# Synthesis of *trans*-7-Hydroxymethyl-2-(2-benz[*d*]isoxazol-3-yl)octahydro-2*H*-pyrido[1,2-*a*]pyrazine



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An efficient synthesis of *trans*-7-hydroxymethyl-2-(2-benz[*d*]isoxazol-3-yl)octahydro-2*H*-pyrido[1,2-*a*]-pyrazine **2** is presented which relies on the equilibration of *cis*-dimethyl piperidinedicarboxylate followed by alkylation with phthalimidoethyl triflate.

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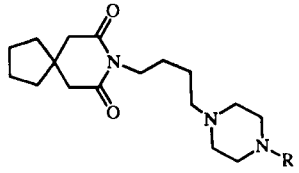
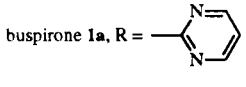
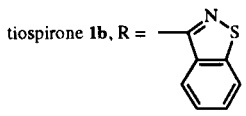
The synthesis of octahydro-2*H*-pyrido[1,2-*a*]pyrazines has been of interest for the study of conformationally restricted analogues of various piperazine based drugs [1]. Within Pfizer Central Research, Dr. Michael Bright has synthesized conformationally restricted analogues related to the serotonergic anxiolytics buspirone **1a** and tiospirone **1b** [2,3]. In this paper we describe an efficient synthesis of the title compound **2**, an intermediate in the preparation of compound **3** from Dr. Bright's laboratory [4].

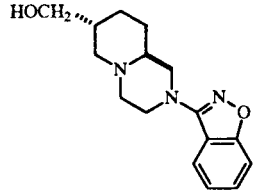


buspirone **1a**, R =

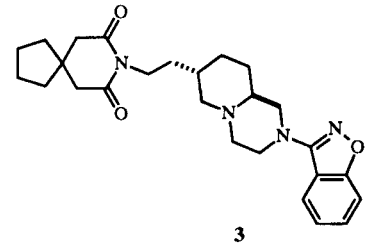


tiospirone **1b**, R =





**2**

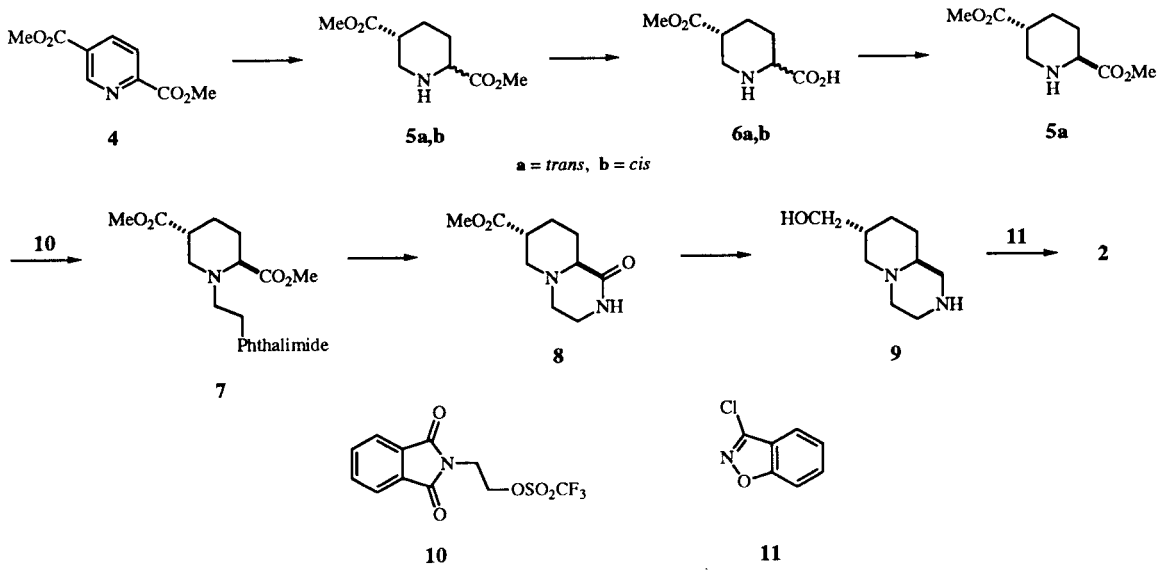


**3**

The synthesis started with the hydrogenation of dimethyl 2,5-pyridinedicarboxylate **4** with platinum oxide in acetic acid at 50 psi giving dimethyl 2,5-piperidinedicarboxylate **5** in 90% yield as a mixture of the predominant *cis* isomer **5b** and the minor *trans* isomer **5a** in a *ca.* 9:1 ratio. While the conversion of *cis*-2,5-piperidinedicarboxylic acid to the *trans* isomer has been described by Mastafanova [5], the harsh conditions (aqueous sodium hydroxide, 200°) caused us to investigate the milder equilibration of amino acids described by Yamada [6] and demonstrated for 2-piperidinecarboxylic acid by Shiraiwa [7]. Following a similar procedure, the mixture of **5a** and **5b** was refluxed in acetic acid with 10 mole % of salicylaldehyde. This caused an increase in the amount of the *trans* diester **5a** in the mixture but was accompanied by the appearance of two new compounds, the mono-esters **6a** and **6b**. After a reaction time of 20 hours, the mixture consisted of only **6a** and **6b** with the former as the major product. Evaporation of the acetic acid and addition of 2-propanol precipitated a solid in 59% yield that consisted of a 3:1 mixture of **6a** and **6b**. The separation of the isomers was accomplished after reesterification to the diester **5a** with thionyl chloride in methanol. Crystallization of the hydrochloride salt of **5a** from the crude diester mixture in 2-propanol afforded analytically pure *trans* **5a** in 67% yield. The reason for the hydrolysis of the ester is not known. One possibility is that water formed in the generation of an iminium intermediate in the equilibration reaction [8] hydrolyzed the activated C-2 ester. Methanol released in the hydrolysis could react with acetic acid to regenerate the water needed to hydrolyze the iminium group and allow the catalytic equilibration to proceed to completion.

To introduce the atoms needed for the piperazine ring, **5a** was treated with a freshly prepared solution of phthalimidoethyl triflate **10** [9] in a biphasic reaction (methylene chloride, aqueous sodium carbonate) at room temperature. This provided compound **7** in high yield as a crystalline solid. In this procedure, the hydrochloride salt of **5a** was used directly by using sufficient sodium carbonate to neutralize the hydrochloric acid. The 2,5–*trans* rela-

Scheme 1




tionship of the ester groups in **7** was confirmed by single crystal X-ray analysis (Figure 1).

The removal of the phthalimido moiety from **7** was carried out with hydrazine hydrate in methanol to provide the lactam derivative **8** as a white solid in close to quantitative yield. The reduction of the lactam carbonyl and ester in **8** was accomplished with excess lithium aluminum hydride in refluxing tetrahydrofuran to provide the water soluble diamine **9**. The hydride reduction worked best by adding solid substrate **8** to a slurry of the hydride, refluxing the mixture for 18 hours and quenching the reaction with 15% sodium hydroxide and a small amount of water to precipitate the aluminum salts which allowed the isolation of **9** in high yield.

To complete the synthesis, 3-chlorobenzisoxazole **11** was prepared in two steps from salicylhydroxamic acid. First, salicylhydroxamic acid [11] was converted to 3-hydroxybenzisoxazole with carbonyldiimidazole in refluxing tetrahydrofuran in 76% yield [12]. Then, 3-hydroxybenzisoxazole was treated with phosphorus oxychloride in pyridine to give **11** in 88% yield [13]. Alkylation of diamine **9** with 3-chlorobenzisoxazole **11** was accomplished in pyridine solution with one equivalent of DBU to

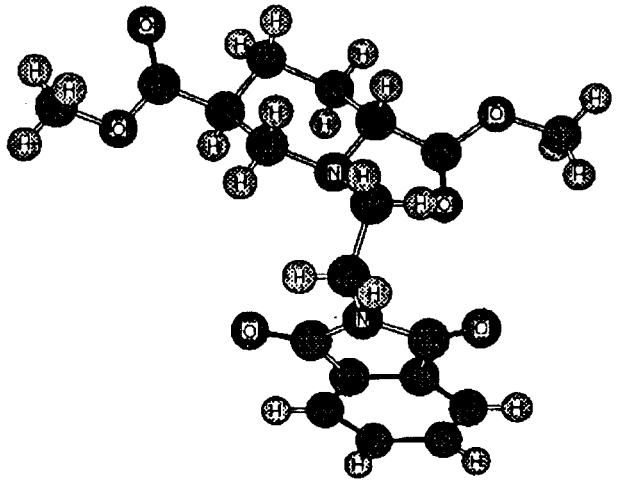


Figure 1. X-ray structure of compound 7 [10].

Table 1

Single-Crystal X-ray Crystallographic Analysis

A. Crystal Parameters

| | |
|---|---|
| formula | $C_{19}H_{22}N_2O_6$ (374.4) |
| crystallization medium | Diethyl ether |
| crystal size, mm | 0.20 x 0.44 x 0.51 |
| cell dimensions | a = 9.141(5)Å |
| | b = 13.372(7)Å |
| | c = 15.48(1)Å |
| | α = 90.00° |
| | β = 90.59(5)° |
| | γ = 90.00° |
| | V = 1892(1)Å$^3$ |
| space group | $P2_1/a$ |
| molecules/unit cell | 4 |
| density calcd, g/cm$^3$ | 1.31 |
| linear absorption factor, cm$^{-1}$ | 7.83 |

B. Refinement Parameters

| | |
|---|---|
| number of reflections | 1944 |
| nonzero reflections (I>3.0σ) | 1714 |
| R-index [a] | 0.062 |
| GOF [b] | 2.37 |
| scale factor | 1.966(5) |
| secondary extinction factor | 168(8) x 10$^{-4}$ |

[a] R-index = $\Sigma \mid\mid Fo \mid - \mid Fc \mid\mid / \Sigma \mid Fo \mid$ [b] GOF = $[\Sigma w(Fo^2-Fc^2)^2/(m-s)]^{1/2}$ where $w = [\sigma^2(F) + \mid g \mid F^2]^{-1}$ g = 0.001

Table 2

Atomic Coordinates (x $10^4$) and Isotropic Thermal Parameters (Å$^2$ x $10^3$)

| | x | y | z | U [a] |
|---|---|---|---|---|
| N(1) | 2296(3) | 582(2) | 6100(2) | 53(1) |
| C(2) | 3655(4) | 1002(3) | 6290(2) | 57(1) |
| C(3) | 4723(4) | 182(3) | 6188(2) | 56(1) |
| C(4) | 3979(4) | -666(3) | 5944(2) | 55(1) |
| C(5) | 2411(4) | -415(3) | 5888(2) | 55(1) |
| C(6) | 6221(4) | 187(4) | 6271(3) | 78(2) |
| C(7) | 6941(4) | -700(4) | 6113(3) | 83(2) |
| C(8) | 6209(5) | -1546(3) | 5888(3) | 81(2) |
| C(9) | 4701(4) | -1539(3) | 5785(3) | 70(2) |
| C(10) | 919(4) | 1104(3) | 6195(2) | 60(1) |
| C(11) | 165(4) | 775(3) | 6997(3) | 58(1) |
| N(12) | 1002(3) | 993(2) | 7778(2) | 48(1) |
| C(13) | 723(4) | 288(3) | 8466(3) | 61(1) |
| C(14) | 1607(5) | 540(3) | 9273(3) | 70(2) |
| C(15) | 1312(5) | 1595(3) | 9567(3) | 77(2) |
| C(16) | 1569(4) | 2314(3) | 8851(2) | 58(1) |
| C(17) | 751(4) | 2026(3) | 8040(2) | 52(1) |
| C(18) | 1120(4) | -757(3) | 8193(3) | 67(2) |
| O(19) | 2225(4) | -997(2) | 7847(2) | 102(1) |
| O(20) | 89(4) | -1392(2) | 8391(2) | 95(1) |
| C(21) | 413(8) | -2240(4) | 8248(4) | 131(3) |
| C(22) | 1215(5) | 3362(3) | 9077(3) | 71(2) |
| O(23) | 515(7) | 3601(3) | 9686(3) | 172(3) |
| O(24) | 1558(4) | 4017(2) | 8513(2) | 91(1) |
| C(25) | 1122(6) | 5046(3) | 8639(3) | 90(2) |
| O(26) | 3854(3) | 1860(2) | 6478(2) | 79(1) |
| O(27) | 1388(3) | -938(2) | 5681(2) | 76(1) |

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalised $U_{ij}$ tensor.

Table 3

Bond Lengths (Å)

| | | | |
|---|---|---|---|
| N(1)-C(2) | 1.392(5) | N(1)-C(5) | 1.377(5) |
| N(1)-C(10) | 1.447(5) | C(2)-C(3) | 1.477(5) |
| C(2)-O(26) | 1.197(5) | C(3)-C(4) | 1.373(5) |
| C(3)-C(6) | 1.374(5) | C(4)-C(5) | 1.475(5) |
| C(4)-C(9) | 1.365(5) | C(5)-O(27) | 1.208(4) |
| C(6)-C(7) | 1.381(6) | C(7)-C(8) | 1.357(6) |
| C(8)-C(9) | 1.387(6) | C(10)-C(11) | 1.494(5) |
| C(11)-N(12) | 1.454(5) | N(12)-C(13) | 1.446(5) |
| N(12)-C(17) | 1.458(4) | C(13)-C(14) | 1.520(6) |
| C(13)-C(18) | 1.505(5) | C(14)-C(15) | 1.507(6) |
| C(15)-C(16) | 1.489(6) | C(16)-C(17) | 1.505(5) |
| C(16)-C(22) | 1.481(6) | C(18)-O(19) | 1.192(5) |
| C(18)-O(20) | 1.308(5) | O(20)-C(21) | 1.450(6) |
| C(22)-O(23) | 1.189(7) | C(22)-O(24) | 1.278(5) |
| O(24)-C(25) | 1.447(5) | | |

Table 4

Bond Angles (°)

| | | | |
|---|---|---|---|
| C(2)-N(1)-C(5) | 111.7(3) | C(2)-N(1)-C(10) | 124.0(3) |
| C(5)-N(1)-C(10) | 124.0(3) | N(1)-C(2)-C(3) | 105.5(3) |
| N(1)-C(2)-O(26) | 124.8(3) | C(3)-C(2)-O(26) | 129.7(3) |
| C(2)-C(3)-C(4) | 108.5(3) | C(2)-C(3)-C(6) | 130.2(4) |
| C(4)-C(3)-C(6) | 121.3(4) | C(3)-C(4)-C(5) | 107.8(3) |
| C(3)-C(4)-C(9) | 121.2(3) | C(5)-C(4)-C(9) | 131.0(3) |
| N(1)-C(5)-C(4) | 106.4(3) | N(1)-C(5)-O(27) | 124.2(3) |
| C(4)-C(5)-O(27) | 129.3(3) | C(3)-C(6)-C(7) | 117.1(4) |
| C(6)-C(7)-C(8) | 121.8(4) | C(7)-C(8)-C(9) | 120.7(4) |
| C(4)-C(9)-C(8) | 117.8(4) | N(1)-C(10)-C(11) | 110.6(3) |
| C(10)-C(11)-N(12) | 112.9(3) | C(11)-N(12)-C(13) | 112.7(3) |
| C(11)-N(12)-C(17) | 109.7(3) | C(13)-N(12)-C(17) | 112.6(3) |
| N(12)-C(13)-C(14) | 111.4(3) | N(12)-C(13)-C(18) | 110.7(3) |
| C(14)-C(13)-C(18) | 108.0(3) | C(13)-C(14)-C(15) | 111.1(3) |
| C(14)-C(15)-C(16) | 110.5(3) | C(15)-C(16)-C(17) | 112.0(3) |
| C(15)-C(16)-C(22) | 113.5(3) | C(17)-C(16)-C(22) | 109.3(3) |
| N(12)-C(17)-C(16) | 113.3(3) | C(13)-C(18)-O(19) | 125.8(4) |
| C(13)-C(18)-O(20) | 111.1(3) | O(19)-C(18)-O(20) | 123.1(4) |
| C(18)-O(20)-C(21) | 116.3(4) | C(16)-C(22)-O(23) | 124.2(4) |
| C(16)-C(22)-O(24) | 115.5(4) | O(23)-C(22)-O(24) | 119.7(4) |
| C(22)-O(24)-C(25) | 119.3(4) | | |

Table 5

Anisotropic Thermal Parameters (Å$^2$ x $10^3$)

| | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| N(1) | 58(2) | 47(2) | 54(2) | -8(1) | -7(1) | -5(1) |
| C(2) | 68(2) | 52(2) | 52(2) | -12(2) | -7(2) | -18(2) |
| C(3) | 57(2) | 59(2) | 50(2) | -2(2) | -4(2) | -5(2) |
| C(4) | 57(2) | 49(2) | 58(2) | -3(2) | -1(2) | -8(2) |
| C(5) | 57(2) | 47(2) | 60(2) | -12(2) | -7(2) | -4(2) |
| C(6) | 62(3) | 88(3) | 84(3) | -12(3) | -13(2) | -14(2) |
| C(7) | 52(2) | 102(4) | 94(3) | -5(3) | -10(2) | 4(2) |
| C(8) | 65(3) | 80(3) | 97(3) | -1(3) | 2(2) | 13(2) |
| C(9) | 64(2) | 58(3) | 87(3) | -3(2) | 3(2) | -3(2) |
| C(10) | 65(2) | 51(2) | 62(2) | -2(2) | -17(2) | 6(2) |
| C(11) | 42(2) | 52(2) | 79(3) | -10(2) | -13(2) | 4(2) |
| N(12) | 50(2) | 41(2) | 53(2) | 0(1) | -5(1) | 1(1) |
| C(13) | 53(2) | 54(3) | 75(3) | -4(2) | 8(2) | 1(2) |
| C(14) | 83(3) | 63(3) | 64(3) | 12(2) | 0(2) | 10(2) |
| C(15) | 96(3) | 70(3) | 64(3) | -1(2) | -0(2) | -5(2) |
| C(16) | 58(2) | 53(2) | 63(2) | -6(2) | -6(2) | 1(2) |
| C(17) | 49(2) | 46(2) | 62(2) | -1(2) | -3(2) | 4(2) |
| C(18) | 76(3) | 53(3) | 72(3) | 5(2) | 6(2) | 2(2) |
| O(19) | 104(2) | 69(2) | 134(3) | 7(2) | 33(2) | 21(2) |
| O(20) | 116(2) | 56(2) | 113(3) | -9(2) | 29(2) | -14(2) |
| C(21) | 192(6) | 50(3) | 151(5) | -13(3) | 41(4) | -13(3) |
| C(22) | 94(3) | 65(3) | 55(2) | -16(2) | 16(2) | -8(2) |
| O(23) | 315(7) | 75(3) | 127(3) | -4(2) | 89(4) | 23(3) |
| O(24) | 126(3) | 54(2) | 95(2) | -5(2) | 22(2) | 6(2) |
| C(25) | 114(4) | 49(3) | 107(4) | -10(2) | -1(3) | 6(2) |
| O(26) | 82(2) | 60(2) | 95(2) | -19(2) | -11(2) | -17(1) |
| O(27) | 62(2) | 54(2) | 112(2) | -22(2) | -20(2) | -9(1) |

The anisotropic temperature factor exponent takes the form: $-2\pi^2-(h^2a^{*2}U_{11} + ... + 2hka^*b^*U_{12}$.

provide the title compound **2** in 49% yield. In the absence of DBU, the alkylation gave much lower yields of **2**.

In conclusion, we have described the synthesis of *trans*-7-hydroxymethyl-2-(2-benz[*d*]isoxazol-3-yl)octahydro-2*H*-pyrido[1,2-*a*]pyrazine **2** in good overall yield from dimethyl 2,5-pyridinedicarboxylate without the necessity of chromatography. Also, the ready availability of the useful *trans*-substituted diamine **9** has been demonstrated in this work. Compound **2** has been converted to the conformationally restricted analogue **3** by Dr. Bright [4].

Table 6

H-Atom Coordinates (x $10^4$) and Isotropic Thermal Parameters (Å$^2$ x $10^3$)

| | x | y | z | U |
|---|---|---|---|---|
| H(6) | 6745 | 781 | 6433 | 91 |
| H(7) | 7989 | -720 | 6163 | 99 |
| H(8) | 6742 | -2154 | 5794 | 93 |
| H(9) | 4175 | -2129 | 5611 | 76 |
| H(10A) | 1101 | 1811 | 6224 | 70 |
| H(10B) | 299 | 962 | 5706 | 70 |
| H(11A) | 2 | 67 | 6965 | 66 |
| H(11B) | -759 | 1114 | 7032 | 66 |
| H(13) | -300 | 338 | 8594 | 72 |
| H(14A) | 1341 | 83 | 9723 | 77 |
| H(14B) | 2629 | 468 | 9151 | 77 |
| H(15A) | 1960 | 1753 | 10040 | 89 |
| H(15B) | 317 | 1650 | 9754 | 89 |
| H(16) | 2598 | 2269 | 8739 | 70 |
| H(17A) | 1052 | 2459 | 7580 | 60 |
| H(17B) | -276 | 2114 | 8140 | 60 |
| H(21A) | 1378 | -2600 | 8455 | 153 |
| H(21B) | 354 | -2563 | 7637 | 153 |
| H(21C) | -290 | -2849 | 8539 | 153 |
| H(25A) | 1699 | 5469 | 8275 | 105 |
| H(25B) | 1284 | 5227 | 9232 | 105 |
| H(25C) | 105 | 5127 | 8495 | 105 |

## EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and were uncorrected. The nmr spectra were obtained on a Bruker WM 300 (300 MHz) spectrometer in deuteriochloroform or deuterium oxide. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer. Mass spectra were determined with a Finnigan 4510 mass spectrometer. Elemental analyses were performed by the Analytical Chemistry Department, Pfizer Central Research.

*trans*-5-(Methoxycarbonyl)piperidine-2-carboxylic Acid **6a** and *cis*-5-(Methoxycarbonyl)piperidine-2-carboxylic Acid **6b**.

Dimethyl *cis*-piperidine-2,5-dicarboxylate (112 g, 0.56 mole) (obtained by hydrogenation of dimethyl pyridine-2,5-dicarboxylate with platinum oxide in acetic acid at 50 psi hydrogen pressure), salicylaldehyde (3 ml, 0.056 mole) and glacial acetic acid (600 ml) were combined and the resulting mixture was heated at 110° for 60 hours. The mixture was cooled to room temperature and evaporated *in vacuo* to a thick oil. 2-Propanol (800 ml) was added to the oil to give a crystalline product which was collected by filtration and dried *in vacuo*, 61.7 g (59%). This product was a 3:1 mixture of the *trans*:*cis* monoesters as determined by $^1$H nmr in deuterium oxide; a peak at 3.13 ppm (t, 1H, J = 14.5 Hz) was diagnostic for the *trans* isomer while a peak at 3.33 ppm (dd, 1H) was diagnostic for the *cis*-isomer.

Dimethyl *trans*-Piperidine-2,5-dicarboxylate Hydrochloride **5a**.

The 3:1 mixture of **6a/6b** (15.1 g, 0.08 mole) was suspended in methanol (200 ml) and stirred under a nitrogen atmosphere at 0° while thionyl chloride (7.35 ml, 0.1 mole) was added dropwise over five minutes. After thirty minutes at low temperature, the mixture was allowed to warm to room temperature and finally was heated at reflux for six hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo* to a thick slurry. 2-Propanol (200 ml) was added to the mixture and the solids were collected by filtration to give the title product, 12.7 g, (67%), mp 207-209°; ir (potassium bromide): ν 1740 cm$^{-1}$; $^1$H nmr (deuterium oxide): δ 4.08 (dd, 1), 3.85 (s, 3), 3.73, (s and m, 4), 3.20 (t, 1), 2.90 (m, 1), 2.43 (m, 1), 2.29 (m, 1), 1.80 (m, 2).

*Anal.* Calcd. for $C_9H_{16}NO_4Cl$: C, 45.49; H, 6.79; N, 5.89. Found: C, 45.34; H, 6.55; N, 5.82.

A sample of the hydrochloride salt (7.88 g, 33 mmoles) was suspended in ethyl acetate (200 ml) and water (100 ml). This was stirred while sodium carbonate was added until the *p*H of the aqueous layer was *p*H 10. The free base **5a** was recovered from the organic layer as a colorless solid from hexanes, 5.8 g (88%), mp 58-60°; ir (potassium bromide): ν 3530, 3330, 1725 cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 3.65 (s, 3), 3.60 (s, 3), 3.28 (m, 2), 2.68 (t, 1), 2.39 (m, 1), 2.05 (m, 2), 1.92 (s, 1, NH) 1.63-1.34 (m, 2); $^{13}$C nmr: δ 174.2, 173.4, 58.1, 52.0, 51.7, 47.6, 41.9, 28.4, 27.0; ms: m/z 201 ($M^+$), 142 ($M^+$ -$CO_2Me$).

*Anal.* Calcd. for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.78; H, 7.46; N, 6.97.

Dimethyl *trans*-1-(2-(Phthalimido)ethyl)piperidine-2,5-dicarboxylate **7**.

2-(Phthalimido)ethanol (22.7 g, 0.12 mole) was stirred in methylene chloride (200 ml) under nitrogen at -5° while a solution of trifluoromethanesulfonic anhydride (35.3 g, 0.125 mole) in methylene chloride (100 ml) was added dropwise. After two hours, tlc (silica gel, ethyl acetate) showed that the reaction was complete. The cold solution was washed with water (2 x), 1*N* hydrochloric acid (2 x), and with brine. The organic solution was dried over magnesium sulfate and filtered. An aliquot was evaporated to give a white solid; $^1$H nmr (deuteriochloroform): δ 7.85 (m, 2), 7.72 (m, 2), 4.73 (t, 2), 4.14 (t, 2). Sodium carbonate (41.8 g, 0.39 mole) was dissolved in water (250 ml). Methylene chloride (200 ml) was added followed by dimethyl *trans*-piperidine-2,5-dicarboxylate hydrochloride **5a** (23.2 g, 0.1 mole). This was stirred at room temperature while the triflate solution from above was added dropwise over 0.5 hour. The reaction was stirred for an additional two hours. The layers were separated and the organic layer was washed with water and brine. After drying the solution over magnesium sulfate, the solvent was evaporated *in vacuo*. Ethyl ether (150 ml) was added followed by hexanes (150 ml). The product was isolated as a colorless solid, 28.7 g (77%), mp 103-106°; ir (potassium bromide): ν 1767, 1745, 1737, 1711, 1702 cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 7.85 (m, 2), 7.70 (m, 2), 3.90 (m, 1), 3.68 (m) and 3.60 (two s) (seven protons total), 3.44 (dd, 1), 3.13 (dd, 1), 2.80 (m, 1), 2.57 (m, 2), 2.40 (t, 1), 1.89 (m, 2), 1.60 (m, 2); $^{13}$C nmr: δ 174.0, 173.5, 168.3, 133.8, 132.3, 123.1, 64.3, 53.2, 52.0, 51.7, 51.6, 40.7, 35.1, 28.1, 25.1; ms: m/z 374 ($M^+$), 315 ($M^+$ -$CO_2Me$).

*Anal.* Calcd. for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48. Found: C, 60.68; H, 5.84; N, 7.46

Single-Crystal X-ray Analysis of **7**.

A sample of **7** was submitted for a single-crystal X-ray study. A representative crystal was surveyed and a 1 angstrom data set (maximum sin θ/λ = 0.5) was collected on a Nicolet R3m/μ diffractometer. Atomic scattering factors were taken from the International Tables for X-ray Crystallography [14]. All crystallographic calculations were facilitated by the SHELXTL system

[15]. All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are summarized in Table 1.

A trial structure was obtained by direct methods. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R-index was 0.062. A final difference Fourier revealed no missing or misplaced electron density. Coordinates, anisotropic temperature factors, distances, and angles are listed in the Tables.

Methyl *trans*-1-Oxo-1,3,4,6,7,8,9,9a-octahydro-2*H*-pyrido-[1,2-*a*]pyrazine-7-carboxylate **8**.

Dimethyl *trans*-1-(2-(phthalimido)ethyl)piperidine-2,5-dicarboxylate **7** (23.9 g, 0.064 mole) was suspended in methanol (400 ml) and stirred mechanically while hydrazine hydrate (8.3 ml, 0.14 mole) was added dropwise over two minutes. The reaction was stirred overnight at room temperature. Methylene chloride (200 ml) was added to the slurry and after 0.25 hour, the slurry was filtered. The filtrate was evaporated to dryness and the solids reslurried in hot methylene chloride. The resulting slurry was cooled to room temperature and the solid collected. All of the solids to this point consisted of the hydrazine side product and were discarded. The lactam was recovered by evaporation of the methylene chloride solution to provide a white solid which was slurried in ethyl ether, collected by filtration and dried *in vacuo*, 13.1 g, (97%), mp 174-177°; ir (potassium bromide): ν 1741, 1661 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 6.50 (s, 1, NH), 3.66 (s, 3), 3.51 (dt, 1), 3.17 (m, 2), 2.83 (dd, 1), 2.59 (m, 3), 2.38 (m, 1), 2.25 (t, 1), 2.18 (m, 1), 1.44 (m, 2); $^{13}C$ nmr: δ 174.0, 170.8, 64.7, 56.9, 51.7, 50.9, 41.4, 41.0, 27.4, 26.5; ms: m/z 212 ($M^+$), 183 ($M^+$ -HCO).

*Anal.* Calcd. for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.52; H, 7.61; N, 13.16.

*trans*-7-(Hydroxymethyl)-1,3,4,6,7,8,9,9a-octahydro-2*H*-pyrido[1,2-*a*]pyrazine **9**.

Methyl *trans*-1-oxo-1,3,4,6,7,8,9,9a-octahydro-2*H*-pyrido-[1,2-*a*]pyrazine-7-carboxylate **8** (70 g, 0.33 mole) was added in portions as a solid to a slurry of lithium aluminum hydride (17.85 g, 0.47 mole) in dry tetrahydrofuran (750 ml) under nitrogen with ice water cooling to keep the temperature <30°. After the addition was complete, the reaction mixture was heated at reflux overnight. The reaction was allowed to cool to room temperature and was quenched carefully by the slow, dropwise addition of water (18 ml) followed by 15% sodium hydroxide solution (18 ml) and finally water (56 ml). The inorganic solids were removed by filtration and then reslurried in hot acetonitrile and filtered to remove any remaining product. The tetrahydrofuran and acetonitrile filtrates were combined and evaporated *in vacuo* to a solid. This solid was reslurried in acetonitrile and filtered to afford the desired amine as a white solid, 38.6 g, (68%), mp 134-137°; ir (potassium bromide): ν 3282, 3143, 3120 $cm^{-1}$; $^1H$ nmr (deuterium oxide): δ 3.45 (m, 2), 2.92-2.68 (m, 5), 2.37 (t, 1), 2.20 (dt, 1), 1.98 (m, 1), 1.81 (m, 3), 1.62 (m, 1), 1.27-0.98 (m, 2); $^{13}C$ nmr: δ 64.9, 61.4, 57.7, 54.4, 49.9, 44.0, 37.7, 28.2, 26.3; ms: m/z 170 ($M^+$).

*trans*-7-Hydroxymethyl-2-(2-benz[*d*]isoxazol-3-yl)-1,3,4,6,7,8,9,9a-octahydro-2*H*-pyrido[1,2-*a*]pyrazine **2**.

*trans*-7-(Hydroxymethyl)-1,3,4,6,7,8,9,9a-octahydro-2*H*-pyrido[1,2-*a*]pyrazine **9** (24.4 g, 0.14 mole) was dissolved in pyridine (46 ml) under nitrogen. 3-Chlorobenzisoxazole **11** (24.2 g, 0.16 mole) [13] was added followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (24 ml, 0.16 mole) and the mixture was refluxed for eighteen hours. The mixture was allowed to cool to 35° and water (25 ml) was added slowly, followed by saturated sodium carbonate solution (200 ml) and finally water to *ca.* 500 ml total volume. After stirring for two hours, the solids were collected and slurried in hot methanol (300 ml). This slurry was allowed to cool to room temperature and the desired product was isolated by filtration and dried *in vacuo*, 20 g (49%), mp 191-193.5°; ir (potassium bromide): ν 3102 (broad), 1610, 1597, 1521, 1450 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 7.70 (d, 1), 7.45 (m, 2), 7.20 (m, 2), 3.98 (m, 1), 3.87 (m, 1), 3.50 (m, 2), 3.30 (dt, 1), 3.04 (d, 1), 2.89 (m, 2), 2.50 (dt, 1), 2.15 (m, 1), 1.86 (m, 3), 1.75-1.29 (m, 3), 1.10 (m, 1); $^{13}C$ nmr (deuteriochloroform): δ 164.0, 161.1, 129.5, 122.3, 122.1, 116.2, 110.5, 66.3, 60.3, 58.7, 54.3, 53.7, 48.3, 39.1, 29.0, 26.7.

*Anal.* Calcd. for $C_{16}H_{21}N_3O_2$: C, 66.88; H, 7.37; N, 14.62. Found: C, 67.10; H, 7.60; N, 14.71.

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