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CYCLIZATION OF ELECTROCHEMICALLY GENERATED NITROGEN RADICALS. A NOVEL SYNTHESIS OF 11-SUBSTITUTED DIBENZO[a,d]CYCLOHEPTENIMINE DERIVATIVES

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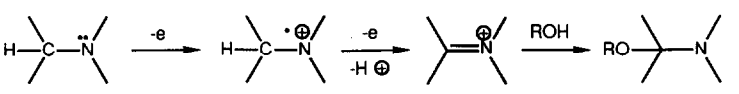
Abstract: A novel and convenient synthesis of 11-substituted dibenzo[a,d]cycloheptimines 10 via annelation of electrochemically generated aminium radicals derived from substituted 5-hydroxylamino-5-methyl-5H-dibenzo[a,d]cycloheptenes 14 is described. The scope and limitations of the reaction as well as the effects of reactor design, current density and electrode material on the yield of 10 and the carbocation rearrangement by-product 28 are discussed.

In recent years, the use of free radical reactions has greatly expanded the range of efficient carbon-carbon bond forming reactions which are available for organic synthesis[1]. The use of nitrogen-based radicals, on the other hand, has attracted much less attention, despite their obvious advantages in the synthesis of alkaloid-like substances. Olefinic aminimum radicals, or aminyl radicals complexed to metals, undergo rapid cyclization[2]. Recent results indicate that neutral aminyl radicals generated from N-chloroamines[2a,b] and from N-hydroxypyridine-2-thione carbamates[2c] undergo similar ring closures.

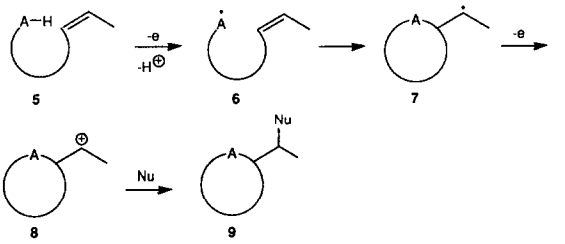
Anodic oxidation has been used frequently to generate nitrogen radicals[3]. Normally, the initially formed aminium radical 2 suffers a further one-electron oxidation accompanied by proton loss to furnish an iminium species 3. Reaction with the solvents leads to α-functionalized amines or amides(4).



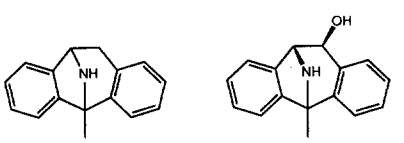
1 2 3 4

In contrast with this, anodic oxidation of lithium alkenylamides initiates a stereospecific cyclization, leading to pyrolidines in modest yield[4].

The manganic acetate-mediated cyclization of carbon radicals has recently found much application in synthesis[6]. Here, the oxidatively generated electrophilic carbon radical 6 adds to a non activated olefin and the new electron rich radical 7 is further oxidized to a carbocation 8. The sequence is terminated by the combination of the carbocation with a nucleophile. (A = Carbon)



In this paper we present an analogous ring closure sequence based on nitrogen centered radicals (A = Nitrogen)[7]. Our aim was to develop methodology suitable for large scale operations which does not generate toxic by-products. Therefore, we turned to electrochemistry, for a non-polluting, selective oxidation method. The scope and limitations of the novel anodic azacyclization will be presented as it pertains to cycloheptimines. Furthermore, development of optimum electrochemical conditions and the problems associated with scale up, will be discussed. Our work was initiated by the need for an efficient synthesis for 11-hydroxy-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine 10, a hydroxylated metabolite of MK-801[8b]. MK-801 (11)[8a] is an important noncompetitive N-methyl-D-aspartate antagonist with in vivo anticonvulsant and neuroprotective activity.

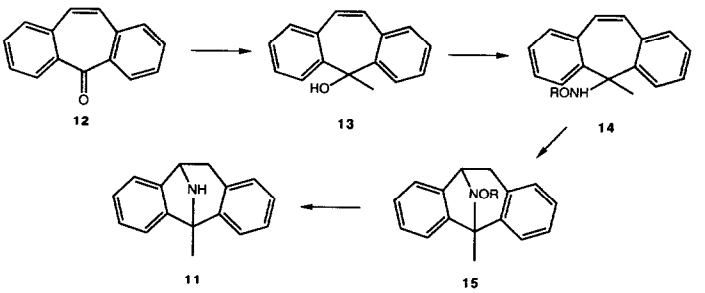


11
MK-801

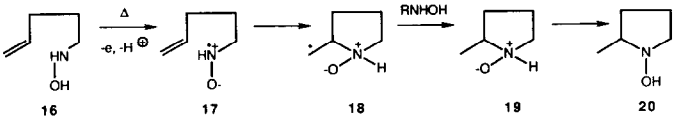
10
11-exo-hydroxy MK-801

Anodic azacyclization

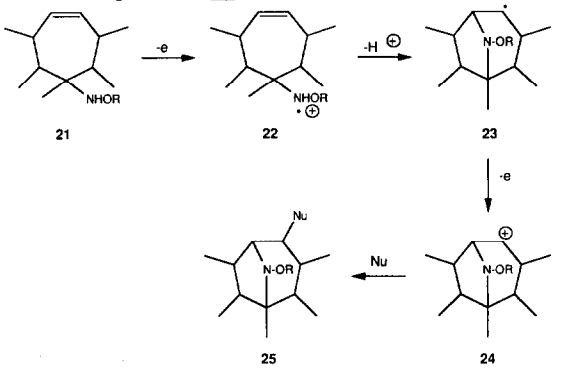
The logical starting material for the synthesis of 10 is the readily available dibenzosuberone (12). In an earlier paper[9], we described the synthesis of MK-801 (11) utilizing this starting material.



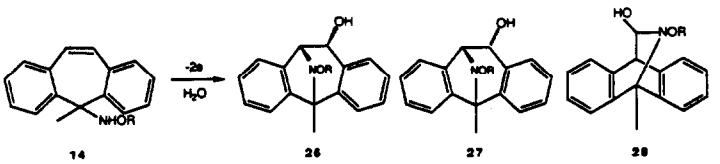
The key step of this sequence is the base catalyzed ring closure: 14→15. The following oxidatively initiated radical chain mechanism was proposed for this type of cyclization [5a].



A more recent study has shown that N,N-disubstituted hydroxylamines ring close by a concerted, two electron process[5b]. Considering the radical mechanism, we reasoned that if such reaction would be conducted in an oxidizing medium, or on the surface of the positively charged anode, hydrogen transfer to radical 18 (18→19) could be prevented by oxidation of 18 to the corresponding carbocation. In our system, this requires that the benzylic radical 23 is oxidized rapidly to carbocation 24. This must be faster than hydrogen transfer to 23 (from 21) and the further oxidation of 22 or its conjugate base. The carbocation 24 thus produced should combine with the nucleophilic solvent to form the desired product 25.



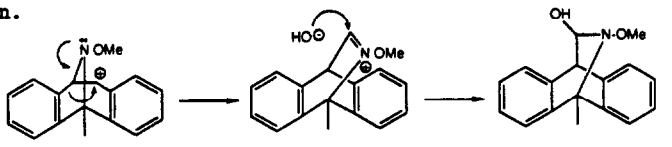
Indeed, electrolysis of methoxylamine 14a afforded a mixture containing the desired ring closure product 26 in 55% yield along with two byproducts: the epimeric alcohol 27 and an isomeric rearrangement product 28. The electrolysis was conducted in a beaker, equipped with a carbon felt anode and a stainless steel cathode, in aqueous THF containing sodium tetrafluoroborate. Since linear sweep voltammetry indicated a half-wave potential of 1.3V, the oxidation was conducted at a constant potential of 1.2V. The coulombic efficiency of the process was 85%.



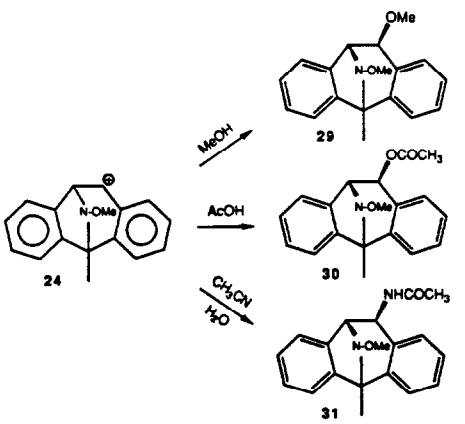
a) R = Me c) R = C(=O)—Me

b) R = H d) R = C(=O)—O—i-Bu

We believe that the mechanism outlined above (21-25) is operative and the products arise from the partitioning of the carbocation (24). Nucleophilic attack from the less hindered exo side leads to the observed product 26, the minor alcohol 27 is the result of endo attack. The major byproduct 28, is clearly the result of rearrangement of the carbocation as shown.



Naturally, the carbocation can react with other nucleophilic solvents besides water. Anodic oxidation in methanol, acetic acid and acetonitrile afforded the analogous methoxy (29), acetoxy (30) and acetamido (31) derivatives.



An O-substituted hydroxylamine is essential for this cyclization. N-alkyl hydroxylamines are known to give nitroso compounds on anodic oxidation[3] and in our hands, no ring closure was observed with 14b. Amino derivative 14 (H replaces OR), probably because of its high oxidation potential, was unreactive. O-Acylhydroxylamines (14c and 14d), on the other hand, entered the anodic process forming 26c and 26d each in 70% in yield. In these cases low levels of the epimeric by-products 27c and 27d were also formed, but rearrangement products analogous to 28 were not observed.

Table I. Anodic Oxidation of O-Substituted-5-Hydroxylamino-5-Methyl-5H-Dibenzo[a,d]Cycloheptenes 14

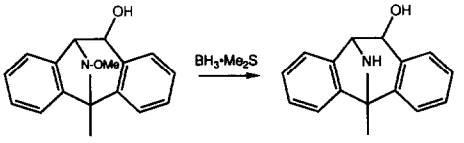
Starting Material	Conditions	Products and Yield
14a	THF, H_2O, $NaBF_4$	26a:55%*, 27a:7%*, 28:12%*
14c	"	26c:70%, 27c:5%
14d	"	26d:70%, 27c:5%
14a	MeOH, THF, $NaBF_4$	29:40%
14a	CH_3COOH, KOAC	30:73%
14a	CH_3CN, $NaBF_4$	31:30%

*These yields were observed using vitrious carbon anode. As shown in Tables II and III, optimization improved the yield of 26a to 85%. Yields were determined using HPLC and ^1H NMR assays.

A probe experiment indicated that the cyclization of 14a can be also achieved with a four molar excess of ceric sulfate in CH_3CN/H_2O, affording 26a in about 50% yield.

Synthesis of 11-hydroxy MK-801 (10)

The synthesis of racemic 10 was completed by reductive cleavage of the methoxy group of 26a.



26a 10

After testing several reagents, reaction with an excess of borane-methyl sulfide followed by hydrolysis with methanolic sulfuric acid accomplished this task in 80% yield. In practice, the crude ring closure mixture was subjected to reduction and pure 11-hydroxy MK-801 (10) was isolated by crystallization. Using optimized conditions for ring closure (flow cell, 75% yield), the overall yield of the process (14a→10) was 58%. Resolution provided the optically pure d-isomer of 10[10].

Electrochemical Optimization

After the small scale synthesis was completed, the experimental variables of the azacyclization reaction was examined in detail. The purpose of this was to improve yield, reduce by-product formation and increase the current efficiency.

The most important variable was the choice of anode material. Table II shows selected data on the effect of anode material on azacyclization (14a→26a). In all cases stainless steel was used as a cathode material. The reactions were run in 70:30 THF:H_2O containing 1% $NaBF_4$ as the supporting electrolyte, at constant potential (1.2V vs SCE). After microscopic examination of the anode materials, it became clear that the best results were obtained with graphite felts which had the largest surface areas (ca. $50m^2/g$) and had been fired at high temperature. Nonfibrous carbon such as pure graphite and reticulated vitrous carbon gave poor results.

TABLE II. Effect of Anode Material

Anode Material[11]	Yield of 26a	Yield of 28a
Platinum foil	0	0
Graphite plate	0*	0
Retriculated vitrious carbon	55%	12%
GSF-2 Graphite felt	50%	20%
GSF-6 Graphite felt	75%	15%
Graphite felt fired at 2300°C	85%	5%

*The major product was the ketone corresponding to 26a.

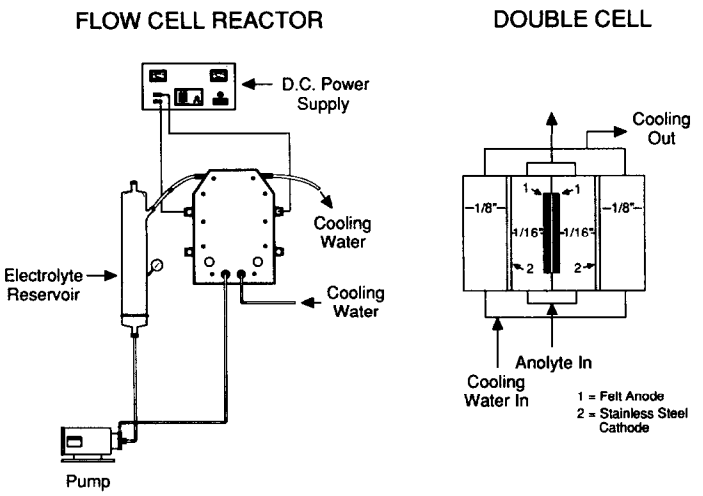
The effect of solvents and supporting electrolytes was also examined. After examining several combinations, we concluded that the optimum solvent for the electrocyclization is 70/30 THF:H_2O containing 1% $NaBF_4$ or $LiOSO_2CF_3$, the latter being preferred due to its higher solubility.

We have also tested the standard reaction (GSF-6 anode, 1.2V vs SCE, 70/30 THF:H_2O 1% $NaBF_4$) at various temperatures and pH ranges. The yield and amounts of byproducts were unaffected at temperatures of 0-60°C and at pH-3-8. At pH ranges below 2 and above 9, the cyclization was retarded. In a standard run, the pH of the reaction mixture did not change during the course of the electrolysis.

When the progress of the reaction was followed, it became apparent that there is some product decomposition parallel with product formation. Thus, product formation reached a maximum before all the starting material was consumed. Optimumum yield, was achieved at 95% conversion.

The effect of current density on yield is important for the scale up of an electrochemical reaction. Our small scale experiments (1-2g) were run in a beaker at constant potential of 1.2 V and current density of 2-7 mA/cm^2. Large scale reactions were conducted at constant current. In these cases, a simple rectifier (AC→DC) and a laboratory variac were used and the current density was increased to 40-80 mA/cm^2. Utilizing these conditions, 75 g of 14a was processed in a 2 l resin kettle. The main drawback of large scale stirred vessel operation is, that because of the relatively large distance between the electrodes (2-5"), significant amount of heat is generated by conductance. Further scale up required the use of a flow cell reactor. The electro flow cell[11] is composed of anode material glued onto graphite plates, interspaced with the stainless steel plate cathode, as shown in Figure 1. The solution of the reactants is passed between the electrodes by a circulating pump. The distance between the anode and cathode is only 1/16 inch, and therefore, very little heat is generated. Cooling is achieved by circulating water between the cell compartments.

Figure I



This equipment was designed for continuous operation. The ring closure of 200 g of 14a required about 5 hrs. of operation. The scale up results are summarized in Table III, using optimized electrochemical conditions.

TABLE III. Scaleup Results

Scale	Conditions	Reactor	Yield of 26a	Yield of 28
1 g	1.2 V const pot	Beaker	85%	5%
75 g	50 mA/cm^2	2 l resin kettle	80%	10%
200 g	50 mA/cm^2	Flow reactor	75%	20%

The major difference between flow reactor operation and stirred vessels is the increased formation of rearrangement product (28). This could be the consequence of the reduced liquid space to electrode surface ratio in the flow reactor. Thus the intermediate carbonium ion has longer time to rearrange prior to reacting with water. This explanation is consistent with the observation that when the flow rate was reduced, the rearrangement product formation further increased (up to 30%).

In conclusion, a novel electrochemical azacyclization was developed and shown to be suitable for larger scale preparations. Normally this type of oxidation is carried out with expensive toxic metals. In this case the oxidation was accomplished by the clean byproduct-free removal of electrons to an anode surface. This illustrates the importance and practicality of electrosynthesis, especially when large scale preparations are involved.

EXPERIMENTAL

^1H and ^{13}C-NMR spectra were obtained in $CDCl_3$ on a Bruker AM300 or WM250 NMR spectrometers and are referred to TMS. Mass spectra were obtained on a Finnegan 450 mass spectrometer. Melting points are uncorrected. Hydrogen and ^{13}C NMR spectra of N-substituted MK-801 derivatives indicated the presence of syn and anti forms (inversion of the nitrogen bridge) at ambient temperature[9]. This phenomenon was also observed with the 11-substituted analogs described in this paper (26, 29, 30 and 31), giving rise to a doubling of NMR signals. Naturally, when the nitrogen substituent was removed (10), only one set of signals were observed.

General Pocedure for Small Scale Electrocyclization

A magnetically stirred beaker equipped with a stainless steel cathode (a spatula) and 2-3 cm^2 size anode was used for small scale ring closures. The electrolysis was conducted at constant potential of 1.2-1.3V (ref: std calomel) until the current dropped to a low level. The progress of the reactions was also followed by HPLC or tlc. When the reaction was complete, the organic solvent was removed on a rotary evaporator. The residue was partitioned between methylene chloride and water, the organic layer was washed with satd. sodium bicarbonate solution and dried over sodium sulfate. The products were purified by silica gel chromatography using methylene chloride, ethyl acetate and hexane as eluents.

10,11-Dihydro-11-hydroxy-5-methyl-12-methoxy-dibenzo[a,d]cycloheptene-5,10-imine(26a)

Anodic oxidation of 14a (1 g) in tetrahydrofuran (45 ml), water (5 ml) and $NaBF_4$ (0.5 g) was carried out utilizing a retriculated vitrious carbon anode. After chromatography, 26a (180 mg) was obtained as resinous solid as a mixture of syn and anti-isomers. ^1H NMR δ 2.01 and 2.05 (s, 3H) 3.6 and 3.73 (s, 3H total), 4.41 and 4.68 (d, J = 12 Hz, 1H total), 4.82 and 5.05 (d, J = 1 Hz, 1H total), 7.05-7.45 (m, 8H). HRMS, found m/z 268.1337, $C_{18}H_{17}NO_3$ requires: 268.1328. LC analysis of the crude product indicated that the mixture contained 26a in 50% and 28 in 20% yield. Improved reaction conditions using graphite felt fired at 2300°C as anode material and lithium trifluoromethane sulfonate as the supporting electrolyte, gave 26a in 80% and 28 in 5% assay yield.

9,10-Dihydro-12-hydroxy-11-methoxy-10-methyl-10,9-(iminomethano)antracen(28).

Later eluting fractions of the above mentioned chromatography contained 75 mg of this rearrangement product (28). ^1H NMR δ 2.18 (s, 3H), 3.7 (s, 3H), 4.34 (d, J = 3 Hz, 1H), 4.68 (s, 1H), 7.05-7.46 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 14.8, 29.3, 50.7, 64.0, 66.0, 92.9, 122.3, 123.0, 124.5, 126.0, 126.6, 126.7, 129.0, 138.6, 139.4, 141.0 and 141.3.

N-(Acetoxy)-5-methyl-5H-dibenzo[a,d]cycloheptene-5-amine (14c)

To a solution of 14b (2.37 g, 10 mmol) triethylamine (1.53 ml, 11 mmol) and a drop of 4-dimethylamino pyridine in methylene chloride was added acetic anhydride (1.07 g, 10.5 mmol). After 4 h reaction at room temperature and extractive workup with 0.5 n HCl, satd. $NaHCO_3$ and satd. brine solution, followed by drying (Na_2SO_4) and evaporation, a yellow oil was obtained. Trituration with hexane produced 1.99 g of 14c, as colorless crystals (67% yield). Mp 96-97°C. ^1H NMR δ 1.75 (s, 3H), 2.32 (s, 3H), 7.18 (s, 2H) 7.23-7.70 (m, 2H), 8.76 (s, 1H). Anal. Calcd. for $C_{18}H_{17}NO$:C, 77.40; H, 6.13; N, 5.01. Found: C, 77.37; H, 6.23; N, 5.28.

5-Methyl-N-[[(2-methylpropoxy)carbonyl]oxy]-5H-dibenzo[a,d]cycloheptene (14d)

The procedure described above, using i-butyl chloroformate produced 14a as a yellow oil. Crystallization from methanol the pure compound was obtained in 35% yield. Mp: 97-99°C. ^1H NMR δ 0.8 (d, 6H) 1.83 (m, 1H), 2.32 (s, 3H), 3.78 (d, t = 8 Hz, 2H), 7.18 (s, 2H), 7.25-7.72 (m, 10H), 8.22 (s, 1H). Anal. Calcd. for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.83; N, 4.15. Found: C, 74.40; H, 6.96; N, 4.25.

N-Acetoxy-10,11-dihydro-11-hydroxy-5-methyl-dibenzo[a,d]cycloheptene-5,10-imine (26c)

Electrocyclization of 14c in THF/H_2O 7:3 and $NaBF_4$ utilizing a graphite felt anode (GF-2) afforded 26c in 70% assay yield. After chromatographic purification and recrystallization from ethyl acetate and hexane, pure 26c was isolated in 55% yield. Mp: 142-144°C. ^1H NMR (syn and anti) δ 1.95 (s, 3H), 2.02 (s, 3H), 4.50 and 4.70 (d, J = 2Hz, 1H), 4.85 and 5.05 (d, J = 1Hz, 1H), 7.04-7.42 (m, 8H). HRMS, found m/z 296.1286, $C_{18}H_{17}NO_3$ requires 296.1287.

10,11-Dihydro-5-methyl-N-[[2-methylpropoxy)carbonyl]oxy] -5H-dibenzo[a,d]cyclohepten-5,10-imin-11-ol (26d)

Electrocyclization of 14d, in THF/H_2O 7:3, and $NaBF_4$, utilizing a graphite felt anode (GF2) and following the general procedure afforded 26d in 70% yield. ^1H NMR (syn and anti) δ 0.92 (d,J = 8Hz, 6H), 2.00 (s, 3H), 2.84 and 3.41 (br.s, 1H), 3.97 (m, 2H); 4.50 and 4.72 (d,J = 1Hz, 1H), 4.94 and 5.13 (d,J = 1Hz, 1H), 7.05-7.45 (m, 8H). HRMS, found m/z 354.1702, $C_{21}H_{23}NO_4$ requires 354.1705.

10,11-Dihydro-11,12-dimethoxy-5-methyl-dibenzo[a,d]cycloheptane-5,10-imine (29)

The electrolysis of 1 g (4 mm) of 14a with 1 g of $NaBF_4$ in 50 ml of methanol afforded 29 in 40% yield. ^1H NMR δ 2.0 (s, 3H), 3.7 (s, 6H), 3.75 (s, 3H), 4.4 (d,J = 1Hz, 1H), 5.0 (d,J = 1Hz, 1h), 7.1-7.4 (m, 8H). HRMS, found m/z 282.1499, $C_{18}H_{20}NO_2$ requires 282.1494.

11-Acetoxy-10,11-dihydro-5-methyl-12-methoxy-dibenzo[a,d]cycloheptene-5,10-imine (30)

Electrolysis of 1 g (4 mm) of 14a with potassium acetate (4.5 g) in 100 ml of acetic acid afforded 30 in 73% yield. ^1H NMR (syn:anti 6:1, major conformer) δ 2.1 (s, 3H), 2.3 (s, 3H) 3.7 (s, 3H); 4.8 (d,J = 2Hz, 1H), 6.0 (d,J = 2Hz, 1H), 7-7.5 (m, 8H).

11-Acetamido-10,11-dihydro-5-methyl-12-methoxy-dibenzo[a,d]cycloheptene-5,10-imine (31)

Electrolysis of 1 g of 14a with $NaBF_4$ (3 g) in 50 ml acetonitrile and 1 ml of water afforded acetamido derivative 31 in 30% yield. ^1H NMR (syn: anti 1:1.5, major conformer) δ 1.9 (s, 3H), 2.1 (s, 3H), 3.6 (s, 3H) 4.7 (d,J = 2Hz, 1H), 5.3 (d, 2Hz, 1H), 7-7.5 (m, 8H). HRMS found m/z 309.1596 $C_{19}H_{21}N_2O_2$ requires 309.1603.

Preparative Scale Electrocyclization of 14a

A 2 l resin kettle was fitted with a 50 cm^2 carbon felt (GSF-6, 5 X 10 cm) anode, a stainless steel (100 cm^2) cathode, a mechanical stirrer, thermometer and N_2 inlet. Into this reaction vessel was added THF (950 ml) and methoxylamine 14a (75 g, 0.3 mole) and a solution of sodium tetrafluoroborate (18 g) in water (400 ml). A constant current of 4 Amps, (28-30 volts) was applied until the LC analysis for starting material was below 5% (6hrs).

Saturated sodium bicarbonate solution was added (pH = 7.5) and the mixture was extracted with methylene chloride. The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered and concentrated to a foam (83.63 g, 104.8% of theory). LC assay indicated that the mixture contained 26a in 55% yield. This material was used without purification for the next step. When the same reaction was performed using graphite felt (fired at 2300°C) as anode material and lithium trifilate as supporting electrolyte, the yield of 26a was 80%.

(+)-10,11-Dihydro-11-exo-hydroxy-5-methyl-dibenzo[a,d]cycloheptene-5,10-imine (10)

To a 2 L 3-necked flask equipped with overhead stirrer, reflux condenser, addition funnel and nitrogen purge, was charged the crude methoxylamine (26a) (103.6 g) and 600 ml tetrahydrofuran. The solution was heated to reflux and borane-methylsulfide (116 ml, 1.16 mole) was added, dropwise, to the refluxing solution. When the addition was complete, the reflux condenser was replaced with a distillation head. Dimethyl sulfide was collected along with some tetrahydrofuran. When HPLC analysis indicated that the reduction was complete (4 hrs.), the cooled mixture was added dropwise to a solution of methanol (500 ml) and 6 M H_2SO_4 (225 ml).

The solution was heated to reflux for 20 min. and 250 ml of solvent was then removed by slow distillation. After the removal of the remaining organic solvents, the pH of the aqueous slurry was adjusted to 11 with KOH. Additional water was added (500 ml) and the product was removed by filtration. Recrystallization of this material from acetonitrile (1500 ml) produced 34.5 g of pure 11-hydroxy MK-801 (10). An additional 12 g of product was obtained by concentration of the mother liquors. Yield of the reduction step was 91%. Mp: 215-218°C. ^{1}H NMR δ 1.91 (s, 3H), 4.44 (d,J = 1Hz), 4.59 (d,J = 1Hz), 7.15-7.40 (m, 8H). Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.97; H, 6.58; N, 5.97.

Flow Reactor Cyclization of 14a

An ESC[11] flow cell reactor fitted with two 100 cm^2 carbon felt anodes (fired at 2300°) and two stainless steel cathodes were used for this reaction. A solution of 14a (200 g, 0.8 mole) lithium trifluoromethanesulfonate (40 g) in tetrahydrofuran (4.85 l) and water (1.65 l) was circulated through the reactor for five hours. A current of 10 A (current density 50 MA/cm^{-2}) was applied and the voltage drop across the electrodes was 17-19 V. The product was isolated as described above. This reaction produced 26a in 75% and 28 in 20% assay yield.

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REFERENCES

1. For recent reviews see: a) Ramaiah, M. Tetrahedron 43, 3541 (1987), b) Giese, B., Radicals in Organic Synthesis: Formation of Carbon-Carbon bonds. Pergamon Press, 1986, c) Curran, D.P., Synthesis, 1988, 417 and 489.
2. a) Gilchrist, T.L. in Comprehensive Organic Chemistry, Barton, D.H.R. and Olis, W.D., Ed., Vol 2, 273, Pergamon Press, 1979, b) Stella, L. Angew Chem. Int. Ed. Engl, 1983, 22, 337, c) Newcomb, M.; Deeb, T.M. J. Am. Chem. Soc. 1987, 109, 3163, d) Surzer, J-M. in Reactive Intermediates, Abramovitch, R.A., Ed., Plenum:New York, 1982, Vol. 2, p. 121-177.
3. Torii, S. Electroorganic Synthesis, Kodansha, Ltd. Tokyo, 1985, Part I, p. 153.
4. Tokuda M.; Yamada, Y.; Takagi, T.; Suginome, H.; Tetrahedron, 1987, 43, 281.
5. a) House, H.O.; Lee, L.F. J. Org. Chem. 1976, 41, 863. House, H.O.; Manning, D.T.; Melillo, D.G.; Fel, L.F.; Haymes, O.R.; Wilkes, B.E. Ibid., 1976, 41, 855. b) Ciganek, E. J. Org. Chem. in print. We thank the author for an advance copy of this paper.
6. Ref. 1b pages: 90, 94 and 182. For a recent summary see Snider, B.B.; Patricia, S.J.; Kates, S.A. J. Org. Chem. 1988, 53 2137.
7. A preliminary account of this work: Karady, S.; Corley, E.G.; Abramson, N.L.; Weinstock, L.M. Tetrahedron Lett. 1989, 30, 2191.
8. a) Britcher, S.F.; Lyle, T.A.; Thompson, W.J. and Varga, S.L. European Patent #0264183, 1988. Christy, M.E.; Anderson, P.S.; Britcher, S.F.; Colton, C.D.; Evans, B.E.; Remy, D.C.; Engelhart, E.L. J. Org. Chem. 1979, 44, 3117. Wong, H.F.; Kemp, J.A.; Priestly, T.; Knight, A.R.; Woodruff, G.N.; Iversen, L.L. Proc. Natl. Acad. Sci. U.S.A. 1986, 83, 7104. b) The original synthesis of the metabolite: Thompson, W.J. et. al. J. Med. Chem. 1990, 33, 789. c) For other synthetic approaches see: Larsen, R.D.; Davis, P.; Corley, E.G.; Reider, P.J.; Rothauser-Lamanec, T.; Grabowski, E.J.J. J. Org. Chem. 55, 299.
9. Lamanec, T.R.; Bender, D.R.; DeMarco, A.M.; Karady, S.; Reamer,R.A.; Weinstock, L.M. J. Org. Chem. 1988, 53, 1768.
10. Resolved with di-p-toluoyl-D-tartaric acid and isolated as the maleate salt, $[a]_D$ (+) 109.2° (C=1 in methanol), by R.D. Larsen and P.J. Reider of these laboratories. See also Ref. 8c.
11. All electrochemical equipment and materials were purchased from the Electrosynthesis Co. Inc., P.O. Box 16, E. Amherst, N.Y. 14051.