STRAINED HETEROCYCLIC SYSTEMS. 17. BASICITIES OF SELECTED ISOQUINOLINES

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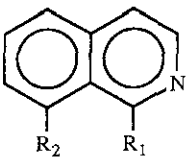
Abstract - The basicities of 7,8-dihydrocyclopenta[*ij*]isoquinoline (**3**) and a series of related compounds were determined spectrophotometrically.

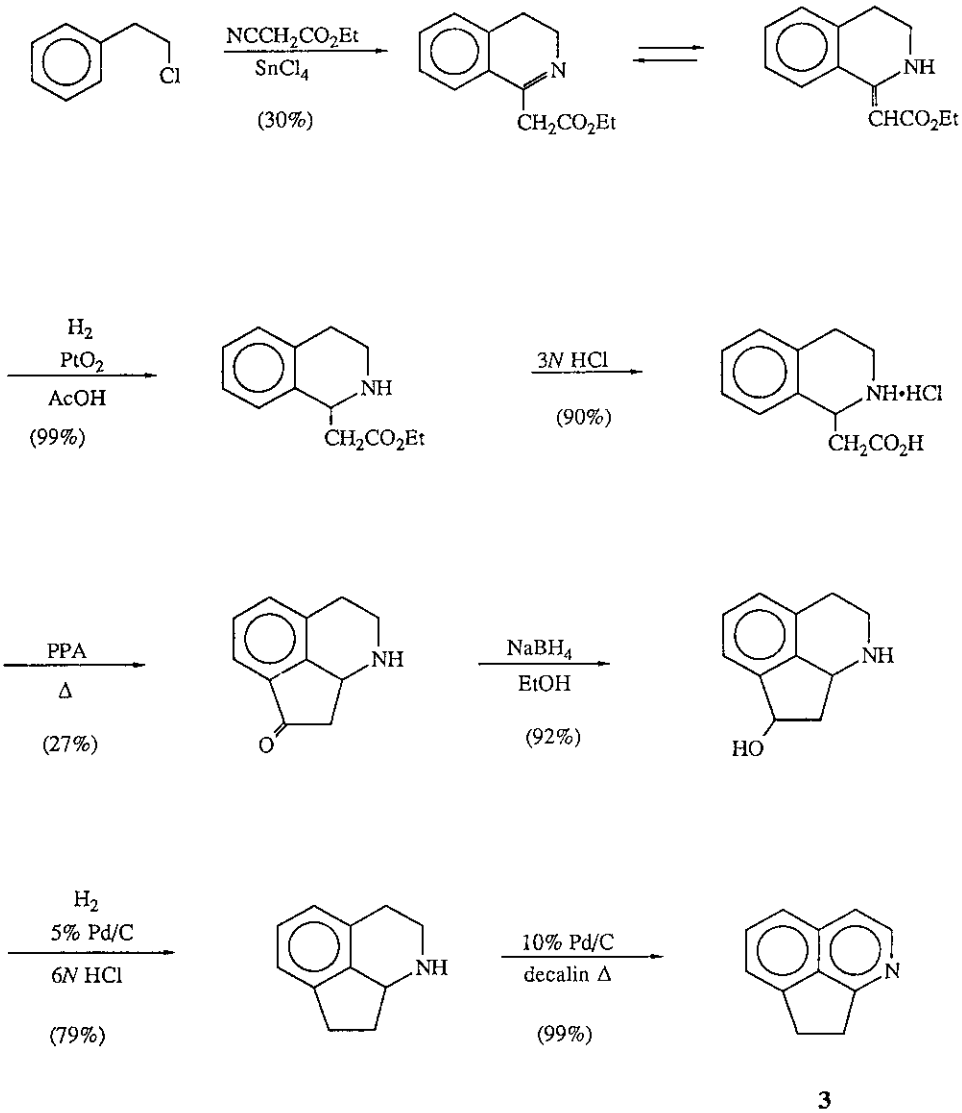
As a continuation of our work on strained quinolines and quinoxalines[1-3] we have extended these studies to the isoquinoline ring system. The target molecule was 7,8-dihydrocyclopenta[*ij*]isoquinoline (**3**), a heterocyclic analog of acenaphthene. That the latter compound possessed a modest amount of strain was known from earlier studies of its reaction kinetics,[4] molecular geometry,[5] thermochemistry,[6] and nmr coupling constants.[7] The Pomeranz-Fritsch reaction with 1-aminoindan was reported to give **3** in only 5% yield.[8] In our hands, the results were no better. The successful preparation of **3** was accomplished in seven steps from β-phenethyl chloride (Scheme I) by the method of Imoto, *et al.* [8,9]



1-5

The basicities of a series of isoquinolines were determined spectrophotometrically. The Table summarizes the substituents for **1-5** and their pK_a values (H_2O, 20 °C). 1-Methylisoquinoline (**2**) incorporates the base-strengthening effect of an α methyl substituent (compared to **1**) and serves as a model compound for **3**. The Δpk_a of 0.16 between **2** and **3** reflects a slight decrease in the basicity of the latter compound, consistent with the modest ring strain of such systems. It was of interest to compare the basicity of **3** to that of indeno[1,2,3-*ij*]isoquinoline (**5**), in which the sp^2 hybridization of C(6b) and C(10a) imposes greater ring strain. Although the pK_a in water is unknown for **5**, its value in 50% aqueous methanol is known.[10] Given the virtual identity of pK_a values for **5** and phenanthridine (**6**) in methanol:water[10] and the value for **6** in water,[11] an approximate pK_a of 4.5 can be estimated for **5** in water (see Table). A suitable model compound was 1-phenylisoquinoline (**4**), for which no basicity data have been reported. Accordingly, the present work included the determination of its pK_a. Compared to **1**, the value for **4** reflects the electron-withdrawing effect of the phenyl substituent. The ΔpK_a of *ca.* 0.8 between **4** and **5** indicates a six-fold difference in basicity.

Scheme I


Cl
NCCH2CO2Et
SnCl4
(30%)
N
CH2CO2Et
NH
CHCO2Et
H2
PtO2
AcOH
(99%)
NH
CH2CO2Et
3N HCl
(90%)
NH•HCl
CH2CO2H
PPA
Δ
(27%)
NH
O
NaBH4
EtOH
(92%)
NH
HO
H2
5% Pd/C
6N HCl
(79%)
NH
10% Pd/C
decalin Δ
(99%)
N

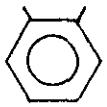
3

EXPERIMENTAL

Compound **2** was purchased from Aldrich Chemical Co., **3** was prepared by the reported method[8] and vacuum sublimed immediately before use; mp 70-73 °C, picrate mp 217-219 °C (lit.[8] mp 68-71 °C, picrate mp 218-222 °C); **4** was a generous gift from Dr. W. Rüger (HOECHST AG).[12] Deionized water was distilled and stored under argon. Glacial acetic acid was distilled from potassium permanganate. Solutions of 0.100 *N* hydrochloric acid and 0.100 *N* sodium hydroxide were prepared by dilution of Acculate standard volumetric solutions (Anachemia Chemicals Inc.). Buffer solutions were prepared with anhydrous sodium acetate and potassium dihydrogen phosphate (Aldrich Chemical Co.). For pH measurements, a Beckman Century SS-1 instrument with a Markson combination/reference electrode was used; the meter was calibrated with certified buffer solutions (Fisher Scientific).

Ultraviolet spectra were recorded on a Cary 219 spectrophotometer in 1-cm cells in a water-jacketed chamber maintained at 20 °C by a Lauda K-2/R bath. The procedure has been described elsewhere.[13,14] The wavelengths of choice for **2**, **3**, and **4** were 333, 344, and 343 nm, respectively. The appropriate buffer was used as a blank for each determination. The data are corrected for ionic strength effects.

Table. Basicities of **1** - **6**

compd	R_1	R_2	solvent	$pK_a^{20\,°C}$	ref.
1	H	H	H_2O	5.40	11
2	CH_3	H	H_2O	6.42 ± .04	15
			H_2O	6.45 ± .02	*a*
3	$-CH_2CH_2-$		H_2O	6.29 ± .02	*a*
4	Ph	H	H_2O	5.28 ± .02	*a*
5			MeOH:H_2O	3.31	10
			H_2O	(4.5)	*b*
6			MeOH:H_2O	3.30	10
			H_2O	4.52	11

[a] This work. [b] Estimated; see text.

REFERENCES

1. W. R. Moomaw, D. A. Kleier, J. H. Markgraf, J. W. Thoman, Jr., and J. N. A. Ridyard, *J. Phys. Chem.*, 1988, **92**, 4892.
2. (a) J. H. Markgraf and W. L. Scott, *J. Chem. Soc., Chem. Commun.*, 1967, 296.
   (b) J. H. Markgraf and R. J. Katt, *Tetrahedron Lett.*, 1968, 6067.
3. J. H. Markgraf and R. J. Katt, *J. Org. Chem.*, 1972, **37**, 717.
4. E. Berliner, D. M. Falcione, and J. L. Riemenschneider, *J. Org. Chem.*, 1965, **30**, 1812.
5. V. Balasubramaniyan, *Chem. Rev.*, 1966, **66**, 567.
6. (a) H. Boyd, R. L. Christensen, and R. Pua, *J. Am. Chem. Soc.*, 1965, **87**, 3554.
   (b) J. F. Liebman and A. Greenberg, *Chem. Rev.*, 1976, **76**, 311.
7. C. K. Fay, J. B. Grutzner, L. F. Johnson, S. Sternhell, and P. W. Westerman, *J. Org. Chem.*, 1973, **38**, 3122.
8. K. Sakane, K. Terayama, E. Haruki, Y. Otsuji, and E. Imoto, *Nippon Kagaku Kaishi*, 1974, 1535.
9. (a) S. G. Agbalyan, A. O. Nshanyan, and L. A. Nersesyan, *Izv. Akad. Nauk Arm. SSR Khim. Nauki*, 1963, **16**, 77 (*Chem. Abstr.*, 1963, **59**, 5132c). (b) W. Sobotka, W. N. Beverung, G. G. Munoz, J. C. Sircar, and A. I. Meyers, *J. Org. Chem.*, 1965, **30**, 3667. (c) E. E. Smissman, S. El-Antably, L. W. Hedrich, E. J. Walaszek, and L.-F. Tseng, *J. Med. Chem.*, 1973, **16**, 109.
10. G. Coppens and J. Nasielski, *Bull. Soc. Chim. Belges*, 1962, **71**, 5.
11. A. R. Osborn, K. Schofield, and L. N. Short, *J. Chem. Soc.*, 1956, 4191.
12. B. Renger, E. Konz, and W. Rüger, *Synthesis*, 1988, 683.
13. R. J. L. Andon, J. D. Cox, and E. F. G. Herington, *Trans. Faraday Soc.*, 1954, 918.
14. C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, N. Shakir, and A. M. White, *Tetrahedron*, 1965, **21**, 1055.
15. M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *J. Chem. Soc., Perkin Trans.* 2, 1973, 1080.

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