Benzyne addition to *N*-alkyl-4-hydroxy-1-methylisoquinolinium salts; a new and convenient synthesis of (±)-5-methyl-10,11-dihydro-5*H*-dibenzo-[*a*,*d*]cyclohepten-5,10-imine (MK801)

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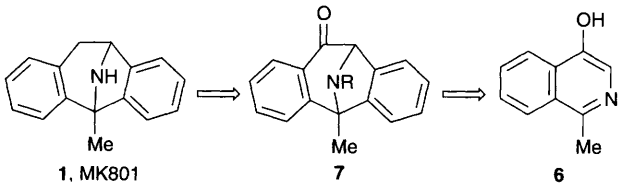
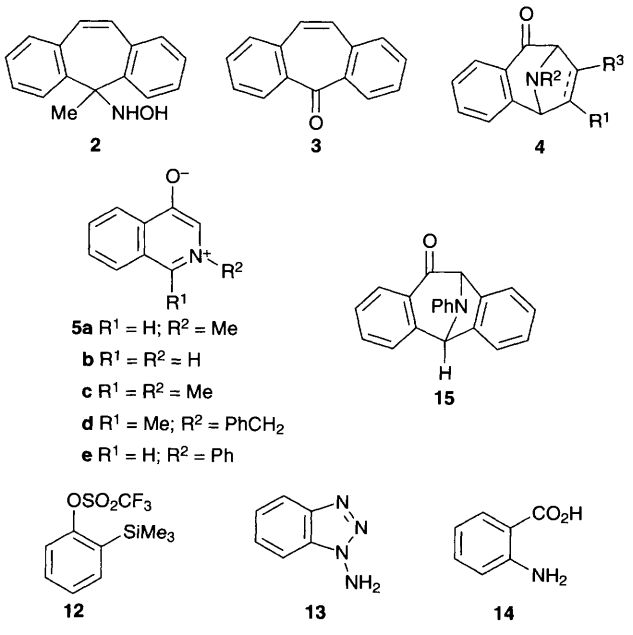
Addition of benzyne, generated by three different methods, to *N*-benzyl-4-hydroxy-1-methylisoquinolinium betaine provides *N*-benzyl-5-methyl-11-oxo-5*H*-dibenzo[*a*,*d*] cyclohepten-5,10-imine which can be converted to MK801.

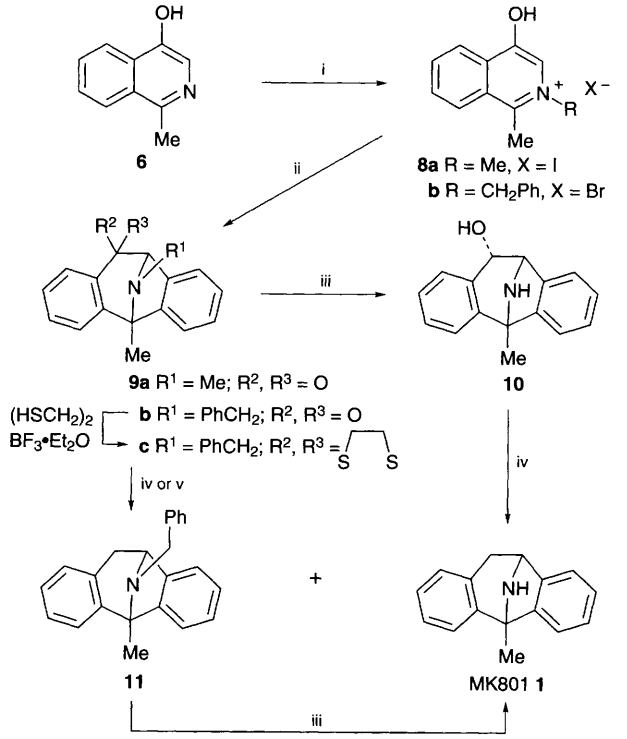
The recent reports that MK801 **1**, which is well known for its anticonvulsant activity, inhibits opioid tolerance and dependence have generated new interest in this channel-blocking antagonist of the NMDA receptor complex.[1,2] The reported synthesis of MK801 involves a transannular ring closure of the 5-methyl-5-hydroxyaminodibenzocycloheptene **2** which is derived from dibenzosubernone **3**.[2] Since the syntheses of MK801 analogues by the reported procedure required that appropriate substituted dibenzosubernone be available, we were interested in exploring other routes to this medicinally important class of compounds. Dennis *et al.*[3–5] reported the synthesis of several benzocycloheptene-5,8-imines **4** *via* the 1,3- dipolar cycloadditions of betaine **5a** with various dipolarophiles. We recently reported significant improvements in this route by forming the betaine *in situ* and conducting the cycloaddition under milder conditions.[6] We also recently reported a high yield, efficient synthesis of 4-hydroxy-1-methylisoquinoline **6**,[7] which suggested that an efficient synthesis of MK801 *via* the retrosynthesis shown in Scheme 1 might be developed.

Here we present a convenient, high-yield cycloaddition of **5c** or **5d** with benzyne and the subsequent conversion of the intermediate **9** to MK801 (Scheme 2). *N*-Methylation of 4-hydroxy-1-methylisoquinoline **6**[7] with methyl iodide provided a 98% yield of 1,2-dimethyl-4-hydroxyisoquinolinium iodide **8a**.† In a one-pot reaction, the betaine **5c**, generated *in situ* from **8a** using triethylamine, was treated with benzyne, generated by treating the *o*-trimethylsilylphenyl triflate **12**[8–10] with excess caesium fluoride in acetonitrile, to give the desired cycloaddition product **9a**, mp 129–130 °C, in 80% yield. If the benzyne was generated by the oxidation of 1-aminobenzotriazole **13** using lead tetraacetate[11,12] in methylene chloride, the yield of **9a** decreased to 27%.‡ Dennis *et al.*[4] reported that the cycloaddition of benzyne, generated by diazotization of anthra-



Scheme 1 Retrosynthetic analysis of MK801





Scheme 2 *Reagents and conditions*: i, MeI, acetone, CH_2Cl_2, room temp. or $PhCH_2Br$, THF, heat; ii, Et_3N, MeCN; CsF, room temp.; 2-TfO-C_6H_4-$SiMe_3$ **12**; iii, 10% Pd/C, HCO_2NH_4, MeOH, heat; iv, 55% HI, red phosphorous, HOAc, heat (used for **9b**); v, Ni_2B, H_2, THF (used for **9c**)

nilic acid **14** with **5a**, gave no isolatable products but found that the reaction of benzyne with **5b** gave 12% of the *N*-phenyl product **15**.[4] Interestingly, it was not established if formation of the phenyl betaine **5e** was required to activate the ring for cycloaddition as had been suggested in other studies by these authors.[5] We also found that none of the desired **9a** was isolated when **5c** was reacted with benzyne, generated by the diazotization of anthranilic acid **14**, using a procedure analogous to that reported by Dennis *et al.*[4] The success of the caesium fluoride/*o*-trimethylsilylphenyl triflate procedure may be due to both the overall milder reaction conditions and to the low solubility of caesium fluoride in acetonitrile which slows the formation of benzyne and allows for efficient cycloaddition.

Since initial attempts to convert **9a** to MK801 were unsuccessful due to difficulty in the *N*-demethylation step, *N*-benzyl-1-methyl-4-hydroxyisoquinolinium bromide **8b** was prepared (85%) and treated with benzyne, generated using the caesium fluoride/*o*-trimethylsilylphenyltriflate **12** procedure, to give the *N*-benzyl analogue **9b** in 74% yield.

Reduction of **9b** with 10% Pd–C and ammonium formate in refluxing methanol[13] gave the known 11-endo alcohol **10**, mp 188–189 °C, lit.,[2] mp 189.5–190.5 °C in 88% yield. Treatment of the ketone **9b** with 55% aq. hydriodic acid and red phosphorous in refluxing acetic acid gave a 1 : 1 mixture of MK801§ and **11** in 89% yield which could be separated by flash chromatography. Debenzylation of **11** using Pd–C and ammonium formate in refluxing methanol gave MK801 in 82% yield. Treatment of alcohol **10** with 55% hydroiodic acid and red phosphorous in refluxing acetic acid also afforded 88% of MK801. Compound **11** was also prepared by conversion of **9b** to the thioketal **9c** (87%) followed by treatment with nickel boride in THF under hydrogen (62%).[14]

In summary a new synthesis of MK801 has been developed. Subjection of known analogues of **12**[9,10,15,16] to the route shown in Scheme 2 will provide C-6 and C-9 substituted and heterocyclic analogues of MK801. The use of other 1-substituted 4-hydroxyisoquinolines will yield new C-5 substituted MK801 analogues. This new synthesis will provide a more efficient route to some previously reported MK801 analogues and a method for synthesizing analogues not previously studied.

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Footnotes

† All new compounds were characterized by elemental analysis of the free base or salt and ^{1}H NMR spectral analysis.

‡ The oxidation of 1-aminobenzotriazole **13** with $Pb(OAc)_4$ has been shown to rapidly produce benzyne even at −78 °C. Thus, the simultaneous addition of $Pb(OAc)_4$ and 1-aminobenzotriazole to a mixture of **8a** and triethylamine in methylene chloride at 0 °C gave the desired cyclized product **9a** in 27% yield after flash chromatography and further purification using HPLC. Apparently, the $Pb(OAc)_4$ indiscriminantly oxidizes organics other than the triazole, thus causing the low yields of the expected product. Several modifications of this procedure including using different mixing rates and using alternate bases for the generation of the betaine did not lead to an increase in the yield of **9a**.

§ The ^{1}H NMR spectrum of the MK801 was identical to that of an authentic sample.

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