obtained from Eastman Kodak Co. and used without purification.

Ammonium Dithiocarbamate.—The procedure previously described employing butyl or amyl alcohol as solvent was used.[8]

2-Mercaptothiazoles.—The same general method was used in the preparation of all the 2-mercaptothiazoles described in Table I. To a stirred suspension of 16.5 g. (0.15 mole) of ammonium dithiocarbamate in 100 ml. of absolute ethanol, at room temperature, was added over a period of fifteen minutes, 0.10 mole of purified halomethyl ketone. During this addition period the temperature of the reaction mixture generally rose to 35–40°. When all the ketone was added, the mixture was stirred for one-half hour, then heated on a water-bath at 60–65° for two hours and finally allowed to cool to room temperature. Alcohol-soluble mercaptothiazoles were isolated by filtering the reaction mixture, washing the solid with two 10-ml. portions of absolute ethanol, evaporating the combined filtrate and washings to dryness and recrystallizing the residue. Alcohol-insoluble mercaptothiazoles were isolated by pouring the reaction mixture, with stirring, into one liter of water containing 200 g. of cracked ice. The mixture was allowed to come to room temperature, the solid separated by filtration and washed on the filter with three 50-ml. portions of water. After air-drying, the material was recrystallized from ethanol.

bis-(Thiazyl-2) Disulfides.—Oxidation of the 2-mercaptothiazoles to the corresponding disulfides was carried out using neutral 30% hydrogen peroxide according to the general directions given by Buchman[5] for the preparation of bis-(4,5-dimethylthiazyl-2) disulfide. The compounds prepared are described in Table II.

Summary

1. Four new *n*-alkyl chloromethyl ketones and two new *p*-alkylphenacyl chlorides have been prepared and described.

2. A series of nine new 2-mercaptothiazoles substituted in the 4-position with *n*-alkyl, aryl and *p*-alkaryl groups has been prepared for evaluation as synthetic rubber modifiers. The properties of these compounds are described.

3. The preparation of eight new bis-(thiazyl-2) disulfides by oxidation of mercaptothiazoles is described.

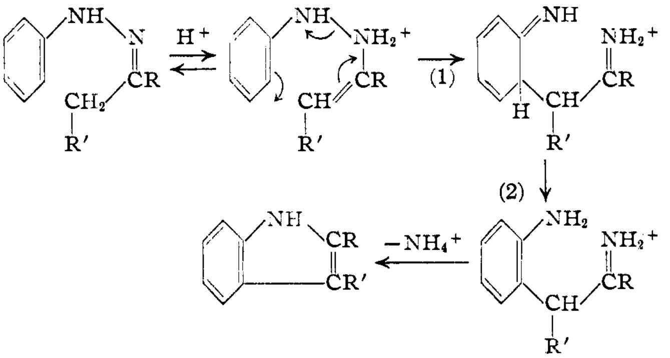
NEW YORK, N. Y. RECEIVED MARCH 4, 1948

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

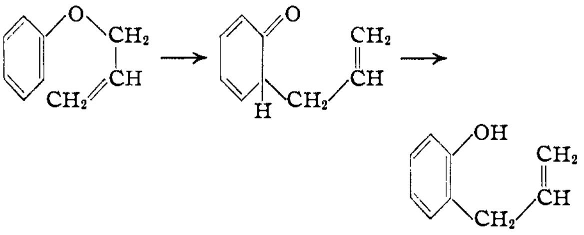
Studies on the Fischer Indole Synthesis. I

BY ROBERT B. CARLIN AND E. E. FISHER[1]

The mechanism proposed by Robinson and Robinson[2] for the Fischer indole synthesis has been supported by the more recent work of Allen and Wilson.[3] The Robinsons observed that the reaction may be considered to be a particular type of "ortho benzidine" rearrangement. If the Robinsons' mechanism for the Fischer indole synthesis is written in the following manner



it is clear that a formal analogy exists between steps 1 and 2 and the two steps which have been proposed to explain the Claisen rearrangement to the ortho-position[4]



Investigations of the Claisen rearrangement have revealed that 2,6-disubstituted phenyl allyl ethers, in which the ortho positions are blocked, often undergo para migration of the allylic group, although the mechanism of the para rearrangement is apparently different from that of the ortho rearrangement.[5] Certain 2,6-dibromo-[6] and 2,6-dichlorophenyl allyl ethers[7] have been shown to undergo both ortho rearrangement, with displacement of a halogen atom, and para rearrangement. The ortho benzidine rearrangement also has its para analog; in fact, many more examples of para benzidine rearrangement than of the ortho rearrangement appear in the literature. The Robinsons recognized that their mechanism for the Fischer indole synthesis suggested the possible occurrence of some para rearrangement concurrently with the normal reaction, but they pointed

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(1) Institute Graduate Fellow in Organic Chemistry, 1947–1948.

(2) Robinson and Robinson, *J. Chem. Soc.*, **113**, 639 (1918); 827 (1924).

(3) Allen and Wilson, THIS JOURNAL, **65**, 611 (1943).

(4) *Cf.* Tarbell, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 16.

(5) Tarbell, *Chem. Rev.*, **27**, 495 (1940).

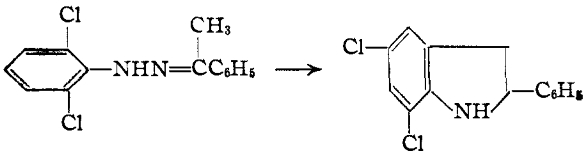
(6) Hurd and Webb, THIS JOURNAL, **58**, 2190 (1936).

(7) Tarbell and Wilson, *ibid.*, **64**, 1066 (1942).

out that such a para rearrangement would lead to *p*-aminobenzyl alkyl (or aryl) ketones or *p*-aminophenylacetaldehydes, which would "normally be isolated as uninviting tars under the conditions of most indole syntheses."

If a 2,6-disubstituted phenylhydrazone were to be subjected to the conditions of the Fischer indole synthesis, analogy with recorded experiments on the rearrangements of 2,6-disubstituted phenyl allyl ethers and of hydrazobenzenes would suggest that the reaction might take either or both of the following courses: (1) ortho rearrangement, with displacement of the corresponding atom or group; (2) para rearrangement. An investigation of the reactions of five 2,6-dichlorophenylhydrazones under the conditions of the Fischer indole synthesis was undertaken in order to discover whether such reactions do occur, and the results of the investigation are reported in this paper.

When the 2,6-dichlorophenylhydrazone of acetophenone was heated with zinc chloride, in the absence of solvents or in the presence of nitrobenzene, *o*-nitrotoluene, phenol, or *p*-cresol, the only pure compound recovered from the reaction mixtures was 2-phenyl-5,7-dichloroindole. The yields of product were generally low (7–25%), but the remaining parts of the reaction mixtures were intractable tars. Solutions of acetophenone 2,6-dichlorophenylhydrazone in purified α-methylnaphthalene or tetralin, when boiled with zinc chloride, gave mixtures from which only unchanged hydrazone was isolated, in yields as high as 50%.



That the product of the reactions was a phenyldichloroindole was shown by its composition and by the fact that it was hydrogenated in the presence of Raney nickel to 2-phenylindole. The positions of the chlorine atoms were established by synthesis of 2-phenyl-5,7-dichloroindole from the 2,4-dichlorophenylhydrazone of acetophenone. Because the conversion of acetophenone 2,6-dichlorophenylhydrazone to 2-phenyl-5,7-dichloroindole apparently involved a migration of a chlorine atom, it seemed possible that similar chlorine migrations might occur during ring closures of other dichlorophenylhydrazones. If such were the case, then the structure of the product could not be considered proved by the fact that it was formed from acetophenone 2,4-dichlorophenylhydrazone. Therefore, both the 2,5- and 3,5-dichlorophenylhydrazones of acetophenone were prepared and converted to phenyldichloroindoles. These compounds were different from each other and from the phenyldichloroindole obtained from the 2,6- and 2,4-dichlorophenylhydrazones of acetophenone. Consequently, it appears most unlikely that chlorine migration occurs in any of these reactions other than that of the 2,6-dichlorophenylhydrazone, where group migration must occur if an indole is to be formed, and the structure of the 2-phenyl-5,7-dichloroindole can be considered proved beyond reasonable doubt.

The 2,6-dichlorophenylhydrazones of *p*-chloroacetophenone, *p*-phenylacetophenone, acetone and cyclohexanone, on treatment with acidic reagents, all gave substituted 5,7-dichloroindoles. The yields of these products varied with the structures of the hydrazones and with reaction conditions, but they never exceeded 33%. In all cases, the structures of the substituted 5,7-dichloroindoles were checked by syntheses from the corresponding 2,4-dichlorophenylhydrazones.

The conversion of 2,6-dichlorophenylhydrazones to 5,7-dichloroindoles appears to have no recorded analog among examples either of the benzidine or of the Claisen rearrangements. It is possible that such analogous reactions do occur, but that they occur to so slight an extent that their products have escaped detection. It is also quite possible that the formation of 5,7-dichloroindoles from 2,6-dichlorophenylhydrazones is accompanied by the formation of para rearrangement products and of 7-chloroindoles, which would result from ortho ring closure with halogen displacement. The comparatively low yields in which the 5,7-dichloroindoles are formed suggests a search of the remaining parts of the reaction mixtures for other products. If chlorine migration occurs intermolecularly during the transformation of 2,6-dichlorophenylhydrazones to 5,7-dichloroindoles, there is a possibility that a suitable halogen acceptor introduced into the reaction mixture might capture some of the chlorine. These problems are under investigation at the present time. Efforts will be made to discover the effects of the conditions of the Fischer indole synthesis upon other 2,6-disubstituted phenylhydrazones.

Experimental[8]

Preparation of Dichlorophenylhydrazines. General Procedure.—Five hundred ml. of concentrated hydrochloric acid was stirred into a solution of 25 g. of dichloroaniline in 100 ml. of glacial acetic acid at room tempera-

TABLE I

PREPARATIONS OF DICHLOROPHENYLHYDRAZINES

Starting dichloroaniline	Yield, %	M. p., °C.	
		Obs.	Reptd.
2,6-[a]	83	100.5–101.5[e]	..
2,5-[b]	54	104.5	105[f]
2,4-[c]	78	94.5	94[g]
3,5-[d]	58	118	118[h]

[a] Seikel, "Organic Syntheses," 24, 47 (1944). [b] Beilstein and Kurbatow, *Ann.*, 196, 215 (1879). [c] Chattaway and Evans, *J. Chem. Soc.*, 69, 850 (1896). [d] Witt, *Ber.*, 8, 145 (1875). [e] White needles. *Anal.* Calcd. for $C_6H_6N_2Cl_2$: C, 40.70; H, 3.42. Found: C, 41.00; H, 3.61. [f] Zettel, *Ber.*, 26, 2472 (1893). [g] Chattaway and Pearce, *J. Chem. Soc.*, 107, 32 (1915). [h] Chattaway and Ellington, *ibid.*, 109, 588 (1916).

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(8) Melting points are corrected.

TABLE II

PREPARATIONS AND PROPERTIES OF DICHLOROPHENYLHYDRAZONES

2,6-Dichlorophenylhydrazone of	No.	Yield, %	M. p., °C.	Stability on standing	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Acetophenone	I	89	63.5	Fair	$C_{14}H_{12}N_2Cl_2$	60.24	4.33	59.99	4.42
Acetone	II	36	...[a]	Fair	$C_9H_{10}N_2Cl_2$	49.79	4.64	49.80	4.70
p-Phenylacetophenone	III	85	173	Good	$C_{20}H_{16}N_2Cl_2$	67.61	4.54	67.55	3.98
p-Chloroacetophenone	IV	95	60	Poor	$C_{14}H_{11}N_2Cl_3$	53.61	3.54	53.76	3.70
Cyclohexanone	V	80	34	Fair	$C_{12}H_{14}N_2Cl_2$	56.04	5.49	55.75	5.19
2-Pentanone	VI	75	...[b]	Good	$C_{11}H_{14}N_2Cl_2$	53.89	5.76	53.76	5.58
2,4-Dichlorophenylhydrazone of									
Acetophenone	VII	86	85[c]	Poor	$C_{14}H_{12}N_2Cl_2$	...	...	...	..
Acetone	VIII	67	42[d]	Poor	$C_9H_{10}N_2Cl_2$	...	..	...	..
p-Phenylacetophenone	IX	83	150	Good	$C_{20}H_{16}N_2Cl_2$	67.61	4.54	67.41	4.54
p-Chloroacetophenone	X	67	139	Good	$C_{14}H_{11}N_2Cl_3$	53.61	3.54	53.55	3.56
Cyclohexanone	XI	69	68	Very poor[g]	$C_{12}H_{14}N_2Cl_2$	...	..	...[g]	..[g]
2,5-Dichlorophenylhydrazone of									
Acetophenone	XII	80	...[e]	Fair	$C_{14}H_{12}N_2Cl_2$	60.24	4.33	60.12	4.45
3,5-Dichlorophenylhydrazone of									
Acetophenone	XIII	..[f]	*ca.* 62[f]	Very poor	$C_{14}H_{12}N_2Cl_2$	...	..	...[f]	..[f]

[a] Liquid, b. p. 115° (3 mm.); $n^{20}D$ 1.5832. [b] Liquid, b. p. 125° (1 mm.); $n^{20}D$ 1.5618. [c] Reported by Bigravi and Kindt, *Gazz. chim. ital.*, **55**, 83 (1925), to be yellow crystals, m. p. 85°. [d] Bülow, *Ber.*, **51**, 399 (1918), gave the m. p. 42°. [e] Distilled in high vacuum; $n^{20}D$ 1.6698. [f] Pronounced decomposition within five minutes after filtration; could not be dried to determine yield or obtain analytical sample without rapid blackening; melting point changes rapidly; sample had to be rearranged to indole immediately after filtration, or no product could be obtained. [g] Dry samples decomposed before analysis even when packed in Dry Ice.

ture, or in 100 ml. of hot 20% hydrochloric acid, and the resulting solution was cooled to 0°. The mixture was treated with a solution of 11 g. of sodium nitrite in 40 ml. of water, and the cold solution of the diazonium salt was filtered rapidly and treated dropwise with a cold solution of 100 g. of stannous chloride dihydrate in 100 ml. of concentrated hydrochloric acid. The insoluble complex salt was collected by filtration, washed with a little saturated aqueous sodium chloride, and the dichlorophenylhydrazine was liberated from the salt by treatment of the latter with aqueous sodium hydroxide. The product was extracted with ether, and the ether solution was concentrated until crystallization of the dichlorophenylhydrazine occurred. Purification could be effected by recrystallization from ether.

Preparations of Dichlorophenylhydrazones. General Procedure.—Liquid ketones were mixed with slightly less than equimolar amounts of dichlorophenylhydrazine, and the mixtures were treated with two drops of glacial acetic acid and warmed on a steam-bath for one to two hours. The same ratios of reacting substances were employed when the ketones were solid, but they were dissolved in about ten times their weight of ethanol. Solid dichlorophenylhydrazones were recrystallized from ethanol, from which they all formed white needles. Liquid products were purified by vacuum or molecular distillation. All liquid dichlorophenylhydrazones were pale yellow in color. The properties of these compounds are given in Table II. All of the dichlorophenylhydrazones discolored to some degree on standing, but the rates of decomposition varied greatly. The column heated "Stability on standing" in Table II indicates varying rates of decomposition, from "Good" (those compounds which discolor slowly and whose melting points change appreciably only after several weeks) to "Very poor" (compounds which decompose too rapidly to permit analytical samples to be prepared).

Preparations of Dichloroindoles from Dichlorophenylhydrazones. Procedure A.—An intimate mixture of dichlorophenylhydrazone with about five times its weight of powdered, anhydrous zinc chloride was stirred vigorously and heated slowly until the onset of reaction, which was often marked by sudden blackening of the molten mixture and evolution of fumes. When the beginning and extent of the reaction could not be determined visually, it was necessary to make preliminary trial runs. When the reaction was over, clean sand was stirred into the melt, the mixture was allowed to cool and then digested on the steam-bath for two to four hours with about 100 times its weight of 2% aqueous hydrochloric acid. The hydrochloric acid solution was removed by decantation and the residue was extracted with benzene. Tars were removed from the benzene solution by allowing it to flow through a short column of activated alumina (80–200 mesh). The benzene was removed by distillation and the product was obtained from the residue by crystallization from a suitable solvent, by high-vacuum sublimation, or by both techniques.

Procedure B.—In some cases, application of Procedure A resulted in excessive charring and tar formation. In these instances, the use of a solvent frequently produced better results.

A mixture of dichlorophenylhydrazone, about five times its weight of anhydrous, powdered zinc chloride, and 50–100 ml. of solvent was stirred vigorously and heated to the effective reaction temperature, established by preliminary trials. After the reaction was complete, the solvent was removed by steam distillation, and the water-insoluble residue was dissolved in benzene. The product was obtained from the benzene solution as in Procedure A. All of the dichloroindoles were white crystalline solids. The methods of preparation and properties of these compounds are given in Table III.

Hydrogenation of 2-Phenyl-5,7-dichloroindole to 2-Phenylindole.—A solution of 0.345 g. of 2-phenyl-5,7-dichloroindole and 0.1 g. of sodium hydroxide in 50 ml. of ethanol was treated with hydrogen at 500 lb./sq. in. pressure, in the presence of 1 g. of Raney nickel, the temperature being held at 75°. The solution of the product was filtered free of catalyst, and the ethanol was removed. Most of the sodium chloride was separated from the residue by washing with water, and the organic

TABLE III

CONVERSION OF DICHLOROPHENYLHYDRAZONES (TABLE II) TO DICHLOROINDOLES

Dichlorophenylhydrazone no.	Procedure	Reaction temp., °C.	Solvent	Dichloroindole	Yield, %	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
I[a]	A	200	None	2-Phenyl-5,7-[d]	7	142	$C_{14}H_9NCl_2$[h]	64.14	3.46	64.10	3.37
	B	180	Nitrobenzene	2-Phenyl-5,7-	11	142					
	B	170	Phenol	2-Phenyl-5,7-	16	142					
	B	200	*p*-Cresol	2-Phenyl-5,7-	26	142					
VII	A	210	None	2-Phenyl-5,7-	22	142					
II	A	200	None	2-Methyl-5,7-[e]	0.5	66.5	$C_9H_7NCl_2$	54.03	3.53	54.33	3.40
	B	165	Nitrobenzene	2-Methyl-5,7-	22	66.5					
VIII	A	190	None	2-Methyl-5,7-	9[g]	66.5[g]					
	B	150	Nitrobenzene	2-Methyl-5,7-	43	66.5					
III	A	260	None	2-(*p*-Biphenylyl)-5,7-[f]	33	214	$C_{20}H_{13}NCl_2$	71.01	3.87	71.59	3.86
IX	A	230	None	2-(*p*-Biphenylyl)-5,7-[f]	50	214					
IV	A	300	None	2-(*p*-Chlorophenyl)-5,7-[d]	21	166	$C_{14}N_8NCl_3$	56.69	2.72	56.41	2.69
X	A	285	None	2-(*p*-Chlorophenyl)-5,7-[d]	36	166					
V	B	60	Nitrobenzene	2,3-Tetramethylene-5,7-[f]	0.3	68	$C_{12}H_{11}NCl_2$	60.04	4.59	59.90	4.36
XI	B	*ca.* 100[b]	Aq. ethanol[c]	2,3-Tetramethylene-5,7-[f]	97	68					
	B	98	Nitrobenzene	. . .	0	. . .					
XII	A	225	None	2-Phenyl-4,7-[e]	33	106	$C_{14}H_9NCl_2$	64.14	3.46	64.16	3.19
XIII	A	277	None	2-Phenyl-4,6-[d]	11	115	$C_{14}H_9NCl_2$	64.14	3.46	64.02	3.64

[a] No rearrangement in α-methylnaphthalene or tetralin at 200° could be detected. [b] On steam-bath. [c] Hydrochloric acid was used in place of zinc chloride as the reaction promoter. [d] Needles from ethanol. [e] High-vacuum distilled from oily product, then recrystallized from petroleum ether (b. p. 65–110°). [f] Plates from ethanol. [g] Bülow, *Ber.*, 51, 399 (1918), reported a 5% yield of a product, m. p. 61°, from this reaction. [h] *Anal.* Calcd.: N, 5.34; Cl, 27.05. Found: N, 5.07; Cl, 26.55.

material was dissolved in ether. Removal of the ether gave a crude product from which 0.25 g. (>90%) of 2-phenylindole, m. p. 188–189°, was obtained by recrystallization from ethanol. A mixture of this compound with an authentic sample[9] of 2-phenylindole showed no melting point depression.

Summary

1. Five 2,6-dichlorophenylhydrazones have been converted to 5,7-dichloroindoles under the conditions of the Fischer indole synthesis. The same 5,7-dichloroindoles have also been prepared from the corresponding 2,4-dichlorophenylhydrazones.

2. The 2,5- and 3,5-dichlorophenylhydrazones of acetophenone have been converted to dichloroindoles which are different from each other and from that obtained from the 2,4- and 2,6-dichlorophenylhydrazones of acetophenone; therefore, only the 2,6-dichlorophenylhydrazones undergo halogen migration under conditions of the Fischer indole synthesis.

3. The conversion of 2,6-dichlorophenylhydrazones to 5,7-dichloroindoles is not analogous to any recorded benzidine or Claisen rearrangement, despite the fact that the simple Fischer indole synthesis, benzidine rearrangement and Claisen rearrangement are formally similar.

PITTSBURGH 13, PA.

RECEIVED MAY 19, 1948

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[9] Shriner, Ashley and Welch, "Organic Syntheses," **22**, 98 (1942).

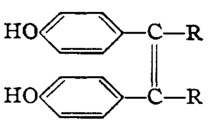
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

α-Methyl-α,β-di-(*p*-hydroxyphenyl)-valeric Acid, an Active Estrogen

BY JAMES H. HUNTER AND JEROME KORMAN

Researches of Dodds and co-workers[1] provided ground work for numerous investigations[2] of synthetic estrogens of the di-*p*-hydroxyphenylethylene (I) and the related ethane (II) types. More recently, extensive studies by Miescher *et al.*[3] have led to potent estrogenic substances of the bis-dehydrodoisynolic acid class (III).

In continuation of studies on synthetic estrogens in this Laboratory,[4] it was considered worth while to incorporate into a single molecule certain of the salient features of II and III above. Ac-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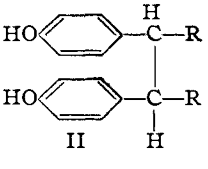
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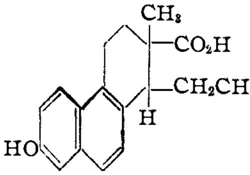
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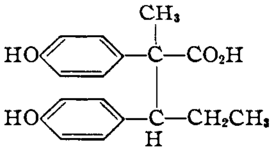
VII

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[1] Dodds, Goldberg, Lawson and Robinson, *Proc. Roy. Soc. London*, **B127**, 140 (1939).

[2] Solmssen, *Chem. Rev.*, **37**, 481 (1945).

[3] (a) Miescher, *Helv. Chim. Acta*, **27**, 1727 (1944); (b) Heer, Billeter and Miescher, *ibid.*, **28**, 1342 (1945); (c) Heer and Miescher, *ibid.*, **28**, 1506 (1945); (d) Anner and Miescher, *ibid.*, **29**, 586 (1946).

[4] Hunter and Korman, THIS JOURNAL, **69**, 2124 (1947).