Synthesis of t-Butyl 2-(2-Methoxycarbonyl-1-methylethylidene)penam-3-carboxylates; Clavulanic Acid Analogues

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4-Acetonylthioazetidin-2-one (2) has been converted in three steps into t-butyl 2-acetylpenam-3-carboxylates (5) and (6). Wittig reaction on these produced t-butyl 2-(2-methoxycarbonyl-1-methylvinyl)penam-3-carboxylates (9) and (10), which were transformed by base catalysis into three racemic isomers [(11), (12), and (13)] of the title compound. Stereochemistry of the products was deduced by n.m.r. spectroscopy, including N.O.E. studies.

CLAVULANIC acid (1) is a microbial metabolite which has potent β-lactamase inhibitory properties.[1] Total syntheses of clavulanic acid and various analogues containing the alkylideneoxazolidine ring system have already been described.[2,3] In this paper, the synthesis of sulphur analogues containing the alkylidenethiazolidine ring is reported.

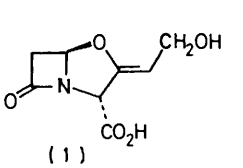
Key intermediates for this work were the 2-acetylpenams † (5) and (6), which contained a functionalized side-chain that appeared suitable for elaboration to the required structures. The corresponding 6-acylamino-2-acetylpenam-3-carboxylate had previously been prepared in these laboratories [4] and similar methodology has now been used to form the 6-unsubstituted system.

RESULTS AND DISCUSSION

The starting material was racemic 4-acetonylthioazetidin-2-one (2), which had originally been made by Bormann [5] from the versatile β-lactam synthon, 4-acetoxyazetidin-2-one. Condensation of (2) with t-butyl glyoxylate gave the α-hydroxy-ester (3) as a mixture of diastereoisomers, which was converted into the α-chloroester (4) using thionyl chloride and pyridine. Unpurified chloride (4) was treated with one equivalent of potassium t-butoxide at −20 to −10 °C to furnish a mixture of products, from which four pure compounds were isolated by a combination of column chromatography and crystallization. The 2-acetylpenams (5) and (6) were the main products, but *O*-alkylation gave some of the 4,7-system, (7) and intramolecular Darzens reaction led to a small amount of the epoxycepham (8).

The acetylpenam (5) was heated with methoxycarbonylmethylenetriphenylphosphorane to cleanly form the unsaturated ester (9). It had been hoped that under base catalysis an equilibrium would be set up, which contained at least some of the compound with an exocyclic double bond. In the event, when (9) was treated with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), the only material isolated was the 2-alkylidenepenam (11). The other 2-acetylpenam diastereoisomer (6) was likewise transformed into a diester (10). Treatment of the latter with DBU again resulted in complete migration of the double bond to the exocyclic position, but three different isomers were obtained. T.l.c. of the reaction indicated that the initial product was the (3*RS*, 5*RS*)-penam (12). However when the reaction was continued until all the (10) had disappeared, the two more thermodynamically stable (3*SR*, 5*RS*)-isomers (11) and (13) were also obtained.

Deconjugation of the double bond in (10) was also attempted by treatment with lithium *N*-isopropylcyclohexylamide at −78 °C followed by acidification. This gave recovered (10) plus the methylene compound (14), which was presumably produced through a chelation effect in the intermediate lithio-derivative.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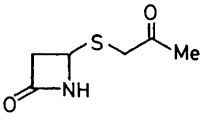
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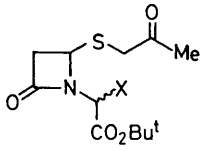
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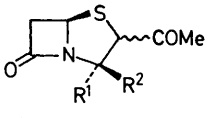
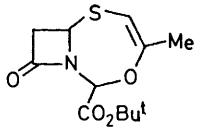
(4) X = Cl


(5) $R^1 = CO_2Bu^t, R^2 = H$
(6) $R^1 = H, R^2 = CO_2Bu^t$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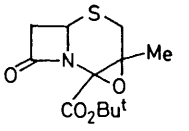
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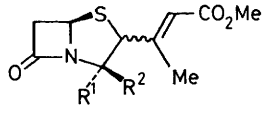
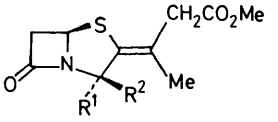
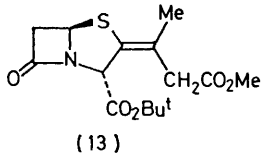

(9) $R^1 = CO_2Bu^t, R^2 = H$
(10) $R^1 = H, R^2 = CO_2Bu^t$


(11) $R^1 = CO_2Bu^t, R^2 = H$
(12) $R^1 = H, R^2 = CO_2Bu^t$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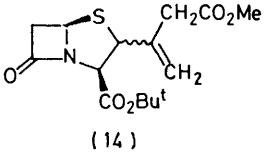
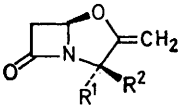

(14)

† The trivial penam numbering system is used in this paper.

Alkylidenepenams (11), (12), and (13) did not exhibit any appreciable activity as antibacterials or β-lactamase inhibitors.

Assignment of Stereochemistry of the Penams.—The n.m.r. spectra of 4,5-fused β-lactam systems normally show the C-3 proton in the ' natural ' series (H-3 and H-5 *trans*) at 0.5—1 p.p.m. to lower field of that in the corresponding ' unnatural ' series (H-3 and H-5 *cis*).[4,6] Thus the clavulanic acid analogue (15) has the C-3 proton at δ 5.00, whereas (16) has this proton at δ 4.43.[3] Alkylidenepenam isomers (11) and (13) both have the C-3 proton signal at δ 5.32, whilst for (12) it is at δ 4.47. Therefore (11) and (13) have the (3*SR*, 5*RS*)-stereochemistry, and (12) has the (3*RS*, 5*RS*)-stereochemistry.



(15) $R^1 = CO_2Me$, $R^2 = H$
(16) $R^1 = H$, $R^2 = CO_2Me$

The n.m.r. data on the intermediates (5), (6), (9), and (10) does not enable assignment of stereochemistries because the relative configurations of the C-2 and C-3 substituents will produce different shielding effects. However, (10) can be assigned the (3*RS*, 5*RS*)-configuration because on isomerization it gives the thermodynamically unfavourable isomer (12), as well as (11) and (13). The other Wittig product (9) is thought to be a (3*SR*, 5*RS*)-isomer because it only gives the ' natural ' product (11) on isomerization.

The problem of geometries about the double bonds in the final products, was solved by investigation of the Nuclear Overhauser Effect (N.O.E.) in these molecules.[7] Inspection of molecular models showed that the distance between the C-3 proton and the olefinic methyl group protons was about 2 Å in a (*Z*)-isomer and >4 Å in an (*E*)-isomer. Therefore one could only expect an appreciable N.O.E. in the (*Z*)-series. Irradiation of the methyl group of (13) at δ 1.81 gave no enhancement of the C-3 proton signal, whereas irradiation of the methyl group of (11) at δ 1.93 resulted in a 14% increase in the integral of the C-3 proton. Hence (11) is the (*Z*)-isomer and (13) the (*E*)-isomer. The effect was even more marked for the ' unnatural ' compound (12), which showed a 25% N.O.E. on the C-3 proton when the methyl group was irradiated at δ 1.84. Therefore although only a single ' unnatural ' isomer was available for study, the large N.O.E. enables (12) to be assigned the (*Z*)-geometry.

A curious feature of the n.m.r. spectrum of the (*E*)-isomer (13) was the temperature dependence of the C=C–CH_2–CO protons. The observed effect was opposite to that normally encountered, in that below −10 °C they appeared as a singlet at δ 3.28, but above 30 °C they produced an AB quartet with lines at δ 3.08, 3.25, 3.30 and 3.47 (90-MHz spectrum). The suggested explanation is that at low temperatures there is hindered rotation of the CH_2CO_2Me group due to proximity of the C-3 substituent and in this conformation the two protons happen to be in the same magnetic environment. At higher temperatures there is free rotation, but the CH_2 is prochiral and the protons become non-equivalent.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded for solutions in chloroform, on a Perkin-Elmer 157 spectrophotometer. ^1H N.m.r. spectra were obtained in $CDCl_3$ with tetramethylsilane as internal standard, using either a Varian EM 360 or a Perkin-Elmer R32 machine. The latter instrument, operating at 90 MHz, was used for N.O.E. and variable-temperature measurements using approximately 7% solutions which had been nitrogen-purged. Mass spectra were obtained with an AEI MS902 or a VG 7070 instrument. The purity of all compounds was tested by t.l.c. on Merck plastic sheets pre-coated with silica gel 60 F_{254} using mixtures of ethyl acetate and light petroleum. Preparative chromatography was carried out on columns of Merck silica gel 60 (finer than 230 mesh ASTM) using the slightly increased pressure provided by a Medcalf Hy-flo pump. When light petroleum is mentioned, it refers to the fraction of b.p. 60—80 °C.

4-*Acetonylthio*-1-[*hydroxy*-(*t-butoxycarbonyl*)*methyl*]-*azetidin*-2-*one* (3).—A solution of 4-acetonylthioazetidin-2-one [5] (1.00 g) and t-butyl glyoxylate (4.60 g) in dry benzene (25 ml) was heated at reflux under argon for 3 h with provision for the removal of water. The cooled product was washed with water (6 × 20 ml), dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel eluting with ethyl acetate–light petroleum (1 : 1) to give a mixture of the two diastereoisomers of the hydroxy-ester (3) as a colourless syrup (1.13 g), $\nu_{max.}$ 3 500, 2 980, 1 765, and 1 730 cm^{-1}; δ 1.49 (9 H, s, Bu^t), 2.26 (3 H, s, COMe), 2.90 (1 H, dd, *J* 16 and 3 Hz, 3-H), 3.41 (1 H, dd, *J* 16 and 5 Hz, 3-H), 3.49 and 3.57 (2 H, 2 × s, SCH_2CO), 4.50 (1 H, br s, exchangeable with D_2O, OH), 4.82 (1 H, dd, *J* 5 and 3 Hz, 4-H), and 5.22 and 5.32 (1 H, 2 × s after D_2O exchange, NCHO).

4-*Acetonylthio*-1-[*chloro*-(*t-butoxycarbonyl*)*methyl*]*azetidin*-2-*one* (4).—A solution of the hydroxy-ester (3) (1.00 g) in a mixture of dry tetrahydrofuran (10 ml) and dioxan (10 ml) was stirred under argon and cooled to −15 °C. It was treated with 2,6-lutidine (0.60 ml) followed by thionyl chloride (0.38 ml). After a period of 3 h the mixture was filtered and the filtrate concentrated. Extraction of the residue with toluene and re-concentration gave the crude α-chloro-ester (4) as a gum (1.02 g); $\nu_{max.}$ 2 960, 1 775, and 1 740 cm^{-1}. This crude material was used in the next stage without further purification.

Cyclization of the Chloride (4).—The crude α-chloro-ester (4) (4.00 g) was dissolved in dry tetrahydrofuran (80 ml) and cooled to −20 °C in an atmosphere of argon. It was treated over a period of 5 min with a 0.98M solution of potassium t-butoxide in t-butanol (13.2 ml) and then allowed to warm to −10 °C. It was stirred at this temperature for 1.5 h and then concentrated. The residue was partitioned between ethyl acetate and brine, and the organic phase was separated, dried (Na_2SO_4), and concentrated to a brown gum (3.05 g). The t.l.c. of this showed four spots and thus four fractions were obtained by chromatography on silica gel (80 g) eluting with ethyl acetate–light petroleum mixtures (1 : 4 grading to 2 : 3). Concentration of the first fraction gave a single isomer of *t-butyl* 4-*methyl*-9-*oxo*-1-*aza*-3-*oxa*-6-*thiabicyclo*[5.2.0]*non*-4-*ene*-2-*carboxylate* (7) (0.17

g) as a colourless gum; $\nu_{max.}$ 2 960, 1 775, 1 750, and 1 615 cm^{-1}; δ 1.50 (9 H, s, Bu^t), 1.90 (3 H, br s, Me), 2.90 (1 H, dd, *J* 15 and 2 Hz, 8-H), 3.45 (1 H, dd, *J* 15 and 5 Hz, 8-H), 4.79 (1 H, dd, *J* 5 and 2 Hz, 7-H), 5.45 (1 H, br s, becoming sharp on irradiation at δ 1.90, 5-H), and 5.69 (1 H, s, 2-H) (Found: M^+, 271.087 8. $C_{12}H_{17}NO_4$ requires *M*, 271.087 8). The second fraction provided a single diastereoisomer of *t-butyl* (3RS, 5RS)-2-*acetylpenam*-3-*carboxylate* (6) also as a gum (0.75 g); $\nu_{max.}$ 2 960, 1 780, and 1 725 cm^{-1}; δ 1.50 (9 H, s, Bu^t), 2.29 (3 H, s, COMe), 2.98 (1 H, dd, *J* 16 and 2 Hz, 6-H), 3.45 (1 H, dd, *J* 16 and 4 Hz, 6-H), 4.21 (1 H, d, *J* 5 Hz, 2-H or 3-H), 4.64 (1 H, d, *J* 5 Hz, 2-H or 3-H), and 4.94 (1 H, dd, *J* 4 and 2 Hz, 5-H) [Found: M^+, 271 (very small); $M^+ - C_4H_8$, 215.025 5. $C_8H_9NO_4S$ requires 215.025 2]. The third fraction (0.38 g) contained mixed products, but crystallization from ethyl acetate–light petroleum gave a pure isomer of *t-butyl* (3SR, 5RS)-2-*acetylpenam*-3-*carboxylate* (5) (0.20 g), m.p. 102—106 °C; $\nu_{max.}$ 2 950, 1 785, 1 740, and 1 720 cm^{-1}; δ 1.48 (9 H, s, Bu^t), 2.29 (3 H, s, COMe), 3.02 (1 H, dd, *J* 16 and 2 Hz, 6-H), 3.51 (1 H, dd, *J* 16 and 4 Hz, 6-H), 4.54 (1 H, d, *J* 2 Hz, 2-H or 3-H), 5.19 (1 H, dd, *J* 4 and 2 Hz, 5-H), and 5.29 (1 H, d, *J* 2 Hz, 2-H or 3-H) (Found: C, 53.1; H, 6.3; N, 5.2; S, 11.7%; M^+, 271.087 8. $C_{12}H_{17}NO_4S$ requires C, 53.1; H, 6.3; N, 5.2; S, 11.8%; *M*, 271.087 8). The mother-liquors from the above crystallization were concentrated and a further crystallization from ethyl acetate–light petroleum gave *t-butyl* 3,4-*epoxy*-3-*methylcepham*-4-*carboxylate* (8) (0.05 g) as fine needles, m.p. 154—155 °C; $\nu_{max.}$ 2 960, 2 920, 1 780, and 1 740 cm^{-1}; δ 1.49 (12 H, s, Bu^t and Me), 2.86 (1 H, dd, *J* 15 and 2 Hz, 7-H), 2.99 and 3.26 (2 H, AB q, *J* 15 Hz, SCH_2), 3.37 (1 H, dd, *J* 15 and 4 Hz, 7-H), and 4.37 (1 H, dd, *J* 4 and 2 Hz, 6-H) (Found: M^+, 271.087 6. $C_{12}H_{17}NO_4S$ requires *M* 271.087 8). The fourth fraction (0.31 g) was a mixture of β-lactam-containing compounds from which none was obtained pure.

t-Butyl (3SR, 5RS)-(E)-2-(2-*Methoxycarbonyl*-1-*methylvinyl*)*penam*-3-*carboxylate* (9).—The 2-acetylpenam (5) (0.100 g) and methoxycarbonylmethylenetriphenylphosphorane (0.246 g) were dissolved in dry benzene (10 ml) and heated at reflux under argon for 48 h. The resulting yellow solution was concentrated and then chromatographed on silica gel [ethyl acetate–light petroleum (3 : 7)] to give the *diester* (9) as a colourless gum (0.100 g); $\nu_{max.}$ 2 970, 1 785, 1 740, 1 725, and 1 650 cm^{-1}; δ 1.47 (9 H, s, Bu^t), 2.23 (3 H, s, C=C–Me), 3.08 (1 H, dd, *J* 16 and 1.5 Hz, 6-H), 3.57 (1 H, dd, *J* 16 and 4.5 Hz, 6-H), 3.68 (3 H, s, OMe), 4.58 (1 H, d, *J* 4.5 Hz, 2-H or 3-H), 4.66 (1 H, d, *J* 4.5 Hz, 2-H or 3-H), 5.19 (1 H, dd, *J* 4.5 and 1.5 Hz, 5-H), and 6.03 (1 H, br s, becoming sharp on irradiation at δ 2.23, C=CHCO) (Found: M^+, 327.116 0. $C_{15}H_{21}NO_5S$ requires *M*, 327.114 0).

t-Butyl(3RS, 5RS)-(E)2-(2-*Methoxycarbonyl*-1-*methylvinyl*)-*penam*-3-*carboxylate* (10).—The other 2-acetylpenam (6) (0.400 g) and methoxycarbonylmethylenetriphenylphosphorane (1.600 g) were heated together in benzene (40 ml) as above for 24 h. Chromatography gave the *diester* (10) as a crystalline solid (0.315 g), m.p. 127—128 °C (from ethyl acetate–light petroleum); $\nu_{max.}$ 2 940, 1 780, 1 730, 1 715, and 1 645 cm^{-1}; δ 1.49 (9 H, s, Bu^t), 2.18 (3 H, d, *J* 1 Hz, C=C–Me), 3.00 (1 H, dd, *J* 16 and 2 Hz, 6-H), 3.52 (1 H, dd, *J* 16 and 4 Hz, 6-H), 3.65 (3 H, s, OMe), 3.74 (1 H, d, *J* 7 Hz, 2-H or 3-H), 4.66 (1 H, d, *J* 7 Hz, 2-H or 3-H), 5.10 (1 H, dd, *J* 4 and 2 Hz, 5-H), and 6.03 (1 H, d, *J* 1 Hz, C=CH–CO) (Found: C, 54.7; H, 6.3; N, 4.2; S, 9.9%. $C_{15}H_{21}NO_5S$ requires C, 55.0; H, 6.5; N, 4.3; S, 9.8%).

t-Butyl (3SR, 5RS)-(Z)-2-(2-*methoxycarbonyl*-1-*methylethylidene*)*penam*-3-*carboxylate* (11).—A solution of the diester (9) (0.048 g) in dry benzene (3 ml) was treated with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) (0.010 g) and stirred at room temperature under argon for 3.5 h. The solution was concentrated and then chromatographed on silica gel [ethyl acetate–light petroleum (3 : 7)] to give the 2-*alkylidenepenam* (11) as colourless needles (0.023 g), m.p. 76—78 °C (from ethyl acetate–light petroleum); $\nu_{max.}$ 2 950, 1 780, 1 735, and 1 655 cm^{-1}; δ 1.45 (9 H, s, Bu^t), 1.93 (3 H, s, C=C–Me), 3.08 (2 H, s, C=C–CH_2), 3.09 (1 H, dd, *J* 16 and 1.5 Hz, 6-H), 3.63 (1 H, dd, *J* 16 and 4 Hz, 6-H), 3.65 (3 H, s, OMe), 5.32 (1 H, s, 3-H), and 5.37 (1 H, dd, *J* 4 and 1.5 Hz, 5-H) (Found: C, 55.1; H, 6.5; N, 4.4%; M^+, 327.114 1. $C_{15}H_{21}NO_5S$ requires C, 55.0; H, 6.5; N, 4.3%; *M*, 327.114 0).

Isomerization of the Diester (10).—A solution of the diester (10) (0.200 g) in dry benzene (10 ml) was treated with DBU (0.040 g). After 3 h at 22 °C the product was chromatographed on silica gel [ethyl acetate–light petroleum (1 : 4)] to give three compounds. The least polar was *t-butyl* (3SR, 5RS)-(E)-2-(2-*methoxycarbonyl*-1-*methylethylidene*)-*penam*-3-*carboxylate* (13), which was obtained as a gum (0.060 g); $\nu_{max.}$ 2 950, 1 780, 1 735 and 1 650 cm^{-1}; δ (at 30 °C) 1.44 (9 H, s, Bu^t), 1.81 (3 H, s, C=C-Me), 3.09 (1 H, dd, *J* 16 and 1.5 Hz, 6-H), 3.16 and 3.38 (2 H, ABq, *J* 15 Hz, C=C–CH_2), 3.63 (1 H, dd, *J* 16 and 4 Hz, 6-H), 3.65 (3 H, s, OMe), 5.32 (1 H, s, 3-H), and 5.34 (1 H, dd, *J* 4 and 1.5 Hz, 5-H) (Found: M^+, 327.114 1. $C_{15}H_{21}NO_5S$ requires *M*, 327.114 0). The next compound was the corresponding (*Z*)-isomer (11) (0.044 g) and the most polar product was *t-butyl* (3RS, 5RS)-(Z)-2-(2-*methoxycarbonyl*-1-*methylethylidene*)*penam*-3-*carboxylate* (12) which was a colourless gum (0.080 g); $\nu_{max.}$ 2 950, 1 780, and 1 735 cm^{-1}; δ 1.47 (9 H, s, Bu^t), 1.84 (3 H, s, C=C–Me), 3.12 (1 H, dd, *J* 15 and 2 Hz, 6-H), 3.20 (2 H, s, C=C–CH_2), 3.39 (1 H; ddd, *J* 15, 4 and 1.5 Hz, becoming a dd, *J*, 15 and 4 Hz on irradiation at δ 4.47; 6-H), 3.64 (3 H, s, OMe), 4.47 (1 H, br s, 3-H), and 4.95 (1 H, dd, *J* 4 and 2 Hz, 5-H) (Found: M^+, 327.114 1. $C_{15}H_{21}NO_5S$ requires *M*, 327.114 0).

t-Butyl (3RS, 5RS)-2-[1-(*Methoxycarbonylmethyl*)*vinyl*]-*penam*-3-*carboxylate* (14).—A solution of *N*-isopropylcyclohexylamine (0.024 g) in dry tetrahydrofuran (3 ml) was stirred under argon at −78 °C and treated with 2.4M n-butyl-lithium solution (0.08 ml). After 10 min the azetidinone (10) (0.050 g) in tetrahydrofuran (1 ml) was added to give a dark green solution. The anion was quenched after 10 min by addition of acetic acid (0.020 g). The reaction mixture was allowed to warm to room temperature and the solvent removed. The residue was partitioned between ethyl acetate and water; the organic phase was separated, washed with brine, dried (Na_2SO_4), and concentrated. Chromatography on silica gel [ethyl acetate–light petroleum (1 : 4)] gave firstly recovered starting material (10) (0.020 g) and then the *methylene compound* (14) as colourless needles (0.010 g), m.p. 93—95 °C (from ethyl acetate–light petroleum); $\nu_{max.}$ 2 960, 1 780, 1 735, and 1 645 cm^{-1}; δ 1.51 (9 H, s, Bu^t) 3.03 (1 H, dd, *J* 16 and 2 Hz, 6-H), 3.18 (2 H, s, side-chain CH_2CO), 3.47 (1 H, dd, *J* 16 and 4 Hz, 6-H), 3.67 (3 H, s, OMe), 3.78 (1 H, d, *J* 8 Hz, 2-H or 3-H), 4.76 (1 H, d, *J* 8 Hz, 2-H or 3-H), 5.00 (1 H, dd, *J* 4 and 2 Hz, 5-H), and 4.82 and 4.68 (2 H, 2 × s, $C=CH_2$) (Found: M^+, 327.114 4. $C_{15}H_{21}NO_5S$ requires *M*, 327.114 0).

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REFERENCES

[1] T. T. Howarth, A. G. Brown, and T. J. King, *J.C.S. Chem. Comm.*, **1976**, 266.
[2] P. H. Bentley, P. D. Berry, G. Brooks, M. L. Gilpin, E. Hunt, and I. I. Zomaya, *J.C.S. Chem. Comm.*, **1977**, 748; P. H. Bentley, G. Brooks, M. L. Gilpin, and E. Hunt, *ibid.*, pp. 905 and 906; P. H. Bentley and E. Hunt, *ibid.*, **1978**, 439.
[3] P. H. Bentley and E. Hunt, *J.C.S. Chem. Comm.*, **1978**, 518.
[4] E. G. Brain, A. J. Eglington, J. H. C. Nayler, N. F. Osborne, R. Southgate, and P. Tolliday, *J.C.S. Perkin I*, **1977**, 249.
[5] D. Bormann, *Annalen*, **1974**, 1391.
[6] A. G. Brown, D. F. Corbett, and T. T. Howarth, *J.C.S. Chem. Comm.*, **1977**, 359.
[7] J. H. Noggle and R. E. Schirmer, ' The Nuclear Overhauser Effect,' Academic Press, New York and London, **1971**.