C-6), 147.9 (s, C-11a), 151.7 (s, C-10a), 154.4 (s, C-10), 171.9 (s, C-15), and 183.1 (s, C-8).

Biological Assay. Antitumor activity was determined by using mouse leukemia cell lines L1210 according to the method previously reported.[3c] The extravesicular Ca^{2+} concentration in sarcoplasmic reticulum was monitored with a Ca^{2+} electrode prepared by the method of Tsien and Rink with modifications.[3b]

Acknowledgment. We thank Mr. Z. Nagahama for help with collections, Mr. T. Hayase of Central Research Laboratories, Mitsubishi Chemical Industries, Ltd., for help with NMR measurements, and Miss M. Hamashima of this institute for technical assistance.

Registry No. 1a, 113321-71-4; 1b, 113351-75-0; 2, 113351-76-1.

Supplementary Material Available: Figures of the HMBC, ^1H-^{13}C COSY, and RTC-COSY spectra of a 3.5:1 mixture (1) of cystodytins A (1a) and B (1b) (4 pages). Ordering information is given on any current masthead page.

Novel Synthesis of the 2,3-Benzindolizine Ring System. Mechanism of Formation, Redox, Electronic Absorption, and Fluorescence Behavior

Franklin D. Saeva* and Henry R. Luss

Corporate Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

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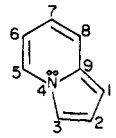
Synthesis of the indolizine ring system 1 has been previously accomplished by the reaction of pyridine with diphenylcyclopropenone by Breslow,[1] Lown,[2] and Wadsworth.[3] In this reaction pyridine and a cyclopropenone condense to form the indolizine nucleus. Indolizines have



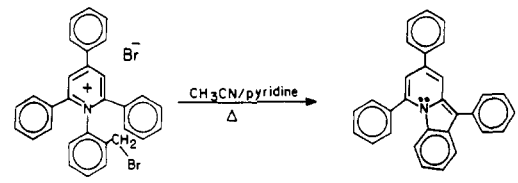
1

recently formed the basis for the synthesis of novel dye classes which have found application in imaging.[4]

We report a novel synthesis of 2,3-benzindolizines by the pyridine-catalyzed reaction of phenyl-substituted pyridinium derivatives via a 1,2-phenyl migration.

Compound 2 was synthesized in a straightforward manner by the reaction of HBr or thionyl bromide with the product of the condensation of triphenylpyrylium chloride with 2-(hydroxymethyl)aniline. The triphenylbenzindolizine 3 was obtained in 83% yield when the pyridinium derivative 2 was heated at reflux in acetonitrile in the presence of pyridine or its derivatives. Triethylamine was found not to be effective at catalyzing the transformation from 2 to 3. The latter are required for the reaction. The structure of 3 was confirmed by its X-ray crystal structure.

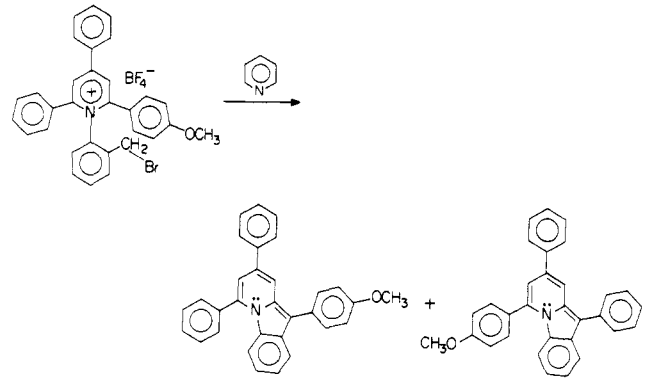
The pyridinium-to-indolizine transformation requires a 1,2-phenyl migration subsequent to ring closure of the



2 3

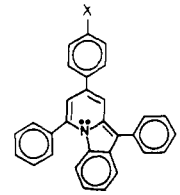
benzylic carbon on the pyridinium ring. Scheme I shows the reactions proposed to account for the observed chemical transformation.

The proposed mechanism involves an initial substitution reaction to form a benzylpyridinium salt which activates the benzylic carbon to deprotonation by pyridine. The pyridinium ylide adds to the triphenylpyridinium ring before loss of pyridine to produce a resonance-stabilized carbocation. The carbocation then undergoes a fast stepwise 1,2-phenyl shift followed by deprotonation to form the indolizine 3. The 4-methoxyphenyl derivative (6) was synthesized from the corresponding hydroxymethyl precursor (5) in order to determine if there was a preference for *p*-anisyl over phenyl migration. Compound 6 was heated at reflux in pyridine for 2 h before purification of the benzindolizine fraction by column chromatography on silica gel with cyclohexane as eluant. Thin layer chromatography on silica gel showed a single spot while field desorption mass spectrometry (FDMS) showed an intense signal corresponding to the expected indolizine (m/e = 425). In addition, ^1H NMR showed the presence of two methoxy signals in a 1:1 ratio, indicating an equal molar mixture of 7 and 8. Cyclic voltammetry showed the mixture to possess a single reversible oxidation wave at +0.64 V (vs SCE in CH_2Cl_2), which produces a cathodic wave at −0.86 V (E_p at 200 mV/s) at slow scan rates. The redox behavior and ^1H NMR spectrum of the mixture of 7 and 8 is entirely consistent with that observed for 3 and 4.



1 : 1

Starting with a [4-(dimethylamino)phenyl]pyrylium derivative, 7-[(dimethylamino)phenyl]indolizine (4) was also synthesized. The redox behavior, electronic absorption, and fluorescence behavior of the two benzindolizines (3 and 4) have been investigated.



3 X = H

4 X = -N(CH$_3$)$_2$

(1) Breslow, R.; Eicher, T.; Krebs, A.; Peterson, R. A.; Posner, J. *J. Am. Chem. Soc.* **1965**, *87*, 1320.
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(3) Wadsworth, D. H.; Bender, S. L.; Smith, D. L.; Luss, H. R. *Tetrahedron Lett.* **1981**, *37*, 3569.
(4) Fletcher, G. L.; Bender, S. L.; Wadsworth, D. H. U.S. Pat. 4577024, March 18, 1986.

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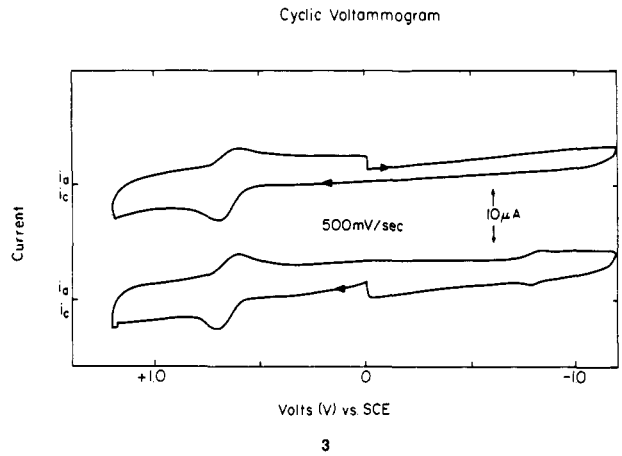
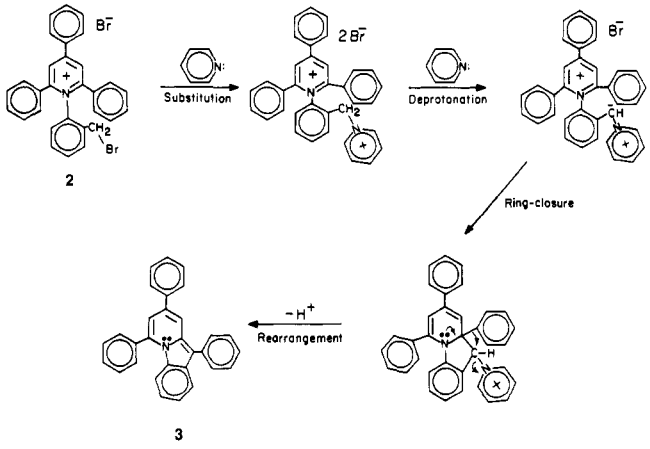


3

Figure 1. Cyclic voltammogram of 3 in methylene chloride containing 0.1 N TBAF.

Scheme I



Compounds 3 and 4 both absorb in the visible region of the spectrum (~450 nm) and exhibit fluorescence at ~590 nm. The magnitude of the Stokes shift, i.e., 138 and 134 nm for 3 and 4, respectively, is indicative of a substantial structural difference between the ground and excited singlet state.

compd	λ_{max} (ϵ_{max})	λ_{max} (fluorescence)
3	452 nm (11 400)	590 nm
4	458 nm (9300)	592 nm

The strongly electron donating dimethylamino group does not significantly affect the wavelength of either the lowest energy electronic transition or the fluorescence over the parent system. This fact is presumably due to an increase in energy of both the highest occupied molecular orbital and excited singlet state to approximately the same extent with dimethylamino substitution.

The indolizines 3 and 4 exhibit reversible one-electron oxidation at +0.66 V and +0.49 V (vs SCE in CH_2Cl_2), respectively. See Figure 1 for the cyclic voltammogram of 3 at 500 mV/s scan rate. No other redox process was observed for 3 and 4 between +1.7 and −1.7 V.

Conclusion

The 2,3-benzindolizine ring system was synthesized by the reaction of *N*-[2-(bromomethyl)phenyl]-2,4,6-triphenylpyridinium bromide with pyridine. The benzindolizine derivative which was formed by a novel 1,2-phenyl migration absorbs in the visible region of the spectrum and exhibits reversible one-electron oxidation at fast scan rates. The presence of a 4-dimethylamino functionality on the 7-phenyl ring does not appreciably influence the electronic absorption and fluorescence behavior of the parent ring system. The oxidation potential, however, is shifted to less anodic values.

Experimental Section

Equipment. A Princeton Applied Research Model 173 potentiostat and Model 175 universal programmer were used in the standard three-electrode configuration to obtain reduction potentials by cyclic voltammetry. A platinum inlay electrode was used as the working electrode along with a platinum auxiliary electrode and a standard calomel electrode (SCE). The electrolyte was 0.1 N tetrabutylammonium tetrafluoroborate (TBAF) previously recrystallized from an ethyl acetate/pentane solvent mixture in dry methylene chloride.

Absorption spectra were run on a Perkin-Elmer Model 330 spectrophotometer equipped with a Model 3600 data station and a Model 600 printer. Proton nuclear magnetic resonance spectra were run on a Varian EM390 spectrometer. Combustion analyses and mass spectra were performed by the Analytical Technology Division of Eastman Kodak Company. Fluorescence excitation and emission spectra were measured on a Perkin-Elmer Model LS-5 spectrofluorimeter equipped with a Perkin-Elmer model 7500 laboratory computer. Data for the crystal-structure determination were collected on an Enraf-Nonius CAD4 diffractometer with graphite-monochromated Mo Kα radiation and are given as supplementary material.[5]

Materials. *N*-[2-(Hydroxymethyl)phenyl]-2,4,6-triphenylpyridinium Chloride. Equal molar quantities (2.6 mmol) of 2,4,6-triphenylpyrylium chloride (EK 14092) and *o*-aminobenzyl alcohol (Aldrich 12,283-1) in 100 mL of absolute ethanol containing a catalytic amount of triethylamine were heated at reflux for 19 h. The reaction mixture was condensed by flash evaporation to ~30 mL and poured into 200 mL of anhydrous ether. The crude product precipitated from solution as a pale yellow solid. Recrystallization from an acetonitrile–diethyl ether solvent mixture provided 0.95 g (87%) of the purified product, mp 267–269 °C: MS, *m/e* 450 (FDMS); ^{1}H NMR (CD_2Cl_2) δ 4.38 (d, 2 H), 6.22 (t, 1 H), 6.9–8.1 (m, 21 H, Ar). Anal. Calcd for $C_{30}H_{24}NOCl$: C, 80.08; H, 5.38; N, 3.11. Found: C, 80.1; H, 5.5; N, 3.1.

***N*-[2-(Bromomethyl)phenyl]-2,4,6-triphenylpyridinium Bromide (2).** *N*-[2-(Hydroxymethyl)phenyl]-2,4,6-triphenylpyridinium chloride (2.12 g) was dissolved in 25 mL of 31% HBr in acetic acid (EK 1161) and allowed to stir at room temperature. The reaction was periodically monitored by ^{1}H NMR until the reaction was complete. The reaction mixture was worked up by pouring into 100 mL of water and collecting the off-white product by suction filtration. Recrystallization from acetonitrile–diethyl ether provided 1.84 g (67% yield) of product, mp 260–262 °C: MS, *m/e* 477 (FDMS); ^{1}H NMR (CD_2Cl_2) δ 4.02 (s, 2 H), 7.0–8.3 (m, 21 H, Ar). Anal. Calcd for $C_{30}H_{23}Br_2N$: C, 64.65; H, 4.16; N, 2.51. Found: C, 64.7; H, 4.2; N, 2.5.

1,5,7-Triphenyl-2,3-benzindolizine (3). Equal molar (2.4 mmol) quantities of 2 and pyridine were dissolved in 40 mL of acetonitrile and refluxed for 15 h and allowed to cool to room temperature. The product that crystallized from acetonitrile as dark red needles was obtained in 83% yield (mp 203–204 °C). The structure of the product was identified from its X-ray crystal structure (see supplementary data).

1,5-Diphenyl-7-[4-(dimethylamino)phenyl]-2,3-benzindolizine (4) was prepared from 4-[4-(dimethylamino)phenyl]-2,6-diphenylpyrylium perchlorate[6] in a manner analogous to compound 3 in 65% yield (mp 197–199 °C); MS, *m/e* 438. Anal. Calcd for $C_{32}H_{26}N_2$: C, 87.64; H, 5.98; N, 6.39. Found C, 87.6; H, 5.9; N, 6.4.

***N*-[2-(Hydroxymethyl)phenyl]-2-(4-methoxyphenyl)-4,6-diphenylpyridinium Tetrafluoroborate (5).** Equal molar quantities (10.8 mmol) of 2-(4-methoxyphenyl)-4,6-diphenylpyrylium tetrafluoroborate (Eastman X52474) and *o*-aminobenzyl alcohol (Aldrich 12,283-1) were dissolved in 100 mL of absolute

(5) Programs used in this study are from the Structure Determination Package (SDP) V3.0, Enraf-Nonius Corp., Delft, Holland (1985).
(6) Reynolds, G. A.; Van Allen, J. A. *J. Heterocycl. Chem.* **1974**, *11*, 405.

ethanol containing a catalytic quantity (0.5 mL) of triethylamine. The reaction mixture was refluxed for 15 h before being condensed to ~30 mL. This solution was added slowly to 200 mL of anhydrous ether at which time the crude product precipitated from solution as a pale yellow solid (5.6 g, 97% yield). Recrystallization from an acetonitrile–diethyl ether solvent mixture provided 5.2 g (90% yield) of the purified product, mp 216–218 °C; MS, *m/e* 444 (FDMS); ^{1}H NMR (CD_2Cl_2) δ 4.32 (s, 2 H), 3.72 (s, 3 H), 3.36 (s, 1 H), 6.70–8.22 (m, 20 H, Ar). Anal. Calcd for $C_{31}H_{26}NO_2BF_4$: C, 70.07; H, 4.93; N, 2.64. Found: C, 70.2; H, 5.0; N, 2.7.

***N*-[2-(Bromomethyl)phenyl]-2-(4-methoxyphenyl)-4,6-diphenylpyridinium Tetrafluoroborate (6).** *N*-[2-(Hydroxymethyl)phenyl]-2-[4-methoxyphenyl]-4,6-diphenylpyridinium tetrafluoroborate (4.4 mmol) was dissolved in 25 mL of thionyl bromide and stirred at room temperature for 15 h. The reaction mixture was poured into 200 mL of water at which time the crude product precipitated from solution. The crude product was collected by suction filtration and air-dried before being dissolved in 100 mL of methylene chloride. This solution was filtered to remove inorganic salts and flash evaporated. Recrystallization from acetonitrile–diethyl ether provided 2.16 g (95% yield) of purified product, mp 254 °C dec; MS, *m/e* 507 (FDMS); ^{1}H NMR (CD_3CN) δ 4.12 (s, 2 H), 3.84 (s, 3 H), 6.95–8.32 (m, 20 H, Ar). Anal. Calcd for $C_{31}H_{25}NOBr{\cdot}BF_4$: C, 62.66; H, 4.24; N, 2.36. Found: C, 62.7; H, 4.3; N, 2.4.

1-[4-Methoxyphenyl]-5,7-diphenyl-2,3-benzindolizine (7) and 1,7-Diphenyl-5-(4-methoxyphenyl)-2,3-benzindolizine (8). *N*-[2-(Bromomethyl)phenyl]-2-(4-methoxyphenyl)-4,6-diphenylpyridinium tetrafluoroborate (**6**) (100 mg, 0.2 mmol) was dissolved in 10 mL of pyridine and refluxed for 2 h. The reaction mixture was then poured into 100 mL of water and extracted with three 100-mL portions of diethyl ether. The combined ether extract was then washed with 10% HCl and dried over $MgSO_4$ before flash evaporation. The mixture of benzindolizines (75 mg, 0.17 mmol) was isolated by chromatographic separation on silica gel by using cyclohexane as eluant. ^{1}H NMR in CD_2Cl_2 showed the presence of two distinct methoxy groups, δ 4.00 (s, 3 H) and 4.05 (s, 3 H) in a 1:1 ratio; MS, *m/e* 425. Anal. Calcd for $C_{31}H_{23}NO$: C, 87.50; H, 5.45; N, 3.29. Found: C, 88.0; H, 5.6; N, 3.4.

Registry No. **2**, 113404-16-3; **3**, 113404-17-4; **4**, 113404-18-5; **5**, 113404-20-9; **6**, 113404-22-1; **7**, 113404-23-2; **8**, 113430-70-9; *o*-$H_2NC_6H_4CH_2OH$, 5344-90-1; 2,4,6-triphenylpyrylium chloride, 40836-01-9; *N*-[2-(hydroxymethyl)phenyl]-2,4,6-triphenylpyridinium chloride, 113404-15-2; 4-[4-(dimethylamino)phenyl]-2,6-diphenylpyrylium perchlorate, 2970-29-8; 2-(4-methoxyphenyl)-4,6-diphenylpyrylium tetrafluoroborate, 2907-13-3; pyridine, 110-86-1.

Supplementary Material Available: X-ray crystallographic data for **3**: crystal data, numbering scheme, positional parameters, displacement parameters (β), bond lengths and angles, and least-square planes (8 pages). Ordering information is given on any current masthead page.

Thermal Cycloelimination of Bis(dialkylamino)cyclopropanes to Amidines and Cycloalkenes

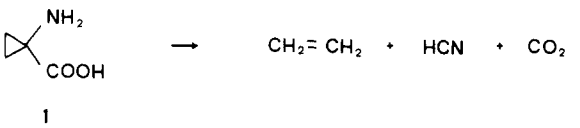
Elmar Vilsmaier,* Gerhard Kristen, and Claus Tetzlaff

Fachbereich Chemie der Universität Kaiserslautern, D 6750 Kaiserslautern, West Germany

Received April 23, 1987

Aminocyclopropanecarboxylic acid (**1**) was shown to be the precursor of the phytohormone ethylene in nature.[1] Investigations[1,2] on the mechanism of ethylene formation from **1** led to an increase of interest in cycloelimination reactions of aminocyclopropane derivatives (Scheme I). So far alkene generation from aminocyclopropanes has required a primary amino function,[1-3] which was shown to be oxidized in the initial step.

Scheme I



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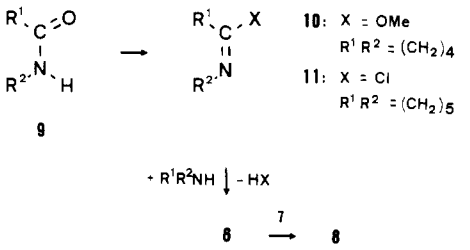
Scheme II



9 **8**

We have found a non oxidatively induced cycloelimination of an aminocyclopropane derivative by flash vacuum pyrolysis of diaminobicyclo[*n*.1.0]alkanes **2**. Thus decomposition of dimorpholinobicyclo[4.1.0]heptane (**2a**) at 700 °C (10^{-5} Torr) gave heterocycle **6a** and cyclohexene (**3a**) in 70% and 93% yield, respectively, indicating a clean cleavage of the cyclopropane unit (Scheme II). The structure of **6a** is established unequivocally by ^{1}H NMR [δ 2.70–2.76 (2 H), 3.21–3.29 (4 H), 3.59–3.75 (10 H), 3 AA'XX' systems], ^{13}C NMR [δ 70.7, 66.9, 65.9 (OCH_2), 52.3, 46.9 (NCH_2), 32.4 (all t), 167.8 (s)], and IR spectroscopy [$\nu_{C=N}$ 1620 cm^{-1}]. Cyclohexene (**3a**) was identified by its ^{1}H NMR spectrum in carbon tetrachloride solution.

Similarily the pyrrolidino and the piperidino compounds **2c** and **2d** were cleaved by flash pyrolysis conditions to give amidines **6c** and **6d**. In these cases small amounts of impurities present could not be removed by distillation, therefore the oily reaction products were isolated and characterized as picrates (yields: **8c**, 88%; **8d**, 84%).

For structural clarification amidines **6c**/**8c** and **6d**/**8d** additionally were prepared by standard procedures[4] from lactams **9** via imidate **10** or imidoyl chloride **11** (Scheme III). The picrates **8c** and **8d** thus obtained and the corresponding picrates resulting from the thermolysis gave identical melting points and IR and ^{1}H NMR spectra.

The bicyclododecane derivatives **2b** and **12** were used to study the stereoselectivity of the cycloelimination. The separation of amidine **6** and cycloalkene was performed by an acidic ion-exchange resin. Cycloundecene was isolable in 89% and 92% yield from the corresponding aminals **2b** and **12**, respectively. Especially the IR and ^{1}H NMR spectra demonstrate the generation of *cis*-cycloundecene (**3b**) from cis aminal **2b** and of *trans*-cycloundecene (**13**) from trans aminal **12** as the main products (Scheme IV). GC–MS investigations[5] showed *cis*-cyclo-

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