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A VERSATILE TOTAL SYNTHESIS OF EPIBATIDINE AND ANALOGS

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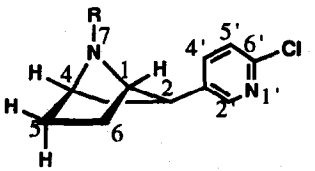
Abstract: A racemic mixture of epibatidine, a potent analgesic alkaloid possessing a 7-azanorbornane structure, has been synthesized *via* a versatile four-step synthetic route: a Diels-Alder reaction of N-carbomethoxy pyrrole and phenylsulfonyl 6-chloro-3-pyridyl acetylene, followed by desulfonation, hydrogenation and deprotection of the amine. *rac* -Epibatidine was resolved to its *d* and *l* enantiomers.

Epibatidine (**1**) represents a new class of alkaloid possessing a 7-azanorbornane structure. It was originally isolated from the skin extracts of an Ecuadoran poison frog, *Epipedobates tricolor*, of the family Dendrobatidae.[1] Only a trace of epibatidine was obtained from the skin extracts of 750 frogs. Its structure was suggested on the basis of high resolution mass spectra and NMR data of the alkaloid and its N-acetyl derivative (**2**).[2] Preliminary biological tests showed that epibatidine has 200 to 500 times the potency of morphine in the hot plate and Straub-tail analgesic assays, respectively, but with negligible (1/8000 of morphine) affinity for the opiate receptors in the receptor binding studies.[2] Further characterization of this novel and potentially useful alkaloid was stymied by the lack of material. The total synthesis of epibatidine is obviously of considerable chemical and pharmacological interest.

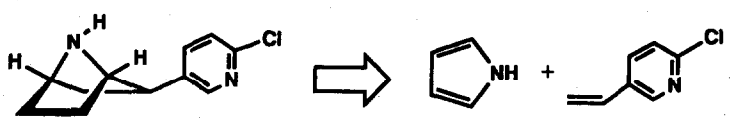


1 R = H

2 R = Ac

A possible entry into the 7-azanorbornane ring system is formally given by the Diels-Alder reaction of a substituted dienophile with pyrrole (Scheme 1).

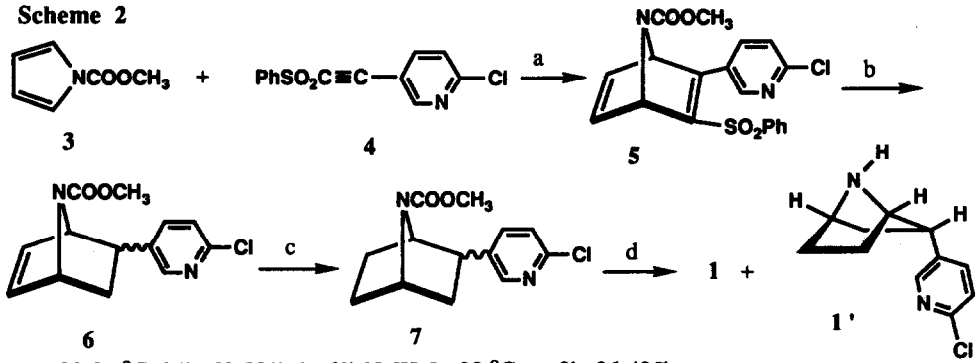
Scheme 1



Unfortunately, pyrrole or its derivatives readily undergo substitution reactions upon treatment with dienophiles,[3] with only a few exceptions reported.[4] Several alternative methods have been reported for the synthesis of the 7-azanorbornane ring system,[5] but the long synthetic route and drastic reaction conditions involved are unsuitable for the synthesis of epibatidine. Most recently, significant progress was made to synthesize the epibatidine ring system and substituted analogs from dipolar cycloadditions of pyrroles *via* their pentaammineosmium (II) complexes.[6]

In exploring alternative approaches, we have noticed that N-carboalkoxy pyrroles, with a decreased aromaticity of the pyrrole ring, have been used successfully in the Diels-Alder reaction with several acetylenic dienophiles.[7,8] Now we report a convenient and versatile process for the synthesis of epibatidine and analogs based on the Diels-Alder reaction of N-carbomethoxy pyrrole (**3**)[9] and phenylsulfonyl 6-chloro-3-pyridyl acetylene (**4**). (Scheme 2).

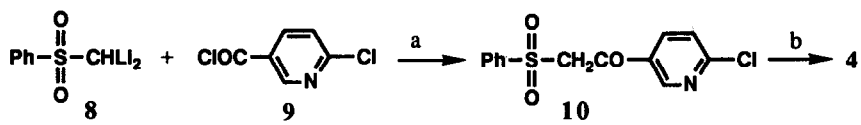
Scheme 2



a: 80-85 °C, 24h, 50-70%. b: 6% Na[Hg], -20 °C -rt, 3h, 36-42%.
c: H_2/10%Pd-C, 5min, 92%. d: 33%HBr/HOAc, 20h.

The starting material (**4**) was prepared in two steps as described in scheme 3:

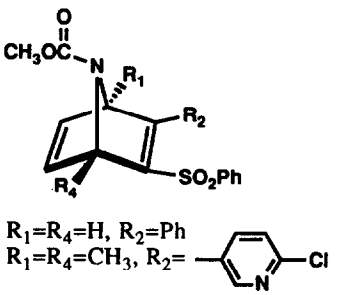
Scheme 3



a: THF, -30 °C, 10min, 50%. b: $ClPO(OEt)_2$, Et_3N/CH_2Cl_2, rt, 24h; t-BuOK/THF, -78°C, 20min. 75%.

The β-ketosulfone (**10**, mp 152-153 °C) was obtained in 50% yield *via* a method reported by Thomsen *et al.*.[10] Phosphorylation with diethyl chlorophosphate and triethylamine at room temperature overnight, followed by elimination with potassium t-butoxide[11] gave 75% of the substituted acetylene (**4**, mp 140-141 °C). The Diels-Alder reaction was performed at 80-85 °C for 24h with excess N-carbomethoxy pyrrole as the solvent. A 70% yield of the adduct was obtained which was recrystallized from methanol to give white crystals (**5**). The structure of this 7-azanorbornadiene derivative was confirmed by X-ray crystallographic analysis (Figure 1). The adduct (**5**) underwent desulfonation,[12,13] and concomitant reduction of the conjugated double bond, with 4 eq 6% sodium amalgam in methanol containing 4 eq sodium dihydrophosphate. The main product (36-42% yield) obtained was a 1:2 mixture of *exo* and *endo* isomers of N-carbomethoxy dehydroepibatidine (**6**) as a colorless oil. MS(CI) m/z 265, 267 (M+1). Reduction of the remaining double bond in (**6**) was readily accomplished by hydrogenation at atmospheric pressure with 10% Pd-C as catalyst. After the calculated volume of hydrogen was absorbed in 5 min, the product (**7**) was obtained in 92% yield as a colorless oil, again as a 1:2 mixture of *exo* and *endo* isomers. MS(CI) m/z 267, 269 (M+1).

Several methods were investigated for the final removal of the N-carbomethoxy protecting group. Hydrolysis with potassium hydroxide[14] in methanol resulted in substitution of the moderately reactive chlorine in the pyridine ring by a methoxy group. Treatment with methyllithium (3 eq)[15] stopped at the formation of N-acetyl epibatidine (**2**) (identical with an authentic sample from acetylation of *rac*-epibatidine as described below), which resisted further cleavage by methyllithium even after a prolonged treatment. This is in accordance with the stability of N-acetyl epibatidine towards hydrolysis observed previously.[2] Finally, the carbamate (**7**) was successfully deblocked by treatment of hydrobromic acid in acetic acid for 24 hours at room temperature.[16] The products isolated from silica gel chromatography, with a mixed solvent system of ethyl acetate, methylene chloride and ammonia methanol as the eluent, were *rac*-epibatidine (**1**, 25%), *rac-endo*-epibatidine (**1'**, 28.4%) and unchanged carbamate (20%). Notably, the recovered starting material is the essentially pure *endo* isomer of (**7**), indicating some stereoselectivity in the cleavage of the N-carbomethoxy group with hydrobromic acid. The *exo*-isomer was apparently cleaved at a higher rate than the *endo*-isomer, presumably because of the proximity of the pyridyl and carbamate groups. The *rac*-epibatidine was obtained as a crystalline white solid, mp 50-51°C, with characteristic spectral data.[17] Both the high resolution mass spectrum of *rac*-epibatidine and the ^{1}H-NMR (GN -500) data of its N-acetyl derivative are in excellent agreement with those published by the original investigators.[2] The *rac-endo*-epibatidine (**1'**) was obtained from chromatography as a more polar component. Its structure was assigned according to its spectroscopic properties[17] which are very similar to those of *rac*-epibatidine. Finaly, *rac*-epibatidine was resolved to its *d* and *l* enantiomers *via* their di-*p*-toluoyl tartaric acid salts, ee>95% (based on their Mosher amides), mp 56-7°C, $[\alpha]_D$ -5.2°, and +5.4° (in chloroform) respectively. The versatility of this synthetic process was demonstrated by the formation of Diels-Alder adducts (**11**) and (**12**) from (**3**) with phenylsulfonyl phenyl acetylene and (**4**) with N-carbomethoxy-2,5-dimethylpyrrole, respectively; different substituents were readily incorporated into the 7-azabicyclo[2.2.1]hepta-2,5-diene system.[17]



11: R_1=R_4=H, R_2=Ph
12: R_1=R_4=CH_3, R_2=

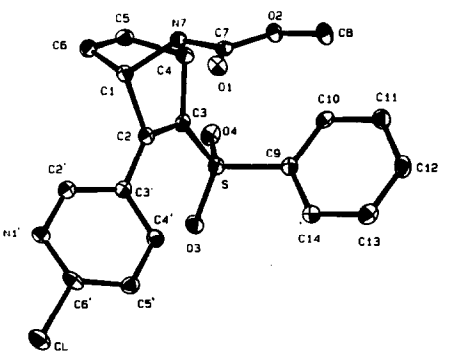


Figure 1. The X-ray crystal structure of adduct (**5**)

In conclusion, a convenient and versatile process has been developed for the synthesis of epibatidine and analogs. Correlation of the absolute configuration of epibatidine with its high analgesic potency is in progress. The availability of synthetic epibatidine and various derivatives from Diels-Alder adducts such as (**5**), (**11**) and (**12**) allows further determination of their pharmacological profiles and potential applications.

Acknowledgement

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17. Selected physical data of compound **1, 1', 5, 11** and **12:**

1: mp 50-51°C, MS(CI) m/z 209, 211 (M+1). H^1-NMR(QE-300, $CDCl_3$) δ(multiplicity, J in Hz): 8.265(d. 2.4, $H_{2'}$), 7.757(dd. 8.1, 2.4, $H_{5'}$), 7.221(d, 8.1, $H_{4'}$), 3.795, 3.560(t, 3.9, br.s. $H_{1,4}$), 2.760(dd. 9.0, 4.8, H_2), 1.988(br.s. H_7), 1.904(dd. 12.0, 9.0, H_{3e}), 1.50-1.65(m, 5H, $H_{3a,5,6}$). ^{13}C-NMR(QE-300, $CDCl_3$) δ: 149.409 ($C_{6'}$), 149.237 ($C_{2'}$), 141.441 ($C_{3'}$), 138.105 ($C_{5'}$), 124.359 ($C_{4'}$), 63.209 (C_1), 56.882 (C_4), 44.952 (C_2), 40.752 (C_3), 31.784 , 30.546 ($C_{5,6}$).

1': oil, MS(CI) m/z 209, 211 (M+1). H^1-NMR δ: 8.219(d. 1.8, $H_{2'}$), 7.447(dd. 8.1, 1.8, $H_{5'}$), 7.252(d. 8.1, $H_{4'}$), 3.760(q. 2H, $H_{1,4}$), 3.289(ddd. 12.0, 4.8, 5.7, H_2), 2.087(br. H_7), 2.120(tdd. 12.3, 4.8, 3.3, H_{3e}), 1.488(dd. 12.3, 5.7, H_{3a}), 1.55-1.72(m, 1H), 1.33-1.43(m, 3H), $H_{5,6}$. ^{13}C-NMR δ: 150.005($C_{2'}$), 149.568($C_{6'}$), 138.812($C_{5'}$), 136.285($C_{3'}$), 124.175($C_{4'}$), 61.535(C_1), 57.955(C_4), 45.337(C_2), 35.311(C_3), 31.433(C_5), 24.553(C_6).

5: mp 109-110°C, MS(CI) m/z 403,405 (M+1). H^1-NMR δ: 8.455(br.s. $H_{2'}$), 7.910(dd. 8.4, 2.4, $H_{5'}$), 7.768(d. 8.1, 2H) 7.644(t. 7.2, 1H) 7.533(t. 7.6, 2H) (PhH), 7.387(d, 8.4, $H_{4'}$), 7.027(s. 2H, $H_{5,6}$), 5.467, 5.447(2s. 2H, $H_{1,4}$), 3.35-3.65 (br. 3H, OCH_3). ^{13}C-NMR δ: 153.489, 148.571, 144.097, 140.486, 139.197, 134.503, 129.858, 128.203, 124.344, 73.504, 69.970, 53.586.

11: MS(CI) m/z 368 (M+1). H^1-NMR δ: 7.048(s, 2H, $H_{5,6}$). 3.50(br.s, 3H, $NCOOCH_3$).

12: MS(CI) m/z 431, 433 (M+1). H^1-NMR δ: 6.790, 6.646(AB, 5.2, 2H, $H_{5,6}$).

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