Pergamon

Tetrahedron Letters 39 (1998) 7431–7434

TETRAHEDRON LETTERS

Beta-lactams Derived from the Reaction of Phenanthridines and 11*H*-Dibenzo[b,e]Azepin-11-one with Phenylvaleryl Chloride. Synthesis of Fused Analogs of the Cholesterol Absorption Inhibitor Sch 48461.

Adriano Afonso,* Stuart B. Rosenblum, Mohindar S. Puar, and Andrew T. McPhail [§]

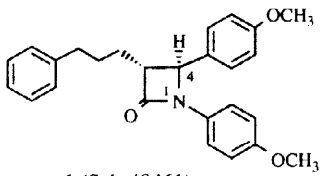
Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033

[§]Duke University, P. M. Gross Chemical Laboratory, Durham, NC 27706, U.S.A

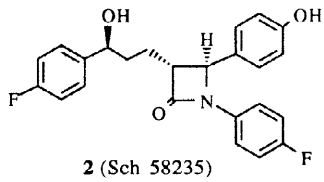
Received 17 June 1998; accepted 17 July 1998

Abstract: Phenanthridines **4** and the 11*H*-dibenzo[b,e]azepin-11-one **17** were used as the imine components in the ketene-imine β-lactam synthesis to provide the fused tetracyclic β-lactams **7, 8 and 18.**

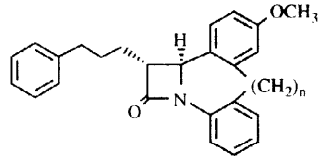
The discovery of 2-azetidinone **1** as a novel cholesterol absorption inhibitor (CAI)[1] led to an extensive structure-activity effort culminating in the development of **2**, which is being evaluated in humans for the treatment of hypercholesterolemia.[2] One of the chemical modifications of **1** that we considered during the early phases of this study, was aimed at determining the conformational requirements for CAI activity of the N_1 and C_4 phenyl groups in this lead molecule. We report here the synthesis of the two fused tetracyclic azetidinones **3** (n=0, 1) which are conformationally rigid analogs of **1**.



1 (Sch 48461)



2 (Sch 58235)

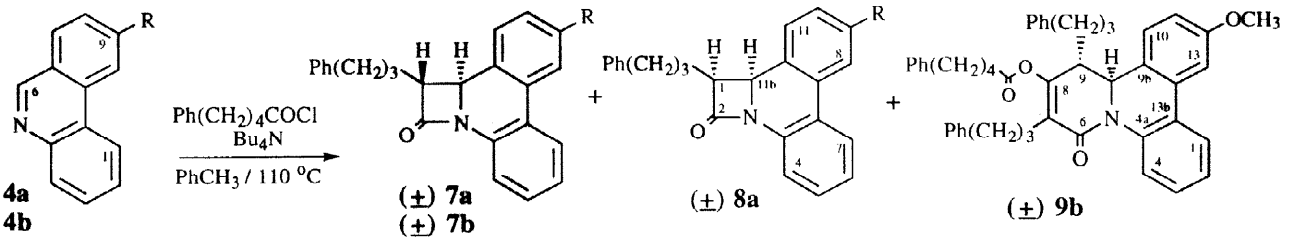


3

The ketene-imine reaction is a convenient method employed for the preparation of β-lactams.[3] This methodology was attractive for preparing compounds **3** from an appropriate aromatic heterocycle. However, there are no prior literature reports on the use of a nitrogen containing aromatic heterocycle as the imine component in the ketene-imine reaction. We have found that phenanthridine (**4a**) reacts with phenylvaleryl chloride (Scheme 1) under the recently reported conditions for the acid chloride-imine reaction[4], to afford in low yield the fused *trans*-betalactam **7a** (6%) and the *cis*-isomer **8a** (1.2%).[5] Similarly, 9-methoxyphenanthridine (**4b**)[6] reacts with phenylvaleryl chloride to afford the desired *trans*-betalactam **7b** (5%) and a detectable trace of the *cis*-isomer.

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01648-7

Scheme 1



a, R = H; b, R = OCH_3

The structure of **7b** was confirmed by X-ray crystallography (Figure 1).[7] A major product isolated in the same reaction of **4b** with phenylvaleryl chloride was characterized as the tetracyclic dihydropyridophenanthridine **9b**. The structure for **9b** was assigned on the basis of INEPT correlations in the NMR (Figure 2).

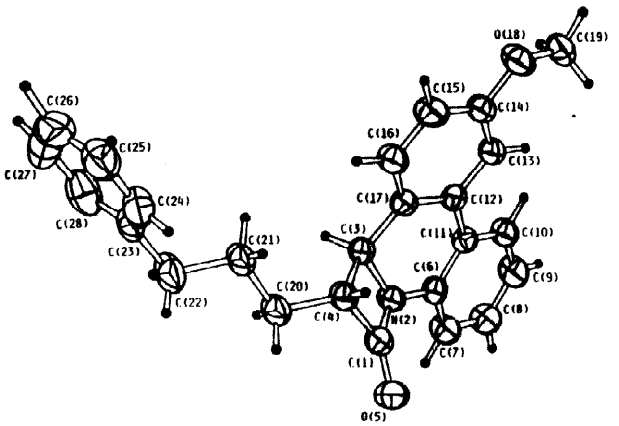


Figure 1. ORTEP Diagram of **7b**

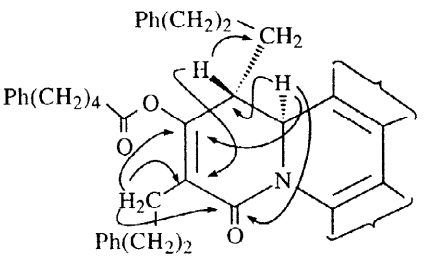
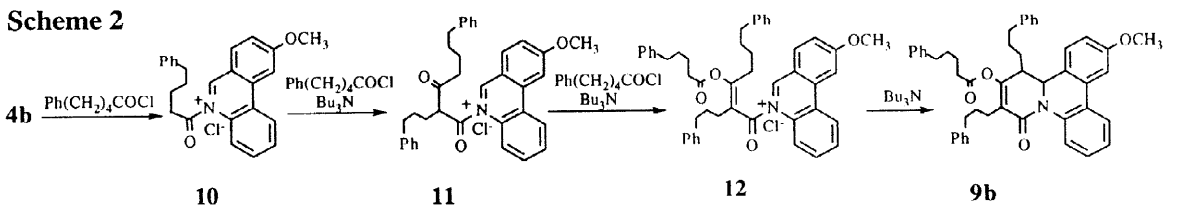


Figure 2. Selected INEPT correlations for **9b**

A possible reaction pathway for the formation of **9b** is shown in Scheme 2. In this pathway, the initial acyliminium chloride **10** reacts with a second molecule of the acid chloride to form a β-dicarbonyl intermediate **11**. Enol acylation of **11** by a third acid chloride molecule forms the vinylogous amide **12** which undergoes a base catalyzed cyclization resulting in **9b**.

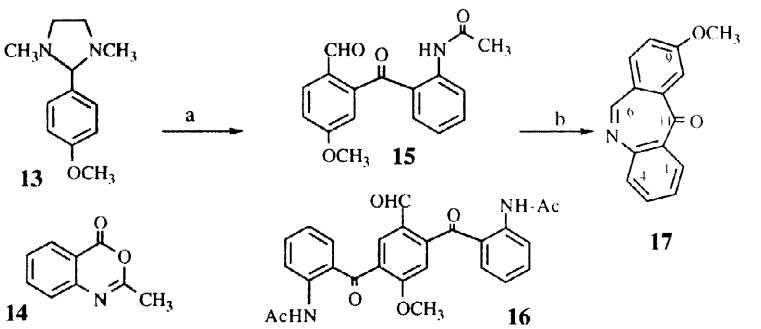
Scheme 2



The ketene-imine reaction was also applied to the tricyclic imine 9-methoxy 11*H*-dibenz[b,e]azepin-11-one (**17**) in order to access the fused betalactam homolog **3** (n=1). The synthesis of **17** is shown in Scheme 3.

Directed *ortho* lithiation of **13** with *tert.*-butyl lithium[8] in Et_2O followed by reaction with 2-methyl-3,1-benzoxazin-4-one (**14**)[9,10] and regeneration of the aldedyde by exposure to dil. HCl afforded after chromatography the *o*-acetamido benzophenone **15** (30%). A diacylated product **16** was also isolated in low yield (2%). Deacetylation of **15** with dil. HCl afforded the desired azepinone **17** (quant).

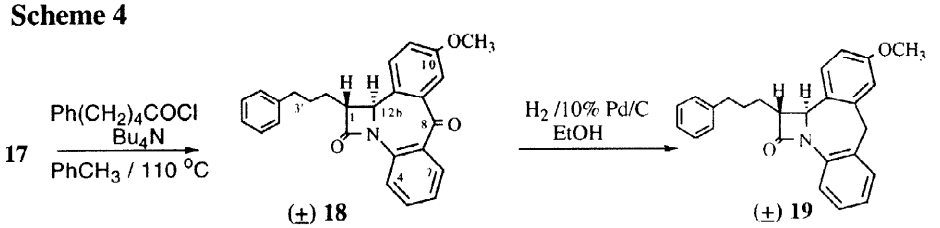
Scheme 3[a]



[a] Reagents: (a) i. 1.7M *t*-BuLi / pentane (2eq) -78 °C, Et_2O, 5h. ii. lithiated **13** added to **14** (1.7 eq), Et_2O, -78 °C- rt, 1h. iii. 0.5N HCl, rt. iv. chromatography/silica-gel (b) 2N HCl, MeOH, 100 °C, 40min.

Reaction of **17** with phenylvaleryl chloride (Scheme 4) under the same conditions[5] used for **4**, afforded the fused betalactam **18** in higher yield (47%) relative to compounds **7**. The increased yield of **18** versus **7** reflects on both the reactivity of the precursor imine and the relative strain differences of the reaction products. Catalytic reduction of the carbonyl group of **18** afforded the desired fused betalactam **19** (80%).[11]

Scheme 4



In summary we report here the application of ketene-imine betalactam synthesis to phenanthridines **4** as the imine component of this reaction. The low yield obtained for the resulting fused tetracyclic betalactams **7** is not surprising since the cyclization step is energetically less favorable and the products are highly strained molecules. The tetracyclic fused betalactams **7a, 7b, 8a** and **19** are conformationally rigid analogs of **1**; the compounds were found to be essentially inactive as CAI agents,[12] thereby demonstrating the importance of conformational mobility of the phenyl groups for the CAI activity of compound **1** and its analogs.

Acknowledgements: The authors thank the Analytical Services for physical data on the new compounds reported herein.

References and Notes:

1. Burnett, D. A.; Caplen, M. A.;Davis, H.R. Jr.; Burrier, R. E.; Clader, J. W. *J. Med. Chem.* **1994**, *37*, 1733.
2. Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H.R. Jr.; Yumibe, N.; Clader, J. W.; Burnett, D. A. *J. Med. Chem.* **1998**, *41*, 973.
3. (a) Georg, G. I.,Ed.; *The Organic Chemistry of betalactams,* Verlag Chemie, New york, 1992, Ch. 6; (b) Ghosez, L.; Marchand-Brynaert, J.; in *Comprehensive Organic Synthesis;* Trost, B. M.; Ed,; Pergamon Press, New York, 1991; Vol. 5, p 90.

4. Browne, M.; Burnett, D. A.; **Caplen, M. A.**; Chen, L.-Y.; Clader, J. W.; Domalski, M.; Dugar, S.; Pushpavanam, P.; Sher, R.; **Vaccaro, W.**; Viziano, M.; Zhao, H. *Tetrahedron Lett.*,**1995**, *36*, 2555.
5. The reaction conditions involved a slow addition of 2 eq. of acid chloride to a refluxing 1M solution of **4a**, **4b** or **17** and 4 eq. of *n*-tributylamine in toluene or heptane and maintaining the reflux for 24 h. The purification of these products required flash chromatography on silica gel (10% Et_2O-hexanes) followed by HPLC on Whatman Porasil columns. Recovered unreacted starting imines ranged from 60-70%. Yields of products are based on the reacted portion of the starting imine.
6. Kessar, S. V.; Gopal, R.; **Singh, M.** *Tetrahedron*, **1973**, *29*, 167.
7. Crystal structure data may be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB2 1EZ (UK).
8. Bevan, F. M.; Euerby, M. R.; Qureshi, S. J. *J. Chem Res.*, **1989**, *(S)*, 116.
9. Errede, L. A.; Oien, H. T.; Yarian, D. R. *J. Org. Chem.* **1977**, *42*, 12.
10. This acylation is best carried out by adding the lithiated **13** to a solution of **14**.
11. Physical data for **7a**: pale yellow oil (6 %); IR (CH_2Cl_2) 1755 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.90-2.20 (m, H_1,$H_{2'}$), 2.78 (t, *J*=7.5 Hz, $H_{3'}$), 3.60 (m, H_1), 4.70 (bs, H_{11b}), 7.10-7.50 (m, 11H), 7.82 (d, *J*= 7.5 Hz, H_8/H_7), 7.84 (d, *J*=7.5 Hz, H_7/H_8); MS (CI) *m* / *z* 340 (MH^+). Anal. Calcd for $C_{24}H_{21}NO$ (0.05xCH_2Cl_2): C, 84.03; H, 6.19; N, 4.08. Found: C, 84.03; H, 6.26; N, 4.21. **8a:** pale yellow wax (1.2 %); IR (CH_2Cl_2) 1755 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.70-2.10 (m, H_1,$H_{2'}$), 2.60 (t, *J*=7.5, 7.5 Hz, $H_{3'}$), 3.90 (dt, *J*=8, 5, 5 Hz, H_1), 5.12 (d, *J*=5 Hz, H_{11b}), 7.0-7.50 (m, 11x**CH**=), 7.85 (d, *J*=7.5 Hz, H_8/H_7), 7.87 (d, *J*=7.5 Hz, H_7/H_8); MS (CI) *m* / *z* 340 (MH^+). Anal. Calcd for $C_{24}H_{21}NO$(0.05xCH_2Cl_2): C, 84.03; H, 6.19; N, 4.08. Found: C, 84.08; H, 6.51; N, 4.09. **7b:** pale yellow crystals (5 %); IR (CH_2Cl_2) 1755 cm^{-1}; mp 114-115 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.95-2.25 (m, $H_{1'}$,$H_{2'}$), 2.83 (t, *J*=7.5 Hz, $H_{3'}$), 3.60 (bt, H_1), 3.93 (s, OCH_3), 4.71 (bs, H_{11b}), 6.96 (dd, *J*=7.5, 1 Hz, H_{10}), 7.15 (d, *J*=7.5 Hz, H_{11}), 7.22-7.52 (m, 8H), 7.45 (d, *J*=7.5 Hz, H_4), 7.88 (d, *J*=7.5 Hz, H_7); HRMS (FAB) calcd for $C_{25}H_{23}NO_2$ 369.1729, found 369.1742. **9b:** colorless oil (20 %); IR (CH_2Cl_2) 1760, 1680, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.50-2.75 (m, 10xCH_2), 3.49 (t, *J*=7.5 Hz, H_9), 3.82 (s, OCH_3), 4.52 (bs, H_{9a}), 6.91 (dd, *J*= 7.5, 1 Hz, H_{11}), 7.28 (d, *J*= 1 Hz, H_{13}), 7.35 (dt, *J*= 7.5, 7.5, 1 Hz, $H_{3/2}$), 7.40 (dt, *J*=7.5, 7.5, 1 Hz, $H_{2/3}$), 7.57 (dd, *J*=7.5, 1 Hz, H_4), 7.58 (d, *J*=7.5 Hz, H_{10}), 7.80 (dd, *J*=7.5, 1 Hz, H_1); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 24.0, 24.3, 28.3, 30.0, 30.8, 32.2, 34.0, 35.5, 35.5 (CH_2), 110.6, 112.5 ($C_{11}C_{13}$), 124.1, 124.3, 125.5, 126.0, 126.5, 126.7, 128.1, 128.3, 128.4, 128.4, 128.6 (CH=), 129.4 (C_{13b}), 141.4, 141.8, 142.2 (aromatic C=), selective INEPT based assignments: 35.3 (C_9), 55.4 (OCH_3), 58.7 (C_{9a}), 123.1 (C_7), 127.5 (C_{9b}), 127.9 (C_3), 134.3 (C_{13a}), 139.3 (C_{4a}), 156.7 (C_8), 159.5 (C_{12}), 163.3 (C_6), 170.9 (C_8-COO); HRMS (FAB) calcd for $C_{47}H_{48}NO_4$ 690.3583, found 690.3578. **15**: pale yellow crystals from ether-hexanes (30 %); mp 138-140 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.30 (s, 3H), 3.90 (s, 3H), 9.81 (s, 1H), 11.55 (bs, 1H); MS (CI) *m* / *z* 298 (MH^+). Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.02; N, 4.71. Found: C, 68.18; H, 5.02; N, 4.69. **16:** white crystals from EtOAc (2 %); mp 252-253 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.31 (s, 3H), 2.33 (s, 3H), 3.86 (s, 3H), 9.89 (s, 1H), 11.55 (bs, 2H); MS (FABS) *m* / *z* 459 (MH^+). Anal. Calcd for $C_{26}H_{22}N_2O_6$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.35; H, 4.92; N, 6.09. **17:** golden yellow needles from EtOAc-hexanes (97 %); IR (CH_2Cl_2) 1640 cm^{-1}; mp 104-105 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.99 (s, OCH_3), 7.34 (dd, *J*=7.5, 1 Hz, H_8), 7.52 (t, *J*=7.5 Hz, H_3), 7.72 (d, *J*=1 Hz, H_{10}), 7.75 (m, H_2,H_4), 7.78 (d, *J*= 7.5 Hz, H_7), 8.20 (d, *J*=7.5 Hz, H_1), 8.77 (s,H_6); MS (CI) *m* / *z* 238 (MH^+). Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67; N, 5.90. Found: C, 75.79; H, 4.52; N, 5.68. **18:** white crystals (47 %); IR (CH_2Cl_2) 1755, 1640 cm^{-1}; mp 99-101 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.75-2.15 (m, H_1,$H_{2'}$), 2.72 (t, *J*=7.5 Hz, $H_{3'}$), 3.79 (dt, *J*=7.5, 1 Hz, H_1), 3.85 (s, OCH_3), 4.90 (d, *J*=1 Hz, H_{12b}), 7.10-7-35 (m, 9H), 7.53 (t, *J*=7.5, Hz, H_6/H_5), 8.05 (d, *J*=7.5 Hz, H_4), 8.27 (d, *J*=7.5 Hz, H_7); MS (CI) *m* / *z* 398 (MH^+). Anal. Calcd for $C_{26}H_{23}NO_3$: C, 78.57; H, 5.83; N, 3.52. Found: C, 79.04; H, 5.05; N, 3.59. **19:** colorless crystals (78 %); IR (CH_2Cl_2) 1740 cm^{-1}; mp 112-113 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.75-2.20 (m, H_1,$H_{2'}$), 2.71 (t, *J*=7.5 Hz, $H_{3'}$), 3.45 (d, *J*=15 Hz, $H_{8\beta}$), 3.65 (m, H_1), 3.80 (s, OCH_3), 4.70 (d, *J*=15 Hz, $H_{8\alpha}$), 5.25 (d, *J*=3 Hz, H_{12b}), 6.70-7.45 (m, 11x**CH**=), 8.10 (d, *J*=7.5 Hz, H_4), % NOE: $H_{12b}H_{8\alpha}$=15.9, $H_{8\alpha}H_{8\beta}$=34, $H_9H_{8\beta}$=21.1. MS (CI) *m* / *z* 384 (MH^+). Anal. Calcd for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65. Found: C, 81.45; H, 6.57; N, 3.54.
12. The compounds showed less than 30% reduction in cholesteryl esters @10 mpk in the CAI assay (for assay details see *ref.* 2) in hamsters.