

## A Convenient Synthesis of the Tetra-aza-macrocyclic Ligands *trans*-[14]-Diene, Tet *a*, and Tet *b*

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A convenient synthesis of 5,7,7,12,14,14-hexamethyl-1,4,8,11-tetra-azacyclotetradeca-4,11-diene (*trans*-[14]-diene) is described. Reduction with sodium borohydride gives the two diastereoisomeric 5,7,7,12,14,14-hexamethyl-1,4,8,11-tetra-azacyclotetradecanes, tet *a* and tet *b*, which are readily separated.

THE macrocyclic ligand 5,7,7,12,14,14-hexamethyl-1,4,8,11-tetra-azacyclotetradeca-4,11-diene (*trans*-[14]-diene) (I) was first described by Curtis.<sup>1,2</sup> Reduction gives two diastereoisomeric hexamethyltetra-azacyclotetradecanes (II) and (III),<sup>3</sup> designated tet *a* (*meso*) and tet *b* (racemic). The chemistry of these ligands has been the subject of a number of reviews.<sup>4,5</sup> *trans*-[14]-Diene was first prepared by the reaction of nickel(II)-

1,2-diaminoethane complexes with acetone.<sup>1,2</sup> Curtis and Hay<sup>6</sup> subsequently prepared the dihydroperchlorate salt of *trans*-[14]-diene in high yield (>80%) by the reaction of the monohydroperchlorate of 1,2-diaminoethane with mesityl oxide or acetone. Kolinski and Korybut-Daszkiwicz<sup>7</sup> have recently found that the monohydroperchlorate of 1,2-diaminoethane reacts with methyl vinyl ketone to give the di(hydroperchlorate)

<sup>1</sup> N. F. Curtis, *J. Chem. Soc.*, 1960, 4409.

<sup>2</sup> M. Blight and N. F. Curtis, *J. Chem. Soc.*, 1962, 3016.

<sup>3</sup> N. F. Curtis, *J. Chem. Soc.*, 1964, 2644.

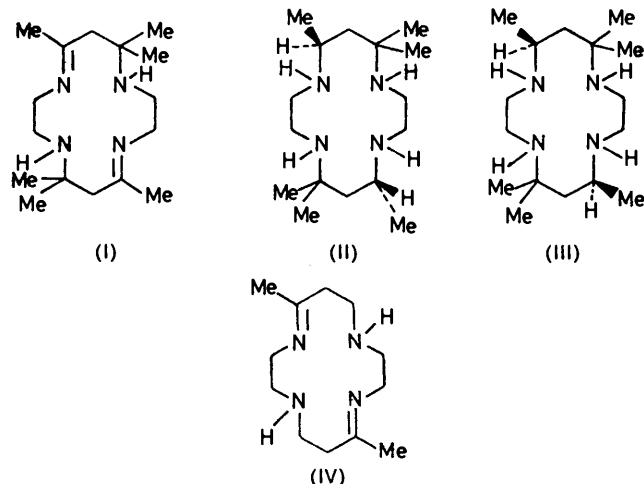
<sup>4</sup> L. F. Lindoy and D. H. Busch, *Prep. Inorg. Reactions*, 1971, **6**, 1.

<sup>5</sup> N. F. Curtis, *Co-ord Chem. Rev.*, 1968, **3**, 3.

<sup>6</sup> N. F. Curtis and R. W. Hay, *Chem. Comm.*, 1966, 524.

<sup>7</sup> R. A. Kolinski and B. Korybut-Daszkiwicz, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1969, **17**, 13.

of 5,12-dimethyl-1,4,8,11-tetra-azacyclotetradec-4,11-diene (IV). The hydroperchlorates of 1,2-diaminoethane



are extremely hazardous materials and violent explosions can occur on heating. We describe here the use of the non-hazardous hydrobromide salts in the synthesis of *trans*-[14]-diene.

#### EXPERIMENTAL

Although the monohydrobromide of 1,2-diaminoethane can be isolated readily, it was found more convenient to prepare it *in situ* by treating the dihydrobromide with 1 equiv. of 1,2-diaminoethane. The 1,2-diaminoethane dihydrobromide was prepared as follows. A solution of 1,2-diaminoethane (10 cm<sup>3</sup>, 0.15 mol) in methanol (100 cm<sup>3</sup>) was cooled in an ice-bath, and concentrated (49%) hydrobromic acid (34 cm<sup>3</sup>, 0.32 mol) was added dropwise. The white precipitate was filtered off. A second crop could be isolated by addition of ether to the filtrate. The product was washed with *n*-butanol then ether, and dried *in vacuo*.

5,7,7,12,14,14-Hexamethyl-1,4,8,11-tetra-azacyclotetradeca-4,11-diene (*trans*-[14]-Diene) Dihydrobromide Dihydrate.—To 1,2-diaminoethane dihydrobromide (11.1 g, 0.05 mol) were added acetone (100 cm<sup>3</sup>) and 1,2-diaminoethane (3.0 g, 0.05 mol). The mixture was stirred and heated at 45 °C for *ca.* 45 min, during which time a copious white precipitate of the macrocycle dihydrobromide formed. The solution was cooled and the product filtered off, washed with ice-cold acetone, then ether, and dried *in vacuo*; m.p. 107–108° (decomp.);  $\nu_{\max}$  1670 cm<sup>-1</sup> (C:N); yield *ca.* 15.4 g (80% based on 1,2-diaminoethane) (Found: C, 40.4; H, 7.9; N, 11.8. Calc. for C<sub>16</sub>H<sub>32</sub>N<sub>4</sub>·2HBr·2H<sub>2</sub>O: C, 40.2; H, 8.0; N, 11.7%).

The same material can be prepared in an exactly analogous manner by heating 1,2-diaminoethane monohydrobromide with acetone. The dihydrobromide of the macrocycle can be kept for 2–3 months without appreciable decomposition.

5,7,7,12,14,14-Hexamethyl-1,4,8,11-tetra-azacyclotetradecane.—(i) *Isomer a (tet a) dihydrate*. *trans*-[14]-Diene dihydrobromide dihydrate (16 g) was dissolved in methanol (200 cm<sup>3</sup>), and sodium borohydride (3 g) was added in small portions to the warmed solution. The solution was

<sup>8</sup> J. L. Love and H. J. K. Powell, *Inorg. Nuclear Chem. Letters*, 1967, **3**, 113.

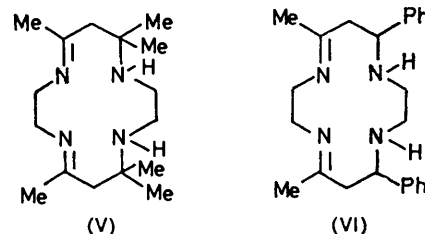
<sup>9</sup> O. H. Hankovszky, K. Hideg, D. Lloyd, and H. McNab, *J.C.S. Chem. Comm.*, 1974, 378.

then heated on a water-bath until effervescence ceased. 2M-Potassium hydroxide solution was then added until the mixture was basic to litmus (pH *ca.* 12), and the solution was cooled to room temperature and filtered. Approximately 50% of the methanol was evaporated off and the resulting solution cooled in an ice-bath. Fine crystals of *tet a* slowly formed; these were filtered off and washed with water. This fraction was essentially pure *tet a* dihydrate, m.p. 146–147° (lit.,<sup>3</sup> 146–148°). The remaining methanol was completely removed from the filtrate, and a second crop of crystals was obtained on cooling in ice (total yield *ca.* 2.5 g). The product can be recrystallised from aqueous methanol. *Tet a* is insoluble in cold water and very sparingly soluble in ether and light petroleum (Found: C, 60.3; H, 12.4; N, 17.7. Calc. for C<sub>16</sub>H<sub>36</sub>N<sub>4</sub>·2H<sub>2</sub>O: C, 60.0; H, 12.6; N, 17.5%).

(ii) *Isomer b (tet b) hydrate*. Potassium hydroxide pellets (*ca.* 10 g) were added to the aqueous filtrate remaining from the previous preparation and the solution was stirred (some *tet b* may crystallise from the strongly basic solution at this stage). The solution was extracted with ether (3 × 100 cm<sup>3</sup>) and the extract dried (Na<sub>2</sub>SO<sub>4</sub>) (continuous ether extraction may be profitably used). The ether was removed to give colourless or very pale yellow crystals of *tet b* monohydrate (*ca.* 5 g), m.p. 101–105° (lit.,<sup>3</sup> 97–105°). The product can be recrystallised from dry ether or light petroleum (Found: C, 63.8; H, 12.5; N, 18.8. Calc. for C<sub>16</sub>H<sub>36</sub>N<sub>4</sub>·H<sub>2</sub>O: C, 63.5; H, 12.7; N, 18.5%). The total yield of *tet a* dihydrate and *tet b* monohydrate is *ca.* 80%.

#### RESULTS AND DISCUSSION

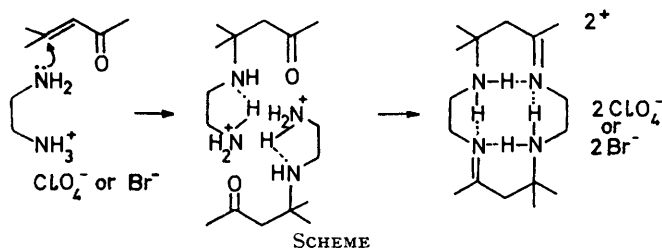
The reaction of 1,2-diaminoethane monohydrobromide with acetone gives *trans*-[14]-diene dihydrobromide dihydrate in high yield (>80%). The reaction appears to be essentially stereospecific, giving only the *trans*-[14]-diene (I). We have obtained no evidence for the *cis*-[14]-diene (V),<sup>8</sup> although this diene is also produced [as its nickel(II) complex] when tris-(1,2-diaminoethane)nickel(II) reacts with acetone.<sup>5,8</sup> Mass spectral evidence has



recently been presented<sup>9</sup> confirming the *trans*-[14]-diene structure for the macrocycle prepared by the reaction of 1,2-diaminoethane monohydroperchlorate with acetone. The mass spectrum of the free base obtained from the diperchlorate on treatment with alkali, gives the correct molecular ion peak ( $M^+$  280) but no fragment corresponding to the loss of 1,2-diaminoethane which would have been expected for the *cis*-[14]-diene. Instead peaks due to the loss of Me<sub>2</sub>C·NH and Me<sub>2</sub>C·NH·[CH<sub>2</sub>]<sub>2</sub>·NH appear. When 1,2-diaminoethane reacts with benzylideneacetone the 14-membered macrocycle formed has the *cis*-configuration (VI).<sup>9,10</sup> It appears that the

<sup>10</sup> K. Hideg and D. Lloyd, *Chem. Comm.*, 1970, 929; *J. Chem. (Soc. (C))*, 1971, 3441.

diamine undergoes a Michael reaction with two molecules of the  $\alpha\beta$ -unsaturated carbonyl compound and the resulting diketone undergoes cyclisation by reaction with a further molecule of the diamine. It is significant that the cyclisations involving monoprotonated diamines give the *trans*-isomers. In this case it appears that a Michael addition of the diamine to the  $\alpha\beta$ -unsaturated ketone gives a substituted  $\beta$ -amino-ketone. A further Michael addition is prevented by protonation (Scheme).



Pairs of  $\beta$ -amino-ketone residues then cyclise by ketimine formation to give the *trans*-[14]-diene which crystallises as the sparingly soluble di(hydroperchlorate) or di-

hydrobromide. A brief report of the isolation of a di(hydrionitrate) salt containing nitric acid of crystallisation has also been published.<sup>11</sup>

In the present reactions it appears that, under the basic conditions employed, acetone undergoes a base-catalysed aldol condensation to give diacetone alcohol, which is subsequently dehydrated to give mesityl oxide. Both diacetone alcohol and mesityl oxide react with the monohydroperchlorate salt of 1,2-diaminoethane to give the di(hydroperchlorate) of *trans*-[14]-diene, suggesting that these compounds are indeed likely intermediates. The free diamine reacts vigorously with mesityl oxide to give tarry polymeric products and the di(hydroperchlorate) and dihydrobromide salts undergo no reaction.

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<sup>11</sup> V. L. Goedken and D. H. Busch, *Inorg. Chem.*, 1971, **10**, 2679.