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1,3,4,7-SUBSTITUTED ISOINDOLES AND ISOINDOLENINES

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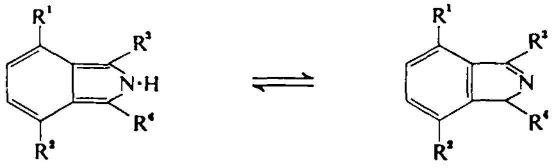
Abstract—Two 1,3,4,7-substituted isoindoles and two 1,3,4,7-substituted isoindolenines have been synthesized by condensing 2,5-disubstituted pyrroles with gamma diketones in the presence of an acid catalyst and in an atmosphere of nitrogen. 1,3,4,7-Tetramethylisoindolenine was also prepared by the reaction between ammonium sulphate and acentonylacetone.

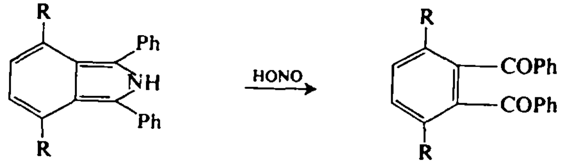
N-UNSUBSTITUTED isoindoles have only recently been synthesized[1,2] and shown to be in equilibrium with their tautomers, isoindolenines.[1] It has now been found that N-unsubstituted isoindoles or their tautomers, isoindolenines, are obtained by condensing 2,5-disubstituted pyrroles with gamma diketones in the presence of an acid actalyst and in an atmosphere of nitrogen.[2a] The method was developed from a process described for the synthesis of N-substituted isoindoles[3] and is applicable to the preparation of isoindoles (I) or isoindolenines (II) substituted in the 1-, 3-, 4- and 7-positions.



I   II

In the presence of trichloracetic acid, 2,5-diphenylpyrrole gave 1,3,4,7-tetraphenylisoindole (I, R^1, R^2, R^3, R^4 = Ph) on condensation with dibenzoylethane, and 1,3-diphenyl-4,7-dimethylisoindole (I, R^1, R^2 = CH_3; R^3, R^4 = Ph) on condensation with acetonylacetone.

The identity of the products was established by elemental analyses, IR spectra, and by the formation of 1,2-dibenzoyl-3,6-diphenylbenzene (III, R = Ph) from I (R^1 R^2 R^3 R^4 = Ph) and of 1,2-dibenzoyl-3,6-dimethylbenzene (III, R = CH_3) from I (R^1 R^2 = CH_3; R^3 R^4 = Ph) when each was treated with an excess of nitrous acid. The opening of the pyrrole ring in these two compounds when they were treated with nitrous acid, is not without parallel. Thus, on similar treatment 2,3,4,5-tetraphenylpyrrole was found to give dibenzoylstilbene.[4]



III

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[1] D. F. Veber and W. Lwowski, *J. Amer. Chem. Soc.* **86**, 4152 (1964).

[2] J. C. Emmett, D. F. Veber and W. Lwowski, *Chem. Comm.* 272 (1965).

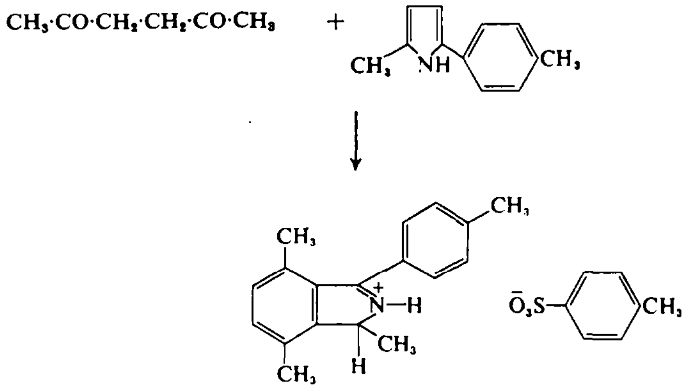
[2a] R. Fletcher, Neth. Pat. Appl. 6413422; *Chem. Abstr.* **63**, 13217 (1965).

[3] F. H. Norton, U.S. Pat. 3007939 (1961).

[4] R. Kuhn and H. Kainer, *Ann.* **578**, 227 (1952).

The elemental analyses of I ($R^1 R^2 R^3 R^4$ = Ph) and I (R^1R^2 = CH_3; $R^3 R^4$ = Ph) were in agreement with the empirical formulae $C_{32}H_{23}N$ and $C_{22}H_{19}N$ respectively. The IR spectra (in Nujol) of both compounds showed absorption at 3400 cm^{-1} which is evidence for the presence of an NH group and therefore the isoindole structures. The isoindole–isoindolenine equilibria of these compounds have not been investigated. However, the complete conjugation of the isoindole structures would be expected to make them the more stable isomers.

The product from the condensation of acetonylacetone and 2-methyl-5-(*p*-tolyl)-pyrrole, using *p*-toluenesulphonic acid as catalyst, was conveniently isolated as the *p*-toluenesulphonic acid salt.



IV

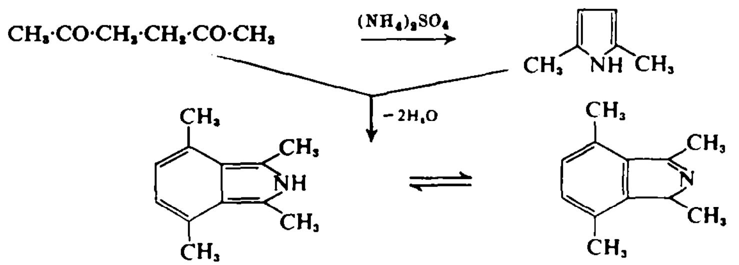
On the basis of elemental analysis and ^1H NMR spectrum, the salt was assigned the structure of 3,4,7-trimethyl-1-(*p*-tolyl)-isoindolenine *p*-toluenesulphonate (IV). The elemental analysis was in agreement with the empirical formula $C_{25}H_{27}NO_3S$. The 60 Mc/sec NMR spectrum of a dilute solution of IV in $CDCl_3$ which is summarized in Table 1, showed no absorption from the $\overset{+}{N}H$ (or $\overset{+}{N}H_2$), presumably because of N quadrupolar broadening. The presence of a $N{\cdot}CH{\cdot}CH_3$ group and also the number of phenyl hydrogens (10) is clear evidence for the isoindolenine rather than the isoindole structure. The unshared pair of electrons on the nitrogen should be more available

TABLE 1. NMR DATA FOR IV MEASURED IN DEUTEROCHLOROFORM AT 60 MC/SEC

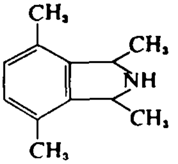
Chemical shift (τ value)	Relative intensity	Multiplet structure	Assignment
Several bands 2·3 to 3·1	10	Not analysed	Phenyl-H of three benzene rings
3·96	1	1:3:3:1 quartet with J = 2 c/sec	$\overset{+}{N}—\underline{CH}—CH_3$ (coupling to $C—CH_3$)
7·00	3	1:1 doublet with J = 2 c/sec	$\overset{+}{N}—CH—\underline{CH_3}$ (coupling to CH)
7·36	3		Four CH_3's attached to benzene rings
7·72	6	None	
8·02	3		

in the isoindolenine tautomer than in the isoindole, thus making it the stronger base, and on salt formation the isoindolenine structure should predominate.

A mixture of 2,5-dimethylpyrrole and acetonylacetone in the presence of sulphuric acid yielded 1,3,4,7-tetramethylisoindolenine (VI). It was found that this compound could also be prepared by refluxing an aqueous solution of acetonylacetone and an ammonium salt which in solution has a pH of less than 7, e.g. sulphate, nitiate, chloride. In both methods of preparation the 1,3,4,7-tetramethylisoindolenine was precipitated by the addition of alkali. It is a yellow solid unstable in air and crystallises from diisopropyl ether in the absence of oxygen as needles, m.p. 143–144°.



V VI



VII

The reaction between the ammonium salt and acetonylacetone presumably involved the initial formation of 2,5-dimethylpyrrole which condensed with unreacted acetonylacetone to yield 1,3,4,7-tetramethylisoindole (V). Tautomerization would then give the isoindolenine (VI). The reaction is apparently related to that which occurred when 2,5-dimethylpyrrole was refluxed with tin and hydrochloric acid.[5] The product in this case was 1,3,4,7-tetramethylisoindoline (VII).

The identity of VI was established by IR and NMR spectra, elemental analysis and by its oxidation and reduction to known compounds.

The IR spectrum shows a strong peak at 805 cm^{-1} which in the absence of a peak in the 700–750 cm^{-1} region is taken as evidence for the presence of two adjacent hydrogen atoms on a benzene ring. Bands in the region of 3150 cm^{-1} were assigned to the NH group of the isoindole tautomer V.

The main bands (summarized in Table 2) of the NMR spectrum measured in deuterochloroform at 60 Mc/sec are associated with structure VI. However, some of the remaining bands (summarized in Table 3) can be regarded as being associated with the isoindole tautomer V. From the relative intensities of the bands at 2·98 and 3·62 an estimate of the abundance ratio VI : V is about 8 : 1. It has been shown that electron donating substituents in the 1-position shift the equilibrium towards the isoindolenine form.[1]

Oxidation of VI with alkaline potassium permanganate gave 3,6-dimethylphthalic

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[5] R. Bonnett and J. D. White, *J. Chem. Soc.* 1648 (1963).

anhydride in low yield, whilst reduction with zinc dust and hydrochloric acid yielded 1,3,4,7-tetramethylisoindoline (VII).

Attempts to extend the ammonium salt reaction to other gamma diketones were unsuccessful.

EXPERIMENTAL

The instability in air of the following isoindoles and isoindolenines necessitated their preparation and isolation under nitrogen.

1,3,4,7-Tetraphenylisoindole (I, $R^1R^2R^3R^4$ = Ph)

A mixture of 2,5-diphenylpyrrole (4·8 g), 1,2-dibenzoylethane (5·3 g), trichloracetic acid (6·3 g) and hexane (100 ml) was refluxed for 17 hr using a Dean and Stark apparatus to remove the water formed. The hexane was removed by distillation and the residual tar triturated with EtOH. The solid which separated crystallized from EtOH to yield 1,3,4,7-*tetraphenylisoindole* (3·6 g; 39%), m.p. 262°. (Found: C, 91·0; H, 5·3; N, 3·3%. $C_{32}H_{23}N$ requires: C, 91·2; H, 5·5; N, 3·3%.) The IR spectrum (Nujol) showed a band at 3400 cm^{-1} (>NH).

Table 2. NMR data for 1,3,4,7-tetramethylisoindolenine associated with structure VI. Measured in deuterochloroform at 60 Mc/sec

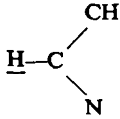
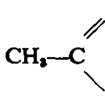
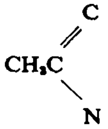
Chemical shift (τ value)	Coupling constants	Assignment
2·98		Aromatic hydrogen
5·26	$J_{geminal}$ = 7 c/sec $J_{aromatic}$ = 2 c/sec	Hydrogen coupled to *geminal* methyl and aromatic methyl
7·42	$J_{aromatic}$ = 2 c/sec	Aromatic methyl coupled to 
7·44		Aromatic methyl
7·61		CH_3—C=N
8·56	$J_{geminal}$ = 7 c/sec	Methyl coupled to *geminal* hydrogen

Table 3. NMR data for 1,3,4,7-tetramethylisoindolenine associated with structure V. Measured in deuterochloroform at 60 Mc/sec.

Chemical shift (τ value)	Assignment
3·62	olefinic hydrogen
6·74	NH
7·31 and 7·39	 and 

4,7-*Dimethyl*-1,3-*diphenylisoindole* (I, R^1R^2 = CH_3; R^3R^4 = Ph)

A mixture of acetonylacetone (4·2 g), 2,5-diphenylpyrrole (8·0 g), *p*-toluenesulphonic acid (13·0 g) and toluene (150 ml) was refluxed for 17 hr using a Dean and Stark apparatus to remove the water produced. The toluene was removed by distillation and the residue was dissolved in ether. The ethereal solution was washed with NaOH and then with water until the washings were neutral. The solution was dried and the ether removed by distillation. The residue which remained, crystallized from EtOH to yield 4,7-*dimethyl*-1,3-*diphenylisoindole* (3·5 g; 32%), m.p. 193°. (Found: C, 88·7; H, 6·7; N, 4·5%. $C_{22}H_{19}N$ requires: C, 88·8; H, 6·4; N, 4·7%.) The IR spectrum (Nujol) showed a band at 3400 cm^{-1} (>NH).

1,2-*Dibenzoyl*-3,6-*diphenylbenzene* (III, R = Ph)

$NaNO_2$aq (400 ml; 40%) was added slowly with stirring to a solution of 1,3,4,7-tetraphenylisoindole (40·0 g) in glacial acetic acid (800 ml) and conc HCl (400 ml) cooled to between 0° and 5°. After stirring the mixture for 2 hr at room temp, the solid which separated was collected by filtration, washed free from acid with water, and dried. It crystallized from acetone to afford 1,2-dibenzoyl-3,6-diphenylbenzene (18·5 g; 44·5%), m.p. 217–218° (lit.[6] 218–219°) identified by a comparison of its IR spectrum with that of an authentic specimen[7] and by mixed m.p. 217–218°.

1,2-*Dibenzoyl*-3,6-*dimethylbenzene* (III, R = CH_3)

Following the above procedure, 4,7-dimethyl-1,3-diphenylisoindole (15·0 g), glacial acetic acid (300 ml), conc HCl (150 ml) and $NaNO_2$aq (150 ml; 40%) gave 1,2-dibenzoyl-3,6-dimethylbenzene (8·5 g; 53%), m.p. 143° (lit.[8] 143–145°). Mixed m.p. showed no depression.

3,4,7-*Trimethyl*-1-(p-*tolyl*)-*isoindolenine* p-*toluenesulphonate* (IV)

A solution of acetonylacetone (4·6 g), 2-methyl-5-(*p*-tolyl) pyrrole (3·5 g) and *p*-toluenesulphonic acid (4·0 g) in toluene (50 ml) was refluxed for 15 hr. The solution was cooled and the solid which separated was collected by filtration. It was recrystallized from EtOH/toluene mixture to give 3,4,7-*trimethyl*-1-(p-*tolyl*)-*isoindolenine* p-*toluenesulphonate* (2·3 g; 45%), m.p. 166°. (Found: C, 71·2; H, 6·6; N, 3·2; S, 7·4%. $C_{25}H_{27}NO_3S$ requires: C, 71·2; H, 6·5; N, 3·3; S, 7·6%.) The NMR data are summarized in Table 1.

1,3,4,7-*Tetramethylisoindolenine* (VI)

(a) A solution of acetonylacetone (4·6 g) in 11% $(NH_4)_2SO_4$aq (80 ml) was refluxed for 18 hr. The solution was cooled and made alkaline with 20% NaOHaq. The precipitate was collected, washed with water until the washings were free from alkali and then dried. It crystallized from diisopropyl ether to give 1,3,4,7-*tetramethylisoindolenine* (2·3 g; 34%) as needles, m.p. 143–144°. (Found: C, 83·3; H, 8·8; N, 7·9%. $C_{12}H_{15}N$ requires: C, 83·2; H, 8·7; N, 8·1%.) The IR spectrum (Nujol) showed a band at 805 cm^{-1} (two adjacent aromatic hydrogens) and several bands in the region of 3150 cm^{-1} (NH associated with the isoindole tautomer IV). The NMR data are summarized in Tables 2 and 3.

Corresponding preparations using ammonium nitrate, chloride or thiocyanate gave the following yields of 1,3,4,7-tetramethylisoinolenine respectively: 12%, 12%, 24%.

(b) To a mixture of acetonylacetone (2·3 g) and 2,5-dimethylpyrrole (2·0 g) was added dropwise and with stirring, 50% H_2SO_4 (7·0 ml). After leaving the solution to stand overnight it was made alkaline with 10% NaOHaq. The precipitate was collected and washed with water until free from alkali. It crystallized from diisopropyl ether as needles (0·9 g; 25·4%). The m.p. and IR spectrum of this compound were identical to those of VI synthesized by the previous method.

1,3,4,7-*Tetramethylisoindoline* (VII)

Zn powder (13·0 g) was added to a stirred solution of VI (8·5 g) in HCl (150 ml; 20%) and after 3 hr the mixture was refluxed for a further 3 hr. The solution was kept for 24 hr and the zinc complex which separated was collected by filtration. It was decomposed by warming with NaOH (60 ml; 20%). The alkaline solution was extracted with ether and the ethereal extract was washed with water and then dried. The ether was removed and the solid residue was crystallized from pet. ether, (b.p. 40–60°) to give VII (2·5 g; 29%), m.p. 73–74° (lit[6] m.p. 72–73°). (Found: C, 82·4; H, 9·7; N, 7·8.

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[6] W. Ried and K. H. Bonnighausen, *Ann.* **639**, 61 (1961).

[7] Kindly supplied by Professor Ried (Univ. of Frankfurt-on-Main).

[8] R. Adams and T. A. Geissman, *J. Amer. Chem. Soc.* **61**, 2083 (1939).

Calc. for $C_{12}H_{17}N$: C, 82·2; H, 9·8; N, 8·0%.) The IR spectrum was identical to that of an authentic sample.[9]

3,6-*Dimethylphthalic anhydride*

KMnO$_4$aq (400 ml; 3%) was added to a vigorously stirred suspension of freshly prepared VI (7·0 g) in KOH (120 ml; 3%) whilst a stream of N_2 was passed through the mixture. When all of the KMnO$_4$ solution had reacted (absence of pink colour) the MnO$_2$ was removed by filtration, and the solution was acidified with conc HCl. The solution was kept overnight and the solid which separated was collected by filtration, washed with water and then dried. It crystallized from pet. ether (b.p. 60–80°)/CHCl$_3$ mixture to give 3,6-dimethylphthalic anhydride (0·13 g; 0·2%), m.p. 142–143°. (lit.[10] m.p. 142–143°). Mixed m.p. showed no depression.

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[9] Kindly supplied by Dr. R. Bonnett, Queen Mary College, London.

[10] Newman and Lord, *J. Amer. Chem. Soc.* **66**, 733 (1944).