

A THEORETICAL INVESTIGATION OF THE STABILITY OF N-UNSUBSTITUTED ISOINDOLES

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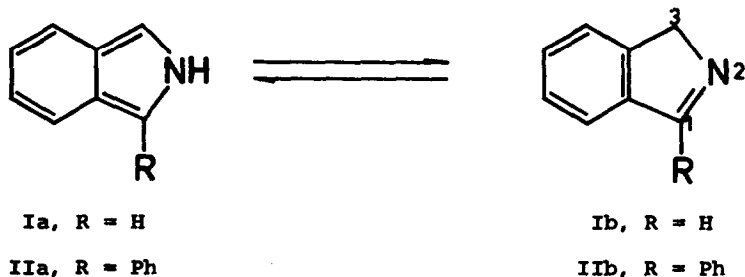
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One of the more interesting problems in the area of nitrogen-containing heterocyclic compounds is that of isoindoles. Although the parent compound, isoindole (I), has resisted isolation, the existence of this unstable species has been shown by trapping with dienophiles (1). Several stable N-substituted derivatives have been known for some time (2-5), but it was only recently that the preparation of 1-phenylisoindole (II), the first stable N-unsubstituted isoindole, was reported (6). In connection with our work in this field, and especially as a result of the observation that benz[f]isoindole (III) and its 1-phenyl-derivative IV are not isolable (7), we have been prompted to investigate the problem of the stability of isoindoles by means of Hückel molecular orbital (HMO) calculations.

Previously reported HMO calculations of isoindole have shown that its instability cannot be explained in terms of delocalization energy (8) or on the basis of electron densities (9). The calculated values for these indices agree closely with those for indole and pyrrole. Similarly, our calculations of the isoindoles under investigation (I - X) do not show any extreme values of reactivity indices, which could explain the stability of II and the instability of I, III and IV. Lwowski (6) has attempted to explain the stability of the isoindoles on the basis of HMO calculations of the delocalization energies (DE) of isoindole, 1-phenylisoindole, and of their corresponding isoindolenine tautomers. From the fact the DE values of the isoindole forms are larger than those of the isoindolenines, it was concluded that the isoindole

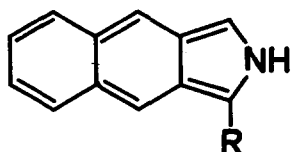
form should be more stable. His results are in agreement with those derived from our calculations. We have found DE values of 2.823 δ and 5.278 δ for isoindole and 1-phenylisoindole; 2.436 δ and 4.838 δ for isoindolenine and 1-phenylisoindolenine, respectively. Analogously, values for IIIa (4.423 δ), IIIb (4.124 δ) and IVa (6.887 δ), IVb (6.525 δ) afford the same qualitative relationship. However, these data do not offer an explanation for the inability to isolate isoindole (I) or the benz[f]isoindoles (III, IV).

The relatively large electron deficiency calculated for position 1 of the isoindolenine form of all compounds studied leads us to conclude that the reactive species responsible for the instability of this series of compounds probably is the isoindolenine, resulting from the tautomeric equilibrium:



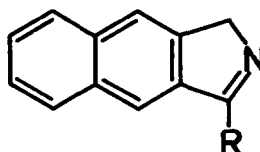
In addition, the striking difference between the stability of isoindole and its N-substituted derivatives, coupled with the observation that 1-phenyl- and 1,3-diphenylisoindole (10) exist almost exclusively in the isoindole form, support the view that the stability is strongly dependent upon this tautomerism. On this basis, a relationship between the difference in the DE (11) of the two tautomers and the stability of the corresponding isoindole, is anticipated. When this difference is sufficiently large so that the isoindolenine species contributes negligibly to the tautomeric equilibrium, the corresponding isoindole will be stable. In support of this proposal, the n.m.r. spectra of the stable IIa and 1,3-diphenylisoindole exhibit no appreciable CH signals characteristics of the isoindolenine tautomer (6, 10). Stable isoindolenines are

known. However, in all of these cases, the electron deficiency in position 1 is compensated by an electron shift from a donating group, as shown by 1-ethoxyisoindolenine (12) and also by the presence of appreciable amounts of the 1-(4-methoxyphenyl)- and 1-(4-dimethylaminophenyl)-isoindolenines (6) in equilibrium with the corresponding stable isoindoles.



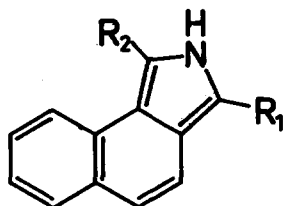
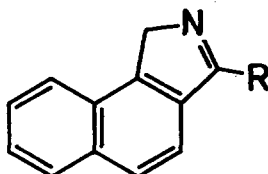
IIIa, R = H

IVa, R = Ph



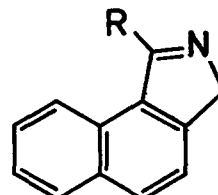
IIIb, R = H

IVb, R = Ph

Va = VIa, R₁=R₂=HVIIa, R₁=Ph, R₂ = HVIIIa, R₁=H, R₂=Ph

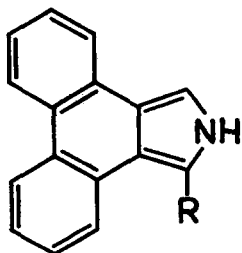
Vb, R = H

VIIb, R = Ph



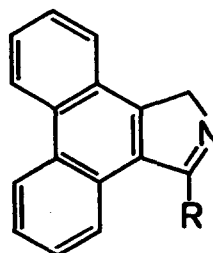
VIB, R = H

VIIIb, R = Ph



IXa, R = H

Xa, R = Ph



IXb, R = H

Xb, R = Ph

TABLE I

No.	DE of tautomers (s)		ΔE^i (s)	p _{ii}	Stability ⁱⁱⁱ
	a	b			
I	2.823	2.436 ^{iv}	0.387	0.01	-
II	5.278	4.838 ^v	0.440	0.25	+
III	4.423	4.124	0.299	0.09	-
IV	6.887	6.525	0.362	0.21	-
V	4.633	4.124	0.509	0.29	(+)
VI	4.633	4.144	0.489	0.29	(+)
VII	7.082	6.525	0.557	0.55	(+)
VIII	7.076	6.543	0.533	0.52	(+)
IX	6.487	5.909	0.578	0.61	(+)
X	8.927	8.308	0.619	1.05	(+)

- ⁱ HMO calculations were made in the usual way; the parameters for the Coulomb and resonance integrals were those of Streitwieser (13).
- ⁱⁱ "Stability index", as described by Zahradnik (14) and calculated for the isoindole structures.
- ⁱⁱⁱ Stability characteristics are given by: + = stable, - = unstable and the predictions for unknown compounds are given in parentheses.
- ^{iv} In the calculation of the isoindolenine structures, the hyperconjugation of the methylene group has been neglected.
- ^v Of the two possible phenyl-substituted isoindolenine tautomers, only that with the higher conjugation (i.e. 1-phenyl-) has been taken into consideration.

The results summarized in Table I satisfactorily explain the observed stabilities of those isoindoles which have been investigated recently (I - IV). A value smaller than 0.387 s (Ia, Ib) has been considered by us to be an indication of instability, whereas a value larger than 0.440 s (IIa, IIb), has been considered an indication of stability. Since the ΔE 's for the pairs IIIa, IIIb and IVa, IVb are smaller than 0.387 s, their reported instability is in accord

with this calculation. For all other compounds, ΔDE for the tautomeric pairs is considerably larger than 0.440 s and, therefore, the probability of their isolation is very high. It is interesting that the stability index P (Table I) afforded the same qualitative conclusions as ΔDE . However, the application of this index, which was developed originally for hydrocarbons, to the isoindole series remains open to question.

It should be noted that Wittig (15) has attempted unsuccessfully to prepare N-methylbenz[f]isoindole and N-methylbenz[e]isoindole by reaction of phenyllithium with the corresponding isoindolinium salts. However, it is not clear whether the inability to isolate these N-methyl analogs of III and V is the result of the extreme reactivity of the intermediate ylids (shown by the formation of rearrangement products) or of the 1,2- or 2,3-naphthoquinoid systems. Our calculations (16) do not suggest an unusually high reactivity for the naphthoquinoid system; however, it is perhaps necessary to use a more refined approximation method in these cases. In agreement with our previous results, when the Dyatkina and Syrkin approximation (11) is applied to the transformation of some isoindolines to isoindoles, the following sequence for ease of formation is found: IXa > Va > Ia > IIIa.

Further investigations, especially those directed toward confirmation of the theoretical data, and including syntheses of some of the unknown isoindoles described here, are now in progress.

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