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Ambident Heterocyclic Reactivity: Alkylation of 2-Substituted-4-methylbenzimidazoles

M. Rezaul Haque and Malcolm Rasmussen*

Chemistry Department, The Faculties, Australian National University,
Canberra, ACT 0200, Australia

Abstract: The regioselectivities were determined for alkylations of 4-methyl-, 2,4-dimethyl-, 2-amino-4-methyl-, 2-chloro-4-methyl-, 2-ethoxy-4-methyl-benzimidazole, and 4-methylbenzimidazolone (as anions in dimethylformamide) with a variety of primary alkylating agents. These $N1/N3$ regioselectivities are correlated with the second order rate constants for benzylation (benzyl chloride / dimethylformamide / 30°) of these heterocyclic anions under comparable conditions. Altering the alkylating agent, $R'CH_2Cl$, causes movement along the loose-tight axis of S_N2 transition state structures and produces substantial changes in regioselectivity. Variations along the early-late S_N2 axis, caused by altering the 2-substituent in the 2-R-4-methylbenzimidazole anions, are much less effective in inducing changes in alkylation regioselectivity. The combined results are consistent with dominant 'steric approach control' for the alkylations, where the magnitude of the steric effect is critically dependent on the length of the developing N - - - C bond in the variable geometry S_N2 alkylation transition states involved. Unequal steric effects of 2-substituents on $N1$ and $N3$ alkylations and their variation with alkylating agent are explained by invoking the geometry of roughly conical 'approach corridors' to the nitrogen alkylation sites. Temperature effects on these regioselectivities are small for most systems.

As part of our continuing investigations of ambident heterocyclic reactivity, we have been studying the factors controlling regioselectivity in the alkylation of purine[1], pyrrolopyridine (azaindole)[2] and benzimidazole[3] ring systems. In benzimidazole alkylations, monosubstitution at the relatively remote 5(6)-position induces only slight regioselectivity, varying from 55:45 to 46:54, between the competitive $N1$ and $N3$ sites by through-bond electronic effects.[3] In the alkylation of 4(7)-monosubstituted benzimidazole systems far more divergent results are obtained, with $N1/N3$ regioselectivity varying between 100:0 and 21:79.[3] These latter alkylation patterns are indicative of competitive electronic, electrostatic field, and steric effects, with specific association effects also important in certain cases. The interplay between the electrostatic field and non-bonded steric interactions are governed by the variable geometries of the S_N2 transition states involved, in particular by the N - - - C distance of the developing N-alkyl bond. Such variable S_N2 transition state geometries are conveniently described by More O'Ferrall - Jencks diagrams[4] which allow the effects of structural variations to be discussed in terms of movement along orthogonal early-late and loose-tight axes.[5]

For the alkylation of 4-methylbenzimidazole anions (2a) by various primary alkyl chlorides, alkylation at the less hindered $N1$ site is favoured in all cases, but the $N1/N3$ regioselectivity [(4a)/(3a)] was found to decrease from 86:14 to 57:43 as the transition state was changed from tight (phenacyl chloride) to very loose (phenoxymethyl chloride).[3] This represents a clear example of 'steric approach control'[6] within variable S_N2 transition states induced by so-called 'perpendicular' effects[7] (movement along the loose-tight axis). In order to investigate the sensitivity of these S_N2 reactions to movements along the orthogonal early-late axis, we

decided to study the alkylations of a series of 2-substituted-4-methylbenzimidazoles (**1**, R ≠ H) as their anions (**2b** - **f**). The 2-substituents, being symmetrically disposed with respect to the $N1$ and $N3$ sites of benzimidazole anions, should not cause steric differentiation between the competitive N-alkylation sites, but may be expected to alter the nucleophilic reactivity of the benzimidazole system by their electronic effects. Such reactivity modification should induce movement along the early-late axis according to the well accepted Bell-Evans-Polanyi (BEP) analysis[8] and Hammond's Principle[9]. These latter concepts underpin our understanding of the widely used Hammett[10] and Brønsted[11] relationships between pK_a and nucleophilic reactivity observed in many nitrogen heterocyclic systems.[12]

a) R = H
b) R = CH_3
c) R = OCH_2CH_3
d) R = Cl
e) R = NH_2
f) R = OH
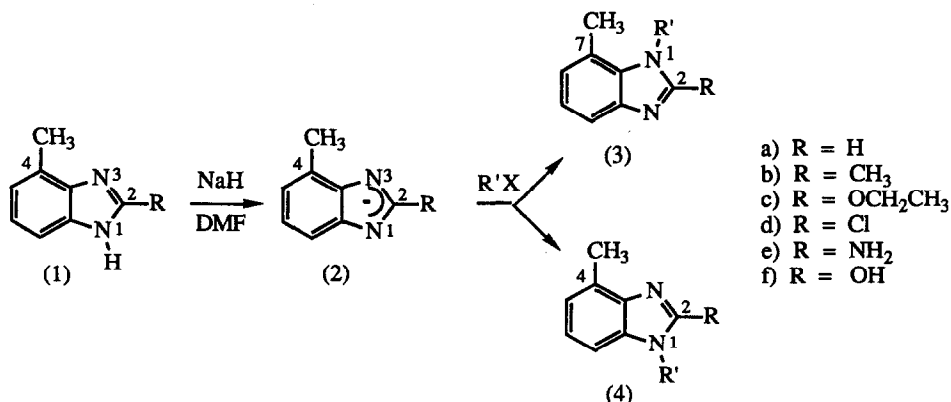
In the current study, we have determined the regioselectivity of alkylation of anionic 2-substituted-4-methylbenzimidazoles (**2a** - **f**) in N,N-dimethylformamide at 30° using a standard range of primary alkyl halides (see Table 1). These results are correlated to changes in the measured second order rate constants for benzylation under comparable conditions and interpreted within the context of modern concepts of ambient nucleophile reactivity[13] and variable geometry S_N2 transition states[5,14].

RESULTS and DISCUSSION

Extensive studies have shown that alkylation of pyridine-type nitrogen sites in heterocycles is sensitive to steric retardation by substituent groups on adjacent sites.[15] This has been particularly well demonstrated in alkylations of 2-mono- and 2,6-disubstituted pyridines, and related 2-substituted quinolines.[16-18] In benzimidazole systems, the steric effects of a 4-methyl group are well established to direct alkylation preferentially to the less hindered $N1$ site.[3] Equilibration of isomeric $N1$- and $N3$-benzyl-4-methyl-benzimidazole[19] (**4a** ⇌ **3a**, R' = $C_6H_5CH_2$) under acidic conditions in dimethylformamide established a thermodynamic preference of 99:1 ($\Delta\Delta G°_{N1/N3}$ 15.2 kJ mol⁻¹) for the $N1$-benzyl system over its congested $N3$ isomer.[3] This steric interaction is moderated by the elongated N - - - CH_2R interaction in the S_N2 alkylation transition states, with alkylation of 4-methylbenzimidazole anions (**2a**) showing $N1/N3$ regioselectivity varying from 58:42 to 87:13 over an extended range of primary alkyl halides, see Table 1. This corresponds to a variation in $\Delta\Delta G^{\ddagger}$ of from 5% to about 30% of the final thermodynamic preference, $\Delta\Delta G°_{N1/N3}$, as the transition state varies from very loose to tight respectively (assuming the $N1$- ⇌ $N3$-benzyl equilibration

$\Delta\Delta G^{\circ}_{N1/N3}$ 15.2 kJ mol^{-1} value is reasonably valid for all five N-alkyl pairs). These results are consistent with previous studies of heterocyclic alkylations. For example kinetic isotope effects[20] and Brønsted coefficients of $\beta \approx 0.3$ to 0.4 for Menschutkin reactions in pyridine systems[17,21] indicate relatively early transition states (for simple alkylating agents), with developing N - - - C bond distances estimated[22] at about 1.81 Å, 22% longer than the final N--C bond (1.48 Å). The amount of steric strain ($\Delta H^{\ddagger}$) in the transition states for quaternization of pyridines bearing α-alkyl substituents is, however, estimated to be about two-thirds of that in the final quaternary salt.[22]

Table 1 Alkylation of 4-Methyl- and 2,4-Dimethyl-benzimidazole Anions (Dimethylformamide, 30°)

Alkylating Agent	4-Methylbenz-imidazole anion (2a)			2,4-Dimethylbenz-imidazole anion (2b)			δS
	$N1$	$N3$	$\Delta\Delta G^{\ddagger}$	$N1$	$N3$	$\Delta\Delta G^{\ddagger}$	($\Delta\Delta G^{\ddagger}_{2b}$ - $\Delta\Delta G^{\ddagger}_{2a}$)
loose							
$C_6H_5CH_2OCH_2Cl$	58	42	0.8	85	15	4.5	3.7
$C_6H_5CH_2Cl$	78	22	3.2	97	3	8.9	5.7
$CH_3(CH_2)_3Cl$	83	17	4.0	95	5	7.4	3.4
$(CH_3)_3COCOCH_2Cl$	85	15	4.3	>99	<1	>12.0	>7.7
$C_6H_5COCH_2Cl$	87	13	4.7	>99	<1	>12.0	>7.3
tight							

$N1$ and $N3$ figures are % of total alkylated product as determined by ^{1}H n.m.r. spectroscopy.
$\Delta\Delta G^{\ddagger}$ = -RT ln($N3$%/$N1$%) kJ mol^{-1}.

The mild electron donation effect of a 4-methyl substituent causes an slight increase in the basicity of both the uncharged (tautomeric) and the anionic forms of benzimidazole (see pK_a values in Table 2). This causes a slightly enhanced nucleophilicity as seen in the almost doubling of the benzylation rate at the $N1$-site in 4-methylbenzimidazole compared to the rate at a single site of unsubstituted benzimidazole anions (see Table 2). The 4-methyl substituent effect on the benzylation rate at the more hindered $N3$-site is, however, a reduction to about 40% of the parent single site rate. These rate effects compare closely with the relative methylation rates (MeI / MeCN / 30°) for pyridine (rel. rate 1), 4-methyl- (rel. rate 2.22) and 2-methyl-pyridine (rel. rate 0.50).[17] These results, together with the observed regioselectivity of these alkylations, see Table 1, confirm the dominance of 'steric approach control' in reactions on this system, with the extent of the control being determined by the length of the developing N - - - C alkyl bond in the (variable) S_N2 transition state.

The addition of a further methyl substituent in the 2-position causes another increase in the basicity, a further slight reduction in the total alkylation rate, see Table 2, and a substantial alteration in the regioselectivity. Although the 2-methyl substituent is symmetrically placed with respect to the competitive $N1$- and $N3$-sites, the steric effects of retarding alkylation at the two sites are clearly unequal. The extra 2-methyl group slightly retards benzylation at the $N1$-site suggesting a small steric retardation almost balanced by an inductive activation, *cf.* the pK_a data. The steric effect at the more congested $N3$-site is, however, a 10-fold reduction in the benzylation rate (Table 2) compared to the reaction at the $N3$-site of 4-methylbenzimidazole anions. This uneven steric effect results in an enhanced regioselectivity for alkylation of 2,4-dimethylbenzimidazole anions (2b) over the 2-unsubstituted system (2a), see Table 1. The extent of this enhancement is, moreover,

dependent on the alkylating agent, with tighter transition states showing greater effects as measured by the differential selectivity parameter, $\delta S = (\Delta\Delta G^{\ddagger}_{2,4\text{-Me}_2} - \Delta\Delta G^{\ddagger}_{4\text{-Me}})$. The graduated steric effect can be understood in terms of substituent interference on roughly conical 'approach corridors' [23], as supported by 3D molecular electrostatic potential maps[24] and by other molecular orbital calculations[25]. The constriction imposed by the symmetrically placed 2-methyl group has a greater impact on the narrower $N3$-approach corridor (roughly $4\pi r^2$ cross sectional area dependence) than on the broader $N1$-corridor, see Diagram 1. Furthermore this constriction should produce a larger percentage effect on $(r^2_{N1} - r^2_{N3})$ for the tighter transition states, with their shorter N - - CH_2 distances and hence narrower corridor cross sections. This is manifest in the increasing $(\Delta\Delta G^{\ddagger}_{2,4\text{-Me}_2} - \Delta\Delta G^{\ddagger}_{4\text{-Me}})$ parameters of Table 1 as the transition states tighten. These graduated regioselectivities thus provide a further clear and convincing demonstration of 'steric approach control' in the alkylation of nitrogen heterocycles with α-substituents.

Table 2   Benzylation rate constants for Benzimidazole Anions (Dimethylformamide, 30.0°)

Anion	$N1$:$N3$ Benzylation Ratio[a]	Rate constants[b]			pK_a[c]
		Total	$N1$-site	$N3$-site	
Benzimidazole	1.0	0.0533	0.0266[d]	0.0266[d]	5.56, 12.86
4-Methylbenzimidazole (2a)	3.7	0.0497	0.0391	0.0106	5.67
2,4-Dimethylbenzimidazole (2b)	33.5	0.0342	0.0332	0.0010	5.88
2-Amino-4-methylbenzimidazole (2e)	18.6	0.0242	0.0229	0.0013	7.6[e]
2-Ethoxy-4-methylbenzimidazole (2c)	5.1	0.0223	0.0187	0.0036	3.71
2-Chloro-4-methylbenzimidazole (2d)	>99	0.0011	0.0011	0.0000	2.8[e]
4-Methylbenzimidazolone (2f)[f]	4.3	0.0220	(0.018)	(0.004)	-2.0[e], 12.0[e]

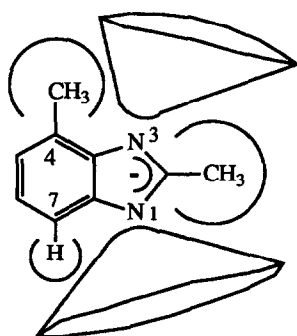[a] From Tables 1 and 3.   [b] Second order rate constants, k_2 ($\pm5\%$) L mol^{-1} sec^{-1} [c] Values from ref. 26
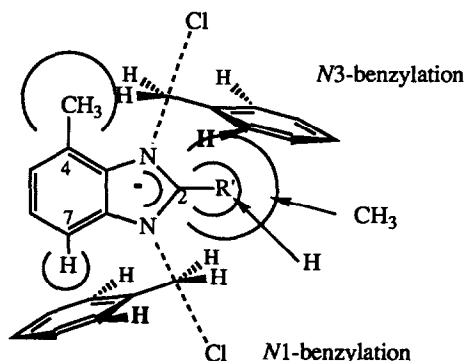[d] The N-Benzylation rate at a single site on the unsubstituted benzimidazole anion is half of the total rate.
[e] Estimated from values quoted in ref. 26   [f] Dianion; 60% $N1$,$N3$-dibenzylation also observed.

Diagram 1   Diagram 2

Replacement of the 2-methyl group in (2b) by an almost isosteric 2-amino group, giving the 2-amino-4-methylbenzimidazole anion (2e), results in a slight (0.71) rate reduction for benzylation, see Table 2, despite

the strong electron donating effect of this α-substituent (see pK_a data, Table 2). Similar effects have been observed in the N-methylation rates of thiazole (MeI / $C_6H_5NO_2$)[27] and 2-substituted pyridine[18] systems. Berg and Gallo have used Brønsted analyses of the rates of N-methylation (MeI / MeCN / 30°) of substituted pyridines to determine *ortho*-steric parameters S°, which indicate a 2-amino group (S° -0.93) to be slightly 'larger' than a 2-methyl group (S° -0.73).[18] It seems likely, however, that the enhanced effective size of *ortho*-amino groups may be due to H-bonded solvation of the amino groups, which would otherwise be slightly smaller than a methyl group. Correspondingly the site selectivities of the 2-amino-4-methyl anions (2e) were slightly *lower* for each alkylating agent than that found in the comparable 2,4-dimethylbenzimidazole anion alkylations, see Table 3, since in the N-alkylation transition states any H-bonded solvent is displaced, leaving the steric effects of the 'bare' groups. A comparison of the site specific benzylation rates of these two anions (Table 2) shows that the 2-amino group causes a small retardation ($k_{rel.}$ 0.69), compared to a 2-methyl group ($k_{rel.}$ 1.0), at the N1-site, but a slight *enhancement* ($k_{rel.}$ 1.3) of rate at the more crowded N3 site. Thus the decrease in selectivity cannot be due solely to the slightly smaller size of a desolvated amino group compared to a methyl group, but is consistent with a shift in the transition state structure to a longer N - - - CH_2R bond (earlier TS) as predicted for a more nucleophilic heterocyclic system, despite an overall rate retardation caused by the need for solvent displacement at the adjacent 2-amino group during both N1 and N3-alkylation.

Table 3   Alkylation of 2-Substituted-4-methylbenzimidazole Anions (Dimethylformamide, 30°)

Alkylating Agent	2-Methyl (2b)			2-Amino (2e)			2-Ethoxy (2c)			2-Chloro (2d)			2-Oxide⁻		
	N1	N3	$\Delta\Delta G^{\ddagger}$	N1	N3	$\Delta\Delta G^{\ddagger}$	N1	N3	$\Delta\Delta G^{\ddagger}$	N1	N3	$\Delta\Delta G^{\ddagger}$	N1	N3	$\Delta\Delta G^{\ddagger}$
loose															
$C_6H_5CH_2OCH_2Cl$	85	15	4.4	78	22	3.2	57	43	0.7	78	22	3.1	20	17	0.4
$C_6H_5CH_2Cl$	97	3	8.8	95	5	7.4	84	16	4.1	>99	<1	≥12	33	8	3.7
$CH_3(CH_2)_3Cl$	98	2	9.8				84	16	4.1	95.5	4.5	7.7			
$(CH_3)_3COCOCH_2Cl$	>99	<1	≥12	98.5	1.5	10.5	86	14	4.6	>99	<1	≥12	71	0	≥11
$C_6H_5COCH_2Cl$	>99	<1	≥12	*	*		96	4	7.8	>99	<1	≥12	*	*	
tight															

N1 and N3 figures are % of total alkylated product as determined by [1]H n.m.r. spectroscopy.
$\Delta\Delta G^{\ddagger}$ = -RT ln(N3%/N1%) kJ mol⁻¹.
On the 4-methylbenzimidazolone dianion; the 1,3-dialkylated product (N,N'-) formed the remaining percentage.
* No alkylated products detected.

The alkylation of 2-ethoxy-4-methylbenzimidazole anions (2c) shows even lower regioselectivity, see Table 3, with the pattern being reasonably comparable to that of 4-methylbenzimidazole itself (Table 1), with the exception of alkylation by phenacyl chloride, the tightest case. Consistent with the lowered basicity of 2-ethoxy-4-methylbenzimidazole, the kinetic studies (Table 2) showed an overall rate retardation ($k_{rel.}$ 0.45) for benzylation of (2c), with the effect being greater at the N3 site ($k_{rel.}$ 0.34) than at N1 ($k_{rel.}$ 0.48), relative to the comparable rates on 4-methylbenzimidazole anions (2a, $k_{rel.}$ 1.0). Berg and Gallo's *ortho*-steric parameter for the ethoxy group is surprisingly large, S°$_{OEt}$ -1.36 (*cf.* Me -0.73, Et -1.08, OMe -1.28).[18] In contrast, cyclohexane A-values give ethoxy groups (A 4.2 kJ mol⁻¹) a smaller 'size' than methyl (A 7.1 kJ mol⁻¹) and ethyl (A 7.5 kJ mol⁻¹).[28] Our results are consistent with a relatively small 'residual size' of the 2-ethoxy group

after allowing for a uniform unfavourable steric effect associated with the need to rotate the ethyl group away from both $N1$ and $N3$ reaction sites during alkylation.

The inductive effect of a 2-chloro group causes a substantial decrease in the basicity the of 4-methyl-benzimidazole system and this is reflected in the low benzylation rates for 2-chloro-4-methylbenzimidazole (2d), see Table 2. The steric requirement of the chloro substituent (van der Waals radius 1.8 Å , longer C-Cl bond 1.7 Å, *ortho*-steric S° -0.54) is smaller than that of a methyl group (v.d.W. radius 2.0 Å, C-CH$_3$ bond 1.52 Å, S° -0.73), and the alkylation pattern shows a corresponding reduced regioselectivity for 2-chloro-4-methylbenzimidazole (2d) compared to 2,4-dimethylbenzimidazole anions (2b), except for benzylation.

The reversed order of regioselectivities for the benzylation and butylation of (2d) compared to (2a) (see Tables 1 and 3) needs explanation. Butylation, with a tighter transition state than benzylation,[14] should involve greater regioselectivity due to its shorter N - - CH$_2$R distance in the transition state. This is seen in the 4-methylbenzimidazole (2a) alkylations, but for the 2-chloro-4-methyl system (2d), this selectivity order is reversed. We attribute this to the peculiar geometric requirements of S$_N$2 reactions in benzyl systems. The relative looseness of the S$_N$2 transition state in benzylations comes from a conjugative electron donation by the phenyl ring coplanar with the pentacoordinate sp^2-hybridized methylene alkylation centre. As indicated in Diagram 2, this specific conformational requirement places extra steric demands on the alkylation transition state; butylations are relatively free from comparable conformational requirements for the propyl group. For (2a) the phenyl group can fit over the edge of the imidazole ring as indicated in the $N3$-benzylation component shown at the top of Diagram 2. In the transition state for $N3$-benzylation of (2d), the 2-chloro group now interferes with this required CH$_2$ - phenyl coplanarity, whereas for $N1$-reaction the absence of a bulky group at C7 (*cf.* the 4-methyl group) allows access to alternate suitable conformations as shown at the bottom of Diagram 2. Thus the steric interference of the 2-chloro group is greater for benzylation than for butylation despite the latter's tighter transition state. Similar, but smaller effects are evident in the butylation versus benzylation selectivity results for the 2,4-dimethyl and 2-ethoxy-4-methyl systems (2b and 2c). Coplanar conformational requirements are also expected for the carbonyl groups and the alkylation methylene centre in the tight transition states of alkylation by phenacyl chloride[29] and *tert*-butyl chloroacetate and these probably contribute to their relatively high regioselectivities.

In an attempt to induce earlier transition states, the alkylation of 4-methylbenzimidazolone dianions (2, R = O⁻) were studied, as the extra electron density and small steric size of a (nominal) 2-oxide substituent were expected to lead to substantially enhanced alkylation rates. The kinetics and regioselectivity analysis of these alkylations were, however, disrupted by the formation of 30 - 60% $N1,N3$-dialkylated material. Second order rate constants, determined at low conversion, established the overall *initial* benzylation rate to be comparable to that of the 2-ethoxy-4-methyl system (2c) and not the enhanced rate expected (see Table 2). The regioselectivities of these dianion alkylations, given in Table 3, must also be considered questionable. Further alkylation of the initially formed $N1$- and $N3$-monoalkylated monoanions proceeds with unknown, different rates, rendering the residual $N1/N3$-monoalkylated product ratio of incalculable significance, although the selectivity ratios seem to conform to the expected pattern.

Table 4   Temperature Dependence of Benzylation Regioselectivities for
2-Substituted-4-methylbenzimidazole Anions (Dimethylformamide)

Temperature	4-Methyl (2a)			2-Ethoxy-4-methyl (2c)			2,4-Dimethyl (2b)			2-Chloro-4-methyl (2d)		
	$N1$	$N3$	$\Delta\Delta G^\ddagger$	$N1$	$N3$	$\Delta\Delta G^\ddagger$	$N1$	$N3$	$\Delta\Delta G^\ddagger$	$N1$	$N3$	$\Delta\Delta G^\ddagger$
30°	78.7	21.3	3.3	83.8	16.2	4.1	97.1	2.9	8.9	>99	<1	>12
60°	78.7	21.3	3.6	82.6	17.4	4.3	95.7	4.3	8.6	95.8	4.2	8.7
90°	78.7	21.3	3.9	81.9	18.1	4.6	94.2	5.8	8.4	92.3	7.7	7.5
$\Delta\Delta H^\ddagger$ / kJ mol^{-1}		0			2.0			11.0			21.5	
$\Delta\Delta S^\ddagger$ / J K^{-1} mol^{-1}		-10.9			-6.9			+7.2			+38.7	

Reaction with benzyl chloride. $N1$ and $N3$ figures are % of total alkylated product as determined by ^{1}H n.m.r. spectroscopy.
$\Delta\Delta G^\ddagger = \Delta\Delta H^\ddagger - T.\Delta\Delta S^\ddagger = -RT \ln(N3\%/N1\%)$ kJ mol^{-1}

Temperature effects on the benzylation regioselectivities of the benzimidazole anions are recorded in Table 4. For 4-methylbenzimidazole anions (2a), the $N1/N3$-benzylation ratio is insensitive to temperature over the 30 - 90°C range studied. 2-Ethoxy-4-methyl- (2c) and 2,4-dimethyl-benzimidazole (2b) anions showed slight decreases in regioselectivity at higher temperatures consistent with a 'normal', temperature induced reactivity-selectivity[30] variation. The 2-chloro-4-methylbenzimidazole system (2d) showed significantly higher temperature sensitivity. The 2-unsubstituted and 2-ethoxy systems (2a and 2c) gave similar $N3/N1$ differential activation parameters, with the larger 2-methyl and chloro substituents of 2b and 2d giving a different pattern. Pronounced temperature sensitivities of alkylations in other ambident anion systems have often been attributed to ionic aggregation effects.[31] The significantly higher temperature sensitivity and large $\Delta\Delta S^\ddagger$ parameter for the 2-chloro system (2d) is consistent with such an effect. It is possible that bidentate coordination of sodium cations by the 2-chloro and adjacent nitrogen sites may cause significant ion-pairing in this latter system, particularly at $N1$ where the absence of a bulky 7-substituent allows better solvation of the exposed face of the chelated sodium cation. The other benzimidazole systems probably exist and react essentially as the 'free anions' with the sodium cations preferably solvated by dimethylformamide.

CONCLUSIONS

Moderate sized 2-substituents cause substantial increases in the regioselectivity of alkylation of anionic 4-methylbenzimidazole systems despite the symmetrical disposition of 2-substituents with respect to the competing $N1$ and $N3$ alkylation sites. The enhancement of $N1/N3$ site selectivity depends on the size of the 2-substituent and is greater for alkylations involving tight S_N2 transition states than those proceeding via loose transition states. This unequal steric effect is consistent with 'steric approach control' involving roughly conical approach corridors. There is some evidence for small changes in regioselectivity caused by shifts along the early-late axis of a More O'Ferrall - Jencks S_N2 transition state diagram as the 2-substituent alters the nucleophilicity of the competing nitrogen alkylation sites. But these effects are slight compared to the more substantive effects of variation along the 'perpendicular', loose-tight axis induced by changing the substituent (R) on the primary alkylating agent, RCH_2Cl.

Overall these results represent a clear example of the subtle but dominant effects of 'steric approach control' in alkylations in 4-substituted benzimidazole systems, where the magnitude of the steric effects is critically dependent on the length of the developing N - - - C bond in the S_N2 alkylation transition states involved.

EXPERIMENTAL

Materials:

The benzimidazoles were synthesized by previously reported routes: 4-methylbenzimidazole[32], 2,4-dimethylbenzimidazole[32], 2-amino-4-methylbenzimidazole[33], 2-chloro-4-methylbenzimidazole[34], 2-ethoxy-4-methylbenzimidazole[35], 4-methyl-2-benzimidazolone[36]. Commercial samples of benzyl chloride and *n*-butyl chloride were distiled before use and phenacyl chloride was recrystallized from petroleum. Benzyl chloromethyl ether[37], and *t*-butyl chloroacetate[38] prepared according to literature procedures were used directly, after establishing their purity by ^1H n.m.r. spectroscopy. *N,N*-dimethylformamide was dried and purified using the procedures of Perrin *et al.* [39] and stored under dry nitrogen, over 4Å molecular sieves.

General Alkylation Procedure

The appropriate benzimidazole (about 0.5 - 1.0 mmole) was dissolved in dry dimethylformamide (10 - 20 mL) to give an about 0.05 M solution. A 5% molar excess of sodium hydride was added and the contents stirred till homogeneous. The alkylating agent (RCH_2X; 95% mole equivalent by weight) in dimethylformamide (5 mL) was then added and the resulting solution kept overnight at 30±0.1° under dry nitrogen. Dimethylformamide was removed by distillation then co-distillation with toluene (3 × 30 mL) (rotary evaporator, about 50°); the residue thus obtained was dissolved in chloroform or dichloromethane (about 30 mL) and washed with saturated aqueous sodium carbonate solution (4 × 30 mL). The residue obtained after evaporation of the dried organic phase was analysed by thin layer chromatography (silica gel, 10 - 20% ethanol / chloroform) and ^1H n.m.r. spectroscopy.

Spectroscopic and Quantitative Analyses

The relative proportions of the two isomers in the crude product mixture, in $CDCl_3$ solution, were determined by by computer generated listing of the integral intensities (p.f.t. ^1H n.m.r. spectroscopy, Varian XL-200E and Varian GEMINI-300) of the alkyl *N*-methylene signals. Careful precautions were taken to avoid saturation and other problems affecting quantitative n.m.r. measurements.[40] All alkylation reactions were performed in duplicate and the results averaged. Estimated uncertainty of these analyses is ±1%, with reproducibility of alkylation product ratios generally ±0.5%.

Most alkylation mixtures were also subjected to preparative t.l.c. or radial chromatography separation (silica gel, ethyl acetate / petroleum) and the individual isomers characterised by m.p., microanalysis, mass spectrometry (EI, 70 eV), uv. (95% ethanol) and ^1H n.m.r. spectroscopy ($CDCl_3$).

Alkylation of 4-Methylbenzimidazole Anions (2a)

Alkylation with Benzyl Chloride

Standard alkylation and isolation procedures were followed using 4-methylbenzimidazole (0.1322 g, 1 mmol.), sodium hydride (0.0465 g, 55.0% in oil, 1.06 mmol.) and benzyl chloride (0.1265 g, 1 mmol.) in dry dimethylformamide (20 mL). The crude mixture (0.2158 g), obtained as a colourless solid, was analysed by t.l.c. and ^1H n.m.r. spectroscopy; both indicated the presence of two isomeric products in unequal amounts. ^1H n.m.r. (200 MHz): δ 2.47 (s, CH_3 [N^3]), 2.70 (s, CH_3 [N^1]), 5.35 (s, CH_2 [N^1]), 5.59 (s, CH_2 [N^3]), 6.9-8.0 (ArH),7.93 (s,1H, H-2 [N^3]), 8.02 (s, 1H, H-2 [N^1]). Integration was extended 20 Hz on each side from the centre of the two *N*-methylene signals; N^1 : N^3 alkylation ratio = 78.7±1.0 : 21.3±1.0% (duplicate run: 77.7±1.0 : 22.3±1.0%).

1-Benzyl-4-methylbenzimidazole (4a, R' = $C_6H_5CH_2$)

The above mixture (0.0514 g) of two isomers were separated on a silica gel (20x20x0.2 cm) t.l.c. plate using ethyl acetate-light petroleum (9:1) as eluent. The major isomer, *1-benzyl-4-methylbenzimidazole* (higher R_f), was obtained on evaporation of the solvent as colourless crystals (0.0372 g); m.p. 81-82°. (Found: C, 80.6; H, 6.3; N, 12.3%. $C_{15}H_{14}N_2$ requires C, 81.1; H, 6.4; N, 12.6%). M.s. m/z (%): 223 (4%), 222 (M+, 21), 221 (1), 131 (5), 92 (8), 91 (100), 77 (5), 65 (17), 51 (8). ^1H n.m.r. (60 MHz): δ 2.70 (s, 3H, CH_3), 5.35 (s, 2H, CH_2), 7.05-7.25 (m, 5H, C_6H_5), 7.28-7.40 (m, 3H, H-5, H-6, H-7), 8.03 (s, 1H, H-2). Uv.: λ_{max} 215, 252, 283.

1-Benzyl-7-methylbenzimidazole (3a, R' = $C_6H_5CH_2$)

The minor isomer, *1-benzyl-7-methylbenzimidazole* (lower R_f), was obtained on evaporation of the solvent as colourless crystals (0.0094 g); m.p. 151-152°. (Found: C, 80.7; H, 6.6; N, 12.5%. $C_{15}H_{14}N_2$ requires C, 81.1; H, 6.4; N, 12.6%). M.s. m/z (%): 223 (6), 222 (M+, 34), 221 (1), 131 (7), 92 (8), 91 (100), 77 (3), 65 (15), 51 (5). ^1H n.m.r. (60 MHz): δ 2.48 (s, 3H, CH_3), 5.60 (s, 2H, CH_2), 7.0 (m, 3H, C_6H_5), 7.18 (t, 1H, J = 8.0, H-6), 7.30 (m, 3H, C_6H_5, H-5), 7.69 (d, 1H, J = 8.0, H-7), 7.92 (s, 1H, H-2). Uv.: λ_{max} 215, 251, 281.

Alkylation of 4-Methylbenzimidazole with n-Butyl Chloride

Standard alkylation and isolation procedures were followed using 4-methylbenzimidazole (0.1321 g, 1mmol.), sodium hydride (0.0481 g, 55.0% in oil, 1.10 mmol.) and n-butyl chloride (0.0925 g, 1 mmol.) in dry dimethylformamide (20 mL). The crude mixture (0.1688 g) was analysed by t.l.c. and ^1H n.m.r.; both indicated the presence of two isomeric products in unequal amounts. ^1H n.m.r.: δ 0.94 (t, $CH_2CH_2CH_2CH_3$ [N^1]), 0.98 (t, $CH_2CH_2CH_2CH_3$[N^3]), 1.30 (m, $CH_2CH_2CH_2CH_3$ [N^1 and N^3]), 1.80 p, $CH_2CH_2CH_2CH_3$ [N^1 and N^3]), 2.63 (s, CH_3 [N^3]), 2.70 (s, CH_3 [N^1]), 4.12 (t, N-CH_2 [N^1]), 4.30 (t, N-CH_2 [N^3]), 7.0-7.25 (ArH), 7.80 (s, 1H, H-2 [N^3]), 7.88 (s, 1H, H-2 [N^1]). The two N-methylene triplets were integrated (extending 16 Hz on each side from the centre of the triplets) N^1 : N^3 alkylation ratio = 82.8±1.0 : 17.2±1.0% (duplicate run, 82.2±1.0 : 17.8±1.0%).

1-Butyl-4-methylbenzimidazole (4a, R' = C_4H_9)

The above mixture (0.0505 g) of two isomers were separated on a silica gel (20x20x0.2 cm) t.l.c. plate using ethyl acetate-light petroleum (9:1) as eluent. The major isomer, *1-butyl-4-methylbenzimidazole* (higher R_f), was obtained as a colourless syrup (0.0377 g) on evaporation of the solvent. (Found: mol wt 188.1313. $C_{12}H_{16}N_2$ requires 188.1313). M.s. m/z (%): 189 (9), 188 (M+, 59), 187 (7), 173 (5), 159 (3), 146 (22), 145 (100), 132 (13), 131 (23), 118 (13), 105 (8), 91 (16), 77 (15), 65 (13), 51 (13). ^1H n.m.r.: δ 0.95 (t, 3H, J_{av} = 7.3, $CH_2CH_2CH_2CH_3$), 1.35 (sextuplet, 2H, J_{av} = 7.5, $CH_2CH_2CH_2CH_3$), 1.86 (pentuplet, 2H, J = 7.5, $CH_2CH_2CH_2CH_3$), 2.68 (s, 3H, CH_3) 4.16 (t, 2H, J_{av} = 7.0, N-CH_2), 7.08 (d, 1H, J = 6.6, H-5), 7.21 (m, 2H, H-6, H-7), 7.88 (s, 1H, H-2). Uv.: λ_{max} 215, 256, 273, 283 nm.

1-Butyl-7-methylbenzimidazole (3a, R' = C_4H_9)

The minor isomer, *1-butyl-7-methylbenzimidazole* (lower R_f), was obtained as a colourless syrup (0.0072 g) on evaporation of the solvent. (Found: mol wt 188.1313. $C_{12}H_{16}N_2$ requires 188.1313). M.s. m/z (%): 189 (6), 188 (M+, 37), 173 (2), 159 (2), 146 (17), 145 (100), 131 (13), 118 (6), 104 (6), 91 (16), 77 (13), 65 (13), 51 (12). ^1H n.m.r.: δ 0.92 (t, 3H, J_{av} = 7.3, $CH_2CH_2CH_2CH_3$), 1.34 (sextuplet, 2H, J_{av} = 7.5, $CH_2CH_2CH_2CH_3$), 1.78 (pentuplet, 2H, J = 7.2, $CH_2CH_2CH_2CH_3$), 2.64 (s, 3H, CH_3), 4.29 (t, 2H, J = 7.2, N-CH_2), 6.96 (d, 1H, J = 7.2, H-5), 7.11 (t, 1H, J_{av} = 7.6, H-6), 7.60 (d, 1H, J = 8.4, H-7), 7.86 (s, 1H, H-2). Uv.: λ_{max} 215, 251, 273, 282 nm.

Alkylation with tert-Butyl Chloroacetate

Standard alkylation and isolation procedures were followed using 4-methylbenzimidazole (0.1324 g, 1mmol.), sodium hydride (0.0462 g, 55.0% in oil, 1.06 mmol.), and *tert*-butyl chloroacetate (0.1505 g, 1mmol.) in dry dimethylformamide (20 mL). The crude mixture (0.2123 g).was analysed by t.l.c. and ^1H n.m.r.; both indicated the presence of two isomeric products in unequal amounts. ^1H n.m.r.: δ 1.27 {s, C(CH_3)_3 [N^3]}, 1.44 {s, C(CH_3)_3 [N^1]}, 2.56 (s, CH_3 [N^3]), 2.68 (s, CH_3 [N^1]), 4.72 (s,CH_2 [N^1]), 4.87 (s, CH_2 [N^3]), 6.96-7.68 (ArH), 7.86 (s, H-2 [N^3]), 7.92 (s, H-2 [N^1]). The two N-methylene singlets were integrated (extending 14 Hz on each side from the centre of the singlets); N^1 : N^3 alkylation ratio = 84.4±1.0 : 15.6±1.0% (duplicate run, 84.8±1.0 : 15.2± 1.0%).

1-tert-*Butyloxycarbonylmethyl-4-methylbenzimidazole (4a, R' = (CH3)3COCOCH2)*

The above mixture (0.0516 g) of two isomers were separated on a silica gel (20x20x0.2 cm) t.l.c. plate using ethyl acetate-light petroleum (8:2) as eluent. The major isomer, *1*-tert.-*butyloxycarbonylmethyl-4-methylbenzimidazole* (higher R_f), was obtained as colourless gum (0.0402 g) on evaporation of the solvent. (Found: mol wt 246.1369. $C_{14}H_{18}N_2O_2$ requires 246.1368). M.s. m/z (%): 247 (2), 246 (M+, 15), 190 (33), 145 (57), 131 (3), 117 (4), 91 (11), 83 (35), 77 (3), 65 (11), 57 (100), 51 (6). ^{1}H n.m.r.: δ 1.46 [s, 9H, -C(CH3)3], 2.70 (s, 3H, CH3), 4.78 (s, 2H, CH2), 7.12 (t,1H, J = 7.5, H-6), 7.17 (bs, 1H, H-5), 7.21 (d, 1H, J = 7.5, H-7), 7.92 (s, 1H, H-2).

1-tert-*Butyloxycarbonylmethyl-7-methylbenzimidazole (3a, R' = (CH3)3COCOCH2)*

The minor isomer, *1*-tert.-*butyloxycarbonylmethyl-7-methylbenzimidazole* (lower R_f), was obtained as colourless crystals (0.0061 g) on evaporation of the solvent; m.p. 126-127°. (Found: mol wt 246.1369. $C_{14}H_{18}N_2O_2$ requires 246.1368). M.s. m/z (%): 247 (2), 246 (M+, 13), 190 (21), 145 (53), 131 (2), 117 (3), 91 (12), 77 (3), 65 (12), 57 (100), 51 (6). ^{1}H n.m.r.: δ 1.30 [s, 9H, C(CH3)3], 2.61 (s, 3H, CH3), 4.96 (s, 2H, CH2), 7.02 (d, 1H, J = 7.0, H-5), 7.17 (t, 1H, J = 7.5, H-6), 7.66 (d, 1H, J = 8.4, H-7), 7.86 (s, 1H, H-2).

Alkylation of 2,4-Dimethylbenzimidazole Anions (2b)

Alkylation with Benzyl Chloride

Standard alkylation and isolation procedure were followed using 2,4-dimethylbenzimidazole (0.1462 g, 1 mmol.), sodium hydride (0.0472 g, 55.0% in oil, 1.06 mmol.) and benzyl chloride (0.1265 g, 1 mmol.) in dry dimethylformamide (20 mL). The crude mixture (0.2038 g), obtained as an almost colourless solid, was analysed by t.l.c. and ^{1}H n.m.r.; both indicated the presence of two isomeric products; one of them being in a very small amount. ^{1}H n.m.r.: δ 2.48 (s,4-CH3 [N^3]), 2.56 (s, 4-CH3 [N^3]), 2.60 (s, 2-CH3 [N^1]), 2.68 (s, 2-CH3 [N^1]), 5.29 (s, CH2 [N^1]), 5.52 (s, CH2 [N^3]), 7.0-7.4 (ArH). The two *N*-methylene singlets were integrated (extending 18 Hz on each side from the centre of the singlets) N^1 : N^3 alkylation ratio = 97.0±1.0 : 3.0±1% (duplicate run, 97.2±1.0 : 2.8±1.0%).

1-Benzyl-*2,4-dimethylbenzimidazole (4b, R' = C6H5CH2)*

The above mixture (0.0542 g) of two isomers were separated on a silica gel (20x20x0.2 cm) t.l.c. plate using ethyl acetate : light petroleum (9:1) as eluent. As the R_f value of the major isomer was only slightly higher than the minor isomer and the proportion of the minor isomer was very small, the latter remained mixed with the major at the lower portion of the band. So from the upper portion of the band, the major isomer, *1*-*benzyl-2,4-dimethylbenzimidazole* was isolated and on evaporation of the solvent gave colourless crystals (0.0223 g); m.p. 42-43°. (Found: C,81.65; H, 6.81; N, 11.84%. $C_{16}H_{16}N_2$ requires C, 81.32; H, 6.82; N, 11.85%). M.s. m/z (%): 237 (2), 236 (M+, 14), 145 (6), 118 (1), 91 (100), 77 (4), 65 (12), 51 (8). ^{1}H n.m.r.: δ 2.60 (s, 3H, 4-CH3), 2.69 (s, 3H, 2-CH3), 5.32 (s, 2H, CH2), 7.02-7.09 (m, 5H, ArH), 7.27-7.32 (m, 3H, ArH). Uv.: λ_{max} 213, 254, 272, 282 nm.

1-Benzyl-*2,7-dimethylbenzimidazole (3b, R' = C6H5CH2)*

The mixture (0.0113 g) of the isomers obtained from the lowest portion of the above chromatographic band were further separated on a silica gel (20x20x0.025 cm) t.l.c. plate using ethyl acetate-light petroleum (9:1) as eluent. From the lower band, the minor isomer, *1*-*benzyl-2,7-dimethylbenzimidazole*, was obtained as colourless crystals (0.0024 g); m.p. 56-57°. (Found: mol wt 236.1313. $C_{16}H_{16}N_2$ requires 236.1313). M.s. m/z (%): 237 (1), 236 (7), 145 (3), 118 (1), 104 (1), 91 (100), 77 (5), 65 (18), 51 (9). ^{1}H n.m.r.: δ 2.50 (s, 3H, 4-CH3), 2.68 (s, 3H, 2-CH3), 5.60 (s, 2H, CH2), 6.92 (m, 2H, C6H5), 7.03 (d, 1H, J = 7.2, H-5), 7.23 (t, 1H, J$_{av}$ = 7.7, H-6), 7.27-7.39 (m, 3H, C6H5), 7.69 (d, 1H, J = 7.8, H-7). Uv.: λ_{max} 212, 253, 271, 280 nm.

Alkylation with Benzyl Chloromethyl Ether

Standard alkylation and isolation procedures were followed by taking 2,4-dimethylbenzimidazole (0.1461 g, 1mmol.), sodium hydride (0.0475 g, 55.0% in oil, 1.08 mmol.) and benzyl chloromethyl ether (0.1503 g, 0.96 mmol.) in dry dimethylformamide (20 mL). The crude mixture (0.2806 g), an almost colourless gum, was analysed by t.l.c. and ^{1}H n.m.r.; both indicated the presence of two isomeric products in unequal amounts. ^{1}H n.m.r.: δ 2.51 (s, 4-CH3 [N^3]), 2.57 (s, 4-CH3 [N^1]), 2.60 (s, 2-CH3 [N^3]), 2.66 (s,

2-CH$_3$ [N^1]), 4.38 (s, -CH$_2$C$_6$H$_5$ [N^1]), 4.40 (s, -CH$_2$C$_6$H$_5$ [N^3]), 5.38 (s, N-CH$_2$ [N^1]), 5.45 (s, N-CH$_2$ [N^3]), 6.91-6.38 (ArH). The two N-methylene singlets were integrated (extending 14 Hz on each side from the centre of the singlets); N^1 : N^3 alkylation ratio = 85.3±1.0 : 14.7±1.0% (duplicate run, 85.5±1.0 : 14.5±1.0%).

1-Benzyloxymethyl-2,4-dimethylbenzimidazole (4b, R' = C$_6$H$_5$CH$_2$OCH$_2$)

The above mixture (0.0524 g) of two isomers were separated on a silica gel (20x20x0.2 cm) t.l.c. plate using ethyl acetate : light petroleum (8:2) as eluent. The major isomer, *1-benzyloxymethyl-2,4-dimethylbenzimidazole* (higher R$_f$), was obtained as a colourless gum (0.0362 g) on evaporation of the solvent. (Found: mol wt 266.1420. C$_{17}$H$_{18}$N$_2$O requires 266.1419). M.s. m/z (%): 267 (1), 266 (M+, 5), 236 (3), 159 (3), 132 (2), 104 (2), 92 (8), 91 (100), 89 (3), 77 (7), 65 (15), 51 (8). ^{1}H n.m.r.: δ 2.66 (s, 3H, 4-CH$_3$), 2.67 (s, 3H, 2-CH$_3$), 4.47 (s, 2H, CH$_2$C$_6$H$_5$), 5.54 (s, 2H, N-CH$_2$), 7.05-7.39 (ArH).

1-Benzyloxymethyl-2,7-dimethylbenzimidazole (3b, R' = C$_6$H$_5$CH$_2$OCH$_2$)

The minor isomer, *1-benzyloxymethyl-2,7-dimethylbenzimidazole* (lower R$_f$), was obtained as colourless crystals (0.0062 g) on evaporation of the solvent; m.p. 131-132°. (Found: mol wt 266.1420. C$_{17}$H$_{18}$N$_2$O requires 266.1419). M.s. m/z (%): 267 (1), 266 (M+, 5), 236 (3), 159 (4), 132 (1), 104 (6), 91 (100), 77 (21). ^{1}H n.m.r.: δ 2.60 (s, 3H, 4-CH$_3$), 2.70 (s, 3H, 2-CH$_3$), 4.54 (s, 2H, CH$_2$C$_6$H$_5$), 5.66 (s, 2H, N-CH$_2$), 7.02 (d, 1H, J = 7.5, H-5), 7.16 (t, 1H, J$_{av}$ = 7.5, H-6), 7.27-7.37 (m, 5H, C$_6$H$_5$), 7.55 (d, 1H, J = 7.5, H-7).

Alkylation with tert-Butyl Chloroacetate

1-tert-Butyloxycarbonylmethyl-2,4-dimethylbenzimidazole (4b, R' = (CH$_3$)$_3$COCOCH$_2$)

Standard alkylation and isolation procedures were followed using 2,4-dimethylbenzimidazole (0.1461 g, 1mmol), sodium hydride (0.0472 g, 55.0% in oil, 1.08 mmol.), and *tert.-butyl* chloroacetate (0.1505 g, 1mmol) in dry dimethylformamide (20 mL). The crude mass (0.2603 g), an almost colourless colourless gum, was analysed by t.l.c. and ^{1}H n.m.r. spectroscopy; both indicated the presence of only one alkylated product, *1-tert.-butyloxycarbonylmethyl-2,4-dimethylbenzimidazole*. The crude product (0.0636 g) was then purified by radial chromatography (SiO$_2$, ethyl acetate) and obtained as a colourless gum (0.0502 g) on evaporation of the solvent. (Found: mol wt 260.1524. C$_{15}$H$_{20}$N$_2$O$_2$ requires 260.1525). M.s. m/z (%): 261 (3), 260 (M+, 16), 204 (62), 159 (93), 145 (5), 131 (2), 117 (3), 91 (12), 85 (63), 83 (100), 77 (4). ^{1}H n.m.r.: δ 1.44 [s, 9H, -C(CH$_3$)$_3$], 2.58 (s, 3H, 4-CH$_3$), 2.66 (s, 3H, 2-CH$_3$), 4.66 (s, 2H, N-CH$_2$), 7.0-7.07 (m, 5H, C$_6$H$_5$), 7.10-7.15 (m, 3H, H-5, H-6, H-7).

A duplicate run, using components of the same scale as above, gave only N1-alkylated product as above.

Alkylation with Phenacyl Chloride

1-Phenacyl-2,4-dimethylbenzimidazole (4b, R' = C$_6$H$_5$COCH$_2$)

Standard alkylation and isolation procedure were followed by taking 2,4-dimethylbenzimidazole (0.1462 g, 1mmol.), sodium hydride (0.0466 g, 55.0% in oil, 0.107 mmol.) and phenacyl chloride (0.1542 g, 1 mmol.) in dry dimethylformamide (20 mL). The crude mass (0.2485 g), an almost colourless solid, was analysed by t.l.c. and ^{1}H n.m.r.; both indicated the presence of only one product. The crude product (0.0752 g) was purified by radial chromatography (SiO$_2$, ethyl acetate) and *1-phenacyl-2,4-dimethylbenzimidazole* obtained as colourless crystals (0.0643 g); m.p. 187-188°. (Found: C, 77.0; H, 6.0; N, 10.7%. C$_{17}$H$_{16}$N$_2$O requires C, 77.3; H, 6.1; N, 10.6%). M.s. m/z (%): 265 (4), 264 (M+, 21), 160 (10), 159 (85), 145 (3), 117 (4), 106 (14), 105 (100), 91 (15), 77 (27). ^{1}H n.m.r.: δ 2.56 (s, 3H, 4-CH$_3$), 2.69 (s, 3H, 2-CH$_3$), 5.49 (s, 2H, CH$_2$), 6.95 (d, 1H, J = 7.5, H-5), 7.09 (m, 2H, H-6, H-7), 7.57 (t, 2H, J$_{av}$ = 7.5, C$_6$H$_5$), 7.70 (t, 1H, J = 7.5, C$_6$H$_5$), 8.02 (m, 2H, C$_6$H$_5$).

A duplicate run, using components of the same scale as above, gave only N1-alkylated product as above.

Alkylation of 2-amino-4-methylbenzimidazole (2e)

Alkylation with Benzyl Chloride

Standard alkylation and isolation procedures were followed using 2-amino-4-methylbenzimidazole (0.1472 g, 1 mmol.), sodium hydride (0.0452, 55.0% in oil, 1.03 mmol.) and benzyl chloride (0.1265 g, 1 mmol.) in dry dimethylformamide (20 mL). The usual work-up procedure gave a brown solid residue (0.2453

g) which was analysed by t.l.c. and ^{1}H n.m.r.; both indicated the presence of two isomeric products in unequal amounts, and some side products, which were not identified. ^{1}H n.m.r.: δ 2.32 (s,CH$_3$, parent heterocycle), 2.43 (s, CH$_3$, [N^3]), 2.52 (s, CH$_3$,[N^1]), 2.66 (s, unidentified), 4.16 (s, unidentified), 5.15 (s, CH$_2$, [N^1]), 5.36 (s, CH$_2$, [N^3]), 6.9-7.4 (ArH). The N-methylene singlets were integrated (extending 6 Hz on each side from the centre of the singlets); N^1 : N^3 alkylation ratio = 94.7±1.0 : 5.3±1.0%. Duplicate run, ^{1}H n.m.r. (CD$_3$OD): δ 2.42 (s, CH$_3$, [N^3]), 2.55 (s, CH$_3$, [N^1]), 3.45 (s, unidentified), 5.32 (s, CH$_2$, [N^1]), 5.55 (s, CH$_2$, [N^3]), 6.8-7.4 (ArH). The N-methylene singlets were integrated (extending 18 Hz on each side from the centre of the singlets); N^1 : N^3 alkylation ratio = 95.0±1.0 : 5.0±1.0%.

2-Amino-1-benzyl-4-methylbenzimidazole (4e, R' = C$_6$H$_5$CH$_2$)

The above mixture (0.0518 g) of two isomers were separated on a silica gel (20x20x0.2 cm) t.l.c. plate using chloroform-methanol (9:1) as eluent. The major isomer, *2-amino-1-benzyl-4-methylbenzimidazole* (R$_f$ = 0.4), was obtained on evaporation of the solvent as pale brown crystals (0.0402); m.p. 193-195°. (Found: C, 75.7; H, 6.5; N, 17.5%. C$_{15}$H$_{15}$N$_3$ requires C, 76.0; H, 6.4: N, 17.7%). M.s. m/z (%): 238 (3), 237 (M$^+$, 14), 146 (19), 104 (3), 92 (11), 91 (100), 77 (7), 65 (16), 51 (6). ^{1}H n.m.r.: δ 2.56 (s, 3H, CH$_3$), 5.16 (s, 2H, CH$_2$), 7.0 (m, 3H, ArH), 7.18 (dd, 2H, ArH), 7.32 (m, 3H, ArH). Uv.: λ$_{max}$ 218, 249, 286 nm.

2-Amino-1-benzyl-7-methylbenzimidazole (3e, R' = C$_6$H$_5$CH$_2$)

The minor isomer, *2-amino-1-benzyl-7-methylbenzimidazole* (R$_f$ = 0.3), was obtained on evaporation of the solvent as pale brown crystals (0.0028 g); m.p. 187-189°. (Found: mol wt. 237.1265. C$_{15}$H$_{15}$N$_3$ requires 237.1266). M.s. m/z (%): 238 (2), 237 (M$^+$, 16), 146 (15), 104 (3), 92 (10), 91 (100), 77 (8), 65 (11), 51 (7). ^{1}H n.m.r.: δ 2.46 (s, 3H, CH$_3$), 5.42 (s, 2H, CH$_2$), 6.86 (d, 1H, ArH), 7.1 (m, 3H, ArH), 7.3 (m, 4H, ArH). Uv.: λ$_{max}$ 218, 248, 285 nm.

Alkylation with Benzyl Chloromethyl Ether

Standard alkylation and isolation procedures were followed using 2-amino-4-methylbenzimidazole (0.147 g, 1 mmol.), sodium hydride (0.0458 g, 55.0% in oil, 1.05 mmol.) and benzyl chloromethyl ether (0.1486 g, 0.95 mmol.) in dry dimethylformamide (20 mL). The brown coloured crude mixture (0.2492 g) was analysed by t.l.c. and ^{1}H n.m.r.; both indicated the presence of two isomeric products in unequal amounts, recovered parent heterocycle and a small amount of benzylated or other alkylated product. ^{1}H n.m.r.: δ 2.26 (s, CH$_3$, from parent heterocycle), 2.50 (s, CH$_3$ [N^3]), 2.53 (s, CH$_3$ [N^1]), 3.12 (s, unidentified), 4.51 (s, CH$_2$ [N^1]), 4.57 (s, CH$_2$ [N^3]), 5.36 (s, CH$_2$ [N^1]), 5.45 (s, unidentified), 5.50 (s, CH$_2$ [N^3]), 5.7 (bs, 2H, NH$_2$), 6.8-7.4 (ArH). Addition of D$_2$O caused a shift in the NH$_2$ signal allowing better integration of the adjacent N-methylene signals (extending 8 Hz on each side from the centre of the singlets); N^1 : N^3 alkylation ratio = 78.5±1.0 : 21.5±1.0 (duplicate run, 78.1±1.0 : 21.9±1.0%).

2-Amino-1-benzyloxymethyl-4-methylbenzimidazole (4e, R' = C$_6$H$_5$CH$_2$OCH$_2$)

The above mixture (0.0506 g) of two isomers were separated on a silica gel (20x20x0.2 cm) t.l.c. plate using chloroform-methanol (9:1) as eluent. The major component, *2-amino-1-benzyloxymethyl-4-methyl-benzimidazole* (higher R$_f$), was obtained on evaporation of the solvent as pale brown crystals (0.0325 g); m.p. 110-112°. (Found: mol wt.267.1371. C$_{16}$H$_{17}$N$_3$O requires 267.1372). M.s. m/z (%): 268 (1), 267 (M$^+$, 7), 159 (9), 146 (15), 104 (2), 92 (9), 91 (100), 77 (6), 65 (12), 51 (5). ^{1}H n.m.r.: δ 2.55 (s, 3H, CH$_3$), 4.53 (s, 2H, C$_6$H$_5$CH$_2$), 5.39 (s, 2H, N-CH$_2$), 6.94-7.2 (m, 3H, ArH), 7.28-7.42 (m, 5H, (ArH).

2-Amino-1-Benzyloxymethyl-7-methylbenzimidazole (3e, R' = C$_6$H$_5$CH$_2$OCH$_2$)

The minor component, *2-amino-1-Benzyloxymethyl-7-methylbenzimidazole* (lower R$_f$), was obtained as pale brown crystals (0.0091 g) on evaporation of the solvent; m.p. 132-134°. (Found: mol wt 267.1371. C$_{16}$H$_{17}$N$_3$O requires 267.1372). M.s. m/z (%): 268 (2), 267 (M$^+$, 9), 159 (9), 146 (17), 104 (3), 92 (10), 91 (100), 77 (7), 65 (14), 51 (6). ^{1}H n.m.r.: δ 2.53 (s, 3H, CH$_3$), 4.62 ((s, 2H, C$_6$H$_5$CH$_2$), 5.58 (s, 2H, N-CH$_2$), 6.82 (d, 1H, J = 7.3, H-5), 6.94 (d, 1H, J = 7.2, H-6), 7.26-7.38 (m, 5H, ArH).

Alkylation with tert-Butyl Chloroacetate

Standard alkylation and isolation procedures were followed using 2-amino-4-methylbenzimidazole (0.1474 g, 1 mmol.), sodium hydride (0.0458 g, 55.0% in oil, 1.05 mmol.) and *tert.*-butyl chloroacetate (0.1505 g, 1mmol.) in dry dimethylformamide (20 mL). Crude brown mixture (0.2482 g) was analysed by t.l.c. and ^{1}H n.m.r.; t.l.c. indicated the presence of only one product and small amount of recovered parent

heterocycle. ^{1}H n.m.r. indicated the presence of two isomeric products in unequal amounts as well as recovered parent heterocycle. ^{1}H n.m.r.: δ 1.46 [s, -O(CH$_3$)$_3$], 2.54 (s, 4-CH$_3$ [N^1]), 2.61 (s, 4-CH$_3$ [N^3]), 4.56 (s, N-CH$_2$ [N^1]), 4.76 (s, N-CH$_2$ [N^3]),5.45 (bs, , NH$_2$ [N^1]), 6.88-7.45 (ArH). The two N-methylene singlets were integrated (extending 18 Hz on each side from the centre of the singlets); N^1 : N^3 alkylation ratio= 98.4±0.5 : 1.6±0.5% (duplicate run, 98.6±0.5 : 1.4±0.5%).

2-Amino-1-tert-butyloxycarbonyl-4-methylbenzimidazole (4e, (CH$_3$)$_3$COCOCH$_2$)

The above product mixture (0.0266 g) was chromatographed on a silica gel (20x20x0.1 cm) t.l.c. plate using chloroform-methanol (9:1) as eluent. From the upper portion of the band, *2-amino-1-tert-butyloxycarbonyl-4-methylbenzimidazole* was obtained as pale brown crystals (0.0156 g) on evaporation of the solvent; m.p. 174-176°. (Found: mol wt 261.1478. C$_{14}$H$_{19}$N$_3$O$_2$ requires 261.1477). M.s. m/z (%): 262 (2), 261 (M$^+$, 14), 205 (100), 160 (66), 146 (8), 133 (18), 104 (7), 91 (14), 77 (17), 65 (19), 57 (98), 51 (13). ^{1}H n.m.r.: δ 1.47 [s, 9H, -C(CH$_3$)$_3$], 2.54 (s, 3H, 4-CH$_3$), 4.55 (s, 2H, N-CH$_2$), 6.85-7.04 (m, 3H, H-5, H-6, H-7).

The minor N3-alkylated isomer was not obtained pure.

Attempted alkylation with Phenacyl Chloride

Standard alkylation and isolation procedures were followed using 2-amino-4-methylbenzimidazole (0.1473 g, 1 mmol.), sodium hydride (0.0458 g, 55.0% in oil, 1.05 mmol.) and phenacyl chloride (0.1543 g, 1mmol.) in dry dimethylformamide. The crude brown mixture (0.2516 g) was analysed by t.l.c. and ^{1}H n.m.r. spectroscopy; both indicated that no apparent alkylation had occurred and some of the reactants had decomposed. The reaction was repeated and allowed to continue for 2 days, but the results were unchanged.

Alkylation of 2-ethoxy-4-methylbenzimidazole (2c)

Alkylation with Benzyl Chloride

Standard alkylation and isolation procedures were followed using 2-ethoxy-4-methylbenzimidazole (0.0882 g, 0.5 mmol.), sodium hydride (0.0232 g, 55.0% in oil, 0.53 mmol.) and benzyl chloride (0.0633 g, 0.5 mmol.) in dry dimethylformamide (10 mL). Crude mixture (0.1421 g) was analysed by t.l.c. and ^{1}H n.m.r.; both indicated the presence of two isomeric products in unequal amounts. ^{1}H n.m.r.: δ 1.43 (OCH$_2$CH$_3$ [N^1 and N^3]), 2.37 (s, 4-CH$_3$ [N^3]), 2.58 (s, 4-CH$_3$ [N^1]), 4.6 (OCH$_2$CH$_3$ [N^1 and N^3]), 5.09 (s, N-CH$_2$ [N^1]), 5.35 (s, N-CH$_2$ [N^3]), 6.7-7.5 (ArH). The two N-methylene singlets were integrated (extending 20 Hz on each side from the centre of the singlets); N^1 : N^3 alkylation ratio = 83.9±1.0 : 16.1±1.0% (duplicate run, 83.5±1.0 : 16.5+±1.0%).

1-Benzyl-2-ethoxy-4-methylbenzimidazole (4c, R = C$_6$H$_5$CH$_2$)

The above mixture (0.0506 g) of two isomers were separated on a silica gel (20x20x0.2 cm) t.l.c. plate using ethyl acetate-light petroleum (1:1) as eluent. The major isomer, *1-benzyl-2-ethoxy-4-methylbenz-imidazole* (higher R$_f$), was obtained as colourless gum (0.0368 g) on evaporation of the solvent. (Found: mol wt 266.1420. C$_{17}$H$_{18}$N$_2$O requires 266.1419). M.s. m/z (%): 267 (2), 266 (M$^+$, 12), 238 (8), 209 (1), 160 (1), 147 (2), 131 (1), 104 (3), 91 (100), 77 (6), 65 (12), 51 (5). ^{1}H n.m.r.: δ 1.52 (t, 3H, J = 7.1, OCH$_2$CH$_3$), 2.67 (s, 3H, 4-CH$_3$), 4.72 (q, 2H, J = 7.1, OCH$_2$CH$_3$), 5.18 (s, 2H, N-CH$_2$), 6.93-7.09 (m, 4H, ArH), 7.24-7.38 (m, 4H, ArH). Uv.: λ$_{max}$ 213, 243, 273, 281 nm.

1-Benzyl-2-ethoxy-7-methylbenzimidazole (3c, R = C$_6$H$_5$CH$_2$)

The minor isomer, *1-benzyl-2-ethoxy-7-methylbenzimidazole* (lower R$_f$), was obtained as colourless gum (0.0082 g) on evaporation of the solvent. (Found: mol wt 266.1420. C$_{17}$H$_{18}$N$_2$O requires 266.1419). M.s. m/z (%): 267 (2), 266 (M$^+$, 12), 238 (6), 175 (1), 147 (3), 131 (1), 104 (2), 91 (100), 77 (5), 65 (10), 51 (4). ^{1}H n.m.r.: δ 1.43 (s, 3H, J = 7.1, OCH$_2$CH$_3$), 2.40 (s, 3H, 4-CH$_3$), 4.62 (q, 2H, J = 7.1, OCH$_2$CH$_3$), 5.40 (s, 2H, N-CH$_2$), 6.83 (d, 1H, J = 7, H-5), 7.02-7.09 (m, 3H, ArH), 7.26-7.35 (m, 3H, ArH), 7.45 (d, 1H, J = 8.1, H-7). Uv.: λ$_{max}$ 213, 273, 281 nm.

Alkylation with Benzyl Chloromethyl Ether

Standard alkylation and isolation procedures were followed by taking 2-ethoxy-4-methylbenzimidazole (0.0882 g, 0.5 mmol.), sodium hydride (0.0232 g, 55.0% in oil, 0.53 mmol.) and benzyl chloromethyl ether (0.0752 g, 0.48 mmol.) in dry dimethylformamide (10 mL). The crude mixture (0.1468 g) was analysed by

t.l.c. and ^{1}H n.m.r.; both indicated the presence of two isomeric products in unequal amounts, plus a very small amount of recovered parent heterocycle. ^{1}H n.m.r.: δ 1.43 (OCH$_2$CH$_3$ [N^1 and N^3]), 2.34 (s, 4-CH3 [from parent heterocycle]), 2.56 (s, 4-CH$_3$ [N^1]), 2.61 (s, 4-CH$_3$ [N^3]), 4.44 (s, CH$_2$C$_6$H$_5$ [N^1]), 4.46 (s, CH$_2$C$_6$H$_5$ [N^3]), 4.5-4.7 (OCH$_2$CH$_3$ [N^1 and N^3]), 5.34 (s, N-CH$_2$ [N^1]), 5.44 (s, N-CH$_2$ [N^3]), 6.8-7.5 (ArH). The two N-methylene singlets were integrated (extending 8 Hz on each side from the centre of the singlets); N^1 : N^3 alkylation ratio = 57.3±1.0 : 42.7±1.0% (duplicate run, 57.7±1.0 : 42.3±1.0%).

1-Benzyloxymethyl-2-ethoxy-4-methylbenzimidazole (4c, R' = C$_6$H$_5$CH$_2$OCH$_2$)

The above mixture (0.0378 g) of two isomers were separated on a silica gel (20x20x0.2 cm) t.l.c. plate using ethyl acetate-light petroleum (1:1) as eluent. The major isomer, *1-benzyloxymethyl-2-ethoxy-4-methyl-benzimidazole* (higher R$_f$), was obtained as colourless gum (0.0176 g) on evaporation of the solvent. (Found: mol wt 296.1526. C$_{18}$H$_{20}$N$_2$O$_2$ requires 296.1525). M.s. m/z (%): 297 (0.6), 296 (M$^+$, 3), 238 (3), 160 (2), 147 (3), 131 (2), 104 (2), 91 (100), 77 (5), 65 (12), 51 (2). ^{1}H n.m.r.: δ 1.52 (t, 3H, J = 7.1, OCH$_2$CH$_3$), 2.64 (s, 3H, 4-CH$_3$), 4.54 (s, 2H, CH$_2$C$_6$H$_5$), 4.70 (q, 2H, J = 7.1, OCH$_2$CH$_3$), 5.46 (s, 2H, N-CH$_2$), 7.05 (d, 1H, J = 7.6, H-5), 7.12 (t, 1H, J = 7.6, H-6), 7.19 (dd, 1H, J = 7.6, H-7), 7.31-7.46 (m, 5H, C$_6$H$_5$).

1-Benzyloxymethyl-2-ethoxy-7-methylbenzimidazole (3c, R' = C$_6$H$_5$CH$_2$OCH$_2$)

The minor isomer, *1-benzyloxymethyl-2-ethoxy-7-methylbenzimidazole* (lower R$_f$), was obtained as colourless gum (0.0138 g) on evaporation of the solvent. (Found: mol wt 296.1526. C$_{18}$H$_{20}$N$_2$O$_2$ requires 296.1525). M.s. m/z (%): 297 (0.8), 296 (M$^+$, 4), 238 (3), 160 (1), 147 (3), 133 (3), 104 (1), 91 (100), 77 (4), 65 (11), 51 (2). ^{1}H n.m.r.: δ 1.49 (t, 3H, J = 7.1, OCH$_2$CH$_3$), 2.68 (s, 3H, 4-CH$_3$), 4.54 (s, 2H, CH$_2$C$_6$H$_5$), 4.63 (q, 2H, J = 7, OCH$_2$CH$_3$), 5.56 (s, 2H, N-CH$_2$), 6.94 (d, 1H, J = 7.7, H-5), 7.11 (t, 1H, J$_{av}$ = 7.7, H-6), 7.28-7.39 (m, 5H, C$_6$H$_5$), 7.41 (d, 1H, J = 7.7, H-7).

Alkylation with tert-*Butyl Chloroacetate*

Standard alkylation and isolation procedures were followed by taking 2-ethoxy-4-methylbenzimidazole (0.0882 g, 0.5 mmol.), sodium hydride (0.0235, 55.05% in oil, 0.54 mmol.) and *tert.*-butyl chloroacetate (0.0752 g, 0.5 mmol.) in dry dimethylformamide (10 mL). Crude mixture (0.1446 g) was analysed by t.l.c. and ^{1}H n.m.r.; both indicated the presence of two isomeric products in unequal amounts and a very small amount of recovered parent heterocycle. ^{1}H n.m.r.: δ 1.44 {-C(CH$_3$)$_3$ [N^1 and N^3]}, 1.45 (OCH$_2$CH$_3$ [N^1 and N^3]), 2.38 (s, 4-CH3 [from parent heterocycle]), 2.53 (s, 4-CH$_3$ [N^3]), 2.58 (s, 4-CH$_3$ [N^1]), 4.55 (s, N-CH$_2$ [N^1]), 4.65 (OCH$_2$CH$_3$ [N^1 and N^3]), 4.78 (s, N-CH$_2$ [N^3]), 6.8-7.5 (ArH). The two N-methylene singlets were integrated (extending 8 Hz on each from the centre of the singlets); N^1 : N^3 alkylation ratio = 86.3±1.0 : 13.7±1.0% (duplicate run, 85.7±1.0 : 14.3±1.0%).

*1-*tert-*Butyloxycarbonylmethyl-2-ethoxy-4-methylbenzimidazole (4c, R' = (CH$_3$)$_3$COCOCH$_2$)*

The above mixture (0.0566 g) of two isomers were separated on a silica gel (20x20x0.2 cm) t.l.c. plate using ethyl acetate-light petroleum (1:1) as eluent. The major isomer, *1-tert.-butyloxycarbonylmethyl-2-ethoxy-4-methylbenzimidazole* (higher R$_f$), was obtained as colourless gum (0.0448 g) on evaporation of the solvent. (Found: mol wt 290.1630. C$_{16}$H$_{22}$N$_2$O$_3$ requires 290.1630). M.s. m/z (%): 291 6), 290 (M$^+$, 15), 234 (10), 189 (12), 175 (2), 161 (42), 147 (1), 133 (28), 118 (3), 104 (8), 91 (4), 77 (10), 65 (6), 57 (100), 51 (3). ^{1}H n.m.r.: δ 1.44, 1.46 [s, t; 12H ; C(CH$_3$)$_3$, OCH$_2$CH$_3$; J(triplet) = 7.1], 2.58 (s, 3H, 4-CH$_3$), 4.56 (s, 2H, N-CH$_2$), 4.64 (q, 2H, J = 7.1, OCH$_2$CH$_3$), 6.90 (d, 1H, J = 7.6, H-5), 6.96-7.07 (m, 2H, H-6, H-7).

*1-*tert-*Butyloxycarbonylmethyl-2-ethoxy-7-methylbenzimidazole (3c, R' = (CH$_3$)$_3$COCOCH$_2$)*

The minor isomer, *1-tert.-butyloxycarbonylmethyl-2-ethoxy-7-methylbenzimidazole* (lower R$_f$), was obtained as colourless gum (0.0052 g) on evaporation of the solvent. (Found: mol wt 290.1630. C$_{16}$H$_{22}$N$_2$O$_3$ requires 290.1630). M.s. m/z (%): 291 (2), 290 (M$^+$, 8), 206 (11), 175 (2), 161 (39), 147 (3), 133 (30), 118 (4), 104 (7), 91 (5), 77 (11), 65 (7), 57 (100), 51 (3). ^{1}H n.m.r.: δ 1.45, 1.46 [s, t; 12H; C(CH$_3$)$_3$, OCH$_2$CH$_3$; J(triplet) = 7.1], 2.51 (s, 3H, 4-CH$_3$), 4.60 (q, 2H, J$_{av}$ = 7, OCH$_2$CH$_3$), 4.78 (s, 2H, N-CH$_2$), 6.85 (d, 1H, J = 7.8, H-5), 7.04 (t, 1H, J$_{av}$ = 7.7, H-6), 7.39 (d, 1H, J = 7.9, H-7).

Alkylation with Phenacyl Chloride

Standard alkylation and isolation procedures were followed using 2-ethoxy-4-methylbenzimidazole (0.0882 g, 0.5 mmol.), sodium hydride (0.0231 g, 55.0% in oil, 0.53 mmol.) and phenacyl chloride (0.0771

g, 0.5 mmol.) in dry dimethylformamide (10 mL). The crude mixture (0.1408 g) was analysed by t.l.c. and [1]H n.m.r.; both indicated the presence of two isomeric products in unequal amounts and some recovered parent heterocycle. [1]H n.m.r.: δ 1.3-1.5 (OCH$_2$CH$_3$ [N^1,N^3 and from heterocycle]), 2.34 (s, 4-CH$_3$ [N^3]), 2.42 (s, 4-CH$_3$ [from parent heterocycle]), 2.58 (s, 4-CH$_3$ [N^1]), 4.5-4.7 (OCH$_2$CH$_3$ [N^1, N^3 and from parent heterocycle]), 5.28 (s, N-CH$_2$ [N^1]), 5.52 (s, N-CH$_2$ [N^3]), 6.78-8.45 (ArH). The Two N-methylene singlets were integrated (extending 20 Hz on each side from the centre of the singlets); N^1 : N^3 alkylation ratio = 95.5±1.0 : 4.5±1.0% (duplicate run, 95.7±1.0 : 4.3±1.0%).

2-Ethoxy-4-methyl-1-phenacylbenzimidazole (4c, R' = C$_6$H$_5$COCH$_2$)

The above mixture (0.0408 g) of two isomers were chromatographed on a silica gel (20x20x0.2 cm) t.l.c. plate using ethyl acetate-light petroleum (1:1) as eluent. The colourless crystals (0.0246 g) obtained from the upper portion of the wide band of the isomeric mixture in the t.l.c. plate was identified as *2-ethoxy-4-methyl-1-phenacylbenzimidazole* ; m.p. 134-135°. (Found: mol wt 294.1369. C$_{18}$H$_{18}$N$_2$O$_2$ requires 294.1368). M.s. m/z (%): 295 (6), 294 (M$^+$, 30), 266 (3), 189 (30), 161 (100), 148 (14), 133 (36), 118 (6), 105 (88), 91 (12), 77 (88), 65 (15), 57 (30), 51 (42). [1]H n.m.r.: δ 1.42 (t, 3H, J = 7.1, OCH$_2$CH$_3$), 2.59 (s, 3H, 4-CH$_3$), 4.64 (q, 2H, J = 7.1, OCH$_2$CH$_3$), 5.35 (s, 2H, N-CH$_2$), 6.83 (dd, 1H, J = 7.1, J = 1.8, H-5), 6.96-7.04 (m, 2H, ArH), 7.54 (m, 2H, ArH), 7.66 (d of t, 1H, J = 7.4, J = 1.8, ArH), 8.03 (dd, 2H, J = 7.1, J = 1.5, ArH).

The minor isomer was not obtained pure.

Alkylation of 2-chloro-4-methylbenzimidazole (2d)

Alkylation with Benzyl Chloride

1-Benzyl-2-chloro-4-methylbenzimidazole (4d, R' = C$_6$H$_5$CH$_2$)

Standard alkylation and isolation procedures were followed using 2-chloro-4-methylbenzimidazole (0.0832 g, 0.5 mmol.), sodium hydride (0.0235 g, 55.0% in oil, 0.54 mmol.) and benzyl chloride (0.0633 g, 0.5 mmol.) in dry dimethylformamide (10 mL). The crude mixture (0.1143 g) was analysed by t.l.c. and [1]H n.m.r.; both indicated the presence of one isomeric product and recovered parent heterocycle. The alkylated product was isolated using radial chromatography (SiO$_2$, ethyl acetate-light petroleum 1:1); the alkylated product eluted first and then the recovered parent heterocycle. Evaporation of the solution of the alkylated product afforded *1-benzyl-2-chloro-4-methylbenzimidazole* as colourless gum (0.0903 g). (Found: mol wt 256.0767. C$_{15}$H$_{13}$N$_2$Cl requires 256.0767). M.s. m/z (%): 258 (1), 256 (M$^+$, 3), 165 (4), 149 (4), 123 (6), 105 (16), 91 (96), 83 (80), 77 (28), 65 (28), 55 (100), 51 (69). [1]H n.m.r.: δ 2.64 (s, 3H, CH$_3$), 5.38 (s, 2H, CH$_2$), 7.05-7.21 (m, 5H, ArH), 7.29-7.35 (m, 3H, ArH). Uv.: λ_{max} 211, 248, 272, 282 nm.

A duplicate run also gave the N1-alkylated isomer as the sole detectable product.

1-Benzyl-2-chloro-7-methylbenzimidazole (3d, R' = C$_6$H$_5$CH$_2$)

Small amounts of a minor isomer, *1-benzyl-2-chloro-7-methylbenzimidazole*, were obtained from alkylation at 90°. Separation of the lower R$_f$ component by preparative t.l.c. gave, on evaporation of the solvent, a colourless gum (0.0028 g). (Found: mol wt 256.0767. C$_{15}$H$_{13}$N$_2$Cl requires 256.0767). M.s. m/z (%): 258 (0.3), 257 (0.1), 256 (M$^+$, 1), 165 (1), 105 (2), 91 (100), 83 (4), 77 (7), 65 (20), 51 (12). [1]H n.m.r.: δ 2.47 (s, 3H, CH$_3$), 5.65 (s, 2H, CH$_2$), 6.98 (m, 3H, ArH), 7.18 (t, 1H, J = 7.6, H-6), 7.31 (m, 3H, ArH), 7.61 (d, 1H, J = 7.6, H-7). Uv.: λ_{max} 212, 250, 274, 283 nm.

Alkylation with Benzyl Chloromethyl Ether

Standard alkylation and isolation procedures were followed using 2-chloro-4-methylbenzimidazole (0.0843 g, 0.5 mmol.), sodium hydride (0.0235 g, 55.0% in oil, 0.54 mmol.) and benzyl chloromethyl ether (0.0751 g, 0.48 mmol.) in dry dimethylformamide (10 mL). The crude mixture (0.1372 g), almost colourless gum, was analysed by t.l.c. and [1]H n.m.r.; both indicated the presence of two isomeric products in unequal amounts and recovered parent heterocycle. [1]H n.m.r.: δ 2.58 (s, CH$_3$ [parent heterocycle]), 2.63 (s, CH$_3$ [N^1]), 2.72 (s, CH$_3$ [N^3]), 4.52 (s, OCH$_2$C$_6$H$_5$ [N^1]), 4.56 (s, OCH$_2$C$_6$H$_5$ [N^3]), 5.61 (s, N-CH$_2$ [N^1]), 5.74 (s, N-CH$_2$ [N^3]), 7.05-7.58 (ArH). The two N-methylene singlets were integrated (extending 18 Hz on each side from the centre of the singlets); N^1 : N^3 alkylation ratio = 77.5±1.0 : 22.5±1.0% (duplicate run, 77.9±1.0 : 22.1±1.0%).

1-Benzyloxymethyl-2-chloro-4-methylbenzimidazole (4d, C6H5CH2OCH2)

The above mixture (0.0417 g) of two isomers was separated on a silica gel (20x20x0.2 cm) t.l.c. plate using ethyl acetate-light petroleum (3:2) as eluent. The R_f value of the components in the mixture were in the following order: major isomer>minor isomer>parent heterocycle. The major isomer, *1-benzyloxymethyl-2-chloro-4-methylbenzimidazole*, was obtained on evaporation of the solvent as colourless gum (0.0257 g). (Found: mol wt 286.0874. $C_{16}H_{15}N_2OCl$ requires 286.0873). M.s. m/z (%): 288 (1), 286 (M+, 2), 258 (1), 180 (1), 116 (1), 104 (1), 91 (100), 77 (3), 65(10), 51 (4). [1]H n.m.r.: δ 2.64 (s, 3H, CH3), 4.53 (s, 2H, OCH2C6H5), 5.63 (s, 2H, N-CH2), 7.12 (d, 1H, J = 7.1, H-5), 7.23 (t, 1H, J = 7.5, H-6), 7.27-7.38 (m, 6H, H-7, C6H5).

1-Benzyloxymethyl-2-chloro-7-methylbenzimidazole (3d, C6H5CH2OCH2)

The minor isomer, *1-benzyloxymethyl-2-chloro-7-methylbenzimidazole*, was obtained on evaporation of the solvent as colourless gum (0.0072 g). (Found: mol wt 286 0874. $C_{16}H_{15}N_2OCl$ requires 286.0873). M.s. m/z (%): 288 (0.4), 286 (M+, 1), 256 (1), 179 (2), 165 (3), 111 (3), 91 (100), 77 (10), 65 (16), 57 (18), 55 (16), 51 (12). [1]H n.m.r.: δ 2.73 (s, 3H, CH3), 4.58 (s, 2H, OCH2C6H5), 5.77 (s, 2H, N-CH2), 7.07 (d, 1H, J = 7.1, H-5), 7.19 (t, 1H, J_{av} = 7.7, H-6), 7.27-7.35 (m, 5H, C6H5), 7.53 (d, 1H, J = 8.2, H-7).

Alkylation with tert-Butyl Chloroacetate

1-tert.-butyloxycarbonylmethyl-2-chloro-4-methylbenzimidazole (4d, R' = (CH3)3COCOCH2)

Standard alkylation and isolation procedures were followed by using 2-chloro-4-methylbenzimidazole (0.0844 g, 0.5 mmol.), sodium hydride (0.0236 g, 55.0% in oil, 0.54 mmol.) and tert.-butyl chloroacetate (0.0752 g, 0.5 mmol.) in dry dimethylformamide (10 mL). The crude mass (0.1214 g), almost colourless gum, was analysed by t.l.c. and [1]H n.m.r.; both indicated the presence of only one alkylated product plus recovered parent heterocycle. The alkylated product was isolated using radial chromatography (SiO2, ethyl acetate-light petroleum = 8:2). Evaporation of the solution of the alkylated product afforded *1-tert.-butyloxycarbonylmethyl-2-chloro-4-methylbenzimidazole* (0.08203 g) as colourless gum. (Found: mol wt 280.0980. $C_{14}H_{17}N_2O_2Cl$ requires 280.0979). M.s. m/z (%): 282 (1), 281 (1), 280 (M+, 2), 178 (11), 143 (2), 116 (3), 91 (3), 77 (2), 65 (3), 57 (100), 51 (3). [1]H n.m.r.: δ 1.44 [s, 9H, C(CH3)3], 2.63 (s, 3H, 4-CH3), 4.78 (s, 2H, CH2), 7.04-7.11 (m, 2H, H-5, H-6), 7.19 (d, 1H, J = 7.8, H-7).

A duplicate run also gave only *N*1-alkylated product and some recovered parent heterocycle.

Alkylation with Phenacyl Chloride

2-Chloro-4-methyl-1-phenacylbenzimidazole (4d, R' = C6H5COCH2)

Standard alkylation and isolation procedures were followed using 2-chloro-4-methylbenzimidazole (0.0843 g, 0.5 mmol.), sodium hydride (0.0237 g, 55.0% in oil, 0.54 mmol.) and phenacyl chloride (0.0772 g, 0.5 mmol.) in dry dimethylformamide (10 mL). The crude mass (0.1085 g), almost colourless solid, was analysed by t.l.c. and [1]H n.m.r.; both indicated the presence of only one alkylated product and recovered parent heterocycle. The alkylated product was isolated by using radial chromatography (SiO2, ethyl acetate-light petroleum = 8:2). Evaporation of the solution of the alkylated product afforded *1-phenacyl-2-chloro-4-methylbenzimidazole* as colourless crystals (0.0634 g); m.p. 91-92°. (Found: mol wt 284.0716. $C_{16}H_{13}N_2OCl$ requires 284.0716). M.s. m/z (%): 286 (1), 284 (M+, 2), 166 (17), 165 (18), 131 (4), 105 (100), 89 (5), 77 (45), 65 (8), 51 (21). [1]H n.m.r.: δ 2.65 (s, 3H, CH3), 5.58 (s, 2H, CH2), 6.95 (d, 1H, J = 8, H-5), 7.09 (d, 1H, J = 7.2, H-7), 7.17 (t, 1H, J = 7.6, H-6), 7.57 (d of t, 2H, J = 7.6, J = 1.6, C6H5), 7.70 (m, 1H, C6H5), 8.05 (m, 2H, C6H5).

A duplicate run gave only *N*1-alkylated product and recovered parent heterocycle.

Alkylation of 4-Methylbenzimidazolone Dianion (2, R = O⁻)

Alkylation with Benzyl Chloride

Standard alkylation and isolation procedures were followed using 4-methylbenzimidazolone (0.0743 g, 0.5 mmol.), sodium hydride (0.0465 g 55.0% in oil, 1.06 mmol.) and benzyl chloride (0.0634 g, 0.5 mmol.) In dry dimethylformamide (10 mL). The crude mixture (0.1382 g) was analysed by t.l.c. and [1]H n.m.r. spectroscopy; t.l.c. indicated the presence of three products, two isomeric monoalkylated products, a dialkylated product and recovered parent heterocycle. [1]H n.m.r. (CD3OD): δ 2.27 (s, CH3 [from parent

heterocycle]), 2.30 (s, CH_3 [dialkyl]), 2.34 (s, CH_3 [monoalkyl]), 5.04 (s, CH_2 [N^1-monoalkyl]), 5.15 (s, CH_2 [dialkyl]), 5.31 (s, CH_2 [N^3-monoalkyl]), 5.38 (s, CH2 [dialkyl]), 6.8-7.5 (ArH). After isolation of the products they were identified as 1-benzyl-4-methylbenzimidazolone, 3-benzyl-4methylbenzimidazolone and 1,3-dibenzyl-4-methylbenzylbenzimidazolone. The three N-methylene singlets (of N^1-monoalkyl, N^3-monoalkyl and N^1,N^3-dialkyl products in the product mixture at 5.13, 5.38 and 5.24 ppm respectively) were integrated (extending 10 Hz on each side from the centre of the singlets); N^1-monoalkyl : N^3-monoalkyl : N^1,N^3-dialkyl product ratio = 32.7±1.0 : 7.4±1.0 : 59.9±1.0% (duplicate run, 32.9±1.0 : 7.8±1.0 : 59.3±1.0%).

1,3-Dibenzyl-4-methylbenzimidazolone

The above mixture (0.0462 g) of the mono- and the dialkylated products were separated on a silica gel (20x20x0.2 cm) t.l.c. plate using ethyl acetate-light petroleum (1:1) as eluent. The R_f value of the components were in the following order: dialkyl>N^1-monoalkyl>N^3-monoalkyl. The dialkyl product, 1,3-dibenzyl-4-methylbenzimidazolone, was obtained on evaporation of the solvent as colourless crystals (0.0236 g); m.p. 86-87°. (Found: mol wt 328.1576. $C_{22}H_{20}N_2O$ requires 328.1576). M.s. m/z (%): 329 (2), 328 (M+, 10), 237 (8), 209 (1), 147 (0.5), 91 (100), 85 (26), 71 (47), 57 (87). ^1H n.m.r.: δ 2.34 (s, 3H, CH_3), 5.15 (s, 2H, CH_2 [N^1]), 5.38 (s, 2H, CH_2 [N^3]), 6.76-7.35 (ArH). Uv.: λ_{max} 213, 285 nm.

1-Benzyl-4-methylbenzimidazolone

The monoalkylated product, *1-benzyl-4-methylbenzimidazolone*, was obtained from the middle band on evaporation of the solvent as colourless crystals (0.0133 g); m.p. 198-200°. (Found: mol wt 238.1106. $C_{15}H_{14}N_2O$ requires 238.1106). M.s. m/z (%): 239 (1), 238 (M+, 7), 149 (17), 134 (3), 106 (6), 91 (100), 79 (8), 77 (6), 65 (14), 51 (6). ^1H n.m.r.: δ 2.39 (s, 3H, CH_3), 5.09 (s, 2H, CH_2), 6.71-7.34 (ArH), 9.47 (bs, 1H, NH). Uv.: λ_{max} 212, 283 nm.

1-Benzyl-7-methylbenzimidazolone

The monoalkylated product, *1-benzyl-7-methylbenzimidazolone*, was obtained from the low R_f band on evaporation of the solvent as colourless crystals (0.0032 g); m.p.203-205°. (Found: mol wt 238.1106. $C_{15}H_{14}N_2O$ requires 238.1106). M.s. m/z (%):.239 (1), 238 (M+,9), 147 (3), 104 (1), 91 (100), 77 (3), 65 (12), 51 (3). ^1H n.m.r.: δ 2.33 (s, 3H, CH_3), 5.32 (s, 2H, CH_2), 6.75-7.35 (ArH), 8.23 (bs, 1H, NH). Uv.: λ_{max} 210, 284 nm.

Alkylation with Benzyl Chloromethyl Ether

Standard alkylation and isolation procedures were followed using 4-methylbenzimidazole (0.0741 g, 0.5 mmol.), sodium hydride (0.0467 g, 55.0% in oil, 1.07 mmol.) and benzyl chloromethyl ether (0.0781 g, 0.5 mmol.) in dry dimethylformamide (10 mL). Analysis of the crude mixture (0.1322 g) by t.l.c. indicated the presence of three products and recovered parent heterocycle. After isolation of the isomeric products, they were identified as 1-benzyloxymethyl-4-methylbenzimidazolone, 3-benzyloxymethyl-4-methylbenzimidazole and 1,3-dibenzyloxymethyl-4-methylbenzimidazolone. ^1H n.m.r. of the isomeric product mixture: δ 2.42 (s, CH_3 [N^1-monoalkyl]), 2.60 (s, CH3 [N^3-monoalkyl]), 2.61 (s, CH_3 [dialkyl]), 4.55 (s, $OCH_2C_6H_5$ [dialkyl]), 4.58 (s, $OCH_2C_6H_5$ [N^1-monoalkyl]), 4.61 (s, $OCH_2C_6H_5$ [N^3-dialkyl]), 4.65 (s, $OCH_2C_6H_5$ [N^3-monoalkyl]), 5.36 (s, N-CH_2 [N^1-dialkyl]), 5.43 (s, N-CH_2 [N^1-monoalkyl], 5.47(s, N-CH_2 [N3-monoalkyl]), 5.50 (s, N-CH_2 [N^3-dialkyl]), 6.8-7.5 (ArH), 8.52 (bs, NH [N^3-monoalkyl]), 9.51 (bs, NH [N^1-monoalkyl). The three N-methylene singlets (N^1-monoalkyl, N^3-monoalkyl and dialkyl products in the product mixture at 5.43, 5.47 and 5.36 ppm respectively) were integrated (extending 6 Hz on each side from the centre of the singlets); N^1-monoalkyl : N^3-monoalkyl : N^1,N^3-dialkyl product ratio = 19.8±1.0 : 17.3±1.0 : 62.9±1.0% (duplicate run, 20.6±1.0 : 17.01.0 : 62.4±1.0%).

1,3-Dibenzyloxymethyl-4-methylbenzimidazolone

The above mixture (0.0451 g,) of two monoalkyl and one dialkyl product were separated on a silica gel (20x20x0.2 cm) t.l.c. plate using ethyl acetate-light petroleum (1:1) as eluent. The R_f values of the components were in the following order: dialkyl>N^1-monoalkyl>N^3-monoalkyl product. The dialkyl product, *1,3-dibenzyloxymethyl-4-methylbenzimidazolone*, was obtained on evaporation of the solvent as colourless gum (0.0244 g). (Found: mol wt 388.1788. $C_{24}H_{24}N_2O_3$ requires 388.1787). M.s. m/z (%): 389 (0.8), 388 (M+, 3), 328 (3), 237 (5), 174 (13), 161 (1), 131 (2), 105 (4), 91 (100), 77 (6), 64 (12), 51 (5). ^1H n.m.r.: δ 2.65 (s, 3H, CH_3), 4.58 (s, 2H, $OCH_2C_6H_5$ [N^1]), 4.64 (s, 2H, $OCH_2C_6H_5$ [N^3]), 5.40 (s, 2H, N-CH_2 [N^1]), 5.55 (s, 2H, N-CH_2 [N^3]), 6.93-7.38 (ArH).

1-Benzyloxymethyl-4-methylbenzimidazolone

The N^1-monoalkyl product, *1-benzyloxymethyl-4-methylbenzimidazolone*, was obtained from the middle t.l.c. band as colourless crystals (0.0074 g); m.p. 152-153°. (Found: mol wt 268.1212. $C_{16}H_{16}N_2O_2$ requires 268.1212). M.s. m/z (%): 269 (0.4), 268 (M+, 2), 238 (4), 162 (5), 147 (2), 107 (2), 91 (100), 73 (18), 65 (11), 51 (7). ^1H n.m.r.: δ 2.42 (s, 3H, CH_3), 4.62 (s, 2H, $OCH_2C_6H_5$), 5.43 (s, 2H, *N*-CH_2), 6.92-7.34 (ArH), 9.54 (bs, 1H, NH [N^3]).

1-Benzyloxymethyl-7-methylbenzimidazolone

The N^3-monoalkyl product, *3-benzyloxymethyl-4-methylbenzimidazolone*, was obtained from the lowest R_f band as colourless crystals (0.0062 g); m.p. 136-137°. (Found: mol wt 268.1212. C16H16N2O2 requires 268.1212). M.s. m/z (%): 269 (1), 268 (M+, 6), 238 (13), 162 (11), 147 (4), 133 (2), 91 (100), 77 (5), 65 (12), 51 (5). ^1H n.m.r.: δ 2.64 (s, 3H, CH_3), 4.65 (s, 2H, $OCH_2C_6H_5$), 5.54 (s, 2H, *N*-CH_2), 6.87-7.32 (ArH), 8.58 (bs, 1H, NH [N^1]).

Alkylation with tert-*Butyl Chloroacetate*

Standard alkylation and isolation procedures were followed using 4-methylbenzimidazolone (0.0741 g, 0.5 mmol.), sodium hydride (0.0464 g, 55.0% in oil, 1.06 mmol.) and *tert.*-butyl chloroacetate (0.0753 g, 0.5 mmol.) in dry dimethylformamide (10 mL). The crude mixture (0.1283 g) was analysed by both t.l.c. and ^1H n.m.r. spectroscopy; t.l.c. analysis indicated the presence of two products in unequal amounts and recovered parent heterocycle. ^1H n.m.r. analysis indicated two major products, one very small product, possibly the N^3-alkylated product and recovered parent heterocycle. After isolation of the major products they were identified as 1-*tert*-butyloxycarbonylmethyl-4-methylbenzimidazolone and 1,3-di*tert*-butyloxycarbonyl-methyl-4-methylbenzimidazolone. ^1H n.m.r. of the crude mixture: δ 1.44-1.47 [OC(CH_3)3], 2.39 (s, 4-CH_3 [N^1]), 2.44 (s, 4-CH_3 [dialkyl]), 4.52 (s, CH_2 [N^1-monoalkyl and N^1-dialkyl]), 4.75 (s, CH_2 [N^3-dialkyl]), 4.87 (s, CH_2 N^3-monoalkyl]), 6.71-7.02 (ArH). The two 4-methyl singlets (each of monoalkyl and dialkyl products) were integrated (extending 7 Hz on each side from the centre of the singlets); N^1-monoalkyl : N^1,N^3-dialkyl product ratio = 71.2+1.0 : 28.8+1.0% (duplicate run, 70.8+1.0 : 29.2+1.0%).

1,3-Ditert-butyloxycarbonylmethyl-4-methylbenzimidazole

The above mixture (0.0463 g) of monoalkyl and dialkyl products were separated on a silica gel (20x20x0.2 cm) t.l.c. plate using ethyl acetate-light petroleum (7:3) as eluent. The dialkyl product, *1,3-ditert-butyloxycarbonylmethyl-4-methylbenzimidazole* (higher R_f), was obtained on evaporation of the solvent as colourless crystals (0.0118 g); m.p. 138-140°. (Found: mol wt 376.1997. $C_{20}H_{28}N_2O_5$ requires 376.1998). M.s. m/z (%): 377 (1), 376 (M+, 7), 264 (12), 219 (16), 174 (5), 147 (8), 109 (6), 97 (13), 91 (5), 83 (14), 77 (3), 56 (100). ^1H n.m.r.: δ 1.45 [s, 9H, C(CH_3)3], 1.46 [s, 9H, C(CH_3)3], 2.44 (s, 3H, 4-CH_3), 4.52 (s, 2H, CH_2 [N^1]), 4.75 (s, 2H, CH_2 [N^3]), 6.72 (d, 1H, J = 7.7, H-5), 6.82 (d, 1H, J = 7.5, H-7), 6.97 (t, 1H, J = 7.7, H-6).

*1-*tert-*Butyloxycarbonylmethyl-4-methylbenzimidazolone*

The monoalkyl product, *1-*tert-*butyloxycarbonylmethyl-4-methylbenzimidazolone* (lower R_f), was obtained on evaporation of the solvent as colourless crystals (0.0261 g); m.p. 197-98°. (Found: mol wt 262.1318. $C_{14}H_{18}N_2O_3$ requires 262.1317). M.s. m/z (%): 263 (1), 262 (M+, 10), 161 (46), 133 (16), 104 (3), 77 (8), 65 (7), 57 (100), 51 (6). ^1H n.m.r.: δ 1.46 [s, 9H, C(CH_3)3], 2.40 (s, 3H, CH_3), 4.53 (s, 2H, CH_2), 6.73 (d, 1H, J = 7.7, H-5), 6.90 (s, 1H, J = 7.7, H-7), 6.99 (t, 1H, J_{av} = 7.7, H-6).

Attempted Alkylation with Phenacyl Chloride

Standard alkylation and isolation procedures were followed by taking 4-methylbenzimidazolone (0.0743 g, 0.5 mmol.), sodium hydride (0.0469 g, 55.0% in oil, 1.07 mmol.) and phenacyl chloride (0.0774 g, 0.5 mmol.) in dry dimethylformamide (10 mL). Both t.l.c. and ^1H n.m.r. analysis of the isolated material indicated that no apparent alkylation had occurred, 4-methylbenzimidazolone remained unchanged and some alkylating agent had decomposed. The reaction was repeated and allowed to continue for 2 days, but the results were unchanged.

Kinetic Measurements

The benzimidazoles (70 - 80 mg) were reacted with freshly prepared, equimolar amounts of sodium methoxide (sodium in dry methanol, 5 mL) under nitrogen. Methanol was removed by co-distillation with toluene and the white solid dried (0.05 mm, 0.5 hr, room temp.). The sodium salts were then dissolved in dry N,N-dimethylformamide (30 mL) containing a known amount (about 0.2 g) of benzonitrile as an internal standard and the solution thermally equilibrated in a constant temperature water-bath ($30.0\pm0.1°$). Benzyl chloride (3 - 4 equiv. in 5 mL dry dimethylformamide) was also equilibrated in the water-bath for 0.5 hr. The two reactant solutions were then rapidly mixed and homogenized. At known intervals over a one hour period, 1.0 mL aliquots of the reaction mixture were withdrawn and quenched with glacial acetic acid (1 mL). These aliquots were analysed by h.p.l.c. using a 12.5×0.45 cm spherisorb S5 ODS2 column using gradient elution with mixtures of (A) 80:20 water / acetonitrile and (B) 60:40 water / acetonitrile containing 0.5% triethylamine and pH adjusted to 5.0 with phosphoric acid. The (residual) benzimidazole concentration in these aliquots was determined by reference to the internal standard peak. Standard benzimidazole / benzonitrile solutions were injected for calibration purposes at the beginning, in the middle, and at the end of each series of h.p.l.c. measurements. The rate constants, k_2, were calculated from a least squares regression analysis using the second order rate law equation. Straight line plots with correlation coefficients of $R^2 = 0.997$ to 1.000 were obtained over periods of up to an hour (5 hr for the sluggish 2-chloro system, **2d**). For the 4-methylbenzimidazolone (**1f**) dianion alkylations, curvature was observed in the second order rate plots and the 'initial rate' constant was determined from the first 3 points (up to 6 min, R^2 1.000).

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