Synthesis and Metal Complexes of Mono-*N*-substituted Tetra-azamacrocycles

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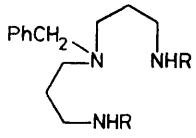
Summary The preparation of *NN'N''*-tritosyl-1,4,7,11-tetra-azacyclotetradecanes opens a general route for the synthesis of mono-*N*-substituted macrocycles and their metal complexes.

FOLLOWING recent reports on interesting properties of macrocycles with additional ligating functions attached to a side chain,[1] a more general synthetic route to mono-*N*-substituted polyazacycloalkanes has become desirable.

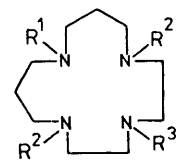
We now describe the preparation of two intermediates which allow specific alkylation at only one of the nitrogen atoms of the macrocycle and give some examples of their synthetic potential. Although many routes, such as template reactions,[2] cyclisation at high dilution,[3] and repetitive ring expansion,[4] lead to cyclic products, the procedure of Richman and Atkins[5] appeared to be the most promising for our purpose, since it is simple, does not require high dilution conditions, and generally provides good yields.



(**1**) R = H
(**2**) R = Ts
Ts = $MeC_6H_4SO_2$-*p*

Compound (**1**), the starting material for our first synthesis, was obtained by treating benzylamine with 2 mol of acrylonitrile and subsequent reduction of the nitrile groups with Raney-nickel.[6] Tosylation according to the procedure of Crossland[7] and precipitation with HCl in ether gave the hydrochloride of the tosylamide (**2**) (yield 72%, m.p. 160—163 °C, lit.[8] m.p. 155—156 °C). Cyclisation of *NOO'*-tritosyldiethanolamine[5] with the disodium salt of (**2**) in dimethylformamide (DMF) solution following the method of Richman and Atkins,[5] gave the crystalline macrocycle (**3**)† [yield 45%; m.p. 161—163 °C; δ ($CDCl_3$) 1·7 (4H, q, CCH_2C), 2·45 (9H, s, PhMe), 2·45 (4H, m, CH_2N), 3·3 (12 H, m, SO_2NCH_2), 3·5 (2H, s, $PhCH_2$), and 7·5 (17H, m, ArH)]. The benzyl group was then removed by catalytic hydrogenation in acetic acid with 10% Pd on charcoal giving compound (**4**) [yield 85%; m.p. 179—181 °C; δ ($CDCl_3$) 1·0 (1H, s, NH), 1·65 (4H, q, CCH_2C), 2·4 (9H, s, PhMe), 2·6 (4H, t, NCH_2), 3·25 (12H, m, SO_2NCH_2), and 7·5 (12H, m, ArH)].

A second reaction sequence with trityl as protecting group was also tested. The mesylated product (**10**)[9] cyclised with the disodium salt of *NN'N''*-tritosyldi(3-aminopropyl)amine in DMF to give the cyclic compound (**11**) [yield 45%; m.p. 175 °C (decomp.); δ ($CDCl_3$) 2·0 (8H, m, CCH_2C and Ph_3CNCH_2), 2·4 (9H, s, PhMe), 3·2 (12H, m, SO_2NCH_2), and 7·25 (27H, m, ArH)]. The trityl group was then removed with HCl in ether yielding the tritosylated

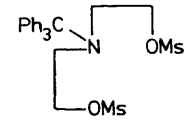


	R^1	R^2	R^3
(**3**)	CH_2Ph	Ts	Ts
(**4**)	H	Ts	Ts
(**5**)	CH_2CONH_2	Ts	Ts
(**6**)	CH_2CH_2CN	Ts	Ts
(**7**)	CH_2CONH_2	H	H
(**8**)	$CH_2CH_2CONH_2$	H	H
(**9**)	$CH_2CH_2CO_2Et$	H	H
(**11**)	Ts	Ts	CPh_3
(**12**)	Ts	Ts	H
(**13**)	Ts	Ts	CH_2CONH_2
(**14**)	Ts	Ts	CH_2CH_2CN
(**15**)	Ts	Ts	CH_2CH_2NHTs
(**16**)	H	H	CH_2CONH_2

Ts = $MeC_6H_4SO_2$-*p*

product (**12**) [yield 91%, m.p. 160 °C (decomp.), δ ($CDCl_3$) 1·5 (1H, s, NH), 2·0 (4H, m, CCH_2C), 2·45 (9H, s, Ph*Me*), 3·05 (16H, m, NCH_2), and 7·5 (12H, m, ArH); *m/e* 663 (M^+)].

Both compounds (**4**) and (**12**) are key intermediates for the preparation of mono-substituted macrocycles since only one secondary amino-group is accessible to alkylation. As examples we have studied the reactions of (**4**) and (**12**) with iodoacetamide, acrylonitrile, and aziridine tosylate whereby compounds (**5**) [yield 88%; m.p. 208—211 °C; δ (Me_2SO) 1·7 (4H, q, CCH_2C), 2·45 (9H, s, Ph*Me*), 2·5 (4H, m, NCH_2), 3·2 (14H, m, $COCH_2N$ and SO_2NCH_2), 6·8 (2H, br s, $CONH_2$), and 7·45 (12H, m, ArH)], (**6**) [yield 86%, m.p. 156—159 °C, δ ($CDCl_3$) 1·7 (4H, q, CCH_2C), 2·45 (9H, s, Ph*Me*), 2·5 (8H, m, NCH_2 and CH_2CN), 3·3 (12H, m, SO_2NCH_2), and 7·5 (12H, m, ArH)], (**13**) [yield 62%, m.p. 162—165 °C, δ ($CDCl_3$) 2·0



(**10**)

Ms = $MeSO_2$

(4H, q, CCH_2C), 2·4 (9H, s, Ph*Me*), 2·6—3·3 (18H, m, NCH_2), and 7·5 (12H, m, ArH)], (**14**) [yield 80%, m.p. 205—207 °C, δ ($CDCl_3$) 1·95 (4H, q, CCH_2C), 2·4 (9H, s, Ph*Me*), 2·45 (2H, t, CH_2CN), 2·8 (6H, m, NCH_2), 3·15 (12H, m, SO_2NCH_2), and 7·45 (12H, m, ArH)], and (**15**) [yield 50%, m.p. 187—189 °C, δ ($CDCl_3$) 1·85 (4H, q, CCH_2C), 2·4 (12H, s, Ph*Me*), 2·65 (6H, t, NCH_2), 3·1 (14H, m, SO_2NCH_2), 5·4 (1H, br s, SO_2NH), and 7·45 (16H, m, ArH)] were obtained.

† Satisfactory elemental analyses were obtained for all new compounds and their metal complexes, except for (**9**), which was only isolated as its metal complexes.

The last step in the synthesis is the removal of the tosyl groups. For small quantities up to 1 g, the electrochemical method[10] appears to be ideal. Compound (**7**) was thus obtained in 51% yield [m.p. 168—170 °C, δ ($CDCl_3$) 1·8 (4H, q, CCH_2C), 2·7 (16H, m, NCH_2), and 3·05 (2H, s, NCH_2CO)]. For larger quantities, however, detosylation is more conveniently achieved with 40% HBr in glacial acetic acid. Compounds (**7**) (yield 42%), (**8**) [yield 79%, m.p. of the tetrahydrobromide 238 °C (decomp.); *m/e* 272 (protonated M^+) and 271 (M^+)], and (**16**) [yield 27%; m.p. 110—111 °C; δ ($CDCl_3$) 1·75 (4H, q, CCH_2C), 2·7 (16H, m, NCH_2), and 3·15 (2H, s, NCH_2CO); *m/e* 258 (protonated M^+) and 257 (M^+)] were prepared by this method. In addition, compound (**9**) was obtained by heating (**8**) with H_2SO_4 and ethanol according to Diamond *et al.*[11]

Compound (**7**) forms crystalline, stable complexes with Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}, and compounds (**8**), (**9**) and (**16**) with Ni^{2+}, Cu^{2+}, and Zn^{2+}.

This work was supported by the Swiss National Science Foundation.

(*Received, 4th October* 1977; *Com.* 1034.)

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