A Study of the Physical and Chemical Properties of the Esters of Indophenols. III. Characterization of Isomeric Esters and Their Reduction Products

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Acetylation of a number of unsymmetrically substituted indophenoxides produced single isomeric esters. Structural determination of these isomers was made using infrared and NMR spectra. Reduction of the indophenyl esters by various methods followed by acetylation afforded routes to the preparation of mono- and diacetates of 4,4′-dihydroxydiarylamines. A discussion is presented of the difficulties in the interpretation of infrared spectra of these reduced compounds for use in the structural determination of the parent indophenyl esters.

Papers I and II in this series[1,2] dealt with the synthesis and physical and chemical properties of indophenyl esters. The authors have also reported[3] details of fine structures of these esters in relationship to their behavior as enzyme substrates. In conjunction with a study on the mechanism of the acylative formation of the isomeric indophenyl esters, involving the catalytic role of pyridine,[4] additional compounds germane to the mechanistic problems were prepared.

Of the first six compounds listed in Table I, only a single isolable isomer could be obtained by acetylation of the corresponding sodium salt using either acetic anhydride alone or in conjunction with pyridine.[1] Therefore, it was not possible to use the comparative infrared studies for structural assignments as was done with the isomeric 2,6-dichloro- and 3′,5′-dichloroindophenyl acetates.[1,5]

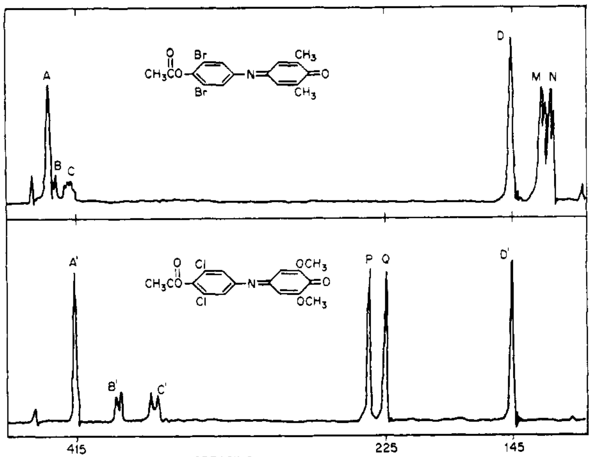

Fig. 1.—NMR spectra of indophenyl acetates at 60 Mc. Tetramethylsilane used as internal reference at 0 with respect to observed resonance peaks

TABLE I

INFRARED ABSORPTION OF INDOPHENYL ESTERS (MICRONS)

Compound	Ester Carbonyl	Quinone Carbonyl
2,6-DiMe IpA	5.67	6.09
3′,5′-DiCl-2,6-DiMe IpA	5.60	6.12
3′,5′-DiBr-2,6-DiMe IpA	5.63	6.08
3′,5′-DiCl-2,6-DiMeO IpA	5.59	6.00
3′,5′-DiCl-InA[a]	5.62	6.01
3′,5′-DiCl-IqA[b]	5.64	5.97
IpA[c]	5.70	6.08
2,6-DiCl IpA[c]	5.69	5.95
3′,5′-DiCl IpA[c]	5.63	6.05

[a] *N*-(4′-Acetoxy-3′,5′-dichlorophenyl)-*p*-naphthoquinonimine. [b] 5-[*N*-(4′-Acetoxy-3′,5′-dichlorophenyl)]-*p*-quinolonimine. [c] These compounds were previously reported.[1-5]

In order to resolve the structures of the dibromodimethyl-(DiBr DiMe IpA) and dichlorodimethoxy-(DiCl DiMeO IpA)-indophenyl acetates, NMR spectra were obtained which are shown in Fig. 1 and summarized in Table II.

The NMR spectra indicate that in both compounds there are two equivalent benzenoid protons which are located down field from the quinoid protons.

In the DiCl DiMeO IpA, due to nonlinearity of the C═N—C bond with respect to the plane of the quinoid ring,[3] it would be expected that: (1) The quinoid protons are magnetically non-equivalent, and (2) the methoxyl protons, if attached to the quinoid ring, should also exhibit non-equivalence. These nonequivalences arise from the magnetic field generated by circulation of the π electrons in the benzene ring which perturb the protons on the proximal side of the quinoid ring.[6] On the other hand, the methoxyl groups would be equivalent if they were situated in the benzenoid ring.

Absorptions characterizing two non-equivalent quinoid protons and two non-equivalent, magnetically shifted protons of the methoxyl groups were obtained. In addition, the two non-equivalent quinoid protons are further split by spin-coupling. Thus, the NMR spectrum supports assignment of structure I.

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(1) D. N. Kramer, R. M. Gamson, and F. M. Miller, *J. Org. Chem.*, **24**, 1742 (1959).

(2) R. M. Gamson, D. N. Kramer, and F. M. Miller, *J. Org. Chem.*, **24**, 1747 (1959).

(3) D. N. Kramer and R. M. Gamson, *J. Biol. Chem.*, **235**, 1785 (1960).

(4) D. N. Kramer, P. Goldberg, F. M. Miller, R. M. Gamson, E. J. Poziomek, and M. N. Levy, in preparation.

(5) C. deBorst, F. N. Hooge, and G. J. Arkenbout, *Nature*, **182**, 1017 (1958).

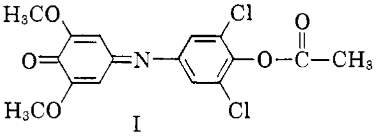
(6) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, 1959, p. 180.

Table II

Summary of NMR Spectra

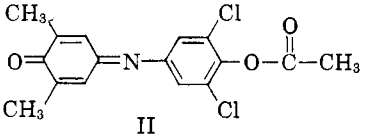
Compound	NMR		Interpretation
Dibromodimethyl	2 protons	A[a]	Equivalent benzenoid protons
(DiBr DiMe IpA)	2 protons	B,C	Multiplet for nonequivalent quinoid protons
	3 protons	D	Acetate methyl protons
	6 protons	M,N	2 doublets, methyl protons, each spin coupled with quinoid protons
Dichlorodimethoxy	2 protons	A′	Equivalent benzenoid protons
(DiCl DiMeO IpA)	2 protons	B′,C′	2 doublets for nonequivalent quinoid protons, spin coupled across quinoid ring
	3 protons	D	Acetate methyl protons
	6 protons	P,Q	2 nonequivalent methoxy groups, magnetically shifted

[a] Letters refer to peaks in Fig. 1.



I

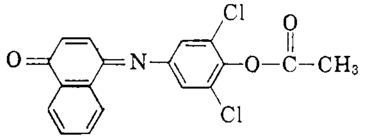
In the DiBr DiMe IpA, similar magnetic shifts are observed with respect to the quinoid protons and the methyl protons as would be expected for reasons stated above. In addition, it is observed that a multiplet is obtained for the two nonequivalent quinoid protons due to spin-coupling with adjacent methyl protons and transannular spin-coupling. Also, there is splitting of the methyl protons due to spin-coupling with the adjacent quinoid protons,[7] thus establishing the position of the methyl groups on the quinoid ring and lending support to the assignment of structure II.



II

The structures of the 2,6- and 3′,5′-dichloroindophenyl acetates have previously been assigned on the basis of infrared[2] and NMR spectra.[3] In the infrared, the quinone carbonyl absorption of the 2,6-isomer was found to be shifted hypsochromically with respect to both the unsubstituted and the 3′,5′-dichloroindophenyl acetates. As noted in Table 1, DiMe IpA, DiBr DiMe IpA, and DiCl DiMe IpA all display a quinoid carbonyl absorption bathochromically shifted with respect to IpA. On the basis of this shift of the quinoid carbonyl absorption, it is concluded that the methyl groups are situated in the quinoid ring. This is to be expected since the methyl groups are known to stabilize the quinoid ring[8] by inductively increasing its electron density, which would therefore, facilitate the stretching of the quinone carbonyl bond. With respect to the DiCl DiMeO IpA, structural assignment on the basis of infrared data is not definitive. However, on the basis of a hypsochromic shift of the ester carbonyl absorption as observed in the 3′,5′-DiCl IpA, the halogens may be assigned to the benzenoid ring. This is in agreement with the NMR data above.

In the case of the indonaphthyl acetate, the assignment of structure III is made on the following basis: The ester and quinoid carbonyl absorptions at 5.63 and 6.05 μ in the 3′,5′-DiCl IpA correspond to those found in the DiCl InA (5.62 and 6.01 μ, respectively). Moreover, the carbonyl absorption of 1,4-naphthoquinone appears at 6.01 μ while the corresponding carbonyl absorption of *N*-2,6-trichloroquinonimine is at 5.97 μ.[9]



III

Reduction of an indophenyl acetate produces a monoacetate of a dihydroxydiphenylamine which, in turn, can be converted to a diacetate. It was expected that the known effects of ortho substituents on the carbonyl absorption of the monoacetate in comparison to the two carbonyl bands of the diacetate would indicate the position of introduction of the second ester grouping and hence would permit deduction of the structure of the monoacetate and its parent indophenyl acetate. Furthermore, the character of the absorption due to the hydroxyl group in the monoacetate would be influenced by substituents ortho to it and therefore, would also serve to characterize those *ortho* substituents.

Thus, the 2,6-DiCl IpA yields compound 1 in Table II which exhibits an ester carbonyl absorption at 5.72 μ. On the other hand, the ester carbonyl absorption of compound 2, derived from 3′,5′-DiCl IpA appears as a doublet at 5.66 μ and 5.69 μ. This hypsochromic shift of the carbonyl absorption in compound 2 is ascribed to the effect of the *ortho* dihalo substituents.[10]

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(7) We are indebted to Dr. L. F. Johnson, Varian Associates, for this interpretation. Dr. Johnson states "It has been our experience that spin-coupling between a proton and an adjacent methyl group on a quinoid-like ring is often observable while spin-coupling in the same situation on a benzene ring is almost never large enough to be observed."

(8) L. F. Fieser and M. Fieser, "Organic Chemistry," D. C. Heath & Co., Boston, 1944, p. 729.

(9) Unpublished data, these laboratories.

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," J. Wiley & Sons, New York, 1954, pp. 153, 156.

TABLE III

ANALYTICAL DATA, REDUCED INDOPHENYL ESTERS

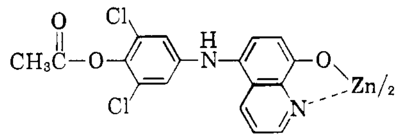
No.	Name	Derived from	Molecular Formula	Calculated % C	Calculated % H	Calculated % O	Calculated % Halogen	Observed % C	Observed % H	Observed % O	Observed % Halogen
1	4′-Acetoxy-3,5-dichloro-4-hydroxydiphenylamine	2,6-DiCl IpA	$C_{14}H_{11}Cl_2BO_3$	53.9	3.5	15.4		53.9	3.7	15.1	
2	4-Acetoxy-3,5-dichloro-4′-hydroxydiphenylamine	3′,5′-DiCl IpA	$C_{14}H_{11}Cl_2NO_3$	53.9	3.5	15.4		54.0	3.5	15.1	
3	4′-Acetoxy-3,5-dimethyl-4-hydroxydiphenylamine	2,6-DiMe IpA	$C_{16}H_{17}NO_3$	70.8	6.3	17.7		70.5	6.5	17.7	
4	4′-Acetoxy-3′,5′-dichloro-3,5-dimethyl-4-hydroxydiphenylamine	3′,5′-DiCl-2,6-DiMe IpA	$C_{16}H_{15}Cl_2NO_3$	56.5	4.4	14.1		56.9	4.7	14.6	
5	4′-Acetoxy-3′,5′-dibromo-3,5-dimethyl-4-hydroxydiphenylamine	3′,5′-DiBr-2,6-DiMe IpA	$C_{16}H_{15}Br_2NO_3$	44.8	3.5		37.2	45.0	3.4		36.7
6	4′-Acetoxy-3′,5′-dichloro-3,5-dimethoxy-4-hydroxydiphenylamine	3′,5′-DiCl-2,6-DiOMe IpA	$C_{16}H_{15}Cl_2NO_5$	51.6	4.1	21.5		51.8	4.9		
7	1-(4-Acetoxy-3,5-dichloroanilino)-4-naphthol	3,5-DiCl InA	$C_{18}H_{13}Cl_2NO_3$	59.7	3.6		19.6	60.5	3.8		19.3
8	5-(4-Acetoxy-3,5-dichloroanilino)-8-quinolinol	3,5-DiCl IqA	$C_{17}H_{12}Cl_2N_2O_3$	56.2	3.3		19.5	55.9	3.5		20.0
9	4,4′-Diacetoxy-3,5-dichlorodiphenylamine	2,6 or 3′,5′-DiCl IpA	$C_{16}H_{13}Cl_2NO_4$	54.2	3.7	18.1	20.0	54.6	4.0	18.1	20.0
10	4,4′-Diacetoxy-3,5-dimethyldiphenylamine	2,6-DiMe IpA	$C_{18}H_{19}NO_4$	69.0	6.1	20.4		69.3	6.4	20.6	
11	4,4′-Diacetoxy-3′,5′-dichloro-3,5-dimethyldiphenylamine	3′,5′-DiCl-2,6-DiMe IpA	$C_{18}H_{17}Cl_2NO_4$	56.6	4.5	16.7		56.3	4.3	16.9	
12	4,4′-Diacetoxy-3′,5′-dibromo-3,5-dimethyldiphenylamine	3′,5′-DiBr-2,6-DiMe IpA	$C_{18}H_{17}Br_2NO_4$	45.9	3.6		33.9	45.9	3.5		33.7
13	4,4′-Diacetoxy-3′,5′-dichloro-3,5-dimethoxydiphenylamine	2,6-DiCl-3′,5′-DiOMe IpA	$C_{18}H_{17}Cl_2NO_6$	52.4	3.7	23.3		52.4	4.3	23.3	
14	1-(4-Acetoxy-3,5-dichloro)-4-acetoxynaphthylene	3,5-DiCl InA	$C_{20}H_{15}Cl_2NO_4$	59.4	3.7			58.9	3.7		
15	5-(4-Acetoxy-3,5-dichloro)-8-acetoxyquinoline	3,5-DiCl IqA	$C_{19}H_{14}Cl_2N_2O_4$	56.3	3.5		17.5	56.0	3.7		17.1
16	4′-Acetoxy-4-hydroxydiphenylamine	IpA	$C_{14}H_{13}NO_3$	69.1	5.4			68.6	5.4		
17	4,4′-Diacetoxydiphenylamine	IpA	$C_{16}H_{15}NO_4$	67.4	5.3			67.4	5.5		

In addition, compound 9, a dihydro diacetate, is obtained by reductive acylation of either the 2,6- or 3′,5′-dihaloindophenyl acetate. The infrared spectrum of compound 9 reveals two ester carbonyl absorptions at 5.67 μ (effect of *ortho* halo substituents) and at 5.79 μ (unsubstituted phenolic ring). Thus, the reduced forms of the indophenyl esters yield compounds having infrared spectra in consonance with known *ortho* substituent effects on the characteristic absorptions of ester carbonyl functions.

The hydroxyl absorption of compound 1 is a broad peak in 2.85–3.00-μ region as compared to a sharp peak at 2.85 μ for compound 2. The broadened hydroxyl absorption in the first case is ascribed to hydrogen bonding with the *ortho* substituted halogens.[11]

Attempts to apply the same correlation in the case of the other dihydroindophenyl acetates were unsuccessful because of wave length shifts which were too small to permit definitive structural assignments.

In the case of the dichloroindoquinolinyl ester, reduction with zinc, acetic acid, and hydrochloric acid led to a pale red solution, indicative of a chelate, presumably IV. However, this product was



IV

not isolable, and the structural assignment is therefore tentative.

Experimental

Preparation of Indophenyl Esters.—The previously reported procedures were employed in attempts to prepare isomeric indophenyl esters of the compounds reported in Table I.

The sodium dichloro dimethoxy indophenoxide was acetylated by both procedures, with and without pyridine. The same product was obtained in either case as orange needles recrystallized from ether and melted at 178–179°.

Anal. Calcd. for $C_{16}H_{13}Cl_2NO_5$: C, 51.9; H, 3.5; Cl, 19.2. Found: C, 5.22; H, 3.9; Cl, 19.1.

Preparation of 4-Hydroxy-4-acetoxydiarylamine Derivatives.—The parent indophenyl acetate (0.1 *M*) was dissolved in 25 ml. of glacial acetic acid to which was added 0.5 g.-atom of powdered zinc metal and 5 ml. of concd. hydrochloric acid. The mixture was magnetically stirred and warmed slightly on a steam bath. Decolorization of the mixture was taken as indiction of the completion of the reaction. The unchanged metal was removed by filtration and the resulting colorless to straw-colored solution was poured into an ice water slush and stirred vigorously. The resulting white precipitate was collected, washed with water, air-dried, and recrystallized from ethanol or ethanol–water to a constant melting point. The properties and analyses of these compounds are given in Tables III and IV.

The dichloroquinolinyl acetate was reduced with hydrogen at atmospheric pressure using palladium-on-charcoal as a

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[11] A. W. Baker, *J. Am. Chem. Soc.*, **80**, 3598 (1958).

Table IV

Physical Constants of Reduced Indophenyl Esters

Compound No.	Appearance	M.P.[a]	Infrared,[b] μ
1	Pale grey microcrystals	119–121	2.84, 2.99, 5.77, 8.16, 8.37
2	Pale pink microcrystals	137–141	2.85, 2.99 (shoulder), 5.67, 5.76, 8.12, 8.38
3	Brown needles	128–129	2.85, 2.97, 5.72, 8.10, 8.23 (shoulder), 8.38
4	Pale tan microcrystals	155–157	2.87, 2.95, 3.00, 5.68, 5.83, 8.17, 8.40
5	Pale tan needles	181	2.86 (shoulder), 2.96, 5.72 (shoulder), 5.79, 8.12, 8.30
6	Tan needles	83–84	2.71, 2.78 (shoulder), 2.89, 5.70, 8.10, 8.32 (broad)
7	Pale tan needles	224–225	2.94, 2.99 (shoulder), 5.78, 8.12, 8.31
8	Tan plates	203–204	2.83, 5.61, 8.17 (shoulder), 8.43
9	White needles	164–165	3.00, 5.67, 5.79, 8.17, 8.35–8.50
10	White plates	174–175	2.94, 5.66, 5.71 (shoulder), 8.11, 8.36
11	Yellow-white needles	178–179	2.97, 5.60 (shoulder), 5.68 (shoulder), 5.71, 8.16, 8.43
12	Tan needles	192–193	2.94, 5.70 (shoulder), 5.73, 8.17, 8.47
13	White needles	168	2.96, 5.57 (shoulder), 5.64 (shoulder), 5.71, 8.3 (broad)
14	Tan needles	164–165	2.95, 5.71, 5.84 (shoulder), 8.35
15	Pale yellow microcrystals	192–196	2.95, 5.65 (shoulder), 5.72, 8.20 (broad), 8.45
16	Light grey plates	119–120	2.94, 5.76, 8.18, 8.39
17	White plates	166–168	2.93, 5.72, 8.20, 8.40

[a] All melting points are uncorrected. Determined using Fisher-Johns melting point apparatus. [b] Potassium bromide pellet. Absorption peaks due to amine, hydroxy, carbonyl, and ester functions are the only ones reported.

catalyst. The ester (0.005 *M*) was dissolved in glacial acetic acid and stirred under a hydrogen atmosphere until no further hydrogen was taken up. The catalyst was filtered and the solvent removed under vacuum. It was recrystallized from ethanol–water.

Preparation of 4,4'-diacetoxydiarylamines.—The 4-hydroxy-4 -acetoxydiarylamine was dissolved in 5 mole excess of acetic anhydride containing one equivalent of pyridine. The solution was stirred for 15 min. and the product isolated as above. These compounds are also listed in Tables III and IV.

Spectra.—Infrared absorption spectra were obtained with a Perkin-Elmer Infracord using a sodium chloride prism and potassium bromide pellets. The NMR spectra at 60 Mc. were obtained by Varian Associates using deuterochloroform as a solvent.

Acknowledgment.—The authors express their gratitude to the Analytical Branch of the Research Directorate, U. S. Army Chemical Research & Development Laboratories for the analyses reported herein. The assistance of Mr. Harold Klapper in the interpretation of NMR spectra and of Mr. Arthur R. Jones, Jr., in the obtaining of infrared spectra are gratefully acknowledged.

Pyrolysis of Esters. XX. Pyrolysis of Cyclohexenyl Acetates[1,2]

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Pyrolysis of methyl *cis*-2-acetoxy-3-cyclohexenecarboxylate at 435° produced a mixture of methyl 2,4-cyclohexadienecarboxylate, methyl 1,3-cyclohexadienecarboxylate and methyl 1,5-cyclohexadienecarboxylate. It was shown that each of these three compounds gave this same mixture when passed through the pyrolysis tube under these indentical conditions. Reduction of this mixture of cyclohexadienecarboxylates gave 4-methylene-2-cyclohexenyl acetate, which, on pyrolysis at 450°, produced a mixture containing toluene, 3-methylenecyclohexene, and bibenzyl. The formation of the bibenzyl indicated the formation of free radicals as a competing reaction during the pyrolysis of the acetate.

As the pyrolysis of esters had been successfully employed to produce a series of isomers of aromatic compounds, such as 4,5-dimethylenecyclohexene,[5] isomeric with *o*-xylene, and 3,6-dimethylenecyclohexene,[6] isomeric with *p*-xylene, an attempt was made to extend this method of synthesis to other unusual isomers of aromatic compounds. In all the cases studied previously the shift of two hydrogen atoms is required for the aromatization of the compounds. In addition to this hydrocarbon series, many cases are described in the literature of iso-

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(1) Previous paper in this series, *J. Org. Chem.*, **26**, 3193 (1962).

(2) This work was supported in part by a grant from the National Science Foundation.

(3) Office of Naval Research Fellow, 1954–1955; Celanese Corp. Fellow, 1955–1956.

(4) Office of Naval Research Fellow, 1955–1957; Goodyear Tire and Rubber Co. Fellow, 1957–1958.

(5) W. J. Bailey and J. Rosenberg *J. Am. Chem. Soc.*, **77**, 73 (1955).

(6) W. J. Bailey and R. Barclay, Jr., *J. Am. Chem. Soc.* **81**, 5393 (1959).