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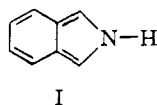
1-Arylisoindoles<sup>1,2</sup>BY DANIEL F. VEBER<sup>3,4</sup> AND WALTER LWOWSKI

RECEIVED MAY 7, 1964

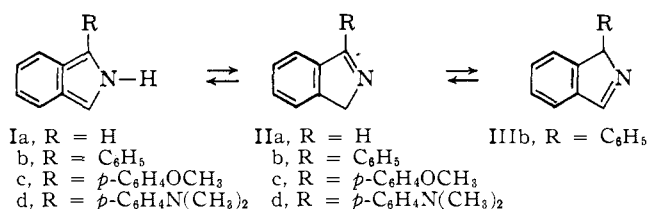
Nitrogen-unsubstituted isoindoles have been synthesized and shown to be in equilibrium with their tautomers, isoindolenines. The chemistry of this heterocyclic system is found to be quite similar to the chemistry of pyrroles.

## Introduction

Since 1893 there have been many reports of unsuccessful syntheses of isoindole (I) and its derivatives.<sup>5-7</sup>



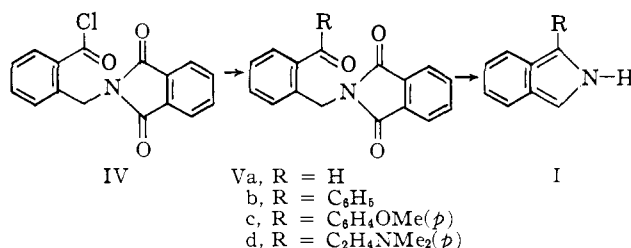
It was not until 1951 that an isoindole was prepared.<sup>8</sup> Both Wittig<sup>9</sup> and Theilacker<sup>10</sup> later reported more versatile synthetic approaches to nitrogen-substituted isoindoles. Since that time a number of synthetic approaches to nitrogen-substituted isoindoles have been devised. However, no nitrogen-unsubstituted isoindoles have been reported. It has been postulated that even if such compounds could be prepared, they would exist in the tautomeric isoindolenine form (II or III). On the other hand, molecular orbital calculations indicate that isoindole should have considerable resonance energy<sup>11,12</sup> and should be more stable than isoindolenine. The zero-order molecular orbital calculations give resonance energies of 50.0 kcal./mole for isoindole (Ia), 42.1 kcal./mole for isoindolenine (IIa), and 79.0 kcal./mole for 1-phenylisoindolenine (IIb).<sup>13</sup> Since benzene has a resonance energy of 32 kcal./mole, then 3-phenylisoindolenine (IIIb) has a predicted resonance energy of 74.1 kcal./mole.



## Results

We were able to prepare the first N-unsubstituted isoindoles from  $\alpha$ -phthalimido-*o*-toluyl chloride (IV)<sup>14</sup>.

- (1) Communicated in part: D. F. Veber and W. Lwowski, *J. Am. Chem. Soc.*, **85**, 646 (1963).  
 (2) Presented at the 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April, 1964.  
 (3) N. I. H. predoctoral fellow, 1962-1964.  
 (4) Taken in part from a dissertation presented to the Yale Graduate School in New Haven, Conn., 1964.  
 (5) S. Gabriel and A. Neumann, *Ber.*, **26**, 705 (1893).  
 (6) R. E. Rose, *J. Am. Chem. Soc.*, **33**, 390 (1911).  
 (7) G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 3295 (1928).  
 (8) G. Wittig, H. Tenhaeff, W. Schoh, and G. Koenig, *Ann.*, **572**, 10 (1951).  
 (9) G. Wittig and H. Streib, *ibid.*, **584**, 1 (1953).  
 (10) W. Theilacker and H. Kalenda, *ibid.*, **584**, 87 (1953).  
 (11) H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.*, **43**, 87 (1947).  
 (12) M. J. S. Dewar, *ibid.*, **42**, 764 (1946).  
 (13) The method and parameters used are described in "Molecular Orbital Theory for Organic Chemists," A. Streitwieser, Jr., Ed., John Wiley and Sons, Inc., New York, N. Y., 1961;  $\beta$  = 16 kcal./mole.  
 (14) J. Bornstein, S. F. Bedell, P. E. Drummond, and C. L. Kosloski, *J. Am. Chem. Soc.*, **78**, 83 (1956).



The ketones Vb and Vc were made by standard Friedel-Crafts reactions; Vd was prepared by first making the anilide (VI) from IV and treating it with phosphorus oxychloride and N,N-dimethylaniline, then water.<sup>15</sup>

The structures of the ketones V were proved by their elemental analyses, n.m.r. spectra, and infrared spectra (Table I).

TABLE I  
SPECTRA OF THE KETONES V

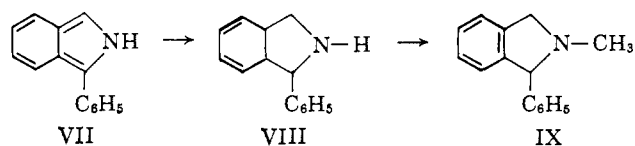
	R =		
	C <sub>6</sub> H <sub>5</sub>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<i>p</i> -Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>
Aromatic protons, $\tau$	2.0-3.0	2.0-3.0	2.0-3.5
CH <sub>2</sub> group, $\tau$	4.94	5.0	4.96
CH <sub>3</sub> group(s), $\tau$	...	6.20	6.96
Phthalimido C=O, cm. <sup>-1</sup>	1770	1770	1770
	1710	1710	1710
Benzophenone C=O, cm. <sup>-1</sup>	1657	1655	1632

Each of these ketones gives an isoindole on treatment with hydrazine hydrate in ethanol. The products could only be purified by sublimation. Attempts to recrystallize any of these isoindoles led only to less pure material. Their instability toward oxygen and heat required that they be stored in a refrigerator under an inert atmosphere. Even with such precautions they generally darkened within a week to a month.

1-Phenylisoindole (Ib) is a very light yellow solid which gives a blue Ehrlich test with *p*-dimethylamino-benzaldehyde in acid. It resinifies in the presence of air and heat and turns to a red tar on treatment with mineral acids. The infrared spectrum in chloroform shows a fairly sharp single N-H absorption at 3460 cm.<sup>-1</sup>. There are no strong absorptions in the region 2000-1600 cm.<sup>-1</sup>. The elemental analysis and molecular weight are also consistent with the isoindole structure. The ultraviolet spectrum shows a striking similarity to that of Theilacker's 1,3-diphenyl-2-methylisoindole.<sup>16</sup> The differences in extinction coefficients and peak positions of the long wave length maxima are predictable on the basis of known differences between 2,5-diphenyl-1-methylpyrrole and 2-phenylpyrrole.<sup>17</sup> The similarity of the ultraviolet spectra of 1-arylisoindoles is demonstrated in Fig. 1. The ultraviolet spectrum has proved to be very useful in determining the presence of the isoindole system.

- (15) C. D. Hurd and C. N. Webb, *Org. Syn.*, **7**, 24 (1927).  
 (16) We are indebted to Professor Theilacker for sending a reproduction of the spectrum of this compound.  
 (17) B. Elpern and F. C. Nachod, *J. Am. Chem. Soc.*, **72**, 3379 (1950); S. M. King, C. R. Bauer, and R. E. Lutz, *ibid.*, **73**, 2253 (1951).

1-Phenylisoindole was reduced with zinc in acetic acid to give a product which analyzes as 1-phenylisoindoline (VIII). The n.m.r. and infrared spectra are also consistent with reduction to the dihydro derivative. On treatment with methyl iodide this compound gives 1-phenyl-2-methylisoindoline (IX), shown to be



identical with a sample prepared according to the method described by Wittig<sup>18</sup> by the identity of their infrared spectra and vapor phase chromatography retention times.

On the basis of these data the structure of our product is clearly established as 1-phenylisoindole. The n.m.r. spectrum, however, contains a small peak at  $\delta$  5.2  $\tau$ , which does not represent an integral number of protons for a monomeric compound. A probable explanation for its presence is that 1-phenylisoindole is in equilibrium with 1-phenylisoindolenine. The  $\delta$  5.2- $\tau$  peak would represent the  $\text{CH}_2$  of the isoindolenine form IIb. An equilibrium is suggested by the fact that the relative height of the  $\delta$  5.2- $\tau$  peak is greater in  $\text{CDCl}_3$  than in  $\text{CCl}_4$ . The difference is small, however, and the results are not conclusive. Therefore, a system where there is a larger proportion of isoindolenine was desired. 1-Ethoxyisoindolenine, reported by Petersen and Tietze,<sup>19</sup> was synthesized and its n.m.r. spectrum was found to be entirely consistent with the isoindolenine structure. It does not indicate the presence of any 1-ethoxyisoindole, nor does the substance give a positive Ehrlich test. This shows that electron-donating substituents favor the isoindolenine form. Thus, 1-*p*-methoxyphenyl- and 1-*p*-dimethylaminophenylisoindole might be expected to exist as some intermediate equilibrium mixture.

2-Phthalimidomethyl-*p*'-methoxy- (Vc) and 2-phthalimidomethyl-*p*'-dimethylaminobenzophenone (Vd) on treatment with hydrazine hydrate in ethanol gave the corresponding isoindoles Ic and d. Their structures are proved by their ultraviolet and infrared spectra ( $\text{N-H}$ ,  $3460 \text{ cm}^{-1}$  in  $\text{CHCl}_3$ ), positive Ehrlich test, and elemental analyses. However, the ultraviolet absorption intensities and n.m.r. spectra differ considerably from those of 1-phenylisoindole. These differences can be interpreted by assuming that some of the isoindolenine form is present.

The n.m.r. spectra of 1-*p*-methoxyphenyl- and 1-*p*-dimethylaminophenylisoindole are more easily interpreted than that of 1-phenylisoindole. 1-*p*-Methoxyphenylisoindole in addition to the  $\text{CH}_2$  peak at  $\delta$  5.19  $\tau$  shows two  $\text{O-CH}_3$  singlets at 6.26 and 6.29  $\tau$ . The spectrum shows a ratio of 0.7  $\text{N-H}$  to 8.7 aromatic protons to 0.6  $\text{CH}_2$  protons to 3  $\text{OCH}_3$  protons (the  $\text{OCH}_3$  peaks had to be integrated together since they are separated by only 2 c.p.s.). This spectrum obviously does not fit any single compound, despite the fact that its elemental analysis corresponds to that of pure 1-*p*-methoxyphenylisoindole. However, if one assumes an isoindole-isoindolenine equilibrium, then the spectrum

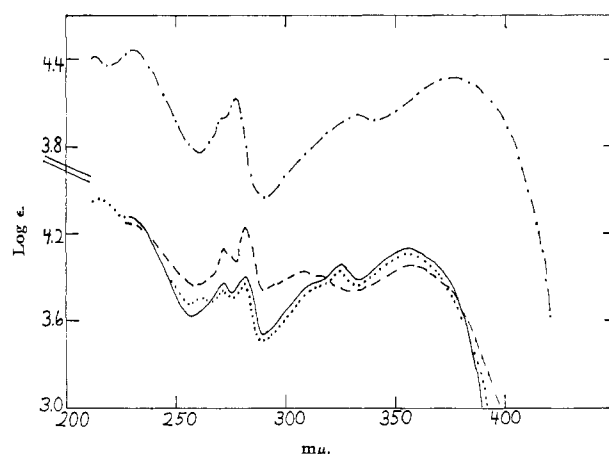


Fig. 1.—Ultraviolet absorption spectra of isoindoles: ---, 1,3-diphenyl-N-methylisoindole; —, 1-phenylisoindole; ·····, 1-phenylisoindole-3-succinic anhydride; - · - ·, 1-*p*-methoxyphenylisoindole.

can be interpreted by converting the isoindolenine spectrum to an isoindole spectrum. This can be done in the following fashion. A  $\text{CH}_2$  group is converted to one aromatic proton and one  $\text{N-H}$  on conversion of an isoindolenine to an isoindole. Thus, the areas ( $\text{N-H} + \frac{1}{2}\text{CH}_2$ ):(aromatic  $\text{CH} + \frac{1}{2}\text{CH}_2$ ):( $\text{OCH}_3$  isoindole +  $\text{OCH}_3$  isoindolenine) should represent a spectrum corrected to 100% isoindole form. This ratio is found to be 1.01:9.04:3.00, just as expected for 1-*p*-methoxyphenylisoindole (1:9:3). The ratio  $\frac{1}{2}\text{CH}_2$  to  $\text{N-H}$  gives the ratio isoindolenine to isoindole as 30.8:69.2. The ratios of the heights of the  $\text{OCH}_3$  peaks gives a ratio of 36.2:63.8. As further evidence that there is a mobile equilibrium between two tautomeric forms, n.m.r. spectra were taken in different solvents. A freshly sublimed, homogeneous sample of 1-*p*-methoxyphenylisoindole was divided into two portions. The spectrum of one portion was taken in  $\text{CDCl}_3$  and gave the results described above. The spectrum of the second sample was taken in diethyl ether- $d_{10}$ . This spectrum was almost that of pure 1-*p*-methoxyphenylisoindole showing only a very small  $\text{CH}_2$  peak at  $\delta$  5.2  $\tau$  and only one observable  $\text{OCH}_3$  peak. A separate sample in benzene was observed to consist of 84% isoindole and 16% isoindolenine based on the  $\text{OCH}_3$  peak heights.

Further evidence for the isoindole-isoindolenine equilibrium is observed in the n.m.r. spectrum of 1-*p*-dimethylaminophenylisoindole (Table II). The spectrum in  $\text{CDCl}_3$  showed the compound to be *ca.* 50-50 mixture of the two tautomers with  $\text{N-CH}_3$  peaks at 6.91 and 6.88  $\tau$ . On addition of a drop of glacial acetic acid only one peak could be observed at 6.893  $\tau$ , intermediate between the two previously observed peaks. If a salt of the dimethylamino group had been formed, a large chemical shift would have been observed. Thus, the addition of acid had made the interconversion of the tautomers fast and the n.m.r. peak position was averaged. In benzene the n.m.r. spectrum showed the mixture to be 80% isoindole, while upon addition of pyridine (1 drop in  $\frac{1}{3}$  ml. to *ca.* 20% solution by volume) the equilibrium was shifted to about 100% isoindole form. (No  $\text{CH}_2$  peak and only one  $\text{N-CH}_3$  peak was observed, the latter not at an average position.) Thus, the equilibration is not catalyzed by weak base. The shift in the equilibrium owing to the

(18) G. Wittig, G. Closs, and F. Mindermann, *Ann.*, **594**, 89 (1955).

(19) S. Petersen and E. Tietze, *ibid.*, **623**, 166 (1959).

presence of pyridine may well be caused by hydrogen bonding in the isoindole form to the free electron pair on the nitrogen in pyridine. This would stabilize only the isoindole form.

TABLE II  
% ISOINDOLE IN VARIOUS SOLVENTS BY N.M.R.

Phenylisoindole	Solvent				
	CCl <sub>4</sub>	CDCl <sub>3</sub>	Ether	THF	Benzene
1-	96	91	..	..	..
1- <i>p</i> -Methoxy-	..	69	99	..	84
1- <i>p</i> -Dimethylamino-	..	50	..	65	80

The ultraviolet spectra of the isoindoles also confirm the presence of the isoindole-isoindolenine equilibrium. The peak positions and general shape of the ultraviolet spectra of Ic and d are very similar to those of 1-phenylisoindole. However, the relative intensities of the peaks are markedly different. The peaks at short wave length have a higher intensity than those of 1-phenylisoindole, while the peaks at longer wave length have a lower intensity. This is consistent with the presence of an equilibrium which has been shifted toward the side which has a shorter wave length absorption in the ultraviolet (*i.e.*, toward the isoindolenine form). The observation that the ratio of the long wave length absorption (358 m $\mu$ ) to the short length absorption (272 m $\mu$ ) is solvent dependent gives a means of measuring the equilibrium in various solvents for 1-*p*-methoxyphenylisoindole. If it is assumed that (1) all the absorption at 358 m $\mu$  comes only from the isoindole tautomer and (2) the extinction coefficient at 272 m $\mu$  of the isoindolenine is twice that of the isoindole (as is reasonable from comparison of benzophenone imines with isoindoles), the fraction of isoindoles in the equilibrium can be determined (Table III).

TABLE III  
1-*p*-METHOXYPHENYLISOINDOLE IN VARIOUS SOLVENTS  
BY ULTRAVIOLET

Solvent	A <sub>358</sub> /A <sub>272</sub>	Isoindole, %
Ethyl ether	1.138	(100)
Ethanol	0.925	90
Acetonitrile	.874	87
Chloroform	.614	70

The value of 100% isoindole in ether is based on the n.m.r. spectrum in ether-*d*<sub>10</sub> (see above). The solvent dependency parallels that of keto-enol equilibria.<sup>20</sup> Valid results are not obtained for 1-*p*-dimethylamino-phenylisoindole for which the first assumption is not true.

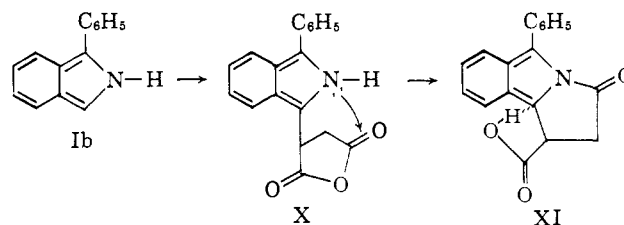
**Chemistry of Isoindoles.**—1-Phenylisoindole is reduced with zinc in acid and condenses with Ehrlich reagent (see above). It exchanges the N-H under neutral conditions in D<sub>2</sub>O. 1-Phenylisoindole reacts almost instantaneously with maleic anhydride in diethyl ether to give a light tan precipitate. This product has an ultraviolet spectrum which is essentially identical with that of 1-phenylisoindole (see Fig. 1). Thus, the isoindole nucleus is still present. The infrared spectrum in KBr shows N-H (3280 cm.<sup>-1</sup>) and carboxyanhydride (1861, 1838, and 1770 cm.<sup>-1</sup>). The n.m.r. spectrum in acetic anhydride shows N-H at  $-0.85 \tau$ , aromatic C-H in the region 1.95 to 3.2  $\tau$ ,

(20) A. S. N. Murthy, A. Balasubramian, C. N. R. Rao, and T. R. Kasturn, *Can. J. Chem.*, **40**, 2267 (1962).

tertiary CH at 4.85  $\tau$  (broad triplet), and CH<sub>2</sub> at 6.52  $\tau$  (1:1:1:1 quartet). The quartet and triplet fit an ABX system where  $\delta_{AB}$  is 4 c.p.s.,  $J_{AB} = 0$  c.p.s., and  $J_{AX} = J_{BX} = 9$  c.p.s., consistent with the presence of a succinamide function. This indicates that the structure of the adduct is that of a substitution product, 1-phenylisoindole-3-succinic anhydride (X) rather than a Diels-Alder adduct.

An elemental analysis could not be obtained since the compound when dissolved in any solvent (benzene, chloroform, acetic anhydride, methyl iodide), rearranged to a product which analyzed as a 1:1 adduct of 1-phenylisoindole and maleic anhydride. The molecular weight (in benzene; vapor pressure osmometer) shows it to be monomeric (calcd. 291, found 300). The ultraviolet spectrum is no longer similar to that of 1-phenylisoindole, but consistent with an additional chromophore. The infrared spectrum in KBr shows significant peaks at 3350 (slightly broad) (N-H or OH), 1800 (C=O), and 1715 cm.<sup>-1</sup> (C=O).

A model of the initially obtained substitution product X shows that one anhydride carbonyl can come very close to the nitrogen atom of the isoindole nucleus. Thus a reaction such as X  $\rightarrow$  XI could take place easily.



1-Carboxy-1,2-dihydro-3-oxo-5-phenyl-3H-pyrrolo[2,3a]isoindole (XI) fits the spectral data of the rearranged product. The carbonyl frequency of 1800 cm.<sup>-1</sup> can be explained as resulting from the carbonyl group being part of a  $\gamma$ -lactam ring containing a nitrogen atom of low electron density. N-Acyl, aromatic heterocycles usually show a high carbonyl absorption frequency. The low electron density on the nitrogen owing to their participation in the aromatic system makes these electrons less available for the normal amide resonance, thereby raising the bond order of the carbon to oxygen bond and correspondingly raising the carbonyl absorption frequency. Assuming that the carbonyl absorption frequency is proportional to the electron density on nitrogen, one can predict the absorption frequency in an N-acylisoindole. Using the data in Table IV, an approximate value of 1750 cm.<sup>-1</sup> for such a carbonyl is obtained.

TABLE IV

Compound	Electron density on nitrogen	Carbonyl frequency of amide, cm. <sup>-1</sup>
Pyrrole	1.692 <sup>21</sup>	1732 <sup>21</sup>
Indole	1.742 <sup>11</sup>	1711 <sup>22</sup>
Isoindole	1.651 <sup>11</sup>	1750 <sup>23</sup>

Since XI is a  $\gamma$ -lactam its carbonyl should be about 30 cm.<sup>-1</sup> higher than an open chain amide<sup>24</sup> raising the carbonyl absorption to about 1780 cm.<sup>-1</sup>. The dif-

(21) W. Otting, *Ber.*, **89**, 1940 (1956).

(22) H. A. Staab, W. Otting, and S. Ueberle, *Z. Elektrochem.*, **61**, 1000 (1957).

(23) Predicted.

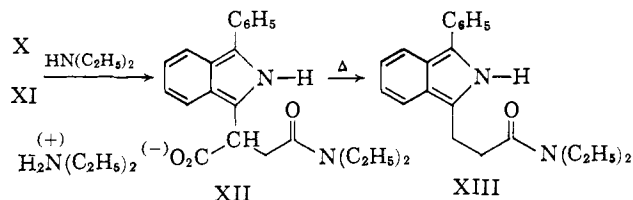
(24) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1960, p. 214.

ference between this and the  $1800\text{ cm.}^{-1}$  found for XI might be caused by hydrogen bonding to the 3-position. Molecular models show this to be quite favorable sterically. Such hydrogen bonding should withdraw electrons from the nitrogen to an even greater extent than expected and further raise the carbonyl frequency. Thus,  $1800\text{ cm.}^{-1}$  is not an unexpected absorption for this compound.

Intramolecular hydrogen bonding also will reduce the intermolecular hydrogen bonding. Thus, the apparent molecular weight is that of a monomer rather than a dimer as is usual for a carboxylic acid.

A reaction such as  $\text{Ib} \rightarrow \text{X} \rightarrow \text{XI}$  has an analogy in the recent work of Taylor and Hand<sup>25</sup> in their study of the maleic anhydride adduct of 1,3-dimethylquinoline. A further analogy to a reaction of this type was observed by Fischer and Neber<sup>26</sup> in the reaction of 4-methyl-3-carbethoxypyrrole-2-propionic acid with acetic anhydride.

The high carbonyl frequency in XI suggests that it should react readily with nucleophiles. This is indeed the case; XI reacts exothermally with diethylamine to give the amide-ammonium salt XII.



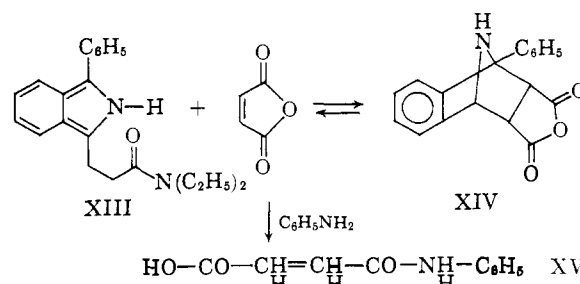
The same compound is obtained on treating X with diethylamine under conditions which preclude rearrangement (very short reaction time). The fact that a common product is obtained from X and XI shows that the rearrangement of X to XI has led only to the formation of bonds which are readily broken (*i.e.*, no new carbon-carbon bonds have been formed).

The infrared spectrum of XII shows ammonium salt N-H as a complex series of bands from  $3400$  to  $2500\text{ cm.}^{-1}$  and carboxylate and amide carbonyl from  $1633$  to  $1598\text{ cm.}^{-1}$ . The ultraviolet spectrum is that of a 1-arylisoindole. The elemental analysis gave results reasonably consistent with this structure, but outside the normal experimental error. Compound XII could not be purified completely owing to its great thermal instability. It loses  $\text{CO}_2$  and diethylamine slowly at room temperature and rapidly on heating, to give 1-phenylisoindole-3-(N,N-diethyl)propionamide (XIII). This compound could be purified and gave a correct analysis. The ultraviolet spectrum is that of a 1-arylisoindole. The infrared and n.m.r. show an N-H ( $3340\text{ cm.}^{-1}$  very broad, hydrogen bonded  $-2.2\tau$  broad) and a hydrogen-bonded amide carbonyl at  $1615\text{ cm.}^{-1}$ . The n.m.r. also shows nine aromatic protons as a complex multiplet from  $1.9$  to  $3.3\tau$ , 8 methylene protons in a broad complex pattern from  $6.3$  to  $7.6\tau$  (4 methylene protons of the two ethyl groups and 4 of the two other methylene groups), and a pair of overlapping triplets at  $8.94$  and  $9.01\tau$  representing a total of six protons. The two ethyl groups give separate n.m.r. signals owing to restricted rotation about the carbon-nitrogen amide bond.<sup>27</sup>

(25) E. C. Taylor and E. S. Hand, *J. Am. Chem. Soc.*, **85**, 770 (1963).

(26) H. Fischer and M. Neber, *Ann.*, **496**, 1 (1932).

1-Phenylisoindole-3-(N,N-diethyl)propionamide (XIII) reacts with maleic anhydride to give a product which analyzes as a 1:1 adduct. The infrared in KBr shows amide carbonyl ( $1615\text{ cm.}^{-1}$ ), N-H ( $3430$  (broad) and  $3279\text{ cm.}^{-1}$ ), and carboxanhydride carbonyl at  $1843$  and  $1770\text{ cm.}^{-1}$ . The ultraviolet spectrum in solution is nearly identical with that of the starting material XIII except that the extinction coefficients are lower. In a KBr pellet, however, the ultraviolet is no longer similar to that of a 1-arylisoindole in KBr.<sup>28</sup> These data indicate that the structure of the adduct is different in solution from that in the solid state. One way in which this is possible is that the formation of a diene adduct with the isoindole nucleus is reversible. This is shown to be the case by treating the adduct with aniline in benzene to give N-phenylmaleamic acid (XV).



Further evidence that this diene addition is reversible is given by the apparent molecular weight of this adduct in solution. This product analyzes as a 1:1 adduct of a material of molecular weight 320 and a material of molecular weight 98. Its molecular weight should therefore be 418. However, its apparent molecular weight as measured in benzene solution by a vapor pressure osmometer is 306 and 265 at initial adduct concentrations of  $0.0412$  and  $0.0187\text{ M}$ . This would be expected if the adduct XIV were dissociating when dissolved. Thus, the product isolated actually is a diene adduct (XIV) of isoindole which easily reverts to its components on being dissolved. These results are similar to those observed by Theilacker<sup>29</sup> in the case of 1,3-diphenyl-2-methylisoindole.

One further reaction of an isoindole with a dienophile has been observed. 1-Phenylisoindole reacts with 1,4-naphthoquinone to give a dark blue 1:1 adduct. The structure of this product was not determined.

It was hoped that the synthetic method described above could be extended to the preparation of the parent heterocycle, isoindole. However, all attempts to hydrazinolyze the aldehyde Va<sup>14</sup> led only to polymers.

### Discussion

The fact that 1-arylisoindoles are in equilibrium with the tautomeric isoindolenines must be due to a fortuitous balance of the factors that determine the relative energies of the tautomers. Zero-order molecular orbital calculations favor the unsubstituted isoindole by  $8\text{ kcal./mole}$  of resonance energy. The steric strain of the tautomers should be slightly less in the isoindolenines (four  $\text{sp}^2$ - and one  $\text{sp}^3$ -hybridized atoms in the five-membered ring) than in the isoindoles (five  $\text{sp}^2$  atoms in the five-membered ring). A rough estimate

(27) R. M. Moriarty, *J. Org. Chem.*, **28**, 1296 (1963).

(28) The ultraviolet spectrum 1-phenylisoindole in a KBr pellet is similar to its spectrum in solution showing maxima at  $360$ ,  $330$ , and  $320\text{ m}\mu$  (shoulder)  $\text{m}\mu$ . The adduct XIV, however, has maxima at  $270$  and  $264\text{ m}\mu$  in KBr.

(29) W. Theilacker and W. Schmidt, *Ann.*, **597**, 95 (1955).

of the  $\sigma$ -bond energies (using the method of Cox<sup>30</sup>) favors the isoindolenines by about 12 kcal./mole. The effects of strain and  $\sigma$ -bond energies must be balanced by the higher resonance energy of the isoindole system to give the observed results.

Introduction of electron-donating substituents in the 1-position shifts the equilibrium toward the isoindolenine form. The 1-position is shown to be electron-rich by the calculations of Dewar<sup>12</sup> and Longuet-Higgins<sup>11</sup> as well as by the observation that maleic anhydride attacks at this position. Therefore electron-donating substituents in this position should destabilize the isoindole form (Table V). On the other hand, the 1-position of the isoindolenine form should be electron deficient owing to the normal carbon-nitrogen double bond resonance. Thus, one would expect electron-donating substituents to stabilize this form.

TABLE V  
EFFECT OF SUBSTITUENTS ON THE ISOINDOLE-ISOINDOLENINE  
EQUILIBRIUM IN CDCl<sub>3</sub>

Phenylisoindole	Equil. constant	$\Delta F_{298}^{\circ}$ , kcal./mole
1-	10.1	1.38
1- <i>p</i> -Methoxy-	2.23	0.48
1- <i>p</i> -Dimethylamino-	1	0.0

Isoindoles can undergo reactions in the nucleus in three ways. The first, and apparently most facile, reaction is electrophilic attack on the 3(1)-position. This is demonstrated by the reaction of 1-phenylisoindole and maleic anhydride to give a substitution in the 3-position and the observation of an Ehrlich reaction. This type of reactivity has also been observed in the case of nitrogen-substituted isoindoles. The facile rearrangement of 1-phenylisoindole-3-succinic anhydride indicates that the nitrogen is a reactive position. However, the fact that reaction with maleic anhydride occurred first at the 3-position indicates that the carbon is more reactive than the nitrogen. Isoindoles can also undergo reaction in the 1- and 3-positions simultaneously as dienes. Since the Diels-Alder reaction with isoindoles has been shown to be reversible in two cases, it must be considered potentially reversible in all cases. If a dienophile can also react irreversibly in some other way with the isoindole nucleus, then the only product observed will be the one which results from the irreversible reaction. Thus, the relative reactivity of isoindoles as a diene cannot be stated on the basis of the data at hand.

### Experimental

**Instruments Used.**—Infrared spectra were taken on a Perkin-Elmer Model 421 grating spectrophotometer. Ultraviolet spectra were taken on a Cary Model 11s recording spectrophotometer. Samples for ultraviolet spectra were weighed on a Mettler Microgrammatic balance. Nuclear magnetic resonance (n.m.r.) spectra were taken on a Varian A-60 analytical n.m.r. spectrometer. Molecular weights were taken on a Mechrolab Model 301a vapor pressure osmometer. Elemental analyses were obtained from either Galbraith Laboratories Inc., Knoxville, Tenn., or Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Elemental analyses of sensitive isoindoles were obtained within 2 hr. after final purification by the Olin Mathieson Corp., New Haven, Conn. Vapor phase chromatographic (v.p.c.) separations were carried out on an Aerograph Model A-90-P gas chromatograph using the column specified in the experimental results.

**Preparation of 2-Phthalimidomethylbenzophenone (Vb).**— $\alpha$ -Phthalimido-*o*-toluyl chloride (IV, 30 g., 0.1 mole) was suspended

in 300 ml. of thiophene-free benzene; 40 g. (0.3 mole) of aluminum chloride was then added with stirring just rapidly enough to maintain a gentle reflux. The addition of 2 equivalents of AlCl<sub>3</sub> leads to a homogeneous red solution. The addition of the third equivalent of AlCl<sub>3</sub> leads to the onset of the reaction and the evolution of HCl. After stirring the solution for 2.5 hr. at room temperature, 50 ml. of water was added cautiously with stirring. The resulting warm, colorless benzene solution was decanted away from the aluminum oxide-water emulsion. The emulsion was washed twice with 100-ml. portions of warm benzene and the combined solutions dried over sodium sulfate and evaporated to leave a viscous oil. This oil was crystallized from 95% ethanol to yield 27 g. (79%) of white crystalline product. Three recrystallizations from ethanol gave a sample of analytical purity (m.p. 107–108°).

*Anal.* Calcd. for C<sub>22</sub>H<sub>15</sub>O<sub>3</sub>N: C, 77.40; H, 4.43; N, 4.10; mol. wt., 341. Found: C, 77.22; H, 4.58; N, 4.05; mol. wt., 351.

**Preparation of 2-Phthalimidomethyl-4'-methoxybenzophenone (Vc).**— $\alpha$ -Phthalimido-*o*-toluyl chloride (IV, 30 g., 0.1 mole) was suspended in a solution of 11 g. (0.1 mole) of anisole in 100 ml. of nitrobenzene, 85 g. of aluminum chloride was carefully added with stirring and cooling with ice over a period of 15 min., and the mixture stirred at room temperature for 1.5 hr., then 250 ml. of 1:1 mixture of concentrated HCl and water was slowly added with cooling and stirring and the mixture stirred for 15 min. The mixture was then extracted three times with 200-ml. portions of benzene. The combined benzene solutions were then evaporated under reduced pressure and the nitrobenzene was removed by steam distillation. The water was decanted from the semisolid product and the product was crystallized from 95% ethanol to give 24 g. (64% yield) of white crystals. Two recrystallizations from ethanol gave analytically pure material, m.p. 102.5–104°.

*Anal.* Calcd. for C<sub>23</sub>H<sub>17</sub>O<sub>4</sub>N: C, 74.38; H, 4.61; N, 3.77. Found: C, 74.12; H, 4.68; N, 3.63.

**Preparation of 2-Phthalimidomethyl-4'-dimethylaminobenzophenone (Vd).**— $\alpha$ -Phthalimido-*o*-toluyl chloride (IV, 30 g., 0.1 mole) was dissolved in 400 ml. of boiling toluene and 25 g. (0.2 mole) of aniline was added cautiously giving a voluminous white precipitate. The mixture was cooled and filtered. The resulting white solid was washed by slurring with water to remove anilinium chloride and dried under vacuum to yield 32.5 g. of  $\alpha$ -phthalimido-*o*-toluanilide (VI). This product was not purified further but was used directly in the next step. Phosphorus oxychloride (60 g.) was slowly added to a mixture of 32.5 g. of the anilide VI and 40.5 g. of N,N-dimethylaniline. When the addition was complete the temperature had risen to 70°. The reaction mixture was then heated to about 100° on a steam bath, at which point an exothermic reaction set in. The temperature continued to rise until it reached 130°, then it dropped. The steam bath was replaced when the temperature reached 110° and the flask temperature was maintained at 95° for 2 hr. The reaction was allowed to cool to 60° and poured into dilute hydrochloric acid (32 ml. of concentrated HCl diluted to 250 ml.). This mixture was allowed to cool and was filtered to remove non-basic by-products. The resulting acidic solution was diluted with 2 l. of water to precipitate the weakly basic product. The product was isolated by filtration and recrystallized from 95% ethanol to give 12.3 g. (31% yield) of green-yellow crystals. Three recrystallizations gave analytically pure yellow material, m.p. 166–167°; the yellow color disappeared on dissolving in concentrated HCl.

*Anal.* Calcd. for C<sub>24</sub>H<sub>20</sub>O<sub>3</sub>N<sub>2</sub>: C, 74.98; H, 5.24; N, 7.29. Found: C, 75.13; H, 5.37; N, 7.12.

**Preparation of 1-Phenylisoindole (Ib).**—2-Phthalimidomethylbenzophenone (Vb, 10 g., 0.229 mole) was dissolved in 200 ml. of boiling 95% ethanol in an Erlenmeyer flask; 7 cc. of 99% hydrazine hydrate was added and the solution boiled for 0.5 hr. Some stirring is required toward the end of the reaction owing to the voluminous precipitate of phthalyl hydrazide. The solution was cooled to 0° and 250 ml. of 5% KOH was added to precipitate the product and dissolve the by-product (phthalyl hydrazide). The product was filtered, dried under vacuum, and sublimed at 85° and 0.01 mm. to give 4.5 g. (80%) of very light yellow product, m.p. 90–100° dec. It gives a blue color with Ehrlich reagent. It was found that isoindoles can best be stored under refrigeration (ca. 0°).

*Anal.* Calcd. for C<sub>10</sub>H<sub>11</sub>N: C, 87.01; H, 5.74; N, 7.25; mol. wt., 193. Found: C, 87.28, 87.20; H, 5.80, 5.89; N, 7.26, 7.21; mol. wt., 206.

<sup>30</sup> J. C. Cox, *Tetrahedron*, **19**, 1175 (1963).

**Preparation of 1-*p*-Methoxyphenylisindole (Ic).**—2-Phthalimidomethyl-4'-methoxybenzophenone (Vc, 4 g., 0.11 mole) was treated with 3 ml. of hydrazine hydrate in 150 ml. refluxing 95% ethanol as described for the preparation of 1-phenylisindole. After cooling the reaction mixture, the product was precipitated as an oil by the addition of 100 ml. of 8% NaOH and 75 ml. of water. On standing overnight the product solidified and was isolated by filtration and dried under vacuum. It was sublimed at 88° and 0.004 mm. to give 1.2 g. (53%) of a light yellow solid. This product is difficult to obtain in a crystalline form, probably because it is a mixture of two tautomers. In crystalline form it has a decomposition temperature of 65–70°. It gives a blue color with Ehrlich reagent.

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>NO: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.82; H, 5.92; N, 6.00.

**Preparation of 1-*p*-Dimethylaminophenylisindole (Id).**—This compound was prepared in the same fashion as 1-*p*-methoxyphenylisindole: 4 g. (0.0105 mole) of 2-phthalimidomethyl-4'-dimethylaminobenzophenone (Vd) yielded 1.2 g. (50%). It was purified by sublimation at 100° at 0.005 mm.; m.p. 90–95° dec. It gives a green color with Ehrlich reagent.

*Anal.* Calcd. for C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>: C, 81.32; H, 6.83; N, 11.86. Found: C, 81.07; H, 6.65; N, 11.60.

**Attempts to Prepare Isoindole (Ia).**—Using the procedure described for 1-phenylisindole, we obtained only a red-brown tar on hydrazinolysis of  $\alpha$ -phthalimido-*o*-tolualdehyde (Va) in ethanol, even with great care to eliminate oxygen. Anything other than this red-brown tar was obtained under only one set of conditions: 1 g. of  $\alpha$ -phthalimido-*o*-tolualdehyde was dissolved in 25 ml. of boiling, peroxide free tetrahydrofuran; 1/3 ml. of 99% hydrazine hydrate was added and the mixture boiled for 10 min. The solution was then cooled and filtered to remove the phthalyl hydrazide. The yellow solution was evaporated to dryness under nitrogen to give a light yellow viscous polymer, which solidified on refrigeration. An attempt to obtain an n.m.r. of this material in CDCl<sub>3</sub> led to the formation of a gel in the n.m.r. tube. The material is oxygen sensitive and gives a red-brown tar on standing in air.

**Preparation of 1-Phenylisindoline (VIII).** (a).—Freshly prepared weakly coppered zinc dust<sup>31</sup> (6 g.) was slowly added to a solution of 2 g. (0.01 mole) of 1-phenylisindole in 30 ml. of glacial acetic acid over a period of 0.5 hr. After stirring for 10 min., 80 ml. of water and 2 g. of Norit were added and the solution stirred for 2 hr. The solution was filtered, neutralized with concentrated aqueous ammonia, and extracted with ether. The ether solution was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under a stream of nitrogen (the product is very sensitive to oxygen). The resulting yellow oil was sublimed at 45° and 0.01 mm. to give 0.78 g. (39% yield) of a white solid, m.p. 54.5–55.0°.

*Anal.* Calcd. for C<sub>14</sub>H<sub>13</sub>N: C, 86.11; H, 6.71; N, 7.17. Found: C, 86.20; H, 6.45; N, 6.97.

(b).—Attempts to hydrogenate 1-phenylisindole under the conditions indicated in Table VI were not successful.

TABLE VI

H <sub>2</sub> press., lb.	Catalyst	Solvent
15	Raney nickel	1-Butanol
44	Raney nickel	1-Butanol
15	Palladium-on-charcoal	Ethanol
15	Platinum-on-charcoal	Ethanol

**Preparation of 1-Phenyl-2-methylisindoline (IX).** (a).—It was found that the procedure used by Wittig<sup>18</sup> to prepare this compound could be modified slightly to give much better results. A solution of phenyllithium prepared from 3.55 g. of lithium and 26.7 g. of bromobenzene in 250 ml. of diethyl ether was slowly added to a stirred suspension of 35 g. of *N*-methylphthalimide in 100 ml. of ether. The solution was stirred for 0.5 hr. and hydrolyzed with 200 ml. of saturated ammonium chloride solution. The ether layer was decanted and the aqueous layer filtered to give 1-phenyl-1-hydroxy-*N*-methylphthalimidine. This product was crystallized from ethyl acetate to give 25 g. (49% yield) of white crystals; 5 g. of this product was continuously extracted from a thimble into a solution of 2 g. of LiAlH<sub>4</sub> in 150 ml. of ether. When extraction was complete (about 2.5 hr.) the mixture was poured into cold 5% NaOH solution and extracted with ether.

(31) Prepared by treating 30 g. of zinc dust with a solution of 1 g. of CuSO<sub>4</sub> in 100 ml. of H<sub>2</sub>O for 5 min., followed by washing with water, methanol, and ether.

The ether extracts were dried over Na<sub>2</sub>CO<sub>3</sub> and the ether evaporated under a stream of nitrogen. The oily product was sublimed at 45° and 0.01 mm. to give 2 g. (46% yield) of white crystalline 1-phenyl-2-methylisindoline, m.p. 55–57°.

(b).—One ml. of methyl iodide was added to a solution of 0.1 g. of 1-phenylisindoline in ether. After 25 min. the solution was filtered and evaporated giving a mixture of 1-phenylisindoline and 1-phenyl-2-methylisindoline. The mixture was easily separated by gas chromatography using 20% GE-SF-96 silicone on 40/60 mesh firebrick (5 ft., 0.5 in. diameter column) at 210°. The 1-phenyl-2-methylisindolines obtained by routes (a) and (b) were shown to be identical by v.p.c. retention times and by the identity of their infrared spectra.

**Preparation of 1-Phenylisindole-3-succinic Anhydride (X).**—A solution of 1.2 g. of maleic anhydride in 100 ml. of ether was added to a solution of 1.7 g. of 1-phenylisindole in 30 ml. of ether.

A precipitate formed almost immediately. After 10 min. the purple solution was filtered and the product washed with ether to give 1.7 g. (69% yield) of a tan solid, m.p. 96–110° dec. This material (X) could not be purified further without rearrangement.

**Preparation of 1-Carboxy-1,2-dihydro-3-oxo-5-phenyl-3H-pyrrolo[2,3a]-isindole (XI).**—1-Phenylisindole-3-succinic anhydride (X, 1 g.) was dissolved in 50 ml. of warm benzene. The solution was allowed to stand for about 2 hr. to cool and for the product to crystallize. The solution was filtered and the product washed with ether to give 0.4 g. (40% yield) of pink crystals. This product can be purified by crystallization from benzene. However, it turns pink to red in air and crimson red on crystallization from xylene. This color is difficult to remove completely; XI turns red on heating above 145° and melts with decomposition at 185–190°, turning purple.

*Anal.* Calcd. for C<sub>18</sub>H<sub>13</sub>O<sub>3</sub>N: C, 74.21; H, 4.50; N, 4.81; mol. wt., 291. Found: C, 74.44, 74.19; H, 4.65, 4.43; N, 4.87, 4.68; mol. wt., 300.

**Preparation of Diethylammonium-1-phenylisindole-3-(*N,N*-diethyl)succinamate (XII).** (a).—Compound XI (1 g.) was dissolved in 10 ml. of diethylamine with gentle warming on a steam bath (warming was unnecessary when run on a larger scale using less diethylamine, as the heat of reaction leads to refluxing). After about 1 min., the product was oiled out in two successive steps by additions of hexane. The first oil fraction was discarded. The solvent was decanted from the second fraction and the residual solvent removed under reduced pressure at about 0° to leave a yellow solid foam. The solid foam was redissolved in diethylamine and the product oiled out in steps as described above. This procedure was repeated two more times to give 0.42 g. (29% yield) of yellow solid, m.p. 70–75° dec. The product decomposes even at room temperature with loss of diethylamine and carbon dioxide. For this reason a good analysis could not be obtained.

*Anal.* Calcd. for C<sub>26</sub>H<sub>35</sub>N<sub>3</sub>O<sub>3</sub>: C, 71.36; H, 8.06; N, 9.60. Found: C, 69.63, 69.91; H, 7.97, 8.14; N, 8.95.

(b).—1-Phenylisindole-3-succinic anhydride (X) was dissolved in diethylamine and worked up in the same fashion as described in (a). The products from both sources were shown to be identical by their infrared spectra. (The only deviation from identity was a small, variable peak at 2340 cm.<sup>-1</sup>, attributed to variable amounts of CO<sub>2</sub> from the thermal decomposition.)

**Preparation of 1-Phenylisindole-3-(*N,N*-diethyl)propionamide (XIII).**—The ammonium carboxylate XII (0.420 g.) was heated at 102° for 24 hr. under a stream of nitrogen. The gaseous products were collected by passing them first through a dilute sulfuric acid solution followed by a barium hydroxide solution. The sulfuric acid solution was made basic and extracted with ether. The ether solution was dried over sodium sulfate and treated with anhydrous hydrogen chloride. The product was shown to be diethylammonium chloride by comparison of its infrared spectrum with that of an authentic sample. A precipitate was formed in the barium hydroxide solution which was shown to be barium carbonate by comparison of its infrared spectrum with that of an authentic sample. The brown residue (0.299 g., 100% yield) was sublimed twice at 100° and 0.001 mm. to give dark brown-yellow XIII, m.p. 40–45°. The loss of weight on heating (0.121 g.) represents a loss of 1 equivalent each of diethylamine and carbon dioxide.

*Anal.* Calcd. for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O: C, 78.71; H, 7.55; N, 8.74; mol. wt., 320. Found: C, 78.95; H, 7.70; N, 8.60; mol. wt., 378.

**Preparation of the 1-Phenylisindole-3-(N,N-diethyl)propionamide-maleic Anhydride Adduct (XIV).**—Crude XIII was prepared by treating 3 g. of XI with diethylamine, evaporating the excess diethylamine, and heating the residue to 100° under nitrogen for 24 hr. The resulting brown oil was dissolved in ether and excess maleic anhydride was added. The more maleic anhydride added the faster the crystallization of adduct, since the reaction is an equilibrium. After standing at room temperature 24 hr., 1.8 g. (44% yield) of adduct was isolated by filtration; XIV can be crystallized from benzene-hexane giving white crystals, m.p. 115–116.5°.

*Anal.* Calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>: C, 71.75; H, 6.26; N, 6.69; mol. wt., 418. Found: C, 71.70; H, 6.36; N, 6.76; mol. wt., 306, 265 (see text).

**Reaction of the Adduct XIV with Aniline.**—A sample of the adduct XIV was dissolved in benzene and a few drops of aniline added to give immediately a precipitate. The solution was filtered and the product washed with dilute HCl to give N-phenylmaleamic acid.

The same compound was isolated by dissolving maleic anhydride in benzene, treating with aniline, and working up in the same fashion. The two products were shown to be identical by their infrared spectra.

**Preparation of 1-Phenylisindole-1,4-naphthoquinone Adduct.**—1,4-Naphthoquinone (1 g.) was dissolved in 100 ml. of ether and this solution was added to a solution of 1 g. of 1-phenylisindole in 30 ml. of ether. After standing 24 hr. at room temperature the reaction mixture was filtered and the dark blue product recrystallized from xylene; yield 0.33 g., 16%, m.p. 222–222.5°.

*Anal.* Calcd. for C<sub>24</sub>H<sub>17</sub>NO<sub>2</sub>: C, 82.03; H, 4.88; N, 3.99. Found: C, 82.26; H, 4.70; N, 3.96.

**Preparation of N-Deuterio-1-phenylisindole.**—1-Phenylisindole (0.1 g.) was dissolved in 2 ml. of dioxane, 99.8% D<sub>2</sub>O was added to the cloud point, and the solution allowed to stand 15 min. An excess of D<sub>2</sub>O was then added to precipitate partially deuterated 1-phenylisindole. Infrared (CHCl<sub>3</sub>) shows N–H at 3460 and N–D at 2560 cm.<sup>-1</sup>.

**Acknowledgment.**—We are indebted to the National Institutes of Health for research grant GM 109 39 in partial support of this work. We also would like to express our thanks to Drs. Rittner and Agahigian of the Olin Mathieson Corp., at New Haven, for their generous help in obtaining elemental analyses and some of the n.m.r. spectra.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, DAVIS, CALIF.]

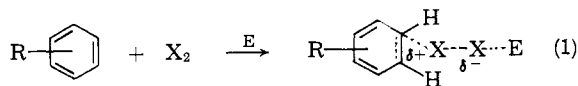
## The Electrophilic Attack of Iodine Monochloride on Hexamethyl- and Hexaethylbenzene in Carbon Tetrachloride

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RECEIVED APRIL 13, 1964

Hexamethylbenzene and iodine monochloride react in carbon tetrachloride at ordinary temperatures in the dark to form pentamethylbenzyl chloride and 2 moles of iodine per mole of starting halogen. Hexaethylbenzene and iodine monochloride undergo a similar reaction. The rates of both processes are third order dependent on iodine monochloride concentration. In their kinetic aspects the reactions closely resemble the ring iodinations of mesitylene and pentamethylbenzene by iodine monochloride in carbon tetrachloride. It is concluded that the side-chain substitution products of hexamethyl- and hexaethylbenzene are formed by way of polar intermediates.

Ring halogenation of alkylbenzenes by elemental chlorine or bromine in a nonpolar medium may take place at ordinary temperatures in the presence of a polar substance E which can function as an electrophile.<sup>1</sup> It seems likely that this electrophile promotes polarization of the halogen-halogen bond by interacting with departing halide ion (eq. 1) in the activation process.



If iodine monochloride is substituted for chlorine or bromine, the halogen itself may assume the role of E.

Mesitylene and pentamethylbenzene react with iodine monochloride in carbon tetrachloride at room temperature to form, respectively, 2-iodomesitylene and 6-iodo-1,2,3,4,5-pentamethylbenzene.<sup>2</sup> Both substitution processes are third order dependent on the ICl concentration of the medium, a fact which has been tentatively explained on the assumption that the dimeric rather than the monomeric form of the polar halogen serves as the reactant E. These ring iodinations are accompanied by minor side reactions in which molecular iodine is formed. There is a growing body of evidence that under polar conditions the halogenation of alkyl-

benzenes may lead to the formation of some side-chain as well as nuclear substitution products.<sup>1b,3,4</sup> The possibility that iodine formation in the iodine monochloride reactions is associated with polar processes leading to alkyl group substitution has now been tested by investigating the products and kinetics of reaction of the mixed halogen with hexamethylbenzene and hexaethylbenzene in carbon tetrachloride. In this regard it is interesting to note that Baciocchi and Illuminati have reported that hexasubstituted alkylbenzenes are readily attacked at the alkyl side chains by chlorine in acetic acid under conditions which provide for nuclear attack on less highly alkylated benzenes.<sup>5</sup>

### Experimental

**The Kinetic Studies.**—Eastman Organic Chemicals hexamethyl- and hexaethylbenzene were used in these experiments without further purification. Spectro Grade carbon tetrachloride, also from Eastman Organic Chemicals, was stored over calcium sulfate for several days before use. The iodine monochloride was prepared from the elemental halogens.<sup>6</sup>

The rates of reaction of the aromatic hydrocarbons and iodine monochloride in carbon tetrachloride were investigated spectrophotometrically. Rate samples were stored in 1-cm. absorption cells in the temperature-controlled ( $\pm 0.1^\circ$ ) housing of a Beckman

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