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STRUCTURAL EFFECTS ON THE ISOINDOLE-ISOINDOLENINE EQUILIBRIUM. SUBSTITUTION IN THE PYRRYL RING[1]

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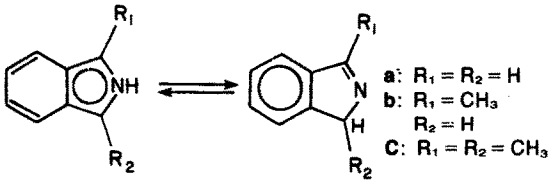
Abstract—The influence of substitution in the pyrryl ring on the isoindole-isoindolenine equilibrium has been studied by NMR spectroscopy. Electron-releasing groups selectively stabilize the isoindolenine tautomer in which the substituent is conjugated with the π-system, while electron-withdrawing groups have the opposite effect. However, sequential introduction of identical groups into the 1- and 3-positions leads, first to a shift of the equilibrium in one direction, then to a shift in opposite direction. Reasons for this behavior are discussed.

Isoindole and its N-unsubstituted derivatives (**1**) are capable of existing in tautomeric equilibrium with the corresponding isoindolenines (**2**).[2] Theoretical predictions that the parent, isoindole (**1a**), by virtue of its

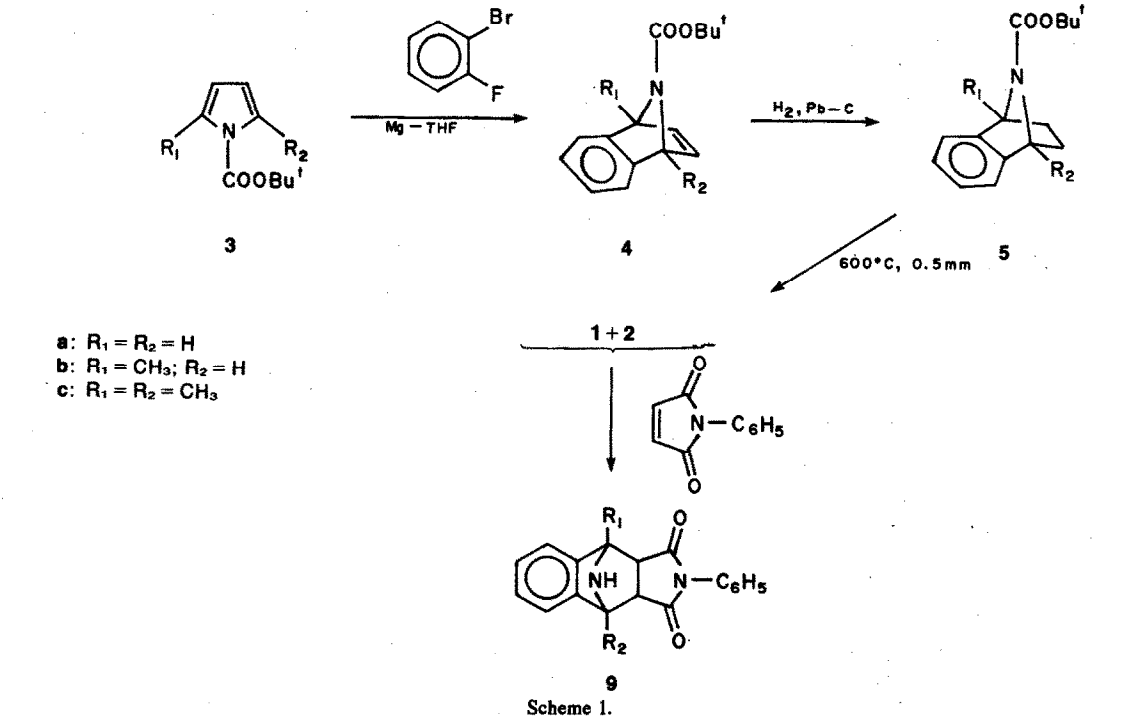


1 **2**

aromaticity, will be more stable than isoindolenine (**2a**), have been verified by our recent NMR studies.[3,4] The delicacy of the energy balance was suggested by an early report that the equilibrium position in the 1-phenylisoindole system is a sensitive function of the substitution pattern and solvent polarity.[5] However, the extent to which the marked overall stabilizing effect of the phenyl group is also responsible for the finely-balanced equilibrium is not clear. For this reason we felt that a more detailed investigation of substituent effects on the equilibrium **1**⇄**2** was necessary to disclose more accurately the manner in which shifts in the equilibrium position are effected.

RESULTS

We were able to synthesize isoindole (**1a**), 1-methylisoindole (**1b**) and 1,3-dimethylisoindole (**1e**) in one step from the tert-butyloxycarbonyl-blocked compounds **3** (Scheme 1). Flash vacuum pyrolysis of these precursors (600°, 0.5 mm)[6] leads to retrograde Diels–Alder reaction with concomitant extrusion of carbon dioxide, ethylene



3 **4** **5**

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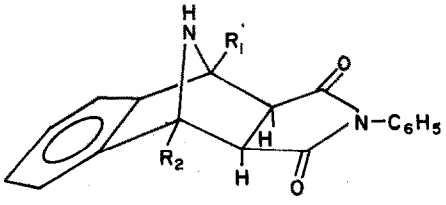
a: $R_1 = R_2 = H$
b: $R_1 = CH_3$; $R_2 = H$
c: $R_1 = R_2 = CH_3$

Scheme 1.

and isobutylene, leaving only the desired heterocycles (1 and 2). The pyrolysis products were collected at −192°; warming of the condensate to 0°C removed the volatile coproducts. UV and NMR spectra indicated the nonvolatile products to be nonequilibrium mixtures of isoindole (1) and isoindolenine (2) tautomers. Although the pyrolysates all decomposed rapidly in air, they reacted smoothly with N-phenylmaleimide, and it was possible to isolate the corresponding exo-adducts represented by the general structure 9.



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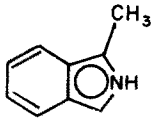
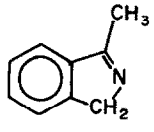
We next investigated the approach to equilibrium of 1 and 2 and the compositions of the equilibrium mixtures. The product mixtures were not at equilibrium when brought to room temperature. The process of equilibration in heptane could be followed by monitoring the time dependence of the long-wavelength UV absorptions of the isoindole tautomers. For both 1-methylisoindole (λ_{max} = 335 nm) and 1,3-dimethylisoindole (λ_{max} = 352 nm) equilibrium was established rapidly (within 10 min and 4 min, respectively) by conversion of isoindole into isoindolenine (1 → 2), whereas conversion of the parent compound (λ_{max} = 320 nm) involved 2 → 1 and was slow (1–2 hr).[3]

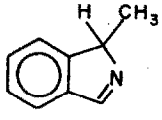
In principle, 1-methylisoindole may exist in any of four tautomeric forms: as an isoindole (1b), as either of two isoindolenines (2b and 5), or as the methylidenisoindole 6. The latter type of structure has actually been observed for 1-benzylisobenzofuran.[7,8] All possible tautomers are easily distinguishable by NMR spectroscopy.



1b



2b



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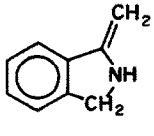

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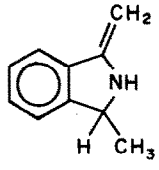
1-*Methylisoindole.* The NMR spectrum in benzene-d_6 at room temperature reveals two methyl resonances (δ2.24,s and δ2.16,t, J = 2 Hz, due to homoallylic coupling to the benzylic protons[9]). Taken together with the absence of olefinic absorptions other than the formal butadienoid protons[4] (which in any case resonate near the aromatic region), this indicates only tautomers 1b and 2b to be present. At equilibrium in benzene-d_6 the mixture's composition is 3:2 in favor of the isoindolenine form 2b.

The solvent-dependency of the equilibrium is strikingly demonstrated when the NMR spectrum is determined in chloroform at room temperature. In this solvent, the mixture consists almost entirely of the isoindolenine tautomer 2b. Only a trace (<1%) of 1b is detectable.

1,3-*Dimethylisoindole.* The appearance in the NMR spectrum of this compound (chloroform-d, room temp.) of a six-proton singlet methyl resonance (δ2.55) and two three-proton methyl doublets (δ1.49, J = 7 Hz; and δ2.49, J = 2 Hz) as well as a broad methine multiplet (δ4.7; coupled to two methyl groups) served to indicate the presence of tautomers 1c and 2c. At equilibrium the mixture consists of the isoindole (1c) and isoindolenine (2c) tautomers in the ratio 1:4, respectively. No evidence for the exocyclic tautomer, 7, was found.



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Deuterium exchange experiments. We had previously shown 1-phenylisoindole (1 and 2, R_1 = H) to undergo deuterium incorporation in the heterocyclic rings of both tautomers when treated with D_2O in $CDCl_3$ solution at room temperature. Under these conditions, exchange was found to be instantaneous, complete and reversible, confirming the existence of a mobile equilibrium.[3] Analogous experiments on 1-methylisoindole and 1,3-dimethylisoindole gave similar results: resonances due to NH and α-hydrogens disappeared and the doublet Me resonance of 2c collapsed to a singlet, owing to replacement of the adjacent 3-proton by deuterium. However, no such α-deuteriation occurs in isoindole itself (1a), although the NH proton does exchange rapidly in both $CDCl_3$ and CD_3CN.[3] No deuterium incorporation in the methyl groups of 1b, 2b and 1c, 2c was observed.

DISCUSSION

Our results, along with data taken from the literature, are summarized in Table 1 and indicate substituents to be capable of profoundly influencing the position of the isoindole-isoindolenine equilibrium. Substituents also exert a pronounced effect on the structure of the isoindolenine tautomer since, in monosubstituted compounds, only one of the two isomeric isoindolenines was observed. Moreover, and of special significance, is our observation that sequential introduction of two identical groups produces opposite effects; the first group causes a shift towards the isoindolenine tautomer whereas the second results in a shift back toward the *o*-quinonoidal tautomer. Finally, electron-releasing substituents exert a differential stabilizing effect on the isoindolenine tautomer.

Table 1. Effects of substitution in the pyrryl ring on the isoindole-isoindolenine equilibrium

R_1	R_2	percent of 1	2	Reference
H	H	100	0	3
CH_3	H	1	99	This work
CH_3	CH_3	20	80	This work
C_6H_5	H	91	9	5
C_6H_5	C_6H_5	100	0	15, 16
COO Et	H	100	0	14
COO Et	COO Et	100	0	14
OEt	H	(0)	(100)	5, 13

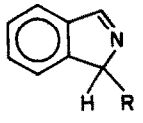
An internally consistent and reasonable explanation for these seemingly erratic variations emerges from consideration of the electronic structures of the parent isoindole and isoindolenine tautomers (**1a** and **1b**). Recent *ab initio* calculations on isoindole (**1a**) indicate the 1- and 3-carbons to be electron-deficient.[10] Electron-releasing groups attached to these positions ought, therefore, to stabilize the molecule. In the same fashion, since the imino C atom of isoindolenine (**1b**) should be electron-deficient relative to the benzylic C atom, attachment of electron-releasing substituents to the former should produce a stabilization of the isoindolenine tautomer, while substitution at the latter position should have essentially no effect on its stability. The net effect on the equilibrium will thus reflect which tautomer is selectively stabilized.

Hückel MO calculations indicate the imino C of isoindolenine (**1b**) to be considerably more electron-deficient than the 1- and 3-carbons of the *o*-quinonoidal tautomer (**1a**) (π-electron density 0.6–0.7 vs 1.0–1.1 for a reasonable range of heteroatom parameters).[11] Thus, electron-releasing groups should selectively stabilize isoindolenine, leading to a shift in the equilibrium away from isoindole, as evidenced by 1-phenylisoindole (approximately 10% isoindolenine[5]), and more dramatically, by 1-methylisoindole, which exists largely in the isoindolenine form (60%, in C_6D_6). Particularly striking in this regard is the case of 1-ethoxyisoindole, which is reported to exist solely as the isoindolenine.[5,13] In contrast, the electron-withdrawing ethoxycarbonyl group should shift the equilibrium toward the *o*-quinonoidal form, as observed. None of the isoindolenine form has been detected for this compound.[14]

These observations are consistent with Veber and Lwowski's finding that electron-releasing substituents at the *para*-position of 1-phenylisoindole increase (to a smaller extent) the amount of isoindolenine in equilibrium with isoindole.[5]

The reason for the exclusive occurrence of a single isoindolenine tautomer (i.e. **2**) is likewise the ability of electron-releasing substituents to stabilize **2** (R_2 = H) by conjugation as opposed to their inability to influence the stability of the π-system when attached to the unconjugated benzylic carbon, as in the alterate structure **8**.

Attachment of a second electron-releasing substituent at the 3-carbon leads to a further stabilization of the isoindole tautomer. However, no overcompensating stabilization of the isoindolenine tautomer occurs in this



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case (the substituent being isolated from the π-system), so the equilibrium moves back toward isoindole, as observed for both 1,3-dimethyl- and 1,3-diphenylisindoles.[15,16] As before, 1,3-bis(ethoxycarbonyl)isoindole exists only in the isoindole form.[14]

In summary, the isoindole-isoindolenine system is a finely-balanced one in which the comparable energies of the two tautomers reflect the fact that each contains one aromatic ring conjugated to a polyenic π-system affording little additional stabilization.[4] Slight perturbations which result in alleviation or exacerbation of charge development can, however, produce major changes in the tautomer distribution.

EXPERIMENTAL

M.ps were determined on a Mel-Temp capillary m.p. apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories (Knoxville, Tenn.).

NMR spectra were taken at room temp. on a Bruker WH-90 pulsed Fourier Transform spectrometer operating at 90 MHz, locked internally to solvent deuterium. Chemical shifts are reported in ppm downfield from internal TMS. IR spectra were recorded on a Beckman IR-10 spectrophotometer. Mass spectra were obtained on a Hitachi Perkin–Elmer RMS-4 medium resolution mass spectrometer.

Preparation of 1*t-butyloxycarbonylpyrroles* **3a–3c**. Compounds **3a**[17] and **3c**[18] were prepared by the general procedure described in the literature. Preparation of the previously unreported **3b** was effected in similar fashion from 2-methylpyrrole. Fractional distillation of crude **3b** through a 46 × 1.5 cm Vigreux column afforded the pure compound (57%): b.p. 58–60° (5 mm); n_D^{25} 1.4745. IR (CCl_4): 2980 and 1743 cm^{-1}; ^1H NMR: $\delta(CDCl_3)$ 1.63 (s, 9 H), 2.39 (s, 3 H), 5.80–6.03 (m, 2 H), 7.05–7.06 (m, 1 H). (Found: C, 66.12; H, 8.25; N, 7.64. $C_{10}H_{15}NO_2$ M = 181.24. Calc.: C, 66.27; H, 8.34; N, 7.73%).

Synthesis of 1,4*-dihydronaphthalen-*1,4*-imines* **4a–4c**. Compounds **4a**[17] and **4c**[17,18] were prepared by the previously published methods. The same route afforded the hitherto unknown compound **4b** from **3b**. Purification by distillation through a semimicro column gave **4b** in 33% yield: b.p. 109–111° (1 mm); n_D^{23} 1.5202. IR (CCl_4): 3050 and 1705 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.26 (S, 9 H), 2.02 (S, 3 H), 5.32 (d, 1 H, J = 2 Hz), 6.51–7.16 (m, 6 H). (Found: C, 74.70; H, 7.48; N, 5.45. $C_{16}H_{19}NO_2$ M = 257.34. Calc.: C, 74.68; H, 7.44; N, 5.44%).

Preparation of 1,2,3,4-*tetrahydronaphthalen*-1,4-*imines* **5a–5c**. Compound **5a** was prepared by the method of Carpino and Barr.[17] Catalytic hydrogenation of adducts **4b** and **4c** in 95% EtOH with 10% Pd-C (40 psi, 20°) gave **5b** and **5c**, respectively. Conversion of **4b** to **5b** was complete in 3 min; longer reaction times led to hydrogenolysis. Reduction of **4c** required 60 min and was trouble-free. The brown oils resulting from removal of catalyst and solvent were distilled in each case through a semi-micro column.

Compound **5b**, yield: 77.4%; b.p. 132–133 (1.7 mm); $n_D^{23.5}$ 1.5142. IR (CCl_4): 2995 and 1702 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.18–1.90 (m, 4 H), 1.33 (s, 9 H), 1.97 (s, 3 H), 5.04 (d, 1 H, J = 4.1 Hz), 6.96–7.20 (m, 4 H). (Found: C, 73.96; H, 8.19; N, 5.37. $C_{16}H_{21}NO_2$ M = 259.36. Calc.: C, 74.10; H, 8.16; N, 5.40%).

Compound **5c**, yield 79%; IR (CCl_4): 2995 and 1700 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.23–2.18 (m, 4 H), 1.39 (s, 9 H), 1.99 (s, 6 H), 6.98–7.20 (m, 4 H).

Synthesis of isoindoles (**1**, **2**)

Isoindoles **1a**, **2a**, **1b**, **2b** and **1c**, **2c** were prepared by pyrolysis of **5a–c**. Passage of compounds **5a–c** through an unpacked Vycor tube maintained at 600 ± 50° (0.5 mm) led to retrograde Diels–Alder reaction with concomitant expulsion of ethylene, isobutylene and CO_2. During the reactions (5–15 min), products were trapped at − 196°. Following the pyrolysis, the trap containing the products under a helium atmosphere was placed in an ice bath for 5–10 min, during which time the volatile coproducts vaporized, leaving behind the white, crystalline isoindoles **1a–c**, **2a–c**. On exposure to air, the crystalline product turned red. Methanolic solns of the isoindoles gave a magenta color on treatment with Ehrlich's reagent. Products were characterized by their Diels–Alder adducts with N-phenylmaleimide.

Spectral data (NMR and UV) for **1a**, **2a** have been reported elsewhere.[3]

1-*Methylisoindole* (**1b**, **2b**). UV (heptane, 25°, equilibrium mixture): λ_{max} 232, 304, 320, 327, 335, 343, and 352 nm. ^1H NMR (25°, equilibrium mixture): δ (C_6D_6) 2.16 (t), 2.24 (s), 4.39 (q), 6.63–7.16 (m), 7.29–7.67 (m); δ ($CDCl_3$) 2.41 (t, 3 H), 4.61 (q, 2 H), 7.19–7.54 (m, 4 H).

1,3-*Dimethylisoindole* (**1c**, **2c**). UV (heptane, 25°, equilibrium mixture): λ_{max} 202, 224, 237, 283, 318, 328, 336, 343, 352, 361, 370 nm. ^1H NMR (25°, equilibrium mixture): δ ($CDCl_3$) 1.49 (d, J = 7 Hz), 2.49 (d, J = 2 Hz), 2.55 (s), 4.60–4.84 (m), 6.71–6.87 (m), 7.09–7.62 (m).

Diels–Alder adducts with N-*phenylmaleimide* (**9a** and **9b**). Adduct **9a** was prepared as reported earlier.[19,20] The Diels–Alder adduct **9b** was prepared as follows. A soln of N-phenylmaleimide (0.133 g, 2 mmol) in 15 ml of ether was added to the cold trap containing a freshly prepared mixture of **1b** and **2b** (obtained from pyrolysis of 0.26 g (1 mmol) of **5b**). The mixture was refrigerated overnight, during which time buff-colored crystals of **9b** separated out. Filtration, followed by recrystallization from chloroform-hexane gave pure **9b**, yield: 51.4%; m.p. 178–180° (dec). IR (CCl_4): 3030 and 1716 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.83 (s, 3 H), 2.29 (broad, 1 H), 2.80 (q, 2 H), 4.79 (s, 1 H), 7.10–7.46 (m, 9 H). (Found: C, 74.59; H, 5.29; N, 9.14 $C_{19}H_{16}N_2O_2$ M = 304.35. Calc.: C, 74.98; H, 5.30; N, 9.21%).

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