Electro-organic Reactions. Part 23.† Regioselectivity and the Stereochemistry of Anodic Methoxylation of *N*-Acylpiperidines and *N*-Acylmorpholines ‡

Peter D. Palasz and James H. P. Utley *
Department of Chemistry, Queen Mary College, London E1 4NS
J. David Hardstone
Pfizer Central Research, Sandwich, Kent CT13 9NJ

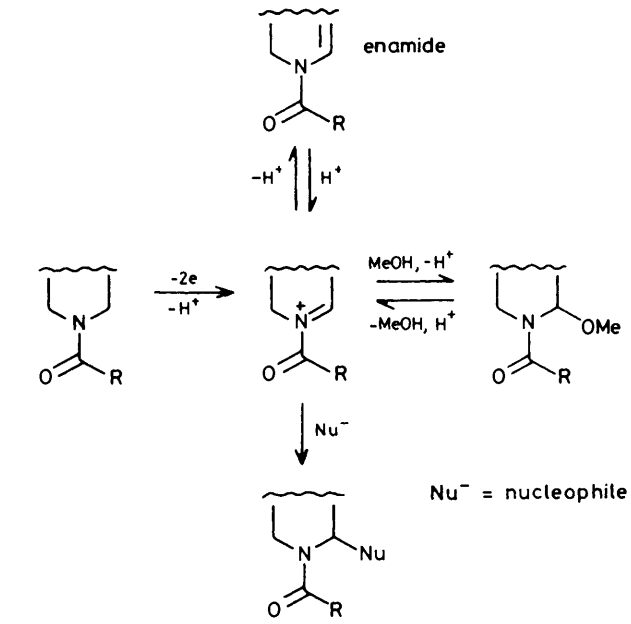
Anodic methoxylation of conformationally biassed *N*-acylpiperidines has been shown to give axial substitution due to steric constraints imposed by relatively slow rotation of the planar *N*-acyl groups. These steric constraints also account for the regioselectivity of the reaction and the axial substitution resulting from nucleophilic displacement of the α-methoxy-function in the presence of aluminium chloride. The *N*-acyl groups adopt *anti*- and *syn*-conformations and their relative proportions are consistent with the steric factors invoked to explain the substitution pattern.

α-Methoxylated amides are versatile intermediates for organic synthesis and in recent years they have become readily accessible through the Ross–Eberson–Nyberg method of anodic methoxylation.[1] This reaction involves the intermediacy of *N*-acyliminium ions and, in the presence of acid catalysts, the methoxylated amides undergo nucleophilic substitution (Scheme 1). This is, therefore, an important method for the α-functionalisation of amides.

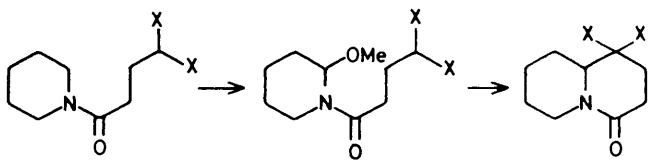
The methoxylated amides have also featured as key intermediates in recent syntheses [2–4] of quinolizidine and benzoquinolizidine derivatives; these routes involve intramolecular nucleophilic displacement of α-methoxylated piperidines (*e.g.* Scheme 2) and the factors influencing such cyclisations [2] raise interesting questions concerning the selectivity and stereochemistry of substitution.

Much interest has focused on the methoxylation of *N*-acylated cyclic amines and lactams, especially on the effects of ring size[1b,5] and ring substitution.[5a,6] It is noteworthy that anodic methoxylation of *N*-acetyl-2-methylpiperidine (1) gives substitution into the 6-position.[6] This result implies that the secondary cation is the attacked species rather than the, expected, tertiary cation. Another pertinent observation is that morpholine-4-carbaldehyde (2) is methoxylated anodically at the 2- rather than at the 3-position; [1b] similar methoxylation of dioxane occurs smoothly.[7]

We report herein on a detailed study of the selectivity and stereochemistry of these reactions and on the stereochemistry of displacement of the α-methoxy group by various nucleophiles. A consistent explanation results.



Scheme 1.



Scheme 2.

Results and Discussion

Selectivity.—The results of anodic methoxylation under comparable conditions of a number of piperidine and morpholine derivatives are collected in Table 1. In each case and, where comparison allows, in accord with earlier reports, α-methoxylation is observed; in the case of the morpholine derivative ^{13}C n.m.r. spectroscopy allows a clear distinction between 2- and 3-substitution. The methoxylated derivatives are prone to decomposition to the corresponding enamides, *e.g.* distillation of 2-methoxymorpholine-4-carbaldehyde (18) gave the corresponding enamide (36). The preferred method of purification is consequently column chromatography, although here too caution must be exercised; 6-methoxy-2-methylpiperidine-1-carbaldehyde (16) was found to decompose to the enamide (37) on a silica column.

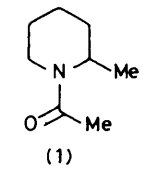
A variety of *N*-deactivating groups have been used and although changes in *N*-acylation do not affect selectivity there are small but observable effects on the ease of oxidation as reflected in the irreversible oxidation peak potentials measured by cyclic voltammetry (Table 2). These differences are

† Part 22, ref. 2.
‡ Presented at the 10th Scandinavian Meeting on Organic Electrochemistry, Sandbjerg, 1982.

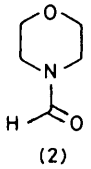
Table 1. Anodic methoxylation [a]

Substrate	Yield (%)	Product
Piperidine-1-carbaldehyde (3)	81	2-Methoxypiperidine-1-carbaldehyde (15)
2-Methylpiperidine-1-carbaldehyde (4)	79	6-Methoxy-2-methylpiperidine-1-carbaldehyde (16)
4-t-Butylpiperidine-1-carbaldehyde (5)	50 [b]	4-t-Butyl-2-methoxypiperidine-1-carbaldehyde (17)
Morpholine-4-carbaldehyde (2)	90	2-Methoxymorpholine-4-carbaldehyde (18)
1,2,3,4-Tetrahydroisoquinoline-2-carbaldehyde (6)	40 [b]	1-Methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbaldehyde (19)
N-Acetylpiperidine (7)	89	*N*-Acetyl-2-methoxypiperidine (20)
N-Phenylacetylpiperidine (8)	59 [b]	*N*-Phenylacetyl-2-methoxypiperidine (21)
N-Phenylacetyl-4-t-butylpiperidine (9)	53 [b]	*N*-Phenylacetyl-4-t-butyl-2-methoxypiperidine (22)
N-Phenylacetyl-2-methylpiperidine (10)	84	*N*-Phenylacetyl-6-methoxy-2-methylpiperidine (23)
N-Phenylacetylmorpholine (11)	50 [b]	*N*-Phenylacetyl-2-methoxymorpholine (24)
N-Phenylacetyl-1,2,3,4-tetrahydroisoquinoline (12)	83	*N*-Phenylacetyl-1-methoxy-1,2,3,4-tetrahydroisoquinoline (25)
N-(3-Methoxymalonyl)piperidine (13)	66	*N*-(3-Methoxymalonyl)-2-methoxypiperidine (26)
N-(4,4-Bisethoxycarbonylbutyryl)piperidine (14)	80	*N*-(4,4-Bisethoxycarbonylbutyryl)-2-methoxypiperidine (27)

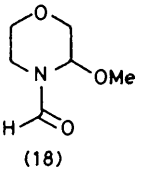
[a] See Experimental section for details of reaction conditions. [b] The lower yields are associated with the use of a flow cell of small anode area; see ref. 2.



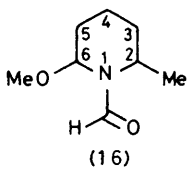
(1)



(2)



(18)



(16)

not significant for preparative-scale work because the electrolyses are run amperostatically at *ca.* 0.06—0.24 A cm^{-2} and under these conditions it is likely that oxidation is at potentials more anodic than those in Table 2. The relatively low oxidation potential measured for 1,2,3,4-tetrahydroquinoline-1-carbaldehyde suggests that in this case it is the aromatic ring which is vulnerable to oxidation and this may explain the extensive polymerisation which is the result of attempted anodic methoxylation. In contrast the corresponding tetrahydroisoquinoline derivative, which is oxidised at a higher potential more in line with the piperidine compounds, is converted smoothly into 1-methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbaldehyde (19).

The ^1H n.m.r. spectra of both starting materials and methoxylated products are complicated by the relatively slow rotation of the *N*-acyl function. Examples of such spectra are given below in the section dealing with stereochemical aspects (Figure 2) but at this stage it is sufficient to note that the accepted explanation of such behaviour invokes considerable double bond character in the C–N bond of the amide group. The barrier to rotation has been measured [8] as in the range 63—84 kJ mol^{-1}. An expected consequence of the planarity of the *N*-acyl group is that a severe steric interaction would result with substituents at the C-2 and -6 positions, particularly should those carbon atoms become trigonal. This is exactly what happens upon formation of *N*-acylium ions at the anode and we suggest that it is this steric effect which directs substitution to the secondary rather than the tertiary position. This is illustrated for the case of 2-methylpiperidine-1-carbaldehyde in Figure 1.

Stereochemistry.—4-t-Butyl-2-methoxypiperidine-1-carbaldehyde (17) is a product of anodic methoxylation which is conformationally biassed and which allows a clear distinction to be made between axial and equatorial substitution. The stereochemistry of this, and other pertinent compounds, proved to be amenable to study by ^1H n.m.r. spectroscopy.

Figure 2 displays the n.m.r. spectra of 4-t-butylpiperidine-1-carbaldehyde (5), 4-t-butyl-2-methoxypiperidine-1-carbaldehyde (17), and 6-methoxy-2-methylpiperidine-1-carbaldehyde (16); the latter two compounds were prepared by anodic methoxylation. For compound (5) H-2 and -6 are clearly made

Table 2. Oxidation peak potential [a] for $R^2N{\cdot}CHR'{\cdot}CH_2{\cdot}X$ ($-(CH_2)_2-$ bridge)

X	Substrate R^1	R^2	$E_{p/2}^{ox}$/V
[*N*-Formyldimethylamine]			2.28
CH_2	H	CHO (3)	2.18
CH_2	H	CO_2Me (28)	2.37
CH_2	H	COMe (7)	1.85
CH_2	H	$COCH_2CO_2Me$ (13)	2.23
CH_2	Me	$COCH_2Ph$ (10)	2.20
O	H	$COCH_2Ph$ (11)	2.33
(1,2,3,4-Tetrahydroisoquinoline-2-carbaldehyde)			2.14
(1,2,3,4-Tetrahydroquinoline-1-carbaldehyde)			1.79

[a] Pt bead anode, $MeCN–Bu_4NBF_4$ (0.1M), 0.3 V s^{-1}; V *versus* Ag wire; irreversible oxidation.

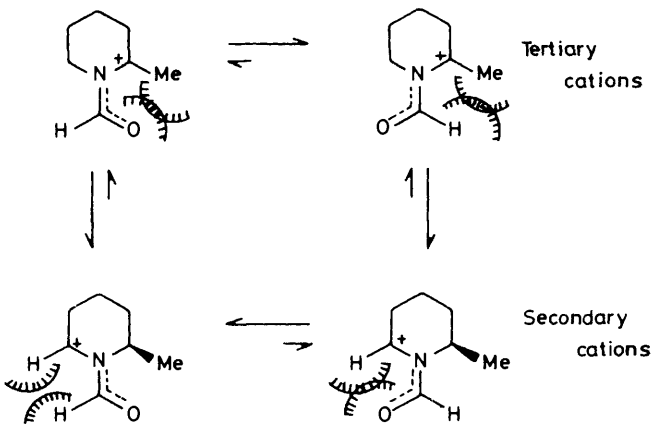


Figure 1. Steric hindrance in tertiary cations

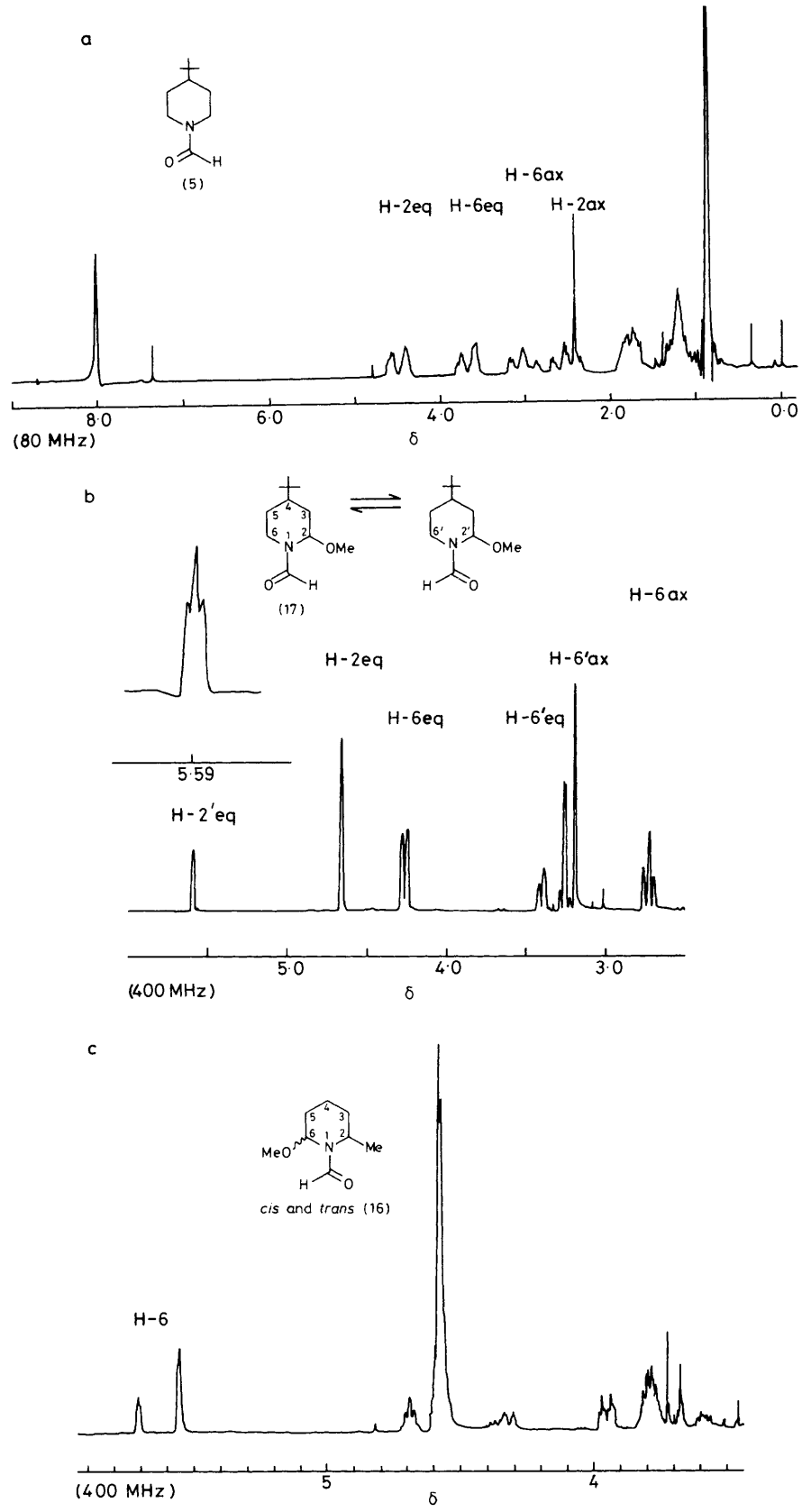
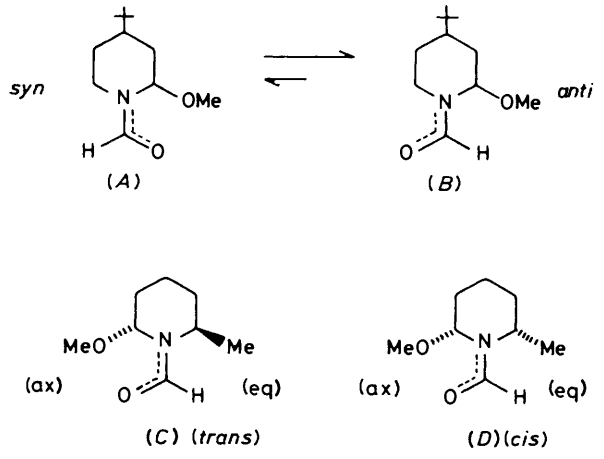


Figure 2. ^{1}H N.m.r. spectra of piperidinecarbaldehydes



inequivalent by the slow rotation of the *N*-formyl group. In all cases strong deshielding is, as expected,[9] experienced by protons in the plane of the carbonyl group. From Figure 2b it is therefore possible to deduce that the *syn*- and *anti*-conformers (*A*) and (*B*) are in the ratio 1 : 3. The assignments given in Figure 2 were confirmed by double irradiation experiments (see Experimental section).

The major conclusion to be drawn from Figure 2 concerns the stereochemical course of the anodic methoxylation reaction. For the conformationally biassed product (17) the signals for H-2 show signs of only very small vicinal coupling (*ca.* 3 Hz). This is compelling evidence for the methoxy-group being, in both the *syn*- and *anti*-case, axial; the H-2 protons are equatorial and involved in small equatorial–equatorial or equatorial–axial couplings to H-3. The large (*J* 10—15 Hz) diaxial coupling which would be expected for the *cis*-isomer (equatorial methoxy) is not seen. The n.m.r. spectrum of *N*-phenylacetyl-4-t-butyl-2-methoxypiperidine (22) similarly shows that for this compound also H-2 is equatorial, *i.e.* the methoxy-group is axial and the effect is not limited to *N*-formyl derivatives. That methoxy is axial in the above compounds is further supported by the absence of signals with large couplings which would have been expected for H-2ax.

A further stereochemical conclusion can be drawn from the n.m.r. spectrum of 6-methoxy-2-methylpiperidine-1-carbaldehyde (16) (Figure 2c). The full spectrum for this compound is complex; the product of anodic methoxylation is a mixture of the *cis*- and *trans*-isomers, each of which can exist in *syn*- and *anti*-forms. It is clear however that the signals at δ 5.71 and 5.55, which show very small couplings, must arise from H-6 equatorial protons in conformations (*C*) and (*D*), *i.e.* in these isomers methoxy is again axial. It is also evident that the ratio of these isomers is *ca.* 2 : 1 although an assignment of *cis* and *trans* was not achieved.

The anodic methoxylation of *N*-phenylacetyl-2-methylpiperidine yields only the *cis*-isomer of *N*-phenylacetyl-6-methoxy-2-methylpiperidine (23). Furthermore it seems that the 2,6-substituents are diaxial; in an n.m.r. experiment irradiation at the position of the methyl resonance (δ 1.25) caused the collapse of the H-2 multiplets into signals with small couplings clearly showing that the 2-methyl group was axial. That the 6-methoxy-group was also axial is confirmed by the small couplings (3 Hz) associated with the H-6 signals at δ 5.90 and 5.03.

The most likely cause of axial substitution in these systems is the severe hindrance to the 2- and 6-equatorial positions occasioned by the planarity of the *N*-formyl and *N*-phenylacetyl functions. Inspection of Dreiding models confirms this probability and the concept is expressed diagramatically in Figure 3. This view supposes that the reactions are under thermodynamic control and there is some support for this;[2] an alternative explanation is that reaction is under kinetic control and proceeding *via* a product-like transition state. Thus there is a single directing influence for both the stereochemistry and selectivity of anodic methoxylation.

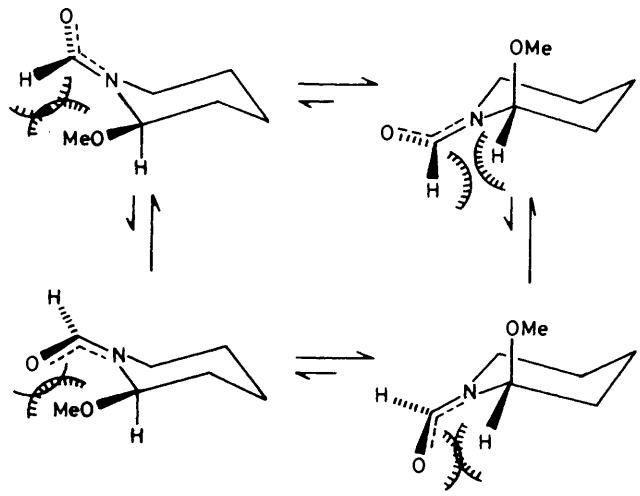
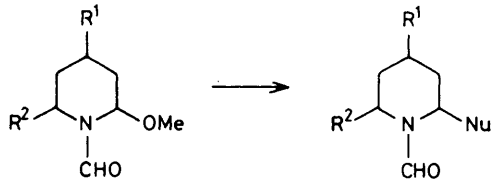


Figure 3. Steric hindrance to equatorial substitution

Table 3. Nucleophilic displacement of methoxy [a]

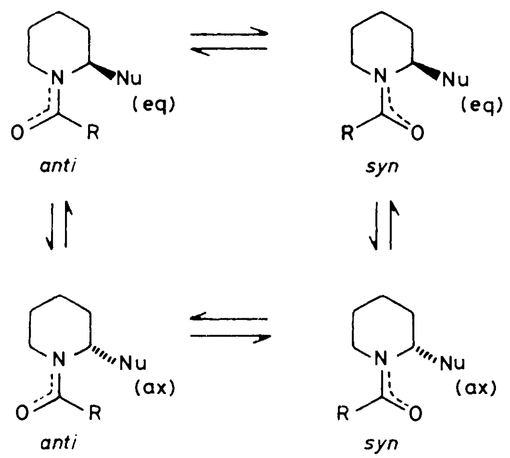


Substrate (I)			Nucleophile (Nu)	Product (II)	Yield (%)
R^1	R^2				
H	H	(3)	C_6H_6	(29)	76
H	H	(3)	$CH_2(CO_2Me)_2$	(30)	21
H	Me	(4)	C_6H_6	(31)	55
H	Me	(4)	$CH_2(CO_2Me)_2$	(32)	31
Bu^t	H	(5)	C_6H_6	(33)	52
Bu^t	H	(5)	$CH_2(CO_2Me)_2$	(34)	29

[a] In the presence of a two-fold excess of aluminium chloride; dichloromethane solvent for reactions with dimethyl malonate (see Experimental section).

The Reactions of α-Methoxyamides with Nucleophiles.—In the presence of acid catalysts, the best of which appears to be aluminium chloride [10] methoxy may be displaced by a variety of nucleophiles (Scheme 2). In the light of the realisation that anodic methoxylation is greatly influenced by the hindered rotation of the *N*-acyl group it is pertinent to examine the stereochemical course of the nucleophilic displacement reaction. The preparative results from such experiments are displayed in Table 3; in several cases the initial product was converted directly into the corresponding amine hydrochloride by treatment with methanolic HCl.

These reactions, which have been found to require two equivalents of aluminium chloride,[11] are believed to involve



Scheme 3.

regeneration of *N*-acylium ion (Scheme 1). Consequently the stereochemical course of substitution should be the same as for the initial methoxylation. Confirmation of this came from an examination of the products of reaction between 4-t-butyl-2-methoxypiperidine-1-carbaldehyde (17) and dimethylmalonate or benzene. The ^{1}H n.m.r. spectra of these products indicate, because of the small couplings involved, that in each case H-2 is equatorial, *i.e.* the dimethylmalonate and phenyl substituents are locked in the axial position. The spectra were completely assigned with the aid of the double irradiation experiments and key results are summarised in the Experimental section.

For the reactions of 6-methoxy-2-methylpiperidine-1-carbaldehyde (16) with dimethylmalonate or with benzene the result is less clear. Substitution with dimethylmalonate gives as the only isolated product *trans*-6-dimethylmalonyl-2-methylpiperidine-1-carbaldehyde (32) and its ^{1}H n.m.r. spectrum is best interpreted in terms of equatorial methyl and axial dimethylmalonate: presumably the bulkier dimethylmalonate group cannot be tolerated in the equatorial position. However, when 6-methoxy-2-methylpiperidine-1-carbaldehyde (16) was allowed to react with benzene in the presence of aluminium chloride a mixture (31) of isomers (2 : 9) was obtained. Attempts to separate these isomers by column chromatography failed, but from the 400 MHz n.m.r. spectrum of the mixture it is apparent that in each isomer the phenyl substituent is predominantly axial.

The Hindered Rotation of the N-*Acyl Function*.—The *N*-acyl function may adopt either a *syn*- or an *anti*-conformation with respect to the α-substituent. Furthermore the *anti* : *syn* ratio is a parameter which will reflect the steric requirements of the 2-substituent; for conformationally mobile systems the possibilities are displayed in Scheme 3. The *anti* : *syn* ratios are readily measured from the n.m.r. spectra. Equatorial H-2 protons are considerably deshielded when in the plane of the carbonyl group. This is the case for the *syn*-conformer and consequently the ratio of integrated areas for the highfield : lowfield H-2 signals is a measure of the *anti* : *syn* ratio. Alternatively, for *N*-formyl derivatives, the measurements may be based on the two signals observed for the formyl proton. The results of such measurements are collected in Table 4 and are organised to highlight differences associated with the *N*-acyl group and differences associated with the 2-substituent.

The results are entirely consistent with the concepts embodied in Figures 1 and 3. As group R, of the RCO acyl

$\ulcorner CHR^3{\cdot}CH_2 \urcorner$

Table 4. *anti* : *syn* Ratios[a] in $XN{\cdot}CHR^2{\cdot}CH_2{\cdot}CHR'$

Substrate				Conformer population (%)	
R¹	R²	R³	X	*anti*	*syn*
H	OMe	H	CHO (15)	70	30
H	OMe	H	$COCH_3$ (20)	55	45
H	OMe	H	$COCH_2CO_2CH_3$ (26)	37	63
H	OMe	H	$CO(CH_2)_2CO_2CH_3$	44	56
H	OMe	H	$CO(CH_2)_2CH(CO_2CH_3)_2$	49	51
H	OMe	H	$COCH_2Ph$ (21)	46	54
H	OMe	Me	$COCH_2Ph$ (23)	36	64
Bu^t	OMe	H	CHO (17)	71	29
Bu^t	OMe	H	$COCH_2Ph$ (22)	43	57
Bu^t	$CH(CO_2CH_3)_2$		CHO (34)	82	18
Bu^t	Ph	H	CHO (33)	50	50
(2-Dimethylmalonylmorpholine-4-carbaldehyde)				73	27
[1-Methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbaldehyde (19)]				65	35
[*N*-Phenylacetyl-1-methoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxaldehyde (25)]				29	71

[a] In $CDCl_3$ solution, precision judged to be ±3%.

group, increases in size the severe interaction between the carbonyl oxygen and the substituted 2-position is offset by the increasingly important interaction between R and the 2-position. Consequently the proportion of the *syn*-conformer increases. The variations are not large, however, which suggests that the 2-substituents can escape major steric interactions, possibly by assuming axial positions (see below). Two features of the results which confirm the above interpretation may be identified. The *anti* : *syn* ratios for 2-methoxypiperidine-1-carbaldehyde (15) and 4-t-butyl-2-methoxypiperidine-1-carbaldehyde (17) are identical within experimental error; it is known that for the conformationally biassed derivative (17) methoxy is axial so the result argues for methoxy also being axial in the conformationally mobile derivative (15). The results for 4-t-butyl-2-(dimethylmalonyl)piperidine-1-carbaldehyde (34) and 4-t-butyl-2-phenylpiperidine-1-carbaldehyde (33) are also consistent with the 2-substituents being axial. The dimethylmalonate group would normally be regarded as bulkier than phenyl yet it influences the *anti* : *syn* ratio only slightly and 2-phenyl substitution perturbs the ratio not at all. Both of these substituents, were they in the equatorial position would clash severely with the carbonyl oxygen of the *syn*-conformer.

Experimental

N-*Acyl Derivatives*.—Many of these are known compounds and were prepared by reaction between the secondary amine and the appropriate acid chloride or, for *N*-formyl derivatives, by reaction with ethyl formate; good agreement was found with published physical data. Compounds either not previously recorded, or inadequately recorded, are as follows.

4-*t*-*Butylpiperidine*-1-*carbaldehyde* (5). This was prepared by treatment of the hydrogencarbonate salt of 4-t-butylpiperidine with ethyl formate, yield 58%, m.p. 53—56 °C; δ 8.01 (s, CHO, 1 H), 4.50 (d, *J* 13 Hz, H-2eq/6eq, 1 H), 3.65 (d, *J* 13 Hz, H-6eq/2eq, 1 H), 3.08 (t, *J* 13 Hz, H-6ax/2ax, 1 H), 2.04 (t, *J* 13 Hz, H-2ax/6ax, 1 H), 1.80 (m, H-3eq/5eq, 2 H), 1.23 (m, H-3ax/4ax/5ax, 3 H), and 0.91 (s, t-butyl, 9 H), *m*/*z* 169 (M^+, 100%) (Found: C, 70.8; H, 11.2; N, 8.1. $C_{10}H_{19}NO$ requires C, 71.0; H, 11.3; N, 8.18%).

Table 5. Double irradiation experiments

Compound	Signal irradiated (δ)	Signal perturbed and interpretation
4-t-Butylpiperidine-1-carbaldehyde (5)	4.50 (d, *J* 13 Hz)	2.04 (d, *J* 13 Hz, H-2ax/6ax)
	3.65 (d, *J* 13 Hz)	3.08 (d, *J* 13 Hz, H-6ax/2ax)
	3.08 (t, *J* 13 Hz)	3.65 (s, H-6eq/2eq)
	2.04 (t, *J* 13 Hz)	4.50 (s, H-2eq/6eq)
	1.20 (m, H-3/4/5)	2.04, 3.08 (d, *J* 13 Hz)
6-Methoxy-2-methylpiperidine-1-carbaldehyde (16)	5.50 (H-6eq)	
	4.60 (H-2)	1.28 (s, CH_3)
	1.30 (CH_3)	4.58, 4.40 (H-2)
N-Phenylacetyl-6-methoxy-2-methylpiperidine (23)	1.25 (CH_3)	4.78br (s, H-2eq)
		4.08 (d, d, *J* 4/2 Hz, H-2eq)
	3.82 ($ArCH_2$)	
N-4-t-Butyl-2-dimethylmalonylpiperidine-1-carbaldehyde (34)	2.60 (H-6ax)	4.40 (s, H-6eq)
	4.04 [d, *J* 12 Hz, $CH(CO_2Me)_2$]	4.45 (s, H-2eq)

N-(3-*Methoxymalonyl*)*piperidine* (13). This was prepared from piperidine and dimethylmalonate, yield 49%, b.p. 110—120 °C at 0.1 mmHg; δ 3.82 (s, OMe, 3 H), 3.05 (m, $COCH_2/NCH_2$, 6 H), and 1.68 [m, $(CH_2)_3$, 6 H]; *m/z* 185.106 (M^+, 100%; $C_9H_{15}NO_3$ requires 185.105).

Electrochemical Equipment and Methods.—This has been adequately described [2] in earlier parts.

Anodic Methoxylation.—This was performed at constant current using undivided flow cells equipped with carbon anodes and stainless steel cathodes; details of the cells and descriptions of typical electrolyses have been published together with physical data for those methoxylated derivatives previously unknown. In summary, however, two flow cells were used the cylindrical carbon anodes of which were 28 mm diameter and, respectively, 80 or 230 mm in length. For a given flow rate (usually 2 l min^{-1}) higher yields were obtained using the longer anode. In a typical electrolysis the *N*-acylpiperidine (0.03 mol) was dissolved in methanol (290 cm^3) containing tetra-n-butylammonium tetrafluroborate (2 g). The current density was 0.07 A cm^{-2}, the solution temperature was maintained at 40—50 °C, and electrolysis was continued to 4 F mol^{-1}. Methoxylated derivatives prepared in the course of this study, and not previously recorded are as follows.

4-*t-Butyl*-2-*methoxypiperidine*-1-*carbaldehyde* (17). This had m.p. 42—43 °C; δ (400 MHz) 8.164, 8.144 (s, CHO, 1 H), 5.580, 4.645 (t, *J* 3 Hz, H-2, 0.29/0.71 H), 4.262, 3.391 (d, d, *J* 13/4 Hz, H-6, 1 H), 3.239, 2.728 (t, d, *J* 13/3 Hz, H-6ax, 1 H), 3.254, 3.182 (s, OCH_3, 3 H), 2.053, 1.975 (d, d, *J* 13/3 Hz, 1 H), 1.73—1.25 (m, 4 H), and 0.851 (s, t-butyl, 9 H); ν(KBr) 2 950, 1 670, 1 420, and 1 020 cm^{-1}; *m/z* 199 ($M^{+\cdot}$, 0.13%) and 28 (100%) (Found: C, 66.3; H, 10.5; N, 7.3. $C_{11}H_{21}NO_2$ requires C, 66.3; H, 10.7; N, 7.0%).

6-*Methoxy*-2-*methylpiperidine*-1-*carbaldehyde* (16). This had b.p. 55—60 °C at 0.1 mmHg; δ 8.37, 8.25, 8.15, 7.99 (s, CHO, 1 H), 5.74, 5.58 (m, H-6, 0.1/0.2H), 4.58 (m, 0.8 H), 4.5—2.25 (m, 1 H), 3.35, 3.30, 3.25, 3.15 (s, OCH_3, 3 H), 1.70 (m, H-3/-4/5, 6 H), 1.41, 1.30, 1.19 (d, *J* 7 Hz, CH_3, 3 H); ν(liquid film) 2 930, 1 660, 1 415, and 1 060 cm^{-1}; *m/z* 157.111 (M^+, 39%; $C_8H_{15}NO_2$ requires 157.110) and 126 (100%).

N-(3-*Methoxymalonyl*)-2-*methoxypiperidine* (26). This had b.p. 135—139 °C at 0.3 mmHg; δ 5.78, 4.90 (m, H-2), 0.63/0.37 H), 4.45 (d, *J* 12 Hz, H-6eq, 0.4 H), 4.0—2.8 (m, 2.6 H), 3.82 (s, H-5′, 3 H), 3.53 (s, H-8, 2 H), 3.38, 3.29 (s, OCH_3, 3 H), and 1.74 (m, H-3/4/5, 6 H), ν(liquid film) 2 920, 1 740, and 1 650 cm^{-1}; *m/z* 215.114 (M^+, 8%; $C_{10}H_{17}NO_4$ requires 215.116) and 84 (100%).

2-*Methoxymorpholine*-4-*carbaldehyde* (18). Although this is a known compound [11] its ^{13}C n.m.r. spectrum is worth noting as it allows a clear distinction to be made between substitution at C-2 and -6, δ (20 MHz) 161.73, 161.24 (d, C-1′), 83.32, 77.13 (d, C-2), 67.35, 65.99, 66.44, 66.07 (t, C-3/5), 55.33, 54.23 (q, C-8), and 41.48, 36.26 (t, C-6).

In some cases the methoxylated derivatives were prone to decomposition to the corresponding enamides, and enamides so prepared are as follows.

N-3-(*Methoxymalonyl*)-2,3-*didehydropiperidine* (35). This had b.p. 90—100 °C and 0.05 mmHg; δ 7.18, 6.50 (d, *J* 8 Hz, =CH, 1 H), 5.63 (m, =CH, 1 H), 3.78 (s, OCH_3, 3 H), 3.72—3.2 (m, 2 H), 3.55 (s, CH_2, 2 H), and 2.2—1.5 (m, 4 H); ν(liquid film) 2 920, 2 860, 1 740, and 1 650 cm^{-1}; *m/z* 183.090 (M^+, 36%; $C_9H_{13}NO_3$ requires 183.089) and 83 (100%).

2,3-*Didehydromorpholine*-4-*carbaldehyde* (36). This had b.p. 90—95 °C at 0.4 mmHg; δ 8.18, 7.90 (s, CHO, 1 H), 6.02, 6.20 (d, d, *J* 1 Hz, 0.44 H), 6.12 (d, *J* 1 Hz, NCH=, 0.66 H), 4.12 (m, =CH, 1 H), and 3.75 (m, NCH_2CH_2O, 4 H); ν(liquid film) 3 090, 2 900, 1 660, and 860 cm^{-1}.

5,6-*Didehydro*-2-*methylpiperidine*-1-*carbaldehyde* (37). This had b.p. 68—73 °C at 0.3 mmHg; δ 8.14, 8.12 (s, CHO, 1 H), 6.98, 6.40 (d, *J* 8 Hz, NCH=, 0.33/0.77 H), 5.10, 4.62, 3.90 (m, 2 H), 2.25—1.50 (m, 4 H), and 1.26, 1.18 (d, *J* 8 Hz, 3 H); ν(liquid film) 3 020, 2 940, 2 840, 1 660, and 760 cm^{-1}; *m/z* 125.084 (M^+, 100%; $C_7H_{11}NO$ requires 125.084) and 110 (98%).

Nucleophilic Displacement Reactions.—Benzene was used as solvent and reactant in the case of phenyl substitution whereas the reactions with dimethylmalonate were carried out in dichloromethane solution. In the latter case equimolar amounts of the methoxylated amide and dimethylmalonate were heated under reflux in the presence of a two-fold excess of good quality aluminium chloride for 1—4 h. In benzene solution the two-fold excess of catalyst related to the amount of methoxylated amide employed. In each case the products were subjected to aqueous work-up and purified by distillation under reduced pressure or column chromatography. New compounds prepared in this fashion are as follows.

2-*Methyl*-6-*phenylpiperidine*-1-*carbaldehyde* (31). This was obtained as a mixture of isomers, as shown by g.l.c. analysis [Hewlett-Packard 5830A, OV17 (3%) column, 200 °C], boiling range 140—145 °C at 0.1 mmHg, yield 55%, δ (400 MHz) 8.490, 8.339, 8.298, 7.591 (s, CHO, 1 H), 7.4—7.2 (m, ArH, 5 H), 6.355, 6.152, 4.812, 4.858 (d, *J* 4 Hz, CHPh, 1 H), 5.262, 5.158, 4.305, 3.707 (m, *J* 7 Hz, CHMe, 1 H), 2.982, 2.907, 2.820 (d, *J* 13 Hz, 1 H), 2.3—2.0 (m, 5 H), 1.773, 1.677 (d, *J* 7 Hz, CH_3, 2.28 H), and 1.771, 1.518 (d, *J* 7 Hz, CH_3, 0.72 H); ν(liquid film) 3 300, 2 700, and 1 660 cm^{-1}; *m/z* 203.131 (M^+, 80%; $C_{13}H_{17}NO$ requires 203.131) and 202 (100%).

N-6-*Dimethylmalonyl*-2-*methylpiperidine*-1-*carbaldehyde* (32). This was formed in 31% yield, m.p. 69—72 °C; δ (400 MHz) 8.118, 8.090 (s, CHO, 0.82/0.18H), 5.158 (d, d, d, *J* 11/6/2 Hz, H-6, 0.18 H), 4.370 (d, t, *J* 11/3 Hz, H-6, 0.82 H), 4.688, 3.880 (m, *J* 7 Hz, H-2, 1 H), 3.980, 3.828 (d, *J* 11 Hz, H-9, 1 H), 3.775, 3.767, 3.735, 3.680 (s, OCH_3, 6 H), 1.702 (m, H-3/4/5, 6 H), and 1.382, 1.779 (d, *J* 7 Hz, CH_3, 3 H); ν(KBr) 2 940, 1 755, 1 660, 1 420, and 1 010 cm^{-1}; *m/z* 257 (M^+, 1%) and 28 (100%) (Found: C, 56.1; H, 7.4; N, 5.5. $C_{12}H_{19}NO_5$ requires C, 56.0; H, 7.4; N, 5.4%).

4-*t*-*Butyl*-2-*dimethylmalonylpiperidine*-1-*carbaldehyde* (34). This was formed in 29% yield, m.p. 77—80 °C, δ (400 MHz) 8.152, 7.981 (s, CHO, 0.82/0.18 H), 5.295 (d, d, *J* 11/3 Hz, H-2eq, 0.18), 4.451, 4.403 (two d side by side, *ca.* *J* 11 Hz, H-2eq/6eq, 1.64 H), 4.036, 3.895 (d, *J* 12 Hz, H-8, 1 H), 3.775, 3.768, 3.711, 3.672 (s, OCH_3, 6 H), 3.025 (d, *J* 13/3 Hz, H-6eq, 0.18 H), 3.300, 2.603 (t, d, *J* 12/3 Hz, H-6ax, 1 H), 1.8—1.0 (m, 5 H), and 0.84 (s, t-butyl, 9 H); ν(KBr) 2 950, 1 750, 1 660, and 1 020 cm^{-1}, *m/z* 299 (M^+, 1%) and 28 (100%) (Found: C, 60.4; H, 8.4; N, 4.6. $C_{15}H_{25}NO_5$ requires C, 60.2; H, 8.4; N, 4.7%).

4-t-*Butyl*-2-*phenylpiperidine*-1-*carbaldehyde* (33). This was formed in 52% yield, b.p. 140—145 °C at 0.3 mmHg, δ 8.25, 8.21 (s, CHO, 1 H), 7.20 (m, ArH, 5 H), 5.81, 4.92 (s, CHPh, 0.5/0.5 H), 4.43, 3.55 (d, *J* 12 Hz, H-6eq, 1 H), 3.05 (t, *J* 12 Hz, H-6ax, 0.5 H), 2.62 (m, 1.5 H), 1.5 (m, 4 H), and 0.92 (s, t-butyl, 9 H); ν(liquid film) 3 020, 2 960, 1 650, and 1 600 cm^{-1}; *m/z* 245.178 (M^+, 66%, $C_{16}H_{23}NO$ requires 245.178) and 244 (100%).

Double Irradiation Experiments.—The assignment of key n.m.r. spectra was supported by the results of double irradiation experiments. The results of typical experiments and their interpretation are summarised in Table 5.

Acknowledgements

We are grateful to the S.E.R.C. for a CASE studentship (to P. D. P.) in collaboration with Pfizer Central Research, to Dr. S. F. Campbell for helpful discussions, and to the Royal Society and the University of London Central Research Fund for equipment grants. N.m.r. spectra were measured by the ULIRS WH-400 N.M.R. Service at Queen Mary College.

References

1 (*a*) S. D. Ross, M. Finkelstein, and R. C. Petersen, *J. Org. Chem.*, 1966, **31**, 128; (*b*) K. Nyberg and R. Servin, *Acta Chem. Scand., Ser. B*, 1976, **30**, 640; (*c*) L. Eberson, J. Hlavaty, L. Johnsson, K. Nyberg, R. Servin, H. Sternerup, and L. G. Wistrand, *ibid.*, 1979, **33**, 113.
2 P. D. Palasz, J. H. P. Utley, and J. D. Hardstone, *Acta Chem. Scand., Ser. B*, 1984, in the press.
3 Z. Blum, M. Ekstrom, and L-G. Wistrand, *Acta Chem. Scand., Ser. B*, 1984, in the press.
4 M. Okita, T. Wakatamatsu, and Y. Ban, *Heterocycles*, 1983, **20**, 401.
5 (*a*) M. Mitzlaff, K. Warning, and H. Jensen, *Liebig's Ann. Chem.*, 1978, 1713; (*b*) Z. Blum, M. Malmberg, and K. Nyberg, *Acta Chem. Scand., Ser. B*, 1981, **35**, 739.
6 T. Shono, H. Hamaguchi, and Y. Matsumura, *J. Am. Chem. Soc.*, 1975, **97**, 4264.
7 T. Shono and Y. Matsumura, *J. Am. Chem. Soc.*, 1969, **91**, 2803.
8 L. Lunazzi, D. Macciantelli, D. Tassi, and A. Dondoni, *J. Chem. Soc., Perkin Trans. 2*, 1980, 717.
9 T. H. Siddall and W. E. Stewart, *J. Mol. Spectrosc.*, 1967, **24**, 290.
10 M. Malmberg and K. Nyberg, *J. Chem. Soc., Chem. Commun.*, 1979, 167.
11 M. Malmberg and K. Nyberg, *Acta Chem. Scand., Ser. B*, 1984, in the press.

Received 19*th July* 1983; *Paper* 3/1235