A Facile Entry to the 2-Azabicyclo[2.2.2]octane-6-one Skeleton via [4+2]-Cycloaddition

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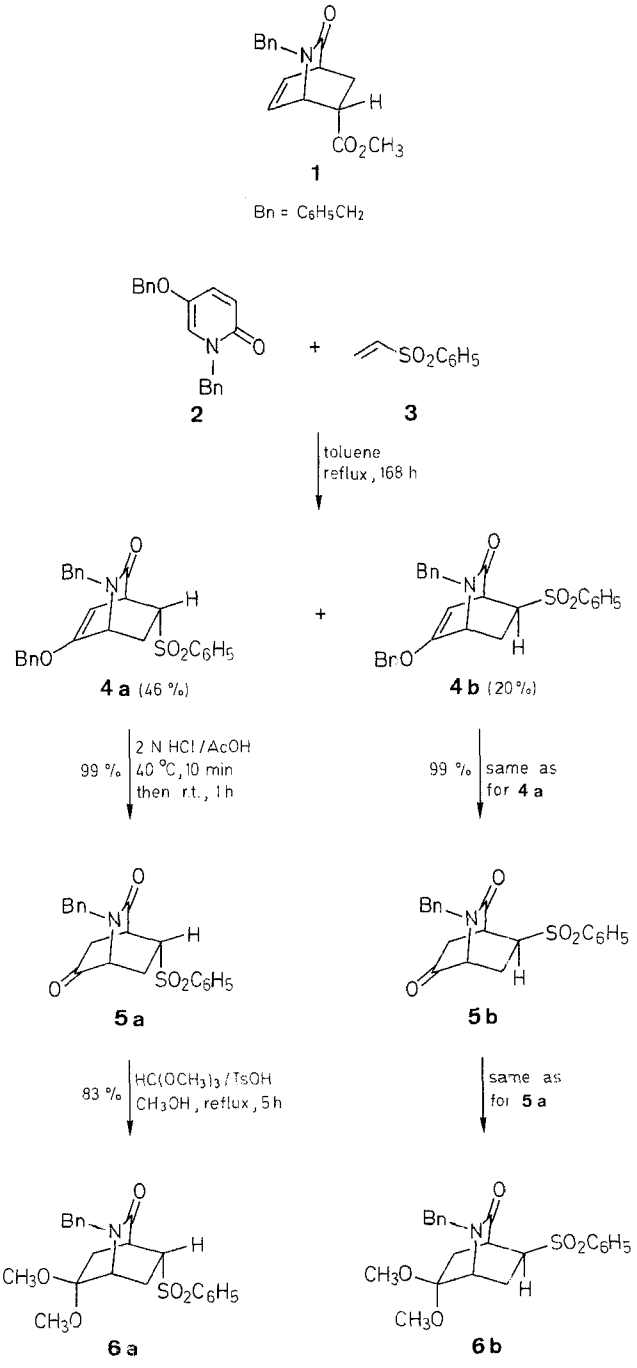
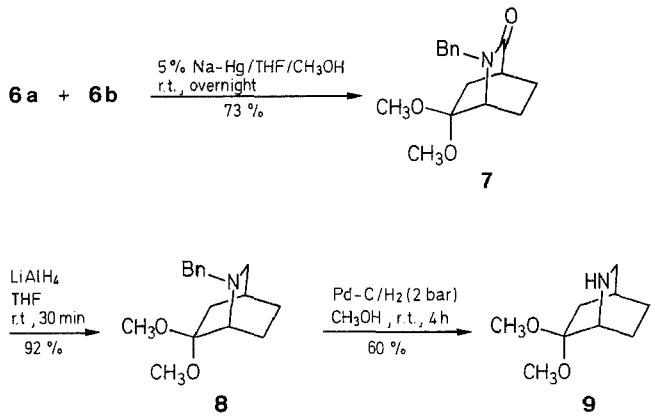
2-Aza-bicyclo[2.2.2]octane-6-one derivatives are prepared from 5-hydroxy-2-pyridone via [4+2]-cycloaddition with phenyl vinyl sulfone as an ethylene equivalent. Complete regiospecificity is observed. The *exo-endo*[15] ratio of the adducts is 7:3. A four step reaction sequence affords 2-aza-6-dimethoxybicyclo[2.2.2]octane, a starting material in the synthesis of desethylibogamine.

There has been considerable interest in the Diels-Alder reaction of *N*-substituted 2(1*H*)-pyridones with dienophiles in recent years. Various dienophiles such as maleic anhydride,[1] benzyne,[2] dimethyl acetylenedicarboxylate,[3] and methyl acrylate[4] yielded azabicyclo[2.2.2]octane derivatives. Blocking of the nitrogen atom by *N*-methylation or benzylation is necessary to prevent nucleophilic addition of the amide group to the dienophile.[5] All these reactions proceed with a low yield of cycloaddition products, suggesting that 2-pyridone system behaves as a neutral diene. Three modifications of the pyridone structure can enhance the reactivity: 1. a vinyl moiety at the nitrogen atom,[6] 2. high pressure (up to 15 kbar)[7] and 3. introduction of a substituent in the 6-position, which has a great influence of the rate of cycloaddition due to a steric effect.[3]

Some of these cycloaddition products are interesting synthetic intermediates. The 2-aza-3-oxobicylo[2.2.2]oct-7-ene-5,6-dicarboxylic anhydride can be transformed to 3-methoxy-2-azabarrelene.[1] The cycloaddition of methyl acrylate to 1-benzyl-2-pyridone led to *endo* Diels-Alder adduct **1** in 17% yield, which was transformed to (±) epiibogamine.[4]





Recently, we have shown that the hydroxy function in the 5-position of 2-pyridone serves as a latent ketone functionality.[8] δ-Aminolaevulinic acid can be synthesized in 3 step.[9] Two factors make the dibenzyl derivative **2** attractive as a diene in the Diels-Alder reaction: 1. a donor substituent in the 5-position of the pyridone influences the reaction rate and the regio- and stereoselectivity of the cycloaddition, and 2. the resulting benzyl enol ether moiety can easily be hydrolized to a ketone.

Here we report that cycloadditon of phenyl vinyl sulfone[10] **(3)** to **2** in boiling toluene furnishes the diastereomers **4a** and **4b** (*exo, endo*).[15] The reaction is completely regiospecific. Isomers **4a** and **4b** can be separated by flash chromatography providing a **4a**:**4b** ratio of 7:3. The epimers can be hydrolyzed in acetic acid with 1 normal hydrochloric acid to give the ketones **5a** and **5b**, respectively.

Desulfonation with sodium amalgam[11] of **5a** or **5b**[12] requires the protection of the ketone as the dimethyl acetal **6a** or **6b**. Reduction of **7** with lithium aluminum hydride in tetrahydrofuran and subsequent debenzylation by hydrogenation over palladium on carbon in methanol provides **9**. During desulphonation of the mixture **6a/6b** or **6a** complete epimerization of **6a** to **6b** occurs. This entry to the 2-azabicyclo[2.2.2]octane-6-one system is an attractive alternative path way to the common procedure developed by Huffman[13] for the synthesis of desethylibogamine.[14] In addition, further derivatization of the adducts **6a** and **6b** is possible via the α-sulfonyl carbanion derivative.

^{1}H-NMR were taken using a Bruker AC 200 MHz FT-spectrometer with TMS as internal standard. R_f values are quoted for Merck silicagel 60 GF_{254} TLC plates of thickness 0.25 mm; detection: UV and iodine vapor. All experiments were carried out under nitrogen atmosphere.

***exo/endo*-2-Aza-2-benzyl-6-benzyloxy-8-phenylsulfonylbicyclo[2.2.2]oct-5-en-3-one (4a/4b):**

To a stirred solution of 1-benzyl-5-benzyloxy-2-pyridone (**2**; 5.82 g, 20 mmol) in toluene (150 mL) is added phenyl vinyl sulfone (**3**; 8.4 g, 50 mmol). This mixture is refluxed for 7d. The solvent is evaporated, and the residual brown oil is flash-chromatographed on silica gel (Merck, 0.015–0.04 μm, 30 cm × 4 cm, 20 mL fractions) using CH_2Cl_2/EtOAc (9:1) as eluent. Evaporation of solvent from the fractions containing pure *exo*-product **4a** gives a residue, which is triturated with ether. Product **4a** is isolated by suction as colorless powder; yield 3.0 g (33%).

A sample for analytic purposes of this *exo*-product **4a** can be recrystallized from EtOH; mp 165–166°C; R_f = 0.48 ($CHCl_3$/EtOAc, 9:1).

Evaporation of the solvent of the remaining fractions provides an *exo/endo*-mixture 3 g. Pure *endo*-product **4b** can be isolated by a second flash chromatography under the above mentioned conditions; yield 1.8 g (20%); mp 117–119°C (EtOH); R_f = 0.35 ($CHCl_3$/9:1); together with 1.2 g (13%) of further *exo* product.

exo-Product **4a**:

$C_{27}H_{25}NO_4S$	calc.	C 70.56	H 5.48	N 3.05
(459.5)	found	70.48	5.41	3.02

MS: *m/z* = 459.

IR (KBr): ν = 2998, 1665 (amide), 1640 (C=C–O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.10–2.17 (m, 2H, H-7); 3.57 (ddd, 1H, *J* = 9 Hz, 4 Hz, 2 Hz, H-8); 3.70 (dd, 1H, *J* = 6.6 Hz, 2.0 Hz, H-4); 4.02 (dd, 1H, *J* = 5, 2.5 Hz, H-1); 4.42 (s, 2H, NCH_2); 4.64 (s, 2H, OCH_2); 4.95 (dd, 1H, *J* = 6.6 Hz, 2.5 Hz, H-5); 7.15–7.69 (m, 15H, H_{arom}).

endo-Product **4b**:

$C_{27}H_{25}NO_4S$	calc.	C 70.56	H 5.48	N 3.05
(459.5)	found	70.31	5.39	2.98

MS: *m/z* = 459.

IR (KBr): ν = 2933, 1676 (amide), 1642 (C=C–O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.10–2.19 (m, 2H, H-7); 3.14 (ddd, 1H, *J* = 7.5 Hz, 6 Hz, 2.8 Hz, H-8); 3.47 (dd, 1H, *J* = 7.2 Hz, H-4); 3.87–3.96, 4.56–4.85 (m, 5H, NCH_2, OCH_2, H-1); 5.28 (dd, 1H, *J* = 7 Hz, 2.5 Hz, H-5); 6.98–7.66 (m, 15H, H_{arom}).

***exo/endo*-2-Aza-2-benzyl-8-phenylsulfonylbicyclo[2.2.2]octane-3,6-dione (5a/5b):**

Enol ether **4a** and **4b** (1.38 g, 3 mmol), AcOH (30 mL) and 2N HCl (10 mL) are stirred for 10 min at 40°C to give a clear solution. Stirring is continued for 1 h at room temperature. Water (150 mL) is added, and the mixture is extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase is washed with sat. aq. $NaHCO_3$ solution (2 × 20 mL) and with water (20 mL), dried (Na_2SO_4) and evaporated. The clear oily residue crystallizes to give colorless needles, which are recrystallized from EtOH.

exo-Dione **5a**; yield: 1.1 g (99%); mp 154–156°C.

$C_{20}H_{19}NO_4S$	calc.	C 65.02	H 5.18	N 3.79
(369.4)	found	64.98	5.22	3.83

MS: *m/z* = 369.

IR (KBr): ν = 1751 (C=O), 1673 (amide), 1450, 1420 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ = 2.13 (ddd, 1H, *J* = 15 Hz, 10.7 Hz, 4.3 Hz, H-7e); 2.46 (ddd, 2H, *J* = 15 Hz, 6.3 Hz, 1.5 Hz, H-7a); 2.55 (d, 2H, *J* = 1.7 Hz, H-5); 3.25 (dd, 1H, *J* = 5 Hz, 2.5 Hz, H-4); 3.54 (ddd, *J* = 10.7 Hz, 6.3 Hz, 2.5 Hz, H-8); 3.80 (dd, 1H, *J* = 4.3 Hz, 1.5 Hz, H-1); 4.24 (d, 1H, *J* = 14.6 Hz, NCH_2); 4.79 (d, 1H, *J* = 14.6 Hz, NCH_2); 7.15–7.89 (m, 10H, H_{arom}).

endo-Dione **5b**; yield: 1.1 g (99%); mp 178–179°C.

$C_{20}H_{19}NO_4S$	calc.	C 65.02	H 5.18	N 3.79
(369.4)	found	65.06	5.13	3.70

MS: *m/z* = 369.

IR (KBr): ν = 1737 (C=O), 1700 (amide), 1454, 1445 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.32–2.50 (m, 2H, H-7a, H-7e); 2.65–2.67 (m, 2H, H-5a, H-5e); 3.03–3.13 (m, 2H, H-4, H-8); 3.43 (d, 1H, *J* = 3 Hz, H-1); 3.73 (d, 1H, *J* = 14.2 Hz, NCH_2); 5.04 (d, 1H, *J* = 14.2 Hz, NCH_2); 6.95–7.76 (m, 10H, H_{arom}).

***exo/endo*-2-Aza-2-benzyl-6,6-dimethoxy-8-phenylsulfonylbicyclo[2.2.2]octane-3-one (6a/6b):**

To a stirred solution of **5a** or **5b** (0.74 g, 2 mmol) in abs. MeOH (30 mL) is added trimethylorthoformate (5 mL) and TsOH (0.2 g). The mixture is refluxed for 5 h. The solvent is evaporated, and the colorless oil is dissolved in CH_2Cl_2 (30 mL). The organic layer is washed with sat. aq. $NaHCO_3$ solution (2 × 30 mL) and with water (30 mL), dried (Na_2SO_4) and evaporated. Treating the residue with EtOH gives a colorless powder, which can be recrystallized from EtOH **(6a)** or from MeOH **(6b)**.

exo-Acetal **6a**; yield: 0.69 g (83%); mp 176–177°C.

$C_{22}H_{25}NO_5S$	calc.	C 63.59	H 6.07	N 3.37
(415.5)	found	63.45	5.93	3.41

MS: *m/z* = 415.

IR (KBr): γ = 1670 (amide); 1500, 1360, 950 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.74 (m, 2H, H-5a, H-5e); 2.55 (m, 1H, H-7e); 2.80–2.91 (m, 2H, H-4, H-7a); 3.12 (s, 3H, OCH_3); 3.24 (s, 3H, OCH_3); 3.33 (m, 1H, H-8); 3.62 (dd, 1H, *J* = 4.5 Hz, 1.3 Hz, H-1); 3.90 (d, 1H, *J* = 14.8 Hz, NCH_2); 5.26 (d, 1H, *J* = 14.8 Hz, NCH_2); 7.17–7.89 (m, 10H, H_{arom}).

endo-Acetal **6b**; yield: 0.69 g (83%); mp 157°C.

$C_{22}H_{25}NO_5S$ (415.5) calc. C 63.59 H 6.07 N 3.37; found 63.64 6.02 3.42

MS: $m/z = 415$.

IR (KBr): $\nu = 1690$ (amide); 1510, 1370, 960, 940 cm^{-1}.

^{1}H-NMR ($CDCl_3$): $\delta = 1.63-2.15$ (m, 4H, H-7, H-5); 2.79 (m, 1H, H-4); 3.10 (s, 6H, OCH_3); 3.39 (ddd, 1H, $J = 10$ Hz, 6.9 Hz, 1.7 Hz, H-8); 3.56 (t, 1H, $J = 6$ Hz, H-1); 3.85 (d, 1H, $J = 14.8$ Hz, CH_2N); 5.36 (d, 1H, $J = 14.8$ Hz, CH_2N); 7.3–8.0 (m, 10H, H_{arom}).

2-Aza-2-benzyl-6,6-dimethoxybicyclo[2.2.2]octane-3-one (7):
To a stirred solution of the diastereomeric mixture of **6a/6b** (0.48 g, 1 mmol) in THF/MeOH (1:2, 30 mL) is added 5% sodium amalgam (Na: 3.3 g, 5 mmol) in portions over 2 h. Stirring is continued overnight. The solution is filtered and evaporated to dryness. The residue is dissolved in CH_2Cl_2(30 mL). The organic layer is washed with sat. aq. NH_4Cl solution (2 × 20 mL), then with water (50 mL), dried (Na_2SO_4) and evaporated. The resultant colorless oil is distilled on a Kugelrohr apparatus (Büchi) (150–250°C, 10^{-3} mbar) to give pure product **7**; yield: 0.2 g (73%). The oil solidifies after some days; mp 68°C.

$C_{16}H_{21}NO_3$ (275.2) calc. C 69.79 H 7.69 N 5.09; found 69.30 7.57 4.91

MS: $m/z = 275$.

IR (KBr): $\nu = 2986$, 1686 (amide), 1676 (amide), 1495, 1470, 1452, 1430 cm^{-1}.

^{1}H-NMR ($CDCl_3$): $\delta = 1.32-2.09$ (m, 6H, H-5, H-7, H-8); 2.68 (m, 1H, H-4); 3.10 (s, 3H, OCH_3); 3.14 (s, 3H, OCH_3); 3.50 (m, 1H, H-1); 3.90 (d, 1H, $J = 14.8$ Hz, NCH_2); 5.23 (d, 1H, $J = 14.8$ Hz, NCH_2); 7.25–7.33 (m, 5H, H_{arom}).

2-Aza-2-benzyl-6,6-dimethoxybicyclo[2.2.2]octane (8):
A mixture of **7** (2.75 g, 10 mmol) with $LiAlH_4$ (0.38 g, 11 mmol) in THF (30 mL) is stirred at room temperature for 30 min. A 2N NaOH solution (20 mL) is added, and the mixture extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase is washed with water (2 × 30 mL), dried (Na_2SO_4) and evaporated. The residual oil is distilled on a Kugelrohr apparatus (Büchi) (120–190°C, 10^{-3} mbar) to give a colorless oil; yield: 2.4 g (92%).

$C_{16}H_{23}NO_2$ (261.2) calc. C 73.53 H 8.87 N 5.36; found 72.99 8.57 5.15

MS: $m/z = 261$.

IR (KBr): $\nu = 2986$, 1686, 1676, 1495, 1470 cm^{-1}.

^{1}H-NMR ($CDCl_3$): $\delta = 1.4-1.85$ (m, 7H); 2.4–2.53 (m, 1H, H-4); 2.77–2.8 (m, 2H, H-3); 3.11 (s, 3H, OCH_3); 3.14 (s, 3H, OCH_3); 3.77 (q, 2H, $J = 12.4$ Hz, NCH_2); 7.23–7.39 (m, 5H, H_{arom}).

2-Aza-6,6-dimethoxybicyclo[2.2.2]octane (9):
A solution of **8** (0.23 g, 0.88 mmol) in MeOH (50 mL) is hydrogenated over Pd–C (93.6 mg) for 4 h (H_2: 2 bar). The mixture is filtered and the solution is evaporated to dryness. The residual oil is distilled on a Kugelrohr apparatus (Büchi) (50°C 10^{-3} mbar); yield: 90 mg (60%).

The oil solidifies after some days in the refrigerator to a waxy solid; mp 25–28°C.

$C_9H_{17}NO_2$ (171.1) calc. C 63.13 H 10.01 N 8.18; found 59.33 9.58 7.72

MS: $m/z = 171.1$ (M^+, 22.9%), 156.0 ($M^+ - CH_3$, 100%), 140.1 ($M^+ - OCH_3$, 25.2%), 124.0 (73%), 111.1 ($M^+ - OCH_3 - HCN$, 38%), 110.1 (73.5%), 81.1 (68.7%).

IR (KBr): $\nu = 3360$, 2960, 1460, 1430 cm^{-1}.

^{1}H-NMR ($CDCl_3$): $\delta = 1.52-1.87$ (m, 7H); 2.66 (s, 1H, NH); 2.87–2.90 (m, 3H, $H^{1,3}$); 3.18 (s, 3H, OCH_3); 3.21 (s, 3H, OCH_3).

Note added in proof:
The recently reported[16] Diels-Alder reactions of 1,3-disulfonyl-2-pyridones represent the first examples of electrophilic [2+4]-cycloadditions in the 2-pyridone series.

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