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Synthesis of (*endo*) 3,9-Disubstituted Diazabicyclo[3.3.1]nonan-7-amines.

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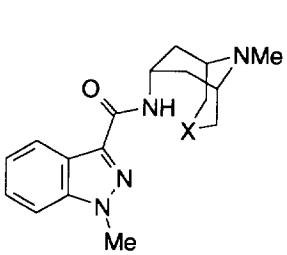
Abstract: The novel synthesis of a series of 3,9-diazabicyclo[3.3.1]nonan-7-amines (4) is reported *via* an alane reduction of a key intermediate oxime (8). The stereoselectivity of the reduction is highly dependent on the size of the 3-aza substituent.

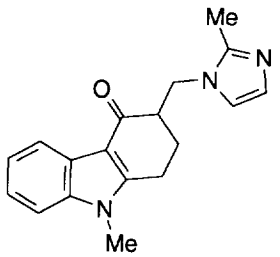
In recent years, potent and selective serotonin $5HT_3$ receptor antagonists e.g. granisetron (1a) and ondansetron (2), have been shown to be effective in the control of cancer chemo- and radio- therapy induced emesis[1]. In addition, $5HT_3$ receptor antagonists, such as (2) and BRL 46470 (3) have been investigated for use in the treatment of various centrally mediated disorders [2-4].



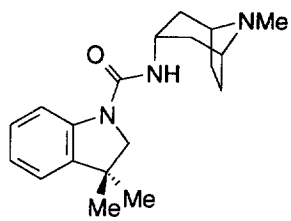
granisetron (1a) X = C

(1b) X = O

(1c) X = N



ondansetron (2)

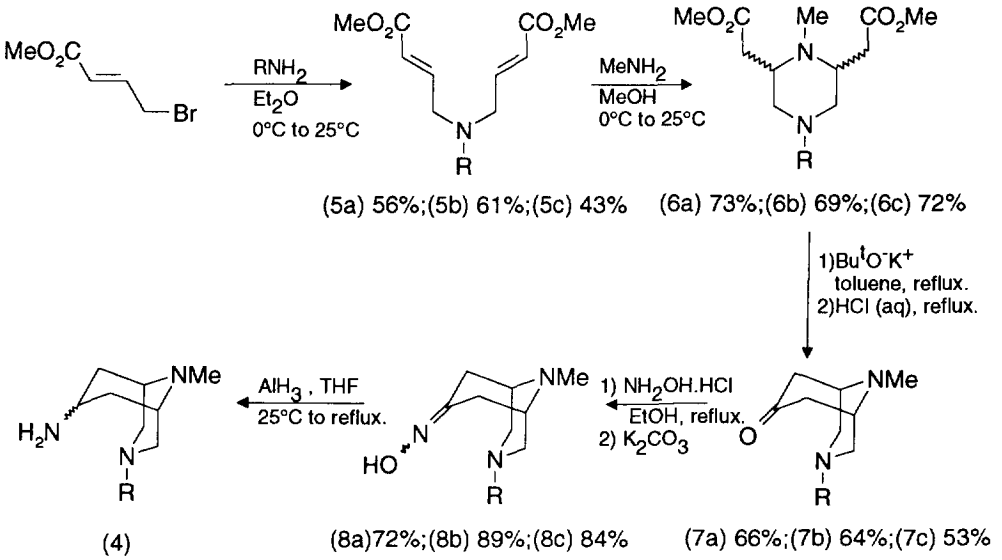


BRL 46470 (3)

We have previously reported that derivatives of tropane and granatane are potent $5HT_3$ receptor antagonists when linked *via* an amide or ester group to either an ortho-methoxyphenyl, indazolyl, 1-indolinyl or ortho substituted anilino aromatic system [5-9]. The effect of introducing a hetero-atom into the granatane ring of (1a) and related compounds has been investigated. The 3-oxagranatane derivatives, such as (1b) which have a lower basicity whilst retaining the chair-chair conformation, were found to retain or enhance potency [10] and consequently, we turned our attention to the 3-azagranatane derivatives such as (1c).

In order to achieve the syntheses of these target structures we required a series of (*endo*) 3-substituted-9-methyl-3,9-diaza-bicyclo[3.3.1]nonan-7-amines (4). A survey of the literature revealed that two syntheses of this ring system were available. Robinson-Schöpf cyclisation had been utilised to afford ketones (7) in only a 7.5% yield [11]. An alternative procedure *via* the dimethyl ester of 4-

hydroxypiperidine-2,6-dicarboxylic acid afforded the requisite ring system *via* a multistep synthesis in 23% yield [12]. However, due to the low yields, neither of these procedures was suitable for rapid synthesis of a series of analogues and an alternative procedure was therefore required. It was envisaged that the ketones (7) could be prepared by Dieckmann cyclisation of the piperazines (6), available in two steps from methyl 4-bromocrotonate.



Scheme I.

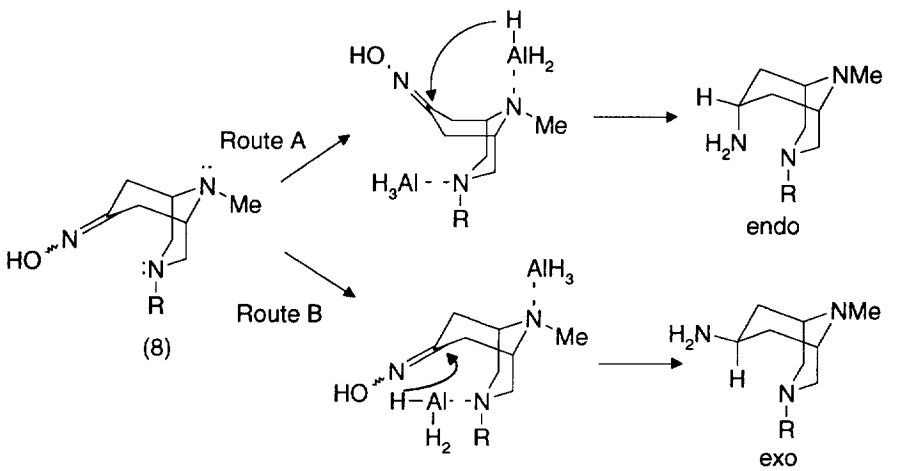
Treatment of commercially available methyl 4-bromocrotonate (Scheme I) with the appropriate primary amine gave moderate yields of unsaturated diesters (5). Subsequent Michael-type addition of methylamine afforded the piperazines (6) as a mixture of *cis* and *trans* isomers (for example a ratio of 70:30 respectively is observed when R = ^{n}Pr). Dieckmann cyclisation using potassium tert-butoxide in toluene, followed by acid hydrolysis and decarboxylation gave the 3-substituted-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-ones (7), in moderate yields (see table 1). It is believed that the moderate yields were a result of cyclisation of the *cis* isomers only, with the *trans* piperazines not undergoing cyclisation. The ketones (7) were converted into the corresponding oximes (8) using standard methodology.

Table 1.

Compd. No.	**R**	**% yield of (4)**	**Boltzmann distribution chair:boat**	**Isomer ratio *exo:endo***
4a	Me	69	77:1	4:1
4b	Et	58	14:1	1:3
4c	^{n}Pr	60	12:1	0:1

We have previously reported that reduction of oximes of ring systems such as granatane, tropane and oxagranatane with alane afforded almost exclusively the respective *endo* amines[6]. However, similar treatment of the oximes (8) with two equivalents of alane in tetrahydrofuran afforded the amines (4), with the *exo* and *endo* isomer ratio depending upon the size of the 3-substituent (see table 1). When R was n-propyl only the expected *endo* amine was isolated. However, where R was methyl and ethyl, mixtures of *exo* and *endo* isomers were obtained in ratios of 4:1 and 1:3 respectively.

A possible explanation for the observed isomeric ratios is based upon the Boltzmann population distribution of the chair and boat conformations of the oximes (8) (Scheme II and table 1). Alane can act as a Lewis acid [13] and as such has the ability to complex to the basic nitrogens of azabicycles. We previously proposed that the stereospecific reduction of the granatane oximes to give almost exclusively the *endo* amine isomer, is due to a kinetically favoured reduction via an intramolecular hydride transfer from the alane complexed to the 9-nitrogen (route A, Scheme II)[5]. However, for the diaza system, there are two possible nitrogen atoms which can complex with the alane, both of which are capable of intramolecular H-transfer (routes A and B), which are expected to lead to *endo* and *exo* isomers respectively. There is either a rapid dynamic equilibration between 3-N and 9-N complexation with alane or both the 3-N and 9-N are complexed. As the proportion of boat conformation increases, the hydride transfer occurs increasingly from the top face *via* the 9-N complexed alane to give the *endo* amine (route A). A possible alternative explanation of reduced ability of the 3-N to complex with alane with increasing size of the R group is unlikely as two molar equivalents of alane were used.



Scheme II.

From molecular mechanics considerations, calculated using the AM1 Hamiltonian[14], the piperazine ring almost exclusively adopts a chair conformation, with the 3-substituent equatorial. In contrast, for the piperidine ring with R = ^{n}Pr, the chair and boat conformations are of similar energies and the Boltzmann population distribution, at 27°C, indicates a 12:1 ratio (92.3% to 7.7%) of the two conformations. However, when R = Me, the energy of the chair form is 2.6Kcal/mol lower than the boat and the

Boltzmann population distribution indicates a 77:1 ratio (98.7% to 1.3%) of the conformations (see table). When R = Et, the calculated Boltzmann distribution between the chair and boat conformations of the piperidine ring is 93.3% to 6.7% (14:1) respectively, that is intermediate between the cases where R = Me and R = ^{n}Pr. Thus, as the proportion of boat conformation increases with increasing size of R, in the order ^{n}Pr > Et > Me, an increasing proportion of *endo* isomer is formed on the reduction with alane. It can be concluded therefore that route A is kinetically favoured over the alternative route B.

In conclusion, a short, versatile and relatively high yielding synthesis of 3-substituted-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-ones (7) has been described. The ketones (7) were converted to the amines (4) by alane reduction of the corresponding oximes (8). Alane has again proved to be a useful reagent for the reduction of azabicyclic oximes by virtue of its Lewis acid complexing properties. However, in this case the degree of stereoselectivity is highly dependent on the size of the 3-aza substituent. The aryl amide derivatives of *endo* amines (4) were found to be potent $5HT_3$ receptor antagonists and full biological evaluation will be reported elsewhere[15].

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