H, NCH_2), 2.68 (s, 3 H, CH_3); ^{13}C NMR δ 177.7 [s, $=C(CH_3)$], 150.2 (s, C-2), 132.3 (d, Ar C), 131.4 (s, C-1), 128.7, 123.8, and 120.2 (d, Ar C), 112.5 and 112.4 (s, CN), 87.0 [s, $=C(CN)_2$], 66.9 (t, CH_2O), 52.6 (t, NCH_2), 23.7 (q, CH_3); IR (KBr) 2240 (CN) cm^{-1}; mass spectrum, m/e 253.119 (M^+, calcd 253.121). Anal. Calcd for $C_{15}H_{15}N_3O$ (M_r 253.304): C, 71.12; H, 5.97; N, 16.59. Found: C, 71.39; H, 5.93; N, 16.48.

***(trans)*-(±)-1,2,4,4a-Tetrahydro-6-methyl[1,4]oxazino-[4,3-*a*]quinoline-5,5(6*H*)-dicarbonitrile (16)** was prepared by reaction of **15** (0.51 g, 2 mmol) in 1-butanol (2 mL) in a similar way as described for **11** and **12**. Reaction time 8 h; yield 83%; mp 172–173 °C (EtOH); ^1H NMR (200 MHz, $CDCl_3$) δ 7.4–7.3 and 7.1–6.95 (m, 4 H, Ar H), 4.50 (dd, 1 H, J = 11.1 and 3.6 Hz, H-4_{eq}), 4.21 (ddd, 1 H, J = 11.7, 4.0, and 1.2 Hz, H-2_{eq}), 3.90 (ddd, 1 H, J = 11.7, 11.7, and 3.1 Hz, H-2_{ax}), 3.86 (dd, 1 H, J = 10.6 and 11.1 Hz, H-4_{ax}), 3.79 (br d, 1 H, J = 11.9, 3.1, and 1.2 Hz, H-1_{eq}), 3.67 [q, 1 H, J = 6.8 Hz, ArC*H*(CH_3)], 3.62 (dd, 1 H, J = 10.6 and 3.6 Hz, H-4a), 3.04 (ddd, 1 H, J = 11.9, 11.7, and 4.0 Hz, H-1_{ax}), 1.86 [d, 3 H, J = 6.8 Hz, ArCH(CH_3)]; ^{13}C NMR δ 143.7 (s, C-10a), 129.0, 127.3, 120.5, and 113.1 (d, Ar C), 121.3 (s, C-6a), 113.8 and 111.6 (s, CN), 68.2 and 66.6 (t, CH_2O), 57.2 (d, NCH), 45.8 (t, NCH_2), 41.4 [s, $C(CN)_2$], 40.1 [d, ArCH(CH_3)], 16.5 (q, CH_3); IR (KBr) 2260 (CN) cm^{-1}; mass spectrum, m/e 253.117 (M^+, calcd 253.121). Anal. Calcd for $C_{15}H_{15}N_3O$ (M_r 253.304): C, 71.12; H, 5.97; N, 16.59. Found: C, 71.34; H, 5.95; N, 16.53.

X-ray Crystal Structure Determination. The crystal data of compounds **9d** and **10** have been reported.[6]

Crystals of (±)-**12a** are monoclinic; space group $P2_1/n$; a = 8.000 (3) Å, b = 22.181 (6) Å, c = 9.338 (4) Å, β = 114.51 (3)°, Z = 4, d_c = 1.24 g cm^{-3}. Reflections measured with an Enraf-Nonius CAD4 diffractometer (MoKα radiation, graphite monochromator, $\omega - 2\theta$ scans, $3 < \theta < 25°$, scan width (ω) (1.0 + 0.34 tg θ)°. The structure was determined and refined by using 1195 reflections with $F_o > 3\sigma(F_o)$. The number of parameters refined was 247 [scale factor, extinction factor, positional and thermal (isotropic for H-atoms, anisotropic for others) parameters of all atoms]. The final R factor was 6.3%. As evident from Figure 1 the C atoms of the ethyl group show large thermal vibrations. Therefore H atoms could not be located for these atoms. Consequently the H atoms for these atoms have been treated as riding atoms.

Crystals of **16** belong to the triclinic space group $P\bar{1}$ with a = 8.683 (4) Å, b = 9.878 (4) Å, c = 10.070 (5) Å, α = 61.76 (3)°, β = 68.53 (3)°, γ = 61.16 (4)°, Z = 2, d_c = 1.23 g cm^{-3}. The experimental conditions were the same as for (±)-**12a**, except for the scan angle (ω), which was taken as (1.5 + 0.34 tg θ)°. The number of reflections used was 1684. The number of parameters refined was 233, and the R factor was 5.3%.

All calculations have been done with SDP.[20]

Acknowledgments. We wish to thank Prof. Dr. C. W. Hilbers (KU, Nijmegen) and the Netherlands Foundation of Chemical Research (SON) for the facilities offered and the use of the 500-MHz NMR apparatus (Nijmegen). This investigation was supported by the Netherlands Foundation of Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO).

Registry No. **1a**, 117607-29-1; **1b**, 117607-30-4; **1c**, 117607-31-5; **1d**, 117607-32-6; **2a**, 117607-14-4; **2b**, 117607-16-6; **3a**, 117607-15-5; **3b**, 117607-17-7; **4c**, 117677-84-6; **4d**, 107743-60-2; **5a**, 117607-18-8; **5b**, 117607-19-9; **7a**, 117677-85-7; **7b**, 117607-33-7; **7c**, 117677-86-8; **7d**, 107743-61-3; **8c**, 117677-87-9; **8d**, 107743-62-4; **9c**, 117677-88-0; **9d**, 107797-44-4; **10**, 107743-63-5; **11**, 117607-20-2; (±)-**12a**, 117607-21-3; (±)-**12b**, 117607-22-4; **12a**, 117677-89-1; **12b**, 117677-90-4; **13**, 117607-23-5; **14a**, 117607-24-6; **14b**, 117607-25-7; **15**, 117607-27-9; **16**, 117607-28-0; (*S*)-(+)-2-(hydroxymethyl)-pyrrolidine, 23356-96-9; (*S*)-2-(chloromethyl)pyrrolidine hydrochloride, 35120-33-3; (*S*)-2-(chloromethyl)-1-pyrrolidinecarboxylic acid phenylmethyl ester, 61350-66-1; (*R*)-2-(chloromethyl)-1-pyrrolidinecarboxylic acid phenylmethyl ester, 117607-12-2; (*R*)-2-methylpyrrolidine hydrobromide, 117607-13-3; 2-fluorobenzaldehyde, 446-52-6; 2-fluoroacetophenone, 450-95-3; (*R*)-3-ethylmorpholine, 74572-05-7; (*R*)-*N*-ethyl-α-methylbenzenemethanamine, 70811-66-4; 1-[2-(4-morpholinyl)phenyl]ethanone, 117607-26-8.

Supplementary Material Available: Lists of atomic positions, bond distances, and bond angles for compounds (±)-**12a** and **16** (8 pages). Ordering information is given on any current masthead page.

(20) Structure Determination Package; Frenz B. A. and Associates Inc., College Station, TX, and Enraf-Nonius, Delft, 1983.

Synthesis of 1,2-Dihydro-1-oxo-3*H*-3-benzazepine and 3-Acyl Derivatives

Rodney C. Schnur* and Randall J. Gallaschun

Central Research, Pfizer Inc., Groton, Connecticut 06340

Received May 23, 1988

Facile preparation of 1-oxo-1,2-dihydro-3*H*-3-benzazepine, **1**, is afforded by an unusual base-induced oxidative elimination of 1-oxo-3-sulfonyl-1,2,4,5-tetrahydro-3*H*-3-benzazepines **6**. This unstable eneamino–ketone can be isolated and characterized as an oil or derivatized after in situ generation. A series of 3-acyl derivatives of **1** were prepared. The chemistry of these derivatives and the mechanism of reaction for their formation is discussed. Molecular mechanics calculations of **1** and related tautomers were neither consistent with the favored tautomer observed experimentally nor predictive of a mechanistic pathway for its formation.

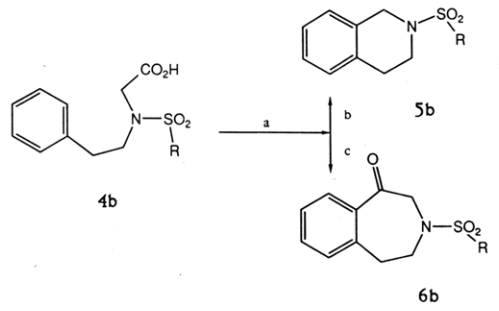
We report the first isolation and derivatization of the unstable parent 1,2-dihydro-1-oxo-3*H*-3-benzazepine, **1**.[1] Its formation occurs via the facile oxidative elimination of sulfinate from sulfonamide with subsequent hydrogen rearrangement and results in introduction of functionality into the unactivated carbons of a tetrahydroazepine ring. This remote functionalization provides access to unique preparative opportunities for a number of biologically important natural or unnatural products containing the benzazepine ring system, e.g. antitumor alkaloids of the cephalotaxine class.[2]

(1) For reviews on azepines, see: Smalley, R. K. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 7, pp 491–546. Proctor, G. R. In *Chemistry of Heterocyclic Compounds*; Rosowsky, A., Ed.; John Wiley and Sons: New York, 1984; Vol. 43, pp 696–737.

(2) For syntheses of the cephalotaxine antitumor compounds, see: Mikolajczak, K. L.; Smith, C. R., Jr. *J. Org. Chem.* **1978**, *43*, 4762. Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507. Tiner-Harding, T.; Ulrich, J. W.; Chiu, F.-T.; Chen, S.-F.; Mariano, P. S. *J. Org. Chem.* **1982**, *47*, 3362. Hiranuma, S.; Shibata, M.; Hudlicky, T. *J. Org. Chem.* **1983**, *48*, 5321.

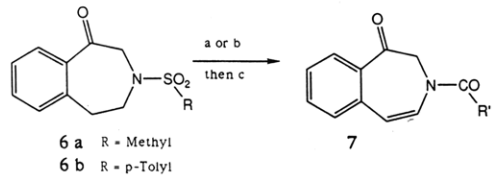
0022-3263/89/1954-0216$01.50/0

Scheme I. Cyclization of *N*-Phenethylglycines[a]



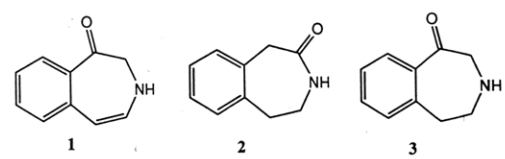
[a] R = 4-tolyl; (a) $SOCl_2$; (b) $AlCl_3$ at 0–20 °C; (c) $AlCl_3$ at −40 °C.

Scheme II. Synthesis of 3-Acyl-1,2-dihydro-1-oxo-3*H*-3-benzazepines[a]



[a] (a) KO-t-Bu, 18-crown-6, THF; (b) NaH, DMF; (c) R′N=C=O or R′COCl.

Compounds **1–3** are members of a series of parent 3-benzazepines with varying oxidation states at proximal carbons of the azepine ring. The chemistry of 3-benzazepines originates with the investigations of von Braun in 1925 and his synthesis of the amide 2-oxo-1,3,4,5-tetrahydro-2*H*-3-benzazepine, **2**.[3] His later attempts to prepare the parent 1-oxo-3-benzazepine **3** involved cyclizing *N*-phenethyl-*N*-tosylglycine, **4b**, but led only to the *N*-tosylisoquinoline derivative **5b** and not benzazepine **6b**.[4] Subsequent successful efforts to prepare 3-benzazepines conducted by numerous investigators involved compounds with an sp^2 center at the 2- (or 4-) position of the seven-member ring.[5] Proctor was the first to observe the formation of the long-sought 1-oxo examples of 3-benzazepines with the isolation of trace amounts of **6b** as a side product in the Friedel–Crafts cyclization of **4b** carried out at 0 °C (where again the major product was isoquinoline **5b**).[6] Attempts to prepare the parent **3** were frustrated further by the chemical sensitivity of the amino–ketone. Hazebroucq's development of an improved low-temperature Friedel–Crafts reaction with **4b** that afforded only **6b**[7] was instrumental in enabling Proctor to succeed finally in preparing parent **3** in 1975. However, to achieve the simple saponification product he employed a sequence of transformations including reduction, hydrolytic detosylation, N-protection, oxidation, and then deprotection to obtain **3**.[8]



(3) Von Braun, J.; Reich, H. *Justus Leibigs Ann. Chem.* **1925**, *445*, 225. Von Braun, J.; Reich, H. *Chem. Ber.* **1925**, *58*, 2765.
(4) Von Braun, J.; Bayer, X. *Chem. Ber.* **1927**, *60*, 1262.
(5) Reviewed in 1966; Hazebroucq, G. *Ann. Chim.* **1966**, *254*, 221.
(6) Proctor, G. R.; Thomson, R. H. *J. Chem. Soc.* **1957**, 2303.
(7) For the methanesulfonamide preparation: Hazebroucq, G.; Gardent, J. *Bull. Soc. Chim.* **1971**, *11*, 3985. For the toluenesulfonamide preparation: Hazebroucq, G.; Gardent, J. *Compt. Rend.* **1963**, *257*, 923.
(8) Lennon, M.; McLean, A.; Proctor, G. R.; Sinclair, I. W. *J. Chem. Soc., Perkin Trans. 1* **1957**, 624. See ref 10.

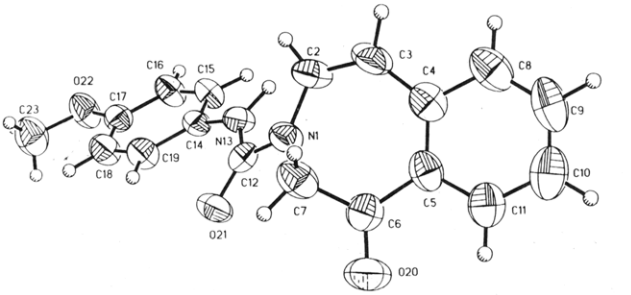
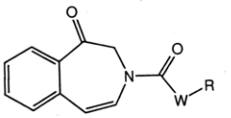


Figure 1. ORTEP drawing of the X-ray structure of compound **7c**.

Table I. 3-Acyl Derivatives of 1



7a–k

compd	R	W	mp, °C	% yield	method[a]
7a	phenyl	NH	197–198	69	E[b]
7b	4-CH_3-phenyl	NH	179–180	66	T
7c	4-OCH_3-phenyl	NH	145–146	66	E
7d	3-CF_3-phenyl	NH	209–210	37	E
7e	2-OC_2H_5-phenyl	NH	119–121	70	E
7f	2-CO_2CH_3-phenyl	NH	171–172	48	E
7g	2,4-$(CH_3)_2$-phenyl	NH	156–158	69	E
7h	$N(CH_3)_2$	bond	119–121	34	C
7i	OC_2H_5	bond	92–92.5	19	C/H[b]
7j	CH_3	bond	65–67	17	C[b]
7k	4-F-phenyl	bond	82–84	22	C/I

[a] The method of preparation employed $KOC(CH_3)_3$ as the base and **6a**. [b] The method of preparation used NaH as base and **6b**. Crystallization solvents are E = ethanol, T = toluene, C = compounds were purified by column chromatography on silica gel eluted with 1:1 ethyl acetate/hexanes and then crystallized where indicated; H = hexanes; I = isopropyl ether.

Our synthetic objective was to prepare 2-acylated derivatives of **3** and embrace a strategy of acylating intermediate **6** rather than the chemically sensitive **3**. The attempted acylation of **6b** by treatment with sodium hydride/DMF and an aryl isocyanate yielded a product retaining its 2-CH_2 group but missing the tosyl group. In addition, the new product incorporated two new functionalities, the desired new acyl group and a double bond. When 4-methoxyphenyl isocyanate was used as the acylating agent, the structure of the product was *N*-(4-methoxyphenyl)-1,2-dihydro-1-oxo-3*H*-3-benzazepine-3-carboxamide, **7c** (Scheme II). Proof of structure was confirmed by X-ray analysis of **7c**, Figure 1.[9]

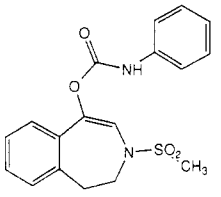
The base-induced oxidative elimination of **6** could be accomplished under a variety of procedures incorporating strong bases such as hydride or alkoxide. Thin-layer chromatography (TLC) monitoring of the reaction mixture revealed an intermediate, shown later to be **1**, which, though unstable, could be isolated. The oil **1** was most efficiently made from **6a** by using 2 equiv of potassium *tert*-butoxide and 1 equiv of 18-crown-6 in THF at 64 °C for a few minutes. Careful temperature control was required to induce elimination of the methanesulfinic acid residue and prevent decomposition of **1** in the strongly basic medium. Heating at higher temperatures or for extended periods at the elimination step resulted in decomposition products.[10] When 1 equiv of strong base was

(9) We gratefully acknowledge Dr. Jon Bordner of Central Research, Pfizer, Inc., for performing X-ray crystallographic analyses.

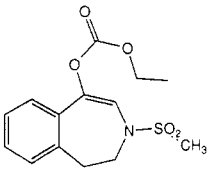
used the product yield was about 50% and starting material was recovered. The use of butyllithium in ether gave only a trace of elimination product along with recovered starting material and several new uncharacterized species. Omission of the cation complexing agent in the THF reaction also resulted in trace sulfinate elimination. Attempts to effect the elimination failed with weaker bases, e.g. 4-(*N*,*N*-dimethylamino)pyridine (DMAP). Thus refluxing **6a** and DMAP in THF gave only unreacted starting material, and when acylating agents were incorporated in these reactions, O-acylated products, e.g. **8** and **9**, were obtained.

Table I shows the products, **7a–k**, resulting from the reaction of benzazepines **6a** or **6b**, strong base, and various substituted aromatic isocyanates (**7a–g**) or acyl halides (**7h–k**). As judged by TLC and NMR analyses of crude reaction mixtures, conversion of the benzazepine to 3-acyl derivatives was uncomplicated by side reactions arising from the benzazepine intermediate under the mild butoxide conditions described above, although when isocyanates were used in the reactions, the formation of carbanilide type side products was observed. Thus, the moderate yields reported in Table I are not optimized and reflect difficulties experienced in purification and recrystallization of products.

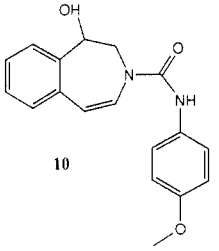
Acylation products, **7**, behaved conventionally in their reduction chemistry. Thus the double bond of **7a** could be cleanly reduced catalytically in alcohol to give **11** while selective hydride reduction of the ketone **7c** with $LiAlH_4$ led to **10**.



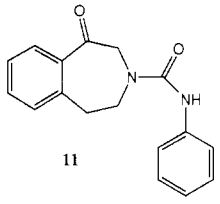
8



9



10



11

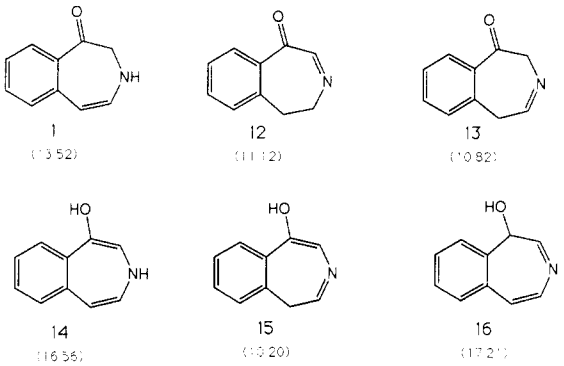
Several steps in the reaction mechanism leading to **1** from **6a** are precedented in the literature or implicated in our experimental results; however, there are still ambiguities. These are addressed below.

The first step in the transformation of **6a** to **1** must be the formation of the enolate of **6a**. When anion formation does not occur, as in the treatment of **6a** with DMAP at elevated temperatures, no sulfinate elimination was observed. Results from Negishi's laboratory[11] suggest that a stabilized anion is required for oxidative desulfonylation to occur. He has shown that with piperidine and piperazine sulfonamides, methylene groups adjacent to the nitrogen must be activated, for example by phenyl or carbonyl substitution, in order for oxidative desulfonylation to occur even in the presence of sodium hydride.[11,12]

(10) Compound **1** appears to be less stable than **3**, which survives 7 days in ethanol at room temperature.

(11) Negishi, E.; Day, A. R. *J. Org. Chem.* **1965**, *30*, 43.

Chart I. AMPAC **Heats of Formation of Benzazepines (kcal/mol)**



1 (-3.52) **12** (11.12) **13** (10.82)

14 (-16.56) **15** (-3.20) **16** (-17.21)

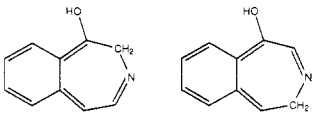
Once formed, the tetrahydrobenzazepine enolate anion readily eliminates sulfinate to yield the dihydro derivative **12**. Chart I shows three possible ketones and the related enol tautomers that could result directly or indirectly from this elimination.[13] Facile sulfinate elimination from 3-benzazepine anion was observed also by Proctor when he isolated the 2-methoxy derivative of **12**.[14] However, the presence of the 2-methoxy group conferred remarkable stability since Proctor was able to vacuum distill his derivative at 150 °C without significant decomposition or isomerization. In our example the α-imino ketone **12** is not stable in either neutral or basic media. Its conversion into **1** could proceed by either proton tautomerizations or by 1,5-hydrogen rearrangement.

Our experimental results indicate that the γ proton (at the 4-position) of **12** is acidic and either this anion or one of its isomers is more readily formed than the anion of ketone **6a** since 1 equiv of base gave approximately 50% **1** and 50% recovered **6a**. Two reaction pathways are resonable leading from the γ anion of **12** to **1**: either, upon quenching the reaction mixture, a series of proton shifts in aqueous base may occur leading to **1** or the conjugated anion of **12** (or **15**), formed in the strongly basic medium, may undergo a sigmatropic 1,5-H shift resulting in the amide anion of **1**. Such 1,5-hydrogen shifts are well precedented in monocyclic azepine[15] and diazepine chemistry[16] but have not yet been definitively shown in 3-benzazepine chemistry.

Unfortunately neither these literature precedents nor our experimental results including molecular mechanics calculations permit definition of a particular reaction

(12) While our data on oxidative desulfonylation eliminations are not definitive of mechanism they suggest that the elimination is of the (E1) anion type rather than one of the bimolecular eliminations. For reviews on syn- and anti-tosylate eliminations and effects of solvent and base upon mechanism, see: Bartsch, R. A.; Zavada, J. *Chem. Rev.* **1980**, *80*, 453. Sicher, J. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 200.

(13) The 2-H and 4-H benzazepines below appear less likely enol tautomers since their AMPAC formation energies are 26.54 and 28.54 kcal/mol, respectively.



A **B**

(14) McKay, W. R.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2435.

(15) See ref 1, pp 506–507. Vogel, E.; Brocker, U.; Junglus, H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1015. Vogel, E.; Altenbach, H.-J.; Drossard, J.-M.; Schmickler, H.; Stegelmeier, H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1016. Carstensen-Oeser, E. *Ber Dtsch. Chem. Ges.* **1972**, *105*, 982. Padwa, A.; Smolanoff, J.; Tremper, A. *J. Org. Chem.* **1976**, *41*, 543. Hassner, A.; Anderson, D. J. *J. Org. Chem.* **1974**, *39*, 3070.

(16) Rothenberger, Otis J.; Moore, J. A. *J. Org. Chem.* **1972**, *37*, 2797.

pathway from **12**. Thermodynamic stabilities of monocyclic azepines have been reported to exhibit the order of 3-H > 4-H > 2-H > 1-H.[15] The least stable 1-H isomer of the monocyclic azepines corresponds to the observed 3-H isomers in the bicyclic case. Since the stability pattern observed in the monocyclic system, where 1,5-H shifts are well precedented, is not reflected in the bicyclics, we performed molecular mechanics calculations on the ketones and enols as a means of rationalizing the experimental results based upon thermodynamic stabilities. The results of those calculations are shown in Chart I.

Molecular mechanics calculations were performed on ketones **1**, **12**, and **13** and their enols **14–16** (Chart I) by using the AMPAC[17] program, which yields heats of formation (energy minimization done in the AMPAC program). Ketone **1** observed experimentally has the highest calculated energy among the first three. Calculations on enols **14–16** (1-hydroxy-3-benzazepines) afforded heats of formation where the structure most likely to yield **1** directly, i.e. **14**, has a relatively high heat of formation. Thus calculated relative stabilities in conjunction with experimental observations suggest that **1** may be a kinetic product, and experimental results obtained thus far are insufficient to provide guidance for favoring a mechanism involving either the equilibrium-driven proton tautomerizations or the sigmatropic 1,5-H migrations leading to **1**.[18] Attempts to further define the mechanism by observing the 1,5-sigmatropic rearrangements of congeners of **6**, for example the 5,5-dideuterio, 5,5-dimethyl, or 5,5-diphenyl analogues, will be the subject of further research.

Experimental Section

All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by the Pfizer Central Research microanalysis laboratory, and results obtained for specified elements are within ±0.4% of the theoretical values (hydrates incorporated as indicated) unless otherwise noted. IR spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer with the stipulated solvents and are reported in reciprocal centimeters. ^{1}H NMR spectra of $CDCl_3$ or $(CD_3)_2SO$ solutions [$(CH_3)_4Si$ as internal standard] were recorded on a Varian A-60, a Perkin-Elmer T-60, or a Brucker 250 spectrometer. High-resolution mass spectral data were recorded on an AEI MS-30. Low-resolution mass spectral data were recorded on a Hitachi RMU6-E spectrometer. For column chromatography, silica gel (Woelm), 0.032–0.063 mm (Universal Scientific Inc.), was used.

1,2-Dihydro-1-oxo-3*H*-3-benzazepine (1). Compound **6a** (1.0 g, 4.18 mmol) and 18-crown-6 (Aldrich, 1.105 g, 4.18 mmol) were dissolved in 30 mL of dry distilled THF and reacted with potassium *tert*-butoxide (0.938 g, 8.36 mmol). The solution was heated to 64 °C (internal temperature) by immersion in a preheated (77 °C) oil bath, cooled to 35 °C, and treated with 5 mL of saturated NH_4Cl, neutralized to pH 7 with 1 N NaOH. After being stirred for 5 min, the mixture was filtered, evaporated in vacuo, diluted with 500 mL of H_2O, and extracted with 2 × 250 mL of EtOAc. The pooled organic layers were washed with 2 × 100 mL H_2O and brine, dried ($MgSO_4$), filtered, and evaporated in vacuo, yielding **1** as a yellow oil that was 90–95% pure by NMR (0.55 g, 82.7%): ^{1}H NMR ($CDCl_3$) δ 3.67 (d, CH_2, J = 3 Hz), 5.10 (br d, NH), 5.43 (dd, H-5, J = 8 and 1 Hz), 6.58 (app dd, H-6), 7.06 (app t, H-7), 7.23 (d, H-4, J = 8 Hz), 7.37 (app t, H-8), 7.98 (dd, H-9, J = 7 and 1 Hz); ^{13}C NMR ($CDCl_3$) δ 54.9, 102.4, 122.8, 129.7, 130.2, 132.5, 134.6, 137.3, 139.7, 188.3; *m/e* 159.0665 (calcd 159.0684).

N-(4-Methoxyphenyl)-1,2-dihydro-1-oxo-3*H*-3-benzazepine-3-carboxamide (7c) [Potassium *tert*-butoxide procedure]. 3-(Methylsulfonyl)-1-oxo-1,2,4,5-tetrahydro-3*H*-3-benzazepine,[7] **6a** (1.0 g, 4.18 mmol), and 18-crown-6 (Aldrich, 1.105 g, 4.18 mmol) were dissolved in 30 mL of dry distilled THF and reacted with potassium *tert*-butoxide (0.938 g, 8.36 mmol). The solution was heated to 64 °C (internal measurement) by immersion into a preheated (77 °C) oil bath for 3–5 min. The resulting mixture was cooled to 35 °C and treated with *p*-methoxyphenyl isocyanate (0.498 g, 4.18 mmol) by dropwise addition. After 5 min the reaction mixture was quenched by pouring into 8.5 mL of 1 N HCl and extracted with 2 × 250 mL of EtOAc. The pooled organic layers were washed with 3 × 100 mL of H_2O and brine and 2 × 100 mL of 5% $NaHCO_3$, dried ($MgSO_4$), filtered, and evaporated in vacuo to an orange-yellow solid, 1.19 g. The crude product was purified of carbanilide by recrystallization from anhydrous EtOH to give **7c** (0.775 g, 66%): mp 145–146 °C; ^{1}H NMR ($CDCl_3$/DMSO) δ 3.78 (s, CH_3), 4.42 (s, CH_2), 5.90 (d, H-5, J = 8 Hz), 6.65–7.4 (m, 8 H, aromatic and vinyl), 8.0 (d, H-9, J = 7 Hz); IR ($CHCl_3$) 1693 (s), 1631 cm^{-1} (s). Anal. Calcd for $C_{18}H_{16}N_2O_3 \cdot {}^1/_4H_2O$: C, 69.11; H, 5.32; N, 8.95. Found: C, 69.12; H, 5.26; N, 8.93.

Ethyl 1,2-Dihydro-1-oxo-3*H*-3-benzazepine-3-carboxylate (7i) [Sodium hydride procedure]. Sodium hydride (50% oil dispersion) (0.602 g, 12.54 mmol), in a 250-mL, three-neck, round-bottom flask fitted with a magnetic stirring bar and a gas inlet connected to a bubbler, was washed free of its oil with 3 × 50 mL of hexanes. To the dry sodium hydride was added 11 mL of dry DMF followed by **6b** (1.0 g, 4.18 mmol) in one portion. After hydrogen gas evolution had ceased (20 min), ethyl chloroformate (0.8 mL, 8.36 mmol) was added dropwise. The mixture was stirred for 10 min, quenched onto 20 mL of 1 N HCl, and extracted with 2 × 250 mL of H_2O, 2 × 100 mL of 5% $NaHCO_3$, and 1 × 200 mL of brine, dried ($MgSO_4$), filtered, and evaporated in vacuo to a red-brown oil. Flash chromatography of the oil with 100 g of silica gel eluted with 15% EtOAc/hexanes yielded a tan solid, which was recrystallized from hexanes to give pure **7i** (0.18 g, 18.6%): mp 92.0–92.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.2 (t, CH_3, J = 7 Hz), 4.3 (q, CH_2, J = 7 Hz), 4.4 (s, CH_2), 5.9 (d, H-5, J = 8 Hz), 7.0–7.5 (m, 4 H, aromatic and vinyl), 8.1 (dd, 1 H, J = 8 and 1 Hz); IR ($CHCl_3$) 1724 (s), 1684 (s), 1639 cm^{-1} (s). Anal. Calcd for $C_{13}H_{13}NO_3 \cdot {}^1/_4H_2O$: C, 66.23; H, 6.06; N, 5.94. Found: C, 65.99; H, 5.57; N, 5.89.

Conditions for O-Acylation of 6a Yielding 8. Compound **6a** (1.00 g, 4.18 mmol) and (dimethylamino)pyridine (1.02 g, 8.36 mmol) were dissolved in 2 mL of DMF at room temperature. Phenyl isocyanate (0.50 g, 4.18 mmol) was added, and after 16 h the reaction mixture was extracted with 100 mL each of ethyl acetate and water. The organic fraction was washed with 2 × 50 mL of 1 N HCl and 100 mL of brine, dried with $MgSO_4$, and evaporated in vacuo to a residue. Column chromatography on silica gel eluted with 50% ethyl acetate/hexane afforded 0.27 g of **8** (18%): mp 148–151 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.96 (s, CH_3), 3.18 (app t, CH_2), 3.93 (app t, CH_2), 7.03 (s, H-2), 7.05–7.6 (m, aromatic, 9 H); IR (KBr) 1740 (s, sh) 1705 cm^{-1} (s); *m/e* 358.1223 (calcd 358.1178).

Ethyl 4,5-Dihydro-3*H*-3-benzazepin-1-yl Carbonate 9. Compound **6a** (1.0 g, 4.18 mmol) and 4-(dimethylamino)pyridine (1.02 g, 8.36 mmol) were dissolved in 2 mL of dry DMF. The solution was treated with a dropwise addition of ethyl chloroformate (0.399 mL, 4.18 mmol), and after being stirred for 30 min, the mixture was quenched by pouring into 100 mL of H_2O and 100 mL of EtOAc. The organic layer was washed with 2 × 50 mL of 1 N HCl and 1 × 50 mL of brine, ($MgSO_4$), filtered, and evaporated in vacuo to a light tan solid, 1.25 g. The crude solid was recrystallized from isopropyl ether, which yielded white crystals, **9** (0.99 g, 76%): mp 103–104 °C; ^{1}H NMR ($CDCl_3$) δ 1.3 (t, CH_3, J = 8 Hz), 2.85 (s, CH_3), 2.9–3.2 (m, CH_2), 3.7–3.9 (m, CH_2), 3.95–4.35 (m, CH_2), 6.9–7.2 (m, 5H); IR ($CHCl_3$) 1763 (s), 1717 cm^{-1} (s). Anal. Calcd for $C_{14}H_{17}NO_5S$: C, 54.01; H, 5.50; N, 4.50. Found: C, 54.23; H, 5.52; N, 4.51.

1-Oxo-*N*-phenyl-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxamide (11). Compound **7a** (0.52 g, 1.86 mmol) was slurried in 50 mL of anhydrous EtOH and treated with 5% Pd/C (0.050 g). The mixture was hydrogenated at atmospheric pressure at 75 °C for 24 h, filtered through Celite, and evaporated in vacuo

(17) AMPAC calculation were performed using the program of Dewar. Dewar, M. J. S. QCPE (AMPAC) **1986**, 506.

(18) MMP2 calculations of the three dihydro-1-oxo-3-benzazepines, **1**, **12**, and **13**, are consistent with the experimental observations, **1** having the lowest strain energy (18.48 kcal/mol). Compounds **12** and **13** have 18.98 and 21.74 kcal/mol, respectively. Calculations were performed using the program of Allinger, N. L.; Yuh, Y. H. QCPE **1981**, 395.

to a yellow solid, 0.55 g. Flash chromatography of the solid with 50 g of silica gel, eluted with 25% EtOAc/hexanes, yielded, after recrystallization from toluene, light yellow crystals of **11** (.072 g, 13%): mp 189–191 °C. Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.28; H, 5.86; N, 10.39.

1-Hydroxy-*N*-(4-methoxyphenyl)-1,2-dihydro-3*H*-3-benzazepine-3-carboxamide (10). Compound **7c** (0.50 g, 1.62 mmol) was dissolved in 4 mL of dry distilled THF and treated with $LiAlH_4$ (0.092 g, 2.43 mmol) dissolved in 10 mL of dry distilled THF by dropwise addition. After 1 h the mixture was quenched by addition of 0.192 mL of H_2O, 0.192 mL of 15% NaOH, and 5.76 mL of H_2O (stirred for 5 min between each addition), filtered, and evaporated in vacuo to a light yellow-white solid, 0.46 g. The solid was recrystallized with 30 mL of anhydrous EtOH, which yielded a white solid, **10** (0.293 g, 58.3%): mp 213–215 °C. Anal. Calcd for $C_{18}H_{18}N_2O_3 \cdot {}^1/_2H_2O$: C, 68.67; H, 5.92; N, 8.90. Found: C, 69.08; H, 5.79; N, 8.88.

Acylation of 1 To Yield 7c. Sodium hydride (60% oil dispersion) (0.075 g, 3.14 mmol), in a 25-mL, three-neck, round-bottom flask fitted with a magnetic stirring bar and a gas inlet connected to a bubbler, was washed free of its oil with 3 × 10 mL of hexanes. To the dry sodium hydride was added 5 mL of dry DMF and **1** (0.499 g, 3.14 mmol). After hydrogen evolution had ceased (20 min), 4-methoxyphenyl isocyanate (0.468 g, 3.14 mmol) was added. The mixture was stirred for 1 h, quenched onto 10 mL of HCl, and extracted with 3 × 100 mL of EtOAc. Pooled organics were washed with 3 × 100 mL of H_2O and brine, dried ($MgSO_4$), filtered, and evaporated in vacuo to a yellow brown oil. Flash chromatography of the oil using 70 g of silica gel eluted with 35% EtOAc/hexanes yielded a yellow solid, **7c** (0.23 g, 23.8%): mp 144–146 °C.

X-ray Crystallographic Analysis of 7c. A large plate crystal of **7c** was obtained by recrystallization from EtOH: $C_{18}H_{16}N_2O_3$; space group $P21/n$; cell constants a = 9.530 (2) Å, b = 27.557 (7) Å, c = 11.924 (2) Å, β = 98.05 (1), z = 8. Lattice constants and intensity data were measured by using graphite-monochromated Cu Kα on a Nicolet R3m/u diffractometer. A total of 3184 unique reflections were observed. The structure was solved by the SHEXTL system and refined to a final R value of 0.065.[8]

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Supplementary Material Available: Cartesian coordinates for the initial and optimized geometries of compounds **1** and **12–16**, as well as the atomic coordinate table for the crystallographic structure, **7c** (28 pages). Ordering information is given on any current masthead page.

Chemistry of the Pyrrolo[3,4-*c*]pyrido[2,3-*d*]pyrimidine System. Synthesis of 6,7-Dihydropyrrolo[3,4-*c*]pyrido[2,3-*d*]pyrimidines, a Novel Ring System with Potential Biological Interest

Tsann-Long Su* and Kyoichi A. Watanabe

Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Division of Graduate School of Medical Sciences, Cornell University, New York, New York 10021

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Two 6,7-dihydropyrrolo[3,4-*c*]pyrido[2,3-*d*]pyrimidines, which contain a novel tricyclic ring system of potential biological interest, were synthesized. 6-(2,5-Dimethoxyphenyl)-6,7-dihydropyrrolo[3,4-*c*]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3a**) was prepared from a pyrido[2,3-*d*]pyrimidine. 6-(Acetoxymethyl)-5-methylpyrido-[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**4**) was oxidized with SeO_2 to the corresponding 5-formyl derivative **5**, which was condensed with 2,5-dimethoxyaniline to form the Schiff base. Reduction of the exocyclic azomethine double bond of the Schiff base with $NaBH_3CN$ to **6** followed by thermal cyclization afforded **3a**. 2,4-Diamino-6-(4-methoxyphenyl)-6,7-dihydropyrrolo[3,4-*c*]pyrido[2,3-*d*]pyrimidine (**3b**) was synthesized by addition of a pyrimidine ring to the dihydropyrrolo[3,4-*c*]pyridine system. 1-(4-Methoxyphenyl)pyrrolidin-3-one (**18**) was condensed with malononitrile to give a Knoevenagel adduct **19**. Treatment of **19** with (*N*,*N*-dimethylamino)methylene chloride in the presence of LDA afforded the 4-[(*N*,*N*-dimethylamino)methylene]pyrrolidine derivative **20**, which was converted into 6-amino-7-cyano-2,3-dihydropyrrolo[3,4-*c*]pyridine (**21**) by treatment with NH_3/MeOH. Cyclization of **21** with *N*,*N*-dimethylguanidine afforded the desired **3b** in high yield.

Chemistry of the pteridine system has been studied extensively since this system is found in the vitamin folic acid (**1**, Figure 1). Folic acid is the essential cofactor in the de novo synthesis of thymidylate and hence DNA. During the biosynthesis of thymidylate, folic acid is converted into 5,10-methylenetetrahydrofolic acid (**2**), which donates a one-carbon unit to 2′-deoxyuridylic acid. Synthesis of derivatives of the hitherto unknown 6,7-dihydropyrrolo[3,4-*c*]pyrido[2,3-*d*]pyrimidine ring system (**3**, Figure 1) has been attempted[1-5] since such derivatives are

* To whom correspondence should be addressed at Laboratory of Organic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY 10021.

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