STABLE 1H- AND 2H-ISOINDOLES * WITH METHYL GROUPS AT THE CARBOCYCLIC SYSTEM [1)]

Richard Kreher and Karl Josef Herd
Institut für Organische Chemie, Technische Hochschule Darmstadt
Petersenstraße 22, D-6100 Darmstadt

4,5,6,7-Tetramethyl-2H-isoindole and 4,7- and 5,6-dimethyl-2H-isoindole are stable and isolable 10π-hetarenes, which can be prepared through a general and *efficient route*. The key step of the reaction sequence is the introduction of a cyclic carbon-nitrogen *double bond* via *elimination* of methanesulfinic acid. The spectroscopic properties of the *tautomeric 2H- and 1H-isoindoles* in solution and the chemical reactivity of the o-quinoid system towards dienophiles with *an activated* CC-double bond have been investigated and elucidated.

The existence of 2H-isoindole was proved by KREHER and SEUBERT [3)] via independent synthesis and chemical reactions and later confirmed by BONNETT and BROWN [4)] via isolation of the parent compound and spectroscopic characterization [5)]. Interest in this field of heterocyclic chemistry has continued in the synthesis of substituted 2H-isoindoles with functional groups at the five or six membered ring system [6)].

Halogen atoms at the carbocyclic moiety exhibit a remarkable effect on the stability of the o-quinoid system [7-9)]. In order to

* DEDICATED WITH BEST WISHES TO PROFESSOR TETSUO NOZOE AT THE OCCASION OF HIS 77TH BIRTHDAY.

evaluate whether electronic or steric stabilization is the dominating effect, the isolation and study of 4,7- or 5,6-dimethyl- and 4,5,6,7-tetramethyl-2H-isoindoles seemed to be of theoretical and practical value.

The synthesis followed the same general route which was successful in the series of the di- or tetra-substituted halogen-2H-isoindoles [8,9]. The starting compounds are obtained by convenient methods; however the previously published procedures must be modified in some order to gain acceptable yields. In an initial step the synthetic precursors (1, $R^n = CH_3$, Z = Br, Cl) were converted by cyclization with methanesulphonamide under basic conditions into the key substances (2, $R^n = CH_3$) with a leaving group at the heteroatom. An effective and practical method consists in the reaction of the two components in relatively concentrated homogeneous medium. The yield of the substituted isoindolines (2, $R^n = CH_3$) is dependent on the reactivity of the bifunctional compounds (1, $R^n = CH_3$) with halogen-methyl groups (Z = Br, Cl).

The critical step is the base induced elimination of methanesulfinic acid introducing the cyclic CN-double bond into the heterocyclic system. Again, the standard conditions [10,11] must be modified to achieve satisfying results. The elimination reaction can be accomplished by treatment with sodium hydride in dimethylsulfoxide. After hydrolysis the reaction products are isolated by filtration (yield 65 - 95 %) under nitrogen atmosphere and purified by sublimation (yield 30 - 50 %). This reaction sequence represents an efficient and general method for the preparation of substituted 2H-isoindoles (3, $R^n = CH_3$) with methyl groups at the carbocyclic moiety.

The spectroscopic data are of considerable interest and significance for the structure of isolated 10π-hetarenes (3, $R^n = CH_3$). The properties are quite different from those of the corresponding halogen substituted 2H-isoindoles (3.2, R^n = Cl, Br) which exist exclusively in the o-quinoid structure (3.2, R^n = Cl, Br). Contrary to this, methyl substituted 2H-isoindoles (3.2, $R^n = CH_3$)

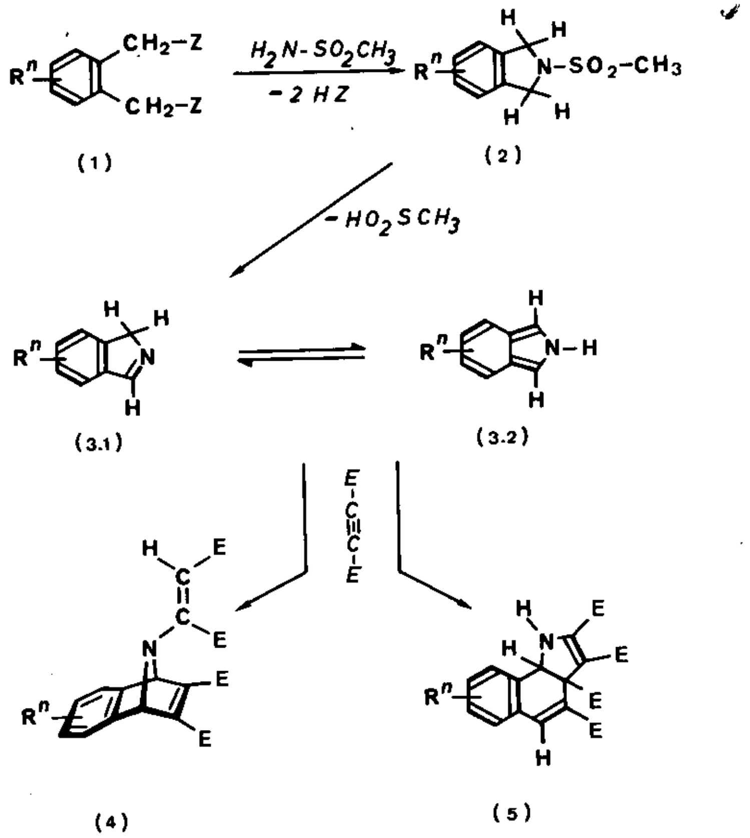

Table 1 : 4,5,6,7-Tetramethyl-isoindole (3a) and 4,7- and 5,6-Dimethyl-isoindoles (3b) and (3c).

(3a), $R^4 = R^5 = R^6 = R^7 = CH_3$: mp ~110 °C (subl. 105 °C/0.01 torr) yield 96% (50%) . - UV (CH_2Cl_2): λ_{max} = 255 (lg ε = 3.77), 295 (3.44), 309 (3.57), 322 (3.62), 334 nm (3.50).

(3b), $R^4 = R^7 = CH_3$ and $R^5 = R^6 = H$: mp 74-77 °C (decomp.) (subl. 50 °C/0.01 torr), yield 75% (50%) . - UV (CH_2Cl_2): λ_{max} = 281 (lg ε = 3.25), 292 (sh, 3.41), 308 (sh, 3.71), 321 (3.84), 334 nm (3.74).

(3c), $R^5 = R^6 = CH_3$ and $R^4 = R^7 = H$: mp 100-103 °C (decomp.) (subl. 75 °C/0.01 torr), yield 95% (30%) . - UV (CH_2Cl_2) : λ_{max} = 250 (log ε = 3.76), 281 (3.33), 294 (3.29), 313 (3.37), 324 (3.40), 337 nm (sh, 3.26).

isomerize to a significant extent into the tautomeric 1H-isoindole form (3.1, R^n = CH_3) in dependence of the solvent. The concentration of the tautomers can be estimated by relevant signals in the ^{1}H-NMR-spectra.

The 4,5,6,7-tetramethyl-2H-isoindole (3.2 a) was found to be the stable tautomeric form in polar solvents (dimethylsulfoxide, acetone); in dioxane the o-quinoid structure is also preferred to a remarkable extent. The equilibrium is displaced towards the 1 H-isoindole form (3.1 a) with decreasing polarity of the solvent. In benzene an equilibrium concentration ratio (3.2 a / 3.1 a) of 64 : 36 is observed, while in chloroform nearly an inverse ratio is measured. This result is supported by the 100 MHz spectrum in chloroform at temperatures from 0 to -30 °C.

For the 4,7-dimethyl compound the predominance of the 2H-isoindole structure (3.2 b) is also established in polar solvents (acetone, dioxane, acetonitrile) but in nonpolar solvents like benzene too. The formation of the tautomeric 1H-isoindole form (3.1 b) can be detected in tetrachloromethane and chloroform; the amount (ca.15%) to be present at equilibrium is relatively small compared with the tetramethyl compound (3.1 a). In the case of the 5,6-dimethyl derivative the 1H-isoindole form (3.1 c) appears to have preference in nonpolar solvents. The concentration of the tautomeric forms could only be estimated, as in solution (benzene, chloroform) decomposition occurred rapidly.

Spectroscopic evidence leads to the conclusion that the positions of the methyl groups have a significant influence upon the stability of the tautomeric forms. The o-quinoid structure (3.2) seems to be favored by substituents in the 4,7-position adjacent to the fused pyrrole system. Methyl groups in the 5,6-position probably contribute inductively to the stabilization of the 1H-isoindole structure (3.1) with the benzenoid moiety.

The 2H-isoindole structure (3.2) is the most reactive form towards dienophiles. Reactions with dimethyl acetylenedicarboxylate lead to the formation of different 1:2-adducts (4) or (5). The 4,5,6,7-

tetramethyl- and the 4,7-dimethyl-2H-isoindole (3.2 a) and (3.2 b) exhibit similar chemical behavior. The initial step seems to be a 1,3-cycloaddition, followed by a Michael addition of the cyclic imino group to the activated triple bond of the dienophile. This subsequent reaction takes a different course in the case of 5,6-dimethyl-2H-isoindole (3.2 c). The reaction sequence is also induced by a 1,3-cycloaddition, but completed by an isomerization process to a tricyclic 1:2-adduct with the structure of a substituted 3a,9b-dihydrobenzo(g)indole (5). It seems conclusive that the isomerization is blocked by the bulky substituents in the 4,7-position. The behavior of 5,6-dibromo-2H-isoindole (3, $R^{5,6}$ = Br) 9), leading to a corresponding adduct with an analogous structure, is consistent with this interpretation.

Table 2 : 1:2-Adducts (4) and (5) of 4,5,6,7-tetramethyl-2H-isoindole (3.2 a) and 4,7-dimethyl- or 5,6-dimethyl-2H-isoindole (3.2 b) and (3.2 c) with dimethyl acetylenedicarboxylate

(4a), mp 208 °C (methanol), yield 14% .- ^{1}H-NMR ($CDCl_3$): τ = 4.48 (s,2H,N-CH), 5.04 (s,1H,CH), 6.12 (s,3H,OCH_3), 6.21 (s,6H,OCH_3), 6.39 (s,3H,OCH_3), 7.72 (s,6H,CH_3), 7.87 (s,6H,CH_3).

(4b), mp 176 °C (methanol), yield 17% .- ^{1}H-NMR ($CDCl_3$): τ = 4.44 (s,2H,N-CH), 4.99 (s,1H,CH), 6.11 (s,3H,OCH_3), 6.20 (s,6H,OCH_3), 6.38 (s,3H,OCH_3), 7.66 (s,6H,CH_3).

(5c), mp 215-217 °C (methanol), yield 18% .- ^{1}H-NMR ($CDCl_3$): τ = 2.32, (s,1H,CH), 4.62 (s,1H,CH), 6.17 (s,3H,OCH_3), 6.21 (s,3H,OCH_3), 6.24 (s,3H,OCH_3), 6.26 (s,3H,OCH_3), 7.73 (s,6H,CH_3).

The experimental results can be summarized under two aspects. The 1H-isoindole form (3.1) seems to be stabilized by the inductive effect of methyl groups (R^n = CH_3) at the carbocyclic system. In a diverse manner halogen atoms (R^n = Cl, Br) cause stabilization of the o-quinoid 2H-isoindole structure (3.2), decreasing the electron density in the heterocyclic 10π-system. Steric effects must also be operative because of the pronounced reactivity and diminished stability of the 5,6-disubstituted 2H-isoindoles (3.2).

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