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STRAINED HETEROCYCLIC SYSTEMS. 19.[1] 1-AZATRIPTYCENE AND DERIVATIVES

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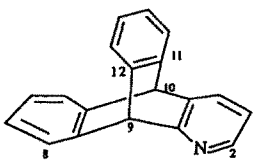
ABSTRACT - The preparations of 1-azatripycene (**1**) and its 9-chloro, 9-deutero, and 1-oxide derivatives are reported The basicity of **1** is compared to model compounds

INTRODUCTION

As a continuation of our studies of strained heterocylic systems, we report here the synthesis of the 1-azatriptycene (**1**) system.[3] Fusion of a strained ring adjacent to the nitrogen atom of an azaarene is known to decrease its basicity,[4] and it should be possible to introduce variable amounts of ring strain via selected bicyclic moieties. Choice of the triptycene (**2**) framework was based on the range of studies assessing strain effects in 2 kinetic acidities, [5,6] electrophilic substitutions, [5,7] NMR coupling constants,[8] and molecular geometries [9] The strain energy of **2** has been estimated to be 26 6 kcal/mole.[10]



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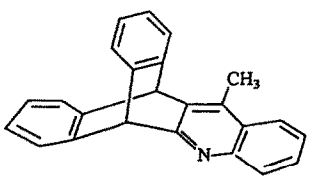

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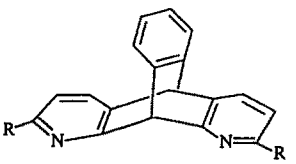

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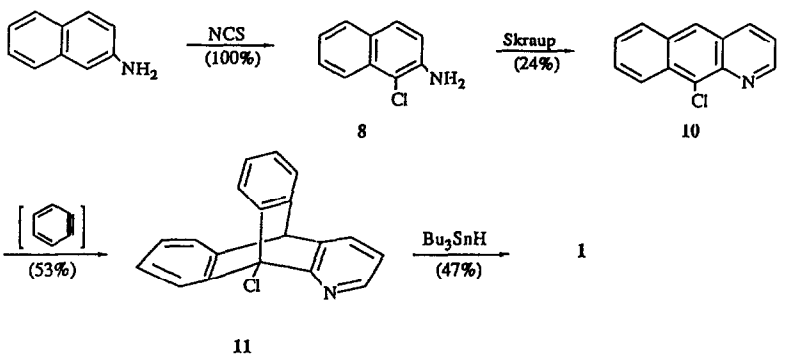
Four azatriptycene systems have been reported, but each contains a feature which would complicate basicity interpretations. The simplest analog is 2-azatriptycene (**3**),[11] but fusion of the strained ring in any position other than adjacent to the hetero atom is virtually without effect.[12] The benzo derivative (**4**)[13] is suitable, except for the base-strengthening effect of the methyl substituent at C(12). Although 2-phenyl-1- azatriptycene (**5**)[14] could be considered a surrogate for **1**, a 2-phenyl substituent decreases the basicity of pyridine and quinoline,[4b,15] thereby masking the anticipated effect of ring strain in the present case Finally, two derivatives of 1,8-diazatriptycene **6** (R = t-Bu; R = Ph) have been reported,[14] but these substituents would also complicate any interpretation of relative basicities. Attempts to prepare **6** (R=H) were unsuccessful.[14]

The basicity of **1**, therefore, remained of interest and two general routes were available for its construction One, utilized in the preparation of **3-5**, involved initial formation of the 9,10-dihydro-9,10-ethanoanthracene framework, followed by construction of the heterocyclic ring The other, patterned after the route to **6**, involved cycloaddition of benzyne to benzo[*g*]quinoline (**7**) The latter sequence, despite recognized difficulties in the preparation of **7**,[16] was simpler and therefore was chosen



RESULTS AND DISCUSSION

The most direct route to **7** is the Skraup cyclization of 2-naphthylamine bearing a substituent at C-1 which can subsequently be removed.[17] Accordingly, 2-naphthylamine was converted to 1-chloro-2-naphthylamine (**8**) by N-chlorosuccinimide (NCS) [18] Condensation of **8** with glycerol by the standard process[16c,17c] gave benzo[*f*]quinoline (**9**) as the major product, an outcome occasionally reported for this reaction [17b,19] The Utermohlen modification,[20] however, circumvented this difficulty and afforded the desired 10-chlorobenzo-[*g*]quinoline (**10**). The low yield reported for the conversion of **10** to **7** under stringent conditions[16c] led us to postpone the hydrodechlorination until the final step

Cycloaddition of benzyne to **10** generated 9-chloro-1-azatriptycene (**11**) Although a variety of methods has been used for the reductive dehalogenation of bridgehead halides, the analogous conversion of **11** to **1** was not readily accomplished Thus, neither magnesium[21] nor chemically activated magnesium,[22] followed by hydrolysis, was effective Cathodic reduction was also unsuccessful [23] The preparation of **1** was accomplished, however, with tributyltin hydride.[24] Analogous reduction of **10** with tributyltin deuteride produced **1**-9d_1, the NMR spectrum of which permitted assignment of the bridgehead protons in **1**

The basicity of **1** was determined titrimetrically and spectrophotometrically and was compared to the pK_a values reported for 2-(phenylmethyl)-pyridine (**12**) and 2-(diphenylmethyl)-pyridine (**13**).[25] The latter compound serves as the best model for the inductive effects, but not the strain effects, present in **1** The half-neutralization potentials (HNP) were determined by potentiometric titrations in acetic anhydride,[21] using quinoline derivatives of known basicity The spectrophotometric measurements were conducted in aqueous solution, using buffers of known pH [22] The results (Table), reflecting the strain-induced decrease in basicity of **1**, were interpreted in our earlier report.[1b]

TABLE. BASICITIES

Compound	Method	$pK_a^{25°}$	Ref.
12	HNP[a]	5.13 ± .01	25a
	UV[b]	5.13 ± .02	25b
13	UV	4.51 ± .03	25b
1	HNP	3.66 ± .10	*c*
	UV	3.66 ± .12	*c*

[a]Potentiometric titration. [b]Spectrophotometric determination. [c]Present work.

The preparation of **1** permitted conversion to the corresponding N-oxide (**14**). Our interest in this derivative stemmed from earlier work on the rearrangement of aromatic N-oxides in acetic anhydride.[29] In particular, our studies on the N-oxide of **13** prompted similar mechanistic considerations for **14**. That investigation will be reported separately, but the present work describes the preparation and characterization of **14**.

EXPERIMENTAL

Melting points were determined on a modified Hershberg apparatus with matched Anschütz thermometers. Liquid chromatography was on neutral alumina (Super 1 activity) with $CHCl_3$ as eluant. Thin layer chromatography was performed on sheets of silica gel (without fluorescent indicator). Gas liquid chromatography was performed on an Aerograph-202-1-B instrument with a 6-ft x 1/8-inch s.s. column packed with 10% DC-710 on 100/120 Chromosorb WHP (column A) and a 5-ft x 1/4-inch s.s. column packed with 20% SE-20 on 60/80 Chromosorb W (column B); helium flow rate was 30 ml/min. Infrared spectra were obtained on a Perkin-Elmer 283B spectrometer. Proton NMR spectra were obtained in $CDCl_3$ on an IBM/Bruker WP-200 SY spectrometer. Mass spectra were determined by Dr. John Occolowitz (Eli Lilly and Co., Indianapolis, Indiana) with a VG ZAB-2SE spectrometer, using a direct probe, ion source temperature of 250 °C, ionizing voltage of 70 eV, and a scanning speed of 10s/decade for regular spectra. High resolution mass spectra were calibrated with perfluorokerosine at a resolution of 25,000. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

1-Chloro-2-naphthylamine (**8**)

CAUTION: The toxicity of 2-naphthylamine requires this substance to be handled with extreme care. To a stirred solution of 2-naphthylamine (0.71 g, 5.0 mmol) in CCl_4 (45 ml) at 45-50 °C was added N-chlorosuccinimide (0.68 g, 5.1 mmol) in small portions over 5 min. The solution was stirred an additional 20 min at 50 °C, cooled, and suction filtered. The filtrate was washed with water (2 x 20 ml), dried (Na_2SO_4) and evaporated to dryness at reduced pressure to give crude **8** (0.90 g, 100%): mp 55-58 °C. The product was recrystallized from ligroine (bp 60-80 °C) to give **8** (0.82 g): mp 59-60 °C (lit.[30] mp 59-60 °C); GLC (column A, 230 °C): retention time 13.3 min.

10-Chlorobenzo[g]quinoline (**10**)

To chilled sulfo-mix (18 g, 88 mmol) were slowly added glycerol (3.7 g, 40 mmol) and then water (6 ml). To the stirred solution at 130 °C **8** (2.1 g, 12 mmol) was added in small portions. After 7 h at 130 °C, the mixture was cooled, basified with 25% NaOH solution (ice bath), diluted with water, and extracted with $CHCl_3$ (5 x 25 ml).

The extracts were washed with brine and extracted with 2N HCl (4 x 25 ml) The acidic extracts were basified and extracted with $CHCl_3$ (4 x 25 ml) The extracts were washed with water, dried (Na_2SO_4), and evaporated to dryness at reduced pressure to give crude **10** (0 62 g, 24%) The product was chromatographed to give yellow crystals of **10** (0 53 g) mp 140 5-142 0 °C (lit [16c] mp 141 °C), GLC (column A, 230 °C) retention time 16 5 min, authentic benzo[*f*]quinoline 6 3 min, TLC (benzene-ethyl acetate 4 1) R_f 0 72, NMR δ 7 43 (1H, dd, $J_{2,3}$ = 3 9 Hz, $J_{3,4}$ = 8.6 Hz, H-3), 7 56 (1H, m, H-7), 7.66 (1H, m, H-8), 8 02 (1H, dd, $J_{6,7}$ = 8 6 Hz, $J_{6,8}$ = 0 9 Hz, H-6), 8 33 (1H, dd, $J_{3,4}$ = 8 6 Hz, $J_{2,4}$ = 1 6 Hz, H-4), 8 35 (1H, s, H-5), 8 60 (1H, dd, $J_{8,9}$ = 8 8 Hz, $J_{7,9}$ = 0 8 Hz, H-9), 9 12 (1H, dd, $J_{2,3}$ = 3 9 Hz, $J_{2,4}$ = 1 6 Hz, H-2), MS (*m/z*) 213 (M^{+})

9-Chloro-1-azatriptycene (**11**)

To a stirred, refluxing solution of **10** (7 0 g, 33 mmol) in 1,2-dimethoxymethane (350 ml, DME) under a N_2 atmosphere were added a portion (10 ml) of a cold solution (A) of isoamyl nitrite (19 1 g, 163 mmol) in DME (26 ml) and then a portion (25 ml over 25 min) of a solution (B) of anthranilic acid (22 4 g, 163 mmol) in DME (125 ml), the reaction solution was refluxed 20 min The cycle of solution A (4 ml), solution B (25 ml) and reflux (20 min) was repeated four times, followed by a final reflux of 90 min The cooled solution was added to 80% aq EtOH (330 ml), basified with 1N NaOH solution (435 ml), diluted with water (400 ml), and extracted with CH_2Cl_2 (5 x 250 ml) The extracts were washed with water, dried (Na_2SO_4), and evaporated to dryness at reduced pressure to give a yellow-brown solid The crude product was chromatographed twice to give **11** (5 0 g, 53%) mp 259-261 °C, GLC (column A, 245 °C) retention time 18 5 minutes, NMR δ 5 41 (1H, s, H-10), 6 99 (1H, dd, $J_{2,3}$ = 5 1 Hz, $J_{3,4}$ = 7 4 Hz, H-3), 7 08-7 13 (4H, m, H-6, 7, 12, 13), 7 38-7 42 (2H, m, H-5, 11), 7 62 (1H, dd, $J_{3,4}$ = 7 4 Hz, $J_{2,4}$ = 1 5 Hz, H-4), 7 79-7 83 (2H, m, H-8, 14), 8 23 (1H, dd, $J_{2,3}$ = 5 1 Hz, $J_{2,4}$ = 1 5 Hz, H-2), HRMS (*m/z*) calcd for $C_{19}H_{12}ClN$ 289 0658, found 289 0666 *Anal* calcd C 78 76, H 4 17, N 4 83, Cl 12 23, found C 78 88, H 4 36, N 4 77, Cl 12 06

1-Azatriptycene (**1**)

A solution of **11** (60 mg, 0 21 mmol), tributyltin hydride (0 16 g, 0 55 mmol), and azo-bis-isobutyronitrile (6 mg, AIBN) in benzene (6 ml) was refluxed 4 5 h A solution of tributyltin hydride (83 mg, 0 29 mmol) and AIBN (4 mg) in benzene (2 ml) was then added dropwise The reaction solution was refluxed an additional 4 5 h, cooled, and evaporated to dryness at reduced pressure to give a pale yellow solid The crude product was dissolved in acetonitrile (5 ml), washed with hexane (4 x 5 ml), and evaporated to dryness at reduced pressure to give **1** (28 mg, 47%) GLC (column A, 245 °C) retention time 7 7 min, no peak at 18 5 min, TLC ($CHCl_3$-DME 1 1) R_f 0 52 The analytical sample was recrystallized from aq EtOH to give **1** mp 268-270 °C, NMR δ 5 39 (1H, s, H-10), 5 55 (1H, s, H-9), 6 99 (1H, dd, $J_{2,3}$ = 5 2 Hz, $J_{3,4}$ = 7 4 Hz, H-3), 7 01 (4H, dd, $J_{5,6}$ = 5 3 Hz, $J_{6,8}$ = 3 2 Hz, H-6, 7, 12, 13), 7 38 (2H, dd, $J_{5,6}$ = 5 3 Hz, $J_{5,7}$ = 3 3 Hz, H-5, 11), 7 45 (2H, dd, $J_{7,8}$ = 5 3 Hz, $J_{6,8}$ = 3 2 Hz, H-8, 14), 7 56 (1H, dd, $J_{3,4}$ = 7 4 Hz, $J_{2,4}$ = 1 4 Hz, H-4), 8 08 (1H, dd, $J_{2\,3}$ = 5 2 Hz, $J_{2,4}$ = 1 4 Hz, H-2), MS (*m/z*) 255 (71 M^{+}), 254 (100), 127 (34) *Anal* calcd for $C_{19}H_{13}N$ C 89 38, H 5 13, N 5 49, found C 89 54, H 5 31, N 5 40

Reduction of **11** (1 0 mmol) with tributyltin deuteride by the same procedure gave **1**-9d_1 (0 77 g, 30%) identical to **1** by GLC and TLC analysis The analytical sample was by preparative GLC (column B, 245 °C) to give **1**-9d_1 mp 269-270 °C, IR (KBr) 2220 cm^{-1}, NMR identical to **1** but no peak at δ 5 55, MS (*m/z*) 256 (74 M^{+}), 255 (100), 254 (46), 253 (11), HRMS (*m/z*) calcd for $C_{19}H_{12}DN$ 256 111076, found 256 109860

1-Azatriptycene N-Oxide (14)

To a cold solution of **1** (25.5 mg, 0 10 mmol) in $CHCl_3$ (0 25 ml) was added a cold solution of *m*-chloroperbenzoic acid (23 7 mg, 80% assay, 0.11 mmol) in $CHCl_3$ (0 7 ml) The reaction solution was refrigerated 2 days, diluted with $CHCl_3$ (7 ml), washed with 1N NaOH solution (2 x 5 ml), and water (2 x 5 ml), dried Na_2SO_4) and evaporated to dryness at reduced pressure to give **14** as a white solid (21 7 mg, 80%) TLC ($CHCl_3$-DME 1:1): R_f 0 17. The analytical sample was chromatographed and vacuum sublimed (200 °C, 0 2 Torr) to give **14** mp 300-301 °C dec.; IR (KBr) 1255 cm^{-1}, MS (*m/z*) 271 (41 M^+), 255 (30), 254 (100) *Anal* calcd for $C_{19}H_{13}NO$ C 84 11, H 4 83, N 5 16, found C 83 69, H 4 85, N 5 00

Basicity Measurements

The procedure for potentiometric titrations has been described [26] The reference compounds were **12**,[25] **13**,[25] and 2-phenylquinoline.[31] The spectrophotometric method has been described;[27] measurements were made at 300 nm

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