Use of the Nuclear Overhauser Effect in the Determination of the Orientation of Aromatic Substitution in Tricyclic Quinoxalinones

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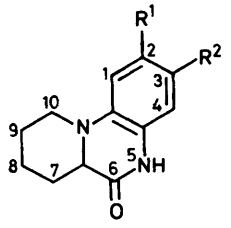
^{1}H N.m.r. nuclear Overhauser enhancement studies involving the amide NH of 7,8,9,10-tetrahydropyrido[1,2-*a*]quinoxalin-6-ones have been used to identify the aromatic proton signals of the quinoxalin-6-ones and to show that bromination with bromine in glacial acetic acid takes place at C-3 whilst nitration with potassium nitrate–concentrated sulphuric acid takes place at C-2.

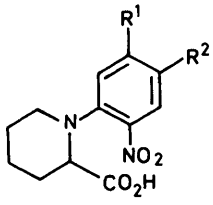
Classical methods for the orientation of groups which have been introduced by substitution onto an aromatic or heteroaromatic ring have often involved lengthy unambiguous syntheses. More recent n.m.r. spectroscopic methods involve chemical-shift and coupling-constant arguments. The nuclear Overhauser effect provides a valuable method for interrelating contiguous protons.[1] An n.O.e. from an NH has been observed on a number of occasions with amides and peptides having been used, for example,[2] to assign the amide proton resonances of NAD. It has considerable potential in heteroaromatic chemistry where a cyclic NH can be identified particularly as an NH will often exchange relatively slowly on an n.m.r. time-scale in solvents such as dimethyl sulphoxide. In this paper we describe the application of this strategy to the determination of the sites of electrophilic aromatic substitution of tetrahydropyrido[1,2-*a*]quinoxalin-6-ones (**1**).[3,4]

Electrophilic aromatic substitution of this ring system may occur either at C-2 or C-4 if the piperidine nitrogen is protonated and the amide directs substitution or at C-3 if sufficient non-protonated material is present. The position of a substituent X may then be determined using a combination of the coupling pattern and n.O.e. effect from the NH to 4-H (see Scheme). An n.O.e. enhancement will also be observed from the NCH_2 to 1-H.

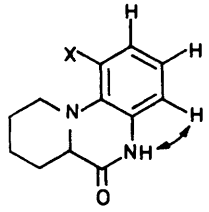
The validity of the method was established using the unsubstituted 7,8,9,10-tetrahydropyrido[1,2-*a*]quinoxalin-6-one (**1**) and its 3-methyl (**2**) and 2-fluoro (**3**) derivatives which were prepared by reductive cyclization[3,5] of the nitro acids (**7**)—(**9**) (see Experimental section). The aromatic proton signals of the parent compound (**1**) determined in [$^2H_6$]dimethyl sulphoxide at 360 MHz comprised: a triplet of doublets at δ 6.72 [*J* 7.5 (t) and 1.5 Hz (d)], a double doublet, at δ 6.80 [*J* 7.5 and 1.5 Hz] overlapping with a second broadened doublet, at δ 6.82 (*J* 7.5 Hz), and a further triplet of doublets at δ 6.89 [*J* 7.5 Hz (t) and 1.5 Hz (d)]. Although the magnitude of the vicinal coupling constants was the same, the relative



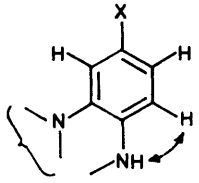
(**1**) $R^1 = R^2 = H$
(**2**) $R^1 = H, R^2 = Me$
(**3**) $R^1 = F, R^2 = H$
(**4**) $R^1 = H, R^2 = Br$
(**5**) $R^1 = NO_2, R^2 = H$
(**6**) $R^1 = H, R^2 = NO_2$



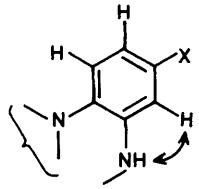
(**7**) $R^1 = R^2 = H$
(**8**) $R^1 = H, R^2 = Me$
(**9**) $R^1 = F, R^2 = H$



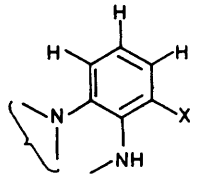
4-H = double doublet (*ortho* + *meta* coupling) n.O.e. enhancement



4-H = doublet (*ortho* coupling) n.O.e. enhancement



4-H = doublet (small *J*, *meta* coupling) n.O.e. enhancement



No 4-H to show n.O.e. enhancement

Scheme.

intensities of the individual lines showed that the doublet δ 6.80 and triplet δ 6.72 arose from adjacent hydrogen atoms whilst the doublet δ 6.82 and the triplet, δ 6.89 represented the other contiguous protons. Irradiation of the NH singlet (δ 10.37) produced a 15% n.O.e. enhancement at δ 6.80 whilst irradiation of the NCH(H) signal (10-H) produced a 16% enhancement at δ 6.82, thus allowing the assignment of the aromatic proton resonances (see Table 1). The aromatic proton signals of the 3-methyl compound (**2**) comprised a 1 H singlet (δ 6.61) and a 2 H singlet (δ 6.69). Irradiation at δ 6.61 produced a 3.3% n.O.e. effect at δ 10.32 (NH) whilst irradiation at 6.69 produced a 10% n.O.e. enhancement at δ 3.67 (10-H). The aromatic signals of the 2-fluoro compound (**3**) were rather more complex because of coupling to the ^{19}F. However irradiation at δ 6.75 produced a 16% n.O.e. enhancement at δ 6.51 and a 6% n.O.e. enhancement on the NH signal (δ 10.40) again allowing a full assignment.

The monobromo (**4**) and mononitro (**5**) compounds were obtained by bromination in acetic acid and nitration with potassium nitrate–concentrated sulphuric acid respectively. In the case of the bromo compound irradiation of the signal at δ 6.93 (d, *J* 2.2 Hz, *meta* coupling) produced a 4% n.O.e. effect at δ 10.51 (NH). Hence substitution has taken place at the 3-position. On the other hand irradiation of the NH in the nitro compound, produced a 13% n.O.e. enhancement on a doublet (*J* 8.5 Hz) at δ 6.92. Hence this nitro compound, which differed from the product (**6**) obtained previously by ring synthesis,[3] is the 2-nitro compound. The full proton spectral assignments are given in Table 1. Hence under the less strongly acidic conditions of the bromination, the piperidine nitrogen dominates aromatic substitution, whilst under the more strongly acidic conditions in sulphuric acid, this nitrogen atom is protonated and the amide directs substitution. A similar dichotomy has previously been observed[6] in the nitration of quinoxalin-2-ol.

Table 1. ^1H N.m.r. spectra of 7,8,9,10-tetrahydropyrido[1,2-*a*]quinoxalin-6-ones [determined in $(CD_3)_2SO$ at 360 MHz]

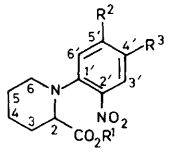
	Compound				
Proton	(**1**)	(**2**)	(**3**)	(**4**)	(**5**)
1-H	6.82	6.69	6.68	6.76	7.51
2-H	6.89	6.69		7.02	
3-H	6.72		6.51		7.65
4-H	6.80	6.61	6.75	6.93	6.92
5 (NH)	10.37	10.32	10.40	10.51	10.40
7a-H	3.42	3.33	3.50	3.48	3.42
7-H	1.43	1.42		1.43	1.43
8-H	1.65	1.64	1.48	1.64	1.68
9-H	1.82	1.80	2.00	1.82	1.84
	2.00	1.99		2.00	2.00
10-H	2.62	2.58	2.66	2.64	2.75
	3.72	3.67	3.72	3.70	3.70
ArMe		2.16			

Experimental

^1H N.m.r. spectra were determined on Bruker WP 80 and WH 360 spectrometers and are tabulated. I.r. spectra were determined as Nujol mulls.

Preparation of (2-Nitrophenyl)piperidine-2-carboxylic Acids.—A solution of 1-fluoro-2-nitrobenzene (7.06 g) and piperidine-2-carboxylic acid (9.7 g) in ethanol (210 ml) containing aqueous sodium hydrogen carbonate (100 ml) was heated under reflux for 4 h and then cooled and washed with ether. It was acidified with dilute hydrochloric acid and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated to give 1-(2-nitrophenyl) piperidine-2-carboxylic acid (8.4 g) which crystallized from ethyl acetate–light petroleum as bright yellow needles, m.p. 79—80 °C (lit.,[34] 79—80 °C) (Found: C, 57.9; H, 5.8; N, 11.1. Calc. for $C_{12}H_{14}N_2O_4$: C, 57.6; H, 5.6; N, 11.2%); $\nu_{max.}$ 3 000 br, 1 700, 1 610, and 1 520 cm^{-1}. Under similar conditions 4-fluoro-3-nitrotoluene (5.8 g) and piperidine-2-carboxylic acid (4.85 g) gave *N*-(*4-methyl-2-nitrophenyl*)*piperidine-2-carboxylic acid* (**8**) (5.5 g), m.p. 85—86 °C (Found: C, 59.1; H, 6.3; N, 10.6. $C_{13}H_{16}N_2O_4$ requires C, 59.1; H, 6.1; N, 10.6%); $\nu_{max.}$ 3 000, 1 700, 1 620, and 1 525 cm^{-1}. 2,4-Difluoronitrobenzene (5.96 g) and piperidine-2-carboxylic acid (4.85 g) similarly gave 1-(*5-fluoro-2-nitrophenyl*)*piperidine-2-carboxylic acid* (**9**) (7.55 g), m.p. 97—98 °C (Found: C, 53.7; H, 5.0; N, 10.4. $C_{12}H_{13}FN_2O_4$ requires C, 53.7; H, 4.85; N, 10.45%); $\nu_{max.}$ 3 000, 1 715, 1 620, and 1 520 cm^{-1}.

Table 2. ^1H N.m.r. spectra of 1-phenylpiperidine-2-carboxylic acids and esters (determined in $CDCl_3$ at 80 MHz)



	Compound				
Proton	R^1—R^3 = H	R^1 = Me, R^2 = R^3 = H	R^1 = R^2 = H, R^3 = Me	R^1 = R^3 = H, R^2 = F	R^1 = R^2 = H, R^3 = NO_2
3'-H	7.78	7.72	7.54	7.9	8.68
4'-H	7.05	7.02		6.96	
5'-H	7.48	7.47	7.23		8.25
6'-H	7.29	7.29	7.23	6.95	7.18
2-H	4.08	4.02	4.04	4.07	4.15
3-H	2.07	2.10	2.05	2.17	2.21
4-H, 5-H	1.67	1.7	1.6	1.7	1.8
6-H	3.05	3.01	2.97	3.10	3.40
	3.46	3.60	3.37	3.63	
OMe		3.60			
OH	10.16		9.9	9.45	8.84
ArMe			2.32		

2,4-Dinitrofluorobenzene (6.98) and piperidine-2-carboxylic acid (4.85 g) gave 1-(2,4-dinitrophenyl)piperidine-2-carboxylic acid (8.3 g), m.p. 134—135 °C (lit.,[3] 130—131 °C) (Found: C, 49.2; H, 4.6; N, 14.0. Calc. for $C_{12}H_{13}N_3O_6$: C, 48.8; H, 4.4; N, 14.2%); $\nu_{max.}$ 1 710, 1 610, 1 530, 1 460, and 750 cm^{-1}.

Methylation.—1-(2-Nitrophenyl)piperidine-2-carboxylic acid (10 g) was heated under reflux in anhydrous methanol (400 ml) containing concentrated sulphuric acid (6 ml) for 5 h. The solution was concentrated, taken up in chloroform (300 ml), and washed with aqueous sodium hydrogen carbonate, dilute hydrochloric acid, and water, dried (Na_2SO_4) and evaporated to give the ester (10 g) as a thick oil, $\nu_{max.}$ 1 740, 1 610, 1 520, 1 350, and 750 cm^{-1}. Under similar conditions 1-(2,4-dinitrophenyl)piperidine-2-carboxylic acid (2 g) gave its methyl ester (2 g), m.p. 86—87 °C (lit.,[3] 86—87 °C); $\nu_{max.}$ 1 740, 1 600, 1 530, 1 500, and 830 cm^{-1}.

Cyclization Reactions.—Method A. A solution of methyl 1-(2-nitrophenyl)piperidine-2-carboxylate (8.0 g) in ethanol (200 ml) containing freshly redistilled cyclohexene (16 ml) and 5% palladium on charcoal (5 g) was heated under reflux for 2 h. The resulting mixture was filtered through Celite and the filtrate evaporated to give a gum which was recrystallized from ethanol–diethyl ether and aqueous ethanol to afford 7,8,9,10-tetrahydropyrido[1,2-*a*]quinoxalin-6-one (**1**) (3.5 g) as a grey solid, m.p. 189—190 °C (lit.,[3] m.p. 189—190 °C).

Method B.[4] 1-(2-Nitrophenyl)piperidine-2-carboxylic acid (2.36 g) was dissolved in water (80 ml) and the pH was adjusted to 9—10 with 50% aqueous sodium hydroxide. Sodium dithionite (7.0 g) was added in small portions and the pH was maintained at *ca.* 9 by the addition of alkali. After a further 1.5 h, the solution was cooled and acidified to pH 2. The product (1.13 g) was filtered off, washed with water, dried, and recrystallized from aqueous ethanol, m.p. 190—191 °C; it was identical (i.r.) with the previously described material.

Using method B 1-(4-methyl-2-nitrophenyl)piperidine-2-carboxylic acid (2.0 g) gave 7,8,9,10-*tetrahydro*-3-*methylpyrido*-[1,2-a]*quinoxalin*-6-*one* (**2**) (0.99 g), m.p. 148—150 °C (Found: C, 69.3; H, 6.8; N, 12.45; $C_{13}H_{16}N_2O\cdot\frac{1}{2}H_2O$ requires C, 69.3; H, 7.1; N, 12.4%); $\nu_{max.}$ 3 260, 1 680, 1 460, and 790 cm^{-1}.

Similarly 1-(5-fluoro-2-nitrophenyl)piperidine-2-carboxylic acid (2 g) gave 2-*fluoro*-7,8,9,10-*tetrahydropyrido*[1,2-a]*quinoxaline*-6-*one* (**3**) (1.13 g), m.p. 195—196 °C (Found: C, 65.4; H, 5.9; N, 12.5. $C_{12}H_{13}FN_2O$ requires C, 65.45; H, 5.9; N, 12.7%); $\nu_{max.}$ 3 100, 1 680, 1 510, 1 460, and 820 cm^{-1}.

Using method A, methyl 1-(2,4-dinitrophenyl)piperidine-2-carboxylate (1.5 g) gave 7,8,9,10-*tetrahydro*-3-*nitropyrido*[1,2-a]*quinoxalin*-6-*one* (**6**) (0.58 g) which crystallized from aqueous ethanol, m.p. 188—190 °C (Found: C, 54.45; H, 4.8; N, 15.3. $C_{12}H_{13}N_3O_3\cdot H_2O$ requires C, 54.3; H, 5.7; N, 15.9%); $\nu_{max.}$ 3 200, 1 660, 1 600, 1 510, and 880 cm^{-1}.

Bromination of 7,8,9,10-*Tetrahydropyrido*[1,2-a]*quinoxalin*-6-*one.*—The quinoxalin-6-one (**1**) (0.2 g) in glacial acetic acid (10 ml) was cooled in ice and bromine (0.05 ml) in acetic acid (2 ml) was added dropwise. The solution was stirred at room temperature for 1 h after which the product was filtered off and washed thoroughly with water. The free base was liberated with concentrated ammonia and recrystallized from aqueous ethanol to afford 3-*bromo*-7,8,9,10-*tetrahydropyrido*[1,2-a]*quinoxalin*-6-*one* (0.2 g) as a red solid, m.p. 225—226 °C (Found: C, 51.7; H, 4.8; N, 9.6. $C_{12}H_{13}BrN_2O$ requires C, 51.3; H, 4.6; N, 10.0%); $\nu_{max.}$ 3 200, 1 680, 1 500, 1 460, 870, and 790 cm^{-1}.

Nitration of 7,8,9,10-*Tetrahydropyrido*[1,2-a]*quinoxalin*-6-*one.*—The quinoxalin-6-one (**1**) (0.4 g) and potassium nitrate (0.2 g) were intimately ground and added over 10 min to ice-cold concentrated sulphuric acid (20 ml). The mixture was then stirred for 40 min after which it was poured onto ice and made alkaline with concentrated ammonia. The product was collected and crystallized from aqueous ethanol to afford 7,8,9,10-*tetrahydro*-2-*nitropyrido*[1,2-a]*quinoxalin*-6-*one* (**5**) (0.3 g) as a brown solid, m.p. 212—214 °C (Found: C, 58.1; H, 5.0; N, 16.9. $C_{12}H_{13}N_3O_3$ requires C, 58.3; H, 5.3; N, 17.0%); $\nu_{max.}$ 1 680, 1 510, 1 460, and 740 cm^{-1}.

Acknowledgements

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