# Imino-Bridged Heterocycles. V [1]. Synthesis of 6,11-Dimethyl-11*H*-benzo[5,6]cyclohepta[1,2-*c*]pyridin-6,11-imine by a Regiospecific Amide to Olefin Cyclization



Daniel G. Brenner [2], Wasyl Halczenko and Kenneth L. Shepard*

Department of Medicinal Chemistry, Merck Sharp and Dohme Research Laboratories, West Point, Pennsylvania 19486

Received April 22, 1985

Attempted utilization of sulfenimines **6a,b** to prepare tertiary carbinamines as intermediates to the desired 6,11-dimethyl-11*H*-benzo[5,6]cyclohepta[1,2-*c*]pyridin-6,11-imine system (**10**) instead gave products resulting from nitrogen-sulfur bond cleavage. The preparation and use of the corresponding sulfonimine **8**, however, led to **10** through a regiospecific base-catalyzed reaction.

*J. Heterocyclic Chem.*, **23**, 145 (1986).

With the discovery that substituents at both bridgehead positions in the anthracenimine structure facilitated anticonvulsant activity [3,4], we were interested in preparing similar analogs in the benzo[5,6]cyclohepta[1,2-*c*]pyridin-6,11-imine system. In earlier papers of this series, selective syntheses of isomeric benzocycloheptapyridines [5,6,7], were described. We anticipated the use of similar methodology for preparing the desired analogs.

Our initial strategy involved generation of the *tertiary* carbinol **2** and investigation of an amino bridging reaction between the potential carbonium ion center at C-11 and C-6. A thermal reaction of **2** with benzylamine was explored to examine the replacement of the C-11 hydroxyl with benzylamino and concomitant cyclization into the C-5,6 olefinic linkage. No such reaction occurred and **2** was recovered unchanged. The carbinol **2** then was treated with benzylamine in the presence of hot pyridine hydrochloride to determine the effects of acid catalysis. Two products, **3** and **4**, were isolated from this reaction, with no evidence of amine insertion. The oxygen-bridged structure **4** was deduced from the analytical data and an examination of the nmr spectrum. The methylene derivative **3** was the only product formed when **2** was treated with hot pyridine hydrochloride, or when co-melted with hydroxylamine hydrochloride. The latter reaction was an attempt to prepare a *N*-hydroxy-bridged structure similar to that reported earlier [7], which could be deoxygenated to the target imino-bridged compound **10**.

The failure, of an aliphatic type amine to undergo an acid-catalyzed bridging reaction may have reflected the

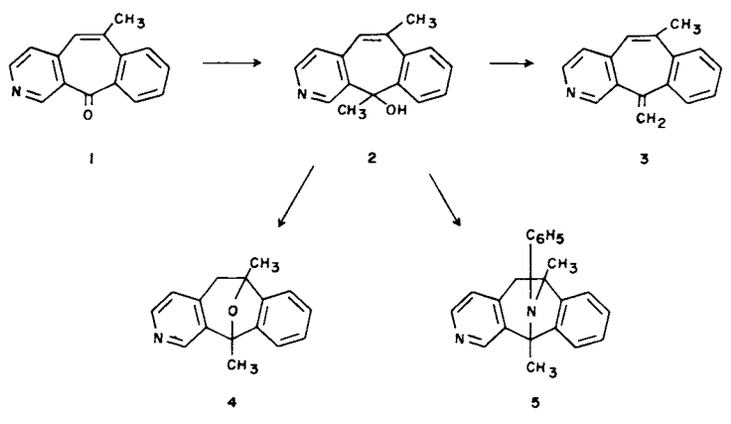
Table 1

Reaction of **2** with Aniline under Acidic Conditions

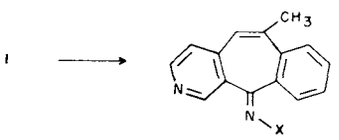
| Acid, solvent | Conditions | Products detected [a] **2** | **3** | **4** | **5** |
|---|---|---|---|---|---|
| Aniline hydrochloride | 125°, 16 hours | [b] | [b] | [d] | [c] |
| Acetic acid | 145°, 18 hours | [b] | [d] | [b] | [c] |
| Trifluoroacetic acid | 85°, 1 hour | [c] | [b] | [d] | [c] |
| Concentrated hydrochloric acid | 40°, 6 hours | [d] | [b] | [d] | [d] |
| Concentrated sulfuric acid | 25°, 2 hours | [b] | [b] | [d] | [d] |
| Titanium tetrachloride, toluene | 25°, 3 hours | [b] | [d] | [d] | [d] |
| Titanium tetrachloride, toluene | 80°, 1 hour | [b] | [c] | [d] | [c] |

[a] Detection by glc, flame ionization, Hewlett-Packard Model 5700A/-3370B, 2 mm × 6' glass 1%, ov-17 GLQ 100/120. [b] Indicates major product(s). [c] Indicates minor product(s). [d] Indicates product not detected.

Scheme I



Scheme 2



6

a X = S-$C_6H_3$ (3,4-$Cl_2$)
b X = S-$C_6H_5$
c X = $CH_3$
d X = $C(CH_3)_3$
e X = $COOC_2H_5$
f X = TMS

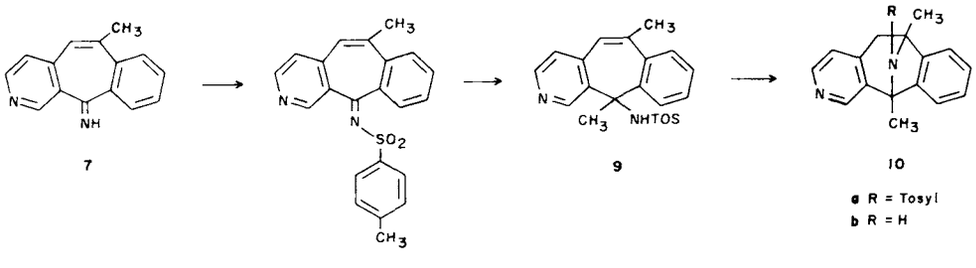
possibility that little or no unprotonated amine was present in the reaction mixture when the C-11 carbonium ion was formed. To examine this possibility, **2** was treated with benzylamine in a less acidic medium, acetic acid. The oxa-bridged derivative **4** was the only material detected in addition to recovered starting material. In an effort to generate a C-11 carbonium ion in the presence of an unprotonated amine, **2** was treated with aniline, a weaker base than benzylamine, in hot acetic acid. The components of the reaction mixture were separated chromatographically, and in addition to **3** and the oxa-bridged **4**, the product **5** resulting from bridging by aniline was isolated and characterized. The singlets exhibited by the methyl groups indicated their attachment to quaternary centers. Their chemical shifts were consistent with those expected based on the single methyl-substituted products seen earlier and the methylene function at C-5 exhibited the characteristic pattern determined for bridged structures [7]. A variety of acidic conditions was employed in an effort to maximize the generation of **5**, but **2** and **3** remained the major products (Table 1). This low yielding and complex step failed to generate aliphatic imino-bridged products and led us to examine alternate pathways for introduction of an amino function at C-11 for cyclization to the C-5,6 olefin.

Two reported methods for preparing tertiary carbinamines seemed appropriate for consideration as solutions to our problem. The first of these, the Ritter reaction [8], was attempted with **2** and generated an unusual bicyclo derivative which will be detailed in a subsequent publication. The second procedure reported by Davis [9] seemed attractive, and once we had developed efficient routes to the requisite sulfenimines, **6a,b** [1a], we attempted to add alkyl lithium or Grignard reagents to the imine linkage. Addition of methyl lithium to an ethereal solution of **6a** produced no detectable addition product at the imine bond, but gave products indicative of nitrogen-sulfur bond cleavage (see Experimental). Similar results were obtained in THF and, when methyl iodide was added prior to acidification, the *N*-methyl imine **6c** was isolated, further substantiating the proposed cleavage reaction. This is in contrast to the reported method of interaction with alkyl lithium reagents, when the sulfenimine is derived from a dialkyl ketone [9]. Attempted addition of methyl magnesium bromide to **6b** gave no reaction at all. This concept still seemed one worth pursuing and other, easily removable, imine nitrogen-protecting groups were explored. However, attempted synthesis of **6d-f** for investigation in alkyl lithium additions proved fruitless in our hands.

Our subsequent analysis of the sulfenimine reaction led us to propose that incorporation of functionality into the structure capable of sterically retarding the attack of the alkyl lithium at the sulfur atom could lead to the desired mode of addition. We chose to look at the sulfonimide type structure **8**, with the added expectation that the anionic charge developed in the addition would be supported by the sulfonyl moiety. Sulfonation of **4** with *p*-toluenesulfonyl chloride occurred in pyridine to give **8** and, as expected, addition of methyl lithium readily produced **9**. Attempted acid-catalyzed ring closure of this intermediate gave small quantities of **3**, but treatment with sodium hydroxide induced a regiospecific intramolecular cyclization to give **10a**. As found earlier, once the imine bridge was formed, it was stable to strongly acidic conditions. Hydrolysis of the amide **10a** with hydrochloric acid-acetic acid produced **10b**, isolated as its fumarate salt. The structures of these products (**10b**) were readily apparent from an inspection of their nmr spectra (see Experimental).

We have demonstrated the regiospecific synthesis of the 6,11-disubstituted benzo[5,6]cyclohepta[1,2-*c*]pyridin-6,11-imine system through a base-catalyzed regiospecific

Scheme 3



7 8 9 10

a R = Tosyl
b R = H

cyclization. The technology illustrated here, as well as that reported earlier [5,6,7], would allow the introduction of a variety of bridgehead substituted imines in 6,11-disubstituted or 6-substituted products by utilization of different alkyl lithium reagents. Substitution on the imine nitrogen itself is available through a reductive amination procedure similar to that used with anthracenimines [3].

## EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected values. The nmr spectra were recorded on a Varian EM390 spectrometer using TMS as an internal standard and microanalyses were performed under the direction of Dr. W. C. Randall.

6,11-Dimethyl-11-hydroxybenzo[5,6]cyclohepta[1,2-*c*]pyridine (**2**).

Methyl magnesium bromide in THF (16 ml, 0.046 mole) was added to a cold (0-5°) solution of **1** [7] (5 g, 0.023 mole) in THF and the resulting mixture was allowed to come to room temperature overnight. The solution was mixed with saturated ammonium chloride solution and extracted with ether. After washing and drying the ether (saturated sodium chloride solution, sodium sulfate), evaporation left 5.24 g of a beige powder, mp 197-200°.

*Anal.* Calcd. for $C_{16}H_{15}NO$ (237.30): C, 80.98; H, 6.37; N, 5.90. Found: C, 80.41; H, 6.49; N, 5.61.

5,6-Dihydro-6,11-dimethyl-6,11-epoxybenzo[5,6]cyclohepta[1,2-*c*]pyridine (**4**).

A mixture of **2** (0.20 g), benzylamine (0.5 ml) and pyridine hydrochloride (1 g) was heated in an oil bath (155-160°) for 2 hours. The reaction mixture was cooled, diluted with water and extracted with ethyl acetate. The extracts were washed with water, saturated sodium chloride solution and dried (sodium sulfate). After filtration and evaporation of the solvent, the residue was subjected to thick-layer chromatography on fluorescent silica (2000 $\mu$) with chloroform-ethyl acetate (1:1, v/v) as eluant. The higher $R_f$ material was identical with **3**. The lower $R_f$ compound was identified as **4**; nmr (deuteriochloroform): $\delta$ 1.77 (s, C6-$CH_3$, 3H), 2.03 (s, CH-$CH_3$, 3H), 2.65 (d, J = 18 Hz, H-5$\alpha$, 1H), 3.22 (d, J = 18 Hz, H-5$\beta$, 1H), 6.78 (d, J = 5 Hz, H-3, 1H), 7.10 (m, H-7, H-8, H-9, H-10, 4H), 8.23 (d, J = 5 Hz, H-4, 1H), 8.43 (s, H-1, 1H).

*Anal.* Calcd. for $C_{16}H_{15}NO$ (237.30): C, 80.98; H, 6.37; N, 5.90. Found: C, 81.25; H, 6.41; N, 5.96.

6-Methyl-11-methylenebenzo[5,6]cyclohepta[1,2-*c*]pyridine (**3**).

A mixture of **2** (1 g) and pyridine hydrochloride (3 g) was heated at 150-160° for 2 hours. The cooled reaction mixture was diluted with water, saturated sodium chloride solution and dried (sodium sulfate). After removal of the solvent the residue was recrystallized from hexane, 0.50 g, mp 114-118°; nmr (deuteriochloroform): $\delta$ 2.38 (d, J = 2 Hz, C6-$CH_3$, 3H), 5.28 (d, J = 2.5 Hz, H-4, 1H), 7.37 (m , H-7, H-8, H-9, H-10, 4H), 8.43 (d, J = 2.5 Hz, H-3, 1H), 8.53 (s, H-1, 1H).

*Anal.* Calcd. for $C_{16}H_{13}N$ (219.27): C, 87.64; H, 5.98; N, 6.39. Found: C, 87.77; H, 5.98; N, 6.49.

5,6-Dihydro-6,11-dimethyl-12-phenylbenzo[5,6]cyclohepta[1,2-*c*]pyridine (**5**).

A mixture of **2** (0.77 g, 3 mmoles), aniline (1.54 g, 16 mmoles) and glacial acetic acid (5 ml) was heated at reflux for 3 hours. The cooled reaction mixture was diluted with water and extracted with chloroform. The organic extract was washed with saturated sodium chloride solution and dried (sodium sulfate). After removal of the solvent, the oily residue was chromatographed on a thick-layer plate (2000 $\mu$) with chloroform-ethyl acetate (1:1, v/v) as eluant. The component with $R_f$ ~0.55 was extracted with chloroform-methanol (1:1, v/v) and evaporated to give 0.13 g of off-white solid. Recrystallization from cyclohexane gave material of mp 186.5-188°; nmr (deuteriochloroform): $\delta$ 1.68 (s, C6-$CH_3$, 3H), 1.94 (s, C11-$CH_3$, 3H), 2.44 (d, J = 18 Hz, H-5$\alpha$, 1H), 2.82 (d, J = 18 Hz, H-5$\beta$, 1H), 6.74-7.34 (m, H-4, H-7, H-8, H-9, H-10, H-12 phenyl, 10H), 8.38 (d, J = 2.5 Hz, H-3, 1H), 8.63 (s, H-1, 1H).

*Anal.* Calcd. for $C_{22}H_{20}N_2$ (312.40): C, 84.58; H, 6.45; N, 8.97. Found: C, 83.74; H, 6.37; N, 8.98.

Reaction of **6a** with Methyl Lithium.

a) Methyl lithium (1.4 *M*, 1.4 ml, 2 mmoles) was added to a cold (-78°) stirred mixture of **6a** [1a] (0.39 g, 1 mmole) and anhydrous ether (10 ml) under nitrogen. The cooling bath was removed and the reaction mixture warmed to 25°. After one hour a tlc probe (fluorescent silica, chloroform-ethyl acetate, 1:1, v/v) indicated only a trace of **6a**. The reaction mixture was treated with water (3 × 25 ml), saturated sodium chloride solution (25 ml) and dried (sodium sulfate). Removal of the dried solvent under vacuum and thick layer chromatography of the residue on silica produced **7**, **1**, **6a**, and methyl 3,4-dichlorophenyl sulfide, identified spectroscopically.

b) The procedure above using THF was followed except that 0.4 ml of methyl iodide was added prior to work-up. Thick layer chromatography produced **6c**, identical in all respects to the previously prepared sample [7].

Attempted Preparation of **6d**.

A solution of titanium tetrachloride (0.8 ml) in toluene (10 ml) was added to a solution of **1** (2 g, 9 mmoles) and *t*-butylamine (2.8 g, 38 mmoles) in toluene (50 ml). No reaction was observed up to 24 hours even with added titanium tetrachloride.

*N*-(*p*-Toluenesulfonyl)-6-methylbenzo[5,6]cyclohepta[1,2-*c*]pyridin-6,11-imine (**8**).

*p*-Toluenesulfonyl chloride (3.83 g, 0.020 moles) was added to a solution of **7** [1a] (4.05 g, 0.018 moles) in pyridine (35 ml) and the resulting reddish solution was stirred at room temperature overnight. The pyridine was removed *in vacuo* and the residue was triturated with cold ethanol. The resulting beige solid was filtered, rinsed with cold ethanol and dried, 5.3 g, mp 166-168°. Recrystallization from ethanol gave mp 169-171°.

*Anal.* Calcd. for $C_{22}H_{18}N_2O_2S$ (374.45): C, 70.56; H, 4.85; N, 7.48. Found: C, 70.71; H, 4.69; N, 7.15.

6,11-Dimethyl-11-*p*-toluenesulfonamidobenzo[5,6]cyclohepta[1,2-*c*]pyridine (**9**).

A solution of methyl lithium in THF (13 ml, 1.4 *M*, 18 mmoles) was added to a solution of **8** (3.5 g, 9 mmoles) in THF (25 ml) and the resulting solution was stirred for 2 hours. The solvent was evaporated and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with saturated sodium chloride solution, dried (sodium sulfate) and evaporated to dryness to give 3.13 g of beige solid. Recrystallization from ethanol gave a white solid, mp 182.5-184°.

*Anal.* Calcd. for $C_{23}H_{22}N_2O_2S$ (390.49): C, 70.74; H, 5.68; N, 7.17. Found: C, 70.98; H, 6.03; N, 7.03.

5,6-Dihydro-6,11-dimethyl-12-(*p*-toluenesulfonyl)benzo[5,6]cyclohepta-[1,2-*c*]pyridin-6,11-imine (**10a**).

Dioxane (24 ml) was added to a solution of **9** (1.2 g) in 50% aqueous sodium hydroxide solution (24 ml). The resulting two-phase mixture was heated to reflux for 2 hours, cooled and diluted with water. The aqueous solution was extracted wtih ethyl acetate and the extracts were washed with water, saturated sodium chloride solution and dried (sodium sulfate). The solvent was evaporated *in vacuo* to give 1.25 g of off-white solid, mp 193-199°. Recrystallization from cyclohexane gave 1.0 g, mp 199.5-201°; nmr (deuteriochloroform): $\delta$ 2.00 (s, C6-$CH_3$, 3H), 2.27 (s, 3H), 2.30 (s, 3H), 2.60 (d, J = 18 Hz, H-5$\alpha$, 1H), 3.73 (d, J = 18 Hz, H-5$\beta$, 1H), 6.79 (d, J = 2.5 Hz, H-3, 1H), 7.00-7.30 (m, H-7, H-8, H-9, H-10, *p*-toluenesulfonyl-H-3', H-5', 6H), 7.74 (d, J = 4 Hz, *p*-toluenesulfonyl-H-2', H-6', 2H), 8.32 (d, J = 2.5 Hz, H-4, 1H), 8.58 (s, H-1, 1H).

*Anal.* Calcd. for $C_{23}H_{22}N_2O_2S$ (390.49): C, 70.74; H, 5.68; N, 7.17. Found: C, 70.77; H, 5.71; N, 7.20.

5,6-Dihydro-6,11-dimethylbenzo[5,6]cyclohepta[1,2-*c*]pyridine-6,11-imine (**10b**).

A solution of **10a** (0.70 g) in concentrated hydrochloric acid (10 ml) and glacial acetic acid (10 ml) was heated under reflux for 5 hours. The cooled reaction mixture was diluted with water (200 ml) and made alkaline by the addition of 20% sodium hydroxide solution. The alkaline solution was extracted wtih methylene chloride and the organic extracts were washed with saturated sodium chloride solution and dried (sodium sulfate). Removal of the solvent left a brown oil (0.30 g) that was converted to a fumarate salt by the additon of fumaric acid (0.15 g) in hot acetone. The solid that formed was recrystallized from acetone to give 0.20 g, mp 186.5-191° dec; nmr (DMSO-$d_6$): $\delta$ 1.67 (s, C6-$CH_3$, 3H), 1.97 (s, C11-$CH_3$, 3H), 2.70 (d, J = 18 Hz, H-5$\alpha$, 1H), 3.15 (d, J = 18 Hz, H-5$\beta$, 1H), 6.63 (s, fumaric acid olefinic, 3H), 7.02 (d, J = 2.5 Hz, H-4, 1H), 7.17-7.66 (m, H-7, H-8, H-9, H-10, 4H), 8.32 (d, J = 2.5 Hz, H-3, 1H), 8.60 (s, H-1, 1H).

*Anal.* Calcd. for $C_{17}H_{16}N_2 + 1.5C_4H_4O$ (422.44): C, 65.40; H, 5.25; N, 6.63. Found: C, 65.51; H, 5.38; N, 6.36.

## REFERENCES AND NOTES

[1a] For paper IV in this series see D. G. Brenner, K. M. Cavolowsky and K. L. Shepard, *J. Heterocyclic Chem.*, **22**, 805 (1985); [b] Presented in part at the Northeast Regional ACS Meeting, Potsdam, New York, June 30-July 3, 1980.

[2] Present address: Department of Biochemistry, University of Leicester, Leicester, LE1 7RH, England.

[3] P. S. Anderson, M. E. Christy, C. D. Colton, W. Halczenko, G. S. Potnicello and K. L. Shepard, *J. Org. Chem.*, **44**, 3127 (1979).

[4] B. V. Clineschmidt, MSDRL, private communication.

[5] W. Halczenko and K. L. Shepard, *J. Heterocyclic Chem.*, **19**, 967 (1982).

[6] D. G. Brenner, W. Halczenko and K. L. Shepard, *J. Heterocyclic Chem.*, **19**, 897 (1982).

[7] D. G. Brenner, W. Halczenko and K. L. Shepard, *J. Heterocyclic Chem.*, **22**, 555 (1985).

[8] L. I. Krimen and D. J. Cota, *Org. React.*, **17**, 213 (1969).

[9] F. A. Davis and P. A. Mancinell, *J. Org. Chem.*, **42**, 398 (1977).