Stereoselective *C*-Alkylation of Di-imine Macrocycles: a Versatile Route to a Series of *meso*-Dialkyl-substituted Macrocyclic Tetramines

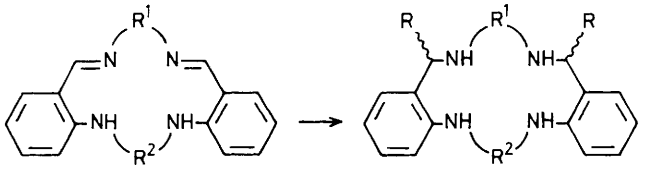
Kim Henrick,[a] Patricia M. Judd,[a] Philip G. Owston,[a] Roger Peters,[a] Peter A. Tasker,*[a] and Ralph W. Turner[b]

[a] *School of Chemistry, The Polytechnic of North London, London N7 8DB, U.K.*
[b] *I.C.I. Pharmaceuticals Division, Macclesfield, Cheshire SK10 4TG, U.K.*

Macrocycles containing two *o*-iminoanilino units undergo stereoselective *C*-alkylation on treatment with Grignard reagents or lithium alkyls to give the *meso*-dialkyl-substituted macrocyclic tetra-amines.

As part of a much wider programme[1] of design and synthesis of tetra-azamacrocycles we have recently considered systematic methods for the preparation of a range of macrocyclic tetra-amines which incorporate alkyl substituents. Often the most troublesome feature in the synthesis of such molecules is the establishment of suitable conditions for cyclisation,[2] which are usually very dependent on the nature and bulk of any alkyl substituents present in linear precursors. Consequently it is desirable to use alkylation of a preformed macrocycle, rather than consider development of conditions for cyclisation of precursors bearing the alkyl substituents. We report here a very effective route to dialkyl derivatives of the dibenzo-annelated tetra-amines (**1**)† by reductive *C*-alkylation[3] of the di-imines (**2**).

Previously it was shown[4] that di-imines of the type (**2**) can give neutral magnesium complexes on reaction with two mol of ethylmagnesium bromide. Addition of an excess of the Grignard reagent results in *C*-alkylation of the imine groups yielding, after hydrolysis, the diethyl-substituted tetra-amines (**1a**—**g**) in good yields (see Scheme 1). Reductive *C*-alkylation was also achieved using methyl-lithium or n-butyl-lithium, in the three cases in which the reaction was attempted, giving (**1h**—**j**) (Scheme 1).



(**2**) (**1a**–**j**)

Scheme 1

		R	R¹	R²	Yield/%	M.p./°C
(**1**);	**a**	Et	$[CH_2]_2$	$[CH_2]_2$	89[a]	164.5
	b	Et	$[CH_2]_3$	$[CH_2]_2$	94[a]	180.0—180.5
	c	Et	$[CH_2]_4$	$[CH_2]_2$	87[a]	120.0
	d	Et	$[CH_2]_5$	$[CH_2]_2$	92[a]	127.5—128.0
	e	Et	*o*-C_6H_4	$[CH_2]_2$	92[a]	78.5—84.0[b]
	f	Et	(*o*-$C_6H_4OCH_2)_2$	$[CH_2]_2$	95[a]	142.5—143.5
	g	Et	*o*-C_6H_4	$[CH_2]_3$	87[a]	162.5—163.5
	h	Me	*o*-C_6H_4	$[CH_2]_3$	78[c]	141.0—142.0
	i	Me	*o*-C_6H_4	$[CH_2]_2$	74[c]	171.0—173.0
	j	Bu[n]	*o*-C_6H_4	$[CH_2]_3$	74[d]	160.0—161.0

[a] (**2**) (1 mmol), EtMgBr (15 mmol), Et_2O–benzene (1 : 1, 20 ml), 25 °C, 0.25 h, followed by hydrolysis with saturated NH_4Cl. [b] Obtained as solidified oil. [c] (**2**) (1 mmol), RLi (14 mmol), Et_2O (15 ml), 25 °C, 0.25 h, followed by hydrolysis. [d] As footnote c, but in thf.

† The unsubstituted tetra-amines (**1**, R = H) were obtained by reduction of the di-imines with $NaBH_4$ under relatively forcing conditions (large excess of reagent in EtOH, 75 °C, 9 h). Reduction of the di-imines which are precursors for (**1d**), (**1e**), and (**1g**) required reaction with an excess of BH_3·tetrahydrofuran (thf).

The resulting free base macrocycles, with the exception of (**1e**), have sharp melting points and give ^1H and/or ^{13}C n.m.r. spectra which are consistent with the presence of only one stereoisomer. An *X*-ray structure determination‡ of (**1b**) shows this to be the *meso*-isomer. Both ethyl groups and the benzylamino N–H bonds are displaced to the same side of the mean plane of the four nitrogen atoms (Figure 1).

The dimethyl-substituted ligand (**1h**) which was obtained from the reaction with the lithium reagent is also a *meso*-isomer as revealed by the structure determination‡ of a copper(II) complex, $[Cu(\mathbf{1h})(dmf)](ClO_4)_2$·dmf (dmf = dimethylformamide). In this complex the ligand more nearly approaches mirror plane symmetry (see Figure 2).

Although definitive evidence for the *meso*-structures is available only for two of the dialkyltetra-amines (**1**), the fact that all the other members of the series [with the exception of (**1e**)] are obtained as single isomers under similar reaction

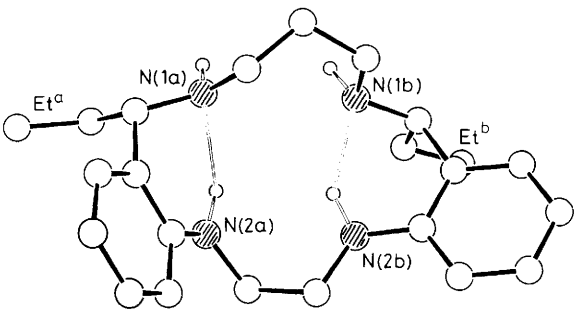


Figure 1. The structure of the *meso*-isomer (**1b**) obtained from the *C*-ethylation of the related di-imine (**2**) with EtMgBr.

‡ *Crystal data:* for (**1b**), 5,11-diethyl-6,7,8,9,10,11,16,17,18,19-decahydro-5*H*-dibenzo[*e*,*n*][1,4,8,12]tetra-azacyclopentadecine, $C_{23}H_{34}N_4$, M = 366.56, orthorhombic, space group *Pbca*, a = 16.382(3), b = 16.502(3), c = 15.848(2) Å, U = 4284.3 Å^3, Z = 8, D_c = 1.134 g cm^{-3}, $F(000)$ = 1600, μ(Mo-K_α) = 0.37 cm^{-1}. 4217 Intensities were recorded ($3 < \theta < 25°$) on a Philips PW1100 diffractometer, and equivalent reflections were averaged to give 1140 unique observed intensities with $I > 3\sigma(I)$ and R 0.065. For $[Cu(\mathbf{1h})(dmf)](ClO_4)_2$·dmf; {(6,20-Dimethyl-6,11,12,13,14,15,20,21-octahydro-5*H*-tribenzo[*b*,*f*,*m*][1,4,8,12]tetra-azacyclopentadecine}(dimethylformamido)copper(II) diperchlorate dimethylformamide, $C_{31}H_{50}Cl_2CuN_6O_{10}$, M = 801.24, monoclinic, space group $P2_1/c$, a = 19.806(6), b = 11.422(3), c = 16.401(4) Å, β = 95.26(3)°, Z = 4, U = 3694.7 Å^3, D_c = 1.444 g cm^{-3}, $F(000)$ = 1660, μ(Mo-K_α) = 7.74 cm^{-1}, R 0.072 for 2022 reflections with $I/\sigma(I) > 3.0$, data collected as above in the range $3 < \theta < 25°$. The dmf solvate molecule is disordered with two sites related by a pseudo 2-fold rotation axis passing through the O and N atoms. One of the perchlorate ions exhibits complex disorder, three sets of oxygen atoms being identified, with site occupation factors of 0.641, 0.304, and 0.062.

The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

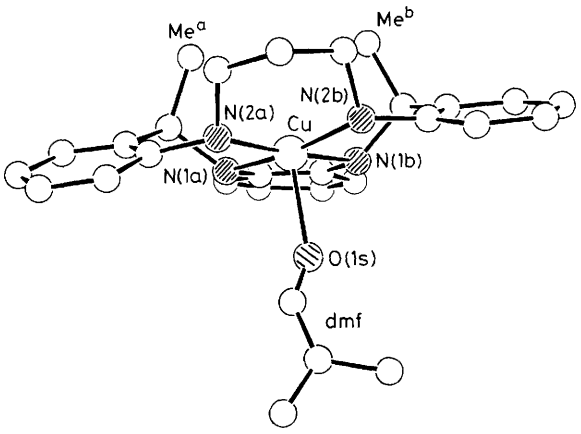


Figure 2. The cationic copper complex of (**1h**), $[Cu(\mathbf{1h})(dmf)]^{2+}$, showing the *meso*-structure of the ligand. Bond lengths from the Cu atom are: N(1a), 2.028(9); N(1b), 2.007(9); N(2a), 2.069(9); N(2b), 2.052(10); O(1s), 2.205(12) Å.

conditions suggests that these are also *meso*-forms. The exception is (**1e**) which appears to be a mixture of *meso*- and racemic-forms as judged by its lower melting point and wider temperature range for melting, and by its more complex ^1H n.m.r. spectrum which contains two well-resolved triplets for the ethyl CH_3 groups.

The stereoselectivity of alkylation of the macrocyclic diimines (**2**) is probably enhanced by the formation of an intermediate magnesium[4] or lithium complex. The rigidity of this species and the displacement of the bridge R^1 to the opposite side of the macrocycle plane from the direction of attack of the first alkyl group R is likely to ensure that the second molecule of alkylating reagent will approach from the same side as the existing R group. Work to establish whether this type of stereoselective alkylation reaction can be applied to other types of imine macrocycles is in progress.

We thank the S.E.R.C. for studentships (to R. P. and P. M. J.) and for diffractometer equipment and computing facilities.

Received, 1st August 1983; Com. 1030

References

1 P. G. Owston, R. Peters, and P. A. Tasker, manuscript in preparation; R. Peters, Ph.D. Thesis, Polytechnic of North London, 1981.
2 G. A. Melsom, 'Co-ordination Chemistry of Macrocyclic Compounds,' ed. G. A. Melsom, Plenum Press, 1979, ch. 2; J. E. Richmans and T. J. Atkins, *J. Am. Chem. Soc.*, 1974, **96**, 2268; F. R. Muller and H. Handel, *Tetrahedron Lett.*, 1982, **23**, 2769.
3 S. Patai, 'The Chemistry of Functional Groups,' J. Wiley, 1970, pp. 266—267.
4 A. J. Greenwood, K. Henrick, P. G. Owston, and P. A. Tasker, *J. Chem. Soc., Chem. Commun.*, 1980, 88.