decomposed with almost explosive force.

Experimental Section

Materials and General Methods. Tetrahydrofuran was purified by distillation over sodium in the presence of benzophenone under dry nitrogen gas. The styrenes used were commercial materials of highest purity and were further purified by distillation over lithium aluminum hydride when necessary. The internal standards, reference samples, and 9-BBN solid and 0.5 M solution in THF were obtained commercially. All operations were carried out under dry nitrogen and followed standard procedures.[15] All glassware and syringe needles were oven dried at 130 °C, assembled while hot, and cooled under a stream of dry nitrogen gas.

All GLC analyses were carried out on a Varian Aerograph Series 2800 instrument equipped with a flame-ionization detector attached in series with a LDC 302 computing integrator and a Sargent Recorder Model SR of 1.25-mV range. The NMR spectra were taken on a Varian Anaspect EM-360 60-MHz NMR spectrometer using tetramethylsilane as an internal reference.

Competitive Relative Rate Experiments. The procedure generally followed that of Brown, Liotta, and Scouten.[6] A THF solution of 0.0025 mol (3 mL) each of styrene and the substituted styrene together with a weighed quantity of a hydrocarbon internal standard was allowed to react in a magnetically stirred system with 0.0025 mol (5 mL) of a standard 0.5 M solution of 9-BBN in THF under a dry nitrogen atmosphere at 25 ± 0.1 °C. All material transfers were carried out by syringes which had been flushed with dry nitrogen. Periodically, minute samples were withdrawn by syringe and analyzed for residual styrenes by GLC, with the internal standard used to determine response factors and yields. Short (a few inches of $^1/_4$-in. diameter aluminum) THEED stripper columns (to remove organoborane compounds) were used in series with SE-30 or Carbowax 20M on Chromosorb W-HP (100/120 mesh) $^1/_8$-in. aluminum columns. The hydrocarbon standards used were undecane, dodecane, and hexdecane, the choice depending on the retention times of the styrenes. Within 1 h or less the residual styrenes ratio reached a constant value, which remained unchanged for periods of 5–20 h, after which time the amounts of residual styrenes gradually decreased. The relative rates were calculated[12] from the samples taken in the plateau region and are given in Table I.

(15) We have found particularly helpful the many detailed experimental procedures and the chapter "Laboratory Operations with Air Sensitive Substances" by Kramer, Levy, and Midland in: Brown, H. C. "Organic Syntheses Via Boranes"; Wiley: New York, 1975.

Regioselectivity Experiments. The various styrenes were hydroborated and oxidized with alkaline hydrogen peroxide in the standard way.[9,15] The yields of the isomeric 1- and 2-phenylethanols were determined by GLC analysis with dodecane or one of the other substituted phenylethyl alcohols as internal standards. The reliability of the analysis for the minor component was checked by analysis of known mixtures of authentic samples in the presence of the internal standard used. The results are shown in Table II.

Preparation of 9-(2-Arylethyl)-9-borabicyclo[3.3.1]nonanes. A THF solution of 0.02 mol (40 mL of a 0.5 M solution) of 9-BBN was added slowly with stirring to 0.02 mol of the appropriate styrene in 10 mL of THF under a dry nitrogen atmosphere. After 16 h the solvent was removed on a rotary evaporator. The crude yields of the light pale yellow oils were all quantitative. **Caution**: Although stable in THF solution, the *m*-nitrostyrene–9-BBN adduct decomposed violently when the solvent was removed. (After this experience, no attempt was made to prepare the *p*-nitrostyrene adduct.) The crude adducts were transferred by disposable plastic syringes to the vacuum distillation apparatus, which contained a dry nitrogen atmosphere. The crude material was stirred magnetically during the vacuum distillation, and the colorless distilled samples were sealed under dry nitorgen. The adducts generated thick white fumes when exposed to air but did not catch fire. The details of the preparations are given in Table III.

Acknowledgment. This work was supported by National Science Foundation Grant CHE-78-09809. We are grateful to Professor W. L. Meyer for a helpful discussion.

Registry No. *p*-Methoxystyrene, 637-69-4; *p*-methylstyrene, 622-97-9; styrene, 100-42-5; *p*-fluorostyrene, 405-99-2; *p*-chlorostyrene, 1073-67-2; *m*-chlorostyrene, 2039-85-2; *m*-nitrostyrene, 586-39-0; *p*-nitrostyrene, 100-13-0; 9-(2-(4-methoxyphenyl)ethyl)-9-borabicyclo[3.3.1]nonane, 75400-50-9; 9-(2-(4-methylphenyl)ethyl)-9-borabicyclo[3.3.1]nonane, 75400-51-0; 9-(2-phenylethyl)-9-borabicyclo[3.3.1]nonane, 67753-90-6; 9-(2-(4-fluorophenyl)ethyl)-9-borabicyclo[3.3.1]nonane, 75400-52-1; 9-(2-(4-chlorophenyl)ethyl)-9-borabicyclo[3.3.1]nonane, 75400-53-2; 9-(2-(3-chlorophenyl)ethyl)-9-borabicyclo[3.3.1]nonane, 75400-54-3; 4-methoxy-α-methylbenzenemethanol, 3319-15-1; α,4-dimethylbenzenemethanol, 536-50-5; α-methylbenzenemethanol, 98-85-1; 4-fluoro-α-methylbenzenemethanol, 403-41-8; 4-chloro-α-methylbenzenemethanol, 3391-10-4; α-methyl-4-nitrobenzenemethanol, 6531-13-1; 4-methoxybenzeneethanol, 702-23-8; 4-methylbenzeneethanol, 699-02-5; benzeneethanol, 60-12-8; 4-fluorobenzeneethanol, 7589-27-7; 4-chlorobenzeneethanol, 1875-88-3; 4-nitrobenzeneethanol, 100-27-6; 9-BBN, 280-64-8.

1,3-Diazepinones. 2. The Correct Structure of Squamolone as 1-Carbamoyl-2-pyrrolidinone and Synthesis of Authentic Perhydro-1,3-diazepine-2,4-dione

Victor E. Marquez,* James A. Kelley, and John S. Driscoll

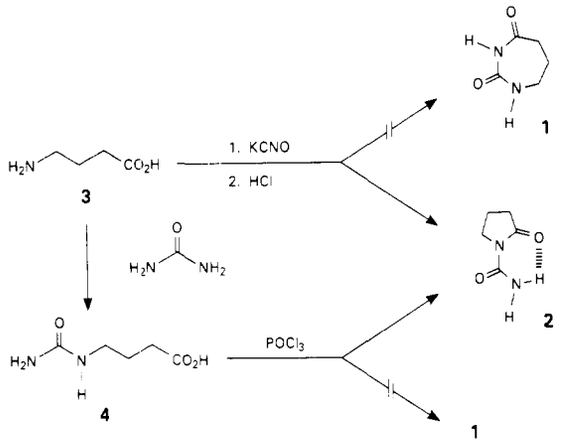
Drug Design and Chemistry Section, Laboratory of Medicinal Chemistry and Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205

Received September 3, 1980

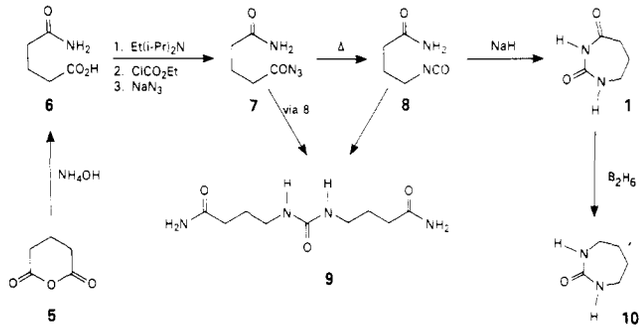
The natural product squamolone, previously reported as 4-oxoperhydro-1,3-diazepin-2-one (**1**), was found to be instead 1-carbamoyl-2-pyrrolidinone (**2**). An unequivocal synthesis of the diazepinedione **1** starting from glutaric acid monoamide (**6**) produced the desired compound in five steps. Diborane reduction of **1** yielded the known perhydro-1,3-diazepin-2-one (**10**, tetramethyleneurea), confirming the seven-membered-ring structure of **1**. A detailed analysis of the IR, NMR, and mass spectra of squamolone (**2**) and its isomer **1** is presented. A one-step synthesis of squamolone (**2**) starting with 4-aminobutyric acid **3** is reported.

The functionalized perhydro-1,3-diazepin-2-one system has been the subject of recent interest in view of the very potent inhibition of cytidine deaminase exhibited by some of its nucleosides.[1] The 5-oxo- and 5-hydroxyperhydro-

Scheme I



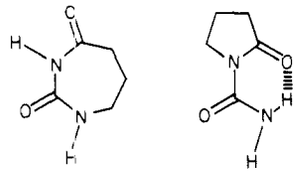
Scheme II



1,3-diazepin-2-one ring systems have been reported[2] and attention has now been focused on the 4-oxo isomer **1**.

Compound **1** was first reported in 1972 as a natural product isolated from the plant *Anona squamosa* and hence named squamolone.[3] Spectral data, including IR, NMR, and mass spectra, as well as a chemical synthesis that produced the identical natural substance were provided to corroborate the structure.[3] A β-D-ribofuranosyl nucleoside having the same seven-membered aglycon **1** has also been reported. However, its synthesis was not accomplished by a direct condensation of **1** with a sugar moiety, but rather by photochemical ring expansion and catalytic hydrogenation of the nucleoside cyclothymidine.[4]

Since we have recently developed methods for condensing saturated cyclic ureas with halosugars,[1] the seven-membered diazepinedione structure **1** was considered as a potential candidate for nucleoside formation. Consequently, the literature procedure for the synthesis of squamolone was reproduced and a material identical with that previously reported was obtained.[3] After the corresponding α and β nucleosides of this material were separated, the NMR spectral data were inconsistent with a structure having the seven-membered aglycon **1** and suggested instead the five-membered aglycon **2**.[5] At about the same time in connection with another study,[6] it was suggested to us that the structure of squamolone was **2** rather than **1** in view of the spectral similarities (IR and NMR) between squamolone and some *N*-alkyl-1-carbamoyl-2-pyrrolidinones.[7]



1 **2**

The present work presents evidence to support the structure of squamolone as **2** and it also describes an unequivocal synthesis of the elusive diazepinedione **1**.

Results and Discussion

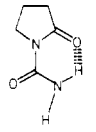
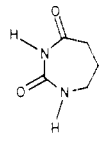
In the short communication reporting the isolation and synthesis of squamolone it was stated that 4-ureidobutyric acid (**4**) cyclized to squamolone (assumed to be **1**) in the presence of phosphoryl chloride.[3] While we were able to develop conditions for this reaction to occur in 56% yield by refluxing a benzene solution of **4** in excess phosphoryl chloride (Scheme I), the preparation of **4** from 4-aminobutyric acid (**3**) and urea, either by simple fusion or by a patented acid-catalyzed procedure,[8] was characterized by low yields. A more efficient synthesis for squamolone was developed by reacting 4-aminobutyric acid (**3**) with an equivalent amount of potassium isocyanate followed by treatment with hydrochloric acid. Part of the material produced was sublimable and the rest was extracted from the inorganic mixture with chloroform to give pure compound identical with that of the original synthesis in excess of 50% yield. A successful application of this procedure has been reported for the synthesis of 5,6-dihydrouracil.[9] However, in contrast to the 5,6-dihydrouracil case, cyclization could potentially occur in two different directions, giving either squamolone (**2**) or its isomeric diazepinedione **1** (Scheme I).

The available spectroscopic evidence was insufficient to unambiguously assign the structure of this product as either **1** or **2**. Therefore, a synthetic route which could produce exclusively the diazepinedione **1** was required to establish the structure of squamolone as **2**. This was accomplished by the sequence of reactions shown in Scheme II. The key starting material was glutaric acid monoamide (**6**), previously described as an oil,[10] which we obtained in crystalline form by simple ammonolysis of glutaric anhydride (**5**) followed by neutralization of the ammonium salt with a cation-exchange resin.

The free carboxylic acid group in **6** was easily transformed into the corresponding isocyanate (compound **8**) by the modified Curtius procedure[11] and the final cyclization step was accomplished with the aid of NaH in tetrahydrofuran. While the desired diazepinedione **1** was not obtained in very high yield (ca. 12% from **6**), the only other product isolated from the reaction was the easily characterizable symmetrical urea **9** which can be formed either during thermal rearrangement of **7** to **8** if heating

(1) Marquez, V. E.; Liu, P. S.; Kelley, J. A.; Driscoll, J. S.; McCormack, J. J. *J. Med. Chem.* **1980**, *23*, 713.
(2) Marquez, V. E.; Liu, P. S.; Kelley, J. A.; Driscoll, J. S. *J. Org. Chem.* **1980**, *45*, 485.
(3) Yang, T. H.; Chen, C. M. *J. Chin. Chem. Soc.* **1972**, *19*, 149.
(4) Kunieda, T.; Witkop, B. *J. Am. Chem. Soc.* **1971**, *93*, 3478.
(5) In the NMR spectra of these nucleosides the anomeric proton appeared as a doublet of doublets with $J_{1',NH} \approx 8$ Hz. After D_2O exchange this signal collapsed to a doublet. Also, irradiation of the anomeric proton caused the NH doublet to collapse to a singlet. Details about the synthesis of these nucleosides will be reported elsewhere.
(6) In a comparative study with 5-oxoperhydro-1,3-diazepin-2-one we initially assumed that **1** was the correct structure for squamolone (178th National ACS Meeting, Washington, D.C., Sept 1979, Division of Organic Chemistry, paper no. 96).
(7) We are indebted to Dr. Reinhard Richter and Dr. E. A. Barsa of the Upjohn Co. for suggesting **2** as the correct structure for squamolone and for providing IR and NMR spectra of *N*-alkyl-1-carbamoyl-2-pyrrolidinones.
(8) Kahr, K. Swiss Patent 380716; *Chem. Abstr.* **1965**, *62*, 16069g.
(9) Roberts, J. L.; Poulter, C. D. *J. Org. Chem.* **1978**, *43*, 1547.
(10) Paris, G.; Gandry, R.; Berlinguet, L. *Can. J. Chem.* **1955**, *33*, 1724.
(11) Weinstock, J. *J. Org. Chem.* **1961**, *26*, 3511.

Table I

compd	mp, °C	IR, cm^{-1}	NMR, δ	mass spectrum, m/z (relative intensity)
 squamolone (2)	143	3360 (s), 3250 (m), 3200 (m), 1740 (s), 1710 (s), 1680 (s), 1580 (s)	2.00 (m, 2), 2.50 (m, 2), 3.80 (t, 2, J = 7 Hz), 5.65 (br s, 1, D_2O exchanged), 8.10 (br s, 1, D_2O exchanged)	128 (30, $M^{+}\cdot$), 85 (100, M − HNCO, m* = 56.5), 56 (19), 42 (66), 30 (69)
 1	217	3200 (m), 3060 (m), 1700 (s), 1660 (m)	1.90 (m, 2), 2.50 (m, 2), 3.10 (m, 2), 3.10 (t, 2, J = 7 Hz, after D_2O), 7.55 (br s, 1, D_2O exchanged), 9.35 (br s, 1, D_2O exchanged)	128 (79, $M^{+}\cdot$), 85 (86, M − HNCO, m* = 56.5), 56 (38), 42 (80), 30 (100)

is too prolonged or during the final cyclization step. Both side reactions are catalyzed by traces of moisture in the reaction mixture. Compounds 1 and 9 proved to be very easily separable by fractional recrystallization from ethanol.

Squamolone and its diazepinedione isomer (1) have different physical properties, with the latter being more similar, as expected, to 5,6-dihydrouracil. Both 1 and dihydrouracil are high melting solids and very insoluble in chloroform. Squamolone (2) is lower melting and is extremely soluble in both chloroform and water.

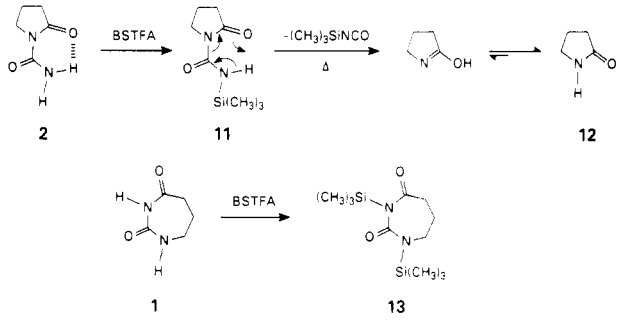
The final chemical proof of the structure of 1 was secured by its successful and very efficient conversion to the known seven-membered diazepinone 10 (tetramethyleneurea)[12] through the action of diborane in THF (Scheme II).

The complete spectral data for squamolone and 1 are shown in Table I. The IR points out an important and characteristic band for a primary hydrogen-bonded amide hydrogen at 3360 cm^{-1} in the spectrum of squamolone which is consistent with structure 2.[13] This band is absent in the spectrum of 1 as well as in the spectrum of 5,6-dihydrouracil. Another important infrared feature is the presence of a strong 1580-cm^{-1} band in the spectrum of 2 which is lacking in the spectra of both 1 and dihydrouracil. This band is possibly associated with an NH deformation band (amide II) from one of the NH_2 hydrogens.[13]

In the NMR spectra the most salient feature is the fact that both compounds show a pair of different NH resonance bands. This nonequivalence of the NH_2 hydrogens in squamolone (2) can be explained in terms of the hydrogen-bonded structure discussed earlier and it was very likely an important element in the original incorrect structural assignment of this compound as the diazepinedione 1.[3] Indeed both 1 and 5,6-dihydrouracil show two distinct NH resonances due to the imide and amide hydrogens, respectively. These bands in the spectra of 1 and 5,6-dihydrouracil are nearly superimposable.

The NMR spectra reveal another important difference with respect to the resonance of the methylene group adjacent to the nitrogen. In squamolone (2), these methylene protons appear as a triplet at much lower field than in 1. This signal at δ 3.80 is similar in chemical shift and multiplicity to the methylene resonance observed in the five-membered 2-pyrrolidinones.[7] In compound 1, the equivalent protons resonate at higher field (δ 3.10) and the signal appears as a triplet only after D_2O exchange, which is consistent with the seven-membered-ring structure. The

Scheme III



identical phenomenon is observed with dihydrouracil.

It is easy to see how the mass spectral evidence contributed to the initial incorrect structural assignment for squamolone, since the mass spectra of both compounds show a remarkable similarity. Unless the spectra are directly compared, the two isomers cannot be differentiated by this technique alone. Both compounds exhibit essentially the same fragmentation pattern, although the relative intensities of the various peaks are different. Loss of isocyanic acid (HNCO, 43 amu) from the molecular ion to form a pyrrolidinonium ion at m/z 85, which is the base peak in 2 and only slightly less intense in 1, is accompanied by a prominent metastable peak at m/z 56.5. Moreover, much of the fragmentation at lower mass can be attributed to further decomposition of this pyrrolidinonium ion, since this part of each spectrum is remarkably similar to that of 2-pyrrolidinone.[14] The immonium ion at m/z 30 is the base peak in the mass spectrum of 1 and is much more abundant than in the spectrum of squamolone (2) since fewer bonds must be broken to form this fragment. The spectrum of 1 also shows a doubly charged ion occurring at m/z 56.6 (relative intensity 2.2%) that does not occur for 2. This fragment may result from opening the diazepinedione ring with concomitant hydrogen migration to allow loss of a methyl radical to form a doubly charged species of mass 113.

Trimethylsilylation allows a more facile differentiation of the two isomers. Squamolone (2), either with excess bis(trimethylsilyl)trifluoroacetamide (BSTFA) at room temperature or with hexamethyldisilazane (HMDS) under reflux for a short time, forms only the monotrimethylsilyl derivative 11 (Scheme III). In the NMR spectrum the broad singlet corresponding to one proton of the primary amide (δ 5.65) disappears while the signal at δ 8.10, cor-

(12) Ulrich, H.; Tucker, B.; Richter, R. J. Org. Chem. 1978, 43, 1544.
(13) Bellamy, L. J. "The Infra-red Spectra of Complex Molecules"; John Wiley & Sons: New York, 1975; pp 231–250.
(14) Budzikiewicz, H.; Djerassi, C.; Williams, D. H. "Mass Spectrometry of Organic Compounds"; Holden-Day, Inc.: San Francisco, CA., 1967; pp 353–355.

responding to the deshielded hydrogen-bonded amide proton, remains almost unchanged at δ 7.80. Prolonged heating in HMDS induces a thermal elimination of (trimethylsilyl)isocyanic acid, possibly in a manner analogous to the loss of isocyanic acid seen in the electron-impact mass spectrum of underivatized **2**. The 2-pyrrolidinone (**12**) formed in this process is immediately silylated under the reaction conditions. When compound **11** is isolated after derivatization with BSTFA at room temperature, it can be rearranged by heat to yield **12**, which was identified by comparison with an authentic sample. Such a rearrangement can be easily followed by gas chromatography (see the Experimental Section). The isomeric compound **1**, on the other hand, was smoothly silylated with BSTFA at room temperature to give only the bis(trimethylsilyl) derivative **13** as determined by GC and GC/MS.

Experimental Section

General. All chemical reagents are commercially available and they were purchased from Aldrich Chemical Co. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 727B spectrometer as Nujol mulls unless otherwise specified. Proton NMR spectra were determined on a Varian T-60 instrument. Chemical shifts are given as δ values with reference to Me_4Si or deuterated sodium 3-(trimethylsilyl)propionate (TSP). Elemental analyses were carried out by the NIAMDD, NIH, and by Galbraith Laboratories, Inc., Knoxville, TN. Low-resolution electron-impact mass spectra were obtained on a Du Pont 21-492B gas chromatograph–mass spectrometer (GC/MS) system interfaced to a VG 2040 data system. Samples were introduced either by direct probe or via a Varian 2740 GC (trimethylsilyl derivatives) coupled to the mass spectrometer by a single-stage glass jet separator. For the silylated mixtures the components were separated on a 1.83 m × 2 mm i.d. glass column packed with 3% OV-17 on 100/120-mesh Gas Chrom Q and operated isothermally or temperature programmed in the range of 90–150 °C. Typical GC operating conditions employed an injector and detector temperature of 260 °C, a 30-mL/min flow rate for both helium carrier gas and hydrogen, and a 300-mL/min flow rate for air. Standard mass spectrometer operating conditions were as follows: transfer line and jet separator, 205 °C; ion source, 255 °C; electron energy, 75 eV; ionizing current, 250 μA; scan speed, 2 s/decade.

4-Ureidobutyric Acid (4). This compound was prepared in very low yield by the method of Kahr.[8] After one recrystallization from ethanol, **4** was obtained as a white solid: mp 174–175 °C (lit.[8] mp 175 °C); IR 3420, 3350, 3200, 1710, 1660 cm^{-1}; NMR (Me_2SO-d_6) δ 1.60 (q, 2), 2.10 (m, 2), 2.95 (q, 2), 5.40 (s, 2, NH_2), 5.95 (t, 1, NH). The yields of **4** improved to 30% by fusing 4-aminobutyric acid and urea at 110–112 °C for 1 h. The mixture was treated with hot ethanol and compound **4** crystallized.

1-Carbamoyl-2-pyrrolidinone (Squamolone, 2). Method A. A suspension of 2.00 g (13.7 mmol) of 4-ureidobutyric acid (**4**) in 100 mL of benzene was refluxed in the presence of 6 mL (65.4 mmol) of $POCl_3$ for 3 h. The solvent was removed in vacuo and the residue was carefully treated with a few milliliters of ice-cold water followed by extraction with twelve 10-mL portions of chloroform. The chloroform layer was dried (Na_2SO_4) and removed to leave **2** as white crystals. One recrystallization from benzene afforded 0.98 g (56%) of **2**, mp 142–143 °C (lit.[3] mp 145–146 °C).

Anal. Calcd for $C_5H_8N_2O_2$: C, 46.87; H, 6.29; N, 21.87. Found: C, 46.98; H, 6.38; N, 21.86.

Method B. A solution of 4-aminobutyric acid (**3**; 2.06 g, 20 mmol) and potassium cyanate (1.64 g, 20 mmol) in 40 mL of water was slowly evaporated at 100 °C under a stream of N_2. The syrupy residue was treated with 40 mL of 6 N HCl and the solution again evaporated to dryness at 50 °C under a stream of N_2. The solid residue was heated at 170 °C for 1 h and part of the sublimed **2** was recovered on a watch glass. The inorganic residue was then thoroughly extracted with $CHCl_3$; this solution was dried (Na_2SO_4) and evaporated to dryness to afford 1.16 g (46%) of **2**, identical with the product obtained from method A. The combined yields with the sublimed material exceeded 50%.

Glutaric Acid Monoamide (6). Glutaric anhydride (10 g, 87.6 mmol) was added cautiously to 100 mL of concentrated ammonium hydroxide at room temperature. The resulting solution was refluxed for 3 h after which it was reduced to dryness in vacuo to a thick syrup. The syrup was treated with excess cation-exchange resin (Bio-Rad AG 50W-X8) and an equivalent amount of water. The resin was then removed by filtration and the solution reduced to dryness and dried overnight in a vacuum oven at 60 °C. The solid material was recrystallized from ethyl acetate (charcoal) to give 8 g (72%) of **6** as crystals: mp 89–91 °C; IR (Nujol) 3350, 3175, 1690, 1650 cm^{-1}; NMR (Me_2SO-d_6) δ 1.70 (m, 2), 2.10 (m, 4), 6.60 (br s, 1), 7.20 (br s, 1), 11.90 (s, 1); mass spectrum, *m/z* (relative intensity) 131 (M^+·, 0.9), 113 (30), 85 (44), 72 (34), 60 (88), 59 (100), 44 (71).

Anal. Calcd for $C_5H_9NO_3$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.79; H, 6.82; N, 10.63.

Perhydro-1,3-diazepine-2,4-dione (1) and 1,3-Bis(3-carbamoylpropyl)urea (9). Glutaric acid monoamide (2 g, 15.2 mmol) was dissolved with the aid of heat in 40 mL of acetone. It was then cooled to room temperature and diisopropylethylamine (3.10 mL, 17.7 mmol) was added immediately. The reaction mixture was cooled to 0 °C and ethyl chloroformate (1.86 mL, 19.4 mmol) dissolved in 6 mL of acetone was added dropwise during the course of 15 min. Stirring at 0 °C was continued for 30 min and NaN_3 (1.5 g, 23 mmol) dissolved in 25 mL of water was added at a fast rate to the solution still maintained at 0 °C. The reaction was kept under stirring at 0 °C for 1 h after which 25 mL of water and 40 mL of ethyl acetate were added. The extraction of the acyl azide was completed with three 40-mL portions of ethyl acetate. The organic layer was dried ($MgSO_4$) for 1 h with stirring and after removal of the drying agent it was reduced to dryness in vacuo at <30 °C to yield 1.30 g (8.32 mmol) of the solid acyl azide **7** (IR 2150 cm^{-1}). The solid was immediately suspended in toluene and refluxed for 5 min. The solvent was removed in vacuo at 40 °C and the solid residue dissolved in 80 mL of freshly distilled THF (over LAH). Part of the solid remained insoluble in THF. This solid was later found to be the symmetrical urea **9** which becomes the only product if heating is prolonged for more than 5 min. In most instances this product was reduced to a minimum under anhydrous conditions and short reflux times. To the solution containing the isocyanate **8** was added 0.799 g (16.6 mmol) of NaH (50% oil suspension) and the mixture stirred for 1 h. After the careful addition of cation-exchange resin and water the resin was removed by filtration and the solution reduced to dryness to afford a solid residue. The solid was treated with hot ethanol (charcoal) and later cooled to afford a first crop (0.2 g, 11%) of shining plates corresponding to **1**, mp 215–217 °C.

Anal. Calcd for $C_5H_8N_2O_2$: C, 46.86; H, 6.29; N, 21.86. Found: C, 46.91; H, 6.20; N, 21.79.

When the original volume of the ethanolic solution was reduced in half, a second and most abundant crop (0.68 g, 38%) of the urea **9** was obtained: mp 201–202 °C; IR (Nujol) 3350, 3170, 1650, 1610, 1570 cm^{-1}; NMR (Me_2SO-d_6) δ 1.50 (m, 4), 2.00 (m, 4), 2.90 (m, 4), 5.85 (br t, 2, J = 6 Hz), 6.60 (br s, 2), 7.20 (br s, 2).

Anal. Calcd for $C_9H_{18}N_4O_3$: C, 46.94; H, 7.87; N, 24.33. Found: C, 46.90; H, 7.81; N, 24.04.

Reduction of Diazepinedione 1 to Tetramethyleneurea (10). Diazepinedione **1** (0.128 g, 1 mmol) was stirred under nitrogen at room temperature while 13 mL of a 1 M diborane solution in THF was added with the aid of a syringe. The reaction was then refluxed under nitrogen for 3 h. After the mixture cooled, 10 mL of a water–THF mixture (1:1) was added followed by 10 mL of 18% HCl. Sodium hydroxide (2.41 g) was dissolved in 10 mL of water and this solution was added slowly until a neutral pH was reached. The water and THF were removed by evaporation and the solid residue was placed in a Soxhlet extractor overnight with refluxing chloroform. A small turbidity in the chloroform solution was removed by filtration and the solution reduced to dryness to yield ~80 mg (70%) of yellowish solid which was triturated with ether and sublimed to give 30 mg of pure tetramethyleneurea (**10**), mp 165–167 °C (lit.[12] mp 166–170 °C), identical in all respects (IR, NMR, and mass spectra) with an authentic sample prepared according to Ulrich et al.[12]

Trimethylsilyation and Gas Chromatography of Squamolone (2) and Its Isomer 1. Microscale silylation was accomplished by solution of 1–2 mg of **1** or **2** in 0.45 mL of a 1:2 mixture

of BSTFA and redistilled acetonitrile at room temperature in a 3.5-mL glass screw-cap vial equipped with a Teflon-lined rubber septum. Silylated products were analyzed by GC on a 3% OV-17 column that was temperature programmed from 90 to 150 °C at 4 °C/min and then held isothermally at the upper temperature. When the injector port temperature was above 200 °C, GC analysis of silylated **2** produced three peaks with retention times of 4.1, 5.7, and 15.9 min. GC/MS analysis and comparison with authentic standards showed that the three peaks were monosilylated 2-pyrrolidinone, 2-pyrrolidinone (**12**), and *N*-(trimethylsilyl)-squamolone (**11**), respectively. Lowering the GC injector port to 190 °C or below resulted in an almost complete disappearance of the first two peaks. In the case of silylated **1** a single GC peak with a retention time of 14.8 min was observed. Silylated **1** is shown as the *N,N*-bis(trimethylsilyl) derivative **13**, since there does not appear to be significant resonance stabilization in the *O*-silyl form.[15] However, other structures for this derivative cannot be excluded.

Registry No. **1**, 75548-99-1; **2** (squamalone), 40451-67-0; **3**, 56-12-2; **4**, 2609-10-1; **5**, 108-55-4; **6**, 25335-74-4; **7**, 75506-69-3; **8**, 75506-70-6; **9**, 75506-71-7; **10**, 19055-93-7; **11**, 75506-72-8; **12**, 616-45-5; **13**, 75506-73-9; glutaric acid monoamide, 25335-74-4.

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Synthesis of Isoquinolines from Indenes[1]

R. Bryan Miller* and James M. Frincke

Department of Chemistry, University of California, Davis, California 95616

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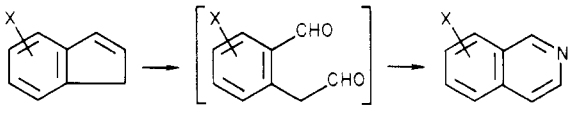
A general procedure for the synthesis of isoquinolines from appropriately substituted indenes is described. Ozonolysis of the indenes followed by reductive workup gives intermediate homophthalaldehydes which are treated with ammonium hydroxide to give the isoquinolines. This "one-pot", three-step reaction sequence was applied to the formation of all of the mono-*C*-methyl-substituted isoquinolines in a regiospecific manner. The procedure is applicable to both electron-withdrawing and electron-donating substituents on the indene system. In this manner the 6- and 7-nitro-, -bromo-, and -iodoisoquinolines were prepared.

In 1964, Fields[2] in a study of amozonolysis of cycloolefins observed that indene is ozonized in the presence of aqueous ammonia and an emulsifier to give an aldehydoamino hydroperoxide which ultimately forms the fully aromatic isoquinoline. We felt that this approach to isoquinolines would offer certain advantages to the more conventional syntheses.[3] By removing the site of heterocyclic ring formation from a position on the homonuclear ring, as it is in Bischler-Napieralski[4] and Pomeranz-Fritsch[5] syntheses, one eliminates the need for activation of that ring toward electrophilic aromatic substitution[6] and ensures regioselectivity in the isoquinoline formation. Also, the product is the fully aromatic isoquinoline and not a dihydro derivative. Since the Fields approach has received little synthetic attention,[7] we undertook a study of the synthesis of isoquinolines from indenes, and the results of that study are presented in this paper.

We chose to pursue a stepwise sequence from the indene to the isoquinoline rather than the heterogeneous procedure of Fields. Thus our general approach could be achieved from an appropriate indene via a homophthalaldehyde intermediate which upon treatment with ammonia should give the fully aromatic isoquinoline (see Scheme I).

Scheme I



Results and Discussion

Isoquinoline from Indene. The initial study to demonstrate the feasibility of our proposed procedure involved the conversion of indene to isoquinoline. It was found that treatment of a methanolic solution of indene with ozone produced a methoxyhydroperoxide[8] which was reduced with dimethyl sulfide[9] to give homophthalaldehyde. Ammonium hydroxide was added to the reaction mixture without workup, and after the mixture was allowed to stand overnight, isoquinoline was produced.

Having demonstrated that this "one-pot", three-step reaction sequence would indeed give isoquinoline from indene, we directed our efforts toward optimizing the yields. First, it was found that the dimethyl sulfide reduction of the methoxy hydroperoxide was best carried out in the presence of solid sodium bicarbonate which presumably removes any acids formed in the ozonolysis and prevents acetal formation between the homophthalaldehyde and the methanol solvent. Next, optimal reaction times were determined for both the reduction and amination steps. Choosing an arbitrary amination time of 24

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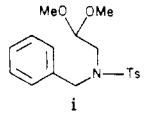

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