Pergamon

Tetrahedron Vol. 50, No. 30, pp. 9167-9174, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00514-1

A Novel Entry Into 1,2,3,4,5,6-Hexahydro-3-benzazocine-4,6-dione And 2-Substituted-2,5,6,7-Tetrahydro-4-benzazonine-1,3-(4H)-dione

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Abstract: **2-Substituted-1,2,3,4,5,6-hexahydro-3-benzazocine-4, 6-diones(1a-d) and 2-methoxy-2,5,6,7-tetrahydro-4-benzazonine-1,3-dione 8 were synthesised through an oxidative ring expansion reaction of 6-methylthio-7-substituted-benzo[a] octem (2a-d) and 7- methylthio-8-methoxy-benzo[a]nonem 7 with sodium periodate in isopropanol respectively.**

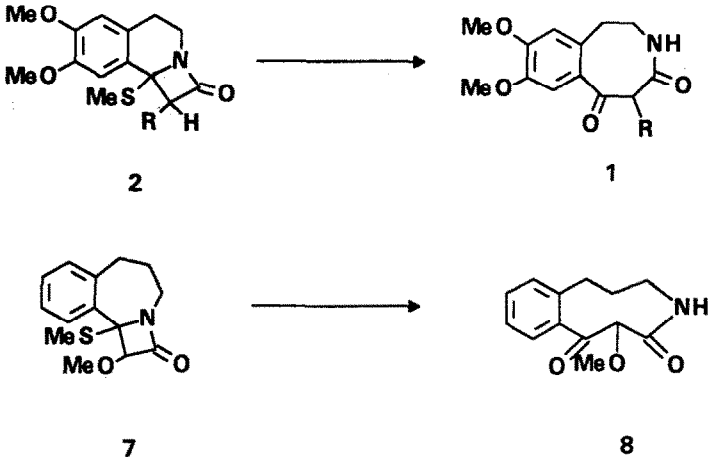
3-Benzazocines are an important class of biologically active substances[1]. Several protracted multistep and usually low yielding syntheses are reported [2] for this system.

For the syntheses of 4-benzazonine the situation is even worse. A single literature report [2i] of a highly specialised synthesis, where the basic aim was to synthesise azacyclotridecadiene has been reported. In the process one of the side products isolated was identified as 4-benzazonine.The fact remains that there is not even a single deliberate attempt to synthesise 4-benzazonine.

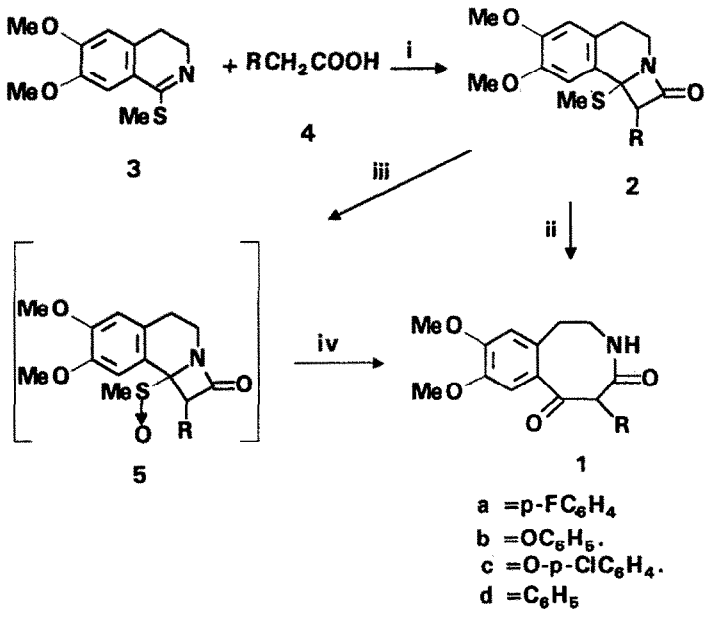
Our interest was to synthesise eight and nine membered nitrogen ring systems, through a simpler route than hitherto described. We decided to use fused tricyclic ring systems as our main intermediates and then open one of the ring junctions to the required ring size.Benzo-six-four and benzo-seven-four membered ring systems were chosen as the starting points. The four membered ring component of the tricyclic is the ß-lactam. ß-Lactams have been used by design [3i] to generate specific chemical substances or accidentally as in the case of 3,4-dihydro-1,4-benzoxazonine-5,7-(2H,6H)-dione[3ii]. However such schemes have not been exploited beneficially to generate a practical synthesis for either hexahydro-3-benzazocines or tetrahydro-4-benzazonines **(Eq.1)**

The key reaction involves oxidative removal of an alkyl thioether group from the benzo[a]octem **2**[4] , possibly through **5** to ring expanded benzazocine-4,6-dione **1**, which proceeds in *ca* 80% (1a=80%; 1b=76%; 1c=76%) isolated yields from **3 (Scheme 1).**

Equation 1



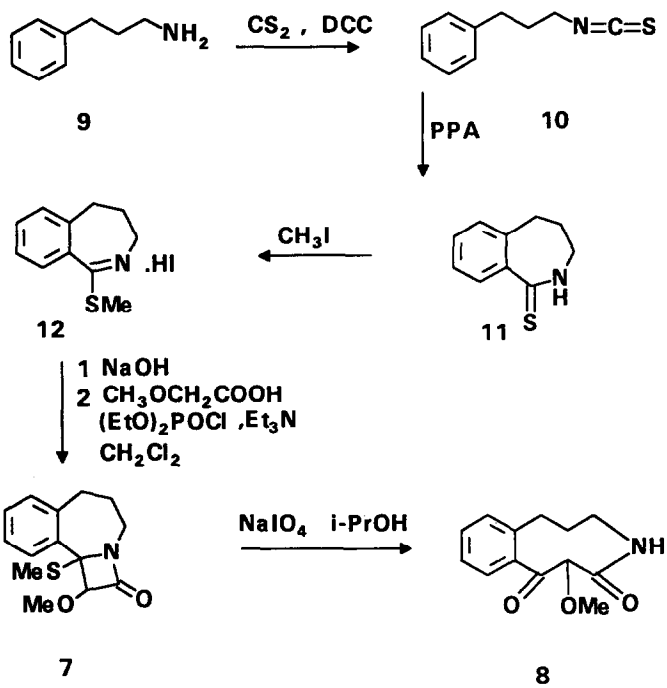
SCHEME 1



(i)$(EtO)_2POCl$, Et_3N, CH_2CL_2 (ii) $NaIO_4$, i-PrOH - H_2O
(iii) m-CPBA , CH_2Cl_2 (iv) i-PrOH - H_2O

It was highly tempting to check the utility of this reaction to generate the nine membered ring systems. When compound **7** was treated with $NaIO_4$ in aqueous propanol, a clean oxidative ring opening resulted into the formation of 2-methoxy-2,5,6,7-tetrahydro-4-benzazonine1,3(4H)-dione **8** in 83% isolated yield.

SCHEME 2



Different benzo[a]octems **2** were synthesised using known methods[5] by reacting 6,7-dimethoxy-dihydro-1-methylthioisoquinoline **3** with substituted acetic acids (*viz.*; 4-chlorophenoxy, 4-fluorophenyl,phenoxy and phenyl acetic acids) diethylphosphochloridate[6] and triethylamine in dichloromethane.

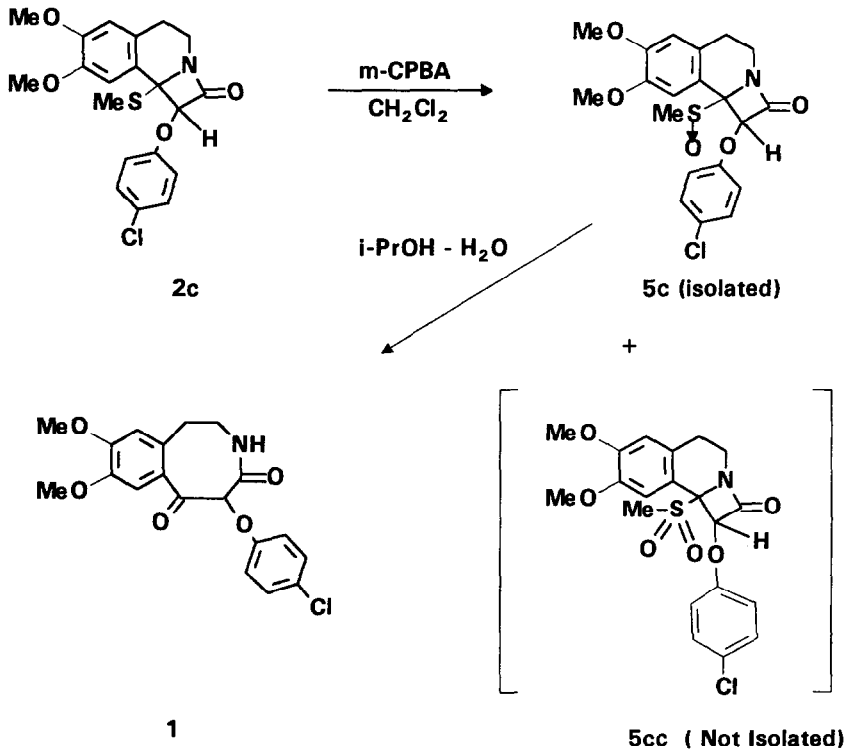
Synthesis of 7-methylthio-8-methoxy-1,2-benzononem **7**, was started from 3-phenylpropylamine **9** which was converted into isothiocyanate[7] **10** followed by cyclisation with PPA to the corresponding 2-benzazepine-1-thione[8] **11. 11** on treatment with methyl iodide gave the corresponding methylthio derivative **12**. Compound **12** was subjected to ß-lactam formation, using methoxyacetic acid triethylamine and diethylphosphochloridate in dichloromethane to give compound **7** in 24% isolated yield **(Scheme 2).**

Benzo[a]octem **(2a-d)** on treatment with 1.2 equivalents of sodium periodate in isopropanol-water (10:1) at 45-50 ^{0}C, gave substituted 5-aryl or aryloxy 1,2,3,4,5,6-hexahydro-3-benzazocine-4,6-dione(**1a-d**) in yields ranging from 68-80%. Similarly when 7-.methylthio-8-methoxy-1,2-benzononem **7** was treated with sodium periodate in isopropanol-water,it gave in 83% the nine membered 2-methoxy-2,5,6,7-tetrahydro-4-

benzazonine-1,3(4H)dione **8**. Compound **8** was analysed correctly and is single spot on TLC,however its ^{1}HNMR indicated that more than one conformer was present.

^{1}H NMR in DMSO at 300 K shows, a slow equilibrium of at least three conformers of approximately 7.5:1.5:1 ratio on the nmr scale. ^{1}H NMR in $CDCl_3$ at 300 K, again indicated a slow equilibrium of two conformers 7:3 ratio on nmr scale. We could observe that H-6 protons were spread between δ 1.75-2.25,similarly H-7 appeared as a multiplet at δ 2.5-2.9, H-5' as multiplet at δ 3-3.2. Methoxy signal appeared at δ 3.4 and another methoxy at δ 3.52, H-5 two protons showed humps at δ 3.8 and 4.23, H-2 two singlets at δ 4.45 and 4.82 , and NH proton at δ 7.68-7.9. On raising the temperature to 393 K in DMSO-d_6 there was a fast equilibrium of the signals; now H-6 appeared at δ 1.75, H-7 between δ 2.5-2.9, H-5 at δ 3.25 and 3.45, methoxy group as a singlet at δ 3.4 , H-2 as a singlet at δ 4.8. Similarly H-4 appeared at δ 7.10 without any splitting. However majority of peaks in DMSO had blurring appearance indicating that the nine membered ring certainly has a flexible conformation.

SCHEME 3



We decided to isolate the possible intermediate **5c.** **2c** was treated with m-CPBA in dry dichloromethane (**Scheme 3),** without treatment of water, reaction was worked up.One pure compound was isolated and was identified as the sulphoxide **5c** (for spectral details see experimental). This indicates that sulphoxide is one of the intermediates.. The rest of the residue was highly polar and on further work up and treatment with water gave **1c** ,thereby indicating that there may be other intermediates such as sulphones **5cc** which can lead to the same compound. When **5c** was heated in isopropanol-water mixture it also gave the required **1c.** We can further speculate that sulphone may be unstable and hence not so easy to isolate from the polar residue. Use of the isolated intermediate to prepare the target compound is not as efficient as that of $NaIO_4$ route.

CONCLUSION

A variety of appropriately substituted alkylthio octems and nonems can be synthesised through known literature methods, therefore the above synthetic sequence will give a ready access to hitherto difficult to synthesise novel benzazocine-4,6-diones and 2-substituted-tetrahydro-4-benzazonine-1,3(4H)dione. These systems can act as versatile intermediates for biologically important classes of compounds.Further we also envisage the use of this reaction to build larger substituted higher as well medium sized nitrogen heterocycles.

EXPERIMENTAL

Melting points were determined on Kofler hot-stage apparatus and are uncorrected. ^1H NMR. spectra were recorded on 90 MHz FT Joel spectrometer using TMS as internal standard. IR spectra were recorded in Perkin-Elmer 157 and Perkin-Elmer 782 spectrophotometer.

General procedure for synthesis of benzo[a] octems (Method A)

To a cold solution of 6,7-dimethoxy-3,4-dihydro-1-methylthioisoquinoline (0.05mol), aryl or aryloxy acetic acid (0.05mol), and triethylamine(0.10 mol) in methylene chloride, diethylphosphochloridate (0.05 mol) in methylene chloride was added under stirring. After 48 hours of stirring, the reaction mixture was washed consecutively with cold water, dilute bicarbonate solution, water, 0.1N hydrochloric acid and water to neutral pH. Organic phase was dried with Na_2SO_4, evaporated under reduced pressure and column chromatographed on florisil to give products.

6-Methylthio-7-(4-fluorophenyl)-2',3'-dimethoxybenzo[a]octem(2a): Prepared through method A. Yield 76%, m.p.154-156° C (Found: C, 64.00; H, 5.60; N, 3.52; S, 8.40. $C_{20}H_{20}NO_3SF$ requires C,64.32; H, 5.39; N, 3.74; S, 8.58%). IR (KBr) 1755 cm^{-1} δ (90 MHz;CDCl3) 1.67 (3H,s, SCH_3), 2.6-3.6 (4H,m,H-3 and H-4), 3.53 and 3.9 (6H,s,OCH_3),4.6 (1H,s,H-7),6.6-7.3 (6H,m,ArH).

6-Methylthio-7-phenoxy-2',3'dimethoxybenzo[a]octem(2b): Prepared through reported method[5].

6-Methylthio-7-(4-chlorophenoxy)-2',3'-dimethoxy benzo[a]octem (2c): Prepared through method **A**. Yield 68%, m.p.260-263°C (Found:C, 58.99; H, 4.74; N, 3.43; Cl, 8.44; S, 7.66. $C_{20}H_{20}ClNO_4S$ requires C, 59.18; H, 4.97; N, 3.45; Cl, 8.73; S, 7.89%). IR (KBr) 1769 cm^{-1}. δ (90 MHz; $CDCl_3$) 2.25 (3H,s, SCH_3), 2.67-3.67 (4H,m,H-3 and H-4),3.8 and 3.90 (6H,2s,OCH_3), 5.23 (1H,s,H-7), 6.60(1H,s,H-4'), 6.75 (1H,s,H-1'),7.0-7.3 (4H,m,ArH).

6-methylthio-7-phenyl-2',3'-dimethoxy benzo[a]octem (2d): Prepared through method **A**. Yield 25%. m.p. 131-131°C (Found: C,67.77; H,6.42; N,3.68; S,9.34. $C_{20}H_{21}NO_3S$ requires C,67.59; H,5.96; N,3.94; S,9.00%). IR (KBr) 1760 cm^{-1} δ (90 MHz; $CDCl_3$) 1.66 (3H,s, SCH_3), 2.53-3.2 (4H,m,H-3 and H-4), 3.83 and 3.89 (6H,2s,OCH_3), 4.58 (1H,s,H-7), 6.66 (1H,s,H-4') ,6.93 (1H,s,H-1'), 7.2-7.5 (5H,m,ArH).

8,9-Dimethoxy-5-(4-fluorophenyl-1,2,3,4,5,6-hexahydro-3-benzazocine-4,6-dione(1a): To a solution of **2a** (10.8 g,0.03 mol) in isopropanol(600 mL) and CH_2Cl_2 (70 mL), sodium periodate (10.7 g, 0.05 mol) in water (60 mL) was added dropwise under stirring. The reaction mixture was heated at 45-50°C for 17h.The solvent was removed under reduced pressure and the residue was treated with water, extracted with EtOAc,organic layer washed with sodium thiosulphate solution, water,driedwith Na_2SO_4 and concentrated in vacuo. Column chromatography ($CHCl_3$-MeOH,95:5) gave **1a** (8.0 g,80%) as white solid, m.p.225-228°C (Found: C,66.45; H, 5.15; N,3.96. $C_{19}H_{18}FNO_4$ requires C, 66.46; H,5.28; N, 4.07%). IR(KBr) 3350, 1680, 1650 cm^{-1}. δ (90 MHz; DMSO-d_6) 2.80-3.80 (4H,m, H-1 and H-2), 3.7 and 3.76 (6H,2s,OCH_3), 5.43 (1H,s,H-5), 6.7-7.6 (6H,m,ArH).

8,9-Dimethoxy-5-phenoxy-1,2,3,4,5,6-hexahydro-3-benzazocine-4,6-dione(1b): The compound **1b** was synthesised in a similar manner to **1a** . Yield 76% (crystallised from EtOAc-$CHCl_3$ mixture). m.p. 243-246°C (Found: C,67.08; H,5.69; N,4.51. $C_{19}H_{19}NO_5$ requires C,66.85 ; H, 5.61; N,4.10%. IR(KBr) 3350, 1709, 1680, 1612 cm^{-1}. δ (90 MHz; TFA-d_1). 2.76-3.4 (4H,m,H-1 and H-2), 3.6 (6H,s,OCH_3), 6.0(1H,s,H-5),6.5 (1H,s,H-10),6.4-7.0 (5H,m,ArH), 7.2 (1H,s,H-7).

8,9-Dimethoxy-5-(4-chlorophenoxy)-1,2,3,4,5,6-hexahydro-3-benzazocine-4,6-dione(1c): Compound **1c** was prepared in a similar manner to that of **1a**. Yield 76% crystallised from EtOAc-CH_2Cl_2, m.p.266 °C. (Found: C,60.36; H,4.53; N, 3.61; Cl, 9.80. $C_{19}H_{18}ClNO_5$ requires C,60.73; H, 4.82; N, 3.72; Cl,9.43%). IR (KBr) 3355, 1724, 1695 cm^{-1} . δ (90 MHz; TFA-d_1) 2.8-4.0 (4H,m,H-1 and H-2), 3.67 (6H,s,OCH_3), 6.08 (1H,s,H-5), 6.55 (2H,d,J=10 Hz, ArH-2' and H-6'), 6.57 (1H,s,H-10), 6.9 (2H,d,J=10 Hz, Ar- H-3'and H-5'), 7.23 (1H,s,H-7).

Method:B

To a cold solution of **2c** (375 mg, 0.9 mmol) in $CHCl_3$ (25mL), MCPBA (225 mg, 1.3 mmol) was added and the reaction mixture left overnight, diluted with excess of $CHCl_3$, washed with water and $NaHCO_3$ solution. The organic layer dried (Na_2SO_4) and the solvent removed in vacuo. The residue was

treated with isopropanol-water (50 mL, 10:1) and refluxed for 2h, during which time a solid separated out. The excess solvent was removed in vacuo and the residue was triturated with water, leaving a white solid ,which was separated, filtered and crystallised from EtOAc-CH_2Cl_2. This compound was found identical to **1c**. Yield (150 mg, 50%)

8,9-Dimethoxy-5-phenyl-1,2,3,4,5,6-hexahydro-3-benzazocine-4,6-dione (1d): The compound **1d** was synthesised in a similar manner as described for **1a**. Yield (68%), m.p. 217-219 ^{0}C. (Found: C,69.40; H, 6.29; N, 4.02. $C_{19}H_{19}NO_4$ 0.25 H_2O requires C,69.20; H, 5.95; N, 4.25%). IR (KBr) 3350, 1700, 1670 cm^{-1}. δ (90 MHz; $CDCl_3$ + DMSO-d_6) 3.0-4.0 (4H,m,H-2 and H-3),3.83 (3H,s,OCH_3), 3.95 (3H,s, OCH_3), 5.30 (1H,s,H-5), 6.73 (1H,s,H-10), 7.05-7.60 (5H,m,ArH), 7.67 (1H,s, H-7).

8-Methoxy-7-methylthio-1,2-benzo[a]nonem (7): A solution of methoxyacetic acid (9.38 mmol) and diethylphosphochloridate (9.41 mmol) in dichloromethane (40 mL) was stirred at room temperature under nitrogen for 20 minutes. To the solution was added, a solution of 4,5-dihydro-1-methylthio (3H) -2-benzazepine (1.74g ,9.09 mmol) and triethylamine (18.79 mmol) in dichloromethane over a period of 15 minutes. Reaction mixture was stirred at room temperature for 48 hours. The reaction mixture was washed successively with water, sodium bicarbonate, water, 1N HCl and water, dried over Na_2SO_4. After removing the solvent the mixture was purified on a silica gel column eluting with 10% EtOAc in petroleum ether as an eluent.Further elution with 25% EtOAc in petroleum ether gave the product. Yield 24% , m.p. 160-161^{0}C. (Found: C,63.80; H,6.22; N,5.48; S,11.72. $C_{14}H_{17}NO_2S$ requires C,63.85; H,6.51; N,5.32; S,12.17%). IR (KBr) 1755 cm^{-1}. δ (CDCl3), 90 MHz isomeric mixture of cis and trans in the ratio 1:3 which are not separated) 1.72-2.04 (2H,m,CH_2), 2.16 and 2.28 (3H,s,SMe), 2.92 -3.68 (4H,m,2CH_2), 3.85 and 3.92 (3H,s,OCH_3), 4.76-4.9 (1H,s,CH), 7.0-7.32 (4H,m,ArH).

2-Methoxy-2,5,6,7-tetrahydro-4-benzazonine-1,3(4H)-dione (8): A solution of sodium periodate (356 mg, 1.6644 mmol) in water (4 mL) was added dropwise to a solution of compound **8** (263 mg, 1 mmol) in 3 mL isopropanol and 2 mL dichloromethane. The reaction mixture was heated at 80^{0}C for 30 minutes. Some solid separated out and was filtered. The filterate was separated into organic and aqueous phase. The organic phase was dried over Na_2SO_4 and the solvent evaporated. The residue was dissolved in chloroform and the solution was washed with sodium thiosulphate and water respectively. After drying with Na_2SO_4 the solvent was evaporated and the mixture was passed through a silica gel column eluting with acetonitrile 10 to 20% gradient in chloroform as an eluant. Yield 83%. (Found C,66.81; H,6.41; N,5.77; $C_{13}H_{15}NO_3$ requires C,66.93; H,6.48; N,6.01%). m.p.149- 150 ^{0}C. IR (KBr) 3320,1650,1680 cm^{-1} . δ (DMSO,270 MHz, 120 ^{0}C Fast equilibrium of all the three conformers) 1.75 (2H,m,H-6), 2.52.9 (2H,m,H-7), 3.25 (1H,m,H-5), 3.4 (1H,m,H-5), 3.4 (3H,s,OMe), 4.8 (1H,s,H-2), 7.18 (1H,m,NH), 7.125 (1H,dd,ArH), 7.25 (2H,m,ArH), 7.36 (1H,m,ArH).

7-(4-Chlorophenoxy)-2',3'-dimethoxy-6-methyloxothiobenzo[a]octem (5c): Compound **2c** (10g, 0.0246m) in dichloromethane (200 mL) was treated with m-CPBA (4.4 g,0.0255m) and stirred overnight. After removal of the solvent the residue was adsorbed in florosil and chromatographed on a silica gel column

eluting with 12-20% acetonitrile in chloroform .Yield.14% m.p.155 °C (Found C,56.99; H,5.05; N,3.63; $C_{20}H_{20}ClNO_5S$ requires C,56.94; H,4.78; N,3.32; Cl,7.6%). IR (KBr) 1760 cm^{-1}. δ (90 MHz; $CDCl_3$) 2.76 (3H,s,SMe), 2.96 (2H,t,CH_2), 3.5 (2H,m,CH_2), 3.86 (3H,s,OMe), 3.9 (3H,s,OMe), 5.28 (1H,s,CH), 6.64 (1H,s,ArH), 6.68 (1H,s,ArH), 7.04 (2H,d,ArH), 7.76 (2H,d,ArH).

ACKNOWLEDGEMENTS

We acknowledge Dr.P.K.Inamdar and his group for providing micro analytical and spectral data and Dr.H.W.Fehlhaber for providing 270 MHz NMR spectra and temperature studies of nine membered ring system.

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(*Received in UK* 4 *May* 1994; *revised* 8 *June* 1994; *accepted* 10 *June* 1994)