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Synthesis, structural and conformational study of selected N-substituted phthalimides

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Abstract: This paper synthesizes N-substituted phthalimides derived from nitrogen heterocycles as potential 5-HT_4 ligands by using the Mitsunobu reaction. Conformational studies of some of the new compounds have been conducted using ^{1}H and ^{13}C-NMR spectroscopy. Proton and carbon resonances were achieved through the application of one-dimensional selective NOE, two-dimensional NMR techniques -homonuclear COSY-45, NOESY and heteronuclear ^{1}H-^{13}C HMQC correlated spectroscopy- and double resonance experiments. The crystal structure of compound **1** was determined by X-ray diffraction.

Keywords: Phthalimides, NMR spectroscopy, structural analysis

1 Introduction

Imides synthesis is of widespread interest as several derivatives of this heterocyclic unit have been found to possess important applications in biology [1-7], synthetic [8-10] and polymer chemistry [11].

There are a number of related applicable methods [1] which may be used to prepare the simplest aliphatic imides. Phthalimides are directly obtained from these general

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methods, but they have also been obtained from a number of unusual starting materials and methods [3-6,12-16]. The reaction of potassium phthalimide with halogenoalkanes and with a variety of other alkylating agents leads to *N*-alkylphthalimide. *N*-substituted phthalimides may be converted into the corresponding primary amines by hydrolysis or hydrazinolysis; these reactions together constitute the Gabriel synthesis of primary amines [17].

During the conventional Gabriel condensation, potassium phthalimide and an organic halide are treated without a solvent or the presence of a non-polar, high-boiling solvent (such as xylene). The insolubility of potassium phthalimide under these conditions prevents the reaction to occur, making necessary prolonged heating and high temperatures (100-150 °C) while giving rise to impure products and low yields. Sheehan *et al.* [18] found that by carrying out the condensations in DMF, in which potassium phthalimide is appreciably soluble, a mild exothermic reaction starts spontaneously at room temperature. The yields are higher and products of high purity can be isolated.

Other solvents have been employed, such as acetonitrile, amyl alcohol, DMSO, etc. Landini *et al.* [19] reported the synthesis of *N*-alkylphthalimides via alkylation of potassium phthalimide with alkyl halides or methane sulfonates in toluene in the presence of catalytic amounts of hexadecyltributylphosphonium bromide ($HDTBP^+Br^-$) in a heterogeneous solid-liquid system.

Mitsunobu [20] reported a one-pot stereospecific synthesis of amines from alcohols via phthalimides using triphenylphosphine and diethyl azodicarboxylate (DEAD). Because the reaction took place under mild neutral conditions with a complete inversion of the configuration of the alcoholic hydroxy group, the system was utilized in the synthesis and transformation of various classes of products [21-23]. However, there are a few examples of Mitsunobu reactions of azamonocyclic alcohols to obtain phthalimides, where the reported yields are low (28 %) [24]. Slightly higher yields (13-64 %) were obtained for non-nitrogen bicyclic alcohols [25].

For many years the authors have been concerned with the synthesis of fused bi- and tricyclic nitrogen heterocycles derivatives with potential pharmacological activities. In an ongoing effort to discover new 5-HT_4 ligands, the authors have synthesized a series of *N*-substituted phthalimides (Figure 1) derived from piperidine and bicyclic nitrogen heterocycles. Furthermore, in spite of the extensive use of the Mitsunobu reaction with simple aliphatic alcohols, there are no apparent reports of the reaction involving the azabicyclic systems. Thus, the authors suggest to investigate the application of this reaction to azabicyclic alcohols.

2 Experimental

2.1 General

All reactions were carried out in an atmosphere of dry argon with carefully dried solvents and oven-dried glassware. Uncorrected melting points were determined in open

capillaries on a Gallenkamp MFB-595-010M apparatus. Microanalyses were conducted using a Heraeus CHN Rapid analyzer. Merck Silica gel 60, 230-400 Mesh, was used for column chromatography; Alugram SIL G/UV_{254} was used for TLC. Infrared spectra were recorded on a Perkin-Elmer model 883 spectrophotometer. ^{1}H and ^{13}C-NMR spectra were recorded on a Varian UNITY-500 spectrometer in the indicated solvents; the values of chemical shifts were expressed in ppm, and coupling constants (J) in Hertz (Hz). Mass spectra (EI, 70 eV) were recorded on a Hewlett-Packard 5988a spectrometer.

2.2 Crystal data for compound 1

$C_{14}H_{16}N_2O_2$, M = 244,293, monoclinic, a = 8.549(1), b = 6.770(1), c = 10.998(1) Å, β = 102,14(1) °, U = 622,29(13) Å^3, T = 298 K, space group $P2_1/m$, Z = 2, μ(Cu-Kα) = 7.145 cm^{-1}. Intensity measurements were performed by $\omega - \theta$ scans in the range 2 °< θ < 65 °. Of the 1203 measured reflections for **1**, 1081 [R(int) = 0.023] were independient; RI = 0.047 and $wR2$ = 0.146 (for 993 reflections with F > 1.0σ(F)). The molecule was at special position x, 1/4, z (two molecules per unit cell). The intensities were corrected for Lorentz and polarization effects. The structure was solved by direct methods. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were included at fixed positions but not refined. All calculations were performed using SIR [26], XRAY80 [27], SHELXL93 [28], and PARST [29] programs.

CCDC-214735 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk.

2.3 General procedure for preparing phthalimides **1-8**

A solution of diethyl azodicarboxylate (DEAD) in anhydrous tetrahydrofuran (THF, 1 ml) was added to a mixture of the alcohol, phthalimide and triphenylphosphine (Ph_3P) in anhydrous THF at room temperature. After stirring for 24 h at room temperature, the solvent was removed *in a vacuum*. Ether was added to the residue to precipitate triphenylphosphine oxide and diethyl hydrazinedicarboxylate, which were filtered off. The filtrate was evaporated and the residue was chromatographed on a Silica gel column eluting with the adequate solvent. The corresponding *N*-alkyl phthalimide thus obtained was recristallized from the adequate solvent.

***N*-(1-Methylpiperidin-4-yl)phthalimide (1)**

DEAD (4.31 mmol, 0.68 ml) in dry THF was added to a solution of **9** (4.31 mmol, 0.5 g), phthalimide (4.31 mmol, 0.64 g) and Ph_3P (4.31 mmol, 1.13 g) in dry THF (9 ml). The crude phthalimide was purified by chromatography using acetone/MeOH (85:15 v/v) as an eluent. Compound **1** was obtained, as a white solid. Crystallization from hexane yielded 0.16 g (15 %). M.p. 143 °C; MS (70 eV, CI): m/z (%): 245 (11) [M^++1]; anal

calc (%) for $C_{14}H_{16}N_2O_2$, C 68.83; H 6.60; N 11.47 found C 68.71; H 6.67; N 11.23.

***N*-(8-Methyl-8-azabicyclo[3.2.1.]octan-3*β*-yl)phthalimide (2)**

DEAD (3.55 mmol, 0.56 ml) in dry THF was added to a solution of **10** (3.55 mmol, 0.5 g), phthalimide (3.55 mmol, 0.52 g) and Ph_3P (3.55 mmol, 0.96 g) in dry THF (8 ml). The crude phthalimide was purified by chromatography using acetone containing increasing quantities of MeOH as eluent to give compound **2**, as a white solid, which was recrystallized from hexane to obtain 0.32 g (33 %); M.p. 123 °C; anal calc (%) for $C_{16}H_{18}N_2O_2$, C 71.09; H 6.71; N 10.36 found C 71.21; H 6.89; N 10.42.

***N*-(9-Methyl-9-azabicyclo[3.3.1]nonan-3*β*-yl)phthalimide (3)**

DEAD (3.22 mmol, 0.51 ml) in dry THF was added to a solution of **13** (3.22 mmol, 0.5 g), phthalimide (3.22 mmol, 0.47 g) and Ph_3P (3.22 mmol, 0.84 g) in dry THF (7 ml). The crude phthalimide was purified by chromatography using acetone/MeOH (9:1 to 8:2, v/v) as eluent and giving compound **3**, as a white solid, which was recrystallized from hexane to obtain 44 mg (18 %); M.p. 122 °C; MS (70 eV, EI): m/z (%): 284 (39) [M^+], 146 (11) [$C_8H_4NO_2^+$], 110 (78) [$C_9H_{16}N^+$]; anal calc (%) for $C_{17}H_{20}N_2O_2$, C 71.81; H 7.09; N 9.85 found C 72.03; H 6.97; N 9.97.

(±)*N*-(1-Azabicyclo[2.2.2]octan-3-yl)phthalimide (4)

DEAD (3.94 mmol, 0.62 ml) in dry THF was added to a solution of **14** (3.94 mmol, 0.5 g), phthalimide (3.94 mmol, 0.58 g) and Ph_3P (3.94 mmol, 1.03 g) in dry THF (5 ml). The crude phthalimide was purified by chromatography using acetone containing increasing quantities of MeOH as eluent and giving **4**, as a white solid. Crystallization from hexane yielded 0.38 g (38 %); M.p. 125 °C; MS (70 eV, EI): m/z (%): 256 (16) [M^+], 255 (67) [M^+-1], 147 (100) [$C_8H_4NO_2^+$], 110 (78) [$C_7H_{12}N^+$]; anal calc (%) for $C_{15}H_{16}N_2O_2$, C 70.29; H 6.29; N 10.93 found C 70.23; H 6.27; N 10.88.

***N*-[6-*Syn*(*anti)*-(2-methyl-2-azabicyclo[2.2.2]octanyl)]-phthalimides (5 and 6)**

DEAD (3.5 mmol, 0.56 ml) in dry THF was added to a solution of **15** and **16** (3.5 mmol, 0.5 g), phthalimide (3.6 mmol, 0.52 g) and Ph_3P (3.5 mmol, 0.92 g) in dry THF (9 ml). The crude phthalimides were purified by chromatography using acetone as eluent to obtain **5**, as a colorless oil, 75 mg (8 %); anal calc (%) for $C_{16}H_{18}N_2O_2$, C 71.09; H 6.71; N 10.36 found C 70.97; H 6.67; N 10.21.

Continued elution produced **6**, as a white solid, 0.14 g (15 %); M.p. 136 °C; anal calc (%) for $C_{16}H_{18}N_2O_2$, C 71.09; H 6.71; N 10.36 found C 70.84; H 6.70; N 10.33.

***N*-[5-*Syn*(*anti)*-(2-methyl-2-azabicyclo[2.2.2]octanyl)]-phthalimides (7 and 8)**

DEAD (4 mmol, 0.64 ml) in dry THF was added to a solution of **17** and **18** (4 mmol, 0.57 g), phthalimide (4 mmol, 0.59 g) and Ph_3P (4 mmol, 1.06 g) in dry THF (9 ml). The crude phthalimides were purified by chromatography using dry acetone as eluent to obtain **7**, as a white solid, 0.22 g (20 %); M.p. 200-202 °C; anal calc (%) for $C_{16}H_{18}N_2O_2$, C 71.09; H 6.71; N 10.36 found C 70.87; H 6.66; N 10.34.

Continued elution gave **8**, as a white solid, 0.04 g (4 %); M.p. 198-200 °C; anal calc (%) for $C_{16}H_{18}N_2O_2$, C 71.09; H 6.71; N 10.36 found C 71.03; H 6.88; N 10.40.

3 Results and discussion

3.1 Chemistry

This paper describes the synthesis of the azamonocyclic and azabicyclic phthalimides **1-8** (figure 1). Although many methods are currently available for these transformations, the authors targeted the synthesis of the phthalimides by using the Gabriel synthesis. 3-chloroquinuclidine was selected as halogenoalkane due to its accessibility and stability, but all attempted methods based on the reaction of potassium phthalimide with 3-chloroquinuclidine in DMF at room temperature and at 70 °C over long reaction times yielded the starting materials.

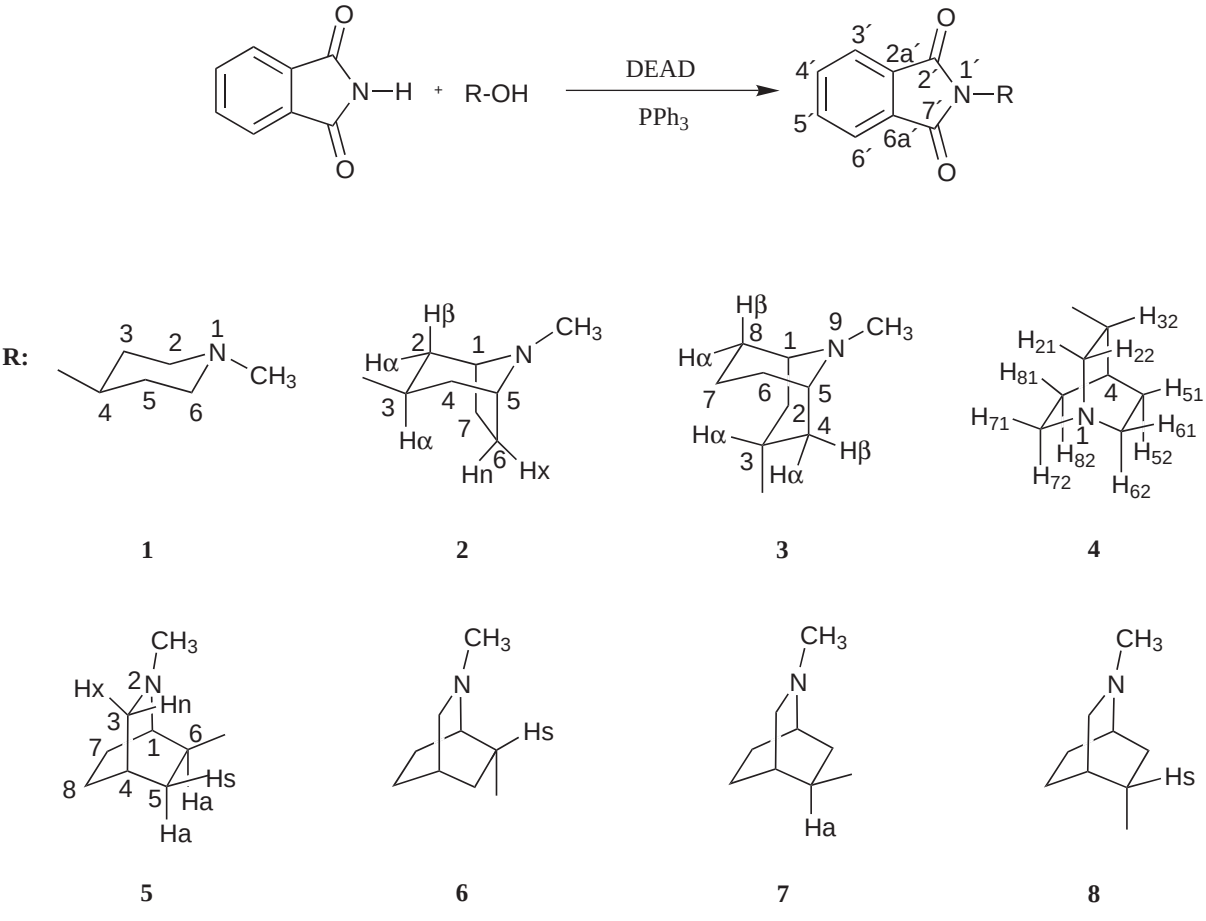

Fig. 1 Synthesis of phthalimides **1-8**.

As mentioned in the introduction, *N*-alkylphthalimides can be obtained by modifying the Gabriel synthesis using HDTBP$^+$Br$^-$[19]. The reaction between 3-chloroquinuclidine and potassium phthalimide whereby HDTBP$^+$Br$^-$ is the catalyst in toluene as a solvent at 100 °C for 24 h and also 72 h gave rise to the starting materials. The same reaction was carried out with a different alkyl chloride 3-*endo*-chlorotropanyl with similar results.

Because alcohols **9**, **10**, **14** are known and commercially available and alcohols **11**

[30], **12** [31], **13** [32], **15** [33], **16** [33], **17** [34], **18**[34] (Figure 2) can conveniently be prepared, the authors sought a method for the direct conversion of alcohols into *N*-substituted phthalimides. The authors decided to synthesize the phthalimides starting from the corresponding alcohols by Mitsunobu reaction [20, 24, 25].

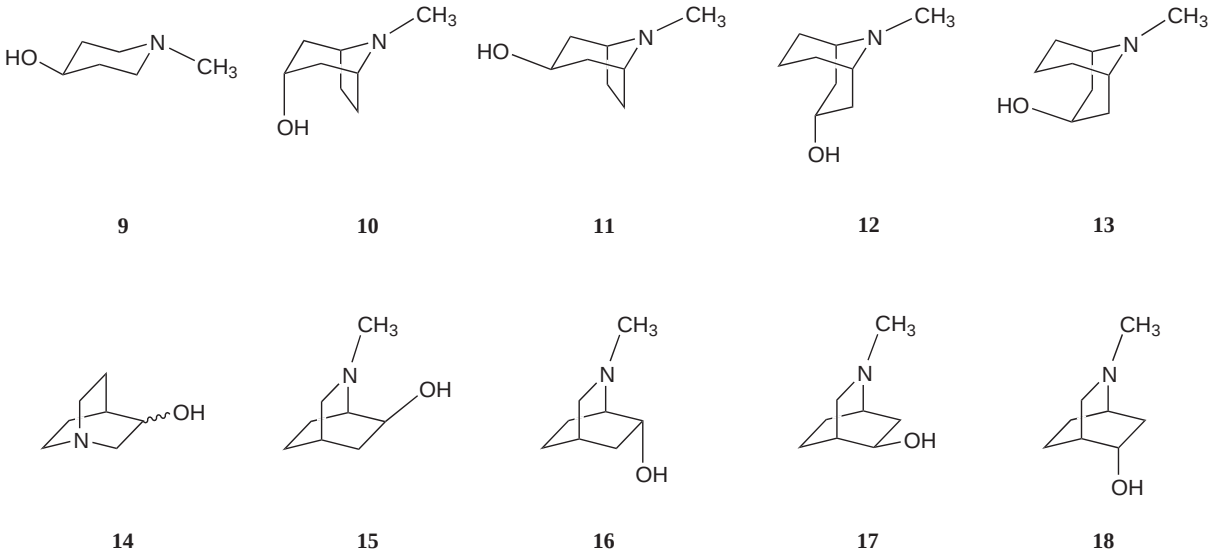

Fig. 2 Alcohols **9-18**.

Classical Mitsunobu reactions entail the activation of an alcohol entity with triphenylphospine and diethyl azodicarboxylate so as to allow the attack of a nucleophile that results in an S2N-like reaction. According to this reaction mechanism, the condensation reaction proceeds with a virtually complete configuration inversion. This accounts for the different behaviour observed between 9-methyl-9-azabicyclo[3.3.1]nonan-3α and β-ols (**13**, **12**) and between 8-methyl-8-azabicyclo[3.2.1]octan-3α and β-ols (**10**, **11**). In this case, starting from 3-α-tropanol (**10**) the β-phthalimide (**2**) was obtained as a result of an S2N type displacement in the oxyphosphonium salt. However, the α-phthalimide was not obtained when the 3β-tropanol (**11**) was used.

Thus, when this reaction was carried out from 9-methyl-9-azabicyclo[3.3.1]nonan-3α-ol (**13**), the corresponding β-phthalimide (**3**) was obtained. However, the attempt to form the α-phthalimide starting from the β-alcohol (**12**), using similar chemistry to that used for the synthesis of the β-phthalimide proved unsuccessful. This can be explained due to the steric hindrance of the α-attack (Figure 3), which also occurs in the case of the alcohol **11**.

For the synthesis of compounds **5-8**, epimeric mixtures (50:50) of *syn* and *anti* alcohols were used and therefore mechanistic conclusions could not be drawn. Nevertheless, in both cases the *anti* phthalimides were obtained as the major products. The structure of compounds **1-8** was determined through NMR studies and, for compound **1**, also by X-ray diffraction.

This method provided the phthalimides (**1-8**) from azabicyclic alcohols yields between 15-38 % and approximated reported literature data for non-nitrogen bicyclic systems. In

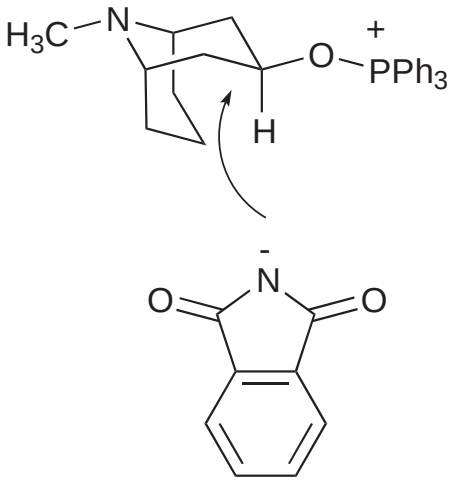

Fig. 3 Steric hindrance for the α attack on compound **12**.

these reactions, unreacted alcohols were not detected, so the low yields must have been due to the formation of by-products.

3.2 Structural study

3.2.1 X ray crystal structure of compound 1

White crystals were obtained by the recrystallization of compound **1** from hexane. All data were collected on a Seifert XRD3000-S diffractometer at room temperature. The molecule has crystallographic C_s symmetry with C13 and C14 of the hexane ring, as well as related C13' and C14' and the attached hydrogen atoms with those of the methyl group, outside the mirror plane (Figure 4). Bond distances and angles in the phthalimide group aligned themselves with those found in literature [35, 36].

The hexane ring has a chair conformation with atoms C12 and N15 0.678 (2) and -0.655 (2) Å, out of the plane formed by C13, C14, C13', C14'. H12 is at axial position.

The molecules stack in chains by means of short contacts (4.12 (1), 4.22 (1) Å) between the centroids of the phthalimide rings and with an interplanar separation of 3.385 (1) Å [37].

3.2.2 NMR spectra

The proton magnetic parameters were deduced from analysis of the spectra performed at 500 MHz, taking into account the coupling modifications observed in the different irradiation experiments.

COSY-45 and NOESY spectra were employed in coordination with the heteronuclear 1H-^{13}C shift correlation HMQC-spectrum for the identification and task of the individual protons (tables 1-3, 5 and 6).

For the ^{13}C-NMR chemical shifts (Table 4), the analysis of the DEPT and HMQC experiments were taking into consideration.

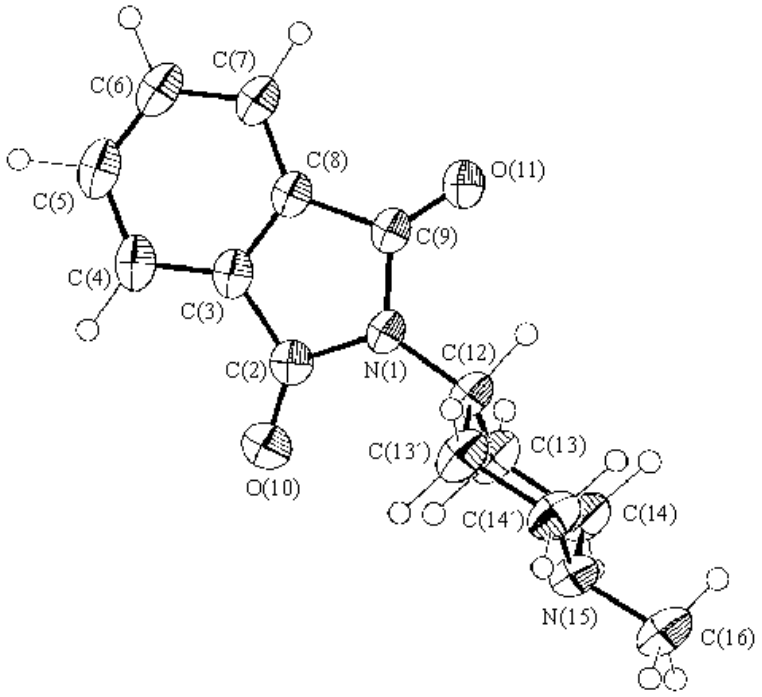

Fig. 4 ORTEP view of compound **1** with the atomic numbering used in the crystallographic study. Displacement ellipsoids are drawn at the 50 % probability level.

The methodology applied to all bicyclic protons in compound **8** is shown as a representative example. The proton spectrum of **8** exhibits a high complexity because all the bicyclic system proton resonances are inequivalent. These differentiate signals due to one proton except those assigned to H1, H7a, H7s, H8a and H4. Figure 5 represents the complete assignment of the ^{1}H-NMR spectrum of compound **8**.

Figure 6 shows the contour plot of the COSY-45 spectrum. The interpretation of this spectrum is based on the unambiguous assignment of the signal at lower field in the aliphatic region to H5. The multiplet at 4.72 ppm is assigned to H5s and appears as multiplet due to vicinal couplings with H4, H6s, H6a and a **W** long-range coupling with H8s.

The analysis of the COSY reveals the correlation between H5s and the signals centered at 2.98, 2.59, 2.01 and 1.69 ppm that correspond to C6a,s protons, H4 and H8s respectively.

The H6s and H6a protons are distinguished on the basis of stereoelectronic factors, the shape of the signals and taking into account the COSY connectivity. The signal centered at 2.98 ppm appears as a multiplet and is assigned to H6a, which resonates at lower field due to the relative disposition of the functional group. H6a shows cross peaks

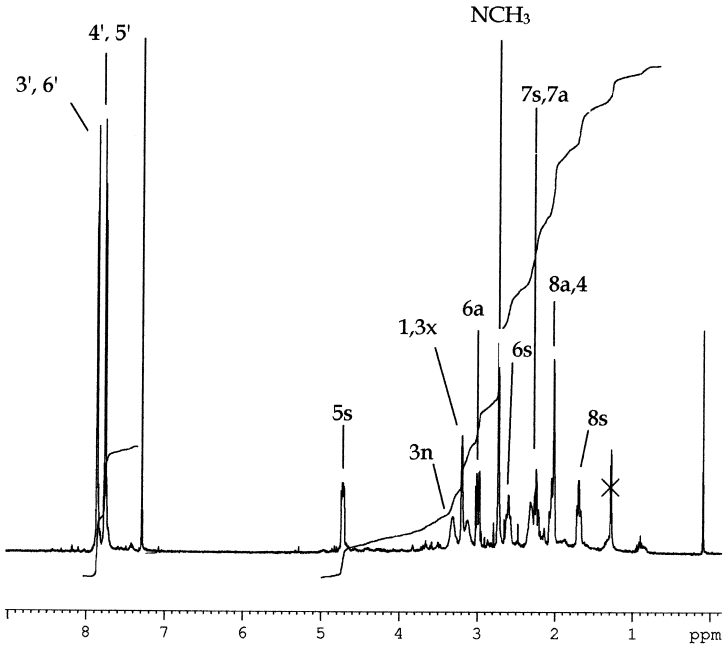

Fig. 5 ^{1}H-NMR spectrum and assignment of compound **8**.

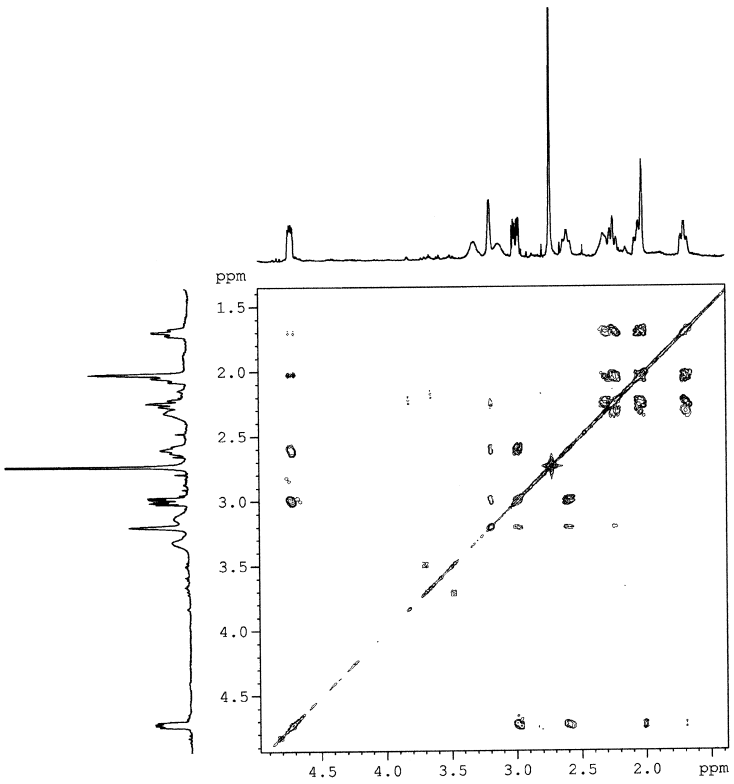

Fig. 6 Section of the COSY-45 spectrum of compound **8**.

with H6s, H5s and with the proton at 3.19 ppm which corresponds to H1. H6a shows in the NOESY spectrum (Figure 7) correlation signals with H6s, H1, and with the proton at 2.24 ppm which should belong to H7a.

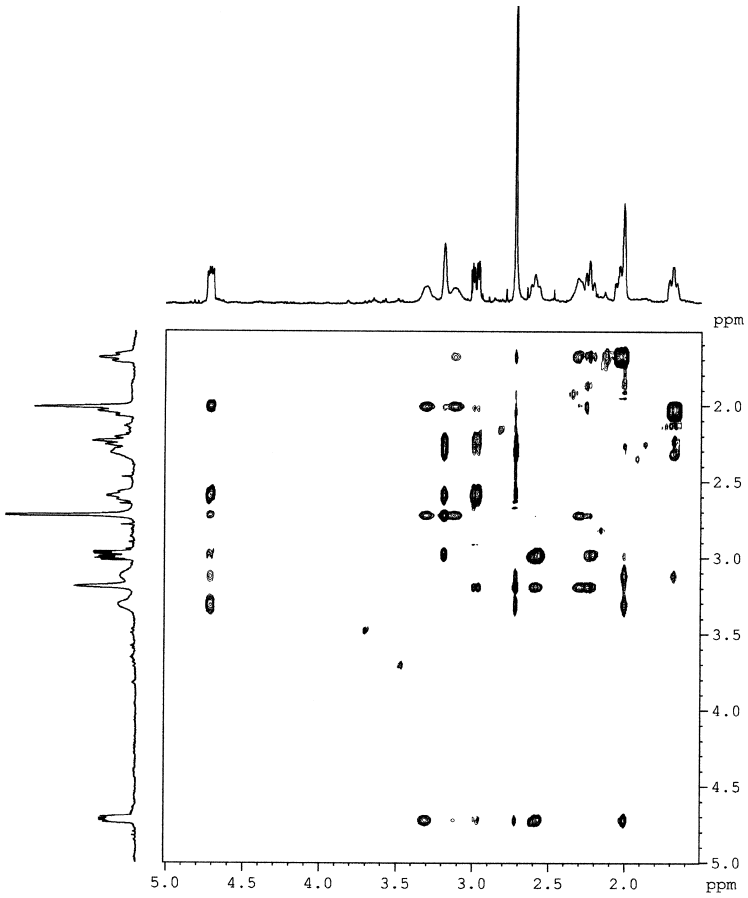

Fig. 7 Section of the NOESY spectrum of compound **8**.

The signal at 2.59 ppm is assigned to H6s and appears as a broaded triplet due to the coupling with H6a, H5s and H1. The COSY as well as the NOESY spectra show cross peaks with H6a, H5s and H1.

The differentiation between the signals corresponding to H3n and H3x, in α-position in respect to the N atom, is based on the shape of the signals and on the observed correlations. The broad signal at lower field (3.31 ppm) is assigned directly to H3n due to a clear correlation signal in the NOESY spectrum with H5s (4.72 ppm), NCH_3 (2.72 ppm) and H4 (2.01 ppm). Moreover, the broad signal at 3.12 ppm can be assigned to H3x, which shows correlation in the NOESY spectrum with H8s (1.69 ppm), NCH_3 (2.72 ppm) and H4 (2.01 ppm). The expanded section of the COSY spectrum (Figure 8) shows a signal at 2.05 ppm, which overlaps partially with H4 (2.01 ppm). This signal can be assigned to H8a, due to the COSY cross peaks with H4, H7a, H8s and the signal at 2.31 ppm. This latter signal can be directly assigned to H7s, through the COSY correlation peak with H8s. NOESY correlations between H8a and H7a corroborates this assignation.

Both protons H7a and H7s show the expected COSY and NOESY cross peaks. The

latter is definitive. Thus, the H7a (2.24 ppm) shows cross peaks with H8a and H6a while H7s (2.31 ppm) correlates with H8s and NCH_3.

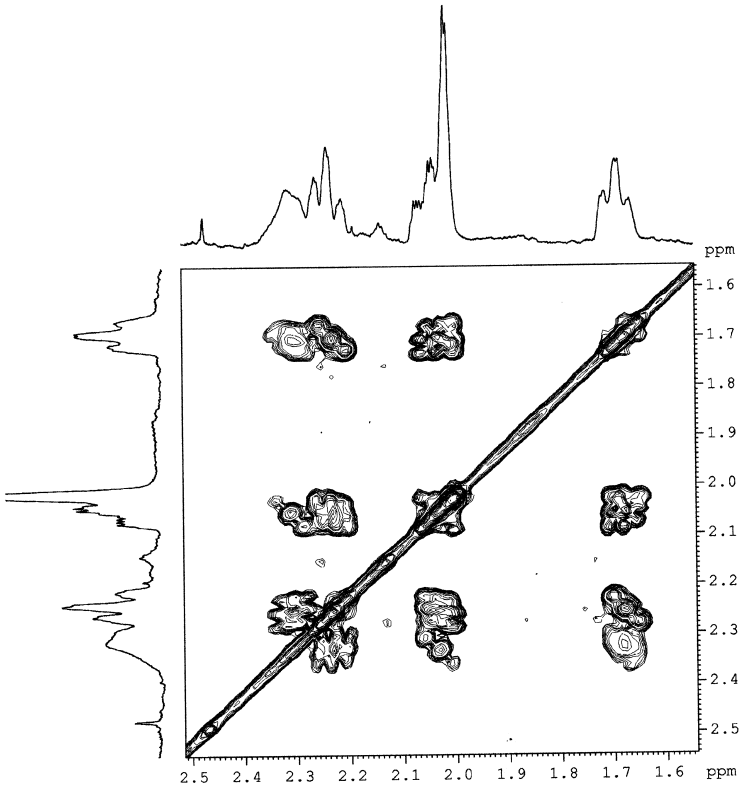

Fig. 8 Expanded section of the COSY-45 spectrum of compound **8**.

All the assignments were corroborated by means of irradiation experiments. The ^{13}C-NMR chemical shifts are tabulated with the signal assignments in table 4. Substituent steric and electronic effects on the ^{13}C chemical shifts and the signal multiplicity obtained from DEPT experiments were taken into consideration. Once the resonances of the respective protons were established, the analysis of the HMQC spectra allowed the distinction between the chemical shift values of the different carbons.

3.3 Conformational study

A conformational study on compounds **1**, **2**, **3** and **8**, as a representative example of the isoquinuclidine derivatives (**5**-**8**), has been presented.

From ^{1}H and ^{13}C-NMR data, the authors postulate that compound **1** adopts a preferred conformation in solution similar to that observed in the crystalline state. The piperidine ring adopts a chair conformation with the phthalimide group in an equatorial position.

In compound **2** the pyrrolidine and piperidine rings adopt a flattened N8 envelope and distorted chair conformation puckered at N8 and flattened at C3 as evidenced by the ^{1}H-NMR spectra where the $W_{1/2}$ value for the H1(5) signals of 9-11 Hz corresponds

to a tropane system with the piperidine ring in a chair conformation. ^{3}JH1(5)-H2(4)β is greater than ^{3}JH1(5)-H2(4)α (Table 2); consequently, the dihedral angle H1(5)-C-C-H2(4)α is greater than H1(5)-C-C-H2(4)β. In the ^{13}C-NMR spectra, the chair conformation adopted by the piperidine ring is confirmed by the δC2(4) values [38-40] (Table 4). The δ of the *N*-substituent (36.96 ppm) is in agreement with an equatorial position for this group [38-40].

The deduced coupling constant ^{3}JH2(4)β-H3 of about 12.0 Hz (Table 2) accounts for a *trans*-coplanar disposition of H2(4)β-C-C-H3; therefore, the phthalimide group is in an equatorial disposition and perpendicular to the piperidine ring.

In compound **3** the bicyclic system can be described in equilibrium between two flattened chair-chair conformations through nitrogen inversion. The following supports these conclusions:

The δC7 value for the β-granatanol (19.80 ppm) [41] is very close to the δC7 value of compound **3** (20.31 ppm); it seems feasible that these compounds should adopt the same preferred conformation in solution.

NOESY spectrum shows a clear correlation between H7α and H3.

In the ^{1}H-NMR spectra the $W_{1/2}$ value of H1(5) ($\sim$11 Hz) is in overall agreement with previously reported values for a flattened chair-chair conformation in related bicyclic systems [42-44].

The values of the coupling constants ^{3}JH2(4)β-H3$\sim$13 Hz and ^{3}JH2(4)α-H3$\sim$6.6 Hz (Table 2) support a slightly flattened chair conformation with the phthalimide group in an *exo* disposition. Also ^{3}JH1(5)-H2(4)β is greater than ^{3}JH1(5)-H2(4)α (Table 2). Therefore the dihedral angle H1(5)-C-C-H2(4)β is smaller than H1(5)-C-C-H2(4)α.

Selective NOESY as well as selective irradiation on the *N*-methyl group show exclusive correlations with the protons attached at bridgehead positions H1(5). Hence, NOE-measurements were not useful tools to assist in the confirmation of the *N*-methyl positions in tropane (**2**) and granatane (**3**) systems.

On the contrary, supported by NOE measurements, bicyclic system **8** can be described as equilibrium between two conformations through nitrogen inversion.

4 Conclusions

This paper describes the Mitsunobu reaction application to the synthesis of *N*-substituted phthalimides beginning with azamonocyclic and azabicyclic alcohols. Although the yields are low, probably due to the formation of by-products in these type of reactions, the readily available starting materials, the mild conditions and the simplified execution, make this synthetic method a simple and convenient process in obtaining these compounds that can not be prepared by other classical methods.

These compounds have also been tested as 5-HT_4 ligands. However, none of them showed pharmacological activity. The lack of activity can be attributed to the trend of hydrolysis of these compounds in an aqueous environment.

When 9-methyl-9-azabicyclo[3.3.1]nonan-3α-ol and 8-methyl-8-azabicyclo[3.2.1] octan-

3α-ol were used, the inverted configuration (β) of the phthalimides was obtained. This is in agreement with an S2N-like mechanism reaction. This theory also explains that the α phthalimides could not be obtained due to the steric hindrance for the α attack in 9-methyl-9-azabicyclo[3.3.1] nonan-3β-ol and 8-methyl-8-azabicyclo[3.2.1]octan-3β-ol.

In conclusion, a complete characterization and structural study of the compounds synthesized have been performed using a multi-technique approach.

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1		**2**		**3**		**4**	
H2(6)eq	2.97(ddt)	H1(5)	3.30 (brs)	H1(5)	3.00 (brs)	H21	3.90 (ddd)
H2(6)ax	2.06 (td)	H2(4)α	1.40 (ddd)	H2(4)α	1.45 (dd)	H22	3.12 (ddd)
H3(5)eq	1.67 (m)	H2(4)β	2.62 (td)	H2(4)β	2.80 (td)	H3	4.40 (ddt)
H3(5)ax	2.58 (qd)	H3	4.50 (tt)	H3	5.02 (tt)	H4	1.91 (qap)
H4	4.10 (tt)	H6(7)x	2.10 (m)	H6(8)α	1.70 (td)	H51	1.78 (dddt)
CH_3	2.31 (s)	H6(7)n	1.75 (m)	H6(8)β	2.04 (tt)	H52	1.67 (dddd)
H3'(6')	7.81 (dd)	CH3	2.51 (s)	H7α	1.86 (td)	H61	2.83 (m)
H4'(5')	7.68 (dd)	H3'(6')	7.80 (dd)	H7β	1.94 (dt)	H62	2.91 (m)
		H4'(5')	7.67 (dd)	CH3	2.67 (s)	H71	3.40 (dddd)
				H3'(6')	7.80 (dd)	H72	2.85 (m)
				H4'(5')	7.68 (dd)	H81	1.94 (dddt)
						H3'(6')	7.81 (dd)
						H4'(5')	7.72 (dd)

Table 1 ^{1}H Chemical shifts (δ, ppm) for compounds **1-4** in $CDCl_3$. *Abbreviations:* brs, broad singlet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dddd, double of double doublet of doublets; dt, doublet of triplets; ddt, doublet of doublet of triplets; dddt, double of double doublet of triplets; m, multiplet; qap, apparent quartet; qd, quartet of doublets; s, singlet; td, triplet of doublets; tt, triplet of triplets.

1		**2**		**3**	
H2(6)eq-H2(6)ax	-10.5	H1(5)-H2(4)α	2.1	H1(5)-H2(4)α	1.9
H2(6)eq-H3(5)ax	4.0	H1(5)-H2(4)β	3.0	H1(5)-H2(4)β	5.5
H2(6)eq-H3(5)eq	2.8	H2(4)α-H2(4)β	-13.2	H1(5)-H6(8)α	a
H2(6)ax-H3(5)eq	2.6	H2(4)α-H3	6.3	H1(5)-H6(8)β	6.3
H3(5)eq-H4	4.0	H2(4)β-H3	12.0	H2(4)α-H3	6.6
H3(5)ax-H2(6)ax	12.0			H2(4)α-H2(4)β	-13.2
H3(5)ax-H3(5)eq	-12.5			H2(4)β-H3	13.2
H3(5)ax-H4	12.5			H6(8)α-H6(8)β	-13.2
				H6(8)α-H7α	13.2
				H6(8)α-H7β	6.3
				H6(8)β-H7α	13.2
				H6(8)β-H7β	6.3
				H7α-H7β	-13.2

Table 2 Coupling constants (J, Hz) deduced from the analysis of the ^{1}H NMR spectra of compounds **1-3.**[a] Not determined owing to the low resolution of the signal.

4					
H21-H3	6.5	H51-H61	10.5	H71-81	11.0
H22-H3	10.5	H52-H4	3.0	H72-H81	5.5
H22-H21	-14.0	H52-H61	7.0	H72-H82	10.5
H22-H72	2.2	H52-H62	11.0	H81-H82	-13.0
H3-H4	2.5	H61-H62	-13.5	H81-H51	3.5
H3-H82	1.5	H61-H71	2.0	H82-H71	4.5
H4-H51	3.0	H62-H51	5.0	H82-H4	3.0
H4-H81	3.0	H62-H21	2.0		
H51-H52	-13.5	H71-H72	-13.0		

Table 3 Coupling constants (J, Hz) deduced from the analysis of the ^{1}H NMR spectra of compound **4**.

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
C1	-	59.54	53.49	-	55.79	64.54	51.53	53.49
C2	55.39	30.62	26.40	48.05	-	-	-	-
C3	28.95	42.55	44.87	50.05	57.00	59.62	52.99	57.64
C4	48.85	30.62	26.40	28.12	26.79	35.36	33.34	32.96
C5	28.95	59.54	53.49	27.82	26.29	20.61	50.06	48.03
C6	55.39	27.01	29.77	47.22	46.79	51.05	25.89	23.73
C7	-	27.01	20.31	47.19	22.04	30.45	23.27	22.48
C8	-	-	29.77	21.67	23.86	28.64	24.82	20.53
$\underline{C}H_3$	46.04	36.96	41.07	-	42.66	41.63	42.17	43.11
$\underline{C}$=O	168.14	168.24	168.27	169.22	169.09	168.86	169.14	169.26
C2a'(C6a')	131.94	131.95	131.94	131.77	131.86	132.02	131.92	131.94
C3' (C6')	133.69	133.83	133.81	133.95	133.87	133.80	133.87	133.85
C4' (C5')	122.96	123.06	122.99	123.04	122.99	122.91	123.00	122.98

Table 4 ^{13}C Chemical shifts (δ, ppm) for compounds **1-8** in $CDCl_3$.

	5	**6**	**7**	**8**
H1	2.49 (dt)	3.05 (t)	2.62 (m)	3.19 (m)
H3x	2.97 (dt)	2.77 (d)	2.95 (dt)	3.12 (dd)
H3n	2.58 (dt)	2.81 (dd)	3.10 (dt)	3.31 (dt)
H4	1.90 (m)	2.50 (m)	1.80 (m)	2.01 (m)
H5a	2.74 (ddt)	1.99 (dd)	4.42 (t)	-
H5s	1.88 (tdd)	2.06 (dd)	-	4.72 (ddt)
H6a	4.74 (ddt)	-	1.70 (ddd)	2.98 (ddd)
H6s	-	4.35 (m)	3.16 (ddt)	2.59 (dddd)
H7a	1.98 (m)	2.00 (m)	1.74 (tddap)	2.24 (m)
H7s	2.00 (m)	1.60 (dtd)	2.02 (dddd)	2.31 (m)
H8a	1.95 (tt)	2.47 (m)	1.58 (dd)	2.05 (m)
H8s	1.60 (m)	1.52 (dddd)	1.50 (m)	1.69 (m)
C$\underline{\mathrm{H}}_3$	2.51 (s)	2.56 (s)	2.51 (s)	2.70 (s)
H3'(6')	7.81 (dd)	7.80 (dd)	7.79 (dd)	7.90 (dd)
H4'(5')	7.69 (dd)	7.69 (dd)	7.68 (dd)	7.75 (dd)

Table 5 ^{1}H Chemical shifts (δ, ppm) for compounds **5-8** in $CDCl_3$. *Abbreviations:* d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dddd, double of double doublet of doublets; dt, doublet of triplets; ddt, doublet of doublet of triplets; dtd, doublet of triplet of doublets; m, multiplet; s, singlet; t, triplet; tdd, triplet of doublet of doublets; tddap, apparent triplet of doublet of doublets; tt, triplet of triplets.

5		**6**		**7**		**8**	
H1-H6a	2.5	H3n-H3x	-9.5	H1-H6a	3.3	H1-H6a	1.8
H1-H7a	4.0	H3x-H4	6.5	H1-H6s	2.5	H1-H6a	4.5
H1-H7s	2.0	H4-H5a	6.5	H1-H7s	4.7	H3n-H3x	-10.6
H3n-H3x	-10.0	H4-H5s	7.0	H3n-H3x	-10.6	H3n-H4	3.0
H3n-H4	< 2.0	H4-H8s	2.5	H3x-H4	3.7	H3x-H4	2.6
H3n-H8a	< 2.0	H5a-H5s	-15.5	H3x-H5a	1.5	H4-H5s	2.5
H3x-H4	2.5	H5a-H6s	< 2.0	H4-H8a	1.5	H5s-H6a	6.6
H3x-H5a	2.0	H5s-H6s	7.5	H5a-H6a	9.7	H5s-H6s	11.4
H4-H5a	2.2	H7a-H7s	-11.5	H5a-H6s	8.8	H5s-H8s	1.8
H4-H5s	5.0	H7a-H8s	10.5	H6a-H6s	-13.5	H6a-H6s	-12.8
H4-H6a	2.5	H7s-H8a	2.0	H6s-H7s	2.5	H6s-H7s	2.6
H4-H8a	~ 2.0	H7s-H8s	5.0	H7a-H7s	-12.8		
H4-H8s	3.0	H8a-H8s	-15.0	H7a-H8s	11.7		
H5a-H5s	-13			H7s-H8s	10.2		
H5a-H6a	7.5			H8a-H8s	-12.8		
H5s-H6a	11.0						
H5s-H8s	2.5						
H7a-H7s	-13.0						
H7a-H8a	11.0						
H7s-H8s	5.0						
H8a-H8s	-11.0						

Table 6 Coupling constants (J, Hz) deduced from the first order analysis of the ^{1}H NMR spectra of compounds **5-8**.