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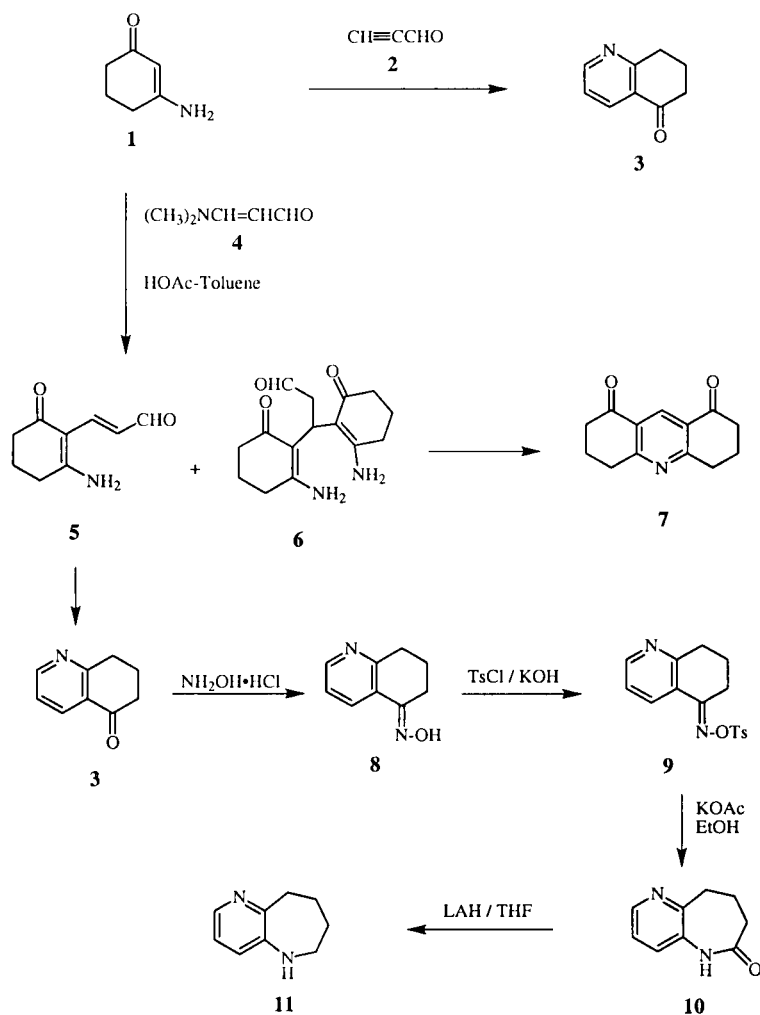
The synthesis of 7,8-dihydro-5(6*H*)-quinolinone (**3**) from commercially available 3-amino-2-cyclohexen-1-one (**1**) and 3-(dimethylamino)acrolein (**4**) in 23% yield avoids the preparation of propynal (**2**). Conversion of 5-(4-methylphenylsulfonyl)-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]azepine (**12**) to 6-(4-methylphenylsulfonyl)-1,4,5,6-tetrahydropyrazolo[3,4-*d*]pyrido[3,2-*b*]azepine (**24**) is described. Removal of the *N*-(4-methylphenylsulfonyl) group with 40% sulfuric acid in acetic acid gave the tricyclic azepine **26**. Application of a similar series of reactions to 5-(4-nitrobenzoyl)-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]azepine (**13**) afforded 6-(4-nitrobenzoyl)-1,4,5,6-tetrahydropyrazolo[3,4-*d*]pyrido[3,2-*b*]azepine (**25**).

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As part of a project to synthesize novel tricyclic azepines, we have investigated methods for the synthesis of the unknown heterocycle 1,4,5,6-tetrahydropyrazolo[3,4-*d*]pyrido[3,2-*b*]azepine (**26**). The synthesis of intermediate 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]azepine (**11**) followed the literature procedure [1] with one excep-

tion (Scheme I). The difficulty in preparing propynal (**2**) [2] needed for the reaction with 3-amino-2-cyclohexen-1-one (**1**) to prepare 7,8-dihydro-5(6*H*)-quinolinone (**3**) [3] prompted the use of 3-(dimethylamino)acrolein (**4**) as an equivalent of **2**. The major product was not the desired **3** but the dimer **7** which probably results from condensation

Scheme 1

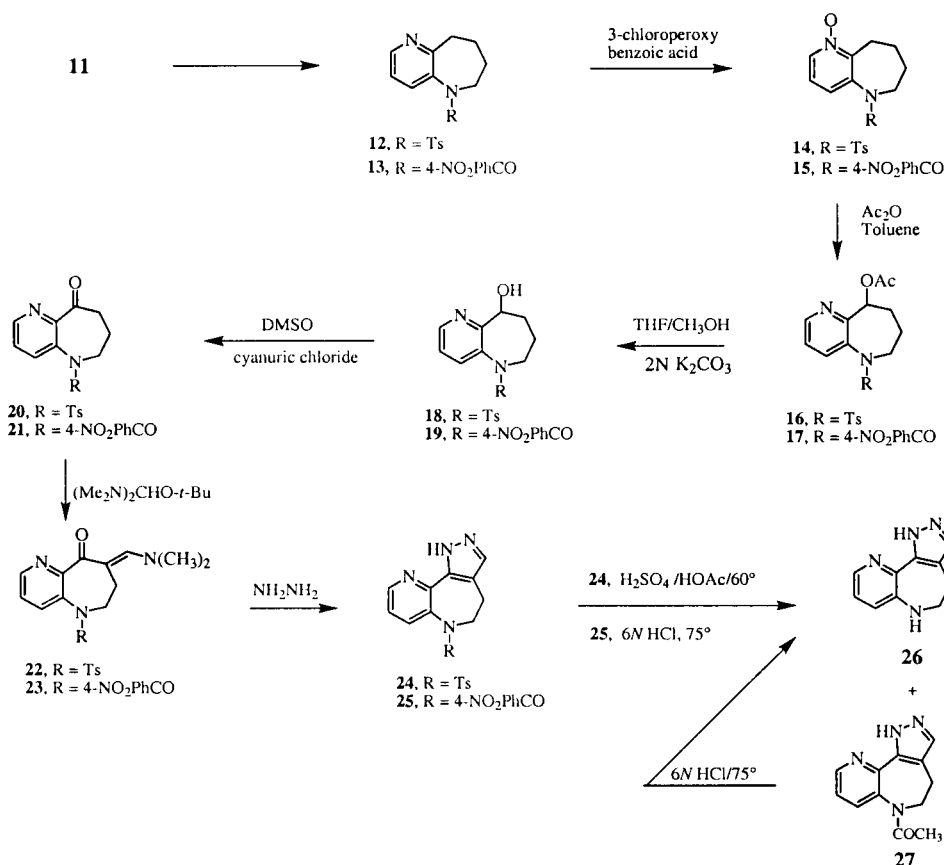


of intermediate **5** with another equivalent of 3-amino-cyclohexen-1-one (**1**) to form **6**. Ring closure of **6** and aromatization by loss of acetaldehyde would give **7**.

Attempts to decrease the formation of **7** by: (a) use of excess acrolein **4**; (b) slow addition of **1** to an excess

benzazepine-5-ones [**5**] were not successful. However, treatment of the *N*-blocked pyrido[3,2-*b*]azepines **12** and **13** with 3-chloroperoxybenzoic acid gave the *N*-oxides **14** (100%) and **15** (85%), respectively, as intermediates for introduction of the 9-keto group (Scheme II).

Scheme 2



acrolein **4** in acetic acid-toluene or; (c) use of trifluoroacetic acid as the acid catalyst failed to increase the yield of **3**. Heating **1** and **4** (neat) at 130-150° gave tar, while the reaction of **1** and malonaldehyde bis(dimethylacetal) in acetic acid gave mainly the undesired dimer **7**. Although the yield of **3** from **1** and **4** was low, the product **3** could be conveniently and selectively isolated in 23% yield by extraction of the reaction product with hot hexane. Compound **3** was converted without event to pyrido[3,2-*b*]azepine **11** by the literature procedure [1] as shown in Scheme I.

Blocking of the amino group in azepine **11** was carried out with tosyl chloride and with 4-nitrobenzoyl chloride to give derivatives **12** and **13**. Attempts to convert **12** or **13** to **20** and **21**, respectively, by oxidation with potassium permanganate in a magnesium sulfate buffer as described in the literature for oxidations of 1-substituted-1,2,3,4-tetrahydro-1-benzazepines [4] to 1,2,3,4-tetrahydro-1-

Introduction of the keto group into the seven member ring was accomplished by rearranging the pyridine *N*-oxides **14** and **15** to give exclusively acetoxylation into the α -methylene group. The rearrangement of *N*-oxides of 2-alkylpyridines or annulated pyridine *N*-oxides with a CH₂ group in the pyridine 2 position is a general procedure for functionalization of the 2-alkyl position [6]. We have extended this reaction to the type with a seven member ring fused to the pyridine ring to give **16** and **17** in good yields.

Hydrolysis of the acetyl group in derivatives **16** and **17** afforded **18** and **19** along with 5-10% of the 4,5-ene products where the acetoxy group had been eliminated. Oxidation of the hydroxyl group with dimethyl sulfoxide-cyanuric chloride [7] gave the keto compounds **20** and **21** in 90% and 49% yield, respectively. The use of dimethyl sulfoxide-acetic anhydride [8] to oxidize the hydroxyl group in **19** gave a less pure product than the dimethyl sulfoxide-cyanuric chloride procedure.

Reaction of the pyrido[3,2-*b*]azepine-9-ones **20** and **21** with *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent) [9] gave the dimethylamino-methylene derivatives **22** and **23**, which on reaction with hydrazine afforded the tricyclic azepines **24** (66%) and **25** (77%), respectively. Detosylation of **24** by a literature procedure [10] afforded a 1:1 mixture of **26** and **27** in an 82% yield.

The *N*-acetyl derivative **27** could be deacylated in 91% yield by heating a solution in 6*N* hydrochloric acid at 75° for 4.5 hours. In a similar manner the *N*-4-nitrobenzoyl derivative **25** was deblocked to give **26** (94%) by heating a solution in 6*N* hydrochloric acid at 75° for 24 hours. Thus, the synthesis of the tricyclic tetrahydropyrazolo[3,4-*d*]pyrido[3,2-*b*]azepine **26** has been accomplished with either an *N*-tosyl or an *N*-4-nitrobenzoyl blocking group and either of the blocking groups readily removed in good yield under acidic hydrolytic conditions.

EXPERIMENTAL

All melting points were determined on a Mel-Temp apparatus and are uncorrected. Thin layer chromatography was performed with Analtech silica GF plates and preparative layer chromatography was performed with Analtech 20 x 20 cm 2000 micron silica gel GF plates. Proton nuclear magnetic resonance spectra (nmr) were recorded on a General Electric QE-300 Fourier transform nuclear magnetic resonance spectrometer. Chemical shifts are reported as δ in units of parts per million relative to an internal standard of tetramethylsilane. Coupling constants are reported in Hertz (Hz). Multiplicities are as follows: s, singlet; d, doublet; t, triplet; m, multiple, br, broad.

7,8-Dihydro-5(6*H*)-quinolinone (**3**).

A mixture of 57.93 g (0.52 mole) of 3-amino-2-cyclohexen-1-one (**1**) and 76.8 g (0.673 mole) of 3-(dimethylamino)acrolein (**4**) in a mixture of 62.5 ml (1.08 moles) of acetic acid and 270 ml of toluene was refluxed overnight under argon. The volatile products were removed under vacuum and to the residue was added 200 ml of toluene and the solvent removed under vacuum. The residue was extracted twice with 500 ml of dichloromethane. To the extract was added carefully solid sodium bicarbonate with stirring and then the extract was washed with 300 ml of saturated sodium bicarbonate. The extract was dried (sodium sulfate) and filtered through a thin pad of hydrous magnesium silicate and the pad washed with dichloromethane. The filtrate was concentrated under vacuum to give a black oil. The product was extracted from the black oil by refluxing with hexane and decanting the hot hexane. The hexane extract was concentrated under vacuum to give 17.30 g (23%) of product **3** as a tan oil (one spot by tlc on silica gel with hexane-ethyl acetate (1:2) as solvent). A sample of the hexane insoluble solid (major component) was crystallized from ethyl acetate-hexane to give white crystals, mp 140-142°, identified as **7**.

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.5; H, 6.1; N, 6.5. Found: C, 72.1; H, 5.8; N, 6.3.

6,7,8,9-Tetrahydro-5-(4-methylphenylsulfonyl)-5*H*-pyrido[3,2-*b*]azepine (**12**).

To a cooled (ice bath) solution of 4.45 g (30 mmoles) of 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]azepine (**11**) and 5.3 g (39 mmoles) of *N,N*-disopropylethylamine in 45 ml of dichloromethane was added 7.58 g (39 mmoles) of 4-methylphenylsulfonyl chloride in 20 ml of dichloromethane. The mixture was stirred at room temperature overnight and was washed with 1*N* sodium bicarbonate, water, brine, and dried (sodium sulfate). The solvent was removed to give 11.2 g of a brown oil. Chromatography on silica gel with ethyl acetate gave 8.04 g (88%) of crystals, mp 76-78°; ¹H nmr (deuteriochloroform): δ 1.56, 1.73, 2.54, 3.75 (m, 8H, 4 x CH₂), 2.42 (s, 3H, CH₃), 7.13-7.20 (m, 1H), 7.22-7.31 (m, 2H), 7.53-7.61 (m, 2H), 7.71-7.79 (m, 1H), 8.36-8.43 (m, 1H); ms: *m/z* 303 (MH⁺).

Anal. Calcd. for $C_{16}H_{18}N_2SO_2$: C, 63.6; H, 6.0; N, 9.3. Found: C, 63.5; H, 6.0; N, 9.1.

6,7,8,9-Tetrahydro-5-(4-methylphenylsulfonyl)-5*H*-pyrido[3,2-*b*]azepine *N*-Oxide (**14**).

A mixture of 8.04 g (26.6 mmoles) of 6,7,8,9-tetrahydro-5-(4-methylphenylsulfonyl)-5*H*-pyrido[3,2-*b*]azepine (**12**) and 9.18 g (53.2 moles) of 3-chloroperoxybenzoic acid in 100 ml of dichloromethane was stirred at room temperature overnight. Additional dichloromethane (150 ml) was added (to dissolve solids) and the solution washed with saturated sodium bicarbonate, water, brine and dried (sodium sulfate). The solvent was removed to give 9.50 g (100%) of a solid (not purified); ¹H nmr (deuteriochloroform): δ 1.57, 1.76, 2.90, 3.75 (m, 8H, 4 x CH₂), 2.42 (s, 3H, CH₃), 7.05-7.11 (m, 1H), 7.22-7.31 (m, 2H), 7.32-7.44 (m, 1H), 7.58-7.68 (m, 2H), 8.20-8.28 (m, 1H).

Anal. Calcd. for $C_{16}H_{18}N_2SO_3$: C, 60.4; H, 5.7; N, 8.8. Found: C, 59.7; H, 5.5; N, 8.0.

6,7,8,9-Tetrahydro-9-hydroxy-5-(4-methylphenylsulfonyl)-5*H*-pyrido[3,2-*b*]azepine, *O*-Acetate (**16**).

A mixture of 0.30 g (0.94 mmole) of 6,7,8,9-tetrahydro-5-(4-methylphenylsulfonyl)-5*H*-pyrido[3,2-*b*]azepine *N*-oxide (**14**), 4 ml of acetic anhydride and 4 ml of toluene was refluxed for 5 hours under argon. The volatile products were removed under vacuum and toluene (25 ml) added and removed three times. The residue was dissolved in 30 ml of dichloromethane and the solution washed with water, 1*N* sodium bicarbonate, brine and dried (sodium sulfate). The solvent was removed and the residual oil was triturated with ethanol to give 0.27 g (84%) of crystals, mp 124-125°; ¹H nmr (deuteriochloroform): δ 1.85 (m, 4H, 2 x CH₂), 2.16 (s, 3H), 2.43 (s, 3H), 3.32 (m, br, 1H, -N-CH), 4.05 (m, br, 1H, N-CH), 5.50 (m, br, 1H, O-CH), 7.18-7.38 (m, 3H), 7.65-7.80 (m, 3H), 8.47-8.49 (m, 1H).

Anal. Calcd. for $C_{18}H_{20}N_2SO_4$: C, 60.0; H, 5.6; N, 7.8. Found: C, 60.0; H, 5.6; N, 7.7.

6,7,8,9-Tetrahydro-9-hydroxy-5-(4-methylphenylsulfonyl)-5*H*-pyrido[3,2-*b*]azepine (**18**).

A mixture of 7.52 g (20.8 mmoles) of 6,7,8,9-tetrahydro-9-hydroxy-5-(4-methylphenylsulfonyl)-5*H*-pyrido[3,2-*b*]azepine *O*-acetate (**16**) and 25 ml of 2*N* potassium carbonate (62.6 mmoles) in 80 ml of methanol-tetrahydrofuran (1:1) was stirred at room temperature overnight. The mixture was concentrated under vacuum and extracted with ethyl acetate. The organic layer was washed with 15 ml of 2*N* citric acid, water, brine and

dried (sodium sulfate). The solvent was removed to give 8.14 g of a brown oil. Crystallization from ether gave 4.94 g (74%) of white crystals, mp 95-98°; ^1H nmr (deuteriochloroform): δ 1.29 (m, 1H), 1.67-1.78 (m, 1H), 1.80-1.97 (m, 1H), 2.10 (m, 1H), 2.42 (s, 3H), 2.88 (m, 1H, -CHOH), 4.05 (m, 1H), 4.47 (m, 1H), 5.49 (d, $J = 2.77\text{ Hz}$, -CHOH), 7.25-7.31 (m, 3H), 7.56-7.61 (m, 2H), 7.83-7.86 (m, 1H), 8.45-8.52 (m, 1H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{SO}_3$: C, 60.4; H, 5.7; N, 8.8. Found: C, 60.4; H, 5.5; N, 8.7.

The residue from the mother liquors showed the presence of a second component which by nmr was identified as 6,7-dihydro-5-(4-methylphenylsulfonyl)-5H-pyrido[3,2-*b*]azepine, a product from elimination of the *O*-acetate moiety.

5,6,7,8-Tetrahydro-5-(4-methylphenylsulfonyl)-9H-pyrido[3,2-*b*]azepin-9-one (20).

To a mixture of 4.90 g (15.4 mmoles) of 6,7,8,9-tetrahydro-9-hydroxy-5-(4-methylphenylsulfonyl)-5H-pyrido[3,2-*b*]azepine (18) in 40 ml of dichloromethane and 11 ml of dimethyl sulfoxide (cooled to -15°) was added 7.09 g (38.4 mmoles) of cyanuric chloride and 6 ml of hexamethylphosphoramide. The mixture was stirred for 1 hour (-15°) and the clear solution was allowed to stand at -18° for 4 hours. To the cold mixture was added 21 ml of triethylamine. The stirred mixture was allowed to warm to room temperature (10 minutes) and was poured into water. The mixture was extracted with dichloromethane and the extract washed with water, brine and dried (sodium sulfate). The solvent was removed and the residue was chromatographed on a silica gel column with ethyl acetate as eluent to give 4.43 g (91%) of crystals, mp 118-120°; ^1H nmr (deuteriochloroform): δ 1.96-2.42 (m, 2H), 2.43 (s, 3H), 3.87 (t, 2H), 7.28 (d, $J = 8.17\text{ Hz}$, 2H), 7.47-7.51 (m, 1H), 7.55 (d, $J = 8.29\text{ Hz}$, 2H), 8.01-8.02 (m, 1H), 8.67-8.71 (m, 1H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{SO}_3$: C, 60.7; H, 5.1; N, 8.9. Found: C, 60.5; H, 5.0; N, 8.6.

8-[(Dimethylamino)methylene]-5,6,7,8-tetrahydro-5-(4-methylphenylsulfonyl)-9H-pyrido[3,2-*b*]azepin-9-one (22).

A mixture of 1.43 g (4.52 mmoles) of 5,6,7,8-tetrahydro-5-(4-methylphenylsulfonyl)-9H-pyrido[3,2-*b*]azepin-9-one (20) and 2 ml (9.04 mmoles) of *tert*-butoxybis(dimethylamino)methane in 30 ml of dichloromethane was refluxed overnight. The solvent was removed and the residue dissolved in dichloromethane and the solution filtered through a thin pad of hydrous magnesium silicate. The filtrate was concentrated to dryness to give 1.42 g (85%) of solid, mp 147-152°; ^1H nmr (deuteriochloroform): δ 2.41 (s, 3H), 2.48 (t, 2H), 3.00 (s, 6H), 3.80 (t, 2H), 7.03 (s, 1H), 7.19 (s, 1H), 7.22 (s, 1H), 7.41-7.47 (m, 3H), 7.87-7.90 (m, 1H), 8.72-8.74 (m, 1H). The compound was used in the next step without further purification.

1,4,5,6-Tetrahydro-6-(4-methylphenylsulfonyl)pyrazolo[3,4-*d*]pyrido[3,2-*b*]azepine (24).

A mixture of 1.47 g (3.8 mmoles) of 8-[(dimethylamino)methylene]-5,6,7,8-tetrahydro-5-(4-methylphenylsulfonyl)-9H-pyrido[3,2-*b*]azepin-9-one (22) and 0.25 mole (7.6 mmoles) of hydrazine in 40 ml of ethanol was refluxed for 3 hours. The solvent was removed under vacuum and the residue dissolved in 50 ml of dichloromethane. The solution was washed with water, brine and dried (sodium sulfate). The solution was filtered through a thin pad of hydrous magnesium silicate and the filtrate concentrated to dryness to give 0.86 g (66%) of a solid (one spot

by tlc on silica gel), mp 48-65°. Washing the filter pad with ethyl acetate gave 0.40 g of slightly impure product.

The solid, mp 48-65°, ^1H nmr (deuteriochloroform): δ 2.27 (s, 3H), 3.05 (t, $J = 5.76\text{ Hz}$, 2H), 3.92 (s-br, 2H), 7.00 (s, 1H), 7.03 (s, 1H), 7.25-7.34 (m, 4H), 8.04-8.08 (m, 1H), 8.48-8.52 (m, 1H), 11.0 (s-br, NH); ms: *ci* 341 (MH^+).

Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_4\text{SO}_2 \cdot \text{H}_2\text{O}$: C, 57.0; H, 5.1; N, 15.6. Found: C, 57.0; H, 4.7; N, 15.4.

1,4,5,6-Tetrahydropyrazolo[3,4-*d*]pyrido[3,2-*b*]azepine (26) and 6-Acetyl-1,4,5,6-tetrahydropyrazolo[3,4-*d*]pyrido[3,2-*b*]azepine (27).

A mixture of 2.97 g (8.7 mmoles) of 1,4,5,6-tetrahydro-6-(4-methylphenylsulfonyl)pyrazolo[3,4-*d*]pyrido[3,2-*b*]azepine (24) in 50 ml of 40% sulfuric acid in glacial acetic acid was stirred at 60° overnight. The mixture was poured into a mixture of ice and water and made basic with solid sodium carbonate (pH 8). The mixture was extracted with dichloromethane and the extract washed with water, brine and dried (sodium sulfate). The solution was filtered through a thin pad of hydrous magnesium silicate and the filtrate concentrated to dryness to give 1.47 g of solid, a 1:1 mixture of two compounds. Chromatography on silica gel with ethyl acetate gave 0.30 g of derivative 26, mp 197-200°; ^1H nmr (deuteriochloroform): δ 2.91-2.98 (m, 2H), 3.38-3.49 (m, 2H), 4.29 (s-br, NH), 6.91-7.04 (m, 2H), 7.49 (s, 1H), 8.08-8.10 (m, 1H), 11.5 (s-br, NH); ms: *ci* 186 (M^+).

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_4 \cdot 1/4\text{H}_2\text{O}$: C, 63.0; H, 5.6; N, 29.4. Found: C, 62.7; H, 5.31; N, 29.7.

The second component isolated by chromatography was identified as the 6-acetyl derivative 27 (0.20 g), mp 221-223°; ^1H nmr (deuteriochloroform): δ 1.98 (s, 1H), 2.82-2.93 (m, 2H), 3.30-3.44 (m, 1H), 4.88-4.89 (m, 1H), 7.27-7.32 (m, 1H), 7.57-7.62 (m, 2H), 8.58-8.62 (m, 1H); ms: *ci* 229 (MH^+).

Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{N}_4\text{O} \cdot 1/4\text{H}_2\text{O}$: C, 61.9; H, 5.4; N, 24.1. Found: C, 61.9; H, 5.2; N, 24.2.

A solution of 28.8 mg of 6-acetyl derivative 27 in 10 ml of 6*N* hydrochloric acid was heated at 75° (oil bath) for 4.5 hours and stirred at room temperature overnight. The solution was made basic with 5*N* sodium hydroxide (pH 10) and extracted with ethyl acetate. The extract was washed with brine and the solvent removed to give 21 mg (91%) of 26; ms: *ei* 187 (MH^+); nmr identical to an authentic sample.

5-(4-Nitrobenzoyl)-6,7,8,9-tetrahydro-5H-pyrido[3,2-*b*]azepine (13).

A mixture of 2.96 g (20 mmoles) of 6,7,8,9-tetrahydro-5H-pyrido[3,2-*b*]azepine (11), 4.45 g (24 mmoles) of 4-nitrobenzoyl chloride and 3.03 g (30 mmoles) of triethylamine in 50 ml of dichloromethane was stirred at room temperature for 4 hours and the mixture was poured into water. The organic layer was separated and washed with sodium bicarbonate, water, brine and dried (sodium sulfate). The solvent was removed to give 6.35 g of tan solid. Trituration with 25 ml of dichloromethane gave 5.50 g (92%) of yellow crystals, mp 231-233°; ^1H nmr (deuteriochloroform): δ 1.55-1.75 (m, 1H), 1.95-2.36 (m, 3H), 2.74-2.93 (m, 1H), 3.12-3.34 (m, 2H), 4.95-5.13 (m, 1H), 6.86-6.95 (m, 2H), 7.30-7.40 (m, 2H), 8.00-8.12 (m, 2H), 8.30-8.40 (m, 1H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_3 \cdot 1/4\text{H}_2\text{O}$: C, 63.7; H, 5.2; N, 13.9. Found: C, 63.6; H, 5.1; N, 13.7.

5-(4-Nitrobenzoyl)-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]azepine, *N*-Oxide (15).

A mixture of 3.57 g (12 mmoles) of 5-(4-nitrobenzoyl)-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]azepine (13) and 2.07 g (24 mmoles) 3-chloroperoxybenzoic acid in 45 ml of dichloromethane was stirred under argon overnight at room temperature. The mixture was washed with 1*N* sodium hydroxide, water, brine and dried (sodium sulfate). The solvent was removed to give 3.7 g of white solid which was triturated with methanol to give 3.21 g (85%) of crystals, mp 231-233°; ¹H nmr (deuteriochloroform): δ 1.56-1.75 (m-br, 1H), 1.92-2.26 (m-br, 3H), 2.72-2.98 (m-br, 2H), 4.25-4.37 (m-br, 1H), 4.93-5.09 (m-br, 1H), 6.43-6.57 (m, 1H), 6.76-6.88 (m, 1H), 7.28-7.50 (m, 2H), 8.01-8.24 (m, 3H); ms: ci 314 (MH⁺).

Anal. Calcd. for C₁₆H₁₅N₃O₄: C, 61.3; H, 4.83; N, 13.4. Found: C, 61.1; H, 4.9; N, 13.3.

9-Hydroxy-5-(4-nitrobenzoyl)-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]azepine, *O*-Acetate (17).

A mixture of 3.21 g (10.2 mmoles) of 5-(4-nitrobenzoyl)-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]azepine, *N*-oxide (15) and 35 ml of acetic anhydride in 35 ml of toluene was refluxed for 5 hours under argon. The mixture was concentrated to dryness under vacuum and toluene (25 ml) added (three times) and the solvent removed after each addition. The residual brown oil was dissolved in dichloromethane and the solution washed with 1*N* sodium bicarbonate, water, brine and dried (sodium sulfate). The solution was filtered through a thin pad of hydrous magnesium silicate and the filter pad washed with ethyl acetate. The filtrate was concentrated under vacuum to give 3.43 g (95%) of crystals (one spot by tlc on silica gel with ethyl acetate as solvent). A sample was recrystallized from ethyl acetate to give white crystals, mp 135-137°; ¹H nmr (deuteriochloroform): δ 1.8-2.05 (m, 2H), 2.12 (s, 0.9H, CH₃), 2.15-2.49 (m, 2H), 2.32 (s, 2.1H, CH₃), 2.82-3.02 (m, 1H, -CHN-), 4.83-4.94 (m, 0.7H, -CHN-), 5.05-5.65 (m, 0.3H, -CHN-), 6.03-6.12 (m, 0.7H, -CHOAc), 6.23-6.32 (m, 0.3H, -CHOAc), 6.8-7.8 (m, 2H), 7.53-7.62 (m, 2H), 8.02-8.13 (m, 2H), 8.40-8.48 (m, 1H); ms: ci 356 (MH⁺).

Anal. Calcd. for C₁₈H₁₇N₃O₅: C, 60.8; H, 4.8; N, 11.8. Found: C, 60.6; H, 5.1; N, 11.8.

9-Hydroxy-5-(4-nitrobenzoyl)-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]azepine (19).

To a solution of 3.3 g (9.28 mmoles) of 9-hydroxy-5-(4-nitrobenzoyl)-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]azepine *O*-acetate (17) in 45 ml of methanol and 26 ml of tetrahydrofuran was added to 25 ml of 2*N* potassium carbonate. The mixture was stirred at room temperature for 3.5 hours and the mixture concentrated under vacuum. The residual aqueous mixture was extracted with ethyl acetate and the extract washed with water, brine and dried (sodium sulfate). The solution was filtered through a thin pad of hydrous magnesium silicate and the pad washed with ethyl acetate. The filtrate was concentrated to dryness to give 2.7 g (93%) of solid (one spot by tlc on silica gel with dichloromethane-ethyl acetate (8:2) as solvent). A sample from a 1 mmole run was crystallized from ethyl acetate to give crystals, mp 182-185°; ¹H nmr (deuteriochloroform): δ 1.5-1.75 (m, 1H), 1.94-2.30 (m, 1H), 2.34-2.50 (m, 1H), 2.60-2.78 (m, 1H), 2.91-3.12 (m, 0.7H, -CHN-), 4.90-5.15 (m, 0.3H, -CHN-; 1H, -CHN-; 1H, -CHO-), 5.59-6.01 (d, 0.7H, OH), 6.40-6.48 (d, 0.3H, OH), 6.80-7.09 (m, 2H), 7.25-7.42 (m, 2H), 8.0-8.14 (m, 2H), 8.40-8.50 (m, 1H); ms: ci 314 (MH⁺).

Anal. Calcd. C₁₆H₁₅N₃O₄: C, 61.3; H, 4.8; N, 13.4. Found: C, 61.2; H, 5.0; N, 13.2.

5-(4-Nitrobenzoyl)-5,6,7,8-tetrahydro-9*H*-pyrido[3,2-*b*]azepin-9-one (21).

To a solution of 1.88 g (6 mmoles) of 9-hydroxy-5-(4-nitrobenzoyl)-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*b*]azepine (19) in 20 ml of dichloromethane and 5 ml of dimethyl sulfoxide cooled to -25° was added 2.43 g (13.2 mmoles) of cyanuric chloride. The mixture was stirred for 2 hours and an additional 8 ml of dichloromethane, 5 ml of dimethyl sulfoxide and 1.2 g of cyanuric chloride was added. The mixture was allowed to stand at -20° for 6 hours and then 8.5 ml of triethylamine was added. The mixture was stirred and after warming to room temperature was poured into water. The mixture was extracted with dichloromethane and the extract washed with water, brine and dried (sodium sulfate). The solution was filtered through a thin pad of hydrous magnesium silicate and the filter pad washed with ethyl acetate. The filtrate was concentrated to dryness to give 2.95 g of solid. Chromatography on silica gel with ethyl acetate as solvent gave 0.91 g (49%) of crystals (one spot by tlc on silica gel with ethyl acetate as solvent). A sample from a 1 mmole run was recrystallized from ethyl acetate to give crystals, mp 188-190°; ¹H nmr (deuteriochloroform): δ 2.14-2.31 (m-br, 2H), 3.93-3.02 (t, 2H), 4.1 (m-br, 2H), 7.14-7.16 (m, 1H), 7.16-7.24 (m, 1H), 7.38-7.43 (m, 2H), 8.05-8.13 (m, 2H), 8.63-8.68 (m, 1H); ms: ci 312 (MH⁺).

Anal. Calcd. for C₁₆H₁₃N₃O₄: C, 61.7; H, 4.2; N, 13.5. Found: C, 61.9; H, 4.4; N, 13.4.

8-[(Dimethylamino)methylene]-5-(4-nitrobenzoyl)-5,6,7,8-tetrahydro-9*H*-pyrido[3,2-*b*]azepin-9-one (23).

A mixture of 0.11 g (0.35 mmole) of 5-(4-nitrobenzoyl)-5,6,7,8-tetrahydro-9*H*-pyrido[3,2-*b*]azepin-9-one (21) and 0.122 g (0.7 mmole) of *tert*-butoxybis(dimethylamino)methane in 5 ml of dichloromethane was refluxed 23 hours and concentrated under vacuum. The residue was dissolved in 3 ml of dichloromethane and filtered through a thin pad of hydrous magnesium silicate. The filter pad was washed sequentially with dichloromethane, ethyl acetate and dichloromethane-methanol (95:5). The dichloromethane-methanol was concentrated under vacuum to give 90 mg (70%) of white solid, mp 124-138°; ¹H nmr (deuteriochloroform): δ 2.28-2.41 (m, 1H), 3.12-3.24 (m, 1H), 3.25 (s, 6H), 3.51-3.92 (m, 1H), 4.50-4.61 (m, 1H), 6.96-7.03 (m, 1H), 7.05-7.14 (m, 1H), 7.36 (s, 1H), 7.39 (s, 1H), 7.97-8.06 (m, 3H), 8.09-8.65 (m, 1H); ms: ci 367 (MH⁺).

Anal. Calcd. for C₁₉H₁₈N₄O₄•1/2H₂O: C, 61.53; H, 5.03; N, 15.11. Found: C, 60.5; H, 5.1; N, 14.6.

1,4,5,6-Tetrahydro-6-(4-nitrobenzoyl)pyrazolo[3,4-*d*]pyrido[3,2-*b*]azepine (25).

A mixture of 1.02 g (2.78 mmoles) of 8-[(dimethylamino)methylene]-5-(4-nitrobenzoyl)-5,6,7,8-tetrahydro-9*H*-pyrido[3,2-*b*]azepin-9-one (23) and 0.17 ml (5.57 mmoles) of anhydrous hydrazine in 40 ml of ethanol was refluxed under argon for two hours and stirred one hour at room temperature. The solution was diluted with dichloromethane and washed with water, brine and dried (sodium sulfate). The solution was filtered through a thin pad of hydrous magnesium silicate and the filter pad washed with ethyl acetate. The filtrate was concentrated to dryness under vacuum to give 0.71 g (77%) of a solid (one spot by tlc on silica gel with ethyl acetate as solvent; Rf 0.61). A sam-

ple was crystallized from ethyl acetate to give light yellow crystals, mp 255-256°; ¹H nmr (deuteriochloroform): δ 2.90-3.09 (m, 2H), 3.10-3.36 (m, 1H), 5.09-5.22 (m, 1H), 6.82-6.96 (m, 2H), 7.14-7.26 (m, 2H), 7.59 (s, 1H), 7.91-8.02 (m, 2H), 8.38-8.48 (m, 1H), 11.4 (s-br, 1H, NH); ms: ci 336 (MH⁺).

Anal. Calcd. for C₁₇H₁₃N₅O₃•1/4H₂O: C, 60.1; H, 4.0; N, 20.6. Found: C, 60.1; H, 3.8; N, 20.1.

1,4,5,6-Tetrahydropyrazolo[3,4-*d*]pyrido[3,2-*b*]azepine **26** from **25**.

A mixture of 40 mg of **25** in 15 ml of 6*N* hydrochloric acid was heated at 75° (oil bath) for 24 hours. The cooled solution was made basic with solid sodium carbonate (*pH* 8) and extracted with ethyl acetate (2 x 40 ml). The extract was washed with brine, dried (sodium sulfate) and the solvent removed to give 21 mg (94%) of azepine **26**; ms: ei 187 (MH⁺); nmr identical to authentic sample.

REFERENCES AND NOTES

- [1] A. Jössang-Yanagida and C. Gansser, *J. Heterocyclic Chem.*, **15**, 249 (1978).
- [2] J. C. Sauer, *Org. Synth.*, Coll. Vol. **4**, 813 (1963).
- [3] F. Zymalkowski and H. Rimek, *Arch. Pharm.*, **294**, 759 (1961).
- [4] R. L. Augustine and W. G. Pierson, *J. Org. Chem.*, **34**, 1070 (1969).
- [5] I. McCall, G. R. Proctor and L. Purdic, *J. Chem. Soc. (C)*, 1126 (1970); G. R. Proctor, W. I. Ross, and A. Tapia, *J. Chem. Soc., Perkin Trans. I*, 1803 (1972); G. R. Proctor and B. M. L. Smith, *J. Chem. Soc., Perkin Trans I*, 862 (1978).
- [6] M. Katada, *J. Pharm. Soc. Japan*, **67**, 51 (1947); V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954); T. Cohen and G. L. Deets, *J. Am. Chem. Soc.*, **94**, 932 (1972); A. McKillop and M. K. Bhagrat, *Heterocycles*, **23**, 1697 (1985); T. W. Bell, Y. M. Cho, A. Firestone, K. Healy, J. J. Liu, R. Ludwig and S. D. Rothenberger, *Org. Synth.*, **69**, 226 (1990); H. Aït Haddou and G. G. A. Balavone, *Synth. Commun.*, **25**, 629 (1995).
- [7] J. D. Albright, *J. Org. Chem.*, **39**, 1977 (1974).
- [8] J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **87**, 4214 (1965); J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **89**, 2416 (1967).
- [9] H. Bredereck, G. Simchen, S. Rebadat, P. Kante Horn, R. Wahl, M. Hoffmann and P. Grieshaber, *Chem. Ber.*, **101**, 41 (1968); T. A. Lessen, D. M. Demka and S. M. Weinreb, *Tetrahedron Letters*, **31**, 2105 (1990); Jean-Pierre Vors, *J. Heterocyclic Chem.*, **28**, 1043 (1991).
- [10] P. D. Carpenter, V. Pesapati and G. R. Proctor, *J. Chem. Soc., Perkin Trans I*, 103 (1979); P. Carpenter and M. Lennon, *Chem. Commun.*, 664 (1973).