

Randall J. Gallaschun and Rodney C. Schnur*

Medicinal Chemistry, Central Research, Pfizer, Inc.,
Groton, CT 06340

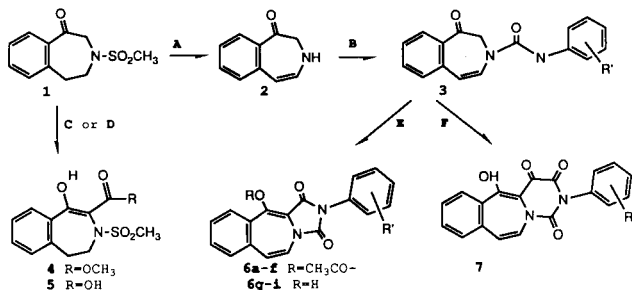
Received October 24, 1989

Two novel tricyclic ring systems derived from 3-benzazepines were synthesized; the first, a 6,7,5-ring, 1*H*-imidazo[5,1-*b*][3]benzazepine-1,3(2*H*)-dione was obtained using an unusual Stiles reaction while the second, an analogous 6,7,6-ring, pyrimido[6,1-*b*][3]benzazepine-1,3,4(2*H*)-trione was prepared with base and oxalyl chloride.

J. Heterocyclic Chem., **27**, 963 (1990).

In our recent paper [1] we reported the synthesis of novel 1,2-dihydro-1-oxo-3*H*-3-benzazepine (**2**) and its 3-acyl derivatives **3**. Herein we describe the observation and use of an unusual Stiles/Finkbeiner reaction [2] of magnesium methyl carbonate on 1-oxo-3-benzazepines **1** and **3** to afford 2-carbonyl substituted derivatives. We have employed this unexpected magnesium methyl carbonate reaction to gain access to polycyclic heterocycles which were previously unknown. Its use, aimed at similar objectives, has precedence in Danishefsky's synthesis of camptothecin precursors [3].

Scheme 1



A, 2 eq. K-O-t-Bu, 1 eq. 18-c-6, THF, NH₄Cl quench, 65°C, 3-5 min; B, 1 eq. R-N-C=O; C, 3 eq. MMC, 9 eq. AcCl; D, 3 eq. MMC, H₂O; E, 4 eq. MMC, DMF, 120°C, 1.5 hr, then 10 eq. AcCl, 0°C, (then 1 eq. 6*N* NaOH, MeOH, rt, 3 hr, for R=H); F, 3 eq. K-O-t-Bu, 1.1 eq. oxalyl chloride, THF 50°C.

In Stiles' original work on intramolecular chelation with magnesium methyl carbonate, chelates of aliphatic ketones were converted after quenching with water to the β -keto acids [2a]. The intermediate chelate in this reaction was found to be superior for mono-alkylation reactions. Finkbeiner found that hydantoin treated with methyl magnesium carbonate (MMC) gave similar chelates [2b] but that the 5-carboxy derivatives decarboxylated readily to return the starting materials. However, treatment of the hydantoin chelates with acyl chlorides or anhydrides gave high yields of 5-acyl hydantoin. In contrast to this result, we have obtained esters and cyclic amides from magnesium methyl carbonate chelates of 1-oxo-3-benzazepines treated with acetyl chloride, Scheme 1.

Initial unsuccessful attempts to acylate 3-benzazepine-1-ones at the 2-position employed a variety of standard methods, however, starting materials were recovered predominantly [1]. When the method of Finkbeiner [2b] was attempted, instead of obtaining the expected 2-acetyl derivative in the reaction of magnesium methyl carbonate with 3-(methylsulfonyl)-1-oxo-1,2,4,5-tetrahydro-3*H*-3-benzazepine (**1**) [4] and acetyl chloride, the only product isolated was the unprecedented 2-carbomethoxy analog **4**. No sulfonic acid elimination was observed from this stabilized anion in contrast to the formation of **2** when **1** was treated with potassium *t*-butoxide and 18-crown-6 [1]. The stan-

Table 1
1*H*-Imidazo[5,1-*b*][3]benzazepine-1,3(2*H*)diones

| Compound No. | R | Recrystallization solvent | Yield | mp (°C) |
|--------------|--------------------|---------------------------|-------|---------|
| 6a | H | ethanol | 44 | 193-194 |
| 6b | 4-CH ₃ | ethanol | 27 | 204-206 |
| 6c | 4-OCH ₃ | ethanol | 14 | 185-187 |
| 6d | 4-Cl | ethanol | 28 | 149-150 |
| 6e | 2-Cl | ethanol | 22 | 222-224 |
| 6f | 2,4-DiF | ethanol | 8 | 222-224 |
| 6g | 4-CH ₃ | [a] | 42 | 179-182 |
| 6h | 4-OCH ₃ | [a] | 55 | 194-196 |
| 6i | 4-Cl | [a] | 35 | 214-216 |

[a] Precipitation by addition of 1*N* hydrochloric acid.

Table 2

Elemental Analysis on 1*H*-Imidazo[5,1-*b*][3]benzazepine-1,3(2*H*)diones

| Compound No. and formula | Calculated | | | Found | | |
|--|------------|------|------|-------|------|------|
| | C | H | N | C | H | N |
| 6a C ₂₀ H ₁₄ N ₂ O ₄ ·2H ₂ O | 62.83 | 4.74 | 7.33 | 62.46 | 4.39 | 7.36 |
| 6b C ₂₁ H ₁₆ N ₂ O ₄ ·1/4H ₂ O | 69.13 | 4.49 | 7.68 | 69.35 | 4.48 | 7.68 |
| 6c C ₂₁ H ₁₆ N ₂ O ₅ | 67.02 | 4.29 | 7.44 | 66.85 | 4.48 | 7.31 |
| 6d C ₂₀ H ₁₃ ClN ₂ O ₄ | 63.09 | 3.44 | 7.36 | 63.11 | 3.68 | 7.33 |
| 6e C ₂₀ H ₁₃ ClN ₂ O ₄ | 63.09 | 3.44 | 7.36 | 62.75 | 3.56 | 7.31 |
| 6f C ₂₀ H ₁₂ F ₂ N ₂ O ₄ | 62.83 | 3.16 | 7.33 | 62.36 | 3.25 | 7.17 |
| 6g C ₁₉ H ₁₄ O ₃ N ₂ ·1/2H ₂ O | 69.71 | 4.61 | 8.55 | 70.11 | 4.41 | 8.55 |
| 6h C ₁₉ H ₁₄ N ₂ O ₄ | 66.47 | 4.70 | 8.16 | 66.80 | 4.64 | 8.03 |
| 6i C ₁₈ H ₁₁ ClN ₂ O ₃ ·1/2H ₂ O | 62.17 | 3.48 | 8.06 | 62.41 | 3.59 | 7.73 |

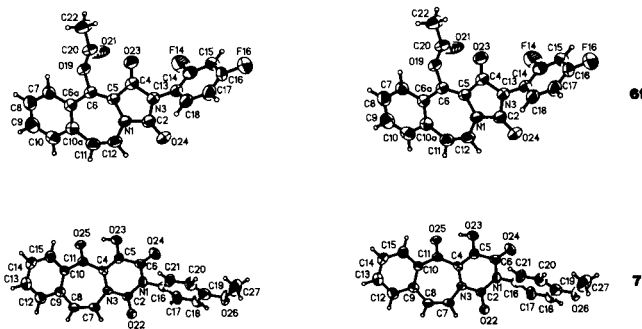
dard Stiles [2] reaction on **1**, *i.e.* treatment of the magnesium chelate with aqueous acid, gave the expected carboxylic acid **5**. This acid decarboxylated at room temperature overnight but could be converted to **4** by immediate treatment with diazomethane.

This unusual Stiles/Finkbeiner reaction product seen in the acetyl chloride procedure afforded the opportunity to generate novel tricyclic heterocycles from **3** under mild reaction conditions. As anticipated the 2-carbomethoxy derivative formed by the reaction of **3** with magnesium methyl carbonate, closed under the basic conditions to give tricyclic heterocycles [5]. A series of tricyclic 6,7,5-ring heterocycles, **6a-6i** were prepared (Table 1). Excess acetyl chloride was necessary to give the acetylated reaction products which were uncontaminated by unacetylated materials, **6a-f**. The use of fewer equivalents of acetyl chloride gave mixtures of heterocycles, *e.g.*, **6b** and **6g** ($R' = CH_3$). Hydrolysis of the 1-acetyl group could be achieved under mild base conditions, as in the preparation of **6g** from **6b**.

Other attempts to produce the 6,7,5-ring system were unsuccessful when the following reagents were used: diethyl carbonate, potassium *t*-butoxide in ethanol; ethyl chloroformate, 4-dimethylaminopyridine in dimethylformamide; ethyl chloroformate, sodium hydride in dimethylformamide; ethyl chloroformate neat. These results suggested that in the absence of chelation conditions the amide nitrogen was acylated first but then failed to cyclize to the carbon-2 of the benzazepine. A more reactive cyclization reagent appeared necessary and led us to try the treatment of **3** ($R' = 4-OCH_3$) with oxalyl chloride and potassium *t*-butoxide. Cyclization occurred which yielded the previously unknown 6,7,6-ring heterocycle, pyrimido-[6,1-*b*][3]benzazepine-1,3,4(2*H*)-trione (**7**). It is possible that phosgene and base would behave in a similar fashion to yield the above imidazobenzazepinediones.

Proofs of the structural assignments of the novel tricyclic heterocycles **6** and **7** were obtained by X-ray diffraction studies on single crystals (Figure 1). The 6,7,5-ring, **6f**, is a $(4n + 2)$ pi-electron aromatic ring system which

Figure 1
X-RAY STRUCTURES OF **6f** AND **7**



displays coplanarity of the three rings, exemplified by the dihedral angles 179.9° and 179.34° inscribed by atoms C4,C5,C6,C6a and C5,C6,C6a,C7, respectively. Lack of coplanarity is seen in **7** due to puckering of the 7-membered ring. The two terminal 6-membered rings of the tricyclic system are planar with the relationship of the two rings embracing a twist and a cup. The degree of twist is measured by the dihedral angle of 28.7° for atoms C15,C10,-C11,O25 while the extent of cupping of the planes is -34.4° inscribed by the dihedral angle for atoms C4,C11,-C10,C15. The pi-bond of the olefin in the 7-membered ring is out of plane with the benzene ring by -25.3° as shown in the dihedral angle of 154.7° for atoms C7,C8,-C9,C12. Crystal data and details of the X-ray study of **6f** and **7** are provided in the experimental section. Fractional coordinates for these structures are listed in Tables 3 and 4.

EXPERIMENTAL

All melting points were taken on a Thomas-Hoover melting apparatus and are uncorrected. Microanalysis were performed by the Pfizer Central Research "Microanalysis" Laboratory, and results obtained for specified elements are within ±0.40% of the theoretical values (hydrates incorporated as indicated) unless otherwise indicated. The ir spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer with the stipulated solvents and are reported in reciprocal centimeters. The ¹H nmr spectra of deuteriochloroform or DMSO-*d*₆ solutions (TMS as the internal standard) were recorded on a Varian A-60, a Perkin-Elmer T-60 or a Bruker 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.

11-Acetyloxy-2-(*N*-phenyl)-1*H*-imidazo[5,1-*b*][3]benzazepine-1,3(2*H*)-dione (**6a**).

A solution of *N*(phenyl)-1,2-dihydro-1-oxo-3*H*-3-benzazepine-3-carboxamide, **3** (R' = H), [1], (0.45 g, 1.60 mmoles), magnesium methyl carbonate (Fluka, 5.39 mmoles, 2.5 *M* in dimethylformamide) and 5 ml of dimethylformamide were heated at 120° for 1.5 hours. The reaction was cooled to 0°, treated with acetyl chloride (1.14 g, 16.0 mmoles) in one portion and stirred at room temperature for 1 hour. This mixture was quenched with 25 ml 1 *N* hydrochloric acid, diluted with 100 ml water and extracted with 3 x 100 ml of ethyl acetate. The pooled organic layers were washed with 2 x 100 ml 5% sodium bicarbonate, 2 x 100 ml water and brine, then dried with magnesium sulfate, filtered and evaporated *in vacuo* yielding a red oil. The crude oil was crystallized from ethanol to give **6a** as red needles (0.24 g, 44%), mp 193-194°; ¹H nmr (deuteriochloroform): δ 2.38 (s, 1H, CH₃), 5.08 (d, 1H, CH, J = 10 Hz), 6.29 (d, 1H, CH, J = 10 Hz), 6.50 (d, 1H, CH, J = 8 Hz), 6.98 (t, 1H, CH, J = 7 Hz), 7.05-7.15 (m, 2H), 7.33-7.55 (m, 5 phenyl protons); ir (dichloromethane): 1773 (C=O), 1725 (C=O), 1647 (O=C-N) cm⁻¹; ms: (m/e) 304.0813 (Calcd. 304.0851).

Compounds **6b-6i** were prepared following the procedure for the synthesis of **6a** (see Table 1).

11-Hydroxy-2-(4-methylphenyl)-1*H*-imidazo[5,1-*b*][3]benzazepine-1,3(2*H*)-dione (**6g**).

pine-1,3(2*H*)-dione (**6g**).

Compound **6a**, (0.13 g, 0.362 mmole) was dissolved in 1 ml of methanol, treated with 6 *N* sodium hydroxide (0.55 μl, 0.362 mmole) and stirred at room temperature for 3 hours. The mixture was then poured into 10 ml diethyl ether. The aqueous layer was washed with 2 x 25 ml diethyl ether, acidified with 1 *N* hydrochloric acid until pH 3 yielding a pale red precipitate. This was collected by filtration and dried *in vacuo* at 110° to yield **6g** (0.05 g, 42%), mp 179-182°; ¹H nmr (deuteriochloroform): δ 2.42 (s, 3H, CH₃), 5.15 (d, 1H, CH, J = 10 Hz), 6.43 (d, 1H, CH, J = 10 Hz), 6.75 (d, 1 phenyl proton, J = 10 Hz), 7.05-7.11 (t, 1 phenyl proton, J = 10 Hz), 7.15-7.24 (t, 1 phenyl proton), 7.35 (d, 4 phenyl protons), 7.78 (d, 1 phenyl proton, J = 8 Hz), 11.75 (s, 1H, OH).

Compound **6h** and **6i** were prepared following the procedure for the syntheses of **6g** (see Table 1).

5-Hydroxy-2-(4-methoxyphenyl)pyrimido[6,1-*b*][3]benzazepine-1,3,4(2*H*)-trione (**7**).

A solution of *N*(4-methoxyphenyl)-1,2-dihydro-1-oxo-[3]benzazepine-3-carboxamide, **3** (R' = 4-OCH₃), (0.50 g, 1.62 mmoles), potassium *t*-butoxide (0.50 g, 4.86 mmoles) and 5 ml of tetrahydrofuran were heated at 50°. To this solution oxalyl chloride (0.16 ml, 1.78 mmoles) was added dropwise. After heating for 5 hours the cooled reaction mixture was quenched with 6 ml of 1 *N* hydrochloric acid, diluted with 100 ml of water and extracted with 3 x 75 ml of ethyl acetate. The pooled organic layers were washed with 3 x 100 ml of brine, dried with magnesium sulfate, filtered and evaporated *in vacuo* to an orange-red solid (0.67 g). Pure **7** was obtained after recrystallization from 50 ml ethanol as red needles (0.25 g, 44%), mp 216-218°; ¹H nmr (deuteriochloroform): δ 3.82 (s, 3H, OCH₃), 6.22 (d, 1H, CH, J = 10 Hz), 6.92 (d, 1H, CH, J = 10 Hz), 7.02 (d, 2, phenyl protons, J = 12 Hz), 7.15 (d, 2 phenyl protons, J = 12 Hz), 7.22 (d, 1 phenyl proton, J = 10 Hz), 7.43 (t, 1 phenyl proton, J = 10 Hz) 7.6 (t, 1 phenyl proton, J = 10 Hz), 7.85 (d, 1 phenyl proton, J = 10 Hz), 12.45 (s, 1H, OH); ir (dichloroformethane): 2835 (CH₃), 1684 (C=O), 1630 (O=C-N), cm⁻¹; ms: (m/e) 362.0876 (Calcd. 362.0909).

Anal. Calcd. for C₂₀H₁₄N₂O₅·H₂O: C, 63.15; H, 4.25; N, 7.36. Found: C, 63.05; H, 3.85; N, 7.20.

Methyl 5-Hydroxy-3-(methylsulfonyl)-4,5-dihydro-3*H*-3-benzazepine-2-carboxylate (**4**).

3-(Methylsulfonyl)-1-oxo-1,2,4,5-tetrahydro-3*H*-3-benzazepine, **1**, (0.50 g, 2.09 mmoles) was dissolved in 5 ml of dimethylformamide and treated with magnesium methyl carbonate (Fluka, 8.50 mmoles, 2.5 *M* in dimethylformamide). After heating at 115° for 1.5 hours the reaction was cooled to 0°. Acetyl chloride (1.30 g, 16.8 mmoles) was slowly added so as to maintain the temperature at 0°. After stirring at 0° for 1.5 hours, the reaction mixture was carefully quenched with 1 *N* hydrochloric acid until a pH of 6 was obtained. The product was isolated by extraction with 3 x 100 ml of diethyl ether. The pooled organic layers were washed with 2 x 100 ml of water and brine, dried with magnesium sulfate, filtered and evaporated *in vacuo* yielding a brown solid. Recrystallization using 50 ml of isopropyl ether afforded yellow prisms of **4** (0.28 g, 44%), mp 144-145°; ¹H nmr (DMSO-*d*₆): δ 2.22 (s, 3H, CH₃), 2.84 (d, 2H, CH₂, J = 8 Hz), 3.34 (br s, 3H, CH₃), 3.83 (s, 3H, OCH₃), 7.39-7.54 (m, 3 phenyl protons), 7.5-7.61 (m, 1 phenyl proton), 12.2 (br s, OH); ir (potassium bromide): 1640 (C=O), 1622 (HO-C=C-C=O) cm⁻¹.

Anal. Calcd. for $C_{13}H_{15}NO_5S$: C, 52.22; H, 5.08; N, 4.71. Found: C, 52.35; H, 5.14; N, 4.73.

Methyl 5-Hydroxy-4,5-dihydro-3-methylsulfonyl-3*H*-3-benzazepine-2-carboxylate (**4**) *via* **5**.

3-(Methylsulfonyl)-1-oxo-1,2,4,5-tetrahydro-3*H*-3-benzazepine, **1**, (1.0 g, 4.18 mmoles) was dissolved in 4 ml of dimethylformamide and treated with magnesium methyl carbonate (Fluka, 10.7 mmoles, 2.5 *M* in dimethylformamide). The reaction was then heated at 120° for 1 hour, cooled to 0° and quenched with 20 ml of 1 *N* hydrochloric acid. The mixture was extracted with 3 x 100 ml of ethyl acetate. The pooled organics were washed with 3 x 100 ml of water and brine, and dried with magnesium sulfate. An aliquot was removed and evaporated *in vacuo* to a brown solid; ¹H nmr (deuteriochloroform): δ 2.28 (s, 3H, CH₃), 2.75-3.1 (br t, 2H, CH₂, J = 8 Hz), 3.80-4.10 (t, 2H, CH₂, J = 8 Hz), 7.39-7.54 (m, 3 phenyl protons), 7.50-7.61 (m, 1 phenyl proton), 13.11-13.41 (br s, 1H, OH). Proton nmr data after 12 hours revealed that the solid decarboxylated ~50% back to starting material **1**. Thus the above procedure on **1** (2.0 g, 8.36 mmoles) was repeated and immediately treated with diazomethane. Diazomethane was generated by dissolving in three portions *N*-methyl-*N*-nitronitrosoguanidine (4.3 g, 29.4 mmoles) in a mixture of 20 ml of 5 *N* sodium hydroxide and 80 ml of diethyl ether at 0°. The ether layer of diazomethane was slowly added to the 0° ethyl acetate solution containing **5** and then stirred at 0° for 1 hour. The mixture was quenched with acetic acid and washed with 3 x 75 ml water and brine, the organic layer was dried with magnesium sulfate, filtered and evaporated *in vacuo* to a brown oil. The oil was dissolved in 20 ml of 1 *N* sodium hydroxide and extracted with 3 x 50 ml of ethyl acetate. The pooled organic layers were washed with 3 x 50 ml of water, dried with magnesium sulfate and evaporated *in vacuo* to a tan solid (0.38 g, 15%) mp 133-135°. Using proton nmr and tlc (1:1 ethyl acetate/hexanes on silica gel) analysis, the product was judged to be identical to **4**, obtained by the earlier procedure.

X-ray Crystallographic Analysis of **6f**.

A large plate crystal of **6f** was obtained by recrystallization from ethanol: $C_{20}H_{12}N_2O_4F_2$; MW = 382.3, space group C2/c; cell

constants $a = 17.607(4)$ Å, $b = 7.570(1)$ Å, $c = 28.110(1)$ Å, $\delta = 90.00^\circ$, $\beta = 113.05(2)$, $\nu = 90.00^\circ$, $V = 3447(1)$ Å³, $Z = 8$. Lattice constants and intensity data were measured by using graphite-monochromated CuK on a Nicolet R3m/u diffractometer. A total of 3104 unique reflections were observed. The structure was solved by the SHEXTL system [6] and refined to a final R value of 0.048.

X-ray Crystallographic Analysis of **7**.

A large plate crystal of **7** was obtained by recrystallization from acetonitrile: $C_{20}H_{14}N_2O_3$; MW = 362.4, space group Pca2, cell constants $a = 15.712(7)$ Å, $b = 15.014(5)$ Å, $c = 7.009(3)$ Å, $\delta = 90.00^\circ$, $\beta = 90.00^\circ$, $\nu = 90.00^\circ$, $V = 1653(1)$ Å³, $Z = 4$. Lattice constants were measured by using graphite monochromated CuK on a Nicolet R3m/u diffractometer. A total of 1698 unique reflections were observed. The structure was solved by the SHEXTL system [6] and refined to a final R value of 0.050.

Supplementary Materials.

Tables of hydrogen atom coordinates, bond angles and lengths and anisotropic thermal parameters are available upon request from the authors.

Acknowledgements.

The authors wish to thank Jon Bordner, X-Ray Diffraction Laboratory, Central Research, Pfizer, Inc. for producing the x-ray structures. In addition we are indebted to Kenneth G. Kraus of Pfizer, Inc., for work on **4** and **5**.

REFERENCES AND NOTES

- [1] R. C. Schnur and R. J. Gallaschun, *J. Org. Chem.*, **54**, 216 (1989).
- [2a] M. Stiles, *J. Am. Chem. Soc.*, **81**, 2598 (1959); [b] H. L. Finkbeiner, *J. Org. Chem.*, **30**, 3414 (1965).
- [3] S. Danishefsky, T. A. Bryson and J. Puthenpurayil, *J. Org. Chem.*, **40**, 1846 (1975).
- [4] G. Hazebrucq and J. Gardent, *Bull. Soc. Chim.*, **11**, 3985 (1971).
- [5] The single reported example of a 6,7,5-benzazepine system is 1*H*-2,3,5,6,11,11a-hexadroimidazo[5,1-*b*][3]benzazepin-3-one; V. Dixit, J. Khanna and N. Anand, *Indian J. Chem.*, **17B**, 72 (1979).
- [6] G. M. Sheldrick, SHEXTL. User Manual, Nicolet Instrument Co., 1981.