tive moiety of an amino group alpha to a free carboxyl group,[13] as in the peptide glutathione, or a β-aspartyl peptide or of a terminal lysine group.[14] (d) The reactivation of air-oxidized inactive material by reduction with either cysteine or glutathione is suggestive of the presence of a sulfhydryl group which is necessary for SSF activity. It therefore appears that cysteine is quite probably a constituent of the structural SSF peptide; since the total sulfur content of proteins in most cases can be accounted for by known sulfur-containing amino acids,[21] and it is unlikely that a new sulfur-containing amino acid is present in the SSF protein. Ergothionine which is present in blood has no SSF activity,[5] nor has this compound been shown to be a component of proteins.

The presence of an SSF protein in mammalian blood and the occurrence of biologically active material in natural products suggest that the factor may be important in mammalian metabolism. The role of this protein in cellular metabolism has yet to be determined.

**Acknowledgment.**—The authors wish to thank Professor J. Lawrence Oncley, University Laboratory of Physical Chemistry Related to Medicine and Public Health, for his aid in interpreting the physical data.

BOSTON, MASSACHUSETTS RECEIVED AUGUST 6, 1951

[21] E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," A.C.S. Monograph 90, page 351, Reinhold Publishing Corp., New York, N. Y., 1943.

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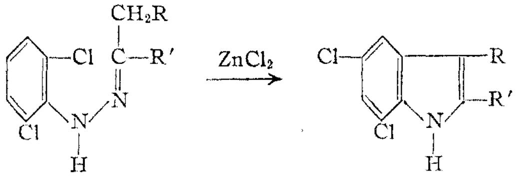
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

# Studies on the Fischer Indole Synthesis. II[1]

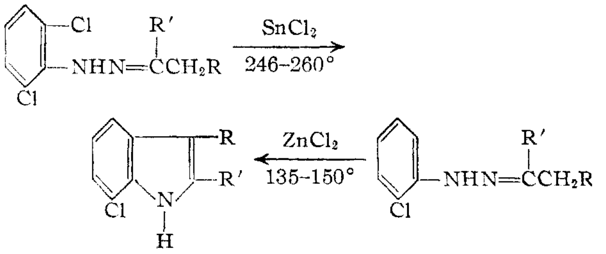
BY ROBERT B. CARLIN, JOHN G. WALLACE[2a] AND E. E. FISHER[2b]

The conversion of five 2,6-dichlorophenylhydrazones to 7-chloroindoles by fusion with stannous chloride, together with the stability of 2-(*p*-chlorophenyl)-5,7-dichloroindole to the same reagent under the same conditions, indicates that chlorine probably migrates in an electron-deficient or "positive" condition during the conversion of 2,6-dichlorophenylhydrazones to 5,7-dichloroindoles by zinc chloride. Failure to observe any evidence of intermolecular chlorine migration from acetophenone 2,6-dichlorophenylhydrazone to any one of three possible halogen acceptors, in the presence of zinc chloride, lends support to the hypothesis that the chlorine migration is intramolecular. A reaction sequence has been proposed to account for the facts now available about the behavior of 2,6-dichlorophenylhydrazones in the Fischer reaction. This reaction sequence includes a mechanism which postulates a six-ring transition state for the step in which the new carbon-to-carbon bond is formed. The ultraviolet extinction curves for three indoles and a carbazole are reported.

The chlorine migration which occurs during the conversion of 2,6-dichlorophenylhydrazones to 5,7-dichloroindoles[3] requires clarification. The work described in this paper was carried out in order to provide evidence bearing on (a) the nature of the migrating chlorine, and (b) the question of inter- or intramolecular chlorine migration.



The available information is consistent with the postulate that a chlorine atom ortho to the hydrazone linkage rearranges to the para position during the course of the acid-catalyzed transformation of 2,6-dichlorophenylhydrazones to 5,7-dichloroindoles. A large number of analogous halogen migration reactions have been observed to occur when aromatic halides having certain structural features are treated with acidic catalysts,[4] and a considerable body of evidence has accumulated to support the theory that in these cases the halogen atoms migrate in an electron-deficient or "positive" condition. Nicolet and Sampey[5] have shown that halogen atoms so located on aromatic rings as to be susceptible to this type of migration are substituted by hydrogen when the aromatic halides are treated with stannous chloride, but that "non-positive" halogens are not attacked. Accordingly, they have used stannous chloride as a diagnostic reagent to establish the presence of positive halogen. Because stannous chloride is an acidic reagent, it might prove capable of promoting the Fischer reaction. Furthermore, if stannous chloride should catalyze Fischer reactions of 2,6-dichlorophenylhydrazones and if positive chlorine is involved in these reactions, then the stannous chloride should also capture the positive chlorine, and 7-chloroindoles should be formed. Actually, in the present work crystalline 7-chloroindoles have been isolated in 3–17% yields from the forbidding black tars formed when 2,6-dichlorophenylhydrazones of acetophenone, β-acetonaph-



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[1] Abstracted from D.Sc. theses by John G. Wallace and E. E. Fisher.

[2] (a) du Pont Pre-doctoral Fellow, 1949–1950; (b) Institute Graduate Fellow in Organic Chemistry, 1947–1948.

[3] (a) R. B. Carlin and E. E. Fisher, THIS JOURNAL, **70**, 3421 (1948); (b) C. S. Barnes, K. H. Pausacker and W. E. Badcock, *J. Chem. Soc.*, 730 (1951).

[4] A bibliography is given by H. Meerwein, P. Hofmann and F. Schill, *J. prakt. Chem.*, **154**, 266 (1940). For a more recent example, see H. T. Huang, D. S. Tarbell and H. R. V. Arnstein, THIS JOURNAL, **70**, 4182 (1948).

[5] B. H. Nicolet and J. R. Sampey, *ibid.*, **49**, 1796 (1927).

thone, *p*-chloroacetophenone, *p*-phenylacetophenone and cyclohexanone were fused at 246–260° with stannous chloride. The structure of each 7-chloroindole was established by its synthesis from the corresponding *o*-chlorophenylhydrazone.

The indoles derived from acetone *o*-chlorophenylhydrazone and zinc chloride and from acetone 2,6-dichlorophenylhydrazone and stannous chloride were opaque white pastes which gave strong Ehrlich indole tests but which resisted all efforts to effect purification by crystallization, high vacuum distillation or sublimation and chromatography. Both pasty indoles changed to clear melts at 49–50°. It is likely that both were 2-methyl-7-chloroindole, but this could not be proved.

Although mixtures from each reaction of a 2,6-dichlorophenylhydrazone with stannous chloride were searched carefully for indoles other than 7-chloroindoles, a by-product was isolated in only one instance. *p*-Chloroacetophenone 2,6-dichlorophenylhydrazone gave 2-*p*-chlorophenyl-7-chloroindole in 6% yield plus an 11% yield of a crystalline solid, m.p. 262°, whose analytical values corresponded to the empirical formula $C_{24}H_{18}NCl_3$. Additional information about this compound will be sought when a new supply of it becomes available.

In connection with the mechanism of chlorine migration during Fischer reactions of 2,6-dichlorophenylhydrazones, the possibility had to be considered that these compounds are converted to 5,7-dichloroindoles by stannous chloride as they are by zinc chloride, but that stannous chloride then reductively removes the chlorine atom at the 5-position, leaving the 7-chloroindole. Though there is much evidence which makes this hypothesis unattractive, nevertheless it was tested by fusing 2-*p*-biphenylyl-5,7-dichloroindole with stannous chloride at 246°. The indole was recovered unchanged in 92% yield, and the presence of no other indole could be detected. Therefore, it seems safe to infer that the stannous chloride induced conversion of 2,6-dichlorophenylhydrazones to 7-chloroindoles does not involve 5,7-dichloroindoles as intermediates, and the reductive removal of the chlorine atom by stannous chloride does not occur subsequent to a chlorine rearrangement identical with that which occurs in the presence of zinc chloride. The evidence strongly suggests that the chlorine atom which is removed, in a positive condition, by stannous chloride is that which migrates at the same stage during the reaction and also in a positive condition in the zinc chloride promoted reaction.

The fact that a chlorine atom apparently migrates from a 2,6-dichlorophenylhydrazone molecule undergoing rearrangement to a stannous chloride molecule might be interpreted superficially as evidence that intermolecular chlorine migration occurs in these cases. However, the tin salt probably is bound to the hydrazone molecule undergoing rearrangement, and abstraction of a chlorine atom by stannous chloride bound to the same molecule would actually constitute intramolecular chlorine migration. Efforts were therefore made to obtain evidence of a true intermolecular chlorine transfer during zinc chloride catalyzed Fischer reactions of acetophenone 2,6-dichlorophenylhydrazone (VI). In the first such effort, VI was heated to 180–190° with zinc chloride in the solvent *p*-cresol, a compound shown by Baddeley and Plant[6] to be an excellent bromine acceptor in aluminum chloride induced intermolecular migrations of aromatic bromine. The only significant product was 2-phenyl-5,7-dichloroindole, isolated in better yield (33%) than has been obtained under any other conditions. Neither 2-phenyl-7-chloroindole nor any chlorinated cresol, the possible products of intermolecular transfer of chlorine from VI to solvent, could be detected in the reaction mixture. An attempt was next made to discover whether an indole (2-*p*-chlorophenyl-7-chloroindole) with no substituent at the 5-position would accept a chlorine atom from VI when the two compounds were heated together with zinc chloride. 2-Phenyl-5,7-dichloroindole and unchanged 2-*p*-chlorophenyl-7-chloroindole were isolated, but no 2-*p*-chlorophenyl-5,7-dichloroindole or 2-phenyl-7-chloroindole could be detected; hence, this attempt to obtain evidence of intermolecular chlorine rearrangement had also failed. Finally, VI and acetophenone phenylhydrazone (XIII) were heated together with zinc chloride. Both "normal" products, 2-phenylindole and 2-phenyl-5,7-dichloroindole, were isolated, but the presence of neither 2-phenyl-5- nor 2-phenyl-7-chloroindole, the possible products of intermolecular chlorine migration, could be detected. Of course, this experiment does not prove that intermolecular chlorine transfer between rearranging phenylhydrazone molecules does not or cannot occur. In the likely event that XIII undergoes the Fischer reaction much more rapidly than VI under identical conditions, then very little unchanged XIII (or XIII in the process of change) would be left to accept chlorine from VI during most of the reaction life of the latter.

Thus, no evidence of intermolecular chlorine transfer could be obtained in the course of this work. Though failure to isolate products of such reactions does not constitute proof that none were formed—particularly when no accounting can be given for substantial fractions of the starting materials—it still seems reasonable to say that the evidence now available supports the postulate that the chlorine migration is intramolecular. Such experimental techniques as chromatography, high vacuum distillation and sublimation and counter-current liquid–liquid extraction were employed in efforts to isolate all of the crystalline material from each mixture in which intermolecular chlorine migration products might have been present. In view of the fact that all "normal" products were obtained in each case and that intermolecular reaction products were obtained in no case, there should be no doubt that intermolecular chlorine migration reactions occurred, if at all, only to a very minor extent.

The information now available about the conversion of 2,6-dichlorophenylhydrazones to 5,7-dichloroindoles may be interpreted in terms of the following reaction sequence.

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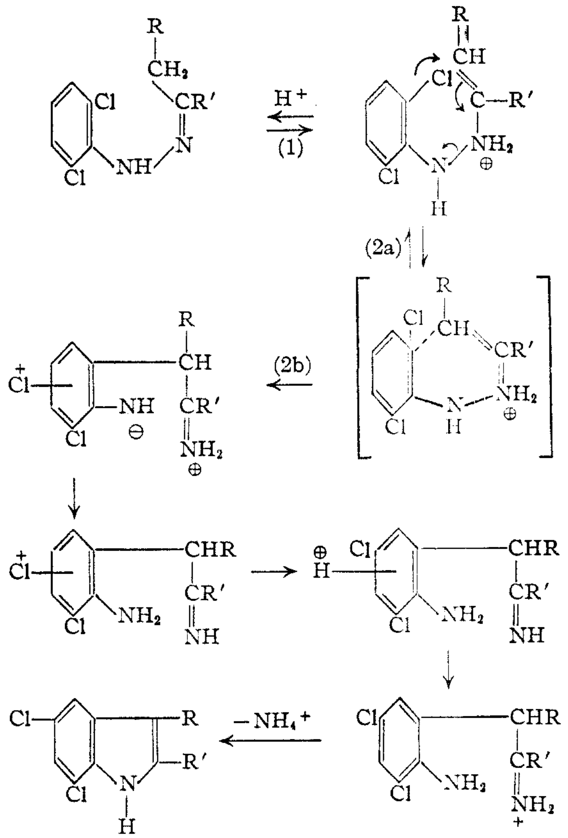
[6] G. Baddeley and J. Plant, *J. Chem. Soc.*, 525 (1943).



The concept of the π-electron complex[7] provides a convenient means of formulating the hypothesis that the "positive" chlorine undergoing migration does not leave the valence atmosphere of the aromatic ring, *i.e.*, that the migration is intramolecular. The above reaction sequence also provides a satisfactory explanation for the fact that the migrating chlorine ultimately appears at the 5-position of the indole, rather than at the 3- or some other position.[8]

The ultraviolet extinction curves for 2-*p*-chlorophenyl-7-chloroindole, 2-phenyl-5,7-dichloroindole and 2-phenylindole (Fig. 1) show that neither the presence of chlorine nor the position of one or more chlorine atoms on the 2-phenylindole ring system can be determined readily by ultraviolet spectroscopy. In Fig. 2 the ultraviolet extinction curve

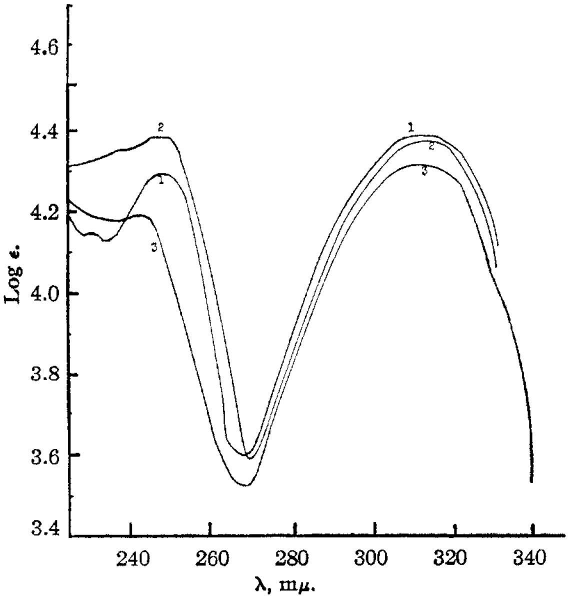


Fig. 1.—The ultraviolet absorption spectra of: 1, 2-(*p*-chlorophenyl)-7-chloroindole; 2, 2-phenyl-5,7-dichloroindole; 3, 2-phenylindole, all in 95% ethanol solution.

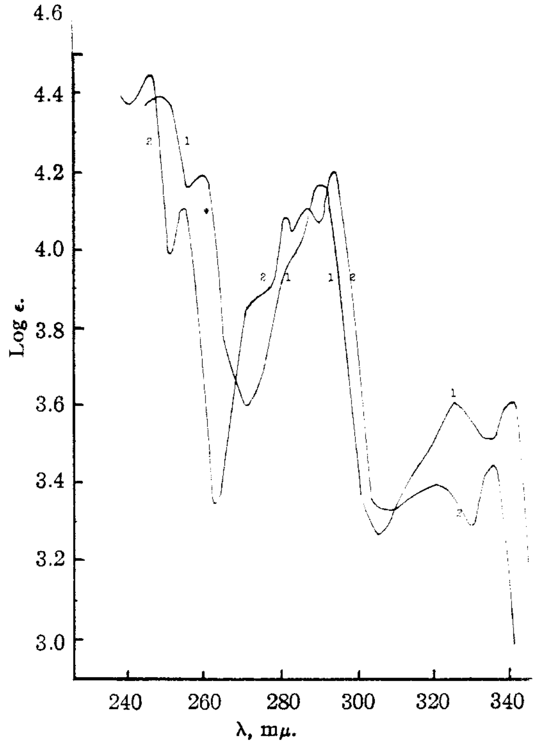


Fig. 2.—The ultraviolet absorption spectra of: 1, 1-chlorocarbazole, in 95% ethanol solution; 2, carbazole, in hexane solution (P. Ramart-Lucas and D. Biquard, *Bull. soc. chim.*, [5] 3, 430 (1936)).

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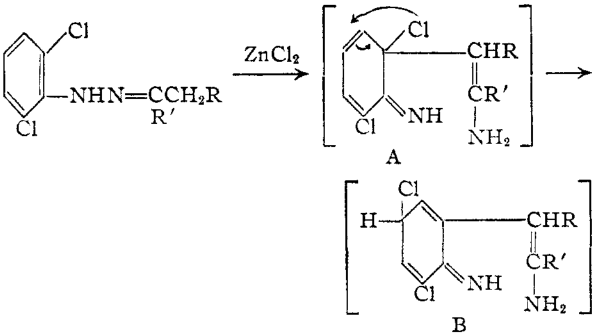
[7] M. J. S. Dewar, *Nature*, 176, 784 (1945); *J. Chem. Soc.*, 406, 777 (1946); "The Electronic Theory of Organic Chemistry," Oxford University Press, London, 1949.

[8] Dr. Philip L. Southwick has suggested an alternative mechanism



Tautomerization of B followed by ring closure affords the 5,7-dichloroindole. The reaction with stannous chloride to yield 7-chloroindoles can be fitted into this scheme if reductive removal of the allylic chlorine atom either of A or B is postulated. Tautomerization and ring closure of such a reduction product would yield the 7-chloroindole. In this case, of course, it is necessary to assume that the substitution of chlorine by hydrogen proceeds more rapidly than the tautomerizations to the 5,7-dichloroindole. This and related mechanisms will be considered in detail elsewhere by Dr. Southwick.

TABLE I

PREPARATIONS AND PROPERTIES OF CHLOROPHENYLHYDRAZONES

| o-Chlorophenylhydrazone of | No. | Yield, % | M.p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|
| Acetone | VII | 57 | ...[a] | $C_9H_{11}N_2Cl$ | 59.00 | 59.34 | 6.02 | 5.91 |
| *p*-Chloroacetophenone | VIII | 87 | 83.5 | $C_{14}H_{12}N_2Cl_2$ | 60.21 | 60.20 | 4.30 | 4.51 |
| *p*-Phenylacetophenone | IX | 74 | 136.5 | $C_{20}H_{17}N_2Cl$ | 74.88 | 74.77 | 5.30 | 5.12 |
| Cyclohexanone | X | 94 | 50.5 | $C_{12}H_{15}N_2Cl$ | ...[b] | ...[b] | ..[b] | ..[b] |
| β-Acetonaphthone | XI | 70 | 142.5 | $C_{18}H_{15}N_2Cl$ | 73.34 | 74.18 | 5.07 | 5.23 |
| Acetophenone | XII | 63 | 52.5 | $C_{14}H_{13}N_2Cl$ | 68.71 | 68.63 | 5.36 | 5.18 |
| 2,6-Dichlorophenylhydrazone of | | | | | | | | |
| β-Acetonaphthone | V | 97 | 132.5 | $C_{18}H_{14}N_2Cl_2$ | 65.65 | 65.73 | 4.25 | 3.96 |

[a] Liquid, b.p. 110–114° (3 mm.), $n^{21}_D$ 1.5816. [b] Sample decomposed before analysis.

TABLE II

CONVERSION OF CHLOROPHENYLHYDRAZONES TO INDOLES

| From chlorophenylhydrazone no. | Procedure | Monochloroindole | Yield, % | M.p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|
| II | A | 2-(*p*-Chlorophenyl)-7- | 6 | 126[i] | $C_{14}H_9NCl_2$ | 64.12 | 64.32 | 3.43 | 3.59 |
| VIII | B[a] | 2-(*p*-Chlorophenyl)-7- | 27 | 126[i] | | | | | |
| III | A | 2-(*p*-Biphenylyl)-7- | 3 | 216.5[j] | $C_{20}H_{14}NCl$ | 79.07 | 79.33 | 4.61 | 4.60 |
| IX | B[b] | 2-(*p*-Biphenylyl)-7- | 32 | 216.5[j] | | | | | |
| IV | A | 2,3-Tetramethylene-7-[f] | 17 | 56[k] | $C_{12}H_{12}NCl$ | ...[h] | ...[h] | ..[h] | ..[h] |
| X | B[c] | 2,3-Tetramethylene-7-[g] | 51 | 56[k] | | | | | |
| V | A | 2-(β-Naphthyl)-7- | 14 | 111[i] | $C_{18}H_{12}NCl$ | 77.83 | 77.79 | 4.32 | 4.32 |
| XI | B[d] | 2-(β-Naphthyl)-7- | 25 | 111[i] | | | | | |
| VI | A | 2-Phenyl-7- | 8 | 112[i] | $C_{14}H_{10}NCl$ | 73.85 | 74.22 | 4.43 | 4.25 |
| XII | B[e] | 2-Phenyl-7- | 65 | 112[i] | | | | | |

[a] At 175°. [b] At 185°. [c] At 135°. [d] At 250°. [e] At 260°. [f] Dehydrogenated by chloranil[11] to 1-chlorocarbazole, m.p. 112°. *Anal.* Calcd. for $C_{12}H_8NCl$: C, 71.46; H, 3.97. Found: C, 71.31; H, 3.76. Previously reported m.p. 109°[11] and 125° (F. Muth and A. Schmelzer, German Patent 511,951 (1921); *C. A.*, **25**, 1262 (1931)). [g] Also dehydrogenated to 1-chlorocarbazole, m.p. and mixed m.p. 112°. [h] Decomposes, turns brown at room temperature. [i] From ethanol. [j] From ethanol–acetone. [k] From benzene–petroleum ether (b.p. 30–60°).

for 1-chlorocarbazole, prepared by the dehydrogenation of 8-chloro-1,2,3,4-tetrahydrocarbazole, is compared with the curve for carbazole itself. This spectroscopic evidence supporting the assignment of the 1-chlorocarbazole structure to the dehydrogenation product was sought because of lack of agreement among reported melting point values for 1-chlorocarbazole (see footnote *f*, Table II).

## Experimental[9]

**Chlorophenylhydrazones.**—The *o*-chlorophenylhydrazones were prepared from *o*-chlorophenylhydrazine[10] and the appropriate ketones by means of the method given previously for the preparation of dichlorophenylhydrazones.[8a] Table I gives the pertinent data for the preparation and properties of seven new chlorophenylhydrazones. In addition, the following 2,6-dichlorophenylhydrazones were prepared[8a] for use in this study: of acetone (I), *p*-chloroacetophenone (II), *p*-phenylacetophenone (III), cyclohexanone (IV) and acetophenone (VI).

**Conversion of Chlorophenylhydrazones to Indoles.**—The conversion of 2,6-dichlorophenylhydrazones to 5,7-dichloroindoles by zinc chloride in the absence of solvent has been reported.[8a] The same procedure was applied to the preparation of 7-chloroindoles from *o*-chlorophenylhydrazones. In Table II, this is "Procedure B."

The conversion of 2,6-dichlorophenylhydrazones to 7-chloroindoles was accomplished by fusion with stannous chloride (Table II, "Procedure A"). Stannous chloride dihydrate in an amount equal to five to eight times the weight of phenylhydrazone to be used was heated at 125° until evolution of water ceased; then the temperature was raised to the fusion temperature or slightly above (246–260°). The 2,6-dichlorophenylhydrazone was added in portions, with stirring, to the melt. After addition of all of the phenylhydrazone, small samples of the mixture were subjected to the Ehrlich test[12] until a positive reaction was shown. The cooled mixture was substantially freed of stannous chloride by heating it on a steam-bath with a liter of 2 *N* hydrochloric acid for three hours. Acid-insoluble material was separated by filtration through a soxhlet thimble, washed with water, dried and extracted with benzene in a soxhlet apparatus. The benzene solution was diluted with benzene to a volume of 1 liter, the diluted solution was dried over Drierite and largely decolorized by permitting it to trickle through one or two 2 × 5 cm. columns of activated alumina. Each column was developed with not more than 250 ml. of benzene or 3:1 benzene–petroleum ether (b.p. 30–60°) until the adsorbed dark colored tars were on the point of passing out of the column. Filtrate and washings were combined, the solvent was removed, and the residual crude indole was subjected to successive high vacuum sublimations and/or distillations until good crystalline product was obtained. The sublimate was then recrystallized from an appropriate solvent. In Table II the methods of preparation and the characterization data are given for five 7-chloroindoles, each of which was obtained both by Procedure A and by Procedure B. In no case was a melting point depression observed when a Procedure A and a Procedure B sample presumably of the same 7-chloroindole were mixed.

A milder procedure for the stannous chloride promoted conversion of 2,6-dichlorophenylhydrazones to 7-chloroindoles, adapted from the method of Nicolet and Sampey[6] was applied to the 2,6-dichlorophenylhydrazones of acetone and *p*-chloroacetophenone. Although both products gave strong

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[9] All melting points are corrected.

[10] Obtained from *o*-chloroaniline by means of the procedure previously employed for the preparation of dichlorophenylhydrazines[8a]; white needles, m.p. 45°. A. Hantzsch and M. Singer, *Ber.*, **30**, 320 (1897), report the m.p. 48°.

[11] B. M. Barclay and N. Campbell, *J. Chem. Soc.*, 580 (1945).

[12] L. H. Chernoff, *Ind. Eng. Chem., Anal. Ed.*, **12**, 273 (1940).

positive Ehrlich tests, no crystalline solid could be isolated from either one, and the method was thereafter abandoned. It consisted in boiling the dichlorophenylhydrazone in a solution containing 10% each of hydrochloric acid and stannous chloride dihydrate until a few drops of the solution gave a positive Ehrlich test. The solution was diluted with water and extracted with ether; the ether solution was washed with aqueous sodium bicarbonate until it was no longer acid, and the ether was replaced by 500 ml. of benzene. The procedure thereafter followed that used for the benzene solution of crude product in "Procedure A."

**By-product from the Fusion of *p*-Chloroacetophenone 2,6-Dichlorophenylhydrazone with Stannous Chloride.**—After removal of the solvent from the decolorized benzene solution ("Procedure A" above), addition of ether to the crude product dissolved most of the oily material, but a white solid remained insoluble. This substance, isolated in 11.8% yield, gave white needles, m.p. 262°, on recrystallization from acetone.

*Anal.* Calcd. for $C_{24}H_{15}NCl_3$: C, 68.03; H, 3.56; Cl, 25.10. Found: C, 68.25; H, 3.49; Cl, 25.17.

The ether solution remaining after removal of the by-product by filtration contained the expected product, 2-(*p*-chlorophenyl)-7-chloroindole.

**Treatment of 2-(*p*-Biphenylyl)-5,7-dichloroindole with Molten Stannous Chloride.**—A 2.33-g. sample of the dichloroindole was treated with molten stannous chloride from 25 g. of stannous chloride dihydrate, and the resulting mixture was treated in accordance with "Procedure A," above. From the mixture 2.14 g. (92%) of crystalline material, m.p. 195–209.5°, was isolated. Fractional crystallization of this crude solid from ethanol and ethanol–benzene gave nothing but white plates, m.p. 215°. All such fractions were subjected to mixed melting point determinations with the original dichloroindole and with 2-(*p*-biphenylyl)-7-chloroindole, m.p. 214°. In no case was a depression observed in melting points of mixtures with the original dichloroindole; but 20–25° depressions were shown by all mixtures containing the 7-monochloroindole.

**Reaction of Acetophenone 2,6-Dichlorophenylhydrazone with Zinc Chloride in *p*-Cresol Solution.**—A mixture of 9 g. of powdered, anhydrous zinc chloride in 40 g. of *p*-cresol was treated with 10 g. of acetophenone 2,6-dichlorophenylhydrazone. When the resulting mixture was heated to 180°, a reaction occurred with sufficient vigor to drive the temperature to 198° without further heating. The mixture was maintained at 180–190° for 20 minutes, cooled and steam distilled. The distillate was treated with sodium hydroxide and shaken with ether. The *p*-cresol liberated by acidifying the aqueous layer gave no test for chlorine. After removal of the ether from the ether layer, the 0.80 g. (18.5%) of residual red oil was identified as acetophenone by the preparation of its 2,4-dinitrophenylhydrazone, m.p. 249°.

The residue from the steam distillation was treated as in "Procedure B" of Paper I.[3a] The filtrate from the alumina column yielded 2.40 g. (25.5%) of 2-phenyl-5,7-dichloroindole, m.p. 140° alone or when mixed with an authentic specimen. The alumina column was eluted with ethanol. Evaporation of the ethanol left 5.0 g. of black, glassy material. Samples of this material were subjected to fractional vacuum sublimation and to chromatographic adsorption from a benzene solution onto activated alumina. Additional small amounts of 2-phenyl-5,7-dichloroindole were obtained from each sample, but no other pure substance could be isolated. Another sample of the black glass was distributed between benzene and 18 *N* sulfuric acid in six separatory funnels. The benzene in funnel no. 1 yielded further amounts of 2-phenyl-5,7-dichloroindole, but no other pure compound could be obtained. In all, 0.70 g. of this indole could be isolated from the 5.0 g. of tar; total yield, 3.10 g. (33%).

**The Reaction of Acetophenone 2,6-Dichlorophenylhydrazone with Zinc Chloride in the Presence of 2-(*p*-Chlorophenyl)-7-chloroindole.**—A mixture of 1.2 g. of acetophenone 2,6-dichlorophenylhydrazone, 0.8 g. of 2-(*p*-chlorophenyl)-7-chloroindole, 70 g. of *p*-cresol and 14 g. of powdered anhydrous zinc chloride was boiled for a half-hour. The organic material was dissolved in 1 liter of benzene, and the *p*-cresol was removed by repeated extractions with 5% aqueous sodium hydroxide. The dried benzene solution was chromatographed, with activated alumina serving as the adsorbent. After development with 500 ml. of benzene, the 2 × 20 cm. column was eluted with acetone, and the dark tar remaining after removal of the acetone was distilled in a high vacuum. An amber glass was collected which resisted all efforts to effect crystallization. The filtrate from the column yielded 0.67 g. of a solid, m.p. 93–106°, after removal of the solvent. This mixture was again chromatographed from a solution in 250 ml. of 10:1 benzene–petroleum ether (b.p. 30–60°), with a 2 × 20 cm. column of activated alumina the adsorbent. After development with 250 ml. of 3:1 benzene–petroleum ether, the column was eluted with acetone. Evaporation of the acetone gave 0.34 g. of a solid, m.p. 82–106°, which, after several recrystallizations from "Mixed Heptanes" and from 1:1 cyclohexane–*n*-hexane gave 2-phenyl-5,7-dichloroindole, m.p. 138–139° alone or when mixed with an authentic specimen. The filtrate from the column yielded 0.19 g. of a white solid, m.p. 100–117°, after evaporation of the solvent. Recrystallization from "Mixed Heptanes" gave 2-(*p*-chlorophenyl)-7-chloroindole, m.p. 123–124° alone or when mixed with an authentic sample. The filtrate from this crop of crystals was evaporated to dryness, and the resulting solid was recrystallized from 1:1 cyclohexane–*n*-hexane. 2-Phenyl-5,7-dichloroindole, m.p. 135–136.5° (no depression when mixed with an authentic sample) was obtained. No other pure compound could be isolated from any fraction.

**Simultaneous Reaction of Acetophenone Phenylhydrazone and 2,6-Dichlorophenylhydrazones with Zinc Chloride.**—A mixture of 1.34 g. of acetophenone 2,6-dichlorophenylhydrazone, 1.035 g. of acetophenone phenylhydrazone, 19 g. of powdered anhydrous zinc chloride and 11 g. of *p*-cresol was stirred and heated slowly until it began to boil at 195°. The jet black mixture was cooled and the organic material extracted into 1 liter of benzene. The *p*-cresol was removed by repeated washings with 5–10% aqueous sodium hydroxide. The dried benzene solution was decolorized by permitting it to trickle through a 2 × 5 cm. column of activated alumina. The column was washed with 500 ml. of benzene and eluted with acetone. Evaporation of the acetone left a black oil. The filtrate and washings from the short column were concentrated to 250 ml. and passed through a 2 × 20 cm. column of activated alumina; then the column was developed with 500 ml. of benzene. Progress of zones throughout chromatography and development could be followed by virtue of the deep blue fluorescence shown by both indoles present when the column or the filtrate was exposed to the radiation from a mercury arc lamp fitted with blue ultraviolet filter. On elution with acetone of that portion of the column which fluoresced and evaporation of the solvent, 0.53 g. (56%) of crude 2-phenylindole, m.p. 150–175°, remained. Recrystallization from ethanol gave white crystals, m.p. 187.5–188°, alone or when mixed with an authentic sample.[13]

The filtrate from the second alumina column gave 0.6 g. (48%) of white solid, m.p. 116–122°. After two recrystallizations from 95% ethanol, 2-phenyl-5,7-dichloroindole, tiny white needles, m.p. 139°, was obtained. There was no melting point depression when a sample was mixed with an authentic one.

The mother liquors from all crystallizations were combined, evaporated to dryness and dissolved, together with the black oil from the first column, in benzene. Another chromatographic procedure was carried out in the manner just described, small amounts of the same two indoles were isolated, but no other indole could be detected.

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[13] Shriner, Ashley and Welch, *Org. Syntheses*, **22**, 97 (1948).