

Substituent Effects on Carbon-13 Chemical Shifts in 1-Substituted Camphenilones and Some Derived *N*-Nitro-imines

By Frances C. Brown and David G. Morris,* Department of Chemistry, University of Glasgow, Glasgow G12 8QQ

In a series of 1-substituted camphenilones (1)—(11) the carbonyl C(2) is markedly shielded by electron-withdrawing substituents. With respect to these camphenilones the corresponding C(2) in a limited series of derived *N*-nitro-imines (12)—(14) is shielded by *ca.* 30 p.p.m. The ^{13}C behaviour of fenchone *N*-nitro-imine is consistent with the existence of configurational isomerism about the C(2)=N bond.

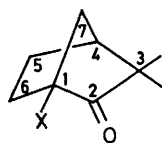
BRIDGEHEAD-substituted fused ring systems have found considerable use as model systems of well defined geometry for the investigation of ^{13}C chemical shift substituent effects where steric interactions caused by the substituent are, in general, slight. The results have relevance for an increased understanding of chemical shift dependence on structural and electronic properties of substituents. Related data are currently available for a number of systems¹⁻⁷ and presently we have examined ^{13}C

RESULTS AND DISCUSSION

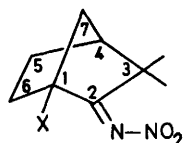
The ^{13}C chemical shift assignments are supported by off-resonance spectra and the methylene C(5) and C(6) were distinguished from C(7) by the 'Grutzner-triplets' in the off-resonance spectra of the former carbons.¹⁰ The ^{13}C chemical shifts of 1-substituted camphenilones are given in Table 1 and in Table 2 are reported the corresponding shifts for some *N*-nitro-imine derivatives.

With respect to the corresponding 1-substituted camphenes the ^{13}C chemical shift trends of the camphenilones are broadly similar. However a few points are noteworthy. No formal correlation exists between C(2) chemical shifts of camphenilones (1)—(11), where electron-withdrawing substituents cause shielding, and those of the corresponding 1-substituted camphenes; the influence of the carbonyl group is to make the shifts of the bridgehead substituent bearing C(1) the most deshielded to date for a tertiary carbon; with respect to the 1-substituted camphenes all carbons γ to oxygen in the camphenilones are shielded. Accordingly, in this latter series, no firm conclusions may be drawn on any steric role of the exocyclic methylene groups on the shielding of the exocyclic methyl groups.

We have also examined the ^{13}C shifts of the derived *N*-nitro-imines (12)—(14) where the nitrogen bonded C(2) absorbs *ca.* 30 p.p.m. upfield from C(2) in the parent ketone (Table 2). The proton-noise decoupled spectrum of fenchone *N*-nitro-imine (13) showed 18 absorptions, and the off-resonance spectrum indicated that the additional absorptions were attributable to configurational isomerism about the C(2)=N bond. However, surprisingly, the largest chemical shift difference between the



- (1) X = H
- (2) X = CH₃
- (3) X = NH₂
- (4) X = OH
- (5) X = Cl
- (6) X = Br
- (7) X = CH₂OH
- (8) X = CO₂H
- (9) X = CO₂CH₃
- (10) X = NO₂
- (11) X = CH₂CO₂CH₂CH₃



- (12) X = H
- (13) X = Me
- (14) X = Cl

chemical shifts of a series of 1-substituted camphenilones (1)—(11) and some derivatives. Previously, investigations of carbonyl ^{13}C chemical shifts in aliphatic systems have centred mainly on alkyl substitution.^{8,9}

¹ T. Pehk, E. Lippmaa, V. V. Sevostjanova, M. M. Krayushkin, and A. I. Tarasova, *Org. Magnetic Resonance*, 1971, **3**, 783.

² G. E. Maciel, H. C. Dorn, R. L. Greene, W. A. Kleschick, M. R. Peterson, and G. H. Wahl, *Org. Magnetic Resonance*, 1974, **6**, 178.

³ G. E. Maciel and H. C. Dorn, *J. Amer. Chem. Soc.*, 1971, **93**, 1268.

⁴ D. G. Morris and A. M. Murray, *J.C.S. Perkin II*, 1975, 734.

⁵ D. G. Morris and A. M. Murray, *J.C.S. Perkin II*, 1975, 539.

⁶ D. G. Morris and A. M. Murray, *J.C.S. Perkin II*, 1976, 1579.

⁷ A. N. Kalinichenko, A. A. Bobyleva, N. A. Belikova, A. F. Plate, T. I. Pehk, and E. T. Lippmaa, *J. Org. Chem. (U.S.S.R.)*, 1974, **10**, 1459.

⁸ F. J. Weigert and J. D. Roberts, *J. Amer. Chem. Soc.*, 1970, **92**, 1347 and references cited therein.

⁹ J. Torri and M. Azzaro, *Bull. Soc. chim. France*, 1974, 1633.

¹⁰ J. B. Grutzner, *J.C.S. Chem. Comm.*, 1974, 64.

two configurational isomers is for C(4), the unique doublet in the off-resonance spectrum. By way of contrast the ^{13}C chemical shifts for the exocyclic methyl carbons differ only slightly (with the proviso that the more shielded 3-methyl group is *endo*). Interestingly, an early observation¹¹ indicated a 6° m.p. range for analytically pure fenchone *N*-nitro-imine, an observation that

after thermolysis, two amides. In order to account for this reaction the authors propose, without evidence, the evolution of nitrous oxide during this reaction. In this connection it is relevant to point out that the presence of nitrous oxide during decomposition of *N*-nitro-imines has previously been confirmed by means of high-resolution mass spectrometry.^{14,16}

TABLE 1

Substituent	^{13}C Chemical shifts (p.p.m.) of 1-substituted camphenilones										
	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)	(C11)
H ^a	50.0	222.0	46.8	46.1	23.3	24.5	34.7	21.4	23.2		
CH ₃ ^a	53.8	222.6	43.1	45.3	24.9	31.8	41.5	21.6	23.3	14.6	
NH ₂	68.96	221.67	46.61	42.02	24.93	32.04	43.39	21.72	23.49		
OH	85.64	220.69	46.23	42.02	24.51	29.65	40.33	21.67	23.70		
Cl	73.79	212.98	47.23	43.54	25.25	33.16	43.61	21.89	23.94		
Br	66.29	212.84	46.90	44.58	25.74	34.95	44.50	22.01	24.04		
CH ₂ OH	60.19	223.79	48.01	45.22	24.19	27.12	37.44	21.45	23.06	62.16	
CO ₂ H	62.77	216.30	48.00	45.20	24.05	28.15	38.51	21.57	23.41	175.2	
CO ₂ CH ₃	63.93	215.34	47.71	45.31	24.11	27.11	38.51	21.69	23.62	170.98	52.06
NO ₂	97.81	207.91	47.98	42.93	24.00	27.34	39.05	21.84	24.02		
CH ₂ CO ₂ CH ₂ CH ₃ [*]	55.33	220.92	47.59	45.32	24.18	30.13	38.90	21.46	23.17	34.08	171.60

^{*} C(12), 60.29; C(13), 14.22 p.p.m.

^{*} Taken from J. B. Stothers, C. T. Tan, and K. C. Yeo, *Canad. J. Chem.*, 1973, **51**, 2893.

TABLE 2

Compound	^{13}C Chemical shifts (p.p.m.) of 1-substituted camphenilone nitro-imines and fenchone oxime									
	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)
(12)	47.18	192.45	44.43	44.43	22.98	26.11	36.54	23.19	25.79	
(13)	52.42	189.85	46.75	45.61	24.45	33.69	42.14	22.61	25.14	15.11
	53.71	189.92	47.41	49.78	24.73	34.03	45.12	23.70	26.00	16.19
(14)	70.25	182.67	47.04	43.56	25.09	36.00	46.84	23.93	26.34	
Fenchone oxime	50.09	172.44	44.19	48.65	25.28	34.22	43.28	22.17	22.97	17.09

we have been able to confirm. Although we have been unable to estimate the proportions of each isomer the ^{13}C spectra suggest that they are present in comparable amounts. The inversion barriers for other imine derivatives are generally high¹² and no attempt has currently been made to estimate the inversion barrier in *N*-nitro-imines; indeed the thermal lability of *N*-nitro-imines¹³ may vitiate such attempts. However we have shown that after melting fenchone *N*-nitro-imine an unchanged spectrum (in CDCl₃) was obtained; further, hydrolysis of fenchone *N*-nitro-imine gives exclusively fenchone as indicated by the ^{13}C chemical shifts and g.l.c. analysis. Interestingly the proton-noise decoupled spectrum of the intermediate fenchone oxime (Table 2) gave no evidence for the presence of configurational isomerism. While 1-chlorocamphenilone *N*-nitro-imine gave no indication of configurational isomerism it was not possible to prepare the *N*-nitro-imines of 1-nitro- and 1-carboxy-camphenilones although hydroxylation of these ketones was possible.

Reaction of nitrimines, *via* initial nucleophilic addition reactions, have been used for formation of nitrones¹⁴ and camphene-1-carboxamide.^{15,16} More recently it has been reported¹⁷ that sequential treatment of fenchone *N*-nitro-imine with cyanide ion and acetic acid gives,

¹¹ F. Tiemann and F. Mahla, *Ber.*, 1896, **29**, 2807.

¹² J. M. Lehn, *Fortsch. Chem. Forsch.*, 1970, **15**, 311.

¹³ L. J. Winters, J. F. Fischer, and E. R. Ryan, *Tetrahedron Letters*, 1971, 129.

EXPERIMENTAL

^{13}C N.m.r. spectra were recorded at natural abundance with a Varian XL 100 spectrometer operating in the pulse Fourier transform mode with a probe temperature of *ca.* 35°. The spectra were determined with CDCl₃ solutions containing tetramethylsilane as an internal standard. Proton-noise decoupling was carried out with a wideband noise decoupler. The spectra were recorded at the University of Glasgow by Dr. D. S. Rycroft.

I.r. spectra were recorded with a Perkin-Elmer 227 spectrophotometer. M.p.s were recorded on a Kofler hot-stage apparatus and are uncorrected.

Camphenilones (4), (5), (8), and (10) were prepared by literature methods.¹⁸

Ester (9) was prepared by treatment of an ethereal solution of acid (8) with ethereal diazomethane in the usual way. Recrystallisation of the crude yellow product from carbon tetrachloride gave analytical material, m.p. 42–44 °C, ν_{max} (KBr) 1725 and 1750 cm⁻¹ (Found: C, 67.6; H, 8.25. C₁₁H₁₆O₃ requires C, 67.3; H, 8.2%).

1-Hydroxymethylcamphenilone.—To a stirred solution of 2-oxocamphenilane-1-carboxylic acid (3.0 g, 1.65 × 10⁻² mol) in anhydrous ether (40 ml) excess of lithium aluminium hydride was added over 2 h. After stirring overnight under reflux excess of hydride was destroyed by continuous addition of a freshly made up aqueous solution of anhydrous

¹⁴ D. G. Morris, *Chem. Comm.*, 1971, 221.

¹⁵ M. Passerini, *Gazzetta*, 1925, **55**, 559.

¹⁶ S. A. Sherrod, R. G. Bergman, G. J. Gleicher, and D. G. Morris, *J. Amer. Chem. Soc.*, 1972, **94**, 4615.

¹⁷ P. J. Kocienski and M. Kirkup, *J. Org. Chem.*, 1975, **40**, 1681.

sodium sulphate. The solution was then filtered and the precipitate washed thoroughly with ether. Ether was then removed to give crude diol, 2-hydroxy-1-hydroxymethyl-3,3-dimethylnorbornane (2.8 g), ν_{\max} 3 300—3 500 cm^{-1} , no carbonyl absorption. This material was used directly in the next stage.

The diol (2.2 g, 1.4×10^{-2} mol) was added to a solution of AnalaR acetic anhydride (1.32 g, 1.3×10^{-2} mol) in dry pyridine (0.8 g) and the solution stirred for 2 h at room temperature. The solution was then added to ether (60 ml) and dilute HCl (20 ml). After removal of pyridine hydrochloride the ether layer was washed with water, brine, and dried (Na_2SO_4). After filtration there remained an oily product (2.2 g), which t.l.c. (CHCl_3 as eluant) indicated to be ca. 90% homogeneous and of higher R_F than diol precursor, ν_{\max} (film) 3 600—3 400, 1 720, and 1 240 cm^{-1} .

This material, taken to be 1-acetoxymethyl-2-hydroxy-3,3-dimethylnorbornane, was oxidised to the corresponding ketone with Jones reagent in the usual way⁴ to give an oil (1.5 g), ν_{\max} 1 750, 1 730, and 1 240 cm^{-1} , no hydroxy absorption.

The acetoxy ketone (1.2 g) was dissolved in methanol (15 ml) and after addition of a concentrated methanolic solution of sodium hydroxide (0.5 g) the solution was stirred under nitrogen for 4 h at 50 °C. After cooling ether was added and the solution acidified with dilute HCl. The ether layer was then washed with NaHCO_3 solution and brine, dried, and filtered and after removal of ether gave product (0.76 g). Pure (7) was obtained by preparative t.l.c. (CHCl_3 eluant) which served to remove the minor impurities of lower R_F . The resultant oil showed ν_{\max} (CCl_4) 1 735 and 3 600—3 400 cm^{-1} , $\delta(\text{CDCl}_3)$ 1.1 (6 H, s), 2.3—1.4 (7 H, m), 3.1br (1 H, s, exchangeable with D_2O) and 3.85 (2 H, d, J 3 Hz) (Found: C, 71.15; H, 9.6. $\text{C}_{10}\text{H}_{16}\text{O}_2$ requires C, 71.4; H, 9.45%).

Ethyl (2-Oxocamphenilane-1-yl)acetate (11)—To 2-oxocamphenilane-1-carboxylic acid (8) (2.1 g, 1.16×10^{-2} mol) dissolved in anhydrous benzene (10 ml) was added oxalyl chloride (3.5 g, 2.76×10^{-2} mol). Gas evolution occurred immediately and the solution was allowed to stir, with protection from moisture for 5 h. Removal of volatiles (rotary evaporator) gave acid chloride (2.3 g), ν_{\max} 1 790 and 1 750 cm^{-1} .

The acid chloride (2 g) was dissolved in anhydrous ether (30 ml) containing triethylamine (1.2 g). To this solution was added an ethereal solution of diazomethane. The solution was filtered and ether removed to leave diazoketone (2.3 g), ν_{\max} 2 170 and 1 650 cm^{-1} . This diazo-ketone was dissolved in ethanol (30 ml) and to this solution was added a slurry of silver oxide (10 g) in ethanol until gas evolution ceased. The mixture was then refluxed for 1 h, filtered and solvent removed to give product (2.1 g), from which pure (11) was obtained as an oil by preparative t.l.c. with 30% ethyl acetate—light petroleum as eluant, R_F ca. 0.60, ν_{\max} 1 740 and 1 705 cm^{-1} (Found: C, 69.45, H, 9.2. $\text{C}_{13}\text{H}_{20}\text{O}_3$ requires C, 69.6; H, 9.0%).

1-Aminocamphenilone (3).—To 2-oxocamphenilane-1-carboxylic acid (2 g, 1.1×10^{-2} mol) in water (5 ml) was added sufficient acetone to effect solution at 0 °C. To this stirred solution was added triethylamine (1.2 g, 1.2×10^{-2} mol) in acetone (15 ml) followed by slow addition of a solution of ethyl chloroformate (1.3 g, 1.2×10^{-2} mol) in acetone (6 ml). After stirring at 0 °C for 30 min a solution of sodium azide

(0.8 g, 1.2×10^{-2} mol) in water (5 ml) was added dropwise at 0 °C and stirring continued for 1 h. The solution was then poured onto excess of ice-water and extracted with ether; the ether solution was dried and removal of ether gave azide (2.1 g), ν_{\max} (film) 2 160, 1 760, and 1 720 cm^{-1} . The azide was heated with toluene (10 ml) with stirring until nitrogen evolution ceased. After removal of toluene (rotary evaporator), 20% HCl solution (15 ml) was added to the residue and the solution refluxed overnight. After removal of most of the water the solution was made alkaline with 40% sodium hydroxide solution, extracted with ether, and after drying (Na_2SO_4) removal of the ether gave an oil (1.3 g), ν_{\max} 3 350, 1 750, and 1 620—1 560 cm^{-1} . This method was found to give a cleaner product than the method of Nickon *et al.*¹⁸

1-Bromocamphenilone (6).—2-Oxocamphenilane-1-carboxylic acid (0.4 g, 24 mmol) dissolved in methanol (5 ml) was titrated with methanolic KOH until phenolphthalein end point. To this solution was added with stirring a solution of silver nitrate (0.39 g, 23 mmol) dissolved in H_2O (2 ml) and MeOH (5 ml). The precipitated silver salt was washed with methanol and dried under vacuum at 70 °C for 24 h. To a stirred suspension of this salt in dry carbon tetrachloride (distilled from P_2O_5) under nitrogen at 0 °C a solution of bromine (0.2 ml) in carbon tetrachloride (5 ml) was added dropwise and the solution warmed to 50 °C for 15 min. The cooled solution was then filtered and after removal of carbon tetrachloride the product was taken up in ether, washed with sodium hydrogen sulphite solution, and dried (Na_2SO_4). After removal of ether the product (370 mg) was purified by preparative t.l.c. with 20% ethyl acetate—petroleum spirit as eluant. The centre of three bands gave (6) as an oil (260 mg), ν_{\max} 1 750 cm^{-1} (Found: C, 49.95; H, 6.2. $\text{C}_9\text{H}_{13}\text{BrO}$ requires C, 49.8; H, 6.05%).

Fenchone N-Nitro-imine. To fenchone oxime¹⁹ (3.3 g, 1.9×10^{-2} mol) in acetic acid (30 ml) was added with stirring a 5% aqueous solution of sodium nitrite (45 ml). After 2 h stirring the precipitate obtained by addition of water was dried and recrystallised from the minimum volume of ethanol to give pure *N-nitro-imine* (2.3 g), m.p. 52—57 °C (lit.,¹¹ 52—58 °C) ν_{\max} (KBr) 1 625, 1 540, and 1 300—1 280 cm^{-1} (Found: C, 60.9; H, 8.2; N, 14.2. $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_2$ requires C, 61.2; H, 8.15; N, 14.3%).

1-Chlorocamphenilone N-Nitro-imine.—To 1-chlorocamphenilone oxime, m.p. 132 °C (0.54 g, 2.9 mmol), dissolved in acetic acid (5 ml) was added with stirring a 5% solution of sodium nitrite (5 ml). After 2 h the *N-nitro-imine* was precipitated by addition of water. Filtration and drying gave crude product (617 mg). Recrystallisation from ethanol gave an analytical sample (430 mg), m.p. 81 °C, ν_{\max} (KBr) 1 630, 1 550, and 1 300 cm^{-1} (Found: C, 50.05; H, 6.25; N, 12.8. $\text{C}_9\text{H}_{13}\text{ClN}_2\text{O}_2$ requires C, 49.8; H, 6.0; N, 12.9%).

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¹⁸ A. Nickon, T. Nishida, J. Frank, and R. Muneyuki, *J. Org. Chem.*, 1971, **36**, 1075.

¹⁹ R. W. Cottingham, *J. Org. Chem.*, 1960, **25**, 1473.