The Halogenation of Some Benzamides Takes Place Preferentially at the *ortho,para* Positions

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The orientation of chlorination and bromination of *N,N*-disubstituted benzamides in aqueous acetic acid is strongly influenced by the nature of the alkyl groups at the nitrogen atom. With large groups, the halogenation takes place fairly selectively at the *ortho*/*para* positions.

The chlorination of aromatic compounds has long been known to take place at the side chain under free radical conditions and at the ring with electrophilic reagents. In the latter case, the orientation follows the classical Holleman rules[1]: some groups direct the substitution to the *ortho*,-*para* positions, others to the *meta* positions[2]. However, in some cases, the results are not always so clear-cut. In the course of other work, it became apparent that whereas benzoic acid, its esters, and benzamide itself undergo electrophilic substitution fairly selectively at their *meta* positions, *N,N*-disubstituted benzamides can behave very differently, showing once again that caution must be exercised in attempting to predict the course of a reaction.

Chlorination

The ring chlorination of aromatics has been extensively investigated. Typically, chlorine in glacial acetic acid is used for reactive substrates, while aqueous acetic acid is preferred for less reactive compounds[3a]. Benzoic acid itself has recently been treated with chlorine in aq. H_2SO_4 solution to give in 58% yield practically exclusively the *meta*-substituted product[3b]. In the present work, the chlorination of various benzoic acid derivatives with chlorine in aqueous acetic acid has been carried out and the reaction mixtures were analysed. Conversions, total yields of monohalogenated products, proportions of the *o*/*m*/*p* isomers, and the various by-products are summarized in Table 1.

Under these conditions, benzoic acid itself gave a very high proportion of the *m*-chloro isomer (*o*/*m*/*p* = 3:97:0) in 41% yield. This result resembles that of the reaction in aqueous sulfuric acid[3b]. Methyl benzoate gave ring-chlorinated products in only 20% yield (*o*/*m*/*p* = 16:84:0); chlorination occurred mainly at the methyl group (52%) instead, and benzoic acid (25%) was also formed. Benzoyl chloride gave mainly benzoic acid with some (24%) *m*-chlorobenzoic acid. Benzamide gave almost the same results.

Table 1. Monochlorination of benzoic acid derivatives Ph−CO−X (1 mmol) with chlorine (80−100 bubbles/min) in 33% (v/v) aqueous acetic acid (8 ml) at 50°C with reaction times 9 h[a]

X	conv. (%)	yield (%)	*o*/*m*/*p*	other products
OH	41	100	3:97:0	−
OMe	46	20	16:84:0	BzOH (25%), $BzOCH_2Cl$ (52%)[34]
Cl	100	0	−	BzOH (76%), *m*-Cl-BzOH (24%)
NH_2	100	trace	−	BzOH (66%), *m*-ClBzOH (28%)
NHEt	34	63	35:46:19	BzOH (23%)
NH*i*Pr	66	84	41:48:11	dichloro (9%)
NH*t*Bu	73	85	35:46:19	dichloro (10%)
NMe_2	78	73	48:28:24	dichloro (9%)
NEt_2	89	68	39:26:35	BzNHEt (10%), Cl-BzNHEt (9%, *o*/*m*/*p* = 29:33:38), dichloro (5%)
$NiPr_2$	100	82	47:11:42	dichloro (12%)[b], BzNH*i*Pr (< 4%), BzOH (< 4%)
DMP	96	85	72:8:20	dichloro (10%)

[a] Bz = benzoyl. − [b] Proportions: 2,3-/2,4-/2,5-/3,4-dichloro = 6:2:70:22.

Various *N*-monosubstituted benzamides were then treated in the same way. It can be seen from Table 1 that the results were very different compared to those obtained with the acid or the ester. Comparing the data for *N*-ethyl (NHEt), *N*-isopropyl (NH*i*Pr) and *N*-*tert*-butyl (NH*t*Bu) benzamides, it is apparent that (i) the conversion increases noticeably; (ii) chlorination takes place at the ring with increasing yields, reaching 85% of monochlorinated products for the higher amides, and (iii) the ratios of isomers are also very different in that the mixtures become more rich in the *o* and *p* isomers (*o*+*p*/*m* = 52:48).

These interesting results prompted us to examine the chlorination of *N,N*-disubstituted benzamides. The results obtained with *N,N*-dimethyl (NMe_2), *N,N*-diethyl (NEt_2),

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and *N,N*-diisopropyl (N*i*Pr$_2$) benzamide, and with *N*-benzoyl-2,6-*cis*-dimethylpiperidine (*N*-BzDMP, see below), show that (i) the conversion increases still further to almost 100%; (ii) the total yields of ring-monochlorinated products are again very high (above 80%); (iii) in this series, in contrast to the results with the *N*-monosubstituted benzamides, the ratio of isomers changes gradually with the size of the substituents, with the larger groups leading to a decrease in the amount of the *meta* isomer formed. The ratio *o*+*p*/*m* increases from about 2.5 to about 10 on going from *N,N*-dimethylbenzamide to the diisopropylbenzamide or *N*-benzoyl-2,6-*cis*-dimethylpiperidine. This remarkable orientation of the chlorination of the benzamide derivatives was beyond our expectations under these very simple reaction conditions and so the reaction was investigated further.

In the case of the diisopropylamide, the by-products formed were examined more closely. They were readily identified as *N*-isopropylbenzamide (a small amount), as well as dichlorinated products (12%). No chlorinated *N*-isopropylbenzamide was found. The dichlorinated products were shown by comparison with authentic samples to be the 2,3, 2,4, 2,5, and 3,4 isomers, and were found in the proportions 6:2:70:22; the 2,6 isomer was absent. The dealkylation of *N*-substituted amides or amines is a known reaction, although the conditions are usually much more vigorous[4].

With regard to the reaction conditions (Table 2), the following statements can be made: (a) reaction time: at 50°C in 33% (v/v) aqueous acetic acid, the time required for complete conversion was found to be 7−9 h. However, the formation of dichlorinated products increased with time from 3 to 12%. The best yield of the monochlorinated products (91%) was obtained after 4.5 h at 77% conversion; (b) temperature: the conversion increased when the temperature was raised from 30 to 50°C (in the same solvent for 9 h), but the yield decreased somewhat due to the increased formation of dichlorinated products. The best compromise seemed to be achieved at 40−45°C; (c) solvent: glacial acetic acid was found to be unsuitable and only moderate results were obtained in water; the best results were obtained in 33% (v/v) aqueous acetic acid.

Other polar solvents could be used (Table 3), such as aqueous trifluoroacetic acid, aqueous nitromethane or a heterogeneous mixture of water and sulfolane. The proportion of the *m*-chloro isomer formed decreased in such media.

In order to gather more quantitative information about the influence of the dialkylaminocarbonyl group, the standard technique of competition was used. When chlorinated in the same flask, *N,N*-diisopropylbenzamide was converted 4 times less rapidly than chlorobenzene to give cleanly a mixture of *N,N*-diisopropylchlorobenzamides (50:15:35) and dichlorobenzenes (34:0.5:65.5).

The formation of the dichlorinated products was investigated by chlorinating both 2-chloro-*N,N*-diisopropylbenzamide and its 4-chloro isomer under the same conditions. The results in Table 4 show that the chlorination in this case takes place essentially at the positions *para* to the *ortho*-chlorine and *ortho* to the *para*-chlorine. Dealkylation of the amido group competes with the chlorination reaction, particularly in the latter case.

Table 2. Study of the monochlorination conditions of *N,N*-diisopropylbenzamide (1 mmol) with chlorine (80−100 bubbles/min) in aqueous acetic solution (8 ml)

conditions	conv. (%)	yield (%)	*o*/*m*/*p*	other products
t (h)[a]				
4.5	77	91	47:13:40	dichloro (3%), BzNH*i*Pr (3%), BzOH (< 3%)
7	97	85	46:10:44	dichloro (7%), BzNH*i*Pr (5%), BzOH (2%)
9	100	82	47:11:42	dichloro (12%), BzNH*i*Pr (< 4%), BzOH (< 4%)
T (°C)[b]				
30−35	67	93	48:14:38	BzNH*i*Pr (4%)
40−45	93	92	47:9:44	dichloro (6%)
50−55	100	82	47:11:42	dichloro (12%), BzNH*i*Pr (< 4%), BzOH (< 4%)
C_{HOAc}[c]				
100	trace	–	–	–
50	84	81	46:11:43	dichloro (8%), BzOH (4%)
30	100	82	47:11:42	dichloro (12%), BzNH*i*Pr (< 4%), BzOH (< 4%)
0	91	66	45:19:36	BzNH*i*Pr (25%), BzOH (4%), dichloro (< 3%)

[a] In 33% (v/v) aqueous acetic acid at 50−55°C. – [b] In 33% (v/v) aqueous acetic acid for 9 h. – [c] In percentage indicated (v/v) acetic acid at 50−55°C for 9 h.

Table 3. Monochlorination of *N,N*-diisopropylbenzamide (1 mmol) with chlorine (80−100 bubbles/min) in other aqueous polar solvents (8 ml)[a] at 50°C with reaction times 9 h

solvent	conv. (%)	yield (%)	*o*/*m*/*p*	other products
CF_3CO_2H/H_2O	35	71	36:18:46	BzOH (13%), BzNH*i*Pr (7%), dichloro (4%)
$MeNO_2/H_2O$	55	55	41:8:51	BzNH*i*Pr (20%), dichloro (2%), BzOH (< 2%), *m*-ClBzOH (2%)
sulfolane/H_2O	99	80	43:5:52	dichloro (11%), BzNH*i*Pr (2%), BzOH (2%), *m*-ClBzOH (3%)

[a] See Experimental Section.

Table 4. Chlorination of 2- and 4-chloro-*N,N*-diisopropylbenzamides (0.42 mmol) with chlorine (80−100 bubbles/min) in 50% (v/v) aqueous acetic acid solution (16 ml) at 70°C with reaction times 9 h

amide	conv. (%)	main product	yield (%)	other products
2-ClBzN*i*Pr$_2$	38	2,5-Cl$_2$	81	2-ClBzNH*i*Pr (8%), 2,3-Cl$_2$ (< 5%)
4-ClBzN*i*Pr$_2$	9	3,4-Cl$_2$	65	4-ClBzNH*i*Pr (22%), 2,4-Cl$_2$ (< 3%)

It might be suspected that under the reaction conditions used, the actual chlorinating reagent is hypochlorous acid (HOCl), most probably in its protonated form[5][6], or possibly acetyl hypochlorite (AcOCl), also in protonated form[7][8][9]. The hydrochloric acid formed in the chlori-

nation makes the medium increasingly acidic. Calcium hypochlorite has been reported to ring-chlorinate activated aromatic compounds such as toluene and anisole in aqueous acetone/acetic acid solution at 0°C[10]. Under these conditions, *N,N*-diisopropylbenzamide was largely unchanged. In contrast, use of calcium hypochlorite in aqueous acetic acid solution led to efficient conversion when three equivalents were used (Table 5). It can be seen that the results closely resemble those obtained with chlorine gas. Acetyl hypochlorite itself has been shown to efficiently halogenate aromatic compounds[7][11], and it could be formed and hydrolysed under the conditions employed[6].

Table 5. Monochlorination of *N,N*-diisopropylbenzamide (1 mmol) with calcium hypochlorite (*n* equiv.) in 33% (v/v) aqueous acetic acid solution (8 ml)

n	*T* (°C)	*t* (h)	conv. (%)	yield (%)	*o*/*m*/*p*	other products
1.5	70	24	20	92	42:21:37	BzNH*i*Pr (4%)
2	70	24	35	91	43:18:39	BzNH*i*Pr (4%)
3	70	24	90	90	49:12:39	dichloro (6%), BzNH*i*Pr (< 2%)
2	50	24	46	93	52:15:33	BzNH*i*Pr (2%)
3	50	16	92	94	46:13:41	BzNH*i*Pr (< 2%), dichloro (3%)
3	50	8	82	94	46:14:40	BzNH*i*Pr (1%), dichloro (< 2%)
3	20	48	63	97	49:15:36	BzNH*i*Pr (1%)

When *N,N*-diisopropylbenzamide was treated with acetyl hypochlorite prepared from chlorine gas and silver acetate[11][12] in acetic acid at 50°C or in $CFCl_3$ at room temperature, essentially no reaction took place. However, in nitromethane at 120°C, a 2% conversion was observed (*o*/*m*/*p* = 48:19:33).

Bromination

For the bromination of deactivated aromatic compounds such as benzoic acid derivatives, a classical technique uses bromine, potassium bromate, and sulfuric acid in aqueous acetic acid at room temperature[13]. It is suggested that the bromine is hydrolysed to hypobromic and hydrobromic acids, and that the former, or its conjugate acid H_2OBr^+, is responsible for the aromatic substitution. The bromide ion is reoxidized to bromine by the potassium bromate, as illustrated in Equations 1−3.

$$Br_2 + H_2O \rightleftharpoons HOBr + H^+ + Br^- \quad (1)$$

$$HOBr + H^+ \rightleftharpoons H_2OBr^+ \quad (2)$$

$$6H^+ + 5Br^- + BrO_3^- \rightleftharpoons 3H_2O + 3Br_2 \quad (3)$$

We first examined the bromination of benzoic acid under Derbyshire and Waters′ conditions[13], which is reported to give 60% of pure *m*-bromobenzoic acid as a precipitate. Extraction of the reaction mixture, conversion of the acids into their methyl esters with diazomethane, and analysis by GLC showed the total yield of *m*-bromobenzoic acid to be 92% (Table 6, run 1). When *N,N*-diisopropylbenzamide was similarly treated (run 2), the conversion was only 52% (bromine was not completely consumed), with the *meta* isomer accounting for only 55% of the mixture formed. Extending the reaction time from 2 to 18 h had no influence on the results (run 3). However, increasing the amount of bromate led to a higher conversion with the same isomer proportions (run 4).

It was later found[14] that the bromination of benzoic acid could be successfully accomplished using potassium bromate and sulfuric acid in aqueous solution. The authors concluded that the bromate was converted by sulfuric acid into bromine and hypobromous acid, which, under the acidic conditions, was responsible for the bromination. Under these conditions[14], *N,N*-diisopropylbenzamide gave a 51% conversion with similar *o*/*m*/*p* proportions (run 5). Addition of one equivalent of potassium bromide led to a higher conversion (77%), with the mixture still rich in the *meta* isomer (run 6). This orientation was rather intriguing, as the disubstituted amide apparently behaved almost like a simple benzoic acid derivative. This led us to speculate that the high concentration of sulfuric acid might be responsible for this behaviour. It is well known that some *o,p*-orienting groups can lead to *meta* substitution when they are protonated. The pK_a values of several disubstituted benzamides have been reported[15]. The authors have observed that these amides can be completely protonated in 60% sulfuric acid solution. Therefore, under Derbyshire and Waters′ conditions (concentrated sulfuric acid/acetic acid/water = 30:50:20, v/v/v), the *N,N*-diisopropylbenzamide is most likely protonated. This would also account for it being less reactive than benzoic acid itself (runs 1 and 2)

This prompted us to reduce the amount of sulfuric acid in the reaction medium. This modification indeed led to a quantitative conversion (96%) to a mixture with *o*/*m*/*p* = 21:12:67 (run 7). Just as in the chlorination of this benzamide, the *o*+*p*/*m* ratio was now very high (88:12). We observed that a slightly better conversion could be obtained when the sulfuric acid or the amide was added last, compared to when the bromate was added last, possibly for solubility reasons (data not shown). Decreasing the amount of bromate (run 8) or bromide (run 9) led to much lower conversion. In aqueous acetic acid, bromine with or without sulfuric acid was completely inactive, even if the reaction was attempted using 4 equiv. of bromine and/or a longer time. Interestingly, when the reaction of potassium bromide and bromate was allowed to proceed for 14 h in the acidic medium before the addition of the amide substrate, the conversion was poor (21%). Bromine was in fact formed, but not consumed.

These facts seem to indicate that the species responsible for the bromination is not formed in the solvolysis of bromine, but in the reaction of bromide ion with bromate. According to the literature, this conversion takes place by way of Equations 4 and 5 and the reverse of Equation 1[16][17].

In order to compare them with *N,N*-diisopropylbenzamide, other aromatic compounds were treated under the bromide/bromate conditions (Table 7). In the case of benzoic acid, selective *meta* bromination and a low conversion was observed (37%, run 2). Heating of the reaction mixture

Table 6. Bromination of benzoic acid (run 1) and *N,N*-diisopropylbenzamide (other runs), 0.3 M in 66% (v/v) aqueous acetic acid at room temperature under different conditions

run	Br_2 (eq)	KBr (eq)	$KBrO_3$ (eq)	H_2SO_4 (l/mol)	*t* (h)	conv. (%)	*o*/*m*/*p*	remarks
1	0.41	0	0.48	1.5	2	100	0:100:0	8% of disub.[13]
2	0.41	0	0.48	1.5	2	52	15:55:30	cond.[13]
3	0.41	0	0.48	1.5	18	42	14:61:25	modified cond.[13]
4	5	0	0.75	1.5	18	86	12:57:31	modified cond.[13]
5	0	0	1	0.8	18	51	10:55:35	cond.[14][a]
6	0	1	0.95	1.5	18	77	13:49:38	
7	0	1	0.95	0.5	18	96	21:12:67	H_2SO_4 last
8	0	0.9	0.2	0.5	18	3	30:20:50	H_2SO_4 last
9	0	0.1	0.95	0.5	18	33	26:22:52	H_2SO_4 last

[a] No acetic acid present, as in ref.[14].

$$2H^+ + Br^- + BrO_3^- \longrightarrow HOBr + HBrO_2 \quad (4)$$

$$H^+ + HBrO_2 + Br^- \longrightarrow 2HOBr \quad (5)$$

at 65°C was necessary to achieve a complete conversion, but this led to the additional formation of 53% of the dibrominated acids (run 3). Methyl benzoate was more easily brominated under these conditions, giving 77% of the *meta*-bromo ester, together with 23% of the dibromo ester (run 4). Nitrobenzene was not converted.

Table 7. Monobromination of *N,N*-diisopropylbenzamide (run 1), benzoic acid (runs 2−3), methyl benzoate (run 4), and nitrobenzene (run 5), 0.3 M in 66% (v/v) aqueous acetic acid, using potassium bromide (1 equiv.), potassium bromate (0.95 equiv.), and sulfuric acid (0.5 ml/mmol substrate)

run	*T* (°C)	*t* (h)	conv. (%)	yield (%)[a]	*o*/*m*/*p*	remarks
1	r. t.	18	96	100	21:12:67	Table 6, run 7
2	r. t.	24	37	100	0:100:0	63% unchanged
3	65°C	22	100	47	0:100:0	53% disub.
4	r. t.	22	96	77	0:100:0	23% disub.
5	r. t.	22	< 5	N. D.	N. D.	

[a] Calculated based on the initial compounds converted.

As far as other benzamides are concerned (Table 8), the bromination of *N,N*-diethylbenzamide was much less selective (compare runs 1 and 2). The di-*n*-octylamide was used to evaluate the possible influence of a long, straight chain on the *o*-bromination. The reaction was much slower, as shown by a lower conversion under the same conditions, and the selectivity was not greater than that with the diethylamide (run 3). A higher temperature did not improve matters. On the other hand, *N*-benzoyl-2,6-*cis*-dimethylpiperidine gave a somewhat higher *o*+*p*/*m* ratio than the diisopropyl derivative, with a remarkable increase in the degree of *para* substitution (run 4).

The carboxamide group resembles acid or ester groups. Nitration of benzamide gives a ratio of isomers *o*/*m*/*p* = 27:70:3[18]. There is no obvious simple electronic reason why substituted amides should react differently. On going from benzoic acid to sodium benzoate, it is known that the orientation changes drastically. Chlorination of the salt gives the monochloro acids (70% conversion, 90% yield, *o*/*m*/*p* = 47:33:20)[19][20]. The Hammett−Brown σ^+ value for the anionic COO^- group is slightly negative in the *para* position, whereas the ester group has a strongly positive value[21].

Table 8. Bromination of (1): *N,N*-diethyl-, (2): *N,N*-diisopropyl-, (3): *N,N*-di-*n*-octylbenzamide, and (4) *N*-benzoyl-2,6-*cis*-dimethylpiperidine (1 mmol) with $KBr/KBrO_3/H_2SO_4$ (1 mmol:0.95 mmol:0.5 ml) in 66% (v/v) aqueous acetic acid (3.5 ml)

amide	*T* (°C)	*t* (h)	conv. (%)	*o*/*m*/*p*
1	r. t.	18	98	11:30:59
2	r. t.	18	96	21:12:67
3	r. t.	20	53	13:42:45
3′	60	48	19	17:33:50
4	r. t.	18	100	6:13:81

As regards the amides, the attachment of large alkyl groups at the nitrogen atom could lead to hindrance of coplanarity, i.e. inhibition of resonance, and therefore modify the behaviour of the group.

Table 9. Correlation between the torsional angle of different *N*-substituted benzamides ($PhCONR^1R^2$) and the *o*/*m*/*p* proportions of their halogenation products

R^1, R^2	H, *i*Pr	Me, Me	Et, Et	*i*Pr, *i*Pr	DMP
torsional angle[a]	28	47	57	65	70
o/*m*/*p*-Cl	41:48:11	48:28:24	39:26:35	47:11:42	72:8:20
o/*m*/*p*-Br			11:30:59	21:13:66	6:13:81

[a] Values reported in ref.[22].

It has been established by NMR measurements, and in some cases by X-ray structure determinations, that as the bulk of the *N*-substituents increases, the carboxamido group is rotated more and more out of coplanarity[22]. It can be seen in Table 9 that the proportions of isomers formed in the halogenation reaction show a correlation with the torsion angle. In order to evaluate this hypothesis, *N*-benzoyl-2,6-*cis*-dimethylpiperidine, which has been reported to display the highest torsion angle, was prepared and submitted to the same reaction conditions. It was found

to lead to the highest *o*+*p*/*m* ratio of substitution products (Table 9).

Finally, hydrolysis conditions of the ring-halogenated diisopropylbenzamides were studied. The usual method for the hydrolysis of carboxylic amides (6 N HCl, reflux, 24 h) was found to be unsuitable in this case. However, in the presence of zinc chloride (Lucas′ reagent[23]), concentrated hydrochloric acid proved very efficient at high temperature. All monohalogenated diisopropylbenzamides were quantitatively transformed into the corresponding acids, together with in some cases a little of the monosubstituted amide derivatives (below 10%) when using the reagents in the ratio amide/conc. HCl/$ZnCl_2$ = 1:5−10:2−10.

Conclusion

A modified technique has been used to accomplish the bromination of aromatic compounds not activated to electrophilic attack. The hindrance to coplanarity in benzamides bearing bulky *N*-substituents has been shown to lead to a substantially higher *o*+*p*/*m* distribution of isomers formed in the ring chlorination or bromination. This shows once again the importance of evaluating the consequences of "small" modifications of a system when attempting to predict the outcome of reactions. Whereas benzoic acids undergo electrophilic substitution almost exclusively at the *m*-position, conversion of the acid into a hindered *N*,*N*-disubstituted amide leads, after substitution and hydrolysis, to the *o*,*p*-substituted isomers. This, of course, can only be applied to compounds sufficiently stable to withstand the rather drastic hydrolysis conditions.

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Experimental Section

^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ or [D_6]DMSO with a Bruker AC 250 spectrometer; chemical shifts are expressed in ppm (δ values) downfield from tetramethylsilane (TMS) or referenced to residual chloroform (δ = 7.27). Coupling constants (*J*) are given in Hz. Mass spectra were recorded with a Nermag R10-10B spectrometer. GC MS was performed using the same mass spectrometer coupled with a capillary column (CPSIL-5CB, 50 × 32 mm). Microanalyses were performed by the Service de Microanalyses of Pierre et Marie Curie University.

The yields and ratios of isomers were determined by gas chromatography (GLC, type Girdel 30) on a capillary column (BP5, SGE, 50 m × 0.22 mm) using the authentic compounds and an internal standard (a similar amide or ester). The starting materials and the authentic samples were prepared by the standard method of treating the appropriate benzoyl chloride with the appropriate amine. The compounds were fully characterized by MS, NMR and microanalysis.

Preparation of Authentic Samples:

o-Chloro-N-ethylbenzamide: M.p. 90−91°C. − ^{1}H NMR ([D_6]DMSO): δ = 1.11 (t, *J* = 18.1, 3 H, Me), 3.24 (m, 2 H, CH_2), 7.40 (m, 2 H, aromatic H), 7.48 (m, 2 H, aromatic H), 8.43 (br., 1 H, NH). − MS (CI, CH_4); *m*/*z*: 184 [M + 1]$^+$, 150, 139. − $C_9H_{10}ClNO$ (183.5): calcd. C 58.86, H 5.49, N 7.63; found C 58.91, H 5.56, N 7.55.

m-Chloro-N,N-diisopropylbenzamide: M.p. 61−62°C. − ^{1}H NMR ($CDCl_3$): δ = 1.06 (br., 6 H, 2 Me), 1.27 (br., 6 H, 2 Me), 3.44 (m, 2 H, 2 CH), 6.98 (m, 1 H, aromatic H), 7.11 (m, 2 H, aromatic H), 7.15 (m, 1 H, aromatic H). − MS (CI, CH_4); *m*/*z*: 240 [M + 1]$^+$, 139. − $C_{13}H_{18}ClNO$ (239.5): calcd. C 65.13, H 7.57, N, 5.84; found C 65.25, H 7.51, N 5.76.

N-(o-Chlorobenzoyl)-2,6-cis-dimethylpiperidine: M.p. 131−132°C. − ^{1}H NMR ($CDCl_3$): δ = 0.95, 1.17 (dd, J_1 = J_2 = 16.0, 3 H, Me), 1.06, 1.20 (dd, J_1 = J_2 = 17.9, 3 H, Me), 1.51 (m, 6 H, 3 CH_2), 3.48, 3.65 (m, 1 H, CH), 4.81 (m, 1 H, CH), 7.07 (m, 2 H, aromatic H), 7.14 (m, 2 H, aromatic H). − MS (CI, CH_4); *m*/*z*: 252 [M + 1]$^+$, 236, 216, 139, 111, 105. − $C_{14}H_{18}ClNO$ (251.5): calcd. C 66.79, H 7.21, N 5.56; found C 66.83, H 7.30, N 5.40.

N-(m-Chlorobenzoyl)-2,6-cis-dimethylpiperidine: M.p. 70−71°C. − ^{1}H NMR ($CDCl_3$): δ = 1.20 (d, *J* = 17.8, 6 H, 2 Me), 1.65 (m, 6 H, 3 CH_2), 4.33 (m, 2 H, 2 CH), 7.13 (m, 1 H, aromatic H), 7.27 (m, 3 H, aromatic H). − MS (CI, CH_4); *m*/*z*: 252 [M + 1]$^+$, 236, 216, 139, 111, 105. − $C_{14}H_{18}ClNO$ (251.5): calcd. C 66.79, H 7.21, N 5.56; found C 66.77, H 7.28, N 5.49.

N-(p-Chlorobenzoyl)-2,6-cis-dimethylpiperidine: M.p. 87−88°C. − ^{1}H NMR ($CDCl_3$): δ = 1.12 (d, *J* = 17.8, 6 H, 2 Me), 1.56 (m, 6 H, 3 CH_2), 4.25 (m, 2 H, 2 CH), 7.13 (d, *J* = 21.0, 2 H, aromatic H), 7.22 (d, *J* = 21.0, 2 H, aromatic H). − MS (CI, CH_4); *m*/*z*: 252 [M + 1]$^+$, 236, 216, 139, 111, 105. − $C_{14}H_{18}ClNO$ (251.5): calcd. C 66.79, H 7.21, N 5.56; found C 66.95, H 7.16, N 5.45.

2,3-Dichloro-N,N-diisopropylbenzamide: M.p. 133−134°C. − ^{1}H NMR ([D_6]DMSO): δ = 1.02 (d, *J* = 16.6, 3 H, Me), 1.12 (d, *J* = 16.7, 3 H, Me), 1.41 (d, *J* = 16.8, 3 H, Me), 1.43 (d, *J* = 16.7, 3 H, Me), 3.37 (m, 1 H, CH), 3.55 (m, 1 H, CH), 7.26 (dd, J_1 = 3.90, J_2 = 19.1, 1 H, aromatic H), 7.40 (t, *J* = 19.1, 1 H, aromatic H), 7.62 (dd, J_1 = 3.90, J_2 = 19.1, 1 H, aromatic H). − MS (CI, NH_3); *m*/*z*: 274 [M + 1]$^+$. − $C_{13}H_{17}Cl_2NO$ (274): calcd. C 56.94, H 6.25, N 5.11; found C 57.12, H 6.21, N 4.99.

2,4-Dichloro-N,N-diisopropylbenzamide: M.p. 97−98°C. − ^{1}H NMR ([D_6]DMSO): δ = 1.04 (d, *J* = 16.6, 3 H, Me), 1.14 (d, *J* = 16.7, 3 H, Me), 1.43 (d, *J* = 16.8, 3 H, Me), 1.46 (d, *J* = 16.8, 3 H, Me), 3.41 (m, 1 H, CH), 3.59 (m, 1 H, CH), 7.35 (d, *J* = 20.5, 1 H, aromatic H), 7.49 (dd, J_1 = 4.75, J_2 = 20.5, 1 H, aromatic H), 7.70 (d, *J* = 4.75, 1 H, aromatic H). − MS (CI, NH_3); *m*/*z*: 274 [M + 1]$^+$. − $C_{13}H_{17}Cl_2NO$ (274): calcd. C 56.94, H 6.25, N 5.11; found C 57.13, H 6.20, N 4.94.

2,5-Dichloro-N,N-diisopropylbenzamide: M.p. 153−154°C. − ^{1}H NMR ([D_6]DMSO): δ = 1.07 (d, *J* = 16.5, 3 H, Me), 1.15 (d, *J* = 16.5, 3 H, Me), 1.43 (d, *J* = 16.5, 3 H, Me), 1.46 (d, *J* = 16.6, 3 H, Me), 3.43 (m, 1 H, CH), 3.57 (m, 1 H, CH), 7.46 (m, 1 H, aromatic H), 7.49 (m, 1 H, aromatic H), 7.55 (m, 1 H, aromatic H). − MS (CI, NH_3); *m*/*z*: 274 [M + 1]$^+$. − $C_{13}H_{17}Cl_2NO$ (274): calcd. C 56.94, H 6.25, N 5.11; found C 57.19, H 6.34, N 4.92.

3,4-Dichloro-N,N-diisopropylbenzamide: M.p. 81−82°C. − ^{1}H NMR ([D_6]DMSO): δ = 1.12 (br., 6 H, 2 Me), 1.40 (br., 6 H, 2 Me), 3.45 (m, 1 H, CH), 3.57 (m, 1 H, CH), 7.30 (dd, J_1 = 4.75, J_2 = 20.5, 1 H, aromatic H), 7.58 (d, *J* = 4.75, 1 H, aromatic H), 7.69 (d, *J* = 20.5, 1 H, aromatic H). − MS (CI, NH_3); *m*/*z*: 274 [M + 1]$^+$. − $C_{13}H_{17}Cl_2NO$ (274): calcd. C 56.94, H 6.25, N 5.11; found C 57.11, H 6.27, N 4.95.

N-(o-Bromobenzoyl)-2,6-cis-dimethylpiperidine: M.p. 134.4−136.1 °C. − ^{1}H NMR ($CDCl_3$): δ = 0.96 (d, *J* = 16.5, 2 H, CH_3), 1.10 (d, *J* = 17.8, 1 H, CH_3*), 1.26 (d, *J* = 17.4, 2 H, CH_3), 1.30 (d, *J* = 18.1, 1 H, CH_3), 1.36−1.64 (m, 6 H, CH_2), 3.47 (m, 9/13 H, CH), 3.68 (m, 4/13 H, CH), 4.81 (m, 1 H, CH*), 7.08 (m, 3 H,

aromatic H), 7.19 (m, 1 H, aromatic H). – ^{13}C NMR ($CDCl_3$): δ = 168.494, 168.144, 139.354, 138.836, 133.286, 132.378, 129.506, 127.390, 127.278, 127.130, 126.777, 119.337, 118.879, 49.816, 49.243, 43.910, 43.729, 30.530, 29.701, 21.416, 21.196, 20.383, 14.047, 13.960. – MS (CI, NH_3); *m/z*: 296 and 298 $[M + 1]^+$, 216, 185 and 183, 105. – $C_{14}H_{18}BrNO$ (296): calcd. C 56.76, H 6.13, N 4.73; found C 56.72, H 6.13, N 4.76.

N-(m-Bromobenzoyl)-2,6-cis-dimethylpiperidine: M.p. 74–75°C. – ^{1}H NMR ($CDCl_3$): δ = 1.25 (d, *J* = 17.7, 6 H, CH_3), 1.48–1.74 (m, 6 H, 3 CH_2), 4.37 (br., 2 H, CH), 7.24 (m, 2 H, aromatic H), 7.47 (m, 2 H, aromatic H). – ^{13}C NMR ($CDCl_3$): δ = 169.540, 139.695, 131.749, 130.039, 128.922, 124.401, 122.543, 46.783 (br), 30.065, 21.127, 14.022. – MS (CI, NH_3); *m/z*: 296 and 298 $[M + 1]^+$, 216, 183 and 185, 114 and 112, 105. – $C_{14}H_{18}BrNO$ (296): calcd. C 56.76, H 6.13, N 4.73; found C 56.69, H 5.98, N 4.80.

N-(p-Bromobenzoyl)-2,6-cis-dimethylpiperidine: M.p. 92.1–93.4°C. – ^{1}H NMR ($CDCl_3$): δ = 1.25 (d, *J* = 17.8, 6 H, CH_3), 1.48–1.74 (m, 6 H, 3 CH_2), 4.37 (br., 2 H, CH), 7.18 and 7.22 (dd, J_1 = 11.6, J_2 = 5.10, 2 H, aromatic H), 7.49 and 7.53 (dd, J_1 = 11.6, J_2 = 5.10, 2 H, aromatic H). – ^{13}C NMR ($CDCl_3$): δ = 170.210, 136.570, 131.553, 127.564, 122.742, 46.783 (br), 30.009, 21.078, 13.964. – MS (CI, NH_3); *m/z*: 296 and 298 $[M^+]$, 216, 183 and 185, 112 and 114. – $C_{14}H_{18}BrNO$ (296): calcd. C 56.76, H 6.13, N 4.73; found C 56.87, H 6.10, N 4.59.

o-Bromo-N,N-di-n-octylbenzamide: ^{1}H NMR ($CDCl_3$): δ = 0.70 (d, *J* = 17.6, 6 H, CH_3), 1.10 (m, 24 H, CH_2), 2.87 (m, 2 H, CH_2N), 3.05 (m, 1 H, CH_2N), 3.58 (m, 1 H, CH_2N), 7.05 (m, 2 H, aromatic H), 7.14 (ddd, J_1 = 17.8, J_2 = 16.2, J_3 = 2.70, 1 H, aromatic H), 7.37 (dd, J_1 = 17.8, J_2 = 1.70, 1 H, aromatic H). – ^{13}C NMR ($CDCl_3$): δ = 168.606, 138.893, 132.695, 129.882, 127.861, 127.438, 119.262, 48.344, 44.571, 31.847, 31.705, 29.412, 29.313, 29.023, 28.974, 28.309, 27.188, 26.542, 22.669, 22.592, 14.130, 14.089. – MS (CI, NH_3); *m/z*: 424 and 426 $[M + 1]^+$, 346, 185 and 183, 128, 122. – $C_{23}H_{38}BrNO$ (424): calcd. C 65.08, H 9.02, N 3.30; found C 65.14, H 9.03, N 3.22.

m-Bromo-N,N-di-n-octylbenzamide: ^{1}H NMR ($CDCl_3$): δ = 0.71 (t, 6 H, CH_3), 1.16 (m, 24 H, CH_2), 2.97 (t, 2 H, CH_2N), 3.27 (t, 2 H, CH_2N), 7.08 (m, 2 H, aromatic H), 7.31 (m, 2 H, aromatic H). – ^{13}C NMR ($CDCl_3$): δ = 169.631, 139.022, 131.879, 129.769, 129.348, 124.817, 122.233, 48.762, 44.624, 31.525, 28.852, 28.388, 27.261, 26.829, 26.262, 22.386, 13.845. – MS (CI, NH_3); *m/z*: 424 and 426 $[M + 1]^+$, 346, 185 and 183. – $C_{23}H_{38}BrNO$ (424): calcd. C 65.08, H 9.02, N 3.30; found C 65.11, H 9.08, N 3.30.

p-Bromo-N,N-di-n-octylbenzamide: ^{1}H NMR ($CDCl_3$): δ = 0.70 (t, 6 H, CH_3), 1.10 (m, 24 H, CH_2), 2.97 (t, 2 H, CH_2N), 3.27 (t, 2 H, CH_2N), 7.02 and 7.06 (dd, 2 H, aromatic H), 7.31 and 7.35 (dd, 2 H, aromatic H). – ^{13}C NMR ($CDCl_3$): δ = 170.463, 136.212, 131.534, 128.204, 123.186, 48.984, 44.837, 31.751, 29.244, 29.063, 28.622, 27.472, 27.034, 26.496, 22.603, 14.072. – MS (CI, NH_3); *m/z*: 424 and 426 $[M + 1]^+$, 344, 234, 183 and 185, 128, 122. – $C_{23}H_{38}BrNO$ (424): calcd. C 65.08, H 9.02, N 3.30; found C 65.21, H 9.06, N 3.24.

N-Ethylbenzamide[24], *N-isopropylbenzamide*[25], *N-tert-butylbenzamide*[26], *N,N-diethylbenzamide*[27], *N,N-diisopropylbenzamide*[27], *N-benzoyl-2,6-cis-dimethylpiperidine*[28], *m-chloro-N-ethylbenzamide*[29], *p-chloro-N-ethylbenzamide*[30], *o-chloro-N-isopropylbenzamide*[31], *m-chloro-N-isopropylbenzamide*[32], *p-chloro-N-isopropylbenzamide*[29], *o-chloro-N-tert-butylbenzamide*[32], *m-chloro-N-tert-butylbenzamide*[29], *p-chloro-N-tert-butylbenzamide*[29], *o-chloro-N,N-dimethylbenzamide*[33], *m-chloro-N,N-dimethylbenzamide*[33], *p-chloro-N,N-dimethylbenzamide*[33], *o-chloro-N,N-diethylbenzamide*[27], *m-chloro-N,N-diethylbenzamide*[27], *p-chloro-N,N-diethylbenzamide*[27], *o-chloro-N,N-diisopropylbenzamide*[34], *p-chloro-N,N-diisopropylbenzamide*[22], *2,6-dichloro-N,N-diisopropylbenzamide*[34], and *chloromethyl benzoate*[35] were synthesized and identified by comparison with literature data.

Chlorination of Benzoic Acid Derivatives with Chlorine in Aqueous Acetic Acid: The typical procedure for this reaction was to heat a mixture of the benzoic acid derivative (1 mmol) in 33% (v/v) aqueous acetic acid (8 ml) to 50°C, and then to pass chlorine (80–100 bubbles/min) through the solution over a period of 9 h with continuous stirring. The reaction vessel was then opened to air to allow the remaining chlorine to dissipate. The mixture was cooled to room temperature and the composition was analysed by GLC (in cases where the mixture was heterogeneous, 10 ml DMF was added). The results are collected in Tables 1 and 2.

Chlorination of N,N-Diisopropylbenzamide with Chlorine in Other Solvents: According to the above procedure, the same reaction was carried out in 66% (v/v) aqueous sulfolane, 66% (v/v) aqueous nitromethane, and 33% (v/v) aqueous trifluoroacetic acid. Work-up procedures were the same as described above (Table 3).

Chlorination of 4-Chloro-N,N-diisopropylbenzamide and 2-Chloro-N,N-diisopropylbenzamide: 4-Chloro-*N,N*-diisopropylbenzamide or 2-chloro-*N,N*-diisopropylbenzamide (100 mg, 0.42 mmol) was dissolved in 50% aqueous acetic acid (16 ml) and the solution was heated to 70°C. At this temperature, chlorine (80–100 bubbles/min) was passed through the solution for a period of 9 h. The subsequent work-up was the same as described above (Table 4).

Competitive Chlorination of N,N-Diisopropylbenzamide and Chlorobenzene: N,N-Diisopropylbenzamide (410 mg, 2 mmol) and chlorobenzene (225 mg, 2 mmol) were dissolved in 50% (v/v) aqueous acetic acid (16 ml) and the solution was heated to 50°C. Chlorine was then bubbled through the solution for 2 h (80–100 bubbles/min). At the end of the reaction, the flask was opened and the contents were allowed to cool to room temperature. Acetone (10 ml) was added to the mixture to dissolve the dichlorobenzene formed. Analysis by GLC showed that 70% of the chlorobenzene and 18% of the diisopropylbenzamide had been consumed, to give 96% and 95% of the corresponding dichlorobenzenes and monochlorodiisopropylbenzamides. The proportion of dichlorobenzene isomers (*o*/*m*/*p*) obtained was 34:0.5:65.5, while the *o*/*m*/*p* ratio of the monochloro-*N,N*-diisopropylbenzamides was 50:15:35.

Chlorination of N,N-Diisopropylbenzamide with Hypochlorous Acid in Aqueous Acetic Acid: A solution of *N,N*-diisopropylbenzamide (205 mg, 1 mmol) in 33% (v/v) aqueous acetic acid (8 ml) was treated with calcium hypochlorite (available chlorine 65%, 330 mg, 3 mmol hypochlorous acid) and the mixture was heated to 50°C for 16 h. After cooling to room temperature, water (30 ml) was added. The mixture was extracted with chloroform (4 × 30 ml) and the combined extracts were dried with $MgSO_4$. Analysis by GLC showed that 92% of the starting material had been consumed to give 94% of the monochloro derivative, with an isomer ratio (*o*/*m*/*p*) of 46:11:43 (Table 5).

Chlorination of N,N-Diisopropylbenzamide with Acetyl Hypochlorite. – (a) In Acetic Acid: To a stirred suspension of silver acetate (802 mg, 4.8 mmol) in acetic acid (24 ml) at room temperature (22°C), was added an acetic acid solution (12 ml) of chlorine (320 mg, 4.5 mmol), followed by *N,N*-diisopropylbenzamide (615 mg, 3 mmol). The mixture was stirred at room temperature (or at 50°C) for 9 h, then filtered, and the filtrate was analysed by GLC.

(b) In Nitrobenzene: The procedure was exactly the same as described above, except for the solvent ($C_6H_5NO_2$) and the reaction temperature (120°C).

(c) In Trichlorofluoromethane: To a stirred suspension of silver acetate (802 mg, 4.8 mmol) in trichlorofluoromethane (30 ml) at 0°C, a trichlorofluoromethane solution (40 ml) of chlorine (320 mg, 4.5 mmol) was added by means of a dropping funnel over a period of 5 min under argon. After the addition was complete, the mixture was stirred for a further 30 min. The dropping funnel was then removed and a solution of *N,N*-diisopropylbenzamide (615 mg, 3 mmol) in trichlorofluoromethane (20 ml) was added. The reaction was allowed to proceed for 9 h at 18°C. However, after filtration, analysis of the filtrate by GLC revealed only starting material.

Bromination of Benzamides with Bromine and Bromic Acid in Aqueous Acetic Acid (Derbyshire and Waters' Method): The benzamide (1 mmol) and bromine (21 µl) were dissolved in a mixture of glacial acetic acid (2.5 ml) and concentrated sulfuric acid (> 95%, 1.5 ml). A solution of potassium bromate (40 mg in 0.5 ml of warm water) was added dropwise with vigorous stirring, the temperature being maintained at 25°C by external cooling. After the mixture had been stirred continuously for a further 1 h, a second, similar portion of potassium bromate solution was added. After a further 1 h, the reaction was terminated by the addition of a solution of sodium metabisulfite until the bromine colour had completely disappeared. The organic compounds were then extracted with diethyl ether. After work-up (Na_2CO_3, H_2O), the conversion percentage and the *o*/*m*/*p* proportion were determined by GLC, using the *p*-chloro derivative of the same amide as an internal standard, as well as authentic samples.

Bromination of Benzamides with a Mixture of Potassium Bromate and Sulfuric Acid (Harrison's Method): Concentrated sulfuric acid (> 95%, 0.8 ml) was added to a well-stirred suspension of the benzamide (1 mmol) and potassium bromate (1 mmol) in water (0.7 ml), with the temperature maintained at 25°C by external cooling (complete dissolution at the end of the addition). After 18 h, the reaction was stopped, and the reaction mixture was worked-up and analysed as above.

Bromination of Benzamides with a Mixture of Potassium Bromide/Potassium Bromate/Sulfuric Acid in Aqueous Acetic Acid: Concentrated sulfuric acid (> 95%, 0.5 ml) was added to a mixture of the benzamide (1 mmol), potassium bromide, and potassium bromate in 66% (v/v) aqueous acetic acid (3.5 ml), with the temperature maintained at 25°C by external cooling. After 18 h, the reaction was stopped, and the reaction mixture was worked-up and analysed as above.

The same experiment was also performed with the amide or the potassium bromate (solution in warm water) being added last.

Hydrolysis of the Benzamides with Concentrated HCl in the Presence of Zinc Chloride: A mixture of the appropriate monohalogenated diisopropylbenzamide, zinc chloride, and hydrochloric acid was heated under reflux with an external oil bath at 160°C for 3 d, with a plastic balloon fitted on top of the condenser to prevent HCl evaporation from the reaction system. At the end of the reaction, the mixture was cooled (solidification), diluted with water, and extracted twice with diethyl ether. The combined organic layers were extracted twice with an aqueous saturated solution of $NaHCO_3$, washed with water, and dried with $MgSO_4$. Removal of the solvent in vacuo left the *N*-monosubstituted amide. The $NaHCO_3$ layer was acidified to pH = 1 and then extracted twice with diethyl ether or ethyl acetate. The combined organic layers were washed with water, and dried with $MgSO_4$. Removal of the solvent gave the acid as a white powder. All products were characterized by NMR, MS, and microanalysis, and by comparison with the authentic compounds.

Typical Example: o-Chloro-*N,N*-diisopropylbenzamide (239.5 mg, 1 mmol) was treated with concentrated HCl (0.83 ml, 10 mmol) and zinc chloride (0.54 g, 4 mmol) under the conditions outlined above, to afford 138 mg of the acid (89%) and 17.7 mg of the monosubstituted amide (9%).

The same procedure was used for *m*-chloro-*N,N*-diisopropylbenzamide (239.5 mg, 1 mmol), *p*-chloro-*N,N*-diisopropylbenzamide (239.5 mg, 1 mmol) and *p*-bromo-*N,N*-diisopropylbenzamide (284 mg, 1 mmol) to give the corresponding acids in yields of 96, 100 and 88% , respectively; 7% of the monosubstituted amide was also detected in the latter case. With *o*-bromo-*N,N*-diisopropylbenzamide (284 mg, 1 mmol), 0.83 ml (10 mmol) of concentrated HCl and 1.35 g (10 mmol) of zinc chloride were used, to give 90% of the acid and no monosubstituted amide was detected. With *m*-bromo-*N,N*-diisopropylbenzamide (710 mg, 2.5 mmol), 1.0 ml (12 mmol) of concentrated HCl and 0.66 g (5 mmol) of zinc chloride were used, to give 90% of the acid and 8% of the monosubstituted amide.

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