Stereoselective Synthesis of *cis* and *trans* 2-Substituted 1-Phenyl-3-azabicyclo[3.1.0]hexanes

Bernard Bonnaud and Dennis C. H. Bigg*

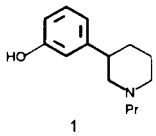
Centre de Recherche Pierre Fabre, 17 avenue Jean Moulin,
F-81106 Castres, France

Received October 29, 1992

The stereoselective synthesis of *cis* and *trans* 2-methyl-1-phenyl-3-azabicyclo[3.1.0]hexanes and 1,2-diphenyl-3-azabicyclo[3.1.0]hexanes from 2-oxo-1-phenyl-3-azabicyclo[3.1.0]hexane is described. The relative stereochemistry of the products was established by nuclear magnetic resonance and molecular modeling studies.

J. Heterocyclic Chem., **30**, 505 (1993).

The synthesis of conformationally-restricted structures containing the phenethylamine moiety as a pharmacophore has given rise to a wide variety of compounds of pharmacological and therapeutic interest. The dopaminergic agonists 3-PPP (**1**) [1,2] and 5-OH DPAT (**2a**) [3], the monoamine oxidase inhibitor tranylcypramine (**3a**) [4], the 5-HT_{1A} agonists **3b** [5] and 8-OH DPAT (**2b**) [6,7], the anorectic agents phenmetrazine (**4a**) and phendimetrazine (**4b**) [8,9], and the antidepressant oxaflozane (**4c**) [10,11] may be singled out from the plethora of examples.



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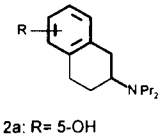
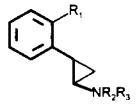
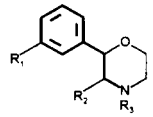


2a: R= 5-OH
2b: R= 8-OH

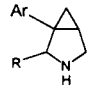


3a: $R_1=R_2=R_3=H$
3b: $R_1=OH$, $R_2=R_3=Pr$



4a: $R_1=R_3=H$, $R_2=Me$
4b: $R_1=H$, $R_2=R_3=Me$
4c: $R_1=CF_3$, $R_2=H$, $R_3=Me$

In pursuance of this approach, and as part of an ongoing program on the use of cyclopropane derivatives in medicinal chemistry, we now describe our efforts to develop stereoselective methods for the preparation of compounds of general structure **5**, related to the above structures, as well as to the analgesic bicifadine (Ar = 4-Me-C_6H_4, R = H) [12].



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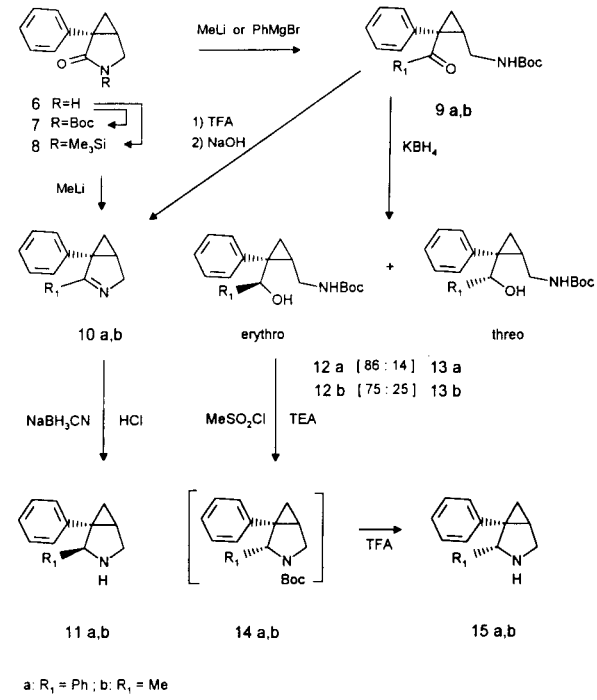
The previously described [13] bicyclic lactam **6** was chosen as a convenient precursor to compounds in both the *cis* and *trans* series, according to the reaction sequences shown in the Scheme [14].

Lactams may be activated towards nucleophilic attack by *N*-acylation or *N*-alkoxycarbonylation and recently it has been reported [15-18] that the *t*-butyloxycarbonyl (*t*-Boc) group is particularly useful in directly attack to the endocyclic (lactam) carbonyl group. Lactam **6** was therefore converted to the *N*-(*t*-Boc) derivative **7** by reaction with di-*t*-butyl dicarbonate. Treatment of **7** with phenylmagnesium bromide or methyllithium gave, respectively, the *t*-Boc-protected amino ketones **9a** and **9b** in good yield. Trifluoroacetic acid treatment of **9a** afforded, after basic workup, the cyclic imine **10a** in essentially quantitative yield.

Scheme



Imine **10b** was prepared by reaction of the trimethylsilyl lactam **8** with methyllithium according to the method described by Hua *et al* [19].

Attempted reduction of imines **10a** or **10b** with sodium borohydride, potassium borohydride, lithium aluminum hydride, or with hydrogen and palladium on charcoal failed to give clean reactions. The use of sodium cyanoborohydride in acidic medium, however, gave **11a** and **11b** in good yield and, somewhat surprisingly, with remarkably

high stereoselectivity [20].

Molecular modeling was carried out using MAD (Molecular Advanced Design) [21-23] in order to gain insight into the factors responsible for the observed stereoselectivity. The results for both **10a** and **10b** indicate that the plane of the phenyl group at the 1-position is almost orthogonal to that of the five-membered ring, with little rotational freedom. In this conformation, illustrated for **10a** in Figure 1, it is apparent that the steric hindrance of the 1-phenyl group in terms of nucleophilic attack on the imine is reduced, relative to the cyclopropane ring, thereby favoring attack on the α-face.

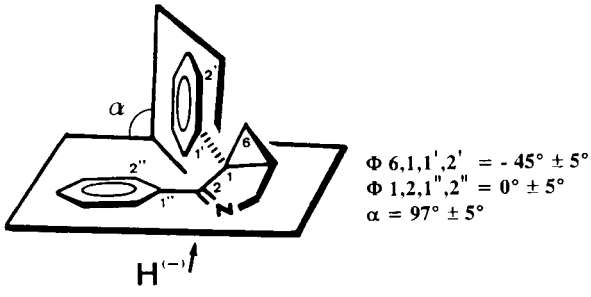


Figure 1. Calculated minimum energy conformation of **10a**.

In order to obtain the *cis* derivatives **15a** and **15b** the protected amino ketones **9a** and **9b** were reduced using potassium borohydride. In both cases the erythro alcohols, **12a** and **12b**, were preponderant. These were converted, after separation by chromatography, to the mesylates which underwent base-induced cyclization [24] to the pyrrolidines with inversion of configuration. The crude carbamates thus obtained, **14a** and **14b**, were deprotected using trifluoroacetic acid to afford the *cis* isomers **15a** and **15b**.

A Nuclear Overhauser Effect (NOE) study was undertaken to establish the geometry of the two pairs of isomers **11a**, **15a** and **11b**, **15b** (Figure 2).

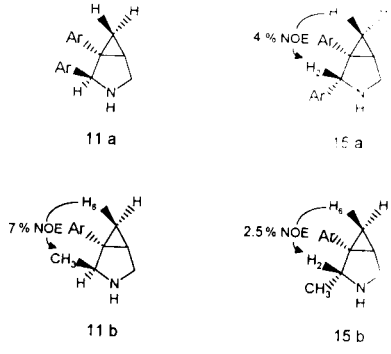


Figure 2. NOE results for compounds **11** and **15**.

In the case of **15a** irradiation of the H_6 proton led to a 4% enhancement of the H_2 signal, whereas no enhancement was observed with **11a**, indicating *cis* and *trans* dispositions of the phenyl rings in **15a** and **11a** respectively. NOE enhancement (2.5%) of the H_2 signal on irradiation of H_6 was also observed for **15b**, in contrast to **11b**. This, coupled with the magnitude of the NOE (7%) between the methyl hydrogens and H_6 observed for **11b**, shows the phenyl and methyl groups to be *trans* for **11b** and *cis* for **15b**. Furthermore, modeling studies showed the methyl group of the *cis* isomer **15b** to be shielded by the aromatic ring. The observed chemical shifts for the methyl protons (0.88 ppm for **15b**, 1.13 ppm for **11b**) are in agreement with this prediction.

In conclusion, the synthetic pathways described above hold promise as general methods for the preparation of stereochemically-defined compounds of structure **5**. The results of the pharmacological evaluation of the novel conformationally-restricted phenethylamines **11a**, **11b**, **15a** and **15b** will be reported elsewhere.

EXPERIMENTAL

Melting points were determined using a Kofler block (Heizbank WME) and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 177 infrared spectrometer. The ^1H and ^{13}C nmr spectra were recorded using a Brucker AC-200 spectrometer and chemical shifts (δ) are reported in ppm relative to tetramethylsilane. Ascending thin-layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualized using a uv lamp or iodine vapor. E. Merck silica gel 60 F (230-400 mesh) was used for column chromatography. The elemental analyses were carried out using a Carlo Erba Model 1106 elemental analyzer.

3-*t*-Butyloxycarbonyl-2-oxo-1-phenyl-3-azabicyclo[3.1.0]hexane (**7**).

A solution of di-*t*-butyl dicarbonate (43.65 g, 0.2 mole) in dichloromethane (50 ml) was added dropwise to a solution of **6** (17.3 g, 0.1 mole) in dichloromethane (170 ml) containing triethylamine (13.9 ml, 0.1 mole) and 4-dimethylaminopyridine (12.2 g, 0.1 mole). The reaction mixture was stirred for 24 hours at room temperature, *N,N*-dimethylaminoethylamine (10.9 ml, 0.1 mole) was then added and stirring continued for a further hour. The reaction mixture was washed with aqueous 0.5*N* hydrochloric acid and then with water. The organic phase was dried (magnesium sulfate), filtered, and evaporated under reduced pressure. The product obtained was recrystallized from hexane to give 23.83 g (87%) of **7**, mp 68-70°; ir (potassium bromide): 1713 and 1744 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.26 (m, 1H), 1.54 (m, 10H), 2.24 (m, 1H), 3.80 (d, 1H), 3.93 (dd, 1H), 7.36 (m, 5H).

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.35; H, 6.92; N, 5.14.

cis-1-Benzoyl-2-*t*-butyloxycarbonylaminomethyl-1-phenylcyclopropane (**9a**).

A solution of phenylmagnesium bromide prepared from bromobenzene (13.35 g, 0.085 mole) and magnesium turnings (2.26 g, 0.093 mole) in tetrahydrofuran (50 ml) was added dropwise under a nitrogen atmosphere to a stirred solution of **7** (20 g, 0.073 mole) maintained at −78°. The reaction mixture was

stirred for 3 hours, allowed to warm to room temperature, and quenched with aqueous 1*N* hydrochloric acid (200 ml). The mixture was extracted with ethyl acetate, the extracts washed with brine, and dried (magnesium sulfate). Filtration, and evaporation of the solvent afforded an oil which was crystallized from diisopropyl ether to give 16.7 g (65%) of **9a** as a white solid, mp 133-135°; ir (potassium bromide): 1662 and 1699 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.38 (m, 10H), 1.64 (dd, 1H), 2.15 (m, 1H), 3.0 (m, 1H), 3.37 (m, 1H), 5.06 (s broad, 1H), 7.26 (m, 8H), 7.9 (d, 2H).

Anal. Calcd. for $C_{22}H_{25}NO_3$: C, 75.18; H, 7.17; N, 3.99. Found: C, 75.50; H, 7.15; N, 4.15.

cis-1-Acetyl-2-*t*-butyloxycarbonylaminomethyl-1-phenylcyclopropane (**9b**).

The procedure described above for the preparation of **9a** but using methyllithium instead of phenylmagnesium bromide gave **9b** in 66% yield, mp 82-84°; ir (potassium bromide): 1713 and 1678 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.23 (dd, 1H), 1.48 (s, 9H), 1.76 (dd, 1H), 2.01 (s, 3H), 2.13 (m, 1H), 3.22 (m, 1H), 3.40 (m, 1H), 4.75 (m, 1H), 7.27-7.37 (m, 5H).

Anal. Calcd. for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.43; H, 7.87; N, 4.87.

1,2-Diphenyl-2,3-dehydro-3-azabicyclo[3.1.0]hexane (**10a**).

Trifluoroacetic acid (28 ml) was added dropwise to a stirred and cooled (0°) solution of ketone **9a** (7.03 g, 0.02 mole) in dichloromethane (28 ml). The solution was allowed to warm to room temperature, stirred for a further hour, and concentrated under reduced pressure. The residual oil was diluted with water and an excess of aqueous 10*N* sodium hydroxide added. The mixture was extracted twice with diethyl ether. The extracts were washed with water, dried (magnesium sulfate), filtered, and the solvent removed under reduced pressure. Purification of the product by column chromatography over silica gel using chloroform as eluent, followed by crystallization from hexane afforded 4.34 g (93%) of **10a** as white crystals mp 106-108°; ir (potassium bromide): 1590 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.8 (t, 1H), 2.03 (m, 2H), 4.09 (d, 1H), 4.28 (dd, 1H), 7.27 (m, 8H), 7.68 (dd, 2H).

Anal. Calcd. for $C_{17}H_{15}N$: C, 87.51; H, 6.48; N, 6.00. Found: C, 87.36; H, 6.53; N, 6.09.

2-Methyl-1-phenyl-2,3-dehydro-3-azabicyclo[3.1.0]hexane (**10b**).

A solution of chlorotrimethylsilane (4.2 ml, 0.033 mole) in toluene (10 ml) was added dropwise to a stirred suspension of lactam **6** (5.19 g, 0.03 mole) and triethylamine (5.2 ml, 0.037 mole) in toluene (60 ml). The stirred reaction mixture was heated at 40° for 4 hours, cooled to 0° and diluted with 60 ml of hexane:diethyl ether (1:1, v/v). The resulting precipitate was removed by filtration and the filtrate concentrated under reduced pressure. The crude *N*-trimethylsilyllactam **8** obtained was taken up in diethyl ether (35 ml) and added dropwise with stirring and cooling (−20°) to 21 ml of a 1.6*M* solution of methyllithium in diethyl ether. After the addition was complete the reaction mixture was stirred for a further 30 minutes at −20°, for 1 hour at 25°, and then poured into a solution of ammonium chloride (1.8 g) in water (60 ml). After stirring for 30 minutes the organic layer was separated, washed with brine, dried (sodium sulfate), and filtered. Evaporation of the solvent followed by chromatography over silica gel using chloroform:methanol (19:1, v/v) as eluent gave 2.8 g (55%) of **10b** as a pale-yellow oil; ir (film): 1610 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.56 (t, 1H), 1.47 (dd, 1H), 1.90 (t, 3H), 2.06 (m, 1H), 3.79 (d, 1H), 4.07 (ddd, 1H), 7.30 (m, 5H).

Anal. Calcd. for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 83.82; H, 7.34; N, 7.91.

trans-1,2-Diphenyl-3-azabicyclo[3.1.0]hexane (**11a**).

To a mixture of imine **10a** (3.62 g, 0.015 mole) and sodium cyanoborohydride (1.46 g, 0.023 mole) in ethanol (36 ml) was added dropwise with stirring 12 ml of a 2*N* ethanolic solution of hydrogen chloride. The reaction mixture was stirred for 2 hours at room temperature then poured into a mixture of 200 ml of brine and 15 ml of an aqueous 2*N* solution of sodium hydroxide and extracted with ethyl acetate. The extracts were washed with brine, dried (magnesium sulfate), filtered, and the solvent evaporated under reduced pressure. The oil obtained was purified by chromatography over silica gel using chloroform:methanol (99:1 v/v) as eluent. Crystallization of the product from dichloromethane:diisopropyl ether gave 2.74 g (75%) of **11a** as a white solid, mp 106-108°; ^1H nmr (deuteriochloroform): δ 1.18 (dd, 1H), 1.28 (t, 1H), 1.74 (t, 1H), 2.21 (s, 1H), 3.17 (d, 1H), 3.36 (dd, 1H), 4.64 (s, 1H), 7.13-7.43 (m, 10H); ^{13}C nmr (deuteriochloroform): δ 12.3, 27.5, 36.0, 49.0, 67.1, 126.1, 127.5, 128.0, 128.1, 128.3, 128.4, 140.3, 142.0.

Anal. Calcd. for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.62; H, 7.26; N, 6.03.

trans-2-Methyl-1-phenyl-3-azabicyclo[3.1.0]hexane (**11b**).

The procedure described above for the preparation of **11a** but using imine **10b** as starting material gave, after chromatography over silica gel using chloroform:methanol (95:5, v/v) as eluent, **11b** in 57% yield as a white solid, mp 43-45°; ^1H nmr (deuteriochloroform): δ 0.80 (t, 1H), 0.89 (dd, 1H), 1.13 (d, 3H), 1.58 (m, 1H), 2.27 (s, 1H), 3.02 (d, 1H), 3.22 (dd, 1H), 3.48 (q, 1H), 7.17-7.36 (m, 5H); ^{13}C nmr deuteriochloroform): δ 9.1, 16.0, 27.3, 37.6, 49.1, 60.3, 126.3, 128.4, 128.7, 141.9.

Anal. Calcd. for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09. Found: C, 83.18; H, 8.75; N, 8.09.

cis-2-*t*-Butyloxycarbonylaminomethyl-1-(α-hydroxybenzyl)-1-phenylcyclopropanes **12a** and **13a**.

Potassium borohydride (9.4 g, 0.174 mole) was added in portions to a stirred solution of **9a** (20.3 g, 0.058 mole) in methanol (500 ml) and the reaction mixture stirred overnight at room temperature. The solvent was evaporated under reduced pressure, water was added to the residue, and the product extracted with ethyl acetate. The extracts were washed with brine, dried (magnesium sulfate), filtered, and the solvent evaporated under reduced pressure. The crude mixture of **12a** and **13a** thus obtained (86:14 by hplc) was purified by flash chromatography over silica gel. Elution with hexane:ethyl acetate (70:30) gave 15.78 g (77%) of the erythro isomer **12a** as a white solid, mp 111-113° (diisopropyl ether:hexane); ir (potassium bromide): 1660 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.91-1.15 (m, 3H), 1.44 (s, 9H), 3.28-3.51 (m, 2H), 4.57 (d, 1H), 5.53 (d, 1H), 6.87-7.14 (m, 11H).

Anal. Calcd. for $C_{22}H_{27}NO_3$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.98; H, 7.73; N, 4.00.

Further elution of the column gave 2.4 g (11.7%) of the threo isomer **13a** as a white solid, mp 126-128° (hexane); ir (potassium bromide): 1644 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.92 (dd, 1H), 1.07 (t, 1H), 1.24-1.35 (m, 1H), 1.42 (s, 9H), 3.19-3.35 (m, 1H), 3.52-3.65 (m, 1H), 4.64 (d, 1H), 5.36 (d, 1H), 6.94-7.11 (m, 11H).

Anal. Calcd. for $C_{22}H_{27}NO_3$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.88; H, 7.80; N, 3.99.

cis-2-*t*-Butyloxycarbonylaminomethyl-1-(α-hydroxyethyl)-1-phenylcyclopropanes **12b** and **13b**.

The reduction of ketone **9b** according to the procedure described above for **9a** afforded a mixture of **12b:13b** (75:25 by hplc) which was separated by flash chromatography over silica gel. Elution with hexane:ethyl acetate (60:40) gave the erythro isomer **12b** in 61% yield, mp 95-97°; ir (potassium bromide): 1679 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.53 (t, 1H), 0.89-1.09 (m, 5H), 1.41 (s, 9H), 3.06-3.21 (m, 1H), 3.26-3.40 (m, 1H), 3.50-3.55 (m, 1H), 4.76 (s, 1H), 6.66 (t, 1H), 7.16-7.31 (m, 5H).

Anal. Calcd. for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.19; H, 8.58; N, 4.85.

Further elution of the column gave the threo isomer **13b** in 15% yield, mp 93-95°; ir (potassium bromide): 1697 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.76 (m, 2H), 0.88 (d, 3H), 1.21-1.32 (m, 1H), 1.40 (s, 9H), 3.02-3.33 (m, 2H), 3.48-3.53 (m, 1H), 4.47 (d, 1H), 7.03 (t, 1H), 7.13-7.34 (m, 5H).

Anal. Calcd. for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.27; H, 8.67; N, 4.89.

cis-1,2-Diphenyl-3-azabicyclo[3.1.0]hexane (**15a**).

A solution of methanesulfonyl chloride (3.45 ml, 0.035 mole) in dichloromethane (5 ml) was added dropwise with stirring to a cooled (0°) solution of **12a** (5.65 g, 0.016 mole) and triethylamine (8.93 ml, 0.064 mole) in dichloromethane (60 ml). After the addition was complete the reaction mixture was allowed to warm to room temperature and stirring continued for a further 24 hours. The reaction mixture was washed twice with water, dried (magnesium sulfate), filtered, and the solvent evaporated under reduced pressure. The crude product **4a** obtained was dissolved in dichloromethane (14 ml), cooled to 0°, and treated with trifluoroacetic acid (14 ml). After stirring for 1 hour at room temperature the solution was concentrated under reduced pressure and the residual oil treated with water and concentrated aqueous sodium hydroxide. The mixture was extracted with diethyl ether and the extracts washed with brine, dried (magnesium sulfate), filtered and the solvent evaporated under reduced pressure. The product obtained was purified by flash chromatography over silica gel using chloroform:methanol (90:10) as eluent to afford 2.15 g (57%) of **15a**, mp 64-66°; ^1H nmr (deuteriochloroform): δ 0.91 (dd, 1H), 1.25 (t, 1H), 2.16 (m, 1H), 2.77 (s, 1H), 3.15 (d, 1H), 3.52 (dd, 1H), 4.59 (s, 1H), 6.97-7.27 (m, 10H); ^{13}C nmr (deuteriochloroform): δ 18.7, 24.6, 37.7, 48.3, 66.7, 125.6, 126.5, 127.6, 127.7, 128.2, 129.0, 141.6, 143.9.

Anal. Calcd. for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.95; H, 7.38; N, 6.00.

cis-2-Methyl-1-phenyl-3-azabicyclo[3.1.0]hexane (**15b**).

The procedure described above for the preparation of **15a** but using **12b** as the starting material gave, after flash chromatography over silica gel using chloroform:methanol (95:5) as eluent, **15b** in 44% yield, mp 93-95° (hexane); ^1H nmr (deuteriochloroform): δ 0.68 (dd, 1H), 0.83 (m, 1H), 0.88 (d, 3H), 1.82 (m, 1H), 1.90 (s, 1H), 2.92 (d, 1H), 3.26 (dd, 1H), 3.46 (q, 1H), 7.16-7.28 (m, 5H); ^{13}C nmr (deuteriochloroform): δ 15.7, 19.8, 22.6, 38.3, 46.7, 58.1, 126.3, 128.2, 129.6, 141.6.

Anal. Calcd. for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09. Found: C, 83.49; H, 8.65; N, 8.07.

Acknowledgements.

The authors wish to thank A. Carlessi and P. Funes for technical assistance.

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