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Rapid and Efficient Entry to Substituted 2-Succinimidobenzoate-3-azabicyclo[3.3.1]nonanes: AE-Bicyclic Analogues of Methyllycaconitine

Philippa A. Coates, Ian S. Blagbrough*, Michael G. Rowan, and Barry V. L. Potter

Department of Medicinal Chemistry, School of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, U.K.

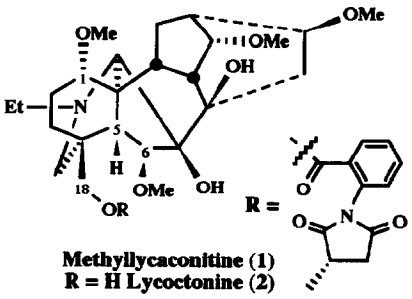
and

David P. J. Pearson and Terence Lewis

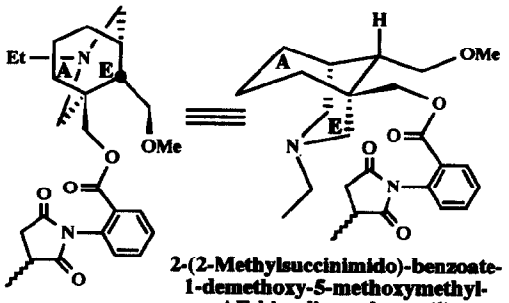
Zeneca Agrochemicals, Jealott's Hill Research Station, Bracknell RG12 6EY, U.K.

Abstract: A double Mannich reaction allows a rapid and efficient entry to substituted 3-azabicyclo[3.3.1]nonane analogues of methyllycaconitine (MLA), a selective antagonist of certain mammalian and insect α-bungarotoxin-sensitive nicotinic acetylcholine receptors.

Methyllycaconitine (MLA) (**1**) (also known as delartine, delsemidine, and mellictine) is the 2-[2-(*S*)-methylsuccinimido]-benzoate ester of the hexacyclic norditerpenoid alkaloid lycoctonine (**2**) [1] and occurs in *Delphinium* and not *Aconitum*, despite its trivial name. These structurally complex alkaloids contain piperidine (E) and cyclohexane (A) rings in a 3-azabicyclo[3.3.1]nonane motif. Neopentyl-like alcohol (**2**) displays considerably less biological activity than its *N*-substituted anthranilate ester (**1**) [2] which continues to find use in Russian medicine [3] as a muscle relaxant for surgery, as it has curare-like activity and apparently blocks neurotransmission. It has been shown that MLA (**1**) is a potent and selective ligand for neuronal over neuromuscular nicotinic acetylcholine receptors (nAChR).[2] MLA is more selective than the snake toxin α-bungarotoxin used for competitive antagonism of neuronal and neuromuscular nAChR.[2] Furthermore, there is continuing interest in MLA (**1**) and its synthetic analogues, as leads for the design and development of insecticides, acting at insect nAChR.[4] We are therefore undertaking structure-activity relationship (SAR) studies of MLA [5] and, in this *Letter*, we present rapid and efficient syntheses of AE-bicyclic analogues, including the 1-demethoxy-5-methoxymethyl analogue (**3**) (racemic) which contains the piperidine (E) and cyclohexane (A) rings of MLA (**1**) as well as the anthranilate moiety.



Methyllycaconitine (1)
R = H Lycoctonine (2)

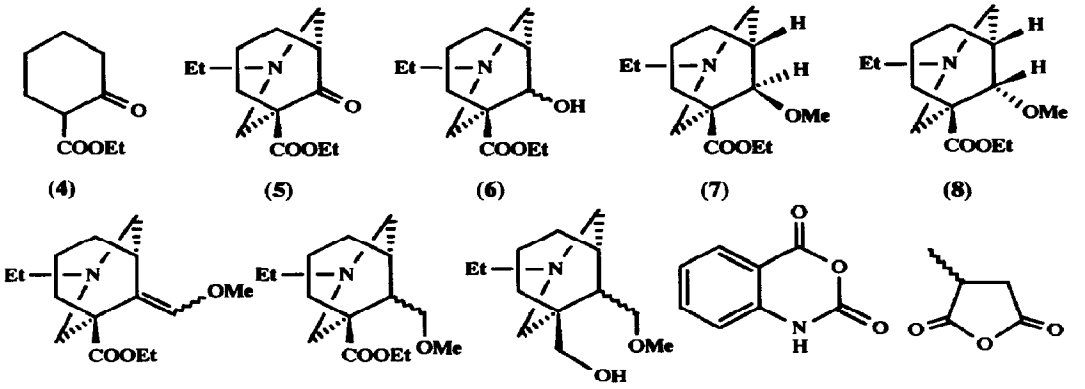


2-(2-Methylsuccinimido)-benzoate-1-demethoxy-5-methoxymethyl-AE-bicyclic analogue (3)

We rationalized that the striking difference in biological activity, more than 10,000 fold, between MLA (**1**) and lycoctonine (**2**) must be, in part, related to the presence of the *N*-succinyl anthranilate ester moiety. In early molecular modelling studies,[6] this ester functional group was compared to the ester found in acetylcholine. The competitive antagonism of nAChR displayed by MLA (**1**) was proposed to be due to the slight distortion of the choline of acetylcholine into the homocholine-like (3-tertiaryaminopropan-1-ol) motif found around the piperidine ring of MLA.[6] Therefore, we have focused our initial synthetic efforts upon the preparation of this functionality by an efficient route which will allow ready access to analogues for biological evaluation. The AE-bicycle is a 3-azabicyclo[3.3.1]nonane which is also found in atisine,[7] cardiopetaline,[8] and related *Aconitum* norditerpenoid alkaloids. Kraus and co-workers have recently published [9] their synthetic approach to the AEBD-tetracycle, and some long-chain fatty acid esters of lycoctonine (**2**) have been prepared by Pelletier and Ross [10] as more lipophilic analogues of MLA (**1**). Benn and Jacyno first reported studies of a monocyclic *N*-methylated piperidine anthranilate ester.[11]

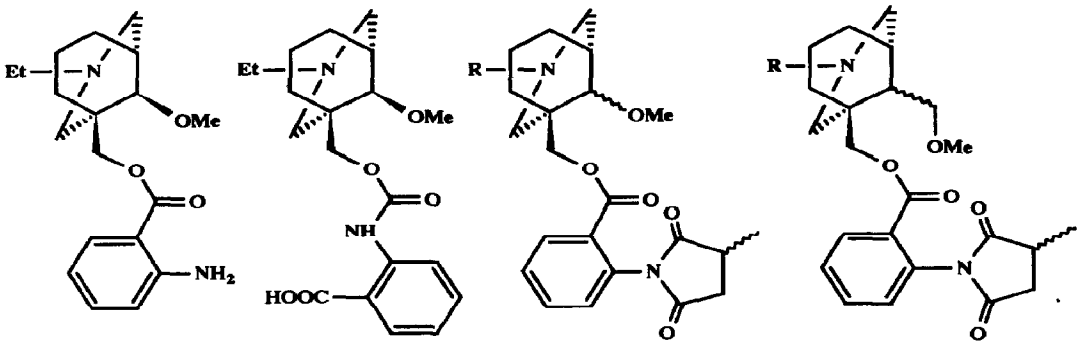
It was immediately apparent that the 3-azabicyclo[3.3.1]nonan-9-one ring system can be prepared from β-keto ester (**4**) which has the correct functionality, appropriately substituted, for the necessary subsequent manipulations. Thus, a double Mannich reaction between keto-ester (**4**), aqueous ethylamine, and aqueous formaldehyde (37%, 2 equiv., EtOH, reflux, 2 h) gave racemic (**5**) (47%).[12] The carboxylic ester carbonyl carbon of (**4**) becomes the neopentyl-type alcohol, equivalent to C-18 of lycoctonine (**2**), of the [3.3.1]bicycle, on reduction and is therefore intrinsic to the design of these MLA (**1**) analogues, not merely a β-keto ester activating group which might later have been removed by decarboxylation. In one series of AE-bicyclic analogues, we decided to exclude oxygenation from C-1 of MLA, and to replace carbon C-6 (norditerpenoid numbering) with an *O*-methyl ether at C-5. Thus, reduction of (**5**) with $NaBH_4$ (EtOH, 25°C, 2 h) gave a mixture of epimeric alcohols (**6**) (81%). *O*-Methylation of (**6**) (NaH, MeI, 1.0 equiv., anhydrous DMF, 25°C, 5 h) gave the required methyl ethers (**7**) (35%) and (**8**) (25%) which were separable on silica gel (hexane-diethyl ether, 2:1) with (**7**) less polar than (**8**), and with no detectable *N*-quaternisation. Characterization of novel ethers (**7**) and (**8**) followed from detailed inspections of their ^{1}H-NMR spectra, in particular, from COSY and nOe experiments as δ 3.53 (d, $J_{5\text{-}9}$ = 3 Hz) and 3.31 (OMe, ax. to cyclohexane) (**7**) and 3.49 (d, $J_{5\text{-}9}$ = 2 Hz) and 3.31 (OMe, eq. to cyclohexane) (**8**) were not diagnostic.

The [3.3.1]bicyclic carbon skeleton can be extended from the ketone at C-5 to C-6 (norditerpenoid numbering) by Grignard- or Wittig-type reactions. In another series of analogues, Wittig reaction of bicyclic cyclohexanone (**5**) was accomplished [nBuLi, (methoxymethyl)triphenylphosphonium chloride, anhydrous THF, 25°C, 16 h] to afford *E*- and *Z*-*exo*-methylidene *O*-methyl ethers (**9**) (44%). Reduction of this mixture of *E*- and *Z*-enol ethers (**9**) by catalytic hydrogenation (5 atm, 10% Pd/C, anhydrous DME, 25°C, 2 h) gave C-5-methyl-*O*-methyl ether (**10**) as a colourless oil (59%). Conversion of the ethyl ester functional groups, in (**7**), (**8**), and (**10**), into the corresponding neopentyl-type alcohols was smoothly accomplished using LAH (anhydrous THF, 25°C, 2 h) e.g. (**10**) gave (**11**) as a colourless oil (90%). We have developed rapid, practical protocols for the conversion of neopentyl-type alcohols into the corresponding anthranilate esters followed by the efficient introduction of the 2-methylsuccinimide ring, in chiral form,[5] as this moiety of MLA (**1**) is also found in related natural product alkaloids, including *inter alia*: anhweidelphinine, ajacusine, barbinine, elatine, glaudelsine, and nudicauline. Isatoic anhydride (**12**), used under basic conditions, efficiently introduces the anthranilate ester, the presence of a basic catalyst promoting the formation of the ester over the carbamate.[13]



(**4**) (**5**) (**6**) (**7**) (**8**)

(**9**) (**10**) (**11**) (**12**) (**13**)



(**14**) (**15**) (**16**) R = CH_3CH_2— (**17**) R = CH_3CH_2—

(**18**) R = $MeOCH_2CH_2$— (**19**) R = $MeOCH_2CH_2$—

Thus, LAH reduction of ester (**7**) gave the desired alcohol which was reacted with isatoic anhydride (**12**), in the presence of the base DMAP, to give anthranilate (**14**) (anhydrous DMF, 60°C, 16 h, 65%) with no detectable isatoate (**15**). Anthranilates derived from (**7**) and (**8**) were converted into diastereoisomeric 2-methylsuccinimides (**16**) by fusing with anhydride (**13**) (125°C, 3 h, 69%); similarly, Wittig reaction product (**9**) was converted, *via* (**10**) and (**11**), into succinimides (**17**) (60%).[5] The basicity of a tertiary amine can be significantly modulated, lowered by essentially a full pKa unit,[14] by the addition of a β-methoxyethyl group. Therefore, β-methoxyethylamine was incorporated in a series of analogues, potentially more lipophilic at physiological pH, parallel to the *N*-ethyl tertiary amines. The colourless oils (**18**) and (**19**) were efficiently prepared by the above strategy. These AE-bicyclic analogues of MLA (**1**) are being tested at sub-types of mammalian and insect nAChR as part of our continuing SAR studies.

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