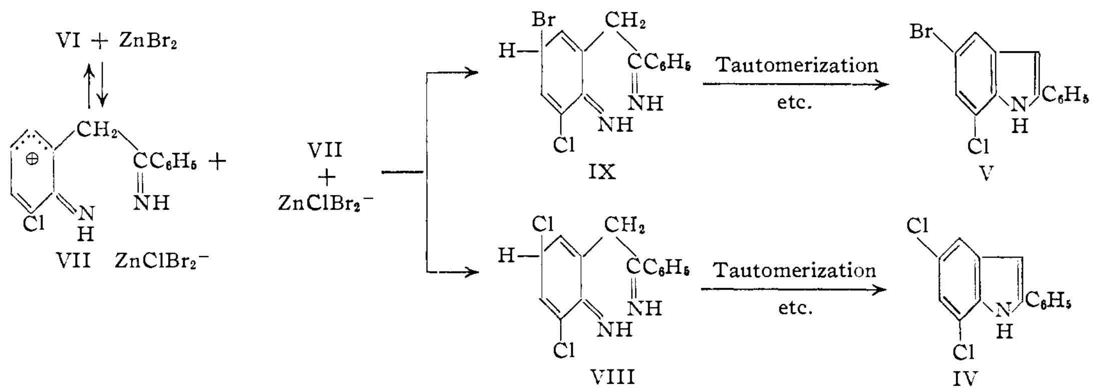
[9] R. B. Carlin and T. J. Kealy, to be published.

[10] A. H. Milne and M. L. Tomlinson, *J. Chem. Soc.*, 2789 (1952).

[11] C. S. Barnes, K. H. Pausacker and C. I. Schubert, *ibid.*, 1381 (1949).

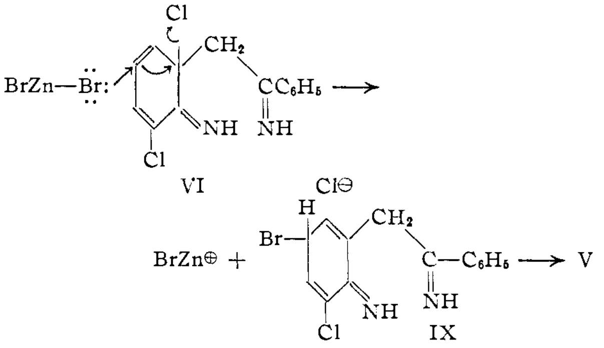
[12] *Cf.* D. Y. Curtin and H. W. Johnson, THIS JOURNAL, **76**, 2276 (1954); **78**, 2611 (1956); H. Conroy and R. A. Firestone, *ibid.*, **75**, 2530 (1953); **78**, 2290 (1956).

viously[13] that VI (or a conjugate acid derived from it) contains an allylic chlorine and that such an intermediate should show reactions characteristic of allylic chlorides. For example, the observations thus far available could be interpreted in terms of a zinc chloride-induced transformation of the SN1 type.

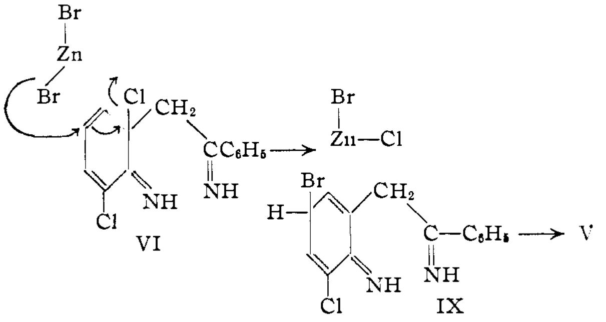


In a like manner, a cation analogous to VII, if attacked by water, should afford the 6-hydroxytetrahydrocarbazole reported by Milne and Tomlinson.[10] The original allylic system of the intermediate VI should, of course, be nearly completely transformed to the isomeric system VIII or IX because the following tautomerization to yield an aromatic ring should be essentially irreversible. The formation of II and III from acetophenone 2,6-dibromophenylhydrazone and zinc chloride can be formulated in the same manner. Furthermore, this mechanism permits a qualitative understanding of the product ratios II:III and IV:V. If one assumes that each bromine of the zinc trihalide anion reacts twice as rapidly as each chlorine with the organic cation, then VII and $ZnClBr_2^-$ should lead to a ratio V:IV 4:1 (observed, about 3:1), and a cation analogous to VII should react with $ZnBrCl_2^-$ to afford about equimolar amounts of II and III (as observed). The assumption that bromine in a complex anion derived from a Lewis acid should react more rapidly than chlorine certainly appears justified in view of the known products of reactions between alkyl chlorides and aluminum bromide[14]; the assumption of a 2:1 rate ratio per halogen, though quantitatively unsupportable, seems to be at least in the correct order of magnitude.[14]

Although the interpretation just given of the behavior of acetophenone 2,6-dihalogenphenylhydrazones in the presence of zinc halides appears to account satisfactorily for the recorded observations, there is no evidence as yet available that serves to eliminate other interpretations. For example, the formation of 2-phenyl-5,7-dichloroindole (IV) from the dichlorophenylhydrazone and zinc bromide might be attributed to an SNi transformation of the intermediate VI to VIII, followed by tautomerization and subsequent formation of IV. Of course, the difference between this and the preceding mechanism advanced to account for the production of IV in this reaction is only in degree of separation of the migrating chlorine from the organic moiety. The formation of 2-phenyl-5-bromo-7- chloroindole (V) in the same reaction might take place by an SN2′ displacement involving the intermediates VI and IX or by an essentially equivalent mechanism involving a six-membered ring transition state,



The presence of 2-phenyl-7-bromoindole (I) in the reaction mixture from acetophenone 2,6-dibromophenylhydrazone and of a monobromotetrahydrocarbazole from cyclohexanone 2,6-dibromophenylhydrazone, both zinc chloride promoted, can only be rationalized when the source of hydrogen that displaces one bromine of the original hydrazone can be identified.



Experimental[15]

3,5-Dibromosulfanilic Acid and its Barium Salt.—The method reported by Orton and Pearson[6] was modified in two ways: one-half the volume of water used in the procedure of Orton and Pearson was employed; and after precipitation of the barium dibromosulfanilate with barium chloride, the solution was neutralized with sodium hydroxide, not barium hydroxide. The yield of dry barium salt was 95%. The

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(13) See ref. 3b, footnote 8.

(14) *Cf.* P. D. Bartlett, F. E. Condon and A. Schneider, THIS JOURNAL, **66**, 1531 (1944).

(15) Melting points are corrected.

dibromosulfanilic acid was obtained by evaporation of its solution on a steam-bath until crystallization occurred.

2,6-Dibromoaniline.—Desulfonation of 3,5-dibromosulfanilic acid and of its barium salt was carried out under a number of sets of conditions. Variables were internally measured temperature of the reaction mixture, temperature of steam introduced if any, nature and strength of acid, the presence or absence of ethylene glycol as a diluent, the use of reflux or immediate steam distillation, and the use of the sulfonic acid or the barium salt. The most consistently good yields of the best product were realized when the barium salt of the dibromosulfanilic acid was steam distilled from 76% sulfuric acid at 170° by a stream of steam preheated to the same temperature. These conditions are essentially those described by Orton and Pearson.[5] A product melting at 82–83.5° (reported[5] 87–88°) was obtained in 60% yield, provided that runs using about 75 g. of material were carried out. Attempts to adapt the procedure to larger runs resulted in the formation of a product too impure to use. Other procedures gave inconsistent results, and crude products never melted higher than 75°.

***o*-Bromonitrobenzene.**—A fine suspension of 69 g. of *o*-nitroaniline in 200 ml. of 48% hydrobromic acid was treated slowly with a solution of 35 g. of sodium nitrite in 65 ml. of water; the temperature of the mixture was held below 10°. The filtered diazonium solution was added slowly to a boiling solution of 40 g. of cuprous bromide in 60 ml. of 48% hydrobromic acid through which a stream of steam was being passed continuously. Steam distillation was continued after addition of the diazonium solution until organic material ceased to distil. The oily steam distillate solidified on cooling to 79 g. (78%) of a yellow product, m.p. 41–42.5°[16] which required no further purification.

***o*-Bromoaniline hydrochloride** was obtained in 80% yield from *o*-bromonitrobenzene by application of the procedure described by Hazlet and Dornfeld.[17] It began to sublime at 150° and melted at 217–220° dec.

2-Bromo-4-chloroaniline was prepared starting with *p*-chloroaniline in 37% yield, using the method of Chattaway and Clemo.[18] The product melted at 65–67° (reported 69°[18]).

2-Chloro-4-bromoaniline.—*o*-Chloroacetanilide was brominated by the method used by Chattaway and Clemo[18] in the bromination of the *para* isomer. Acid hydrolysis in ethanol of the bromination product gave white needles, m.p. 70.5–72° (reported[19] 70–71°), in 82% over-all yield.

2,4-Dichloroaniline.—Acetanilide was chlorinated by means of the procedure reported by Reed and Orton.[20] Acid hydrolysis in ethanol gave a 54% over-all yield of white needles, m.p. 63–65° (reported[16] 63°).

2,6-Dichloroaniline was prepared as described in "Organic Syntheses."[5]

Halophenylhydrazines.—All but two of these substances were prepared by the procedure described earlier.[3] One of the exceptions was *o*-bromophenylhydrazine, which was prepared by the method of Meyer and Lecco.[21] This method departs from the standard one only by virtue of the fact that the usual amount of hydrochloric acid is reduced by one-half. The other exception was 2,4-dibromophenylhydrazine, which was prepared by brominating acetylphenylhydrazine and hydrolyzing the product in accordance with the report by Humphries and Evans.[22] The yields in which these halophenylhydrazines were obtained and their properties are given in Table I.

Halophenylhydrazones.—The general method described previously[3a] was employed. Acetophenone 2,4- and 2,6-dichlorophenylhydrazones have been reported in an earlier paper in this series[3a]; the yields from the preparations and the properties of nine other ketone halophenylhydrazones are summarized in Table II.

TABLE I

PREPARATIONS AND PROPERTIES OF SOME HALOPHENYLHYDRAZINES

Halophenylhydrazine	Yield, %	M.p., °C. Obsd.	M.p., °C. Repptd.
2,6-Dibromo-	70	107–109	110[a]
2,6-Dichloro-	68	101–102	100.5–101.5[3a]
2,4-Dibromo-	79	91.5–92	92[b]
2,4-Dichloro-	95	94–95	94.5[3a]
2-Chloro-4-bromo-	83	90.5–91.5[c]	....
2-Bromo-4-chloro-	71	96–97[d]	....
o-Bromo-	61	44–46	48[e]

[a] E. Votocek and R. Lukes, *Bull. soc. chim.*, **35**, 868 (1924). [b] A. Michaelis, *Ber.*, **26**, 2190 (1893). [c] Calcd. for $C_6H_6N_2BrCl$: C, 32.53; H, 2.73. Found: C, 32.67; H, 3.06. [d] Calcd. for $C_6H_6N_2BrCl$: C, 32.53; H, 2.73. Found: C, 32.52; H, 2.82. [e] M. Busch and E. Meussdorffer, *J. prakt. Chem.*, [2] **75**, 137 (1907).

2-Phenylhaloindoles. General Procedure.—A modification of the earlier procedure[3a] was used for the preparation of all the pure 2-phenylhaloindoles. A mixture of the acetophenone halophenylhydrazone with five times its weight of anhydrous zinc chloride was heated until a solution of a small sample in 5 ml. of acetone gave a strong red-purple color when treated with 5 ml. of Ehrlich reagent (a 2% solution of *p*-dimethylaminobenzaldehyde in 85% phosphoric acid); then the mixture was held at constant temperature for 10 to 20 minutes. The mixture was cooled and digested with 2% aqueous hydrochloric acid until the solid mass disintegrated.

When this procedure led to a flocculent, dark solid, the latter was removed by filtration, dried and extracted in a Soxhlet apparatus with petroleum ether (b.p. 65–110°) for three to four hours. Removal of the solvent from the extract solution left a residue that was purified by high vacuum sublimation, by recrystallization or by a combination of both methods. When the product from the acid digestion was an oil or a tar, it was extracted into chloroform, and the solution was concentrated to a volume of 20–30 ml. and then poured into about ten times its volume of petroleum ether (b.p. 65–110°). The finely divided solid that precipitated was collected, dried and extracted in a Soxhlet apparatus as in the preceding method. The chloroform–petroleum ether filtrate and the petroleum ether extract were combined, the solvents were removed and the residue purified as before.

This method was much more rapid, and yields from it were better than from the earlier procedure[3a]; for example, 2-phenyl-5,7-dichloroindole, formerly obtained in 19% over-all yield from 2,4-dichlorophenylhydrazine,[3a] was isolated in 34% yield when the new procedure was used. The yields and properties of five new 2-phenylhaloindoles are listed in Table III.

2-Methyl-5,7-dibromo-3-indoleacetic Acid.—A mixture of 24 g. of dihalophenylhydrazone XVII (Table II), 125 g. of anhydrous zinc chloride and an equal volume of clean sand was heated at 150° for 20 minutes. The mixture was digested with 2% aqueous hydrochloric acid, and the organic material was extracted into ether. The ether was removed and the residue was boiled with 10% methanolic potassium hydroxide for 45 minutes. Most of the methanol was removed, and the remaining solution was filtered free of a small amount of dark solid, extracted with ether, and then neutralized with hydrochloric acid. The dark brown solid (13 g.) that precipitated yielded 5.5 g. of a pale yellow crystalline acid after protracted sublimation at 1 μ. From this crude acid, 3 g. of white crystalline product, m.p. 215° dec., was obtained after several recrystallizations from glacial acetic acid. The white acid gave no Ehrlich test, but after fusion a sample gave an immediate red coloration with the Ehrlich reagent.

Anal. Calcd. for $C_{11}H_9O_2NBr_2$: C, 38.07; H, 2.61. Found: C, 38.14; H, 2.71.

1,3-Dibromocarbazole.—The dibromophenylhydrazone XV (Table II) was heated at 150° with zinc chloride in the absence of a solvent or diluent. The product was isolated and purified by methods employed previously[3a]; it melted at 93.5–94° and was presumably 6,8-dibromo-1,2,3,4-tetrahydrocarbazole, although it was not characterized. Instead it was subjected to dehydrogenation by chloranil in

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(16) A. F. Holleman, *Rec. trav. chim.*, **19**, 365 (1900), reported the m.p. 41–42°.

(17) S. E. Hazlet and C. A. Dornfeld, THIS JOURNAL, **66**, 1781 (1944).

(18) F. D. Chattaway and G. R. Clemo, *J. Chem. Soc.*, **109**, 89 (1916).

(19) G. B. Heisig, THIS JOURNAL, **50**, 143 (1928).

(20) W. W. Reed and K. J. P. Orton, *J. Chem. Soc.*, 1543 (1907).

(21) V. Meyer and M. T. Lecco, *Ber.*, **16**, 2976 (1883).

(22) J. E. Humphries and R. Evans, *J. Chem. Soc.*, 1676 (1925).

TABLE II

PREPARATION AND PROPERTIES OF SOME KETONE DIHALOPHENYLHYDRAZONES

Acetophenone halophenylhydrazone	No.	Yield, %	M.p., °C.	Formula	Carbon, %		Hydrogen, %	
					Calcd.	Found	Calcd.	Found
2,4-Dibromo-	X	56	84–85	$C_{14}H_{12}N_2Br_2$	45.68[a]	45.86[a]	3.29[a]	3.48[a]
2,6-Dibromo-	XI	72	81–82	$C_{14}H_{12}N_2Br_2$	45.68[a]	45.83[a]	3.29[a]	3.47[a]
o-Bromo-	XII	65	78–79	$C_{14}H_{13}N_2Br$	58.15	58.52	4.53	4.56
2-Chloro-4-bromo-	XIII	90	84.5–85.5	$C_{14}H_{12}N_2BrCl$	51.96	52.25	3.74	3.71
2-Bromo-4-chloro-	XIV	54	78–79	$C_{14}H_{12}N_2BrCl$	51.96	51.83	3.74	3.71
Cyclohexanone halophenylhydrazone								
2,4-Dibromo-	XV	90	69.5–70	$C_{12}H_{14}N_2Br_2$	...[b]	...[b]	...[b]	...[b]
2,6-Dibromo-	XVI	88	58–59	$C_{12}H_{14}N_2Br_2$	...[b]	...[b]	...[b]	...[b]
Ethyl levulinate halophenylhydrazone								
2,4-Dibromo-	XVII	95	70–71	$C_{13}H_{16}N_2O_2Br_2$	39.82	40.01	4.11	4.26
2,6-Dibromo-	XVIII	68	...[c]	$C_{13}H_{16}N_2O_2Br_2$	39.82	39.65	4.11	4.23

[a] Sample prepared by E. E. Fisher.[4] [b] Compound decomposed too rapidly to permit analysis. [c] Pale yellow oil, b.p 140° (*ca.* 1 mm.), $n^{30}D$ 1.5702.

TABLE III

PREPARATION AND PROPERTIES OF SOME 2-PHENYLHALOINDOLES

2-Phenylhaloindole	From halophenylhydrazone no.	Yield, %	M.p., °C.	Formula	Carbon, %		Hydrogen, %	
					Calcd.	Found	Calcd.	Found
5,7-Dibromo- (II)	X	44	148.5–149.5	$C_{14}H_9NBr_2$	47.89[a]	47.84[a]	2.58[a]	2.58[a]
5,7-Dibromo-[b] (II)	XI[b]	8[b]	148–149[b]					
7-Bromo- (I)	XII	38	117–118	$C_{14}H_{10}NBr$	61.78	62.15	3.70	3.90
5-Bromo-7-chloro- (V)	XIII	50	139–139.5	$C_{14}H_9NClBr$	54.84	55.04	2.96	3.14
5-Chloro-7-bromo- (III)	XIV	44	143–143.5[c]	$C_{14}H_9NClBr$	54.84	54.98	2.96	3.33

[a] Sample prepared by E. E. Fisher. [b] Prepared by heating halophenylhydrazone XI and zinc bromide in nitrobenzene at 165° for ten minutes. The nitrobenzene was steam distilled from the reaction mixture, and the residue was treated in accord with the general procedure. [c] Recrystallized from "mixed heptanes." All others were recrystallized from ethanol.

accordance with the procedure reported by Barclay and Campbell.[8] The crude dibromocarbazole was recrystallized from commercial heptanes. A 3.5% over-all yield was obtained of a white crystalline product, m.p. 108–109°.

Anal. Calcd. for $C_{12}H_7NBr_2$: C, 44.34; H, 2.17; Br, 49.18. Found: C, 44.75; H, 2.23; Br, 50.28.

Reaction of Cyclohexanone 2,6-Dibromophenylhydrazone (XVI) with Zinc Chloride.—A mixture of 30 g. of XVI, 150 g. of zinc chloride, and about three times as much clean sand was heated on a steam-bath for a half hour. The internal temperature did not exceed 110°. The reaction mixture was digested with dilute hydrochloric acid and then extracted with benzene. The benzene solution was dried ("Drierite"), freed of tars by passage through a short column of alumina, and the benzene was removed. The residue, 17 g. of a yellow oil, was not purified but was dissolved in xylene, and the solution was boiled with 20 g. of chloranil for 24 hours. The cooled mixture was filtered free of solids, which were washed with benzene. The combined benzene and xylene solutions were washed with 100 ml. of a 2.5% aqueous sodium hydroxide solution containing 10 g. of sodium hydrosulfite, and the organic solvents were removed by steam distillation. The residue was extracted into ether, and the solution was dried ("Drierite"). Removal of the ether left a glass from which 3.5 g. of a yellow pasty material was obtained by sublimation at 1 μ. Four recrystallizations from petroleum ether (b.p. 65–110°) alternated with three vacuum sublimations gave 0.5 g. of a white crystalline solid, m.p. 124–125°. When a solution of a sample in concentrated sulfuric acid was treated with a few drops of nitric acid, a deep green-blue color developed, as is characteristic of most carbazoles.[8] Although its composition indicates a monobromocarbazole, the melting point does not accord with those reported for any of the four monobromocarbazoles,[8] which are as follows: 1-bromo-, 111–112°; 2-bromo-, 250–251°; 3-bromo-, 201–202°; 4-bromo-, 104–105°.

Anal. Calcd. for $C_{12}H_8NBr$: C, 58.56; H, 3.27; N, 5.69. Found: C, 58.18; H, 3.35; N, 5.84.

A solution of 0.4 g. of the presumed monobromocarbazole, m.p. 124–125°, in 60 ml. of ethanol was hydrogenated in the presence of Raney nickel at 75° for nine hours at 600 p.s.i. The solution was filtered free of catalyst, and the bomb and the catalyst were rinsed with hot ethanol. The combined ethanol solution was concentrated until crystallization began and then cooled. The product was carbazole, m.p. and mixed m.p. 245–246°. The ethanol mother liquors were diluted with water and filtered to remove additional precipitated carbazole. The filtrate contained bromide ion, but no chloride ion could be detected.

Reaction of Acetophenone 2,6-Dibromophenylhydrazone with Zinc Chloride.—A slurry of 250 g. of anhydrous zinc chloride in a solution of 47 g. of acetophenone 2,6-dibromophenylhydrazone in 300 ml. of nitrobenzene was stirred and heated at 170–180° for ten minutes. Nitrobenzene was removed by steam distillation, and the residue was extracted into benzene. Removal of the benzene left a residue which was subjected to high vacuum sublimation. The small amount of sublimate, at one stage of its attempted fractional crystallization, yielded two crystalline types, prisms and needles, which were separated mechanically. The prisms, m.p. 108–114°, yielded pure **2-phenyl-7-bromoindole** (I), m.p. and mixed m.p. 117–118.5°, after two recrystallizations from petroleum ether (b.p. 65–110°). The needles, m.p. 132–135°, were slightly impure 139° material isolated earlier by Fisher.[4]

The residue from the sublimation was dissolved in benzene, the solution was concentrated and then poured, with stirring, into about 250 ml. of commercial "heptanes." The flocculent black precipitate was collected by filtration and extracted in a Soxhlet apparatus with petroleum ether (b.p. 65–110°) for 24 hours. Removal of the solvent from the extract left 5 g. of an amorphous solid from which 3.4 g. of semi-crystalline material was obtained by vacuum sublimation. The residue in the Soxhlet thimble was extracted for 48 hours with commercial heptanes; evaporation of the solvent from this extract and subsequent sublimation afforded another 0.8 g. of product. Recrystallization of the total sublimate (4.2 g.) from petroleum ether (b.p. 65–110°) gave 1.16 g. of nearly colorless needles, m.p. 138–139°. A second crop, m.p. 134–137°, 0.38 g., was obtained after concentrating the mother liquor. Total yield of this product was about 5%. It will be referred to subsequently as mixture A.

Anal. Calcd. for phenyldibromoindole $C_{14}H_9NBr_2$: C, 47.89; H, 2.58; N, 3.99; mol. wt., 351. Calcd. for phenylbromochloroindole $C_{14}H_9NBrCl$: C, 54.84; H, 2.96; N, 4.57; mol. wt. 306. Calcd. for equimolar mixture: C, 51.22; H, 2.76; N, 4.27; mol. wt., 328. Found: C, 51.09, 51.57, 50.99, 52.73; H, 3.10, 2.90, 2.76, 2.64; N, 4.16, 4.37; Br (all halogen calcd. as Br), 46.12, 45.14; mol. wt. (Menzies-Wright), 348.

Hydrogenation of Mixture A.—A solution of 0.111 g. of mixture A and 0.2 g. of sodium hydroxide in 50 ml. of ethanol was hydrogenated at 50 p.s.i. in the presence of Raney nickel for four hours at room temperature. The mixture was filtered free of catalyst, and the latter was extracted with boiling ethanol, which was added to the original filtrate. The ethanol solution was evaporated to dryness, the residue was washed free of sodium halides with distillled water, and the organic material was dissolved in ether. The water solution gave good qualitative tests both for chloride and for bromide ions. The ether solution yielded, after removal of the solvent, a crude product from which 0.056 g. of a white crystalline product, m.p. 185–187°, was obtained by recrystallization from ethanol. No m.p. depression was observed when this sample was mixed with authentic[23] 2-phenylindole.

Reaction of Acetophenone 2,6-Dichlorophenylhydrazone with Zinc Bromide.—A slurry of 300 g. of anhydrous zinc bromide in a solution of 73 g. of acetophenone 2,6-dichlorophenylhydrazone in 500 ml. of nitrobenzene was stirred and heated at 150–175° for ten minutes. After removal of the nitrobenzene by steam distillation, the mixture was subjected to the general procedure described previously. Extraction and sublimation gave 23.6 g. of a pasty yellow material, from which 12.1 g. of faintly yellow needles, m.p. 134.5–136°, were obtained by crystallization from ethanol. Recrystallization from petroleum ether (b.p. 65–110°) yielded fine, white needles, m.p. 139–139.5°, hereafter referred to as "mixture B." The mother liquors from the first crop of crystals yielded a second crop of the same m.p. No other crystalline material could be isolated from the reaction mixture. There was no m.p. depression when mixtures B and A were mixed, and mixture B and 2-phenyl-5-bromo-7-chlorindole also showed no m.p. depression. In view of the fact that there is no appreciable m.p. depression in any of the mixtures of 2-phenyl-5,7-dihaloindoles, the failure of mixture B to show m.p. depressions with other compounds and mixtures of the series discloses nothing about its constitution.

Anal. Calcd. for phenyldichloroindole $C_{14}H_9NCl_2$: C, 64.14; H, 3.46; N, 5.34. Calcd. for phenylbromochloroindole $C_{14}H_9NBrCl$: C, 54.84; H, 2.96; N, 4.57. Calcd. for mixture 70 mole % (*ca.* 75 wt. %) in $C_{14}H_9NBrCl$: C, 57.33; H, 3.09; N, 4.78. Found: C, 57.21, 57.14; H, 3.09, 3.18; N, 4.79.

Spectra of Indoles.—Ultraviolet absorption spectra were measured with a Beckman Model DU quartz spectrophotometer. Solutions in ethanol were about 3×10^{-5} *M*.

Infrared spectra were measured with a Perkin-Elmer Model 21 double beam spectrophotometer equipped with a sodium chloride prism. The spectra were determined in carbon disulfide solutions of 20 mg. per ml. concentrations.[24]

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[23] R. L. Shriner, W. C. Ashley and E. Welch, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 725.

[24] The ultraviolet and infrared spectra referred to in this paper have been deposited as Document number 5111 with the ADI Auxiliary Publication Project Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be obtained by citing the Document number and by remitting $1.25 for photoprints or $1.25 for 35 mm. microfilm, in advance by check or money order payable to: Chief, Photoduplication Service, Library of Congress.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

Preparation of Triazines by the Reaction of Biguanide and Esters[1]

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Compounds of type II and III have been synthesized by the reaction of phenyl biguanide or *p*-chlorophenyl biguanide and biguanide, respectively, with appropriate esters. Methylation experiments with 4,6-diamino-2-methyl-*s*-triazine have demonstrated that conventional techniques useful for 2-aminopyrimidine derivatives fail. Successful methylation can be achieved with methylamine hydrochloride at higher temperatures.

In previous work,[3] compounds of type II were synthesized as precursors for the synthesis of vinyltriazines. When some of these compounds were screened for biological activity,[4] it was found that they exhibited some anti-rheumatic and diuretic properties. It was therefore of interest to synthesize compounds of type II, R = CH_2Cl, X = Cl; R = CHBrCl, CF_3, $CHCl_2$, X = H and type III, R′ = CHBrCl, CH_2Cl, $CHCl_2$ to test their activity in the above mentioned areas. The general reaction is diagrammed in the reaction scheme.

Compounds of type III, R′ = CH_2Cl, CHBrCl and $CHCl_2$, were synthesized from the appropriate α-haloester and biguanide. All attempts to synthesize biguanide according to the procedure described by Rackmann[5] failed, guanylurea being isolated in every case as evidenced from the melting point, preparation of the picrate and a mixed melting point with an authentic sample of guanylurea. Biguanide was then synthesized according to the procedure described by Smolka and Friedrich[6] and the free base by that of Slotta and Tschesche.[7]

Although Thurston has reported the reaction of biguanide with haloesters to give haloalkyl guanamines,[8] compound III, R′ = CH_2Cl, was not de-

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[1] This is the thirteenth in a series of articles concerned with the synthesis of monomers and their precursors; for the twelfth paper in the series, see C. G. Overberger and Alexander Lebovits, THIS JOURNAL, **78**, 4792 (1956).

[2] This paper comprises portions of theses presented by Francis W. Michelotti in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School and Philip M. Carabateas for the degree of Bachelor of Science at the Polytechnic Institute of Brooklyn.

[3] (a) C. G. Overberger and S. L. Shapiro, THIS JOURNAL, **76**, 93 (1954); (b) S. L. Shapiro and C. G. Overberger, *ibid.*, **76**, 97 (1954); (c) C. G. Overberger and S. L. Shapiro, *ibid.*, **76**, 1061 (1954).

[4] These compounds and subsequent ones reported here were suggested for biological activity by the Eli Lilly Co. and will be reported separately.

[5] K. Rackmann, *Ann.*, **376**, 169 (1910).

[6] A. Smolka and A. Friederich, *Monatsh.*, **10**, 86 (1889).

[7] K. H. Slotta and R. Tschesche, *Ber.*, **62B**, 1396 (1929).

[8] J. T. Thurston, U. S. Patent 2,463,471, March 1, 1949.