Unique Synthesis of 1,4,7,10-Tetraazacyclododecane

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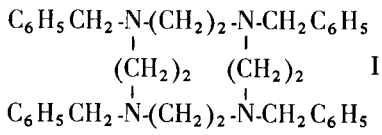
Sir:

Recent work (1) in this laboratory on the synthesis and nucleophilic properties of small ring compounds has resulted in the isolation of an unusual ring system. Following the reaction of *N*-benzylaziridine with tetramethyl-1,3-cyclobutanedione a small amount of a solid was isolated which was the result of a low order polymerization of the aziridine. Detailed analytical studies showed this compound to be 1,4,7,10-tetrabenzyl-1,4,7,10-tetraazacyclododecane (I).



I

Reduction of 1,4-ditosyl-1,4,7,10-tetraaza-2,5,8,11-cyclododecanetetrone with lithium aluminum hydride in tetrahydrofuran has been reported to give the 1,4-ditosyl derivative, m.p. 35° (2), however the preparation of the precursor, a cyclic polypeptide is a lengthy and low yielding synthetic process. Several other tetraamide derivatives of this ring system have been reported (3,4,5,6), these are all cyclic polypeptides and are the products of relatively difficult synthetic procedures.

The title compound I was prepared in nearly quantitative yields by refluxing a mixture of 10 g. of *N*-benzylaziridine, 0.05 g. of *p*-toluenesulfonic acid (PTSA) in 75 ml. of 95 percent alcohol for six hours. The precipitated white solid was recrystallized from absolute alcohol to give pure I (96%), m.p. 142-143° (picrate, prepared in ethanol, unstable, m.p. 136-137° dec.).

Anal. Calcd. for $C_{36}H_{44}N_4$: C, 81.15; H, 8.32; N, 10.51; M.W. 532.7. Found: C, 81.20; H, 8.25; N, 10.46; M.W. (7), m/e 532 (M^+), 441 (M^+-$C_6H_5CH_2$). The n.m.r. spectrum (7) (deuteriochloroform) revealed a singlet (area 16) at 2.66 ppm (ring protons); a singlet (area 8) at 3.40 p.p.m. (benzyl protons) and a multiplet (area 20) at 7.15 p.p.m. for the aromatic protons.

This appears to be an isolated reaction as aziridine, *N*-methylaziridine, *N*-phenylaziridine and *N*-(β-hydroxyethyl)aziridine in the presence of acid catalysis give only high molecular weight polymers. *N*-(*n*-Butyl) aziridine, however, when treated with acid catalysis (PTSA) gave *N,N'*-dibutylpiperazine (13%), b.p. 99° (4.5 mm.), picrate (m.p. 268-269° dec.); (lit. (8) b.p. 126-128° (12 mm.), picrate (m.p. 270-271° dec.). No other low molecular weight polymerization products were isolated.

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(7) Mass spectra were run on a Hitachi RMU-6E spectrometer at a resolution of 2,500 (M/ΔM). NMR spectra were run (deuteriochloroform) on a Varian HA-100 spectrometer at 100 mc. (tetramethylsilane = 0.00 ppm).

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