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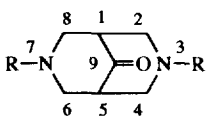
Synthesis and Metal Complexes of Symmetrically *N*-Substituted Bispidinones

David St.C. Black[a*], Glen B. Deacon[b] and Michael Rose[c]

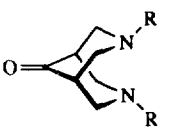
[a]School of Chemistry, University of New South Wales, Sydney 2052, Australia
[b]Department of Chemistry, Monash University, Clayton, Victoria 3168 Australia
[c]Department of Organic Chemistry, University of Sydney, Sydney 2006, Australia

Abstract: The symmetrically substituted bispidinones (9-23) were prepared by the Mannich reaction. The bispidinone (28) can be used to generate the diaminoethyl derivative (25) and the diphenoxy ether (32). The crystal structure of the glycinic bispidinone (20) is reported. Metal complexes of bispidinones (4), (35-54) were prepared with copper, palladium and platinum.

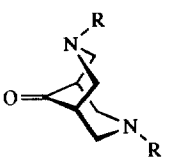
The 3,7-diazabicyclo[3.3.1]nonan-9-one (1) ring system (bispidinone) can adopt the chair-chair (1a), chair-boat (1b), or boat-boat (1c) conformations. More commonly the twin-chair and chair-boat conformations have been reported.[1] We were interested in preparing bispidinone derivatives that could adopt the twin-chair conformation and investigating their use as bidentate ligands. The derived metal complexes would then contain a novel backbone of two fused piperidinone rings. This was relevant to a wider project in which structurally diverse amine adducts of platinum and palladium were to be synthesised and surveyed for potential anti-tumor activity.



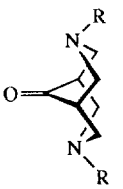
(1)



(1a)



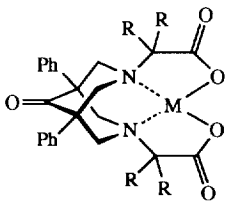
(1b)



(1c)

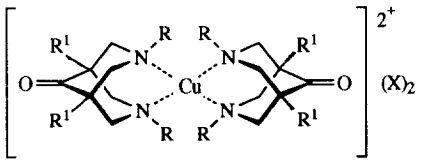
Surprisingly there have only been a few examples of bispidinone derivatives binding metals. These include the quadridentate complexes (2),[2] the 2:1 adducts (3),[3] and the 1:1 adduct (4).[4] In all cases divalent transition metals have been employed, the most common being copper. Attempts to bind other divalent group II metals to bispidinones were unsuccessful.[5] These bispidinones (2-4) do not contain ring substituents at positions 2, 4, 6 and 8. Bispidinones that are substituted in these β-positions have only been prepared with small amines and most commonly ammonia.[6] In contrast a wide variety of aliphatic amines have been incorporated into bispidinone skeletons that remain unsubstituted in these positions.[2,7] The possible correlation between metal complex formation in bispidinones without β-substituents and the opportunity to

explore synthesis of bispidinones with a wide variety of amines, directed our study towards these types of adducts. Bispidinones unsubstituted at β-positions need to be prepared with formaldehyde.



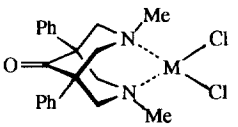
R = Me : M = Co, Ni, Cu, Zn
R = H : M = Co, Ni, Cu,

(2)



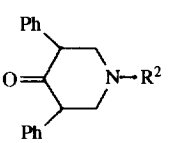
R^1 = Ph : R = H : X = CH_3COO^-
R^1 = H : R = Me : X = ClO_4^-

(3)



(4)

The first synthesis of a bispidinone where formaldehyde constituted the aldehyde fragments in both rings was reported[8] after attempts to generate γ-piperidinones (5) from dibenzyl ketone (6), paraformaldehyde and a primary amine were unsuccessful. Instead bicyclic ring formation readily occurred to provide the bispidinone skeleton without any observable formation of monocyclic product. In this synthesis, the two condensation reactions necessary to form a piperidinone skeleton (Mannich reactions) occur twice to generate the fused symmetrical ring systems on both sides of the ketone.



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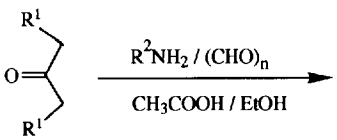
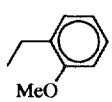
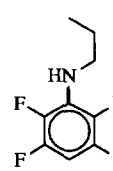


(6) R^1 = Ph
(7) R^1 = SPh
(8) R^1 = Me

(9-23)

Using this methodology the symmetrically substituted bispidinones (9-23) were prepared by Mannich cyclisation reactions between the acetone derivatives (6-8), paraformaldehyde and the acetate salts of a variety of amines (see Table 1). Some derivatives have been reported previously[7a, 8, 2a] and are included since they are relevant to this study or have been prepared by modified methods. The yields ranged from 1-74% reflecting both the ease of the reactants to generate the bispidinone skeleton and the effectiveness of the method of isolation of the bispidinones. Generally good yields could be obtained in derivatives that crystallized, or could be induced to precipitate directly from the reaction mixture. The rendering of the reaction mixture alkaline and aqueous could be used to precipitate the free base of the bispidinones, whilst treating the reaction mixture with acids could precipitate the acidic salt of the bispidinone. This method was employed for bispidinones that were either unable to precipitate cleanly as the free base or were recovered as hygroscopic amorphous solids. When precipitation of bispidinones would not occur aqueous acidic extractions were undertaken. These were inefficient and yields of bispidinones recovered by this method were usually quite low.

Table 1. Preparation of Symmetrically N-Substituted Bispidinones (9-23)

Compound	R^1	R^2	Yield%	Method[a]	Compound	R^1	R^2	Yield%	Method[a]
(9)[b]	Ph	Me	5 72	A B	**(17)**[b]	Ph		72	C
(10)[b]	Ph	CH_2Ph	74	C	**(18)**[b]	Ph		42	D
(11)	SPh	Me	25	C	**(19)**[b]	Ph		74	C
(12)	SPh	CH_2Ph	18	D	**(20)**	Ph		1	A
(13)	Me	Me	16	B	**(21)**	SPh		6	D
(14)	Me	CH_2Ph	5	B	**(22)**	Ph		44[c]	B
(15)	Ph		45	D	**(23)**	Ph		35	A
(16)	Ph	$CH(Ph)_2$	21	C					

[a] Method: A aqueous acid extraction; B precipitation of salt derivative; C crystallisation from reaction mixture; D precipitation from reaction mixture rendered alkaline. [b] Previously reported. [c] Triperchlorate salt.

Dibenzyl ketone (6) was the most effective ketonic substrate observed in these syntheses. The dimethyl (9) and dibenzyl (10) bispidinones of this ketone (6) were prepared in a significantly greater yield than the analogous dimethyl (11) and dibenzyl (12) derivatives of 1,3-diphenyl mercapto acetone (7)[9] and the dimethyl (13) and dibenzyl (14) adducts from diethyl ketone (8). Comparatively the solubilities of these bispidinones correlated well with the trends in yields. Other bispidinone derivatives of dibenzyl ketone (6) containing functional groups at nitrogen that effectively increased the solubility of the product, such as the hydroxyethyl (18), picolyl (22), methoxyphenyl (15) and the carboxyethyl ester (20), were also found to be produced in diminishing yield. The lowering of yields in the synthesis of bispidinones with greater solubility may reflect a tendency for bispidinones to be more vulnerable to reverse reactions when they are intimately associated with the equilibrium environment of the Mannich reaction.

The benzhydryl derivative (16) could only be synthesised with an excess of acetic acid. This was needed to produce a homogeneous reaction environment. Although this bispidinone (16) crystallized from the

reaction mixture it was isolated only in a modest yield. This possibly reflects steric hindrance at positions 3 and 7 and may represent a limit to the size of substituents that can be incorporated onto the nitrogen atoms.

Glycine was used to prepare the bispidinone (19). This compound was tentatively assigned by its melting point which was in agreement with the reported value.[2a] The adduct (19) was extremely insoluble and could not be characterised by conventional nmr spectroscopy. The insolubility of this bispidinone (19) was rationalised by considering a zwitterionic structure. An infrared spectrum supported this structure, displaying absorption bands at 1600 cm^{-1} characteristic of carboxylate ions found in amino acids, and a broad band between 2700 and 2300 cm^{-1} consistent with amine salts.

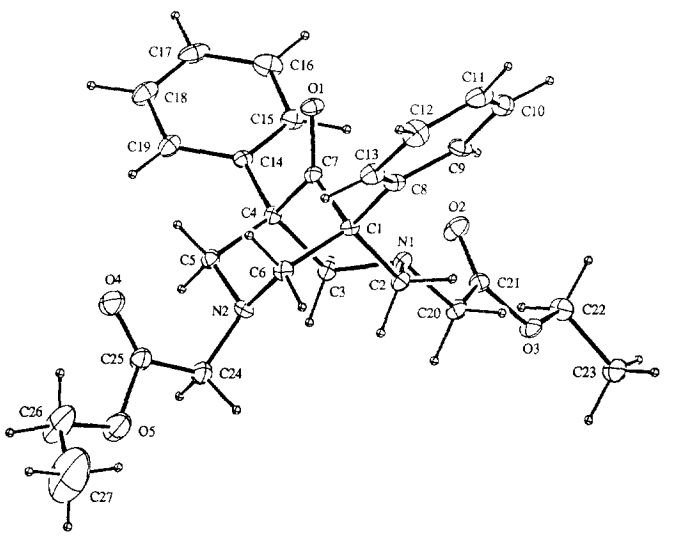


Figure 1 **The crystal structure of the glycinic bispidinone (20)**

The bispidinone derivatives (20) and (21) were prepared from glycine ethyl ester. A crystal structure of the adduct (20) revealed that in the solid state this molecule (20) existed equally in two forms. Both forms exhibited the chair-boat configuration with an exo orientation of the glycine moiety in the chair ring and an endo orientation of the glycine moiety in the boat ring. The glycine fragment of the chair ring was in the plane of the *N,N*-axis, whilst the glycine fragment of the boat ring was rotated by 47° on either side of the *N,N*-axis giving two equivalent conformations. The crystal structure of one of these conformations is represented (see Figure 1).

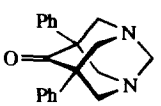
The extremely low yields of compounds (20) and (21) may reflect difficulties of employing amino acids in bispidinone synthesis. The failure to incorporate a series of α or β amino acids, other than glycine, into bispidinones has been observed.[2b] Additionally it was reported[10] that amino acids introduce problems in the environment of the Mannich reaction, due to variations in structure and solubility characteristics. Despite this the utility of the esters of amino acids in the bispidinone preparations suggests that protected amino acids, in which the amino acid moiety may be treated as a free amine, may be encouraged in these syntheses.

The picolyl bispidinone (22) was initially isolated as a hydrochloride salt, and the free base was recovered as an amorphous solid which was extremely soluble in common organic solvents. The adduct (22)

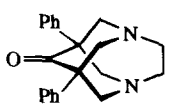
was purified and stored as a perchlorate salt. Analytical data suggested the inclusion of three equivalents of this acid in the salt. Bispidinones can form three centre hydrogen bonds,[11] in which both nitrogen atoms are co-ordinated to an acidic proton. In the perchlorate salt of the picolyl derivative (22) four nitrogen atoms are present, and although each is capable of undergoing protonation, accommodation of these acidic protons is consistent with protonation of both pyridine rings and a three centre hydrogen bond within the bispidinone.

The novel amine tetrafluorophenylethylenediamine[12] was employed to generate the bispidinone (23). Significantly only a Mannich reaction occurred at the primary amine site. Although this amine is a diamine the fluorophenyl group appears capable of deactivating the adjacent secondary amine towards the Mannich reaction. This particular reaction also required an excess of acetic acid to effect a homogeneous reaction environment.

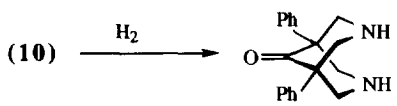
Bispidinones unsubstituted (24) or containing aminoethyl fragments (25) at nitrogen are not accessible by the Mannich reaction. Use of ammonium acetate or 1,2-diamino ethane in these reactions generates the adamantanone (26)[3a] and diaza adamantanone (27)[13] structures respectively.



(26)



(27)



(24)

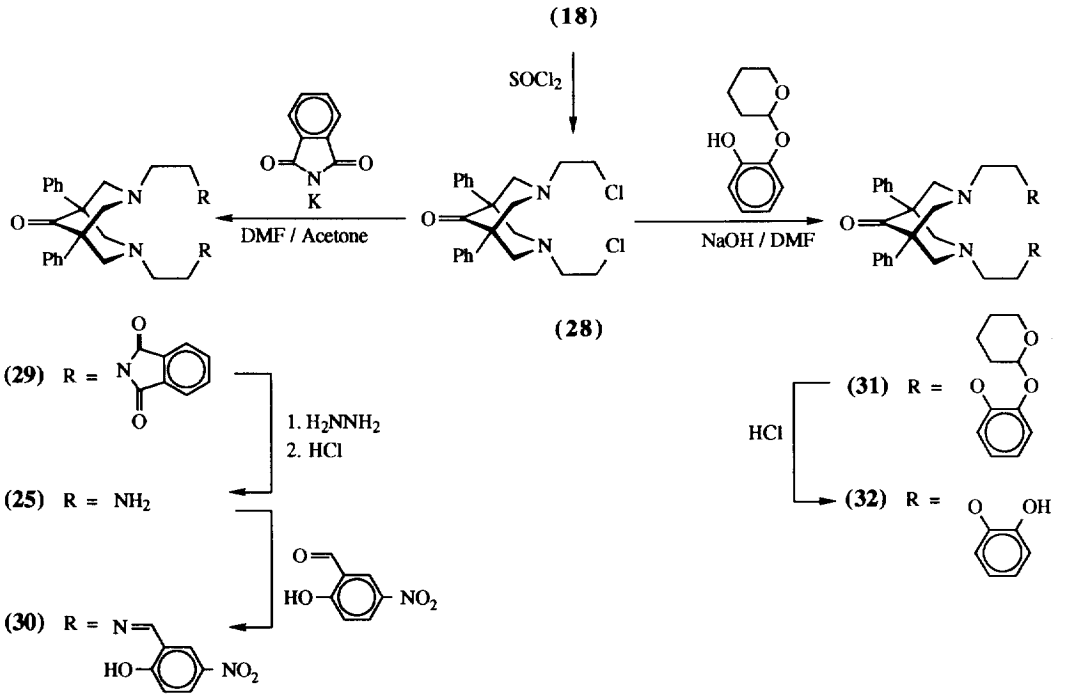
Hydrogenation of the dibenzyl bispidinone (10) gave the N-unsubstituted derivative (24). Although this preparation had been reported[14] in alcohol with palladium/carbon, it was found that hydrogenation in this solvent would only proceed if a catalytic amount of perchloric acid was added. Alternatively hot ethyl acetate has recently been applied as a solvent system for this reduction.[15]

The diaminoethyl bispidinone (25) was prepared by a Gabriel synthesis. Addition of potassium phthalimide to the dichloroethyl bispidinone (28) in a mixture of acetone and dimethyl formamide gave the phthalimido derivative (29) in 80% yield. Hydrolysis with ethanolic hydrazine and an acidic extraction liberated the bispidinone (25) quantitatively. The dichloroethyl bispidinone (28) was obtained by the facile treatment of the dihydroxyethyl bispidinone (18) with thionyl chloride. The diaminoethyl bispidinone (25) was a highly soluble amorphous solid and was characterised through the preparation of the Schiff base derivative (30).

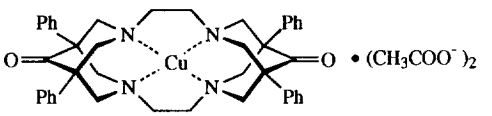
This method of synthesis was significant as previous attempts to prepare the phthalimido bispidinone (29) by alkylation of the *N*-unsubstituted bispidinone (24) with bromoethyl phthalimide had been unrewarding. Also the removal of the phthalimido group of (29) with hydrazine carefully exploited the known lack of reactivity that the carbonyl group of bispidinones display towards non-ionic nucleophiles.[1]

The dichloroethyl bispidinone (28) was investigated in a Williamson like synthesis.[16] Catechol protected as the tetrahydropyranyl[17] ether was condensed with the bispidinone (28) in hot dimethyl formamide with sodium hydroxide as a base. The resulting ether (31) was hydrolysed to the diphenoxy ether (32), which was isolated as a hydrochloride salt. The overall yield for these transformations was 46%, calculated for the monohydrochloride. A novel Mannich reaction with ethylenediamine, copper acetate, and the ketone (6) gave a complex that was assigned the structure (33). The assembly of this macrocycle (33)

was regarded to occur upon an ethylenediamine copper template. Proof of structure was tentative, as only analytical data and an infrared spectrum could be obtained. Examination by ^1H nmr was not undertaken due to the paramagnetic nature of this copper (II) species.



Analytical data was not collected on the free bases of the new bispidinones, but rather on their metal complexes. In this sense the metal complexes are regarded as suitable derivatives of the bispidinones. Complexes were not prepared for a few bispidinones, however their structures were rationalised by a spectroscopic comparison to the characterised adducts.



(33)

The bispidinone skeleton was clearly characterised by ^1H nmr, ^{13}C nmr and infrared spectroscopy (see Table 2). ^1H nmr spectroscopy identified the protons of the 1,5-disubstituted bispidinone ring system as an AB quartet. This pattern derives from the geminal couplings between the isolated axial and equatorial protons and can be interpreted in two ways. One interpretation is that in which these protons are fixed in a symmetrical configuration, the other in which there is an average representation of the axial and equatorial protons of the bispidinone in different conformations that are in a rapid equilibrium on the nmr time scale.

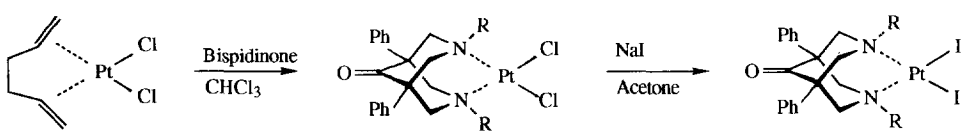
Bispidinones with 1,5 phenyl substituents,[11] or containing sp^2 nitrogen atoms are reported[14] to adopt two degenerate chair-boat conformations that can interconvert rapidly on the nmr time scale. We reason that the majority of bispidinones prepared here would behave in a similar manner. However, the picolyl perchlorate (22) contains an internal hydrogen bond and would be expected to adopt a twin-chair conformation. The unsubstituted bispidinone (24) is also capable of an intramolecular hydrogen bond and might also adopt this conformation.

Axial protons are more strongly shielded than equatorial protons and the lower field doublet of the AB pattern has been assigned accordingly. The chemical shifts, in deuterated chloroform, of the axial protons range between 2.26-3.17 ppm and the equatorial protons range between 3.03-3.88 ppm for bispidinones examined as their free bases. The nmr spectra of the salts (22) and (32) were recorded in deuterated dimethylsulfoxide where the axial and equatorial protons were observed to resonate at higher fields. This may reflect deshielding of the bispidinone ring upon protonation although solvent effects have not been considered. Coupling constants for the axial and equatorial protons range between 10.65-11.93 Hz.

In the ^{13}C nmr spectra of symmetrically substituted bispidinones individual signals were observed for the equivalent methylene and the bridgehead carbon atoms. The chemical shifts of these carbons ranged between 53-69 ppm. Generally it was observed that the carbonyl group of bispidinones behaved as ketones. Their ^{13}C resonances ranged between 200-215 ppm, and in the infrared absorbances were observed in the region between 1720-1750 cm^{-1}.

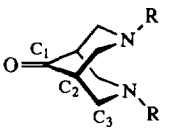
Bispidinones readily formed metal complexes with the transition metals of copper, nickel, palladium and platinum. Analytical data were used to determine the ratio of ligand to metal in the complexes. In some instances these data best fitted structures with the inclusion of water. The infrared spectra of these complexes gave at least weak absorptions in the range 3600-3100 cm^{-1} consistent with the presence of water.

Complexes were prepared by combining alcoholic solutions of both a bispidinone and a relevant divalent copper, nickel or palladium metal precursor. Alternative solvents such as acetonitrile, acetone and water could also be used in the copper case. This approach was not suitable for the preparation of platinum complexes due to the reducing effect of alcohols on this metal. Acidic or aqueous/organic reaction mixtures were briefly investigated but predominantly led to the production of unwanted salts. Only the *cis*-diiodo platinum complex (38) could be prepared in aqueous dioxan from the tetraiodo platinate anion and the bispidinone (24). A general ligand displacement reaction of hexadiene from the dichloro platinum hexadiene (34)[18] was effective for the generation of *cis*-dichloro platinum bispidinones (37), (40) and an anion exchange reaction of (40) with sodium iodide gave the *cis*-iodo complex (41).



(34) (37) R = H (40) R = Me (41) R = Me

Table 2. The ^{1}H n.m.r. chemical shifts (δ)[a,d] of axial and equatorial protons, with their coupling constants (J)[b], the ^{13}C n.m.r. chemical shifts (δ)[a,d] of ring carbons, and the carbonyl absorptions (υ)[c] in some symmetrical bispidinones.



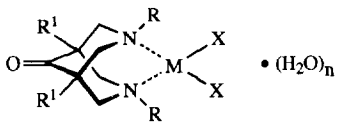
Bispidinone	δ ax	δ eq	J ax eq	δ C1	δ C2	δ C3	υ (carbonyl)
(9)	3.09	3.53	10.91	211.1	54.1	67.1	1723
(10)	3.13	3.55	10.85	211.0	54.4	64.9	1732
(11)	2.80	3.12	11.34	204.1	60.0	66.4	1723
(12)	2.83	3.12	11.29	204.0	60.7	63.5	1720
(13)	2.26	3.03	11.20	215.8	64.3	68.4	1733
(14)	2.37	3.03	10.79	215.7	64.7	65.5	1734
(15)	3.16	3.58	10.73	211.6	54.7	64.9	1727
(16)	3.08	3.59	11.00	211.1	54.4	63.2	1733
(17)	3.14	3.54	10.80	211.0	54.3	65.0	1732
(18)	3.23	3.66	11.41	209.8	54.7	65.2	1731
(20)	3.40	3.70	10.78	210.0	54.7	64.6	1755, 1739, 1724
(21)	3.12	3.43	11.48	203.4	61.1	63.2	1722, 1740
(22)[e,f]	3.96	4.12	11.48	204.2	53.2	62.2	1748
(23)	3.21	3.56-3.60[g]	10.98	209.7	54.0	65.2	1730
(24)	3.71	3.88	11.93	210.1	56.1	61.1	1689
(27)	3.24	3.65	10.65	210.1	54.5	64.9	1726
(28)	3.10	3.50	10.75	210.4	54.0	65.2	1775 1720
(29)	3.20	3.60	10.72	209.8	54.4	65.3	1720
(31)[f,h]	3.96	4.33	11.47	-	-	-	-

[a] In ppm. [b] In Hz. [c] In cm^{-1}. [d] Spectrum recorded in deuterated chloroform. [e] Triperchlorate salt [f] Spectrum recorded in d^6-dimethyl sulfoxide. [g] Overlapping signals. [h] Hydrochloride salt

The resulting metal complexes usually precipitated or crystallized from the reaction mixture. When this did not occur the reaction mixtures were concentrated and precipitation was prompted by the addition of a solvent with low dissolving power for the complex. Alternatively reaction residues were washed or crystallized with solvents that enabled efficient isolation of the complex. In this regard solvent selection was often peculiar to the individual solubilities of the ligands and complexes.

Bidentate transition metal complexes were formed with bispidinones that could co-ordinate through only both terminal nitrogen atoms. The yields ranged between 40-83% (see Table 3). Surprisingly it was possible to prepare the copper (44) and palladium (45) complexes of the dibenzyl bispidinone (10) as this requires accommodation of both benzyl groups around the metal centre. In the *cis*-platinum complexes it was possible to observe different absorbances in the far infrared region between the dichloro (37), (40) and diiodo derivatives (38), (41) respectively. The unique absorbance bands of 324 cm^{-1} in the adduct (37) and 336 cm^{-1} in (40) were characteristic of υ(Pt-Cl) stretching frequencies reported[19] for *cis*-dichloro platinum adducts.

Table 3. Bidentate transition metal complexes (4), (35-46) of some bispidinones



Complex	R^1	R	M	X	n	Yield%	υ(Pt-Cl)[a]
(35)	Ph	H	Cu	Cl	0	76	-
(36)	Ph	H	Pd	Cl	0	56	-
(37)	Ph	H	Pt	Cl	0	46	324
(38)	Ph	H	Pt	I	2	42	-
(4)[b]	Ph	Me	Cu	Cl	0	83	-
(39)	Ph	Me	Pd	Cl	1	63	-
(40)	Ph	Me	Pt	Cl	0	40	336
(41)[c]	Ph	Me	Pt	I	3	10	-
(42)	SPh	Me	Cu	Cl	1	70	-
(43)	Me	Me	Cu	Cl	0	63	-
(44)	Ph	CH_2Ph	Cu	Cl	0	45	-
(45)	Ph	CH_2Ph	Pd	Cl	1	72	-
(46)	Ph		Cu	Cl	0.5	58	-

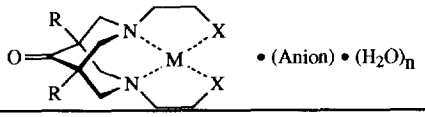
[a] In cm^{-1}. [b] Previously reported. [c] Prepared from complex (40)

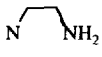
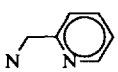
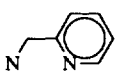
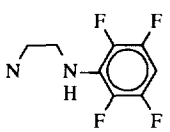
Quadridentate transition metal complexes were generated from bispidinones containing two additional co-ordination sites (see Table 4).

The dichloroethyl bispidinone (28) gave the 1:2 copper complex (47). It was anticipated that this ligand should have produced a 1:1 adduct similar to the bidentate complexes described. The $[CuCl_4]^{2-}$ ion has been reported[20] and the 1:2 species (47) was rationalised as a quadridentate complex, in which the chlorine atoms were involved in the additional bridging of copper. The glycinic esters (20) and (21) generated the neutral complexes (48) and (49) respectively. Synthesis of the complex (48) has also been reported[2a] from the free glycinic bispidinone (19). However the gross insolubility of this bispidinone (19) made this preparation impractical.

Generally complexes of bispidinones containing two additional nitrogen donor sites were derived from metal perchlorates. The infrared spectrum of the nickel perchlorate complex (50) exhibited a strong broad absorption at 1104 cm^{-1} and a medium absorption at 917 cm^{-1}. These bands have been reported[21] in other nickel complexes to indicate the presence of ionic perchlorate and supported the proposed quadridentate structure. The copper perchlorate (52) of the picolyl bispidinone (22) had similar absorptions in the infrared and was also assigned this structure. By analogy the 1:1 complex (54) was regarded to be a quadridentate complex. The dicopper perchlorate (51) displayed absorption bands characteristic of ionic perchlorate and similar to those of both the copper (52) and nickel (50) complexes. The structure of (51) was proposed as a quadridentate complex which had associated an extra mole of copper perchlorate. The picolyl bispidinone (22) gave a 1:2 palladium complex (53), which we rationalised as the Magnus salt structure depicted.

Table 4. Quadridentate transition metal complexes (47-54) of some bispidinones



Complex	R	N X	M	Anion	n	Yield%	$\upsilon(ClO_4^-)$[a]
(47)	Ph		Cu	$CuCl_4^{2-}$	1	49	-
(48)	Ph		Cu	-	0.25	54	-
(49)	SPh		Cu	-	2	71	-
(50)	Ph		Ni	$(ClO_4^-)_2$	2	24	1104sb, 933m
(51)	Ph		Cu	$Cu(ClO_4^-)_2 \cdot (ClO_4^-)_2$	0	30	1100s, 932m
(52)	Ph		Cu	$(ClO_4^-)_2$	2	74	1102sb, 932m
(53)	Ph		Pd	$PdCl_4^{2-}$	0	69	-
(54)	Ph		Cu	$(Cl^-)_2$	0	63	-

[a] In cm^{-1}; s = strong, b = broad, m = medium.

In summary, the Mannich reaction can be used to prepare bispidinone derivatives containing diverse functionalities at nitrogen, provided care is taken in the selection of the ketone and amine. These Mannich cyclisation reactions are not general but subject to subtle influences from the substrates. Functional group transformations on the nitrogen substituents have been demonstrated. Significantly the bispidinones were found to be efficient ligands in the preparation of a wide variety of transition metal complexes.

Crystallography

Crystal data. (20). $C_{27}H_{32}N_2O_5$, M 464.6, monoclinic, space group $P2_1/c$, a 12.516(6), b 15.465(3), c 30.719(16)Å, β 119.21(2)°, V 5190(4)Å^3, D_c 1.19 g cm^{-3}, Z 8, μ_{Mo} 0.77 cm^{-1}. Crystal size 0.14 by 0.17 by 0.29 mm, $2\theta_{max}$ 40°, min. and max.transmission factors 0.94 and 0.96. The number of reflexions was 3027 considered observed out of 4803 unique data, with R_{merge} 0.017 for 192 pairs of equivalent 0kl reflexions . Final residuals R, R_w were 0.048, 0.063 for the observed data.

Structure Determination. Reflexion data were measured with an Enraf-Nonius CAD-4 diffractometer in θ/2θ scan mode using graphite monochromatized molybdenum radiation (λ 0.7107Å). Data were corrected for absorption using the method of de Meulenaer and Tompa[22]. Reflexions with $I > 3\sigma(I)$ were considered observed. The structure was determined by direct phasing and Fourier methods. Hydrogen atoms were included in calculated positions and were assigned thermal parameters equal to those of the atom to which

they were bonded. Positional and anisotropic thermal parameters for the non-hydrogen atoms were refined using full matrix least squares. Reflexion weights used were $1/\sigma^2(F_o)$, with $\sigma(F_o)$ being derived from $\sigma(I_o) = [\sigma^2(I_o) + (0.04I_o)^2]^{1/2}$. The weighted residual is defined as $R_w=(\Sigma w\Delta^2/\Sigma wF_o^2)^{1/2}$. Atomic scattering factors and anomalous dispersion parameters were from International Tables for X-ray Crystallography.[23] Structure solution was by MULTAN80[24] and refinement used BLOCKLS, a local version of ORFLS.[25] ORTEP-II[26] running on a Macintosh IIcx was used for the structural diagram, and an IBM 3090 computer was used for calculations. The structure and atom numbering scheme for one of the molecules in the asymmetric unit is shown in Fig. 1. Material deposited with this journal comprises all atom and thermal parameters, interatomic distances, angles and torsional angles, and observed and calculated structure factors.

EXPERIMENTAL

General Information

^{1}H n.m.r. spectra were recorded at 500 MHz with a Bruker AM-500 spectrometer, and refer to deuterochloroform solutions with chloroform (7.26 ppm) or to d^6-dimethylsulfoxide solutions with dimethylsulfoxide (2.05 ppm) as internal standards. Signals refer to deuterochloroform solutions unless otherwise stated. Signals due to exchangeable protons (NH) were identified by exchange with deuterium oxide. The usual notational conventions are used. ^{13}C n.m.r. spectra were recorded at 125.77 MHz with a Bruker AM-500 spectrometer, and refer to deuterochloroform solutions with chloroform (77.0 ppm) or to d^6-dimethylsulfoxide solutions with dimethylsulfoxide (39.8 ppm) as internal standards. Signals refer to deuterochloroform solutions unless otherwise stated. Low resolution mass spectra were obtained on an A.E.I. MS12 spectrometer at 70eV and 8000V accelerating potential at 210° ion source temperature. Infrared spectra were recorded with a Perkin Elmer 580B with far infrared option spectrophotometer and refer to paraffin mulls of solids. Microanalyses were performed by Dr. H.P. Pham of the UNSW Microanalytical Unit.

General procedure for the synthesis of bispidinones

To an ice cold solution of an amine (50 mmol, 2 eq) in ethanol (10 ml) neutralised by the slow addition of glacial acetic acid (3.0 ml), was added paraformaldehyde (3.0 g, 0.1 mol, 4 eq), a ketone (5, 6, or 7) (25 mmol, 1 eq) and ethanol (20 ml). Additional glacial acetic acid was employed when the amine acetate was insoluble. The resulting suspension was heated gently under reflux for 5 hours. The reaction was then worked up by one of the following methods:

Method (A) The solvent was removed and the residue was taken up with dichloromethane/2N hydrochloric acid. The aqueous phase was collected and the pH was made basic by the addition of a 20% sodium hydroxide solution. Extraction with dichloromethane and evaporation gave the bispidinone.

Method (Bi) The solvent was removed and the residue was dissolved in a small volume of ethanol for compound (11) or acetone for compound (22). Addition of concentrated hydrochloric acid (11) or 2N hydrochloric acid (22) precipitated the bispidinone hydrochloride salt which was filtered and washed with dichloromethane (11) or acetone (22). The free base was liberated by partitioning the hydrochloride salt between dichloromethane (11) or ethanol (22) and a 22% sodium hydroxide solution, and heating until the salt had dissolved. For (22) the ethanol was removed, and dichloromethane was added. The organic phase was collected, washed with a saturated sodium chloride solution, dried ($MgSO_4$) and concentrated to give the bispidinone.

Method (Bii) The reaction mixture was cooled to ambient temperature and diluted with ether (300 ml). The pH was adjusted to 3 with an aqueous perchloric acid solution (70%) and the mixture was stored in the cold overnight. The bispidinone perchlorate salt was collected and partitioned between dichloromethane and a 20% sodium hydroxide solution. Extraction of the organic phase, followed by drying (Na_2SO_4) and concentration gave the crude bispidinone.

Method (Ci) The bispidinone crystallized from the reaction mixture, this was collected and washed with ethanol.

Method (Cii) The reaction mixture was stored in the cold overnight. The bispidinone was collected and washed with ethanol.

Method (Ciii) The reaction mixture was cooled and diluted with an equal volume of water. The crystallized bispidinone was washed with a solution of 1:1 ethanol/water.

Method (Di) The reaction mixture was cooled to ambient temperature and made basic by the addition of concentrated ammonium hydroxide. The solvent was evaporated, and addition of water prompted the precipitation of the bispidinone.

Method (Dii) The reaction mixture was cooled overnight. The solution was made basic by the addition of a 20% soidium hydroxide solution and dilution with an equal volume of water, ethanol for (20), prompted the crystallization of the bispidinone.

Washing the reaction mixture refers to the following: The solvent was removed and the residue was taken up in dichloromethane/water. The organic phase was collected and washed repeatedly with water until the pH of the aqueous phase was neutral, followed by a saturated sodium chloride solution and then dried (Na_2SO_4). Solvent removal gave the crude bispidinone.

2-Methoxybenzylamine

This was used in the synthesis of the bispidinone (15) and was prepared as follows. Under a nitrogen atmosphere a suspension of lithium aluminium hydride (10.0 g, 0.26 mol) in dry tetrahydrofuran (100 ml) was heated under gentle reflux. A solution of 2-methoxybenzaldoxime (15.8 g, 0.11 mol) in dry tetrahydofuran was slowly introduced, and the resulting mixture was maintained under a steady reflux for 48 h. After cooling, water (6 ml) and a 20% sodium hydroxide solution (60 ml) were cautiously added. The precipitate was filtered and washed well with ethanol. The combined filtrates were concentrated, and the residue partitioned between dichloromethane/20% sodium hydroxide solution. The organic phase was collected and evaporated to give the crude amine as a dark oil (6.3 g) which was used in a Mannich reaction without any further purification or characterization.

***1,5-Diphenyl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one* (9)**

This compound was prepared following the general description using an ethanolic methylamine solution (33%) (6.0 ml, 50 mmol) and dibenzylketone (5.0 g, 24 mmol). Work up by *method (A)* gave (9) as a viscous oil that crystallized from ethanol (0.40 g, 5%); work up by *method (Bii)* gave (9) as a viscous oil that crystallized from ethanol (5.5 g, 72%), m.p. 164-165 (lit.[8] 150-151°). υ_{max} 2802, 2790, 1723, 1183, 1153, 721, 702 cm^{-1}. ^1H n.m.r. δ 2.48, s, 6H, NMe; 3.09, d, 4H, J_{axeq} 10.91 Hz, Hax; 3.53, d, 4H, J_{axeq} 10.91 Hz, Heq; 7.21-7.34, m, 10H, aryl. ^{13}C n.m.r. δ 45.6, NMe; 54.1, CPh; 67.7, CH_2; 126.6, 127.0, 127.9, aryl CH; 145.2, aryl C; 121.1, CO. *m/z* 320 (M, 9%), 58 (100).

***Dichloro(1,5-diphenyl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one)copper(II)* (4)**

Hot solutions of the bispidinone (9) (306 mg, 1.0 mmol) in ethanol (10 ml) and copper(II) chloride hydrate (167 mg, 1.0 mmol) in ethanol (5 ml) were combined. The mixture was heated gently until green crystals had precipitated. After cooling the title complex (4) was collected, washed with ethanol, and dried (377 mg, 83%), m.p. 180-182° (Found: C, 55.4; H, 5.4; N, 6.1. $C_{21}H_{24}Cl_2CuN_2O$ requires C, 55.4; H, 5.3; N, 6.2%). υ_{max} 1375, 730, 699, 302, 186 cm^{-1}.

***Dichloro(1,5-diphenyl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one)palladium(II)* (39)**

Solutions of the bispidinone (9) (103 mg, 0.32 mmol) in methanol/acetone (5:2) (7 ml) and sodium tetrachloropalladate(11) (118 mg, 0.83 mmol) in methanol/acetone (5:2) (7 ml) were combined. Additional acetone (2 ml) was added and after stirring overnight the title complex (39) had precipitated as a yellow powder. This product was collected, washed successively with methanol, dichloromethane, and light petroleum and dried (100 mg, 63%), m.p. 240° (Found: C, 49.0; H, 4.8; N, 5.7. $C_{21}H_{24}Cl_2N_2OPd.H_2O$ requires C, 48.9; H, 5.0; N, 5.4%). υ_{max} 1737, 732, 705, 325, 188 cm^{-1}.

***Dichloro(1,5-diphenyl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one)platinum(II)* (40)**

Solutions of the bispidinone (9) (166 mg, 0.52 mmol) in dry chloroform (3 ml) and dichloro $^4\eta$-hexa-1,5-diene platinum(II) (165 mg, 0.48 mmol) in dry chloroform (3 ml) were combined. The resulting mixture was heated under a gentle reflux for 21 h, during which time the title complex (40) precipitated. After cooling this product was collected, washed successively with dichloromethane and light petroleum and dried (114 mg, 40%), m.p. 285° (Found: C, 42.7; H, 4.2; N, 4.8. $C_{21}H_{24}Cl_2N_2OPt$ requires C, 43.0; H, 4.1; N, 4.8%). υ_{max} 1737, 732, 703, 336, 302 cm^{-1}.

***Diiodo(1,5-diphenyl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one)platinum(II)* (41)**

To a suspension of the dichloroplatinum(II) bispidinone (40) (122 mg, 0.42 mmol) in acetone (20 ml) and water (2 ml) was added a solution of sodium iodide (0.16 g, 1.1 mmol) in water (5 ml). The resulting mixture was heated under a gentle reflux overnight and then evaporated to a small volume. The title complex (41) was filtered, washed successively with water and light petroleum and dried (33 mg, 10%), m.p. 190° (Found: C, 30.8; H, 3.3; N, 3.0. $C_{21}H_{24}I_2N_2OPt.3H_2O$ requires C, 30.6; H, 3.6; N, 3.4%). υ_{max} 1735, 731, 691, 212, 190 cm^{-1}.

***1,5-Diphenyl-3,7-dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9-one* (10)**

This compound was prepared following the general method using benzylamine (5.5 ml, 50 mmol) and dibenzyl ketone (5.0 g, 24 mmol). Work up by *method (Ci)* and recrystallization from chloroform/methanol gave the bispidinone (10) (17.5 g, 74%) as colourless crystals m.p. 168-170° (lit.[8] 161-162°; lit.[7a] 165-166°). υ_{max} 1732, 748, 705 cm^{-1}. ^{1}H n.m.r. δ 3.13, d, 4H, J_{axeq} 10.85 Hz, Hax; 3.55, d, 4H, J_{axeq} 10.85 Hz, Heq; 3.75, s, 4H, NCH_2Ph; 7.17-7.45, 20H, m, aryl. ^{13}C n.m.r. δ 54.4, CPh; 61.9, NCH_2Ph; 64.9, CH_2; 126.6, 126.9, 127.4, 127.8, 128.4, 129.0, aryl CH; 138.0, 142.7, aryl C; 211.0, CO. *m/z* 472 (M, 7%), 91 (100).

***Dichloro(1,5-diphenyl-3,7-dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9-one)copper(II)* (44)**

Solutions of the bispidinone (10) (314 mg, 0.67 mmol) in acetonitrile (10 ml) and copper(II) chloride hydrate (114 mg, 0.67 mmol) in acetonitrile (10 ml) were combined. The resulting mixture was heated gently for 15 min and then concentrated. The residue was taken up in hot ethanol, filtered and then concentrated. Dichloromethane was then added to the remainder and the resulting mixture was gently warmed and filtered. Solvent removal gave the complex (44) as a foamed solid which was triturated with ether, collected as a lime

yellow powder, and dried (182 mg, 45%), mp 135-138° (Found: C, 63.9; H, 5.3; N, 4.8. $C_{38}H_{32}Cl_2CuN_2O$ requires C, 63.4; H, 5.4; N, 4.5%). υ_{max} 1745, 1514, 1501, 755, 703, 199, 186 cm^{-1}.

***Dichloro(1,5-diphenyl-3,7-dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9-one)palladium(II)* (45)**

Solution of the bispidinone (10) (175 mg, 0.37 mmol) in dioxan (5 ml) and sodium tetrachloropalladate(II) (141 mg, 0.36 mmol) in methanol (4 ml) were combined. The resulting mixture was stirred overnight during which time the title complex (45) had precipitated as a pink powder. This product was collected, washed successively with methanol, and light petroleum and dried (169 mg, 72%), m.p. 210° (Found: C, 59.4; H, 4.8; N, 4.3. $C_{33}H_{32}Cl_2N_2OPd.H_2O$ requires C, 59.4; H, 5.1; N, 4.2%). υ_{max} 1742, 754, 704, 353 cm^{-1}.

***3,7-Dimethyl-1,5-bis(phenylthio)-3,7-diazabicyclo[3.3.1]nonan-9-one* (11)**

This compound was prepared following the general description using an ethanolic methylamine solution (33%) (6.0 ml, 50 mmol) and 1,3-bis(phenylthio)acetone[9] (7.1 g, 25 mmol). Work up by *method (Bi)* and crystallization from dioxan gave the bispidinone (11) as colourless crystals (2.5 g, 25%), m.p. 98-100°. υ_{max} 1732, 1440, 1187, 1148, 755, 729, 699 cm^{-1}. ^1H n.m.r. δ 2.21, s, NMe; 2.80, d, 4H, J_{axeq} 11.34 Hz, Hax; 3.12, d, 4H, J_{axeq} 11.34 Hz, Heq; 7.25-7.56, m, 10H, aryl. ^{13}C n.m.r. δ 44.4, NMe; 60.0, CSPh; 66.4, CH_2; 128.5, 128.8, aryl CH; 130.8, aryl C; 135.8, aryl CH; 204.1, CO. *m/z* 384 (M, 10%), 232(100).

***Dichloro(3,7-dimethyl-1,5-bis(phenylthio)-3,7-diazabicyclo[3.3.1]nonan-9-one)copper(II)* (42)**

Hot solutions of the bispidinone (11) (91 mg, 0.34 mmol) in ethanol (5 ml) and copper(II) chloride hydrate (114 mg, 0.78 mmol) in ethanol (3 ml) were combined. The resulting mixture was heated gently until bright green crystals precipitated. After cooling, the title complex (42) was collected, washed with ethanol and dried (123 mg, 70%), m.p.175-176° (Found: C, 46.7; H, 4.8; N, 5.3. $C_{21}H_{24}Cl_2CuN_2OS_2.H_2O$ requires C, 47.0; H, 4.8; N, 5.2%). υ_{max} 3327-3189, 3016, 1748, 1337, 1294, 1214, 1140, 1059, 1037, 831, 771, 751, 695, 303 cm^{-1}.

***3,7-Dibenzyl-1,5-bis(phenylthio)-3,7-diazabicyclo[3.3.1]nonan-9-one* (12)**

This compound was prepared following the general procedure using benzylamine (5.5 ml, 50 mmol) and 1,3-bis(phenylthio)acetone[9] (7.1 g, 25 mmol). Work up by *method (Dii)* and recyrstallization from dioxan/light petroleum gave the bispidinone (12) (2.1 g, 18%) as colourless crystals m.p. 155-160°. υ_{max} 1720, 1440, 756, 730 cm^{-1}. ^1H n.m.r. δ: 2.83, d, 4H, J_{axeq} 11.29 Hz, Hax; 3.12, d, 4H, J_{axeq} 11.29 Hz, Heq; 3.46, s, 4H, NCH_2Ph; 7.15-7.40, m, 20H, aryl. ^{13}C n.m.r. δ 40.6, NCH_2Ph; 60.7, CSPh; 63.5, CH_2; 127.4, 128.3, 128.4, 128.7, aryl CH; 130.8, aryl C; 135.6, 2 aryl CH; 137.2, aryl C; 204.0, CO. *m/z* 536 (M, 3%), 91 (100).

***1,3,5,7-Tetramethyl-3,7-diazabicyclo[3.3.1]nonan-9-one* (13)**

This compound was prepared following the general procedure (x5) using an ethanolic methylamine solution (33%) (30 ml, 250 mmol) and diethyl ketone (12 ml, 110 mmol). Work up by *method (Bii)* gave a yellow oil that was re-extracted with n-hexane. Evaporation gave the bispidinone (13) (3.5 g, 16%) as a colourless oil that slowly crystallized m.p. 55-60°. υ_{max} 2808, 2780, 2765, 1733, 1445, 1288, 1135, 1120, 1107, 1031 cm^{-1}. ^1H n.m.r. δ 0.96, s, 6H, CMe; 2.23, s, 6H, NMe; 2.26, d, 4H, J_{axeq} 11.20 Hz, Hax; 3.03, d, 4H, J_{axeq} 11.20 Hz, Heq. ^{13}C n.m.r. δ 19.7, ring Me; 45.4, NMe; 64.3, ring C; 68.4, CH_2; 215.8, CO. *m/z* 196 (M, 17%), 58 (100).

***Dichloro(1,3,5,7-tetramethyl-3,7-diazabicyclo[3.3.1]nonan-9-one)copper(II)* (43)**

Hot solutions of the bispidinone (13) (134 mg, 0.7 mmol) in ethanol (5 ml) and copper(II) chloride hydrate (169 mg, 1.0 mmol) in ethanol (3 ml) were combined. The resulting mixture was heated gently for 15 min and then left to stand at ambient temperature overnight. The title complex (43) precipitated as green crystals. These were collected, washed with ethanol and dried (146 mg, 63%), m.p.176-177° (Found: C, 35.7; H, 6.4; N, 7.90. $C_{11}H_{20}Cl_2CuN_2O.2H_2O$ requires C, 36.0; H, 6.5; N, 7.6%). υ_{max} 3613-3469 wb, 1748, 1432, 1258, 1077, 1063, 1022, 307 cm^{-1}.

***1,5-Dimethyl-3,7-dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9-one* (14)**

This compound was prepared following the general procedure (x5) using benzylamine (28.4 ml, 260 mmol) and diethyl ketone (13.2 ml, 125 mmol). Work up by *method (Bii)* and crystallization from ethanol gave the bispidinone (14) (2.2 g, 5.0%) as colourless crystals m.p. 84-86°. υ_{max} 2810, 2784, 2775, 1734, 1445, 1288, 1135, 1120, 1108, 1030 cm^{-1}. ^1H n.m.r. δ 0.95, s, 6H, Me; 2.37, d, 4H, J_{axeq} 10.79 Hz, Hax; 3.03, d, 4H, J_{axeq} 10.79 Hz, Heq; 3.53, s, 4H, NCH_2Ph; 7.26-7.33, m, 10H, aryl. ^{13}C n.m.r. δ 20.0, ring Me; 46.7, ring C; 61.3, NCH_2Ph ; 65.5, ring CH_2; 127.1, 128.3, 128.7, aryl CH; 138.4, aryl C; 125.7, CO. *m/z* 348 (M, 10%), 91 (100).

***1,5-Diphenyl-3,7-di(2-methoxybenzyl)-3,7-diazabicyclo[3.3.1]nonan-9-one* (15)**

This compound was prepared following the general procedure using 2-methoxybenzylamine (6.8 g, 50 mmol) and dibenzyl ketone (5.0 g, 24 mmol). Work up by *method (Di)* deposited a resin which was powdered and triturated with water. Filtration and cyrstallization from ethanol gave the title bispidinone (15) (5.6g, 45%) as colourless crystals m.p. 68-70° . υ_{max} 1727, 1493, 1245, 755 cm^{-1}. ^1H n.m.r. δ 3.16, d, 4H, J_{axeq} 10.73 Hz, Hax; 3.58, d, 4H, J_{axeq} 10.73 Hz, Heq; 3.77, s, 4H, benzyl CH_2; 3.86, s, 6H, OMe; 6.90-7.45, m, 18H, aryl. ^{13}C n.m.r. δ 54.7, CPh; 55.2, OMe; 55.4, benzyl CH_2; 64.9, ring CH_2; 110.5, 120.3, aryl CH; 126.3, aryl C; 126.4, 127.0, 127.8, 128.4, 130.6, aryl CH; 143.1, 157.9, aryl C; 211.6, CO. *m/z* 532 (M, 3%), 121 (100).

***1,5-Diphenyl-3,7-dibenzhydryl-3,7-diazabicyclo[3.3.1]nonan-9-one* (16)**

This compound was prepared following the general procedure (x0.2) using benzhydrylamine (1.8 ml, 10 mmol), dibenzylketone (1.0 g, 4.8 mmol) and additional glacial acetic acid (10 ml). Work up by *method (Cii)* gave the bispidinone (16) (0.43 g, 21%) as colourless crystals m.p. 270-272°. υ_{max} 1733 cm^{-1}. ^1H n.m.r. δ 3.08, d, 4H, J_{axeq} 11.00 Hz, Hax; 3.59, d, 4H, J_{axeq} 11.00 Hz, Heq; 4.63, s, 2H, $NCH(Ph)_2$; 7.14-7.50, m, 30H, aryl. ^{13}C n.m.r. δ 54.4, CPh; 63.2, CH_2; 75.3, $NCH(Ph)_2$; 126.6, 127.1, 127.4, 127.7, 128.1, 128.6, aryl CH; 141.3, 142.0, aryl C; 211.1, CO. *m/z* 624 (M, 2%), 167 (100).

***1,5-Diphenyl-3,7-diallyl-3,7-diazabicyclo[3.3.1]nonan-9-one* (17)**

This compound was prepared following the general procedure using allylamine (3.7 ml, 50 mmol), and dibenzylketone (5.0 g, 24 mmol). Work up by *method (Cii)* gave the bispidinone (17) (4.8 g, 72%) as colourless crystals m.p. 118-120° (lit.[7a] 119-120°). υ_{max} 1732, 937, 723, 702 cm^{-1}. ^1H n.m.r. δ 3.14, d, 4H, J_{axeq} 10.80 Hz, Hax; 3.22, d, J 6.47 Hz, allyl NCH_2; 3.54, d, 4H, J_{axeq} 10.80 Hz, Heq; 5.20, d, 2H, J_{trans} 10.70 Hz, olefinic CH_2 trans; 5.72, d, 2H, J_{cis} 17.50 Hz, olefinic CH_2 cis; 5.96, ddt, 2H, J 6.47 Hz, J_{trans} 10.70 Hz, J_{cis} 17.50 Hz, olefinic CH; 7.22-7.35, m, 10H, aryl. ^{13}C n.m.r. δ 54.3, CPh; 60.5, allyl NCH_2; 65.0, ring CH_2; 118.1, olefinic CH_2; 126.6, 126.9, 127.9, aryl CH; 135.1, olefinic CH; 142.9, aryl C; 211.0, CO. *m/z* 372 (M, 6%), 84 (100).

***Dichloro(3,7-diallyl-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one)copper(II)* (46)**

Hot solutions of the bispidinone (17) (222 mg, 0.6 mmol) in ethanol (10 ml) and copper(II) chloride hydrate (1.03 g, 0.6 mmol) in ethanol (10 ml) were combined. The resulting mixture was heated gently for 15 min during which time the title complex precipitated as green crystals. After cooling these were collected, washed with ethanol and dried (178 mg, 58%), m.p.215° (Found: C, 58.3; H, 5.6; N, 5.4. $C_{25}H_{28}Cl_2CuN_2O.0.5H_2O$ requires C, 58.2; H, 5.63; N, 5.4%). υ_{max} 3691-3171 wb, 1744, 1505, 990, 944, 700, 300, 185 cm^{-1}.

***3,7-Bis(2-hydroxyethyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one* (18)**

This compound was prepared following the general procedure using ethanolamine (3.0 ml, 50 mmol) and dibenzyl ketone (5.0 g, 24 mmol). Work up by *method (Dii)* gave the bispidinone (18) (3.8g, 42%) as colourless crystals m.p. 182-184° (lit.[8] 176-177°). υ_{max} 3477-3202, 1731, 1501, 1358, 1313, 1173, 1140, 1072, 1056, 1043, 945, 886, 812, 783, 765, 725, 712 cm^{-1}. ^1H n.m.r. δ 2.73, t, 4H, J 5.20 Hz, NCH_2; 3.23, d, 4H, J_{axeq} 11.41 Hz, Hax; 3.66, d, 4H, J_{axeq} 11.41 Hz, Heq; 3.73, t, 4H, J 5.20 Hz, CH_2OH; 7.26-7.37, m, 10H, aryl. ^{13}C n.m.r. δ 54.7, CPh; 58.3, CH_2OH; 58.6, exocyclic NCH_2; 65.2, ring CH_2; 127.3, 127.4, 128.0, aryl CH; 138.2, aryl C; 209.8, CO. *m/z* 380 (M, 5%), 88 (100).

***9-Oxo-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonane-3,7-diethanoic acid* (19)**

A mixture of glycine (2.0 g, 27 mmol), paraformaldehyde (1.6 g, 53 mmol) and dibenzyl ketone (2.0 g, 10 mmol) in ethanol (20 ml) was heated gently under reflux for 2 h. Water (5 ml) was added and the gentle reflux was continued overnight. After cooling the reaction mixture, addition of water (10 ml) prompted the precipitation of a crystalline solid. This mixture was heated gently under reflux for 24 h and filtered hot. The crystalline product, tentatively assigned as the title bispidinone (19) was washed with water, recrystallized from N,N-dimethylformamide and dried (3.0 g, 74%), m.p. 244-247° (dec). (lit.[2a] 248-249°). υ_{max} 2700-2300, 1730, 1600, 1360, 1195, 705, 613 cm^{-1}.

***Diethyl 9-oxo-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonane-3,7-diethanoate* (20)**

To a solution of glycine ethyl ester hydrochloride (8.0 g, 57 mmol), in hot ethanol (40ml), was added a solution of sodium acetate (4.7 g, 57 mmol) in hot water (10 ml). This mixture was gently boiled for 15 min, allowed to cool, and filtered. Paraformaldehyde (7.15 g, 240 mmol) and dibenzyl ketone (10.0 g, 240 mmol) were introduced and the resulting suspension was heated gently under reflux for 5h . Work up by *method (Ai)* and crystallization from ethanol gave the bispidinone (20) (144 mg, 1%) as colourless crystals m.p. 62-63°. υ_{max} 1755, 1739, 1724, 1204, 1188, 1160, 704 cm^{-1}. ^1H n.m.r. δ 1.31, t, 6H, J 7.15 Hz, CH_3; 3.40, d, 4H, J_{axeq} 10.78 Hz, Hax; 3.49, s, 4H, NCH_2; 3.70, d, 4H, J_{axeq} 10.78 Hz, Heq; 4.21, q, 4H, J 7.15 Hz, OCH_2; 7.21-7.35, m, 10H, aryl. ^{13}C n.m.r. δ 14.2, CH_3; 54.7, CPh; 58.5, OCH_2; 60.6, exocyclic NCH_2; 64.6, ring CH_2; 126.7, 126.9, 127.9, aryl CH; 142.3, aryl C; 170.1, ester CO; 210.0, ketone CO. *m/z* 464 (M, 3%) 105 (100).

***9-Oxo-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonane-3,7-diethanoato copper(II)* (48)**

Solutions of the bispidinone (20) (111 mg, 0.24 mmol) in ethanol (5 ml) and copper(II) acetate monohydrate (85 mg, 0.43 mmol) in water (5 ml) were combined. The resulting mixture was heated under a gentle reflux for 2 h. During this time a purple solid precipitated from the reaction solution. This was filtered, suspended in water (15 ml) and heated under a gentle reflux for a further 2 h. After cooling, the title complex (48) was collected as a purple powder, washed with ethanol and dried (61 mg, 54%), m.p. 290° (dec) (Found: C, 58.2; H, 4.6; N, 6.0. $C_{23}H_{22}CuN_2O_5.0.25\ H_2O$ requires C, 58.2; H,4.7; N, 5.9%). υ_{max} 3922-3192w, 1740, 1646, 1341, 1326, 1315, 706, 348 cm^{-1}.

***Diethyl 9-oxo-1,5-bis(phenylthio)-3,7-diazabicyclo[3.3.1]nonane-3,7-diethanoate* (21)**

This compound was prepared by the method reported for compound (20) using bis(phenylthio)acetone[9] (13.0 g, 48 mmol) as the ketone. Work up by *method (Di)* and slow crystallization from ethanol gave the bispidinone (21) (1.2g, 6%) as colourless crystals m.p. 63-65°. υ_{max} 1740, 1722, 1278, 1260, 1200, 1185, 1122, 1030 cm^{-1}. ^1H n.m.r. δ 1.20, t, 6H, J 7.12 Hz, CH_3; 3.12, d, 4H, J_{axeq} 11.48 Hz, Hax; 3.28, s, 4H, NCH_2; 3.43, d, 4H, J_{axeq} 11.48 Hz, Heq; 4.12, q, 4H, J 7.12 Hz, OCH_2; 7.25-7.52, m, 10H, aryl. ^{13}C n.m.r. δ 14.2, CH_3; 57.4, OCH_2; 60.5, NCH_2; 61.1, CSPh; 63.2, ring CH_2; 128.5, 128.8, aryl CH; 130.6, aryl C; 135.8, aryl CH; 169.9, ester CO; 203.4, ketone CO. *m/z* 528 (M, 2%), 304 (100).

***9-Oxo-1,5-bis(phenylthio)-3,7-diazabicyclo[3.3.1]nonane-3,7-diethanoato copper(II)* (49)** To a solution of the bispidinone (21) (176 mg, 0.33 mmol) in ethanol (10 ml) was added a solution of copper(II) acetate monohydrate (69 mg, 0.35 mmol) in water (2 ml). The resulting mixture was then heated under a gentle reflux for 1 h. During this time the title complex (49) precipitated as a blue powder. This product was collected, washed with ethanol and dried (125 mg, 71%), m.p. 270° (dec). (Found: C, 48.2; H, 4.3; N, 4.9. $C_{23}H_{22}CuN_2O_5S.2H_2O$ requires C, 48.5; H,4.6; N, 4.9%). υ_{max} 3592-3052, 1645, 1608, 1343, 1322, 1074, 750, 725, 321, 190 cm^{-1}.

***1,5-Diphenyl-3,7-di(2-pyridylmethyl)-3,7-diazabicyclo[3.3.1]nonan-9-one* (22)**

This compound was prepared following the general procedure using 2-aminomethylpyridine (6.6 ml, 64 mmol) and dibenzyl ketone (5.3 g, 25 mmol). The reaction mixture was washed and worked up by *method (Bi)*. This gave the bispidinone (22) (5.2 g, 44%) as a foamed solid that could be powdered, m.p. 57-60°.

Triperchlorate Salt

To the free base (22), dissolved in ether, was added aqueous perchloric acid (70%) until the pH was 3. The resulting salt was collected, triturated with ethylacetate, filtered, and dried under reduced pressure. (Found: C, 45.8; H, 4.5; N, 6.9. $C_{31}H_{30}N_4O.(HClO_4)_3.2H_2O$ requires, C, 46.0; H, 4.2; N, 6.9%). υ_{max} 1748, 1108, 767, 627 cm^{-1}. ^1H n.m.r. δ (d^6-dimethylsulfoxide) (triperchlorate salt) 4.00, d, 4H, J_{axeq} 11.48 Hz, Hax; 4.12, d, 4H, J_{axeq} 11.48 Hz, Heq; 4.50, s, 4H, NCH_2Py; 7.33-7.42, m, 10H, aryl; 7.81, t, 1H, J 6.54 Hz, H5 Py; 8.00, d, 1H, J 9.70 Hz, H3 Py; 8.34, t, 1H, J 7.78 Hz, H4 Py; 8.76, d, 1H, J 5.37 Hz, H6 Py. ^{13}C n.m.r. δ (d^6-dimethylsulfoxide) (triperchlorate salt) 32.2, CPh; 58.3, NCH_2Py; 62.6, ring CH_2; 125.7, 126.6, 128.1, 128.5, 128.6, aryl CH; 135.0, aryl C; 143.0, 146.3, aryl CH; 150.2, aryl C; 204.2, CO. *m/z* (free base) 474 (M, 1%), 135 (100).

***(1,5-Diphenyl-3,7-bis(2-pyridylmethyl)-3,7-diazabicyclo[3.3.1]nonan-9-one) copper(II) perchlorate* (52)**

Solutions of the bispidinone (22) (147 mg, 0.31 mmol) in ethanol (5 ml) and copper(II) perchlorate hexahydrate (120 mg, 0.32 mmol) in ethanol (2 ml) were combined. The title complex (52) precipitated as a purple solid. This was collected, washed with ethanol, and dried under reduced pressure (166 mg, 74%). (Found: C, 48.5; H, 4.0; N, 7.14. $C_{31}H_{30}Cl_2CuN_4O_9.2H_2O$ requires C, 48.1; H, 4.4; N, 7.2%). υ_{max} 3924-3416, 1745, 1618, 1492, 1307, 1164, 1102, 997, 767, 742, 725, 704, 194 cm^{-1}.

***(1,5-Diphenyl-3,7-bis)(2-pyridylmethyl)-3,7-diazabicyclo[3.3.1]nonan-9-one) palladium(II) tetrachloropalladate(II)* (53)**

Solutions of the bispidinone (22) (105 mg, 0.22 mmol) in methanol (5 ml) and sodium tetrachloropalladate(II) (70 mg, 0.23 mmol) in methanol (6 ml) were combined. The mixture was stirred overnight and concentrated. The residue was powdered in acetone, filtered, and taken up with a small volume of water. Addition of acetone to this solution deposited the title complex (53) as a fine powder which was

collected, washed with acetone and dried (66 mg, 69%), m.p. 248-250°. (Found: C, 44.9; H, 4.2; N, 6.8. $C_{31}H_{30}Cl_4N_4OPd_2$ requires C, 45.0; H, 4.2; N, 6.8%). υ_{max} 3765-3220, 1738, 1304, 772, 742, 724, 707, 191 cm^{-1}.

***1,5-Diphenyl-3,7-bis(2,3,5,6-tetrafluorophenylaminoethyl)-3,7-diazabicyclo[3.3.1]nonan-9-one* (23)**

This compound was prepared following the general procedure using N-(2,3,5,6-tetrafluorophenyl)ethylenediamine (11.0 g, 53 mmol), dibenzyl ketone (15.0 g, 24 mmol), water (10 ml) and additional glacial acetic acid (3.0 ml). The reaction mixture was washed and cyrstallization from ether/light petroleum gave the bispidinone (23) (5.65 g, 35%) as colourless crystals m.p. 152-153°. υ_{max} 1730, 1650, 1525, 1500, 1350, 1250, 1178, 1167, 1140, 1110, 1070 cm^{-1}. ^1H n.m.r. δ 2.86, t, 4H, J 5.68 Hz, NCH_2; 3.21, d, 4H, J_{axeq} 10.98 Hz, Hax; 3.56-3.60, m (t and d overlapping), 8H, $CH_2NC_6F_4$ and Heq; 4.65, s, 2H, D_2O exch, NH; 6.43, m, 2H, p-C_6F_4H; 7.15-7.35, m, 10H, aryl. ^{13}C n.m.r. δ 45.2, CH_2NH; 54.2, CPh; 56.2, exocyclic NCH_2; 65.2, ring CH_2; 93.5, CH (C_6F_4H); 126.7, 127.1, 128.1, aryl CH; 128.5, t, C (C_6F_4); 137.3, dt, CF; 142.0, aryl C; 164.2, dt, CF; 209.7, CO. *m/z* 525 (3%), 43 (100).

***(1,5-Diphenyl-3,7-bis(2,3,5,6-tetrafluorophenylaminoethyl)-3,7-diazabicyclo[3.3.1]nonan-9-one) copper(II) chloride* (54)**

Hot solutions of the bispidinone (23) (63 mg, 0.09 mmol) in ethanol (5 ml) and copper(II) chloride hydrate (89 mg, 0.5 mmol) in ethanol (3 ml) were combined. The resulting mixture was heated gently until green crystals precipitated. After cooling, the title complex (54) was collected, washed with ethanol, and dried (46 mg, 63%), m.p. 204-205°. (Found: C, 51.7; H, 3.4; N, 6.8. $C_{35}H_{30}Cl_2CuF_8N_4O$ requires C, 51.9; H, 3.7; N, 6.3%). υ_{max} 3026, 1742, 1655, 1532, 1516, 1179, 1154, 1080, 286, 205, 190 cm^{-1}.

***1,5-Diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one* (24).**

A solution of 3,7-dibenzyl-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (10) (10.0 g, 21 mmol), in glacial acetic acid (100 ml) and ethanol (20 ml) was treated with seven drops of an aqueous perchloric acid solution (70%). Palladium/charcoal (10%, 1.0 g) was added and the reaction mixture was stirred under a hydrogen atmosphere, at ambient temperature and atmospheric pressure, until uptake of this gas ceased (ca. 2 days). The reaction mixture was filtered, and solvent evaporated at ambient temperature under reduced pressure. The residue was suspended in a 20% sodium hydroxide solution and extracted with dichloromethane. The organic extracts were dried (Na_2SO_4), and concentrated to give the crude bispidinone (24) as a white solid, which was recrystallized from ethanol (5.1 g, 83%), m.p. 204-205° (lit[24] 205-206°). υ_{max} 3049, 1689, 707 cm^{-1}. ^1H n.m.r. δ 2.50-3.25, no observed signal, 2H, D_2O exch, NH; 3.71, d, 4H, J_{axeq} 11.93 Hz, Hax; 3.88, d, 4H, J_{axeq} 11.93 Hz, Heq; 7.26-7.39, m, 18H, aryl. ^{13}H n.m.r. δ 56.1, CPh; 61.1, CH_2; 127.1, 127.4, 128.0, aryl CH; 138.2, aryl C; 210.1, CO. *m/z* 292 (M, 16%), 248 (100).

***Dichloro(1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one)copper(II)* (35)**

Hot solutions of the bispidinone (24) (186 mg, 0.64 mmol) in ethanol (10 ml) and copper(II) chloride hydrate (186 mg, 0.64 mmol) in ethanol (10 ml) were combined. The title complex (35) precipitated as pale blue crystals. These were collected, washed with ethanol, and dried. (208 mg, 76%), m.p. 189-191° (Found: C, 51.4; H, 4.6; N, 6.3. $C_{19}H_{20}CuCl_2N_2O.H_2O$ requires C, 51.3; H, 4.9; N, 6.3%). υ_{max} 3674-3484, 1737, 702, 287, 202 cm^{-1}.

***Dichloro(1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one)palladium(II)* (36)**

Solutions of the bispidinone (24) (101 mg, 0.35 mmol) in dioxan/methanol (2/1) (15 ml) and sodium tetrachloropalladate(II) (105 mg, 0.36 mmol) in dioxan/methanol (2/1) (6 ml) were combined. The resulting

mixture was stirred overnight and concentrated. The title complex (36) was suspended in water, collected, washed successively with dichloromethane and light petroleum and dried. (92 mg, 56%), m.p. 315-317° (Found: C, 48.3; H, 4.2; N, 6.2. $C_{19}H_{20}Cl_2N_2OPd$ requires C, 48.6; H, 4.3; N, 6.0%). υ_{max} 33205, 3112, 1745, 1344, 1190, 1073, 906, 757, 741, 702, 331, 319 cm^{-1}.

***Dichloro(1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one)platinum(II)* (37)**

Solutions of the bispidinone (24) (110 mg, 0.38 mmol) in dry chloroform (10 ml) and dichloro $^4\eta$-hexa-1,5-diene platinum(II) (121 mg, 0.35 mmol) in dry chloroform (10 ml) were combined. The resulting mixture was heated under a gentle reflux overnight and concentrated. The crude title complex (37) was powdered in dichloromethane, filtered, washed with light petroleum and dried. (91 mg, 46%), m.p. >350° (Found: C, 41.8; H, 3.8; N, 5.2. $C_{19}H_{20}Cl_2N_2OPt$ requires C, 40.9; H, 3.6; N, 5.0%). υ_{max} 3191, 3094, 3059, 1743, 1343, 756, 702, 324 cm^{-1}.

***Diiodo(1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one)platinum(II)* (38)**

Solutions of potassium tetrachloroplatinate(II) (176 mg, 0.42 mmol) in water (2 ml) and potassium iodide (0.7 g, 4.2 mmol) in water (3 ml) were combined. The resulting mixture was stirred for 0.5 h, and then a solution of the bispidinone (24) (122 mg, 0.42 mmol) in dioxan (10 ml) was introduced. The reaction solution was then stirred overnight during which time the title complex (38) precipitated as a pale yellow powder. This was collected, washed successively with water, acetone, light petroleum and dried. (132 mg, 42%), m.p. 275° (Found: C, 29.3; H, 2.8; N, 3.3. $C_{19}H_{20}I_2N_2OPt.2H_2O$ requires C, 29.3; H, 3.1; N, 3.6%). υ_{max} 3869-3454, 1739, 901, 201 cm^{-1}.

***1,5-Diphenyl-3,7-di(2-chloroethyl)-3,7-diazabicyclo[3.3.1]nonan-9-one* (28)**

Under a nitrogen atmosphere an ice cold solution of the dihydroxyethyl bispidinone (18) (8.3 g, 22mmol), in dichloromethane (50 ml) was treated with thionyl chloride (12 ml, 165 mmol). The reaction mixture was heated under a gentle reflux for 2 h, and concentrated. The residue was taken up in water/ethanol (2:1) and the mixture was made basic by the addition of a 20% sodium hydroxide solution. This was extracted with dichloromethane and the organic extract was concentrated to a small volume. Addition of ethanol precipitated the product, which after filtration and washing with ethanol gave the dichloro bispidinone (28) (8.5 g, 93%) as pale yellow crystals, m.p. 150-155° (lit.[8]154-155°). This product was used in further synthesis without any purification although it can be recrystallized from acetone/ethanol. υ_{max} 1726, 720 cm^{-1}. ^{1}H n.m.r. δ 2.97, t, 4H, J 6.47, NCH_2; 3.24, d, 4H, J_{axeq} 10.65 Hz, Hax; 3.65, d, 4H, J_{axeq} 10.65 Hz, Heq; 3.68, t, 4H, J 6.47, CH_2Cl; 7.24-7.37, m, 10H, aryl. ^{13}C n.m.r. δ 41.5, CH_2Cl; 54.5, CPh; 58.3, exocyclic NCH_2; 64.9, ring CH_2; 126.8, 128.1, aryl CH; 142.5, aryl C; 210.1, CO. *m/z* 147 (M, 1%), 106 (100).

***Copper(II) chloride complex* (47)**

Solutions of the bispidinone (28) (228 mg, 0.55 mmol) in acetonitrile (5 ml) and copper (II) chloride hydrate (95 mg, 0.55 mmol) in acetonitrile (20 ml) were combined. The resulting mixture was heated under a gentle reflux for 15 min and concentrated. Addition of ethanol to the residue precipitated lime green crystals, that were collected, washed with ethanol, dried and assigned the structure (47) (82 mg, 49%), m.p. 165-166° (Found: C, 39.5; H, 3.9; N, 3.7. $C_{32}H_{26}Cl_4N_2O.H_2O$ requires C, 39.2; H, 4.0; N, 4.0%). υ_{max} 3452, 3348, 1744, 1073, 1055, 700, 302, 189 cm^{-1}.

***1,5-Diphenyl-3,7-bis(2-phthalimidoethyl)-3,7-diazabicyclo[3.3.1]nonan-9-one* (29)**

Under a nitrogen atmosphere a suspension of the dichloroethyl bispidinone (28) (11.0 g, 26 mmol), potassium phthalimide (15.0 g, 81 mmol), in N,N-dimethylformamide (20 ml) and acetone (5 ml) was stirred

and heated at 120° for 12h. The acetone was evaporated, and the remaining solution was partitioned between dichloromethane/water. The organic phase was collected, washed repeatedly with water until the pH of the aqueous phase was neutral, and then concentrated to give the crude phthalimide (29)) (13.5 g, 80%) as colourless crystals, m.p. 205-207°. υ_{max} 1775, 1720, 1400, 723 cm^{-1}. ^1H n.m.r.δ 2.74, t, 4H, J 6.48, NCH_2; 3.10, d, 4H, J_{axeq} 10.75 Hz, Hax; 3.50, d, 4H, J_{axeq} 10.75 Hz, Heq; 3.81, t, 4H, J 6.48, CH_2NPth; 7.16-7.87, m, 18H, aryl. ^{13}C n.m.r.δ 35.7, CH_2Pth; 54.0, CPh; 54.1, exocyclic NCH_2; 65.2, ring CH_2; 123.3, 126.6, 126.8, 127.9, aryl CH; 132.0, phthalimide C; 134.1, aryl CH; 142.3, aryl C; 168.2, phthalimide CO; 210.4, ketone CO. *m/z* 638 (M, 1%), 217 (100).

***3,7-Bis(2-aminoethyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one* (25)**

A suspension of the diphthalimido bispidinone (29) (13.5 g, 21mmol), in ethanol (100 ml) was treatedwith hydrazine hydrate (7.0 ml, 142mmol). This mixture was then heated under reflux for 2 h, during which time a volumous clag had formed. Concentrated hydrochloric acid (30 ml) and water (30 ml) were added and the reaction mixture was reheated under reflux for an additional 1h. After the ethanol was removed, the remaining suspension was filtered, and the collected salts were washed well with 2N hydrochloric acid. The acidic filtrate was treated with concentrated ammonium hydroxide until basic, and then extracted with dichloromethane. Drying of the organic extracts (K_2CO_3) gave the diaminoethyl bispidinone (25) (7.7 g, 97%) as a clear orange oil that waxed.^1H n.m.r.δ 1.4, sb, 4H, D_2O exch, NH_2; 2.2-2.8, m, 8H, NCH_2CH_2N; 3.0, d, 4H, J_{axeq} 10 Hz, Hax; 3.5, d, 4H, J_{axeq} 10 Hz, Heq; 7.1-7.4, sb, 10H, aryl.

***[3,7-Bis(2-aminoethyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one]nickel(II) perchlorate* (50)**

Solutions of the bispidinone (25) 25 mM in tetrahydrofuran (10 ml, 0.25 mmol) and nickel(II) perchlorate hexahydrate (105 mg, 0.29 mmol) in ethanol (15 ml) were combined. Fine yellow crystals separated and acetone (10 ml) was added. The resulting mixture was heated gently under reflux for 24 h and left to cool. The title complex (50) was collected, washed with light petroleum, and dried. (39 mg, 24%) (Found: C, 29.7; H, 3.5; N, 6.2. $C_{23}H_{30}Cl_2N_4NiO_9.2H_2O$ requires C, 29.7; H, 3.7; N, 6.0%). υ_{max} 3609-3412, 1744, 1104, 996, 932, 626, 239, 213, 199, 184 cm^{-1}.

***Copper(II)perchlorate complex* (51)**

Solutions of the bispidinone (25) 25 mM in tetrahydrofuran (10 ml, 0.25 mmol) and copper(II) perchlorate hexahydrate (200 mg, 0.54 mmol) in ethanol (10 ml) were combined. The resulting mixture was heated gently under reflux until fine lavender crystals precipitated. After cooling, this compound was collected, washed with light petroleum, dried, and assigned the structure (51) (67 mg, 30%), (Found: C, 30.4; H, 3.5; N, 6.3. $C_{23}H_{30}Cl_4Cu_2N_4O_9$ requires C, 30.6; H, 3.3; N, 6.2%). υ_{max} 3606-3543, 1742, 1100, 1007, 991, 932, 728, 702, 626, 195 cm^{-1}.

***3,7-Bis-(5-nitrosalicylidenaminoethyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one* (30)**

Filtered solutions of the bispidinone (25) (381 mg, 1 mmol) in ethanol (5 ml) and 5-nitro salicylaldehyde (337 mg, 2 mmol) in ethanol (10 ml) were combined. The title compound (30) precipitated as yellow crystals. These were collected, washed with ethanol and dried (357 mg, 53%), m.p. 98-100°. υ_{max} 3700-3400, 1720, 1650, 1612, 1320cm^{-1}. ^1H n.m.r. δ2.92, t, 4H, J 5.93 Hz, NCH_2; 3.20, d, 4H, J_{axeq} 10.72 Hz, Hax; 3.60, d, 4H, J_{axeq} 10.72 Hz, Heq; 3.83, t, 4H, J 5.93 Hz, CH_2N=C; 7.00, d, 2H, J_{34} 9.12 Hz, H3 aryl ($HOC_6H_3NO_2$); 7.17-7.36, m, 10H, aryl; 8.21, dd, 2H, J_{34} 9.12 Hz, J_{45} 2.91 Hz, H4 aryl ($HOC_6H_3NO_2$); 8.23, d, 2H, J_{45} 2.91 Hz, H5 aryl ($HOC_6H_3NO_2$); 8.42, s, 2H, N=CH; 14.72, sb, 2H, OH.^{13}C n.m.r. δ 54.4, CPh; 55.4, 56.7, (NCH_2CH_2N); 65.3, ring CH_2; 116.7, aryl C ($HOC_6H_3NO_2$); 119.2, 126.7, 127.0, 128.1,

128.3, 128.4, aryl CH; 138.9, aryl C (Ph); 142.1, aryl C ($HOC_6H_3NO_2$); 164.9, CH; 169.3, aryl C ($HOC_6H_3NO_2$); 209.8, CO. *m/z* 444 (2%), 103 (100).

***3,7-Bis-(2-hydroxyphenoxyethyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one* (32)**

To a solution of the bispidinone (28) (2.67 g, 6 mmol) and 2-(2-hydroxyphenoxy)tetrahydropyran[17] (2.63 g, 13 mmol) in N,N-dimethylformamide (20 ml), was added a solution of sodium hydroxide (0.73 g, 18 mmol) in water (5 ml). The resulting mixture was heated at 120°, under a nitrogen atmosphere for 16 h. After cooling the reaction mixture was partitioned between dichloromethane and water. The organic phase was collected, washed well with water, passed through an alumina pad, and concentrated. This gave compound (31) as a dark oil, which was used directly, without further purification or characterization, to generate the title compound (32). To the ether (31) was added a 2N hydrochloric acid solution (25 ml), the resulting mixture was boiled for 30 min and left to cool. Addition of ethanol prompted the precipitation of the title hydrochloride (32) as a white salt. This compound was collected, washed with ethanol and dried (1.66 g, 46%) (calculated for the monohydrochloride), m.p. 205° (dec). ^{1}H n.m.r. δ ($CDCl_3$/$(CD_3)_2SO$ 1:2) 3.37, t, 4H, J 4.70 Hz, NCH_2; 3.96, d, 4H, J_{axeq} 11.47 Hz, Hax ; 4.21, t, 4H, J 4.70 Hz, CH_2O; 4.33, d, 4H, J_{axeq} 11.47 Hz, Heq; 6.60-7.35, m, 18H, aryl; 8.93, sb, 2H, OH.

***Bisacetato(6,13,16,19-tetraphenyl-1,4,8,11-tetraazapentacyclo[9.3.3.3^{4,8}.1^{6,9}.1^{13,6}]docosan-21,22-dione)-copper(II)* (33)**

A filtered solution of copper(II) acetate monohydrate (954 mg, 5 mmol) in water (8 ml) and ethanol (3 ml) was neutralized by the addition of 1,2-diaminoethane (636 ml, 9.5 mmol). Paraformaldehyde (1.25 g, 42 mmol), dibenzyl ketone (2.0 g, 95 mmol) and ethanol (10 ml) were introduced and the resulting suspension was heated gently under reflux for 4 h. After cooling, the reaction mixture was filtered, concentrated, and the residue was partitioned between dichloromethane and water. The organic phase was collected, filtered through a Celite pad and concentrated. The remainder was taken up in hot ethanol, filtered through a Celite pad, evaporated to a small volume and, upon addition of ether, deposited a pale green powder. This product was collected, dried, and assigned the structure (33). (38.5 mg, 1%), m.p. 168-170°. (Found: C, 67.9; H, 6.1; N, 6.9. $C_{46}H_{50}CuN_4O_6$ requires C, 67.5; H, 6.1; N, 6.9%). υ_{max} 1672, 702cm^{-1}.

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