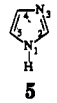
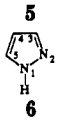
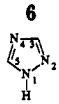
Table I. Aqueous pK_as and Calculated $\bar{I}_{S,min}$

molecule	pK_a[a]	$\bar{I}_{S,min}$[b] (eV)
 1	5.2	N: 12.45 C_3: 13.62 C_5: 13.62
 2	2.1	N: 12.85 C_4–C_5: 14.51
 3	1.1	N: 12.97 C_5: 14.12
 4	0.4	N: 13.11 C_2–C_3: 14.35 C_5–C_6: 14.35
 5	6.95	N_3: 12.14 C_4–C_5: 12.32
 6	2.52	N_2: 12.87 C_4–C_5: 12.68
 7	2.45	N_2: 12.96 N_4: 13.52
 8	2.53	N: 12.81 S: 13.05 C_4–C_5: 13.43
 9	0.8	N: 13.12 C_4–C_5: 13.27 O: 17.24
 10	-2.97	N: 13.63 C_4–C_5: 13.65 O: 16.89
 11	(-2.31)[c]	N: 13.54
 12	(-1.77)[c]	N_2: 13.46 N_1: 13.62 N_4: 13.81 C_6: 15.18 C_3: 15.51

[a] The pK_a values were determined experimentally and are taken from ref 16. [b] The locations of the $\bar{I}_{S,min}$ are indicated by designating the atom or bond above which they are found, e.g., N, C_3, C_4–C_5. When the $\bar{I}_{S,min}$ is closer to atom A in a bond than atom B, the atom closer to $\bar{I}_{S,min}$ is italic, e.g., C_4–C_5. [c] Estimated pK_a, using correlation presented in Figure 3.

positions, while, for isoxazole, they are observed above the ring nitrogen and above the C_4–C_5 bond, closer to C_4.

In Table I are listed experimentally determined pK_a values[16] for **1–10** and the locations and magnitudes of the lowest surface $\bar{I}(r)$ for molecules **1–12**; these will be designated as $\bar{I}_{S,min}$. The locations of the $\bar{I}_{S,min}$ are the points at which, on the average, the least amount of energy is required to remove an electron from the surface of the molecule; thus these sites are expected to be the most reactive toward electrophiles.

Looking first at the $\bar{I}_{S,min}$ values of the ring nitrogens, it is seen in Figure 3 that these correlate very well with the pK_as of **1–10**. The linear correlation coefficient is 0.99. The basicities of the ring nitrogens of the azines and azoles increase (as indicated by the corresponding increase in pK_a) as $\bar{I}_{S,min}$ decreases. Thus, the magnitude of the ring nitrogen $\bar{I}_{S,min}$ provides an index of its relative basicity. It is particularly noteworthy that there exists such a good correlation between a gaseous phase and a solution phase property.

The locations of the $\bar{I}_{S,min}$ associated with the ring carbons or carbon–carbon bonds are also indicative of favored sites for electrophilic attack. For example, the carbon $\bar{I}_{S,min}$ of pyridine (Figure 1) are above the β positions (C_3 and C_5), consistent with its known greater susceptibility to electrophilic attack at these carbons.[11,16] The $\bar{I}_{S,min}$ above the C_4–C_5 double bond in isoxazole is closer to C_4 (Figure 2), in agreement with the observation that the carbon β to the nitrogen is the preferred site for electrophilic attack.[16]

The relationship between experimentally determined pK_a values and ring nitrogen $\bar{I}_{S,min}$ presented in Figure 3 allows us to estimate pK_a values that have not yet been determined for members of the azine and azole families. For example, we predict the pK_as of *s*-triazine (**11**) and 1,2,4-triazine (**12**) to be -2.31 and -1.77, respectively. Thus, both triazines are expected to be much less basic than even the least basic diazine, pyrazine (**4**), which has a pK_a of 0.4.

Summary

We have computed average local ionization energies, $\bar{I}(\mathbf{r})$, on the molecular surfaces of a series of azines and azoles. The locations of the lowest values of $\bar{I}(\mathbf{r})$ on the surface ($\bar{I}_{S,min}$) indicate sites that are favored for electrophilic attack. The magnitudes of the ring nitrogen $\bar{I}_{S,min}$ correlate linearly with measured pK_as; the correlation coefficient is 0.99. This relationship provides a predictive capability for determining the aqueous acidities of molecules within the azine and azole classes. Possible extensions of this approach to other types of compounds are being investigated.

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An Efficient Synthesis of 2-Methyl-5,6,7,8-tetrahydro-4*H*-furo[2,3-*d*]azepines

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In the course of developing novel agents for the treatment of central nervous system disorders, we required an efficient synthesis of 2-methyl-5,6,7,8-tetrahydro-4*H*-furo[2,3-*d*]azepine. A survey of the literature revealed very few references to this fused ring system, and the only known synthesis[1] was impractical due to a very low overall yield.

We have developed an efficient synthesis of this fused azepine system. The key reaction is based on a Claisen

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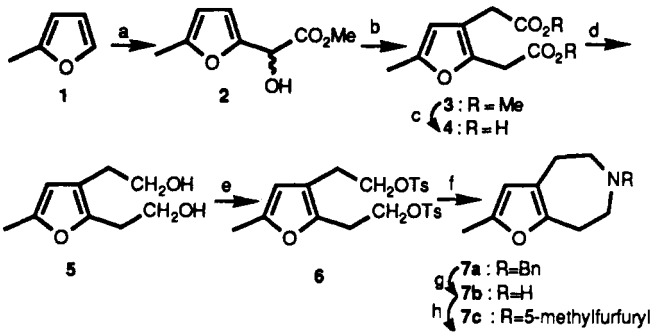
Scheme I[a]



[a] Reagents: (a) methyl glyoxalate/chloroacetic acid (75%); (b) trimethyl orthoacetate/Decalin (y/y = 1/6)/hexanoic acid (67%); (c) NaOH(aq) (92%); (d) BH_3/THF (88%); (e) TsCl/Et_3N/DMAP; (f) RNH_2/dioxane/K_2CO_3/reflux (77% from 4); (g) ACE-Cl/dichloroethane, then MeOH/reflux (75%); (h) 5-methylfurfural/4A sieves/NaOAc/$NaBH_3CN$ (75%).

ortho ester rearrangement of 2-furanglycolate **2** to give diester **3** from which the desired azepine ring skelton was formed via a few synthetic manipulations (Scheme I). The prerequisite 5-methyl-2-furoglycolic acid methyl ester (**2**) was prepared in good yield by condensing 2-methylfuran (**1**) with methyl glyoxalate[3] via a slight modification of the known procedure.[4] The Claisen ortho ester rearrangement of methyl 5-methyl-2-furanglycolate **2** requires a higher temperature than the reported procedure.[2] Specifically, the rearrangement was carried out in Decalin and trimethyl orthoacetate with a volume ratio of 6/1 so that the temperature of the reaction pot could reach 180 °C. In this manner the desired dimethyl ester **3** was obtained in 67% yield. Exhaustive hydrolysis of **3** gave the diacid **4** from which diol **5** was formed via borane reduction. Conversion of the diol **5** to the ditosylate **6** proceeded quantitatively through standard procedures. This ditosylate **6** was extremely unstable upon attempted isolation in neat form. On several occasions, the ditosylate **6** turned to black tar while on the high vacuum line to remove the last traces of solvent after column purfication. Fortunately, the compound was found to be stable if kept in solution; therefore, a 0.5 M stock solution of **6** in dioxane was prepared and this can be stored in the refrigerator for months without any significant decomposition. Azepine formation was carried out in refluxing dioxane with solid K_2CO_3 as base, adding the appropriate amines via syringe pump to afford the desired azepines **7** in good yield (75–90% from diol **5**). Dealkylation of *N*-benzylazepine **7a** with ACE-Cl[5] afforded N-unsubstituted azepine **7b** from which other substituted amines (e.g., **7c**) were synthesized via reductive alkylation with various aldehydes.[6]

In conclusion, we have developed a practical and efficient synthesis of the 2-alkylfuro[2,3-*d*]azepine skeleton. The key reaction involves a Claisen ortho ester rearrangement of 5-alkyl-2-furanglycolate with an orthoacetate. This synthetic sequence provides easy access to a series of novel 2-alkylfuro[2,3-*d*]azepine derivatives **7** in which various substitutions at the nitrogen atom of the azepine nucleus can be easily incorporated to examine structure–activity relationships.

Experimental Section

Proton magnetic resonance spectra were recorded at 300 or 500 MHz in $CDCl_3$ unless otherwise noted. Chemical shifts are reported as δ values (ppm) relative to Me_4Si as an internal standard unless otherwise indicated. Mass spectra were obtained with Hewlett Packard HP5965 (CI) and Kratos MS50 (FAB, HRMS) spectrometers. Elemental analyses and the above determinations were performed by the Analytical Research Department, Abbott Laboratories. Thin-layer chromatography (TLC) was carried out by using E. Merck precoated silica gel F-254 plates (thickness 0.25 mm). Column chromatography was carried out using Merck silica gel 60, 230–400 mesh. Melting points are uncorrected and were determined on a Thomas-Hoover melting point apparatus. Anhydrous solvents were purchased from Aldrich (Milwaukee, WI) and reactions requiring anhydrous solvents were performed under a nitrogen atmosphere. Final product solutions were dried over Na_2SO_4, filtered, and evaporated under reduced pressure on a Büchi rotary evaporator.

5-Methyl-2-furoglycolic Acid Methyl Ester (2). To a solution of freshly distilled methyl glyoxalate (16.6 g, 0.188 mol) in 2-methylfuran (55.0 mL, 0.61 mol) under a nitrogen atmosphere was added chloroacetic acid (7.1 g, 75 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight. Excess 2-methylfuran was removed under reduced pressure. The residue was diluted with diethyl ether (200 mL). The ethereal solution was carefully poured into ice-cold saturated $NaHCO_3$ (150 mL) with vigorous stirring. The organic layer was separated and the aqueous layer was further extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with saturated $NaHCO_3$ and brine, dried, filtered, and concentrated. The crude product was chromatographed (EtOAc/hexane, 1/5–1/2) to yield a waxy solid, which was recrystallized from Et_2O/hexane to give the desired compound **2** (23.9 g, 75%) as a low-melting white solid. This material decomposed slowly at room temperature and therefore should be stored in the refrigerator and used within 2 weeks of its preparation. **2**: ^1H NMR δ 2.28 (d, J = 0.7 Hz, 3 H, CH_3), 3.29 (br d, J = 5.9 Hz, 1 H, OH), 3.83 (s, 3 H, OCH_3), 5.14 (d, J = 5.9 Hz, 1 H), 5.94 (dm, J = 0.7, 3.3 Hz, 1 H, C-4H), 6.27 (d, J = 3.3 Hz, 1 H, C-3H); MS m/e 188 $(M + NH_4)^+$, 170 $(M + NH_4 - H_2O)^+$, 171 $(M + H)^+$. Anal. Calcd for $C_8H_{10}O_4 \cdot {}^1/_4H_2O$: C, 54.99; H, 6.02. Found: C, 55.19; H, 5.80.

2,3-Bis(carbomethoxymethyl)-5-methylfuran (3). To a solution of **2** (25.4 g, 0.149 mol) in Decalin (450 mL) were added trimethyl orthoacetae (76 mL, 0.597 mol) and hexanoic acid (1.9 mL, 0.015 mol) in a 1 L flask fitted with a 30-cm Vigreux column topped with a distillation head and a condenser. The reaction mixture was heated to reflux in an oil bath, and methanol was distilled by varying the bath temperature in the range 170–190 °C. More hexanoic acid was added when distillation of methanol desisted. In this manner three portions of hexanoic acid were added over the reaction course (2.0, 2.0, 4.0 mL). After 10 h, excess ortho ester was removed under reduced pressure and the Decalin layer was extracted with methanol (3 × 200 mL). The methanolic extracts were concentrated and the residue was extracted again with methanol (2 × 50 mL, 2 × 25 mL). The second batch of methanolic extracts was concentrated to give a dark orange oil (63 g). Upon refrigeration two layers formed, which were separated. The crude heavy layer (35.5 g) was chromatographed (EtOAc/hexane, 1/5–1/2) to yield the pale yellow oil **3** (22.6 g, 67%) and starting material (1.67 g, 6%): ^1H NMR δ 2.24 (d, J = 0.7 Hz, 3 H), 3.36 (s, 2 H), 3.62 (s, 2 H), 3.69 (s, 3 H), 3.71 (s, 3 H), 5.95 (br s, 1 H); MS m/e 227 $(M + H)^+$, 244 $(M + NH_4)^+$; exact mass calcd for $C_{11}H_{14}O_5$ 226.0841, found 226.0842. Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.39; H, 6.25. Found: C, 58.09; H, 6.22.

2,3-Bis(carboxymethyl)-5-methylfuran (4). To an ice-cold solution of **3** (17.4 g, 76.9 mmol) in methanol (150 mL) under a nitrogen atmosphere was added 2.0 N NaOH (80 mL) dropwise. The reaction mixture color changed from clear yellow to orange during the addition. The reaction mixture was allowed to stir at room temperature overnight. Methanol was removed under reduced pressure. The aqueous phase was acidified with 1.0 N HCl and extracted with EtOAc (3 × 300 mL). The combined

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(7) A control experiment was carried out as follows. Diol **5** (412 mg, 2.4 mmol) was carried through this two-step sequence to give *N*-benzyl analogue **7a** (450 mg) in 77% overall yield. Therefore, the individual yield of each step is 88%.

extracts were washed with brine, dried, filtered, and concentrated to give a yellow solid (13.2 g), which was recrystallized from Et_2O/hexane to yield a white solid (10.6 g, 70%): ^1H NMR δ 2.25 (d, J = 0.74 Hz, 3 H), 3.35 (s, 2 H), 3.66 (s, 2 H), 5.92 (br s, 1 H). Anal. Calcd for $C_9H_{10}O_5$: C, 54.53; H, 5.09. Found: C, 54.59; H, 5.22. Mp: 133-135 °C.

2,3-Bis(2-hydroxymethyl)-5-methylfuran (5). To an ice-cold solution of 4 (3.4 g, 17.2 mmol) in anhydrous THF (160 mL) was added a 1.0 M Borane-THF complex (86 mL) via syringe. The reaction mixture was allowed to stir in the ice-bath for 20 min and then at room temperature for 2 h. The reaction mixture was carefully poured into ice-cold saturated aqueous $NaHCO_3$; then it was extracted with EtOAc (3 × 200 mL). The combined extracts were washed with saturated $NaHCO_3$ and brine, dried, filtered, and concentrated to give a pale yellow oil. The residue was chromatographed (EtOAc) to yield diol 5 as a colorless oil (2.87 g, 98%): ^1H NMR δ 2.24 (s, 3 H), 2.47-2.60 (m, 1 H), 2.56 (t, J = 6 Hz, 2 H), 2.60-2.73 (m, 1 H), 2.80 (t, J = 6 Hz, 2 H), 3.73 (t, J = 6 Hz, 2 H), 3.82 (t, J = 6 Hz, 2 H), 5.81 (s, 1 H); MS m/e 171 $(M + H)^+$, 188 $(M + NH_4)^+$; exact mass calcd for $C_9H_{14}O_3$ 170.0943, found 170.0942. Anal. Calcd for $C_9H_{14}O_3 \cdot {}^1/_8H_2O$: C, 62.66; H, 8.34. Found: C, 62.86; H, 8.05.

2,3-Bis[2-(*p*-tosyloxy)ethyl]-5-methylfuran (6). A solution of the following composition was allowed to stir at room temperature for 48 h: 5 (2.87 g, 16.8 mmol), *p*-tosyl chloride (12.8 g, 67.1 mmol), triethylamine (9.35 mL, 67.1 mmol), and DMAP (0.10 g, 0.82 mmol) in anhydrous THF (75 mL). The reaction mixture was filtered through a fritted glass funnel (4-8 μm), rinsing the solids with Et_2O. The filtrate was concentrated to a small volume (40-50 mL) and quickly diluted with Et_2O (200 mL). The organic phase was washed with 10% citric acid (100 mL), saturated $NaHCO_3$ (2 × 100 mL), and brine, dried, and concentrtion to give a clear yellow oil (14.3 g). The crude was chromatographed (EtOAc/hexane, 1/10-1/2). The product fractions were concentrated to a volume of approximately 50 mL; then anhydrous dioxane (60 mL) was added. The volume of the solvents was reduced to about 20 mL and the solution was transferred to a flask containing K_2CO_3 (15 g). Assuming a 90% yield,[7] more dioxane (10 mL) was added to achieve a stock solution of 0.5 M concentration, which was stored in the refrigerator under nitrogen. At no time should this product be handled in fully concentrated form, whether crude or purified. The neat compound will decompose within minutes.

6-Benzyl-2-methyl-5,6,7,8-tetrahydro-4*H*-furo[2,3-*d*]azepine (7a). A mixture of K_2CO_3 (5.0 g, 36 mmol) and 6 (0.5 M stock solution, 4.4 mL, 2.2 mmol) was further diluted with anhydrous dioxane (11 mL) and heated to reflux. Benzylamine (0.82 mL, 7.5 mmol) in anhydrous dioxane (10 mL) was added via syringe pump over 2 h and the reaction mixture was heated to reflux overnight. The solids were filtered off and rinsed thoroughly with CH_2Cl_2. Volatiles were removed under reduced pressure to yield a yellow residue, which was chromatographed (EtOAc/hexane, 1/5) to give a clear yellow oil. This free base was treated with oxalic acid to form the salt, a white powder (0.68 g, 93%): ^1H NMR (DMSO-d_6) δ 2.16 (s, 3 H), 2.53-2.62 (m, 2 H), 2.84-2.92 (m, 2 H), 3.02-3.13 (m, 4 H), 4.08 (br s, 2 H), 5.87 (s, 2 H), 7.31-7.50 (m, 5 H); MS m/e 242 $(M + H)^+$. Anal. Calcd for $C_{18}H_{21}NO_5 \cdot 0.4H_2O$: C, 63.86; H, 6.49; N, 4.14. Found: C, 63.97; H, 6.26; N, 4.12. MP 127-129 °C dec.

2-Methyl-5,6,7,8-tetrahydro-4*H*-furo[2,3-*d*]azepine (7b). 1-Chloroethyl chloroformate (1.10 mL, 10.2 mmol) was added dropwise to an ice-cold solution of 7a (0.50 g, 2.1 mmol) in anhydrous 1,2-dichloroethane (14 mL). The reaction mixture was allowed to stir at room temperature for 1 h and then was washed with saturated $NaHCO_3$ (25 mL), and the aqueous phase was back-washed with CH_2Cl_2 (25 mL). The organic extracts were washed with brine, dried, filtered, and concentrated to give a clear brown oil (1.33 g). To the crude carbamate was added anhydrous methanol (14 mL), and the solution was heated to reflux for 1 h. The solvent was removed under reduced pressure and the pink residue was triturated with Et_2O to yield the hydrochloride, a pink powder (0.35 g, 90%): ^1H NMR (DMSO-d_6) δ 2.18 (s, 3 H), 2.70 (t, J = 6 Hz, 2 H), 2.99 (t, J = 6 Hz, 2 H), 3.21 (t, J = 6 Hz, 2 H), 3.22 (t, J = 6 Hz, 2 H), 5.93 (s, 1 H), 9.26 (br s, 1 H); MS m/e 152 $(M + H)^+$. Anal. Calcd for $C_9H_{14}NOCl$: C, 57.73; H, 7.54; N, 7.49. Found: C, 57.57; H, 7.49; N, 7.38. MP 204-206 °C dec.

2-Methyl-6-(5-methylfurfuryl)-5,6,7,8-tetrahydro-4*H*-furo[2,3-*d*]azepine (7c). To a mixture of 7b (100 mg, 0.53 mmol), 5-methylfurfural (80 μL, 0.80 mmol), anhydrous NaOAc (88 mg, 1.07 mmol), and dried, powdered 4A molecular sieves (0.53 g) in anhydrous methanol (2.1 mL) was added sodium cyanoborohydride (67 mg, 1.07 mmole) in one portion. The reaction mixture was allowed to stir overnight at room temperature. To the chilled reaction mixture was added 1.0 N NaOH (10 mL), and the resulting aqueous phase was extracted with Et_2O (3 × 20 mL). The extracts were washed with brine, dried, filtered, and concentrated to give a clear yellow oil. The crude oil was chromatographed (EtOAc/hexane, 1/9-1/5) to yield a clear yellow oil. This free base was treated with oxalic acid to form the salt, an off-white powder (134 mg, 75%): ^1H NMR (CD_3OD) δ 2.19 (s, 3 H), 2.32 (s, 3 H), 2.83 (t, J = 6 Hz, 2 H), 3.10 (t, J = 6 Hz, 2 H), 3.42-3.50 (m, 4 H), 4.45 (s, 2 H), 5.86 (s, 1 H), 6.12 (d, J = 3 Hz, 1 H), 6.60 (d, J = 3 Hz, 1 H); MS m/e 246 $(M + H)^+$. Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.88; H, 6.32; N, 4.18. Found: C, 60.91; H, 6.34; N, 4.16. Mp 145-147 °C.

Cyclialkylation Studies. 1. A Practical Synthetic Approach to the 2,3:6,7-Dibenzobicyclo[3.2.2]nona-2,6-diene System

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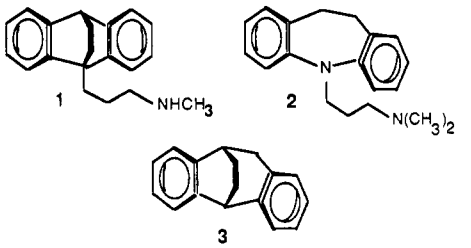
One of the useful antidepressant drugs, maprotiline (1), has a dibenzobicycloalkadiene structure, and another, imipramine (2), has a dibenzoazacycloheptadiene structure. We thought it might be interesting to synthesize molecules incorporating a structure related to both of these compounds, such as amino derivatives of 2,3:6,7-dibenzobicyclo[3.2.2]nona-2,6-diene (3).



Two very different syntheses of the tetracyclic hydrocarbon 3 have been published.[1,2] The earlier synthesis[1] affords 3 in low yield in seven steps from an expensive starting material. The later report[2] came from this laboratory as part of a study of acid-catalyzed cyclidehydrations; the formation of 3 in good yield was an unexpected observation in this study. In order to achieve a practical synthesis of derivatives of 3 with potential valuable medicinal properties, we have reexamined some of the steps in the synthesis of 3.

We now report an efficient and practical synthesis from readily available starting materials, beginning with lactone 4 (Scheme I).[3] The reduction of lactone 4 was a bottleneck for a practical synthesis. Catalytic hydrogenation was sensitive to trace impurities in the lactone and variations of Clemmensen-type reduction were attempted with little

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