Phytochemistry, Vol. 27, No. 7, pp. 2083 2087, 1988.
Printed in Great Britain.

0031-9422/88 $3.00+0.00

CORIANDRIN, A NOVEL HIGHLY PHOTOACTIVE COMPOUND ISOLATED FROM *CORIANDRUM SATIVUM*

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(*Received* 21 *September* 1987)

Key Word Index—*Coriandrum sativum*; Umbelliferae; photoactive constituents; furocoumarins; furoisocoumarins; coriandrin; dihydrocoriandrin; chemotaxonomy.

Abstract—Extracts of *Coriandrum sativum* L. were analysed for photoactive constituents using HPLC analysis and photobiological assay. Two new photoactive furoisocoumarins, named coriandrin and dihydrocoriandrin, were isolated, and their structures determined by ^1H and ^{13}C NMR and X-ray crystallography.

INTRODUCTION

Coriander, *Coriandrum sativum* L., is an umbelliferous, aromatic annual plant, native to the eastern Mediterranean. The name coriander derives from the ancient Greek word for bedbug, for if the fruit is bruised in the unripe state, it gives off a penetrating, nauseating bug-like odour. When the fruit ripens, this unpleasant smell disappears. Coriander is cultivated mainly for the fruits which are globular, very aromatic, with a bittersweet, spicy taste. They are highly esteemed as a general seasoning agent and finely ground coriander fruits are a major ingredient of curry powder. A liqueur is made in France with coriander flavour and sugar coated fruits were once a popular candy in Scotland. Internally, in the form of an infusion, coriander is useful as a carminative and in the treatment of intestinal disorders. It also has antispasmodic and expectorant properties. Externally, it is used in ointment for the treatment of rheumatism and arthritis. The distilled oil, which may constitute as much as 1% of the fruit, is used in the food industry, pharmaceutics, and perfumery.

Fresh coriander leaves, also known as cilantro or Chinese parsley, are also very popular in Chinese, Indian and Mexican cuisine. Only young plants with ternate-pinnate leaves, not yet divided into narrow linear segments, are used. Leaves have a heavy odour and are used in soups, chutneys, for flavouring curries and wine. In North America, until recently, cilantro was available only in special Chinese and Indian stores. However, because of the recent trend in promoting new exotic food plants, cilantro is now sold in many big supermarkets.

During our search for photoactive constituents in umbelliferous food plants, we isolated two new photoactive compounds from coriander leaves. This paper reports on the isolation and identification of these new compounds.

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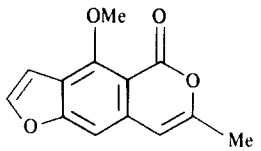
RESULTS AND DISCUSSION

Young coriander plants were analysed for photoactive constituents using our sensitive bioassay [1]. The plants in this stage have *ca* 5–10 ternate-pinnate leaves, and feathery leaves typical of the mature plants are only just starting to develop. The leaves have a very strong odour which some people find disagreeable. Our analysis revealed the presence of several photoactive compounds in all parts of the young coriander plants, and TLC and HPLC analysis confirmed that none of these substances are the furocoumarins commonly associated with umbelliferous plants. The major photoactive compound was eventually isolated in sufficient quantity for complete identification. A second compound, present in much lesser quantity, was also isolated. The amount obtained allowed only for the determination of the mass spectrum and ^1H NMR spectrum, but this was satisfactory for the assignment of a structure. The other photoactive compounds were present in concentrations insufficient for further analysis.

The major component was shown to be present in moderate concentrations in all parts of the plant. Using HPLC analysis, we determined its concentration in leaves as 45.20 μg/g wet weight, and in petioles as 19.26 μg/g weight. The amount of this compound was higher in roots than in leaves, but accurate quantification was difficult because of other interfering substances. It exhibited a parent peak in the mass spectrum at m/z 230, suggesting a molecular formula of $C_{13}H_{10}O_4$. Clearly evident in the ^1H NMR spectrum were a methoxy group (4.20 ppm), an aromatic methyl coupled to a single olefinic proton [2.25 (3H) and 6.28 ppm (1H, $J = 0.8$ Hz], and three aromatic protons [7.56, 7.05, 7.01 ppm] which are intercoupled and suggestive of a benzofuran in which the furan ring is unsubstituted and adjacent to a single proton (coupling through oxygen to H-2 of the furan, $J = 0.8$ Hz [2]). The data were suggestive of a furobenzopyrone, but did not permit of an unambiguous structure assignment.

The structure of the major constituent, hereafter called coriandrin, was therefore identified by X-ray crystallo-



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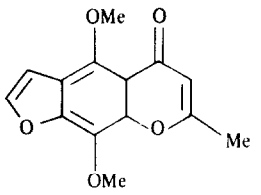

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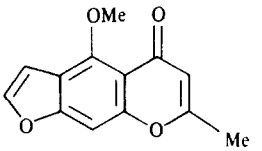

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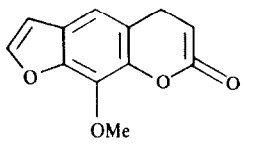

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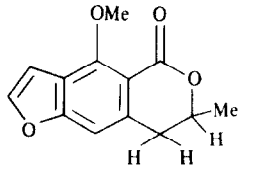

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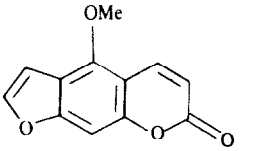

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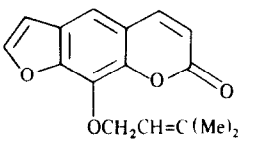

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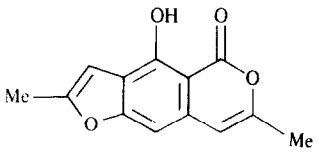

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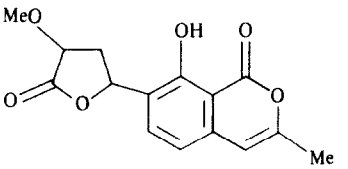

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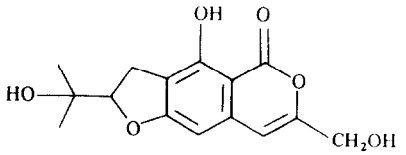

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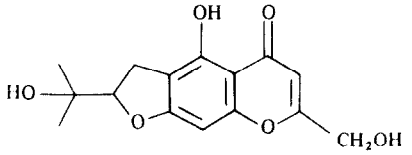

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graphy as 4-methoxy-7-methyl-5H-furo[2,3-*g*] [2]benzopyran-5-one (**1**). Figure 1 is an ORTEP drawing of this compound, giving the atomic labelling scheme and a display of the thermal motion ellipsoids scaled to enclose 50% probability. Interatomic distances are shown on the Figure, and confirm that the central ring is aromatic with a mean bond length of 1.396 Å. The double bonds in the furan and pyrone rings are similar in length, as are the four C–O single bonds therein. Bond lengths and angles are similar to those found in furobenzopyrones (e.g. khellin, **2** [3]) but the peri- substituent effect [as seen between the pyrone carbonyl (C1–O12) and the aromatic methoxyl (C9–O10) is pronounced. Bond angles are distorted, with the very short carbonyl bond being displaced outwards, away from the central ring (C9A–C1–O12 angle of 127.7° vs the O2–C1–O12 angle of 115.2°), and the methoxyl group displaced in the opposite fashion away from the carbonyl (C9A–C9–O10 angle of 125.2° vs C8A–C9–O10 angle of 116.9°).

Based upon this structure, the NMR spectra can thus be assigned as follows. In the ^{1}H NMR spectrum, the H-8 proton is coupled only to the C-7 methyl (0.8 Hz, confirmed by decoupling); H-9 appears at 7.05 ppm, long-range coupled to H-2 (0.8 Hz), with H-2 (7.56 ppm)

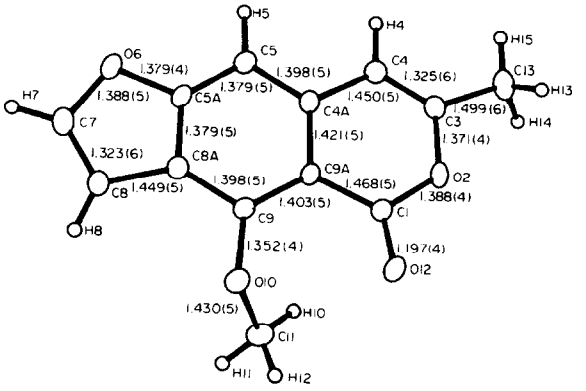

Fig. 1. ORTEP drawing of coriandrin, giving the atomic labelling scheme and a display of the thermal motion ellipsoids scaled to enclose 50% probability. Interatomic distances are shown in Å, with estimated standard deviations in parentheses.

and H-3 (7.01 ppm) exhibiting typical furan coupling (2.4 Hz). To assign the ^{13}C NMR spectrum, a *J*-modulation experiment was conducted to distinguish the signals for quaternary carbons from methine and methyl carbons, and the aromatic CH's assigned from a ^{13}C–^{1}H chemical shift correlation experiment. Assignment of the quaternary carbons is made by a 2D experiment in which the parameters are optimized for three bond $^{3}J_{C-H}$ coupling (Table 1); all atoms are positively assigned, with the exception of those resonating at 159.9 and 159.7 ppm which are too close for absolute identification. The assignment given (see Experimental) is based on a comparison with literature data [4–7].

Coriandrin is structurally similar to the furochromone visnagin (**3**). Visnagin and khellin have been previously studied for photoactivity, and the bioassay detection limit for visnagin reported at 10–20 μg using the fungus *Penicillium expansum* as a test organism [8]. Visnagin was also found to have weak photomutagenic potency [9]. Phototoxicity and genotoxicity of visnagin and khellin were studied by Abeysekera *et al.* [10], who concluded that the behaviour of these furochromones resembles that of the structurally related furocoumarins. Visnagin was phototoxic to a variety of microorganisms, although less so than the furocoumarin 8-MOP (8-methoxypsoralen, **4**). It was also found to be genotoxic but again less than 8-MOP. Visnagin and its structural analogues were studied intensively for their spasmolytic and vasodilating activities, and were recently found to have a capacity to affect the relative levels of high density and low density lipoprotein in the serum of Japanese quail [11].

The minor component exhibited a mass two units higher ($C_{13}H_{12}O_4$) than coriandrin, and was identified as the 7,8-dihydro derivative from the ^{1}H NMR spectrum. The signals due to the benzofuran portion of the molecule were basically unchanged, indicating that any alteration in the structure had occurred in the pyrone ring. The clean signals due to the C-7 methyl doublet and H-8 quartet had been replaced with a complex coupled system consisting of a geminally coupled, magnetically inequivalent methylene group (2.99 and 2.93 ppm, J_{gem} = 16.0 Hz), each proton of which is coupled to an adjacent methine (4.55 ppm, J = 11.8 and 2.0 Hz) which is itself further coupled to the methyl (1.48 ppm, J = 6.2 Hz). This compound is thus a furodihydroisocoumarin [12], identified as 7,8-dihydro-4-methoxy-7-methyl-5H-furo-[2,3-*g*] [2]benzopyran-5-one, **5** (dihydrocoriandrin).

Using our sensitive bioassay [1], the photoactivity of the new compound coriandrin was determined. The detection limit was 5×10^{-9} g/spot, only about 5 × less active than 8-MOP. Dihydrocoriandrin was much less active. For comparison, visnagin in this bioassay had a detection limit of 5×10^{-8} g/spot. Under certain conditions however, photoactivity of coriandrin may actually be higher than the photoactivity of 8-MOP, since the UV spectrum of coriandrin has a prominent peak at 340 nm,

Table 1. Chemical shift correlations obtained from long range coupling 2D experiment

	Frequency F2			Frequency F1			
	Col	[Hz]	[ppm]	Row	[Hz]	[ppm]	Intensity
1	271	12061.898	159.8266	1 87	2272.359	7.5713	1.206
				2 173	2104.648	7.0125	.410
2	299	11879.606	157.4112	1 607	1257.561	4.1901	4.753
3	347	11567.106	153.2704	1 302	1852.700	6.1730	.265
				2 911	663.848	2.2119	10.008
4	443	10942.106	144.9888	1 83	2280.660	7.5989	.279
				2 172	2106.730	7.0194	5.759
5	638	9672.575	128.1668	1 420	1622.600	5.4063	.173
6	745	8975.960	118.9363	1 88	2269.946	7.5632	.943
				2 165	2120.647	7.0658	.213
7	886	8057.991	106.7727	1 166	2118.159	7.0575	1.504
				2 302	1853.520	6.1757	.786
8	898	7979.866	105.7375	1 88	2270.750	7.5659	1.820
9	921	7830.127	103.7534	1 168	2113.352	7.0415	.525
				2 301	1855.244	6.1815	1.173
				3 910	664.789	2.2150	3.846
10	947	7660.856	101.5105	1 167	2116.115	7.0507	2.066
				2 300	1856.979	6.1872	.526

while 8-MOP has no peaks at wavelengths longer than 300 nm. Other biological properties will be investigated further when larger quantities of coriandrin are available from synthesis.

Coriander is known to cause allergic symptoms, although only in a small proportion of the population. Suhonen *et al.* [13] described a patient with rhinitis and throat irritation as an allergic reaction to powdered coriander. Positive skin test reactions to powdered coriander [14] and to oil of coriander [15] were also reported. Oil of coriander is considered to be an allergen, and has therefore been removed from certain brand-name cosmetics [16]. The main volatile constituent of coriander oil is linalool [17], which is considered to be an allergen, capable of provoking contact dermatitis [18]. Coriander fruits were also found to contain a furocoumarin bergapten (5-MOP) [19]. We have also found small amounts of 5-MOP **6**, 8-MOP **4**, and another photoactive compound, most likely imperatorin **7**, in coriander fruits. Also detected were two other unknown photoactive compounds [20]. No allergic reactions to fresh coriander leaves have been reported so far.

The isolation of a new benzopyran from young coriander plants opens the question about its taxonomic significance. The genus *Coriandrum*, represented by two species, namely *C. sativum* L. and *C. melphitense* Ten. & Guss., belongs to the tribe Coriandreae, of the subfamily Apioideae of the Umbelliferae. The tribe Coriandreae has six genera, each genus of which is represented by one or two species, with the exception of the genus *Schrenkia* which has seven species [21]. Besides coriander, two species of *Bifora* were investigated for phenolics, and furocoumarins were found in the fruits of both species [22]. The chemical character of the tribe Coriandreae is otherwise unknown.

Coriandrin and dihydrocoriandrin are the first examples of the 5H-furo[2,3-*g*][2]benzopyran ring system to be identified from natural sources, although numerous examples of natural benzofurans [23] and [2]benzopyrones (isocoumarins) [23] are known. One other 5H-furo[2,3-*g*][2]benzopyran, pyrocanescin (**8**), has been reported [24] as the pyrolysis product of the fungal metabolite canescin (**9**). A report [25] identifying angelicain (**10**) as a member of this family has subsequently [26] been corrected (**11**).

EXPERIMENTAL

Furochromone standard. Visnagin was purchased from Aldrich Chemical Co.

Plant material. Young cilantro plants were purchased from local vegetable stands. For HPLC quantification, leaves, petioles, and roots were analysed separately. Samples of known weight were coarsely chopped and extracted several times with EtOAc. Combined extracts (300 ml) were evapd under red. pressure. The residue was dissolved in an appropriate amount of EtOAc, filtered through 0.5 μm millipore AP2001000 filter and directly analysed by HPLC and TLC.

HPLC and TLC. A Varian 500 HPLC system equipped with a Rheodyne 7125 loop injector was used with detection by UV at 286 nm. A Varian MCH-10 (4 mm × 30 cm) column was employed, with 35% acetonitrile in H_2O as solvent and a flow rate of 2 ml/min. A coriandrin standard, dissolved in $CHCl_3$, was used at a concn of 10 μg/ml. For TLC analysis, Merck precoated silica gel K60 sheets (without fluorescent indicator) were used, and two-dimensional chromatograms were developed, the first elution being conducted with $CHCl_3$, the second with hexane–pentane–EtOAc (7:7:6). Visualization was performed with UV 250–300 nm light.

Photobiological assay. This photobiological assay has been described previously [1]. The DNA repair deficient mutant, *Escherichia coli* B_s-1 (*rec*$^+$,*exr*$^-$,*hrc*$^-$), which is extremely sensitive to ultraviolet radiation and to chemical alkylating agents [27], was used as a test microorganism.

Isolation. Young cilantro plants were trimmed of roots and coarsely chopped. The plant material (4.8 kg) was extracted twice with a total of 16 l of EtOAc over a period of 72 hr. The organic extract was reduced *in vacuo* to give a thick green gum which was dissolved in a small volume of MeOH and chromatographed on a 2.5 cm × 40 cm open column packed with silicic acid. The eluent was hexane–Et_2O (1:1). Fractions (20 ml) were monitored by TLC and photobiological assay. Frs 11–13 contained coriandrin, frs 14–16 contained dihydrocoriandrin. The final purification was done by semi-prep. HPLC using an MCH-10 column (8 mm × 50 cm), eluting with 50% acetonitrile in H_2O using UV detection at 286 nm. The yield was *ca* 20 mg coriandrin and 1 mg dihydrocoriandrin.

Characterization. Coriandrin was obtained as colourless needles (MeOH), mp 142–143°; ν_{max}^{KBr} cm^{-1}: 1718 (C=O), 1660 (arom), 1602 (arom), 1565 (arom), 1329 (MeO), 1105 (furan), 1086 (furan), 1050 (furan), 830 (furan), and 767 (furan); λ_{max}^{MeOH} nm (log ε): 286 (1.03), 298 (1.30) and 340 (0.38); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.56 (1H, *d*, *J* = 2.4 Hz, H-2), 7.05 (1H, *d*, *J* = 0.8 Hz, H-9), 7.01 (1H, *dd*, *J* = 2.4, 0.8 Hz, H-3), 6.18 (1H, *q*, *J* = 0.8 Hz, H-8), 4.20 (3H, *s*, MeO), and 2.25 (3H, *d*, *J* = 0.8 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9 (C-5), 159.7 (C-9a), 157.4 (C-4), 153.3 (C-7), 145.0 (C-2), 136.7 (C-8a), 118.9 (C-3a), 106.7 (C-4a), 105.7 (C-3), 103.8 (C-8), 101.5 (C-9), 61.42 (MeO), and 19.30 (Me); EIMS (probe) 70 ev, *m/z* (rel. int.): 230[M$^+$] (90), 201 (100), 187 (40), 183 (30), 159 (92), 144 (47), and 129 (71); X-ray: the colourless needle-shaped crystal was mounted on a glass fibre in the direction of its greatest length, and photographed using Weissenberg and precision cameras with CuK_α radiation. The symmetry was found to be monoclinic and an approximate unit cell was established. The crystal was then transferred to a Nonius CAD-4 diffractometer using MoK_α radiation on which all further work was done. The unit cell was refined by least squares from 14 pairs of reflections (at $\pm 2\theta$) in the range 2θ = 21–48°. The crystal data are: $C_{13}H_{10}O_4$, M_r 230.22, space group *C*2/*c* (No. 15), *a* = 19.666(4) Å, *b* = 3.858 (2) Å, *c* = 28.101(6) Å, β = 106.02(2)°, *V* = 2049 (1) Å^3, *T* = 20°, *Z* = 8 molecules per cell, D_{meas} = 1.483 g/cm^3 (flotation in CCl_4/m-xylene), D_{calc} = 1.492 g/cm^3, λ = 0.71069 Å, μ = 11.93 cm^{-1}, needle length 0.97 mm, cross section 0.404 × 0.060 mm, no absorption correction applied. Intensity measurements were done for 1 quadrant ($k,l \geq 0$) in the range 2θ = 0–50°, using the Nonius variable speed $\omega/2\theta$ scan and a prescan rate of 2.75°/min. Background counting was half of the peak counting time. A set of three standards 3,0,0;0,10,0;0,0,2 were measured before each batch of 50 reflections. 1468 measurements consisting of 194 standards and 1274 reflections were obtained. Lorentz and polarization corrections were applied and equivalent measurements were averaged to obtain a final file with 1087 entries. 187 reflections having $I < 2.5\sigma(I)$ were suppressed in the subsequent calculations. Structure solution and refinement: The programs used were SHELX-76 [28] and ORTEP [29]. The atomic scattering factors were those given in the SHELX-76 program [28, 30]. The structure was solved using direct methods, and refined by standard Fourier synthesis techniques and by least squares minimizing $\Sigma w\Delta^2$ (where *w* is a weight derived from the counting statistics, $w = 1/(\sigma^2(F) + 0.001F^2)$, and $\Delta = (|F_o| - |F_c|)$. Initially carbon atomic scattering factors were used for all the ring atoms. O(2) and O(6)

were identified as the oxygen atoms by abnormally low temperature parameters. The hydrogen atoms of the methoxy group were placed at their calculated positions (C–H = 1.08 Å). The hydrogen atoms of the C(13) methyl group were first calculated and then the group as a whole was refined as a rigid body. The hydrogen atoms were treated as isotropic scatterers, and the heavier atoms were allowed the freedom of anisotropic thermal motion. U_{iso} was refined for those hydrogen atoms whose positional coordinates were refined. The hydrogen atoms fixed at calculated positions were assigned U_{iso} values of 0.05Å^2. The final residuals were $R = 0.0524$, $R_g = \sqrt{(\Sigma w\Delta^2/\Sigma wF_o^2)} = 0.0555$. The convergence was good with the final maximum (shift/esd) = 0.10. The final difference map had no important features, maximum 0.289 eÅ^{-3}, minimum 0.104 e Å^{-3}. The number of measurements, 1087, was sufficient to determine the 194 parameters well. Supplementary Tables containing fractional atomic co-ordinates and temperature parameters, bond angles, hydrogen atom parameters, anisotropic thermal parameters, bond angles involving hydrogen atoms, selected intermolecular distances, and observed and calculated structure amplitudes have been deposited.*

Dihydrocoriandrin, ^{1}H NMR (250 MHz): δ 7.55 (1H, *d*, *J* = 2.3 Hz, H-3), 7.02 (1H, *d*, *J* = 0.8 Hz, H-9), 6.99 (1H, *dd*, *J* = 2.3, 0.8 Hz, H-2), 4.55 (1H, *ddq*, *J* = 11.8, 2.0, 6.2 Hz, H-7), 4.17 (3H, *s*, MeO), 2.99 (1H, *dd*, *J* = 16.0, 11.8 Hz, H-8′), 2.93 (1H, *dd*, *J* = 16.0, 2.0 Hz, H-8″), 1.48 ppm (3H, *d*, *J* = 6.2 Hz, Me); EIMS (probe) 70 eV, *m/z* (rel. int.): 232[M$^+$] (37), 189 (13), 188 (31), 186 (25), 173 (71), 171 (65), 159 (62), 131 (50), 130 (100), 102 (44), and 89 (54).

Coriandrin gave a positive colour test when treated with alkaline *m*-dinitrobenzene, which Schönberg and Sidky [31] have used to identify the presence of a 2-methyl-4-pyrone or 2-methylchromone functionality. Obviously, the 6-methyl-2-pyrone or 3-methylisocoumarin, in which the methyl group is equally activated by conjugation to the carbonyl group, is also sensitive to this reagent.

Acknowledgements—This research was supported by grants from the Medical Research Council of Canada (MJAS), the Natural Sciences and Engineering Research Council of Canada (MJAS, GWB) and the University of Victoria (MJAS, GWB, GAP). The cooperation of Bruker Spectrospin Canada Ltd. and Dr C. Rodger in the obtaining of the detailed ^{13}C spectra is gratefully acknowledged. Mrs K. Beveridge is thanked for technical assistance in the X-ray work.

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