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A Comparison of the Reactions of Some Ethyl *N*-Arylcarbamates with Those of the Corresponding Acetanilides. II* Amidomethylation with *N*-Hydroxymethylphthalimide

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Abstract

The reactions of some ethyl *N*-arylcarbamates and of the corresponding acetanilides towards 1 equiv. of *N*-hydroxymethylphthalimide in concentrated sulfuric acid at 50° have been compared with one another. In the case of certain *para*-substituted compounds, amidomethylation occurs more readily *ortho* to the carbamate group than to the *N*-acetyl group. The diagnostic use of (D_6)benzene as a ^{1}H n.m.r. solvent, particularly for the structural elucidation of the *ortho*-(phthalimidomethyl)-phenylcarbamates and -acetanilides, is reported. Acidic treatment of the *ortho*-(phthalimidomethyl)phenylcarbamates, but not of the corresponding acetanilides, gave 8-substituted isoindolo[1,2-*b*]quinazolin-12(10*H*)-ones. Amidomethylation of the parent anilines is also described.

Introduction

We have recently reported the results of a study in which the nitrations of some ethyl *N*-arylcarbamates with sodium nitrate (1 equiv.) in concentrated sulfuric acid solution at 0–5° were compared with those of the corresponding acetanilides.[1] Except in the case of the unsubstituted analogues, nitration has a significantly greater tendency to occur *ortho* to the carbamate group than to the *N*-acetyl group. On the basis of competitive reactions, we have suggested that this difference in reactivity is due to steric factors.

We were interested to learn whether this difference in reactivity was shown by other reagents and, in the present work, we report the results of a similar comparative study where the reagent used was *N*-hydroxymethylphthalimide in concentrated sulfuric acid, i.e., the conditions of the Tscherniac–Einhorn reaction.[2] This reagent has been used widely for the introduction of the phthalimidomethyl group (and, hence, after suitable removal of the phthaloyl substituent, the aminomethyl group) into aromatic and other substrates (cf.[2–5]). Recently, we and others have described its reaction with a variety of *N*,*N*-

* Part I, *Aust. J. Chem.*, 1985, **38**, 723.

[1] Rosevear, J., and Wilshire, J. F. K., *Aust. J. Chem.*, 1985, **38**, 723.
[2] Hellmann, H., *Angew. Chem.*, 1957, **69**, 463.
[3] Zaugg, H. E., and Martin, W. B., *Org. React.*, 1965, **14**, 53.
[4] Zaugg, H. E., *Synthesis*, 1970, 49.
[5] Zaugg, H. E., *Synthesis*, 1981, 85.

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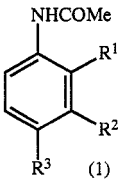
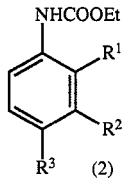
dialkylanilines,[6] and with 1,3,3-trimethyl-2-methyleneindoline (Fischer's base).[7] In addition, we report its reaction with the corresponding anilines. Prior to our work, the reactions of *N*-hydroxymethylphthalimide with aniline,[8] acetanilide,[8,9] *p*-toluidine[8] and *p*-methylacetanilide[8] had been reported. We chose to investigate the amidomethylations of aniline, *p*-toluidine, *p*-chloroaniline and *p*-nitroaniline, and those of the corresponding acetanilides and ethyl *N*-arylcarbamates. The amidomethylation of ethyl *N*-(4-bromophenyl)carbamate was also investigated.

Results and Discussion

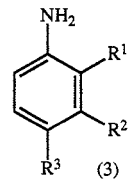
Our results, presented in Table 1, are for amidomethylations with 1 equiv. of *N*-hydroxymethylphthalimide at 50°, the temperature previously used for the corresponding reactions with *N*,*N*-dialkylanilines.[6]



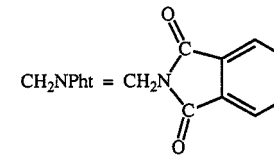
(1)



(2)



(3)



The structures of the amidomethylation products obtained are given by the general formulae (1)–(3) (R^1, R^2 or $R^3 = CH_2NPht$); their melting points and analytical data are presented in Table 2. Several of the reactions gave mixtures of products which were separated into their components by a combination of differences in solubility (usually in ether), crystallization, and chromatography on silica gel. The ^1H chemical shifts (in $CDCl_3$ solution) of the aliphatic protons of the isomeric phthalimides obtained from the same reaction differed significantly from one another. Scheme 1 shows the relevant chemical shifts for those isomers obtained from the amidomethylation of the derivatives of 4-chloroaniline (similar differences in chemical shifts were found for the corresponding derivatives of *p*-toluidine). It was later found that the use of (D_6)benzene induced significant (and diagnostic) solvent shifts; some examples of this solvent effect will be discussed below. However, structural assignments based on chemical shifts alone were uncertain because the effect of the phthalimidomethyl group on the protons of a neighbouring substituent can be either shielding or deshielding (cf.[6]). Unequivocal assignments based on chemical evidence were forthcoming when it was discovered that acidic (sulfuric acid) hydrolyses (with concomitant decarboxylation) at 100° of those carbamates which contain a phthalimidomethyl substituent located *ortho* to the carbamate group [general formula (4)] gave cyclic amides [general formula (5)]. Thus, hydrolysis of the carbamate (4b) [(A) in Scheme 1] gave 8-chloroisoindolo[1,2-*b*]quinazolin-12(10*H*)-one (5b). In contrast, hydrolysis of

[6] Gale, D. J., and Wilshire, J. F. K., *Aust. J. Chem.*, 1975, **28**, 2447.
[7] Gale, D. J., Lin, J., and Wilshire, J. F. K., *Aust. J. Chem.*, 1977, **30**, 689.
[8] Ota, M., Kaneyuki, H., and Matsui, K., *Nippon Kagaku Zasshi*, 1960, **81**, 1849 (*Chem. Abstr.*, 1962, **56**, 2373b).
[9] Maki, R., Ishida, Y., Satako, K., and Oda, R., *J. Chem. Soc. Jpn (Ind. Chem. Sect.)*, 1954, **57**, 44 (*Chem. Abstr.*, 1955, **49**, 10907h).

Table 1. Amidomethylation of the phenyl ring in ethyl *N*-arylcarbamates, acetanilides and anilines

N-Hydroxymethylphthalimide (1 equiv.) was used. Unless otherwise stated, concentrated sulfuric acid (97–99%) was the solvent, and the temperature was 50°. Yields are based on the amount of *reagent* used; those in **bold** type were obtained by ^{1}H n.m.r. analysis

Substrate	Derivatives isolated[A] and yields
Aniline	3-CH_2NPht **44%**, 4-CH_2NPht **44%**
Acetanilide	2-CH_2NPht 18%, 4-CH_2NPht 57%
Ethyl *N*-phenylcarbamate	2,4-$(CH_2NPht)_2$ 71%, (2-+4-CH_2NPht)[F]
Ethyl *N*-phenylcarbamate[B]	2,4-$(CH_2NPht)_2$ 61%, (2-+4-CH_2NPht)[F]
Ethyl *N*-phenylcarbamate[C]	2-CH_2NPht 21%, 4-CH_2NPht 42%
Ethyl *N*-phenylcarbamate[D]	2-CH_2NPht 31%, 4-CH_2NPht 62%
p-Toluidine	3-CH_2NPht 75%
4-Methylacetanilide	2-CH_2NPht 16%, 3-CH_2NPht 75%
Ethyl *N*-(4-methylphenyl)carbamate	2-CH_2NPht **42%**, 3-CH_2NPht **25%**, 2,5-$(CH_2NPht)_2$ 10%
Ethyl *N*-(4-methylphenyl)carbamate[B]	2-CH_2NPht **50%**, 3-CH_2NPht **39%**, 2,5-$(CH_2NPht)_2$ 2%
Ethyl *N*-(4-methylphenyl)carbamate[E]	2-CH_2NPht **39%**, 3-CH_2NPht **22%**, 2,5-$(CH_2NPht)_2$ 4%
4-Chloroaniline	3-CH_2NPht 72%
4-Chloroacetanilide	2-CH_2NPht 12%, 3-CH_2NPht 68%
Ethyl *N*-(4-chlorophenyl)carbamate	2-CH_2NPht 67%, 3-CH_2NPht 16%
4-Nitroaniline	no reaction (see Experimental)
4-Nitroacetanilide	no reaction (see Experimental)
Ethyl *N*-(4-nitrophenyl)carbamate	2-CH_2NPht 75%
Ethyl *N*-(4-bromophenyl)carbamate	2-CH_2NPht 73%

[A] Mono- or bis-(phthalimidomethyl) derivatives. [B] Conc. H_2SO_4 at 0–5°. [C] '90%' H_2SO_4 at 50°. [D] '90%' H_2SO_4 at 0–5°. [E] '95%' H_2SO_4 at 50°. [F] Analysis uncertain, see Experimental.

Table 2. Phthalimidomethyl derivatives: melting points and analytical data

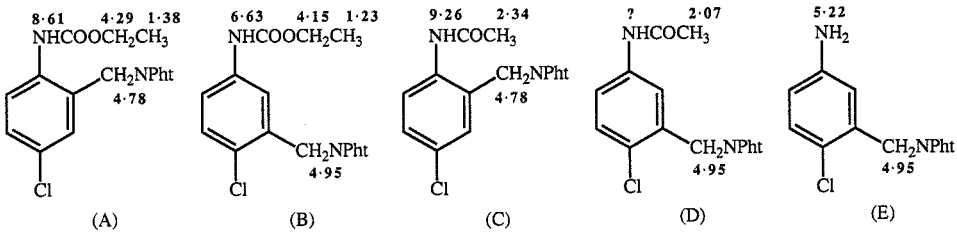
For data of some bis derivatives, see Experimental

Substitution 2-R^1	Substitution 3-R^2	Substitution 4-R^3	M.p. (°C)	Molecular formula	Found (%) C	Found (%) H	Found (%) N	Requires (%) C	Requires (%) H	Requires (%) N
Ethyl *N*-arylcarbamates [general formula (2)]										
CH_2NPht	H	H	116–117	$C_{18}H_{16}N_2O_4$	66·8	4·9	9·3	66·7	5·0	8·6
H	H	CH_2NPht	188–190	$C_{18}H_{16}N_2O_4$	67·2	5·1	8·5	66·7	5·0	8·6
CH_2NPht	H	Me	160–161	$C_{19}H_{18}N_2O_4$	67·3	4·6	8·9	67·1	4·4	8·7
H	CH_2NPht	Me	161–163	$C_{19}H_{18}N_2O_4$	67·6	5·6	8·3	67·4	5·4	8·3
CH_2NPht	H	Cl	184–186	$C_{18}H_{15}ClN_2O_4$	60·2	4·1	7·8	60·3	4·2	7·8
H	CH_2NPht	Cl	190–192	$C_{18}H_{15}ClN_2O_4$	60·2	4·1	7·9	60·3	4·2	7·8
CH_2NPht	H	NO_2	207–208	$C_{18}H_{15}N_3O_6$	58·9	4·5	11·3	58·5	4·1	11·4
CH_2NPht	H	Br	200–201	$C_{18}H_{15}BrN_2O_4$	53·3	3·5	6·5	53·6	3·8	7·0
Acetanilides [general formula (1)]										
CH_2NPht	H	H	204–206[A]	$C_{17}H_{14}N_2O_3$						
H	H	CH_2NPht	224–226[A]	$C_{17}H_{14}N_2O_3$						
CH_2NPht	H	Me	227–228[B]	$C_{18}H_{16}N_2O_3$	69·8	5·2	9·1	70·1	5·2	9·1
H	CH_2NPht	Me	217–218[A]	$C_{18}H_{16}N_2O_3$						
CH_2NPht	H	Cl	241–243	$C_{17}H_{13}ClN_2O_3$	61·9	3·9	8·4	62·1	4·0	8·5
H	CH_2NPht	Cl	216–218	$C_{17}H_{13}ClN_2O_3$	62·2	4·0	8·1	62·1	4·0	8·5
Anilines [general formula (3)]										
H	CH_2NPht	Me	238–239	$C_{16}H_{14}N_2O_2$	72·3	5·5	10·7	72·2	5·3	10·5
H	CH_2NPht	Cl	242–244	$C_{15}H_{11}ClN_2O_2$	63·2	4·1	9·7	62·8	3·9	9·8
H	H	CH_2NPht	203–205[C]	$C_{15}H_{12}N_2O_2$						

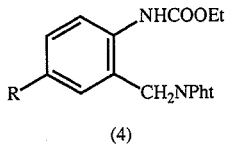
[A] In good agreement with m.p. reported.[8] [B] Lit.[8] 218°. [C] Lit. 207–208° (Barnes, R. A., and Godfrey, J. C., *J. Org. Chem.*, 1957, **22**, 1038).

the isomeric carbamate (B) gave the parent aniline (E), which was also obtained by the reaction *N*-hydroxymethylphthalimide with 4-chloroaniline. Since the aniline (E) was readily converted into its carbamate (B) and *N*-acetyl (D) derivatives, the structures of phthalimides (A)–(E) were all rigorously assigned. From the ^{1}H chemical shift data presented in Scheme 1, it will be seen that a phthalimidomethyl group exerts a significant deshielding effect on the protons [$COOCH_2CH_3$, $COCH_3$ and NH (where observable)] of a neighbouring group, presumably because of the anisotropic effect of the rigid phthaloyl group.

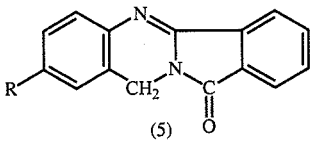
The amidomethylation results obtained with each group of compounds will be discussed in turn.



Scheme 1. δ values ($CDCl_3$ solution) for some protons of phthalimides derived from *p*-chloroaniline and its derivatives.



(4)



(5)

(a) R = H	(d) R = Me
(b) R = Cl	(e) R = Br
(c) R = NO_2	(f) R = NH_2

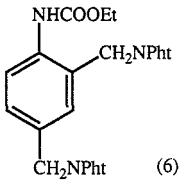
Amidomethylation of Acetanilides

The amidomethylations went readily at 50°C, except in the case of 4-nitroacetanilide, which was found to be unreactive (see also below). Reaction with acetanilide gave a mixture (*c.* 1 : 3) of 2- and 4-(phthalimidomethyl)acetanilide; reactions with 4-methyl- and 4-chloro-acetanilide gave mixtures of the corresponding 2- and 3-(phthalimidomethyl)acetanilides, the latter isomer predominating in each case, i.e., substitution had occurred mainly *meta* to the *N*-acetyl group. Except for some differences in the proportions of isomers obtained, our results for the amidomethylation of acetanilide and of its 4-methyl analogue are in general agreement with those reported by earlier workers[8] who, however, did not have access to ^{1}H n.m.r. analysis. Disubstituted derivatives were not encountered in any of these amidomethylations.

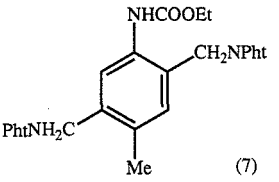
Amidomethylation of Ethyl N-Arylcarbamates

Unlike the corresponding acetanilides, all the carbamates studied, including the 4-nitro compound, were amidomethylated smoothly at 50°. Disubstitution was the main reaction in the case of ethyl *N*-phenylcarbamate where the corresponding 2,4-bis(phthalimidomethyl) derivative (6) was obtained. In the

case of the 4-methylphenylcarbamate (2; $R^1 = R^2 = H$, $R^3 = Me$), the major product was a mixture of the corresponding 2- and 3-phthalimidomethyl derivatives, the former predominating; a minor product (10% yield) was the corresponding 2,5-bis(phthalimidomethyl) derivative (7). In both amidomethylations, however, disubstitution was suppressed almost completely when some water was added to the solvent. With '90%' sulfuric acid (see Experimental); amidomethylation of ethyl *N*-phenylcarbamate gave a mixture (*c.* 1 : 2) of the corresponding 2- and 4-(phthalimidomethyl)phenylcarbamates (practically no disubstituted product was formed). Similarly, amidomethylation of the 4-methyl analogue in '95%' sulfuric acid gave a mixture of the corresponding 2- and 3-phthalimides with only 4% of the disubstituted product (7). It is interesting to note that the use of a lower (0–5°) reaction temperature had little effect on the reaction outcome (see Table 1), although higher overall yields of products were obtained. With the other carbamates studied (see Table 1), monosubstituted phthalimidomethyl derivatives were obtained exclusively.



(6)



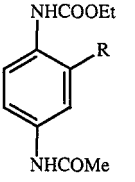
(7)

Our results (see Table 1) show that, when the *para*-position is substituted (i.e., when $R^3 = Me$, Cl, NO_2 or Br), amidomethylation occurs either predominantly or exclusively *ortho* to the carbamate group. This substitution effect differs, therefore, from that found with the corresponding acetanilides where amidomethylation occurred mainly *meta* to the *N*-acetyl group (see above). In this regard, amidomethylation resembles nitration (cf.[1]) of the same two series of compounds, although the two reactions differ significantly from one another in that *ortho*-nitration of the acetanilides (cf.[1]) studied either did not occur or did so to a very minor extent (e.g., with 4-chloroacetanilide), whereas considerable *ortho*-amidomethylation of the corresponding acetanilides did occur (see Table 1). Although the actual nature of the reactive species involved in reactions with *N*-hydroxymethylphthalimide has not been established (cf.[10,11]), we suggest that the transition state leading to the formation of the *ortho*-(phthalimidomethyl)acetanilides is less crowded (by virtue of some flexibility about the $ArCH_2$–N bond) than is that leading to the formation of the corresponding *ortho*-nitroacetanilides. Hence, formation of the *ortho*-(phthalimidomethyl)acetanilides is less subject to steric hindrance than is that of the corresponding nitro derivatives. On the other hand, the transition state leading to the formation of the corresponding *ortho*-(phthalimidomethyl)-phenylcarbamates is even less crowded (by virtue of the presence of the flexible ester-type group); hence, the observed greater tendency in favour of *ortho*-amidomethylation. Finally, it should be noted that amidomethylation, like nitration (cf.[1]), of the mixed carbamate amide (8a) gave only one product which, on the basis of the foregoing discussion, must have structure (8b).

[10] Zaugg, H. E., Kotre, A. M., and Fraser, J. E., *J. Org. Chem.*, 1969, **34**, 11.
[11] Zaugg, H. E., DeNet, R. W., Fraser, J. E., and Kotre, A. M., *J. Org. Chem.*, 1969, **34**, 14.

Amidomethylation of Anilines

Except for 4-nitroaniline, which was unreactive, amidomethylation proceeded smoothly. When the *para*-position was blocked, i.e., when $R^3 = Me$ or Cl, substitution occurred exclusively *meta* to the amino group to give the corresponding 3-phthalimidomethyl derivatives. Amidomethylation of aniline gave a mixture (*c.* 1 : 1) of the 3- and 4-(phthalimidomethyl)anilines; this could not be separated into its components. Assignment of structure to these components is based on the ^1H n.m.r. spectrum of the mixture in $(CD_3)_2SO/C_6D_6$ (1 : 1) (see discussion in next section), and on the spectrum in $(CD_3)_2SO$ of the mixture of acetanilides obtained by acetylation of the reaction mixture. The aromatic portion of the latter spectrum showed *inter alia* the signals (*para*-substituted pattern) expected for 4-(phthalimidomethyl)acetanilide (1; $R^1 = R^2 = H$, $R^3 = CH_2NPht$) [also obtained by the amidomethylation of acetanilide (see above)] as well as two discernible one-proton signals, namely an *ortho*-coupled doublet and a di-*ortho* triplet, the latter signal being diagnostic for *meta* substitution (cf.[12]). Hence the second component of the acetylated mixture is 3-(phthalimidomethyl)acetanilide (1; $R^1 = R^3 = H$, $R^2 = CH_2NPht$). Support for this deduction comes from the similarity of the aromatic portion (apart from the phthalimido group signal) of the spectrum of the acetylated mixture with that of a synthetic mixture (1 : 1) of 3- and 4-methylacetanilide.



(8a) R = H
(8b) $R = CH_2NPht$

It should be noted that in those amidomethylations which failed, i.e., those of 4-nitro-aniline and -acetanilide (see above), *N,N'*-methylenebisphthalimide $[(PhtN)_2CH_2]$, which presumably arises from decomposition of the reagent, was isolated.

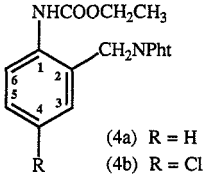
^1H N.M.R. Spectra: Benzene-Induced Solvent Shifts

The structures of most of the amidomethylation products obtained were determined by suitable transformations (see earlier discussion) or by ^1H n.m.r. spectroscopy in either $CDCl_3$ or $(CD_3)_2SO$ solution. However, the ^1H n.m.r. spectra of several of the compounds in either of these solvents were too complex for unequivocal structural assignments to be made. With such compounds, the use of C_6D_6 either alone or as a cosolvent caused significant (and diagnostic) solvent shifts. For some signals, particularly those due to the phthalimido group protons (observed as an AA'BB' pattern), the solvent shifts were considerably upfield (designated positive); for others, the shifts were considerably downfield (designated negative); for a few only, the shifts were negligible.

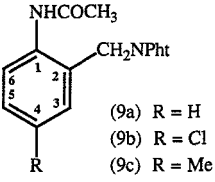
The solvent shifts $[\delta(CDCl_3) - \delta(C_6D_6)]$ were particularly marked in the case of the 2-(phthalimidomethyl)-phenylcarbamates and -acetanilides [data for

[12] Zanger, M., *Org. Magn. Reson.*, 1972, **4**, 1.

the unsubstituted analogues (4a) and (9a) respectively, and for the 4-chloro derivatives (4b) and (9b) respectively are presented in Table 3]. Noteworthy is the large downfield shift experienced by H6, and the large upfield shifts experienced by the NCH_2 and phthalimido group signals. The resultant dispersion of signals proved to be particularly useful for assigning structures to the minor products, namely carbamate (4a) and acetanilide (9a), obtained by the amidomethylation of ethyl *N*-phenylcarbamate and acetanilide respectively. In $CDCl_3$ solution, the multiplet due to the phthalimido group protons obscures the other aromatic signals, whereas in C_6D_6 solution, the H3 and H6 signals (each revealed as a doublet of doublets) are separated not only from the phthalimido group multiplet, the AA'BB' pattern of which is now revealed as two well separated branches, but also from each other and from the signals of other aromatic protons. The individual assignments of the H3 and H6 multiplets are tentative and are based on the observation (see Table 3) that the H6 signals of the chloro derivatives (4b) and (9b) experience greater downfield solvent shifts than do the H3 signals.



(4a) R = H
(4b) R = Cl



(9a) R = H
(9b) R = Cl
(9c) R = Me

Table 3. ^{1}H n.m.r. solvent shift data for compounds (4a,b) and (9a,b)

$\Delta\delta = \delta(CDCl_3) - \delta(C_6D_6)$

Proton(s)	$\delta(CDCl_3)$	$\delta(C_6D_6)$	$\Delta\delta$	$\delta(CDCl_3)$	$\delta(C_6D_6)$	$\Delta\delta$
	Amide (9a)			Carbamate (4a)		
$COCH_3$	2·35	2·21	0·14			
$COOCH_2CH_3$				1·38	1·14	0·24
$COOCH_2CH_3$				4·30	4·21	0·09
CH_2N	4·81	4·29	0·52	4·83	4·38	0·45
PhtN[A]	7·77	6·77	1·00	7·77	6·77	1·00
	7·87	7·24	0·63	7·87	7·24	0·63
H3	*c.* 7·95[B]	7·63	*c.* 0·32	*c.* 7·80[B]	7·62	*c.* 0·18
H5(H4)[C]	?	?	?	?	?	?
H6	*c.* 7·95[B]	8·63	*c.* −0·68	*c.* 7·80[B]	8·37	*c.* −0·57
NH	9·27	9·22[D]	0·05	8·64	9·04	−0·40
	Amide (9b)			Carbamate (4b)		
$COCH_3$	2·34	2·15	0·19			
$COOCH_2CH_3$				1·38	1·13	0·25
$COOCH_2CH_3$				4·29	4·18	0·11
CH_2N	4·77	4·08	0·69	4·78	4·21	0·57
PhtN[A]	7·76	6·77	0·99	7·76	6·84	0·92
	7·89	7·18	0·71	7·89	7·24	0·65
H3	7·56	7·69	−0·13	7·54	7·65	−0·11
H5(H4)	7·28	7·08	0·20	7·25	7·06	0·19
H6	7·95	8·42	−0·53	7·80	8·14	−0·34
NH	9·26	9·84	−0·58	8·60	8·90	−0·30

[A] AA'BB' pattern (multiplets not assigned); solvent shift values arbitrary. [B] Signals obscured; solvent shifts arbitrary. [C] H4 and H5 solvent shifts for amide (9a) and carbamate (4a) not assignable. [D] Signal very broad.

We presume that the marked solvent shifts observed for these 2-substituted compounds arise because of the interaction between the aromatic solvent and the three contiguous carbonyl groups (two from the phthalimido group and one from the carbamate or amide group) [for a review of aromatic solvent-induced shifts (ASIS), cf.[13]]. Similar diagnostic shifts were found for the other 2-phthalimidomethyl-substituted compounds prepared in this investigation (relevant ^{1}H n.m.r. data are to be found in the Experimental).

Of the 3-phthalimidomethyl-substituted derivatives prepared, only the 3-substituted 4-methylphenyl carbamate (2; $R^1 = H$, $R^2 = CH_2NPht$, $R^3 = Me$) was sufficiently soluble in C_6D_6 for solvent shifts to be measured; these shifts, although of considerable magnitude (see Experimental), did not lead to a diagnostic separation of the aromatic (H2, H5 and H6) signals from those of the phthalimido group protons.

C_6D_6-induced solvent shifts were also useful for determining the structures of the bisphthalimides (6) and (7) [$(CD_3)_2SO$ was ineffective in this regard]. Thus, the 1,2,4-trisubstitution pattern of the bisphthalimide (6) was revealed, as were the *two* methylene singlets of the bisphthalimide (7). Finally, the ^{1}H n.m.r. spectrum in $C_6D_6/(CD_3)_2SO$ (1 : 1) solution of the mixture of phthalimides obtained by the amidomethylation of aniline (see above) revealed the presence of a di-*ortho* triplet (diagnostic for *meta*-substitution), and hence indicated that 3-(phthalimidomethyl)aniline was present in the mixture.

Preparation of 8-Substituted Isoindolo[1,2-b]quinazolin-12(10H)-ones [General Formula (5)]

It was mentioned above that sulfuric acid treatment at 100° of the *ortho*-substituted carbamate (4b) gave the quinazolinone derivative (5b). The analogous carbamates (4c–e) (where $R = NO_2$, Me and Br respectively) were also converted into the corresponding quinazolinone derivatives (5c–e), although it was later found that sulfuric acid containing some water (see Experimental) at 100° gave better yields (>80%), particularly in the case of the methyl analogue (5d). Surprisingly, the unsubstituted carbamate (4a) was converted into the known parent quinazolinone derivative (5a)[14–17] only with difficulty. With concentrated or '90%' sulfuric acid, a product, the structure of which was not ascertained, was obtained; with '75%' sulfuric acid, this product was also obtained together with a poor yield (17%) of the desired derivative (5a). Reaction of the phthalimide (8b), obtained by amidomethylation of the mixed carbamate amide (8a), with concentrated sulfuric acid brought about quinazolinone formation with concomitant hydrolysis of the *N*-acetyl group to give the amino derivative (5f) in high yield; this compound has been obtained by another route.[18] It is of interest to note that the related *ortho*-(phthalimidomethyl)acetanilides [general formula (9)] were recovered essentially unchanged (but in reduced yield) by similar treatment with concentrated sulfuric acid alone or with water

[13] Laszlo, P., *Prog. N.M.R. Spectrosc.*, 1967, **3**, 348.
[14] Gabriel, S., *Ber. Dtsch. Chem. Ges.*, 1912, **45**, 712.
[15] Spiessens, K. I., and Antennuis, M. J. O., *Bull. Soc. Chim. Belg.*, 1981, **90**, 1167.
[16] Kametani, T., Nyu, K., Yamanaka, T., and Takano, S., *J. Heterocycl. Chem.*, 1971, 1071.
[17] Kametani, T., Jpn Pat. No. 7,242,750 (16 December 1972) (*Chem. Abstr.*, 1973, **78**, 72192x).
[18] Kabbe, H.-J., *Justus Liebigs Ann. Chem.*, 1978, 398.

added; only in the case of the chloro-substituted acetanilide (9b) was there evidence (^{1}H n.m.r. spectrum) that a trace of the desired chloroquinazolinone derivative (5b) had been formed.

Several quinazolinone derivatives of general formula (5) are known,[14–19] having been prepared from the corresponding (2-aminobenzyl)phthalimides, which in turn were prepared *in situ* either from the parent 2-aminobenzylamines[18] or by reduction of the corresponding (2-nitrobenzyl)phthalimides.[14–17,19] In the present work, the *ortho*-substituted carbamates [general formula (4)] are essentially protected (2-aminobenzyl)phthalimides.

Other Acidic Reactions

It was mentioned above that the reaction of *N*-[4-chloro-3-(phthalimidomethyl)-phenyl]carbamate [compound (B) in Scheme 1] with sulfuric acid at 100° gave the corresponding aniline derivative (E) (in 69% yield). However, the same reaction with the corresponding 4-methyl analogue (2; $R^1 = H$, $R^2 = CH_2NPht$, $R^3 = Me$) gave a poor yield (12%) of the corresponding aniline derivative (3; $R^1 = H$, $R^2 = CH_2NPht$, $R^3 = Me$), i.e., ease of removal of the carbamate function is dependent on the nature of the substituent R^3. After some experimentation, it was found that the use of '90%' sulfuric acid at 100° gave the desired aniline derivative in somewhat better yield (30%). Conversion of the *para*-substituted carbamate (2; $R^1 = R^2 = H$, $R^3 = CH_2NPht$) [obtained from the amidomethylation of ethyl *N*-phenylcarbamate (see above)] into the parent aniline derivative (3; $R^1 = R^2 = H$, $R^3 = CH_2NPht$) also required some experimentation before it was found that the use of '75%' sulfuric acid gave the desired derivative but in low yield (20%). Finally, the 3-(phthalimidomethyl)acetanilides, prepared in this investigation (see Table 1), were recovered unchanged (but in reduced yield) after treatment with sulfuric acid alone or with water added.

We suggest that, during treatment of these (phthalimidomethyl)-phenylcarbamates or -acetanilides with sulfuric acid (alone or with water added), two competing processes can occur: (i) hydrolysis (followed by decarboxylation in the case of the carbamates) to give the parent anilines, or (ii) removal of the phthaloyl group to give the parent benzylamine (cf.[6,7]). When the former process predominates, the corresponding anilines will be produced (and the *ortho*-substituted anilines will cyclize to the corresponding quinazolinone derivatives); otherwise, the corresponding *N*-substituted or parent 2-aminobenzylamines, or decomposition products derived therefrom, are likely to be formed.

Experimental

Melting points are uncorrected. Elemental analyses were carried out by the Australian Microanalytical Service, Melbourne. ^{1}H n.m.r. spectra (for 0·4 M solutions in $CDCl_3$ unless otherwise stated) were obtained either on a Varian A60D or on a JEOL FX90Q spectrometer. In $CDCl_3$ solution, the signals for the phthalimido group protons occur as a narrow symmetrical multiplet (AA'BB' pattern) centred at δ *c.* 7·8; in $(CD_3)_2SO$ solution, they occur as a broad singlet centred at δ 7·9; in C_6D_6 solution, they occur as two well separated symmetrical multiplets centred at δ 6·8 and 7·2 (see also Table 3). I.r. spectra were recorded in KBr discs on a Perkin–Elmer 297 spectrophotometer. ν(C=O) maxima were observed at 1765 (sharp) and 1700 (broad) (phthalimido group absorptions), at 1660–1680 ($NHCOCH_3$) and at 1720–1740 cm^{-1} (NHCOOEt). '95%', '90%', '80%' and '75%' sulfuric acid refer to solutions

[19] Downes, A. M., and Lions, F., *J. Am. Chem. Soc.*, 1950, **72**, 3053.

obtained by mixing concentrated sulfuric acid (97–99% A.R. grade) (95, 90, 80 and 75 ml) with water (5, 10, 20 and 25 ml respectively). Merck silica gel 60 was used for the column chromatography; the light petroleum used had b.p. 60–80°.

Amidomethylation Reactions

Unless otherwise stated, these reactions were carried out on a 20 mmol scale in concentrated sulfuric acid at 50° for 3 h. The descriptions of the reactions with ethyl *N*-phenylcarbamate (2; $R^1 = R^2 = R^3 = H$) and its 4-methyl analogue (2; $R^1 = R^2 = H$, $R^3 = Me$) are typical for those where mixtures of products were obtained. Many of the phthalimides formed were sparingly soluble in ether, and therefore a partial separation could often be achieved by a preliminary ether extraction. Silica gel chromatography (*c.* 10–15 g per g of product) was generally accomplished as follows: elution with (*a*) benzene (or light petroleum) containing increasing amounts of methylene chloride, (*b*) methylene chloride alone, and (*c*) methylene chloride containing increasing amounts of ethyl acetate. Mid-zones were analysed by ^1H n.m.r. spectroscopy.

(i) *With Ethyl* N*-Phenylcarbamate (2;* $R^1 = R^2 = R^3 = H$*)*

(A) *In concentrated sulfuric acid.*—*N*-Hydroxymethylphthalimide (3·54 g, 20 mmol) was added in portions to a stirred solution of ethyl *N*-phenylcarbamate (3·30 g, 20 mmol) in concentrated sulfuric acid (20 ml) at room temperature. After the reagent had dissolved, the solution was stirred at 50° at 3 h, and then poured into ice/water to give a colourless sticky solid which was separated by an ether extraction into an ether-insoluble solid (2·26 g; m.p. 200–204°) and an ether-soluble solid (2·39 g). The ether-insoluble solid was essentially pure *ethyl* N*-[2,4-bis(phthalimidomethyl)phenyl]carbamate* (6), m.p. 208–210° (from ethanol) (Found: C, 67·3; H, 4·6; N, 8·9. $C_{27}H_{21}N_3O_6$ requires C, 67·1; H, 4·4; N, 8·7%). ^1H n.m.r. [$(CD_3)_2SO$]: δ 1·24, t, $COOCH_2CH_3$; 4·10, q, $COOCH_2CH_3$; 4·68, s, CH_2N (at C2?); 4·72, s, CH_2N (at C4?); 7·01, br s, H3; 7·18, br d, H5; 7·33, d (*Jc.* 8 Hz), H6; 9·07, br s, NH. ^1H n.m.r. (sat. C_6D_6): δ 1·13, t, $COOCH_2CH_3$; 4·18, q, $COOCH_2CH_3$; 4·37, s, CH_2N (at C2?); 4·60, s, CH_2N (at C4?); 7·82, d (*Jc.* 2 Hz), H3; 8·25 d (*Jc.* 8 Hz), H6; 9·01, br s, NH. The H5 signal was obscured. Chromatography of the ether-soluble solid gave the corresponding *2-phthalimide* (4a) (see below), m.p. 108–110° (from ethanol), in 3% yield (0·21 g) followed by a solid (1·76 g), which crystallized from ethanol to give a further quantity (0·70 g) of the above bisphthalimide; the filtrate from this crystallization yielded a solid which was estimated (^1H n.m.r. analysis) to be a mixture (*c.* 1 : 1) of the bisphthalimide and the corresponding *4-phthalimide* (see below). On the basis of starting reagent used, the total yields of products were estimated to be: 2,4-bisphthalimide, 71%; 2-phthalimide, *c.* 3%; 4-phthalimide, *c.* 5%.

When the same reaction (40 mmol scale) was carried out at 0–5° for 3 h, the 2,4-bisphthalimide was obtained in 61% yield. The ether-soluble solid, which appeared to be a mixture of the 2,4-bisphthalimide, and the 2- and 4-phthalimides, could not be separated into its components by chromatography.

(B) *In '90%' sulfuric acid.*—Reaction in '90%' sulfuric acid (20 ml) at 50° for 3 h gave an ether-insoluble solid (1·64 g), m.p. 182–187°, and an ether-soluble solid (3·76 g). The former solid was *ethyl* N*-[4-(phthalimidomethyl)phenyl]carbamate* (2; $R^1 = R^2 = 4$, $R^3 = CH_2NPht$), m.p. 187–189° (from ethanol). ^1H n.m.r.: δ 1·28, t, $COOCH_2CH_3$; 4·19, q, $COOCH_2CH_3$; 4·97, s, CH_2N; 6·72, br s, NH; 7·35, br s, H2, H3, H5, H6. Chromatography of the ether-soluble solid, and elution with methylene chloride/light petroleum (4 : 1) gave *ethyl* N*-[2-(phthalimidomethyl)phenyl]carbamate* (4a) (1·24 g), m.p. 116–117° (from ethanol). ^1H n.m.r. (see Table 3). Elution with methylene chloride/ethyl acetate (9 : 1) gave a further quantity (1·01 g) of the above 4-phthalimide. After ^1H n.m.r. analysis [estimation of their respective NH peaks (located at δ 9·14 and 9·63) in $(CD_3)_2SO$ solution] of a mid-zone (0·21 g), the total yields of the 2- and 4-phthalimides were 21 and 42% respectively.

When the same reaction (30 mmol scale) was carried out at 0–5°, the ether-insoluble solid (5·13 g) was essentially pure 4-phthalimide. Silica gel (65 g) chromatography gave the 2-phthalimide (2·48 g) followed by a mixture (2 : 3; 1·47 g) of the 2- and 4-phthalimides. The yields of the 2- and 4-phthalimides were 31 and 62% respectively.

(ii) *With Ethyl N-(4-Methylphenyl)carbamate (2; $R^1 = R^2 = H$, $R^3 = Me$)*

The reaction in '95%' sulfuric acid, which gave a lower proportion of the bis(phthalimidomethyl) derivative, was used to obtain pure samples of the monophthalimides.

(A) *In '95%' sulfuric acid.*—Reaction (45 mmol scale) in '95%' sulfuric acid (65 ml) gave an ether-insoluble solid (2·10 g) and an ether-soluble solid (11·59 g). Crystallization of the ether-insoluble solid from benzene gave *ethyl N-[4-methyl-2,5-bis(phthalimidomethyl)phenyl]carbamate* (7) (0·92 g), m.p. 276–278° (Found: N, 8·9. $C_{28}H_{23}N_3O_6$ requires N, 8·5%). ^{1}H n.m.r. [$(CD_3)_2SO$]: δ 1·16, t, $COOCH_2CH_3$; 2·29, s, Ar**Me**; 4·01, q, $COOCH_2CH_3$; 4·69, s, 2×NCH_2; 6·97, s, H3 or H6; 7·02, s, H6 or H3; 8·89, br s, NH. In $(CD_3)_2SO/C_6D_6$ (1 : 1) solution, the corresponding signals were located at δ 1·14; 2·22; 4·05; 4·70, s, NCH_2; 4·82, s, NCH_2; 7·07, s, H3 or H6; 7·38, s, H6 or H3; 9·05, br s, NH.

The solid recovered from the recrystallization filtrate was added to the ether-soluble solid, and the combined solids were chromatographed on silica gel (65 g). Elution with benzene/light petroleum (2 : 1) gave *ethyl N-[4-methyl-2-(phthalimidomethyl)phenyl]carbamate* (4d) (4·63 g), m.p. 160–161° (from ethanol). ^{1}H n.m.r.: δ 1·37, t, $COOCH_2CH_3$; 2·28, s, Ar**Me**; 4·28, q, $COOCH_2CH_3$; 4·79, s, CH_2N; 7·12, dd (*J c.* 2 and 8 Hz), H5; 7·32, d (*J c.* 2 Hz), H3; 7·66, d (*J c.* 8 Hz), H6; 8·52, br s, NH. In saturated C_6D_6 solution, the corresponding signals were located at δ 1·15, 2·01, 4·22, 4·42, 6·81, 7·45, 8·23 and 8·95. Elution with benzene containing increasing amounts of methylene chloride gave a mid-zone (2·28 g), which contained the 2- and 3-phthalimides in the ratio 3 : 2 [integration of ArMe singlets ($CDCl_3$ solution)]. Elution with benzene/ethyl acetate (9 : 1) gave *ethyl N-[4-methyl-3-(phthalimidomethyl)phenyl]carbamate* (2; $R^1 = H$, $R^2 = CH_2Pht$, $R^3 = Me$) (2·54 g), m.p. 161–163° (from ethanol) (mixed m.p. with the 2-phthalimide was 145–152°). ^{1}H n.m.r.: δ 1·24, t, $COOCH_2CH_3$; 2·42, s, Ar**Me**; 4·15, q, $COOCH_2CH_3$; 4·81, s, CH_2N; 6·70, br s, NH; 7·09, d (*J c.* 8 Hz), H5; 7·14, br s, H2; 7·40, dd (*J c.* 2 and 8 Hz), H6. ^{1}H n.m.r. (sat. C_6D_6): δ 0·92, t, $COOCH_2CH_3$; 2·23, s, Me; 3·91, q, $COOCH_2CH_3$; 4·58, s, CH_2N; 6·79, br s, NH; 7·32, d (*J c.* 8 Hz), H5; 7·35, dd (*J c.* 2 and 8 Hz), H6; H2 and NH not resolved. The overall yields of 2,5-bisphthalimide, and of the 2- and 3-phthalimides were 4, 39 and 22% respectively.

(B) *In sulfuric acid.*—Reaction (20 mmol scale) and workup as described in experiment (A) above gave the following compounds (yields in parentheses): 2,5-bisphthalimide (10%), 2-phthalimide (42%), 3-phthalimide (25%). The monophthalimides were not isolated; their yields were derived by ^{1}H n.m.r. analysis ($CDCl_3$; integration of the ArMe singlets). When the same reaction was carried out at 0–5° for 3 h, the yields (monophthalimides not isolated) were: 2,5-bisphthalimide, 2%; 2-phthalimide, 50%; 3-phthalimide, 39%.

(iii) *With Other Carbamates (2; $R^1 = R^2 = H$, $R^3 = Cl$, Br, NO_2 or NHCOMe)*

Reaction (20 mmol scale) with ethyl *N*-(4-chlorophenyl)carbamate (2; $R^1 = R^2 = H$, $R^3 = Cl$) gave a product which was separated into two components by a combination of ether extraction and silica gel chromatography. The less soluble (in ether) and less strongly adsorbed component (obtained in 67% yield) was *ethyl N-[4-chloro-2-(phthalimidomethyl)phenyl]carbamate* (4b), m.p. 184–186° (from ethanol). ^{1}H n.m.r. (see Table 3). The more soluble and more strongly adsorbed component (obtained in 16% yield) was *ethyl N-[4-chloro-3-(phthalimidomethyl)phenyl]carbamate* (2; $R^1 = H$, $R^2 = CH_2NPht$, $R^3 = Cl$), m.p. 190–192° (from ethanol) (mixed m.p. with the 2-phthalimide was 170–185°). ^{1}H n.m.r.: δ 1·23, t, $COOCH_2CH_3$; 4·15, q, $COOCH_2CH_3$; 4·95, s, CH_2N; 6·58, br s, NH; 6·88, d (*J c.* 8 Hz), H6; 7·10, d (*J c.* 2 Hz), H2; 7·33, dd (*J c.* 2 and 8 Hz), H5.

Reaction (10 mmol scale) with ethyl *N*-(4-bromophenyl)carbamate (2; $R^1 = R^2 = H$, $R^3 = Br$) gave an ether-insoluble solid (2·61 g) and an ether-soluble solid (1·26 g). Both solids contained *ethyl N-[4-bromo-2-(phthalimidomethyl)phenyl]carbamate* (4e), m.p. 200–201° (from ethanol/methylene chloride), which was isolated by silica gel chromatography. ^{1}H n.m.r. [$(CD_3)_2SO$]: δ 1·26, t, $COOCH_2CH_3$; 4·13, q, $COOCH_2CH_3$; 4·77, s, CH_2N; 7·38, m, H3/H4/H6; 9·14, br s, NH. ^{1}H n.m.r. (C_6D_6): δ 1·13, t, $COOCH_2CH_3$: 4·17, q, $COOCH_2CH_3$; 4·18, s, CH_2N; 7·19, m, H5; 7·81, d (*J c.* 2 Hz), H3; 8·10, d (*J c.* 8 Hz), H6; 8·92, br s, NH. The ether-insoluble solid contained a strongly adsorbed impurity (0·15 g), m.p. 265–277°, which appeared (^{1}H n.m.r. spectrum) to be a bis(phthalimidomethyl) derivative. The ether-soluble solid contained the starting carbamate and a strongly adsorbed solid, m.p. 183–210° (from

methylene chloride/ethanol), which appeared (^{1}H n.m.r. spectrum) to be impure 3-phthalimide (2; $R^1 = H$, $R^2 = CH_2NPht$, $R^3 = Br$). Neither of these impure solids was investigated further. The total yield of carbamate (4e) was estimated to be 73%.

Reaction (15 mmol scale) with ethyl *N*-(4-nitrophenyl)carbamate (2; $R^1 = R^2 = H$, $R^3 = NO_2$) gave an ether-insoluble solid (3·83 g) and an ether-soluble solid (0·82 g). The former solid was essentially *ethyl N-[4-nitro-2-(phthalimidomethyl)phenyl]carbamate* (4c), m.p. 207–208° (from aqueous acetic acid). ^{1}H n.m.r. [$(CD_3)_2SO$]: δ 1·30, t, $COOCH_2CH_3$; 4·21, q, $COOCH_2CH_3$; 4·89, s, CH_2N; 7·87, d (*J c.* 8 Hz), H6; 8·03, d (*J c.* 2 Hz), H3; 8·17, dd (*J c.* 2 and 8 Hz), H5; 9·56, br s, NH. ^{1}H n.m.r. (sat. C_6D_6): δ 1·10, t, $COOCH_2CH_3$; 4·06, s, CH_2N; 4·12, q, $COOCH_2CH_3$; 7·86, dd, H5; 8·32, d (*J c.* 8 Hz), H6; 8·45, d (*J c.* 8 Hz), H3; 9·10, br s, NH. The ether-soluble solid contained (^{1}H n.m.r. analysis) a further quantity of the 2-phthalimide together with starting carbamate (2; $R^1 = R^2 = H$, $R^3 = NO_2$). The total yield of 2-phthalimide (4c) was 75%, and the recovery of starting carbamate was 15%.

Reaction (10 mmol scale) with ethyl *N*-(4-acetamidophenyl)carbamate (8a) gave *ethyl N-[4-acetamido-2-(phthalimidomethyl)phenyl]carbamate* (8b), m.p. 258–260° (from aqueous acetic acid), in 87% yield. ^{1}H n.m.r. [$(CD_3)_2SO$]: δ 1·25, t, $COOCH_2CH_3$; 1·94, s, $COCH_3$; 4·11, q, $COOCH_2CH_3$; 4·73, s, CH_2N; 7·16, br s, H3; 7·21, d (*J c.* 8 Hz), H6; 7·64, dd (*J c.* 2 and 8 Hz), H5; 8·99, br s, NHCOOEt; 9·83, br s, $NHCOCH_3$.

(iv) *With Acetanilide*

The reaction product was separated into two components by a combination of crystallization from ethanol followed by chromatography of the ethanol-soluble fraction. The less soluble (in ethanol) and more strongly adsorbed component was 4-(phthalimidomethyl)acetanilide (1; $R^1 = R^2 = H$, $R^3 = CH_2NPht$), m.p. 224–226° (from ethanol) (lit.[8] 221°). ^{1}H n.m.r. [$(CD_3)_2SO$]: δ 2·03, s, Me; 4·73, s, CH_2; 7·25 (*J c.* 8 Hz), H2/H6; 7·56, d (*J c.* 8 Hz), H3/H5; 6·72, br s, NH. The more soluble and less strongly adsorbed component was 2-(phthalimidomethyl)acetanilide (9a), m.p. 204–206° (from ethanol/methylene chloride) (lit.[8] 202°). ^{1}H n.m.r. data (see Table 3). The yields of the 2- and 4-phthalimides were 18 and 57% respectively.

(v) *With 4-Methyl- and 4-Chloro-acetanilide*

Reaction (30 mmol scale) with 4-methylacetanilide (1; $R^1 = R^2 = H$, $R^3 = Me$) gave a product which was separated into two components by a combination of extraction with ether, crystallization of the ether-insoluble solid from methylene chloride/ethanol, and silica gel chromatography. The less soluble (in methylene chloride/ethanol) and more strongly adsorbed component was 4-methyl-3-(phthalimidomethyl)acetanilide (1; $R^1 = H$, $R^2 = CH_2NPht$, $R^3 = Me$), m.p. 217–218° (from ethanol) (lit.[8] 216°). ^{1}H n.m.r. [$(CD_3)_2SO$]: δ 1·93, s, $NHCOCH_3$; 2·32, s, ArMe; 4·71, s, CH_2; 7·09, br d (*J c.* 8 Hz), H5; 7·14, br s, H2; 7·55, dd (*J c.* 2 and 8 Hz), H6; 9·74, br s, NH. *The other component (isolated by chromatography)* was 4-methyl-2-(phthalimidomethyl)acetanilide (9c), m.p. 227–228° (from hexane/methylene chloride) (lit.[8] 218°). ^{1}H n.m.r. [$(CD_3)_2SO$]: δ 2·08, s, $NHCOCH_3$; 2·21, s, ArMe; 4·71, s, CH_2; 6·99, br s, H3; 7·03, dd, H5; 7·13, br s (*J c.* 8 Hz), H6; 9·53, br s, NH. The yields of the 2- and 3-phthalimides, by ^{1}H n.m.r. analysis [$(CD_3)_2SO$; ArMe singlets] of the crude initial reaction product, were 16 and 75% respectively.

Reaction (25 mmol scale) with 4-chloroacetanilide (1; $R^1 = R^2 = H$, $R^3 = Cl$), and workup as described above for the 4-methyl analogue, gave two isomeric compounds. The more soluble and less strongly adsorbed isomer (obtained in 12% yield) was *4-chloro-2-(phthalimidomethyl)acetanilide* (9b), m.p. 241–243° (from ethanol/methylene chloride). For ^{1}H n.m.r. data, see Table 3. The other isomer (obtained in 68% yield) was *4-chloro-3-(phthalimidomethyl)acetanilide* (1; $R^1 = H$, $R^2 = CH_2NPht$, $R^3 = Cl$), m.p. 216–218° (from ethanol). ^{1}H n.m.r.: δ 2·07, s, Me; 4·95, s, CH_2; 7·30, d (*J c.* 8 Hz), H6; 7·58, dd, H2. The remaining signals were obscured by the phthalimido group signal.

(vi) *With 4-Nitroacetanilide and 4-Nitroaniline*

Reaction with both these compounds led to the same result. With 4-nitroacetanilide (50 mmol scale), a yellow solid (7·89 g) was obtained. Crystallization of a sample (3·0 g)

from ethanol gave *N,N'*-methylenebisphthalimide [$(PhtN)_2CH_2$] (0·69 g), m.p. 220–226°, raised to 228–229° (lit.[20] 226°) by recrystallization from methylene chloride/ethanol. ^{1}H n.m.r. [$(CD_3)_2SO$]: δ 5·65, s, CH_2; 7·78, m (AA'BB' pattern), phthalimido group protons. The filtrate from the first crystallization contained (^{1}H n.m.r. spectrum) starting 4-nitroacetanilide. With 4-nitroaniline (26 mmol), a yellow solid (2·25 g) was obtained. Crystallization from ethanol/chloroform gave *N,N'*-methylenebisphthalimide (1·29 g), m.p. 228–229°. The filtrate contained (^{1}H n.m.r. spectrum) 4-nitroaniline.

(vii) *With Aniline*

When the reaction mixture (30 mmol scale) was poured onto ice/water, no precipitation occurred. However, basification with ammonia gave a yellow solid (7·01 g), m.p. 144–186°, which was a mixture of 3-(phthalimidomethyl)aniline (3; $R^1 = R^3 = H$, $R^2 = CH_2NPht$) and 4-(phthalimidomethyl)aniline (3; $R^1 = R^2 = H$, $R^3 = CH_2NPht$). This mixture could not be separated into its components, either by crystallization or chromatography (on alumina). ^{1}H n.m.r. [$(CD_3)_2SO$]: δ 4·58, s, CH_2 (4-phthalimide); 4·63, s, CH_2 (3-phthalimide); 5·08, br s, NH_2; 6·42–6·57, m, aromatic protons; 6·88–7·06, m, aromatic protons; 7·86, br s, phthalimido group protons. The *para*-substitution pattern [doublets (*J c.* 8 Hz) centred at δ 6·50 and 6·97] of the 4-phthalimide [see section (viii)] was readily discernible in the two aromatic multiplets. The addition of an equal volume of C_6D_6 to the solution caused a dispersion of the lower-field aromatic multiplet into a doublet (*J c.* 8 Hz) centred at δ 7·19, and a triplet (*J c.* 8 Hz) centred at 7·01; the former signal was assigned to H3/H5 of the 4-phthalimide, and the latter [a di-*ortho* triplet (cf.[12])] to H5 of the 3-phthalimide. This solvent-induced dispersion, which indicated that the original low-field aromatic multiplet represented two protons of the 4-phthalimide and one proton of the 3-phthalimide, enabled the proportions (*c.* 1 : 1) of the two isomers to be calculated (by integration of the original spectrum).

A portion (1·50 g) of the reaction product was acetylated by stirring its solution in pyridine (15 ml) with acetic anhydride (1·5 ml) for 5 h at room temperature. The reaction mixture was poured onto ice/hydrochloric acid to give an inseparable mixture of the 3- and 4-(phthalimidomethyl)acetanilides as an oily solid (1·42 g). The following tentative ^{1}H n.m.r. assignments [$(CD_3)_2SO$] are based on the availability of 4-(phthalimidomethyl)acetanilide (1; $R^1 = R^2 = H$, $R^3 = CH_2NPht$) [see section (iv)] for comparison: δ 2·02, s, Me (not assigned); 2·04, s, Me (not assigned); 4·72, s, CH_2 (4-isomer); 4·75, s, CH_2 (3-isomer); 7·00, br d (*J c.* 8 Hz), H4 (3-isomer); 7·24, d (*J c.* 8 Hz), H2/H6 (4-isomer); 7·26, t (*J c.* 8 Hz), H5 (3-isomer); 7·51, m, H2/H6 (3-isomer); 7·54, d (*J c.* 8 Hz), H3/H5 (4-isomer); 7·87, br s, phthalimido group protons; 9·93, br s, NH. Integration based on the signals centred at δ 7·00, 7·24 and 7·26 indicated that the proportions of the 3- and 4-isomers formed was *c.* 1 : 1.

(viii) *With* p-*Toluidine*

Reaction in '95%' sulfuric acid followed by basification of the diluted reaction mixture with ammonia gave *4-methyl-3-(phthalimidomethyl)aniline* (3; $R^1 = H$, $R^2 = CH_2NPht$, $R^3 = Me$) as an ether-insoluble yellow solid (4·46 g, 75% yield), m.p. 238–239° (from acetone) [m.p. not reported (cf.[8])]. ^{1}H n.m.r. [$(CD_3)_2SO$]: δ 2·20, s, Me; 4·61, s, CH_2; 4·79, br s, NH_2; 6·82, br s, H2; 6·36, dd (*J c.* 2 and 8 Hz), H6; 6·82, d (*J c.* 8 Hz), H5. The *N*-acetyl derivative (1; $R^1 = H$, $R^2 = CH_2NPht$, $R^3 = Me$) was prepared by stirring a solution of the parent aniline (0·62 g) in pyridine (10 ml) with acetic anhydride (1·0 g) at room temperature for 16 h. Dilution with water gave the derivative, m.p. 219–221°, in 77% yield after crystallization (from aqueous ethanol); this compound was identical (mixed m.p. and ^{1}H n.m.r. spectrum) with the major isomer, m.p. 217–218°, obtained by the amidomethylation of 4-methylacetanilide [see section (v)]. The corresponding ethyl carbamate (2; $R^1 = H$, $R^2 = CH_2NPht$, $R^3 = Me$) was prepared (cf.[21]) by treating a stirred suspension of the parent aniline (266 mg) in pyridine (5 ml) at 0° with a solution of ethyl chloroformate (324 mg, 3 equiv.) in acetone (5 ml). After 2 h, dilution with water gave the colourless derivative, m.p. 158–161° (from aqueous ethanol), in

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71% yield, which was identical (mixed m.p. and ^{1}H n.m.r. spectrum) with the minor isomer, m.p. 161–163°, obtained by the amidomethylation of ethyl *N*-(4-methylphenyl)carbamate [see section (ii)].

(ix) *With 4-Chloroaniline*

Similar reaction gave *4-chloro-3-(phthalimidomethyl)aniline* (3; R^1 = H, R^2 = CH_2NPht, R^3 = Cl) as a yellow solid, m.p. 242–244° (from aqueous pyridine), in 72% yield. ^{1}H n.m.r. [$(CD_3)_2SO$]: δ 4·69, s, CH_2; 5·22, s, NH_2; 6·36, br s, H2; 6·45, dd (*J c.* 2 and 8 Hz), H6; 7·07, d (*J c.* 8 Hz), H5. The corresponding *N*-acetyl and ethyl carbamate derivatives were prepared [see section (viii)] in 81 and 75% yields respectively. The acetyl derivative (1; R^1 = H, R^2 = CH_2NPht, R^3 = Cl), m.p. 216–218° (from ethanol/methylene chloride), was identical (mixed m.p., and ^{1}H n.m.r. spectrum) with the major isomer obtained by the amidomethylation of 4-chloroacetanilide [see section (v)]. The carbamate derivative (2; R^1 = H, R^2 = CH_2NPht, R^3 = Cl), m.p. 191–192° (from ethanol), was similarly identical with the minor isomer obtained by the amidomethylation of ethyl *N*-(4-chlorophenyl)carbamate [see section (iii)].

Preparation of 8-Substituted Isoindolo[1,2-*b*]quinazolin-12(10*H*)-ones [General Formula (5)]

Unless otherwise stated, '90%' sulfuric acid was used. A solution of ethyl *N*-[4-bromo-2-(phthalimidomethyl)phenyl]carbamate (4e) (360 mg) in '90%' sulfuric acid (3·5 ml) was heated at 100° in a boiling-water bath for 7 h. Vigorous evolution of carbon dioxide occurred to give a yellow solution which was poured onto ice/water to give *8-bromoisoindolo[1,2-b]quinazolin-12(10H)-one* (5e) (250 mg, 89% yield), m.p. 215°, as a yellow solid. The analytical sample (from aqueous ethanol) had m.p. 215–216° (Found: C, 64·2; H, 3·0; N, 14·8. $C_{15}H_9BrN_2O$ requires C, 64·5; H, 3·3; N, 15·0%). ν_{max}: 1640 (C=N), 1725 cm^{-1} (C=O). ^{1}H n.m.r. [$(CD_3)_2SO$]: δ 4·91, s, CH_2 (the aromatic portion of the spectrum was not amenable to first-order analysis).

The *8-chloro analogue* (5b), m.p. 206–208° (from aqueous ethanol) was obtained in 80% yield (Found: C, 66·9; H, 3·6; N, 10·3. $C_{15}H_9ClN_2O$ requires C, 67·0; H, 3·8; N, 10·4%). Spectroscopic data are as for the 8-bromo analogue (see above). The *8-nitro analogue* (5c) (from aqueous acetic acid), m.p. 288–290°, was obtained in 94% yield (2 h reaction was sufficient) (Found: C, 64·2; H, 3·1; N, 15·0, $C_{15}H_9N_3O_3$ requires C, 64·5; H, 3·3; N, 15·1%). ν_{max}: 1640, 1730 cm^{-1}. ^{1}H n.m.r. [$(CD_3)_2SO$]: δ 5·07, s, CH_2; 7·60, d (*J c.* 8 Hz), H6. The *8-methyl analogue* (5d) ('75%' sulfuric acid used for 7 h), m.p. 218–220°, was obtained in 89% yield (Found: C, 77·9; H, 5·0; N, 10·9. $C_{16}H_{12}N_2O$ requires C, 77·4; H, 4·9; N, 11·3%). ν_{max}: 1645, 1720 cm^{-1}. ^{1}H n.m.r. [$(CD_3)_2SO$]: δ 2·33, s, Me; 4·89, s, CH_2.

The 8-amino analogue (5f) was obtained as an orange solid by heating (5 h at 100°) a solution of ethyl *N*-[4-acetamido-2-(phthalimidomethyl)phenyl]carbamate (8b) (700 mg) in concentrated sulfuric acid (7 ml). Basification (ammonia) was required to obtain maximum yield (95%) (436 mg). The analytical sample had m.p. 270° (dec.) (from aqueous ethanol) (lit.[18] 287–288°) (Found: C, 72·5; H, 4·1; N, 16·5. Calc. for $C_{16}H_{11}N_3O$: C, 72·3; H, 4·5; N, 16·9%). ν_{max}: 1640 (C=N), 1680 (C=O), and 3365, 3465 cm^{-1} (aromatic NH_2). ^{1}H n.m.r. [$(CD_3)_2SO$]: δ 4·78, s, CH_2; 5·54, s, NH_2 (exchangeable with deuterium oxide); 6·47, br s, H9; 6·52, dd (*J c.* 2 and 8 Hz), H7; 7·13, d (*J c.* 8 Hz), H6.

The parent compound, isoindolo[1,2-*b*]quinazolin-112(10*H*)-one (5a), was obtained in poor yield as follows. A solution of ethyl *N*-[2-phthalimidomethyl)phenyl]carbamate (4a) (303 mg) in '75%' sulfuric acid (4 ml) was heated at 100° for 2 h. The cooled solution was poured onto ice/water to give a yellow solid (100 mg), m.p. >360°, which was isolated by filtration. ν_{max}: 1775 (C=O), 1660 cm^{-1} (C=N). This solid was insoluble in the usual ^{1}H n.m.r. solvents. The filtrate from this solid was basified cautiously with ammonia to give the desired compound (5a) in 17% yield (37 mg), m.p. 178–181°. Crystallization from aqueous ethanol give yellow leaflets, m.p. 186–187° (lit.[15] 182–183°). ν_{max}: 1650 (C=N), 1725 cm^{-1}(C=O). ^{1}H n.m.r.: δ 4·97, s, CH_2. Reaction [400 mg carbamate (4b)] with '90%' sulfuric acid (4 ml) gave only the insoluble yellow solid (349 mg), m.p. >360°.

Other Acidic Reactions

(A) *With ethyl* N-*[4-chloro-3-(phthalimidomethyl)phenyl]carbamate (2;* $R^1 = H$, $R^2 = CH_2NPht$, $R^3 = Cl$*).*—Reaction (H_2SO_4, 100°, 4 h) of this carbamate (0·90 g) gave, after dilution (water) and basification (ammonia), the parent aniline (3; $R^1 = H$, $R^2 = CH_2NPht$, $R^3 = Cl$) (0·498 g, 69% yield), m.p. 237–239° (from ethanol), which was identical (mixed m.p. and ^1H n.m.r. spectrum) with the compound obtained by the amidomethylation of 4-chloroaniline [see section (ix)].

(B) *With ethyl* N-*[4-methyl-3-(phthalimidomethyl)phenyl]carbamate (2;* $R^1 = H$, $R^2 = CH_2NPht$, $R^3 = Me$*).*—Reaction ('90%' H_2SO_4, 100°, 3 h) of this carbamate (217 mg) gave, after dilution (water), an acid-insoluble solid (36 mg, m.p. 270–278°, which was not investigated further, and an acid-soluble solid (52 mg, 30% yield), which was liberated by basification (ammonia). The latter solid, m.p. 238–240° (from ethanol/methylene chloride), was identical (mixed m.p. and ^1H n.m.r. spectrum) with the parent aniline (3; $R^1 = H$, $R^2 = CH_2NPht$, $R^3 = Me$), which had been obtained previously by the amidomethylation of *p*-toluidine [see section (viii)]. The use of concentrated sulfuric acid for this reaction gave a much poorer yield (12%) of less pure parent aniline.

(C) *With ethyl* N-*[4-(phthalimidomethyl)phenyl]carbamate (2;* $R^1 = R^2 = H$, $R^3 = CH_2NPht$*).*—Reaction ('75%' H_2SO_4, 100°, 4 h) of this carbamate (2·62 g) gave, after dilution (water) and removal (Celite) of a small amount of an acid-insoluble solid (discarded), a yellow solution which was basified (ammonia) to give crude 4-(phthalimidomethyl)aniline (3; $R^1 = R^2 = H$, $R^3 = CH_2NPht$). Purification by chromatography [alumina; methylene chloride/ethyl acetate (4 : 1) as eluent] gave the pure compound, m.p. 203–205° (from methylene chloride/ethanol) (lit.[22] 207–208°), in 20% yield (405 mg). ^1H n.m.r. [$(CD_3)_2SO$]: δ 4·58, s, CH_2; 5·04, s, NH_2 (signal exchangeable with D_2O); 6·50, d (*J c.* 8 Hz), H2/H6; 7·01, d (*J c.* 8 Hz), H3/H5; 7·84, s, phthalimido group.

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