Tetrahedron Vol 33, pp 1931 to 1934 Pergamon Press 1977 Printed in Great Britain

FORMATION OF ENAMINE SCHIFF BASES BY RING CLEAVAGE OF PYRIDINE

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(*Received in USA 20 December 1976; Received in UK for publication 16 March 1977*)

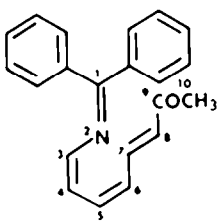
Abstract—On treatment with diphenyldichloromethane or anisal chloride in the presence of acetone and aqueous sodium hydroxide, pyridine undergoes condensation and ring cleavage to yield the enamine Schiff bases 1,1-diphenyl-2-azadeca-1,3Z,5Z,7E-tetraen-9-one (1) and 1-(4-methoxyphenyl)-2-azadeca-1E,3Z,5Z,7E-tetraen-9-one (7). The reaction proceeds through attack of acetonyl carbanion on the initially formed bis-pyridinium salt, followed by ring scission with elimination of one equivalent of pyridine. The structure and stereochemistry of the 2-azatetraene (1) was confirmed by X-ray crystallography.

The condensation of *o*-dihydroxyphenols with diphenyldichloromethane in the presence of pyridine and acetone, followed by treatment with aqueous sodium hydroxide, was first reported by Bradley *et al.*[1] as a method for synthesis of diphenylmethyl ether derivatives. However, attempted mono-diphenylmethylenation of ellagic acid by this technique gave rise to a yellow crystalline compound, m.p. 124–5°, which had none of the properties expected of the desired product, neither reducing ammoniacal silver nitrate nor giving any color with alcoholic ferric chloride solution. Since the m.p. and spectroscopic properties differed from those of ellagic acid bis-diphenylmethyl ether[2] the latter structure was eliminated. Repetition of the reaction in the absence of ellagic acid gave the same crystalline product, indicating that it must be formed by condensation of the other reactants.†

The mass spectrum showed the molecular ion at *m/e* 301, which together with the elemental analysis established the molecular formula as $C_{21}H_{19}NO$. The product is therefore formally derived from equimolar quantities of diphenyldichloromethane, pyridine and acetone. Prominent ions at *m/e* 258 $[M-CH_3CO]^+$, 224 $[M-C_6H_5]^+$, 167 $[(C_6H_5)_2CH]^+$ and 165 [fluorenyl]$^+$[3] were also observed in the mass spectrum.

The IR spectrum indicated the presence of an α,β-unsaturated ketone group (1690 and 1675 cm^{-1}) and both *cis*- (705 and 695 cm^{-1}) and *trans*- (965 cm^{-1}) double bonds in the molecule but no –NH absorption was observed. The UV spectrum exhibited intense absorption at 372 nm, indicative of a polyenone structure, while acidification induced a pronounced bathochromic shift to 424 nm, characteristic of a conjugated azomethine.[4]

The 100 MHz NMR spectrum was also consistent with a highly conjugated molecule, showing a single acetyl group signal at δ2.38 and a complex pattern due to sixteen protons, between δ6.1 and 7.8, which was not interpretable *a priori*. However, upon addition of a 0.44 mole ratio of Pr(fod)$_3$ shift reagent, six protons of this multiplet were displaced to higher field giving a first-order spectrum which could be interpreted as a triene fragment terminated at one end by the acetyl group and at the other by an azomethine function. Based on the reasonable assumption that the shift reagent should be co-ordinated with the CO group,[5] each proton of the triene system was identified by the decreasing magnitude of the upfield shift with increasing distance from the acetyl moiety and the coupling constants thus assigned for each proton. By the use of these values the complex pattern of the unshifted spectrum was interpretable and the remaining ten protons were assigned to the two phenyl groups which could be attached only to the azomethine group. The compound must therefore be the enamine Schiff base 1, the magnitude of the coupling constants (Table 1) indicating *cis, cis, trans* stereochemistry as shown. The ^{13}C NMR spectrum was in accord with the above structure, particularly significant signals occurring at 27.7 ($-CH_3$), 121.4 (C_3), 130.8 (C_8), 167.6 (C=N–) and 198.1 (C=O) ppm. The remaining ^{13}C signals are tentatively assigned as in Table 1.[6]



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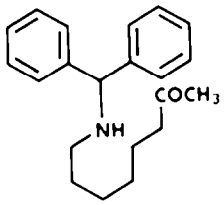

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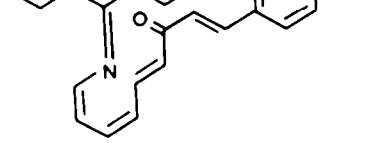

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Chemical evidence in favor of the enamine Schiff base structure 1 was obtained by catalytic hydrogenation over 10% Pd–C to give an octahydro derivative 2 as a colorless oil, which exhibited a one proton singlet at δ4.80 in the NMR spectrum, assignable to the $(C_6H_5)_2CH-N$

† Bradley *et al.*[1] reported the formation of considerable quantities of an uncharacterized oily by-product on reaction of diphenyldichloromethane with methyl gallate. This material is probably identical to the crystalline product now isolated and characterized.

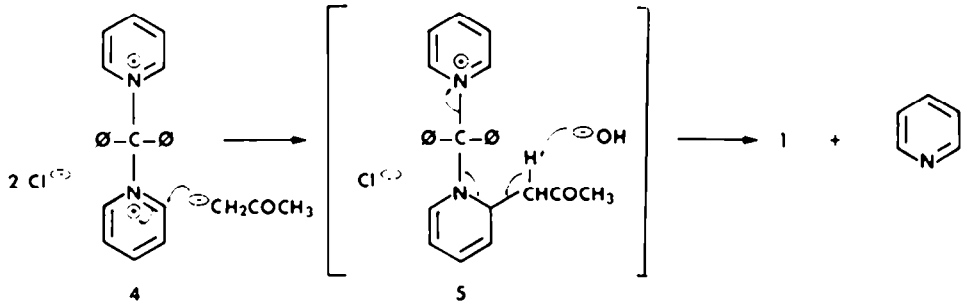
Table 1. ^1H and ^{13}C NMR data for 2-Azatetraenes 1 and 7

Position in Compound 1	δ^1H (J) ppm (Hz)[a]	δ^1H (J) ppm (Hz)[b]	$\delta^{13}C$ ppm[c]	Position in Compound 7	δ^1H (J) ppm (Hz)[a]
1	—	—	167.6	1	8.32
3	6.84 (8,1.5)	6.80 (8)	121.4	3	7.03 (7.5,1)
4	6.62 (12,8,1)	5.68 (12,8)	135.7	4	6.64 (12,7.5,1)
5	7.54 (12,11,1.5,1)	7.16 (12,12)	137.5	5	7.55 (12,11,1.5,1)
6	6.32 (11,11,1,1)	4.80 (12,11)	139.1	6	6.25 (11.5,11,1,1)
7	7.75 (15.5,11,1)	3.48 (16,11)	139.7	7	7.77 (15,11.5,1)
8	6.21 (15.5,1)	1.10 (16)	130.8	8	6.20 (15,1)
C = O	—	—	198.1	MeO-	3.88
CH_3-	2.38	0.59	27.7	CH_3-	2.30
C_6H_5-	7.1-7.9	7.1-7.8	126.9-133.4	2',6'-	7.87 (8.5)
				3',5'-	7.03 (8.5)

[a] In $(CO_3)_2$ CO [b] In Pr(fod)$_3$ /$CDCl_3$ [c] In $CDCl_3$, ppm from TMS

proton. Only the phenyl ring proton resonances occurred at lower field than this methine proton, the remaining signals appearing as double doublets at δ2.40 and 2.57 ($-CH_2$ groups adjacent to -NH and $\rangle C{=}O$), a singlet at δ2.08 ($-COCH_3$) and as an eight-proton multiplet at δ1.2–1.7.

Treatment of the reaction product 1 with anisaldehyde, in the presence of aqueous sodium hydroxide, gave an orange crystalline product, m.p. 122–123°, having λ_{max} 405 nm, indicative of increased conjugation due to formation of a *p*-methoxycinnamyl moiety. The NMR spectrum of this compound established its structure as the anisal derivative 3. However, reaction of the enamine Schiff base 1 with hydroxylamine hydrochloride did not give the expected product but rather a quantitative yield of benzophenone oxime. This must arise by acid-catalyzed cleavage of the Schiff base linkage followed by oximation of the benzophenone thus formed, or by direct transamination.



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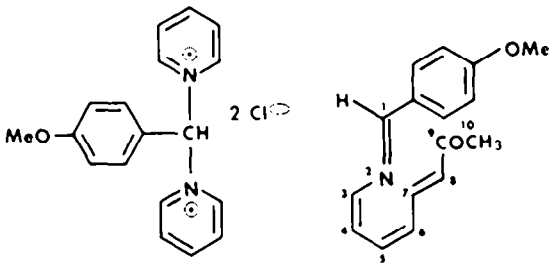
The reaction mechanism involved in the condensation of diphenyldichloromethane, pyridine and acetone is not readily apparent, although the N and C (3) to C (7) atoms of the product 1 must be generated through cleavage of the pyridine ring. However, in the only previous report of the isolation of a conjugated enamine Schiff base, Olofson and Zimmerman[7] postulated OH ion attack on a bisiminium cation to give the labile azatrienal $C_6H_5CH{=}N(CH{=}CH)_2CHO$. By analogy, formation of the considerably more stable azatetraenone 1 could occur by reaction of diphenyldichloromethane with two equivalents of pyridine to give the bispyridinium salt 4. Attack at the 2-position of one of the pyridinium rings by the carbanion generated from acetone in the presence of base would then give the intermediate monopyridinium salt 5. Subsequent abstraction of a proton from the acetonyl substituent, accompanied by cleavage of the dihydropyridine ring and expulsion of the remaining pyridinium ion as a neutral species[7,8] would produce the enamine Schiff base 1. The *cis, cis, trans* stereochemistry of the product is consistent with the postulated reaction mechanism, formation of the *trans* α,β-double bond proceeding through a less hindered planar transition state than for a *cis* α,β-double bond.[17] An alternative but less likely mechanism, in view of the good yield of azatetraene and the possibility of competitive Michael additions, might be cleavage to form an azatrienal which could then undergo aldol condensation with acetone.

In order for an enamine Schiff base to be formed by such a route the initial reaction product (e.g. 4) must be a bispyridinium salt which can only be produced from a dihalide. Since diphenylmethyl-*bis*-(pyridinium chloride) 4 could not be isolated in crystalline form, the condensation of *p*-anisal-*bis*-(pyridinium chloride)[9] 6 with acetone in the presence of base was carried out in order to investigate the mechanism and generality of the reaction.

A suspension of the bispyridinium salt **6** in acetone gave upon treatment with aqueous sodium hydroxide solution a yellow-orange, crystalline product, m.p. 108–110°. Analytical, chemical and spectral data established the structure of this compound as the *p*-anisal-2-azatetraene **7**, analogous to the diphenylmethyl-2-azatetraene **1**. Thus, the compound analyzed for $C_{16}H_{15}NO_2$ and showed prominent peaks in its mass spectrum *m/e* 255 $[M]^+$, 212 $[M-COCH_3]^+$ and 121 $[MeOC_6H_4CH_2]^+$. The IR spectrum exhibited absorption due to an α,β-unsaturated ketone group (1690 and 1673 cm^{-1}) and the UV spectrum showed intense absorption at 375 nm. The *cis, cis, trans* stereochemistry of the triene fragment of the azatetraene **7** was established from the coupling constants (Table 1) in the NMR spectrum, which was directly interpretable without recourse to the use of the shift reagent necessary to elucidate the structure of the corresponding diphenyl compound **1**. The azomethine proton gives rise to a singlet at δ8.32[7,10,11] and the molecule presumably possesses the highly favored[11,12] E-configuration about the C=N double bond as shown in structure **7**.



6 **7**

†Detailed X-ray data will be published elsewhere.

In a reaction analogous to that observed with enamine Schiff base **1**, treatment of the *p*-anisal compound **7** with hydroxylamine hydrochloride yielded β-anisaldoxime. On catalytic hydrogenation **7** gave an octahydroderivative as a colorless oil.

In view of the unique nature of the enamine Schiff bases resulting from the pyridine ring cleavage reaction, the diphenyl compound **1** was subjected to X-ray crystallographic analysis.† The structure was thereby established as 1,1-diphenyl-2-azadeca-1, 3*Z*, 5*Z*, 7*E*-tetraen-9-one and the conformation of the molecule, thermal motion of the atoms and numbering system are illustrated in the ORTEP[13] drawing (Fig. 1).

The double bonds in the conjugated chain of the molecule have a *Z*, *Z*, *E* configuration while both benzene rings are essentially planar within experimental error, the maximum deviation of the rings from their least-squares planes being 0.01 Å. The molecule is appreciably twisted, resulting in a dihedral angle between the benzene rings of 77.9°. The observed orientation appears to provide minimum intramolecular steric hindrance between the H atoms attached to C(12) and C(22) of the adjacent rings.

The atoms in the conjugated chain exhibit greater thermal motion with increasing distance from the benzene rings. This effect is particularly noticeable for the C atoms, as illustrated in Fig. 1 by the larger size of the thermal ellipsoids for C(9) and C(10) compared to C(1). The greater thermal motion of C(10) is presumably also due to Me torsion. One of the benzene rings in the molecule [C(11) to C(16)] appears to exhibit greater waggling motion than the other, a phenomenon for which there is no obvious explanation.

The average bond lengths and angles of the two benzene rings are in good agreement with the expected values of 1.39 Å and 120°. The bond lengths in the

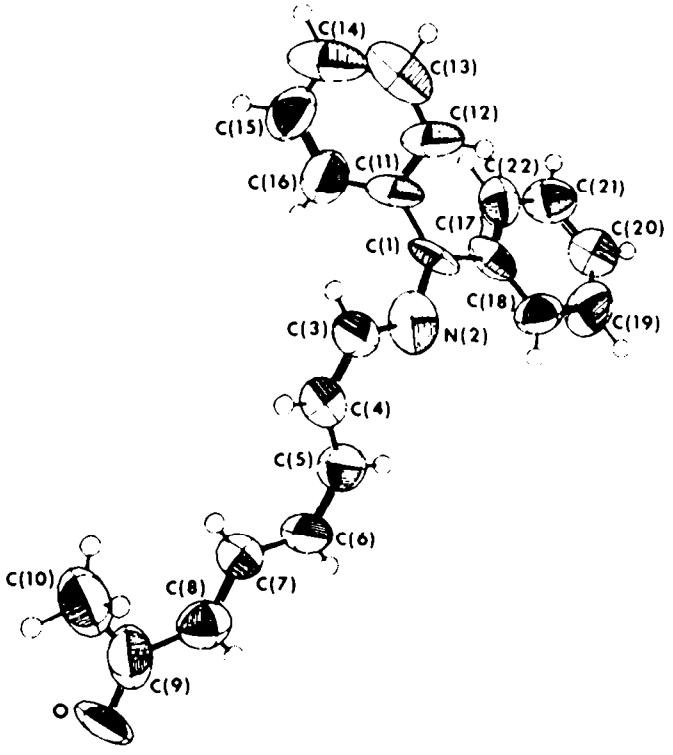


Fig. 1. ORTEP drawing of 1,1-Diphenyl-2-aza-1,3*Z*,5*Z*,7*E*-tetraen-9-one (**1**) showing conformation and thermal motion of the atoms.

ethylenic chain show that the single bonds are slightly shorter (1.465 Å) and the double bonds slightly longer (1.353 Å) than would be expected for a non-resonating $sp^2 - sp^2$ system[14] for which these values should be 1.479 and 1.338 Å respectively.

Although a number of synthetic routes of 2 - aza - butadienes have been developed,[2] with the exception of the labile 1 - phenyl - 2 - aza - 1,3,5 - trien - 6 - al prepared by Olofson *et al.*[7,9] additional 2-azapolyenes, such as the 2-azatetraenes (1 and 7) have not been reported. These novel types of enamine Schiff bases are quite stable at room temperature and therefore could prove useful as model compounds for studying the reactions of related compounds postulated as intermediates in a number of biochemical mechanisms.[16] In addition, the dual enamine—carbonyl functionality at opposite ends of the polyene system suggests that the 2-azapolyenones may be useful as synthetic intermediates for preparation of complex polyenes such as insect pheromones, particularly since *cis* double bonds are often difficult to prepare selectively. Expansion of the range of 2-azapolyene products by use of a variety of bis-pyridinium salts and nucleophiles should greatly enhance the utility of this reaction.

EXPERIMENTAL

M.ps are uncorrected. ^{1}H NMR spectra were determined on a modified Varian HA-100 and ^{13}C NMR spectra on a Jeolco PFT-1M instrument. Mass spectra were obtained with a CEC 110 double-focusing mass spectrometer at 70 eV. IR spectra were measured on a Perkin Elmer 237 B grating spectrophotometer and UV spectra on a Cary 15 spectrophotometer.

1,1-*Diphenyl*-2-*azadeca*-1,3*Z*,5*Z*,7*E*-*tetraen*-9-*one* (1). Diphenyldichloromethane (2.6 g) in dry acetone (50 ml) was added to pyridine (8.7 g) in dry acetone (50 ml) and the soln kept at room temp. overnight with exclusion of moisture. A soln of NaOH (4.4 g) in H_2O (50 ml) was added slowly and the resulting deep red soln stirred for 2 hr, then poured into H_2O (1000 ml). The red-brown ppt which slowly separated was filtered off without suction, washed thoroughly with H_2O and air-dried. Recrystallization from aq. acetone gave bright yellow needles, m.p. 124–125°, (2.3 g, 70%). (Found: C, 81.1; H, 6.26. Calc. for $C_{21}H_{19}NO$, 0.5 H_2O: C, 81.3; H, 6.45%. Found: m* *m/e* 301.1458. Calc. for $C_{21}H_{19}NO$: m* *m/e* 301.1466). MS: mass (rel. ab.): 301 (25.5), 258 (23.7), 180 (34.6), 167 (62.5), 165 (100), 104 (17.3), 77 (69.4), 43 (41.1). NMR spectra, (^{1}H and ^{13}C): see Table 1. UV spectrum: λ_{max}^{EtOH} nm (log ϵ), 228 (4.01), ~276 (3.78), 372 (4.58). $\lambda_{max}^{EtOH\ HClO_4}$ nm (log ϵ), 253 (4.35), 424 (4.40). IR spectrum (CCl_4): 1690, 1675, 1595, 1252, 965, 705, 695 cm^{-1}.

1,1-*Diphenyl*-2-*azadecan*-9-*one* (2). The azatetraene (1; 0.5 g) in THF (100 ml) was shaken with H_2 over 10% Pd–C at 45 psi for 3 hr. The catalyst was filtered off and the solvent evaporated under vacuum to give a colorless oil. (Found: m* *m/e* 309.2092. Calc. for $C_{21}H_{27}NO$: m* *m/e* 309.2093). MS: mass (rel. ab.): 309 (2.8), 252 (2.9), 232 (16.4), 168 (14.3) 167 (100), 165 (17.5) 152 (8.1), 43 (30.4). NMR spectrum ($CDCl_3$): 8H, m, δ1.16–1.70; 3H, s, δ2.11; 2H, dd, J = 7, 8 Hz, δ2.40; 2H, dd, J = 6, 6.5 Hz, δ2.57; 1H, s, δ4.81; 10H, m, δ7.12–7.46. IR spectrum (CCl_4): 3650, 2940, 2855, 1725, 1498, 1455, 1363, 1160, 1060, 705 cm^{-1}.

1,1 - *Diphenyl* - 11 - (4 - *methoxyphenyl*) - 2 - *azaundeca* - 1,3,5,7,10 - *pentaen* - 9 - *one* (3). A soln of 1 (1.0 g) and anisaldehyde (1.0 g) in EtOH (40 ml) was treated with 5% NaOH aq. (40 ml) and the mixture stored at room temp. for 4 hr. The soln was poured into H_2O (500 ml), the orange ppt filtered off, washed with H_2O and recrystallized from $CHCl_3$–MeOH, m.p. 122–123°, (1.1 g, 82%). (Found: C, 81.1; H, 5.94. Calc. for $C_{29}H_{25}NO_2$, 0.5 H_2O: C, 81.3; H, 6.24%). MS: mass (rel. ab.): 419 (45.4), 258 (23.7), 238 (20.2), 181 (20.6), 180 (47.2), 167 (100), 165 (55.2), 161 (63.0), 104 (24.2), 77 (41.5). NMR spectrum ($CDCl_3$): 3H, s, δ3.82; 1H, dd, J = 11, 11 Hz, δ6.31; 1H, dd, J = 8, 11 Hz, δ6.51; 1H, d, J = 15 Hz, δ6.57; 1H, d, J = 6 Hz, δ6.79, 1H, d, J = 16 Hz, δ6.84. 2H, d, J = 9 Hz, δ6.90 Hz; 12 H, m, δ7.1–7.9; 2H, d, J = 9 Hz, δ7.52; 1H, d, J = 16 Hz, δ6.65. UV spectrum: λ_{max}^{EtOH} nm (log ϵ), 248 (4.10), 405 (4.49).

Reaction of 1 *with hydroxylamine hydrochloride.* Compound 1 (0.25 g) in EtOH (10 ml) was treated with hydroxylamine hydrochloride (0.5 g) and NaOAc (0.5 g) in H_2O (10 ml). The bright yellow soln was warmed on a steam-bath for 1 hr and the resultant colorless soln poured into H_2O (100 ml). The white, crystalline product was filtered off, washed with H_2O and air dried, giving benzophenone oxime as white needles (0.15 g, 94%), m.p. and m.m.p. 143–144°. IR spectrum identical with known sample.

1 - (4 - *Methoxyphenyl*) - 2 - *azadeca* - 1*E*,3*Z*,5*Z*,7*E* - *tetraen* - 9 - *one* (7). *p*-Anisal-*bis*-(pyridinium chloride)[9] (3.4 g) in acetone (200 ml) was treated with NaOH (4.4 g) in H_2O (50 ml) added dropwise and the soln stirred at room temp. for 1 hr. The mixture was poured into H_2O (1000 ml), kept at 0° overnight and the yellow product filtered off without suction and washed with H_2O. Recrystallization from aq. acetone gave yellow plates, m.p. 108–110° (2.3 g, 92%). (Found: m* *m/e* 255.1253. Calc. for $C_{16}H_{17}NO_2$: m* *m/e* 255.1259). MS: mass (rel. ab.): 255 (28.8), 212 (42.6), 134 (14.8), 121 (100), 104 (21.6), 77 (36.0), 51 (16.4), 43 (19.8). NMR spectrum: see Table 1. UV spectrum: λ_{max}^{EtOH} nm (log ϵ), 243 (3.81), ~305 (3.81), 375 (4.63). IR spectrum (CCl_4): 1690, 1673, 1605, 1545, 1250, 1166, 965 cm^{-1}.

1-(4-*Methoxyphenyl*)-2-*azadecan*-9-*one*. The azatetraene (1.0 g) in THF (250 ml) was shaken with H_2 over 10% Pd–C at 50 psi for 4 hr. The catalyst was filtered off and the solvent evaporated under vacuum to give a colorless oil. (Found: m* *m/e* 263.1890. Calc. for $C_{16}H_{25}NO_2$: m* *m/e* 263.1885). MS: mass (rel. ab.): 263 (2.4), 206 (3.4), 150 (7.8), 142 (3.3), 136 (5.0), 121 (100), 78 (4.2), 43 (16.6). NMR spectrum ($CDCl_3$): 8H, m, δ1.10 – 1.74; 3H, s, δ2.12; 2H, dd, J = 6, 6.5 Hz, δ2.41; 2H, dd, J = 6.5, 7 Hz, δ2.61; 2H, s, δ3.72; 3H, s, δ3.79; 2H, d, J = 8 Hz, δ6.85; 2H, d, J = 8 Hz, δ7.22.

Reaction of 7 *with hydroxylamine hydrochloride.* Compound 7 (0.25 g) in EtOH (10 ml) on treatment with a soln of hydroxylamine hydrochloride (0.5 g) and NaOAc (0.5 g) in H_2O (10 ml) gave *β*-anisaldoxime (0.09 g), m.p. and m.m.p. 132–133°. IR spectrum identical with known sample.

Acknowledgements—The authors wish to express their thanks to Miss G. Secor and Dr. W. F. Haddon for elemental and mass spectral analyses, to Ms. M. Benson and Dr. D. L. Dreyer for NMR spectra and to Dr. K. L. Stevens for helpful discussions.

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