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Ambident Heterocyclic Reactivity: Intramolecular Alkylations of 2,4-Disubstituted Benzimidazoles

M. Rezaul Haque and Malcolm Rasmussen*

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

Abstract: Alkali induced intramolecular cyclizations of 2-(3-chloropropyl)- and 2-(4-chlorobutyl)-4-substituted benzimidazoles bearing 4-nitro-, 4-amino-, and 4-methyl groups show enhanced N3/N1 regioselectivity compared to the corresponding intermolecular alkylations with 1-chlorobutane. The observed N1:N3 cyclization ratios vary from 94:6 to 10:90, with the largest preference for reaction at the 'congested' N3-site occurring in the 5-membered ring formation. In contrast, related base induced reactions of (2-benzimidazolyl)methyl chloroacetate and 3-(2-benzimidazolyl)propyl chloroacetate give excellent yields of macrocyclic dimeric systems. These results are interpreted as involving interplay between electrostatic field, through-bond electronic, and steric approach control factors within variable geometry S_N2 transition state structures. Calculations (AM1 and molecular mechanics) on these systems and conformational analysis of the expected transition states for the intramolecular cyclizations do not support any appreciable use of out-of-plane approach trajectories for these heterocyclic *N*-alkylation reactions. © 1997 Elsevier Science Ltd.

Previous studies on the regioselective alkylation of substituted benzimidazoles have shown such systems to be sensitive models for the investigation of interacting steric, electronic and thermodynamic effects in ambident N-alkylation reactions.[1-3] Monosubstitution at the relatively remote 5(6)-position of benzimidazole induces only slight regioselectivity, varying from 55:45 to 46:54, between the competitive N1 and N3-sites by through-bond electronic effects.[1] In the alkylation of 4(7)-monosubstituted benzimidazole systems, however, far more divergent results were obtained, with N1/N3 regioselectivity varying between 100:0 and 21:79.[1,4] 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 were found to be 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.[1-3,5] Such variable S_N2 transition state geometries are conveniently described by More O'Ferrall - Jencks diagrams[6] which allow the effects of structural variations to be described in terms of movement along orthogonal early-late and loose-tight axes.[7]

Subsequent studies of the alkylation of 2,4-disubstituted benzimidazole anions[2,3] in our laboratories have confirmed most of the concepts above, as well as giving some insight into the question of allowed "approach corridors"[2,3] or "reaction windows"[8-10] for alkylation at nitrogen lone pairs; see Fig. 1. In particular, we observed an increase in the differential selectivity patterns, $\delta s = (\Delta\Delta G^{\ddagger}_{2,4\text{-}Me_2} - \Delta\Delta G^{\ddagger}_{4\text{-}Me})$ [11] for alkylations of the 2,4-dimethyl- *vs* 4-methyl-benzimidazole anions as the S_N2 transition states become progressively tighter.[2]

This was interpreted as support for roughly conical approach channels or corridors[2,3] (see Fig. 1), as indicated by 3D molecular electrostatic potential maps[12] and by other molecular orbital calculations[9,10,13]. The constriction imposed by the symmetrically placed 2-methyl group has a greater impact on the narrower N3-approach corridor (rough $4\pi r^2$ cross sectional area dependence) than on the broader N1-corridor as indicated in Fig. 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 was manifest in the increasing ($\Delta\Delta G^{\ddagger}_{2,4\text{-}Me_2}$ - $\Delta\Delta G^{\ddagger}_{4\text{-}Me}$) parameters as the transition states tightened.[2] These graduated regioselectivities thus provide a clear and convincing demonstration of 'steric approach control' in the alkylation of nitrogen heterocycles bearing α-substituents.

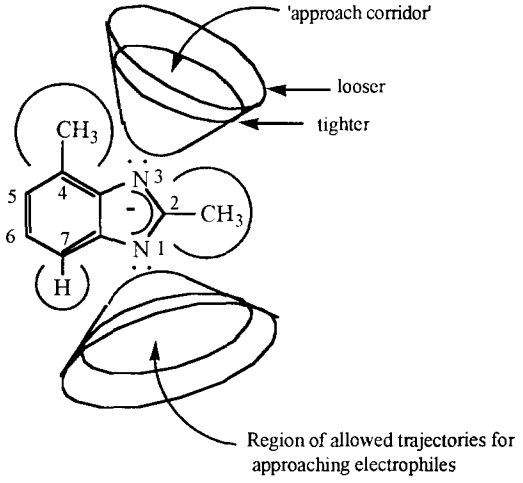
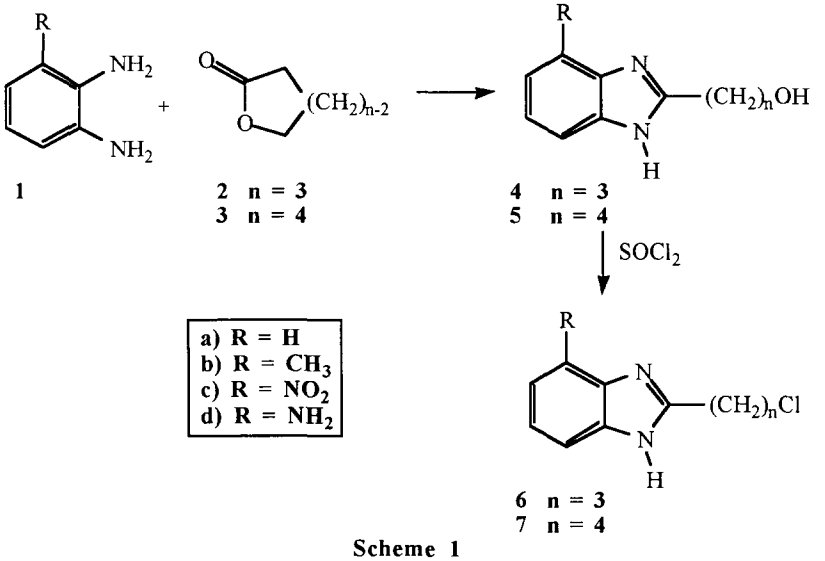


Figure 1

To gain further information on the question of possible reaction trajectories involving non-colinear and particularly out-of-plane approach[8,13,14], at least in the earlier stages of these alkylations, we decided to investigate intramolecular alkylations (cyclizations) in 4-substituted-2-haloalkyl-benzimidazole systems. Here the conformational preferences of cyclizations forming different sized rings, particularly five and six membered, should influence the possible approach trajectories. Precedence for this concept can be found in the intramolecular alkylation of enolates, where cyclization to five membered rings gives the thermodynamically less favoured enol ethers (O-alkylation, involving constrained, in-plane approach) whereas six membered ring formation gives the thermodynamically preferred cyclic ketone (C-alkylation, from accessible out-of-plane approach on the π system) in keeping with Baldwin's rules.[15-17] It was also hoped that further information may be gathered from the regioselectivities of cyclizations involving modified ω-chloroalkyl groups, such as the reactive α-chloroether[18], $-(CH_2)_n$-O-CH_2Cl, and α-chloroketone[19], $-(CH_2)_n$-CO-CH_2Cl, groups where the special geometric requirements for conjugation and the altered N --- C bond lengths in the S_N2 transition states[18,19] should produce further restrictions on available approach trajectories during the intramolecular alkylations.

Preparation of 2-Chloroalkylbenzimidazole Systems

2-(3-Hydroxypropyl)- and 2-(4-hydroxybutyl)-4(7)-substituted-benzimidazoles (**4b,c** and **5b,c**) were prepared from the appropriately substituted 1,2-benzenediamines (**1**), using established literature procedures[20], as indicated in Scheme 1. Reaction of these primary alcohols (**4b,c** and **5b,c**) with thionyl chloride gave the corresponding 2-chloroalkylbenzimidazoles (**6b,c** and **7b,c**), isolated as their stable hydrochloride salts.[21] The free bases **6b,c** were isolated after passing the hydrochlorides through short columns of silica gel eluted with ethyl acetate. Reduction of the 4(7)-nitro compounds (**6c, 7c**) gave the corresponding 2-chloroalkyl-4(7)-aminobenzimidazoles (**6d, 7d**), again isolated as their more stable (di)hydrochloride salts.



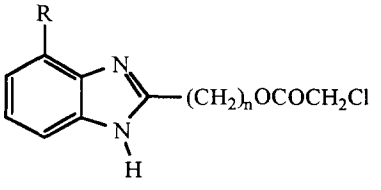
1 **2** **n = 3** **3** **n = 4** **4** **n = 3** **5** **n = 4**

a) R = H
b) R = CH_3
c) R = NO_2
d) R = NH_2

6 **n = 3** **7** **n = 4**

Scheme 1

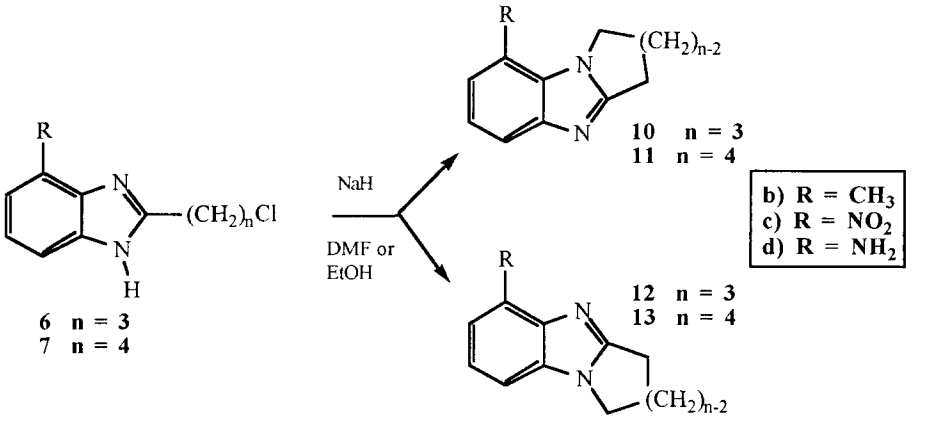
All our attempts to prepare 2-substituted benzimidazole systems with ω-chloromethyl ketone, $(CH_2)_nCOCH_2Cl$, and ω-chloromethyl ether, $-(CH_2)_nOCH_2Cl$, side chains failed. However, reaction of (2-benzimidazolyl)methanol[22], prepared from 1,2-benzenediamine (**1a**) and glycolic acid, with chloroacetyl chloride readily gave (2-benzimidazolyl)methyl chloroacetate, **8a**, isolated as its stable hydrochloride salt. Similar reaction of the methyl-diamine **1b** gave (4-methyl-2-benzimidazolyl)methanol; chloroacetylation of this and the homologue **4a** yielded respectively (4-methyl-2-benzimidazolyl)methyl chloroacetate, **8b**, and 3-(2-benzimidazolyl)propyl chloroacetate, **9a**, again both isolated as their hydrochloride salts.



8 **n = 1** **a) R = H**
9 **n = 3** **b) R = CH_3**

ALKYLATION RESULTS AND DISCUSSION

Addition of sodium hydride, two equivalents for mono-hydrochloride salts, **6/7b,c**, and three equivalents for dihydrochloride salts, **6/7d**, to the solutions of these hydrochloride salts in dimethylformamide or ethanol produced anions which spontaneously cyclized to form the corresponding isomeric tricyclic fused ring benzimidazole compounds[21,23,24], 5- and 8-substituted 2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazoles (6-5-5) and 6- and 9-substituted 1,2,3,4-tetrahydropyrido[1,2-a]benzimidazoles (6-5-6), see Scheme 2. The ratios of the isomeric products were determined by proton n.m.r. spectroscopy on the crude mixtures, with the assignment of the isomeric structures following the procedures outlined in earlier papers.[1-3] In most cases, the individual isomers were subsequently isolated by preparative t.l.c. and their structural assignments confirmed by spectral comparison with known compounds.[21,23,24]



Scheme 2

The observed regioselectivity of the intramolecular alkylations of the anions from **6b-d** (n = 3) is given in Table 1. These N1/N3 ratios were found to be equivalent (within experimental errors) in both ethanol and dimethylformamide. The intramolecular cyclization reactions of the anions from **7b-d** (n = 4), were consequently performed only in ethanol, giving regioselectivities as listed in Table 1. For comparison, the related N1/N3-*inter*molecular alkylation ratios of the corresponding 4-nitro-, 4-methyl- and 4-amino-benzimidazole anions with 1-chlorobutane (in dimethylformamide at 30°)[2,3] are also given in Table 1.

Contrary to the distinct preference of *inter*molecular butylation at the less hindered N1-sites of all three model 4-monosubstituted-benzimidazole anions[2,3], *intra*molecular cyclizations in the 4-methyl and 4-nitro systems, **6b,c** and **7b,c**, showed preferred reaction at the *more hindered* N3-site (see Table 1)! The enhanced reaction at the sterically hindered N3-sites was more pronounced in the formation of the smaller 5-membered rings (**6b-d** → **10** + **12**) than in the cyclizations to the 6-membered ring systems (**7b-d** → **11** + **13**). We have argued previously[2,3] that the (intermolecular) butylation of 4-monosubstituted benzimidazole anions is under dominant steric approach control, with smaller modulations of the N1/N3 ratios induced by the electrostatic field and electronic effects of the 4-substituent, see Table 1. Related alkylations of 2-methyl-4-substituted benzimidazole anions show an enhanced dominance of steric effects, giving significantly higher N1/N3 ratios; butylation of 2,4-dimethylbenzimidazole anions gave a 98 : 2 N1/N3-ratio, corresponding to a

regioselectivity of $\Delta\Delta G^{\ddagger}$ -10 kJ/mol.[2] Thus the preferential cyclization of **6b,c** and **7b,c** to the more crowded N3-sites of these 2,4-disubstituted systems was completely unexpected.

Table 1 Intramolecular Cyclization of 2-(3-Chloropropyl)- (**6b-d**) and 2-(4-Chlorobutyl)- (**7b-d**) 4-substituted Benzimidazoles (NaH, ethanol, 30°)

Substrate:	**6 (n = 3)** [A]			**7 (n = 4)**			**4-R-BI** [B]		
Cyclization reactions: [C]	N1-%	N3-%	$\Delta\Delta G^{\ddagger}$	N1-%	N3-%	$\Delta\Delta G^{\ddagger}$	N1-%	N3-%	$\Delta\Delta G^{\ddagger}$
Products:	**12**	**10**	kJ/mol	**13**	**11**	kJ/mol	**14**	**15**	kJ/mol
c) R = NO_2	10.3	89.7	5.46	47.9	52.1	0.21	76.4	23.6	-3.0
b) R = CH_3	34.3	65.7	1.64	49.3	50.7	0.07	83.0	17.0	-4.0
d) R = NH_2	56.4	43.6	-0.65	71.7	28.3	-2.34	93.7	6.3	-6.8

[A] The corresponding values found for cyclization in dimethylformamide solution are: **6c**) NO_2: 10.6%, 89.4%, 5.37; **6b**) CH_3: 36.5%, 63.5%, 1.40; **6d**) NH_2: 56.9%, 43.1%, -0.70 kJ/mol.

[B] Intermolecular alkylation of 4-monosubstituted benzimidazole anions {4-R-BI$^-$, c) R = NO_2; b) R = CH_3; d) R = NH_2} with 1-chlorobutane in dimethylformamide at 30°; results from ref. 2,3.

[C] N1 and N3 values are % of total product as determined by ^1H n.m.r. spectroscopy; estimated uncertainty ± 1%, reproducability better than ± 0.5%. $\Delta\Delta G^{\ddagger}$ = -RT ln(N1% / N3%) kJ/mol.

Some insight into the factors controlling this enhanced reactivity of the N3-sites was obtained from molecular mechanics and semi-empirical molecular orbital calculations on the isomeric pairs of cyclized 4-methyl systems, **10/12b** and **11/13b**, and on model 1,4- and 1,7-dimethylbenzimidazole systems. Using fully optimized geometries, both molecular mechanics (CHARMm, Quanta Version 3.2)[25] and semi-empirical molecular orbital (AM1)[26] calculations indicate all the 1,4-alkylated isomers to be more stable than their corresponding 1,7-alkylated isomers, due to unfavourable peri interactions in the latter 1,7-dialkylated systems. The isomeric energy gap is calculated to be largest for the dimethyl pair, slightly smaller for the six membered cyclic pair, **11b** and **13b**, and significantly smaller for the five membered cyclic isomers, **10b** and **12b**; see Table 2. Earlier equilibration studies on the $N^1 \leftrightarrows N^3$-benzyl-4-methylbenzimidazole system under acidic conditions in dimethylformamide at 125° indicated a 99:1, ΔG° = 15.2 kJ/mol, preference for the sterically less hindered 1,4-disubstituted system.[1]

Careful inspection of the calculated, optimized geometry of 1,7-dimethylbenzimidazole indicated significant non-bonded steric repulsion between the 7-methyl and N1-methyl groups, with calculated H_3C --- CH_3 distances, see Fig. 2, of 3.178 Å (CHARMm) and 3.167 Å (AM1) for 1,7-dimethylbenzimidazole. The corresponding 7-CH_3 --- *N*1-CH_2 distance in the six membered ring compound **11b** was calculated to be slightly longer at 3.186 Å (CHARMm) and 3.194 Å (AM1). For the five membered cyclic compound **10b**, the corresponding calculated C---C distance was significantly longer, 3.299 Å and 3.432 Å (CHARMm, AM1). Comparison of the geometries in the isomeric pairs, see Table 2 and Fig. 2, also indicated significant angle distortions about the N1- and 7-methyl groups in 1,7-dimethylbenzimidazole, similar but slightly less distortion for **11b**, and little detectable angle distortion for **10b**, when compared to their corresponding 1,4-isomers. These calculations indicate that the unfavourable 1,7-non-bonded interactions are progressively reduced, but not completely eliminated, by 'tying back' the N-alkyl group with the fused ring (increasing γ angle, see structures

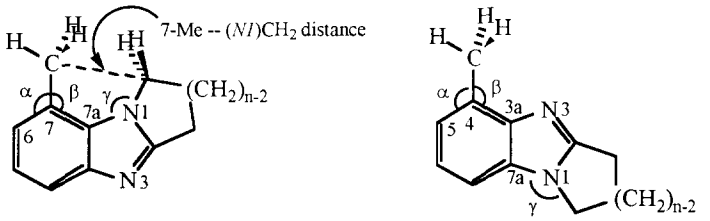
Table 2. Calculated Optimized Geometries[a] and Energies[a,b] of Isomeric 1,4- and 1,7-disubstituted Benzimidazole systems.

	1,4-Me_2BI	1,7-Me_2BI	**13b**	**11b**	**12b**	**10b**
7-Me---(*N1*-)$CH_{2/3}$						
C --- C distances[a] Å		3.167		3.194		3.432
H --- H distances[a] Å		2.329/2.364		2.311/2.413		2.664/2.675
α, (4/7)Me-C4/7-C5/6 angle[a]	121.9°	121.0°	121.9°	121.1°	121.8°	122.0°
β, (4/7)Me-C4/7-C3a/7a angle[a]	120.5°	122.2°	120.5°	122.1°	120.4°	121.2°
γ, C7a-N1-$CH_{2/3}$ angle[a]	126.8°	127.9°	128.4°	128.8°	140.3°	140.4°
AM1 (ΔH_f)[a]	267.68	270.05	205.43	207.43	274.73	275.90
$\Delta\Delta E^b$ kJ/mol	-2.4		-2.0		-1.2	
CHARMm[c] strain energies	21.06	25.77	29.05	31.70	37.23	38.85
$\Delta\Delta E^b$ kJ/mol	-4.7		-2.7		-1.6	

[a] Semi empirical AM1 molecular orbital calculations; enthalpies of formation, ΔH_f, in kJ/mol.

[b] $\Delta\Delta E = \Delta E_{1,4} - \Delta E_{1,7}$

[c] QUANTA Version 3.2, Polygen Corporation; total strain energies in kJ/mol.



10b n = 3
11b n = 4

12b n = 3
13b n = 4

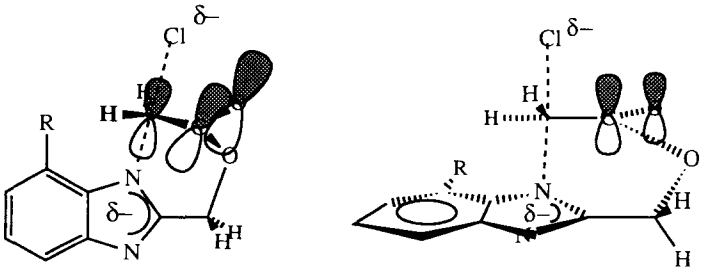
Figure 2.

10/11b and **12/13b**). The six-membered rings of **11b** and **13b** are calculated (AM1) to adopt standard half-chair conformations (cf. cyclohexene) with one of the N1-CH_2 hydrogens inserted between the facing CH_2 hydrogens of the peri 7-methyl group in **11b** ('gear' or 'cogwheel' effect[27]). The five membered rings are calculated (AM1) to prefer a fully eclipsed, planar conformation, with two roughly equidistant H --- H interactions between the N1-CH_2 group and the peri 7-methyl hydrogens as shown in structure **10b**, Fig. 2. The 1,7-dimethyl interaction geometry surprisingly is calculated (AM1) to prefer eclipsed 7-CH_2 --- (N1)-CH_2 groups similar to the cyclopentyl system **10b**, rather than adopt the 1,7-cogwheel conformation seen in **11b**. Related calculations, including some on cycloalkeno-fused pyridine systems, have been successfully used by J.I.Seeman for deriving quantitative measures of steric effects in intermolecular heterocyclic alkylations.[28]

Extrapolation of the trends, calculated for the ground state geometries of these 1,7-disubstituted systems, to the much 'looser' geometries of the S_N2 transition states, should see the 1,7-interactions diminish further. The 7-methyl : N1-alkyl **H** ---- **H** interaction distances in these transition states, assuming an expected **N** ---- CH_2 distance of 1.82 Å (25% extension)[29], are estimated to be about 0.25 Å longer than in the final cyclized products (see Table 2). Studies of kinetic isotope effects and Brønsted analyses, have also indicated that such Menschutkin-like reactions have early transition states with about 20-30% N --- C bond formation[30], although activation parameters for similar reversible N-alkylation reactions suggest[31] that some 60-70% of the non-bonded steric interaction in such N-alkylations is already incurred at the transition states for reactions at pyridine-like sites. At these extended distances in the transition states, the 1,7-non-bonded steric interactions may actually be attractive (Lennard-Jones, Van der Waals) and this seems a possible explanation for the preferential cyclization to the 'more hindered' N3-site of the 4-methyl-2-chloroalkylbenzimidazole anions.

The regioselectivity of the 4-nitro- and 4-amino-2-chloroalkyl cyclizations follow a similar pattern, but with the enhanced N3-alkylation being moderated by the electronic effects of the 4-substituent.[1] The reduced N1/N3- butylation ratio for 4-nitrobenzimidazole anions, compared to the 4-methyl system (see Table 1), has been attributed to a favourable electrostatic field effect of the 4-nitro group enhancing electrophilic attack at the adjacent N3-site, despite the increased steric bulk of the nitro group ($NO_2 > CH_3$).[1] This strong electrostatic field effect is most dramatically evident in the 5-membered cyclization (**6c** → **10c** + **12c**), where steric interactions are minimised by the tight cyclopentyl ring formation and the N1/N3 alkylation ratio is now 10.3 : 89.7, indicating a strong 5.46 kJ preference for cyclization to the 'congested' N3-site adjacent to the 4-nitro group.

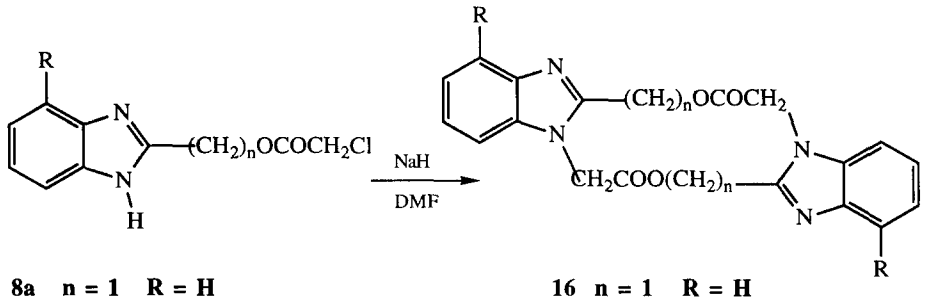
From studies of intermolecular alkylations, the electrostatic field and through-bond electronic effects of the amino group in 4-aminobenzimidazole anions are considered to reinforce steric effects and favour reaction at the 'open' N1-site.[1] The results of the intramolecular cyclizations in Table 1 imply that the steric effect is dominant in this 4-aminobenzimidazole system, since in the five membered cyclization of **6d**, where the attacking alkyl halide group is severely restrained (enforced in-plane approach), only a *slight* preference for reaction at the N1-site is observed. This indicates that the combined electronic and electrostatic effects of the 4-amino group are small, only slightly retarding attack at the N3-site. For the more 'normal' approach geometries involved in cyclohexyl formation (**7d** → **11d** + **13d**) and in the intermolecular alkylations of 4-aminobenzimidazole anions, the increasing amounts of N1-alkylation may thus be directly attributed to enhanced steric effects associated with normal 'unrestrained' approach trajectories.



a) In-plane approach geometry b) Perpendicular approach geometry

Figure 3

The enhanced reactivity of α-chloromethyl ketones and esters towards nucleophilic displacements derives from the conjugate interaction of the carbonyl π-bond with the N---C_α---X axis of the S_N2 transition states; this requires the carbonyl C--O σ axis to remain perpendicular to the N---C_α---X axis during the reaction.[19] Inspection of Dreiding models of the expected S_N2 transition state for cyclization of **8a** (assuming a linear N---C_α---X geometry) indicated that conformational constrictions cause the carbonyl C--O axis to be about 30° off perpendicular to the N---C_α---X axis, see Fig. 3a. Further, the constraints of ring formation cause twisting within the ester function, reducing its conjugative stability, and also cause the carbonyl π-system to overlap partially and unfavourably with one face of the heterocyclic π-system. These geometric constraints would be further exacerbated by the relatively short N---CH_2 distances in the tight S_N2 transition states involved in displacements adjacent to carbonyls[19]. All these difficulties are reduced, however, if a perpendicular approach geometry, involving *initial* attack through the π-system to the nitrogen , is assumed, see Fig. 3b. Such an out-of-plane initial approach geometry can thus be expected to be preferred for six-membered ring formation reaction on conformational grounds, but would be inaccessible within the chain length restrictions of five-membered ring formation.



8a n = 1 R = H
9a n = 3 R = H

16 n = 1 R = H
17 n = 3 R = H

Instead of the expected entropically favoured *intra*molecular cyclization to the six-membered ring of a 6-5-6 tricyclic system, base treatment of **8a** gave, however, the symmetric dimeric pentacyclic compound, **16** in excellent yield. Similarly, base induced alkylation of **9a** gave the dimeric **17** also in excellent yield. These results indicate that preliminary *inter*molecular alkylations, with subsequent macro-cyclization of the dimers, forming 12- and 16-membered rings respectively, were favoured. These dimerization processes and subsequent large ring cyclizations are expected to be entropically less favourable than initial intramolecular cyclizations forming 6- and 8-membered rings.[32] Earlier studies of the related alkylation of benzimidazolone anions with α,ω-dibromoalkanes, Br-$(CH_2)_n$-Br, revealed tricyclic monomer formation for n = 3,4 (O,N-alkylation; 6 and 7-membered rings) and n = 10,12 (N,N'-alkylation; 13 and 15-membered rings), with the intermediate cases, n = 5 - 8, giving pentacyclic dimers (16 to 22-membered ring formation) in preference to entropically disfavoured formation of monomeric 8 to 11 membered rings.[33] Attempted cyclization of the 4-methyl analogue, **8b** R=CH_3, under comparable basic conditions (NaH in dimethylformamide) yielded only decomposition products. Clearly the extra geometric constraints of reaction at the ω-chloromethyl ester groups cause very significant retardation of *intra*molecular cyclization, enough to allow the normally less efficient *inter*molecular alkylation

process to become competitive. For the macrocyclic ring formation, there is sufficient conformational flexibility to achieve the 'normal' (acyclic) geometry[19] in the transition states of these α-carbonyl methylation reactions.

As out-of-plane approach geometries are expected to minimise the conjugation problems in the intramolecular cyclizations of these α-chloroester systems (**8a,b**, see above), the implied retarded rate of such 6 and 8-membered cyclizations indicates insignificant use of out-of-plane approach trajectories in these heterocyclic *N*-alkylations. Thus the regioselectivity associated with six-membered ring formation for the ω-chloroalkyl cyclizations (**7b-d** → **9/11b-d**), which is intermediate between that shown in the intermolecular butylation and the intramolecular 5-membered cyclizations (**6b-d** → **8/10b-d**), see Table 1, may most simply be attributed to the intermediate geometries involved with diminished angle strain, but retained in-plane approach of the CH_2 - **Cl** axis to the heterocyclic nitrogen centre.

CONCLUSIONS

Intramolecular *N*-alkylations of 4-substituted-2-haloalkylbenzimidazoles under basic conditions proceed smoothly to form tricyclic 6-5-5 and 6-5-6 heterocyclic systems (**9/11** and **10/12**) with enhanced N3/N1 regioselectivity compared to the corresponding intermolecular butylation reactions. The constrained approach geometries involved in cyclizations to both N1 and N3 sites reduce the steric effect of the 4-substituent, particularly for five-membered ring formation, allowing the electrostatic field and electronic effect of the substituent to dominate the regioselectivity. Thus cyclizations of 2-(3-chloropropyl)- and 2-(4-chlorobutyl)-4-*nitro*benzimidazole give dominant alkylation at the more 'crowded' N3-site. The corresponding 4-*methyl*benzimidazole systems give similar but lower preference for N3-cyclization, whereas the 4-*amino* systems show a definite preference for cyclization to the less hindered N1-site. In all cases, the reactivity at the congested N3-site is larger in 5-membered ring formation than in 6-membered rings, with the corresponding intermolecular alkylation being dominated by the steric effect and giving large N1-selectivity for alkylations of all three 4-substituted benzimidazole systems (4R = NO_2 , CH_3, and NH_2).

The additional conformational constraints involved in cyclizations with chloromethyl ester groups in the 2-alkyl chain, retard intramolecular alkylations sufficiently to allow intermolecular dimerizations to become competitive. Conformational analyses of the possible approach geometries to the transition states for such chloromethyl ester cyclizations do not support the concept of allowed non-planar approach with initial interaction with the heterocyclic π-system at the nitrogen alkylation site. The observed reactivities and regio-selectivities are most simply interpreted as involving essentially in-plane, although not necessarily co-linear, approach trajectories.

EXPERIMENTAL

Syntheses:

*3-(4-Methyl-2-benzimidazolyl)-1-propanol (**4b**)*

A mixture of 2,3-diaminotoluene (1.22 g, 0.01 mole), γ-butyrolactone (1.3 g, 0.015 mole) and 4M hydrochloric acid (5 mL) was refluxed for one hour. After cooling, the solution was made alkaline with saturated sodium carbonate solution and the product extracted with chloroform (4 × 30 mL). After evaporation of the dried solution (rotary evaporator), the residue was recrystallised from ethanol-water as colourless crystals

(1.66 g, 87%); m.p. 164-165°. (Found: C, 69.19; H, 7.73; N, 14.68%. $C_{11}H_{14}N_2O$ requires C, 69.45; H, 7.42; N, 14.72%). Mass spectrum: m/z 191 (3), 190 (M^+, 10), 189 (2), 173 (3), 159 (25), 146 (100), 145 (15), 131 (6), 116 (1), 104 (4), 91 (3), 77 (8), 65 (3), 51 (7%). ^1H n.m.r. (d^6-DMSO): δ 1.96 (p, 2H, J_{av} = 7.2, $CH_2\mathbf{CH_2}CH_2OH$), 2.51 (s, 3H, CH_3), 2.88 (t, 2H, J = 7.4, $\mathbf{CH_2}CH_2CH_2OH$), 3.52 (t, 2H, J = 6.3, $CH_2CH_2\mathbf{CH_2}OH$), 4.72 (bs, 1H, $CH_2O\mathbf{H}$), 6.91 (d, 1H, J = 7.1, H-5), 7.01 (t, 1H, J_{av} = 7.6, H-6), 7.28 (d, 1H, J = 6.3), 12.15 (bs, 1H, NH).

*3-(4-Nitro-2-benzimidazolyl)-1-propanol (**4c**)*

A mixture of 3-nitro-1,2-benzenediamine (1.53 g, 0.01 mole), γ-butyrolactone (1.3 g, 0.015 mole) and 20% hydrochloric acid (5 mL) was refluxed overnight under nitrogen. After cooling, the solution was made alkaline with saturated sodium carbonate solution and the product extracted with ethyl acetate (4×30 mL). The residue (1.89 g), obtained on evaporation of the dried solution, was purified by radial chromatography (SiO_2, ethyl acetate). On evaporation of the solvent the product was obtained as pale yellow crystals (1.59 g, 72%); m.p. 136-137°. (Found: C, 54.02; H, 5.10; N, 18.83%. $C_{10}H_{11}N_3O_3$ requires C, 54.30; H, 5.01; N, 19.00%). Mass spectrum: m/z 222 (0.9), 221 (M^+, 1), 191 (20), 177 (100), 160 (6), 144 (12), 131 (20), 116 (3), 104 (5), 90 (7), 77 (3), 63 (10), 52 (4%). ^1H n.m.r. (d^6-DMSO): δ 1.97 (p, 2H, J_{av} = 7, $CH_2\mathbf{CH_2}CH_2OH$), 3.02 (t, 2H, J = 7.5, $\mathbf{CH_2}CH_2CH_2OH$), 3.52 (t, 2H, J = 6.3, $\mathbf{CH_2}OH$), 7.41 (t, 1H, J = 8.1, H-6), 8.05 (dd, 1H, J = 7.6, J = 1.1, H-5), 8.11 (d, 1H, J = 8.2, H-7).

*4-(4-Methyl-2-benzimidazolyl)-1-butanol (**5b**)*

A mixture of 2,3-diaminotoluene (0.1223 g, 1 mmol.), δ-valerolactone (0.1505 g, 1.5 mmol.) and 4M hydrochloric acid (5 mL) was refluxed for one hour. After cooling, the solution was made alkaline with saturated sodium carbonate solution and the product extracted with chloroform (4×30 mL). Then the solvent was removed from the dried solution and the residue on recrystallization from ethanol-light petroleum gave colourless crystals (0.1912 g, 95%); m.p. 140-141°. (Found: C, 70.51; H, 7.89; N, 13.65%. $C_{12}H_{16}N_2O$ requires C, 70.56; H, 7.89; N, 13.71%). Mass spectrum: m/z 205 (3), 204 (M^+, 20), 187 (3), 173 (9), 160 (53), 159 (100), 146 (92), 131 (8), 118 (4), 104 (9), 91 (10), 85 (3), 77 (23), 65 (8), 51 (10%). ^1H n.m.r. (CD_3OD): δ 1.59 (p, 2H, J_{av} = 8.2, $CH_2\mathbf{CH_2}CH_2CH_2OH$), 1.90 (p, 2H, J_{av} = 8, $CH_2CH_2\mathbf{CH_2}CH_2OH$), 2.52 (s, 3H, CH_3), 2.91 (t, 2H, J = 7.5, $\mathbf{CH_2}CH_2CH2CH_2OH$), 3.59 (t, 2H, J = 6.4, $\mathbf{CH_2}OH$), 6.96 (d, 1H, J = 7.8, H-5), 7.06 (t, 1H, J = 7.8, H-6), 7.30 (d, 1H, J = 7.8, H-7).

*4-(4-Nitro-2-benzimidazolyl)-1-butanol (**5c**)*

A mixture of 3-nitro-1,2-benzenediamine (1.53 g, 0.01 mole), δ-valerolactone (1.51 g, 0.015 mole) and 4M hydrochloric acid (10 mL) was refluxed overnight under nitrogen. After cooling, the solution was made alkaline with saturated sodium carbonate solution and the product extracted with ethyl acetate (4×30 mL). The residue (1.94 g), obtained on evaporation of the dried solution, was purified by radial chromatography (SiO_2, ethyl acetate). On evaporation of the solvent the product was obtained as pale yellow crystals (1.76 g, 75%); m.p. 135-136°. (Found: C, 55.70; H, 5.78; N, 17.72%. $C_{11}H_{13}N_3O_3$ requires C, 56.16; H, 5.57; N, 17.86%). Mass spectrum: m/z 236 (2), 235 (M^+, 6), 218 (8), 204 (6), 190 (100), 177 (87), 161 (16), 144 (31), 130 (45), 103 (16), 90 (25), 76 (16), 63 (44), 51 (22%). ^1H n.m.r. (d^6-DMSO): δ 1.49 (p, 2H, J_{av} = 7, $CH_2\mathbf{CH_2}CH_2CH_2OH$), 1.82 (p, 2H, J_{av} = 7.5, $CH_2CH_2\mathbf{CH_2}CH_2OH$), 2.94 (t, 2H, J = 7.5,

$\mathbf{CH_2}CH_2CH_2CH_2OH$), 3.43 (t, 2H, J = 6.5, $\mathbf{CH_2}OH$), 7.35 (t, 1H, J = 8.1, H-6), 8.02 (d, 1H, J = 7.8, H-5), 8.07 (d, 1H, J = 8.2, H-7).

*2-(3-Chloropropyl)-4-methylbenzimidazole Hydrochloride (**6b**.HCl)*

To 3-(4-methyl-2-benzimidazolyl)-1-propanol (0.19 g, 1 mmol.) was added thionyl chloride (1 mL) and the mixture heated at 80° for one hour. Excess thionyl chloride was then removed by evaporation and four successive co-distillations with toluene on a rotary evaporator. The product was recrystallised from ethanol-toluene as colourless crystals (0.23 g, 94%); m.p. 210-211°. (Found: C, 53.48; H, 5.86; N, 11.25; Cl, 29.27%. $C_{11}H_{14}N_2Cl_2$ requires C, 53.89; H, 5.76; N, 11.43; Cl, 28.92%). Mass spectrum: m/z 210 (2), 211 (1), 208 (M^+, 8), 172 (12), 146 (100), 131 (5), 118 (2), 104 (4), 77 (9), 65 (4), 51 (9%). ^1H n.m.r. (d^6-DMSO): δ 2.41 (p, 2H, J_{av} = 7.4, $CH_2\mathbf{CH_2}CH_2Cl$), 2,61 (s, 3H, CH_3), 3.31 (t, 2H, J = 7.4, $\mathbf{CH_2}CH_2CH_2Cl$), 3.79 (t, 2H, J = 6.3, CH_2Cl), 7.32 (d, 1H, J = 7.3, H-5), 7.41 (t, 1H, J = 7.7, H-6), 7.58 (d, 1H, J = 7.7, H-7).

*2-(3-Chloropropyl)-4-methylbenzimidazole (**6b**)*

2-(3-Chloropropyl)-4-methylbenzimidazole hydrochloride (0.0264 g) in ethanol was passed through ~1 cm thickness of silica gel with ethyl acetate as eluent; evaporation of the eluent gave the free base as colourless crystals (0.0204, 91%); m.p. 97-98°. (Found: C, 63.12; H, 6.45; N, 13.13; Cl, 16.89%. $C_{11}H_{13}N_2Cl$ requires C, 63.31; H, 6.28; N, 13.42; Cl, 16.99%). Mass spectrum: m/z 210 (2), 209 (1), 208 M^+, 6), 172 (94), 146 (100), 131 (5), 116 (6), 104 (8), 91 (8), 77 (21), 65 (11), 51 (20%). ^1H n.m.r. ($CDCl_3$): δ 2.33 (p, 2H, J_{av} = 6.8, $CH_2\mathbf{CH_2}CH_2Cl$), 2.57 (s, 3H, CH_3), 3.12 (t, 2H, J = 7.3, $\mathbf{CH_2}CH_2CH_2Cl$), 3.61 (t, 2H, J = 6.2, CH_2Cl), 7.05 (d, 1H, J = 6.8, H-5), 7.15 (t, 1H, J = 7.6, H-6), 7.39 (d, 1H, J = 7.8).

*2-(3-Chloropropyl)-4-nitrobenzimidazole Hydrochloride (**6c**.HCl)*

To 3-(4-nitro-2-benzimidazolyl)-1-propanol (0.2214 g, 1 mmol.) was added thionyl chloride (~2 mL) and the mixture warmed at 80° for one hour. Then excess thionyl chloride was removed by evaporation and four successive co-distillations with toluene on a rotary evaporator. The product was recrystallised from ethanol-toluene as colourless crystals (0.2564 g, 93%); m.p. 187-188°. (Found: C, 43.20; H, 4.11; N, 14.88; Cl, 25.82%. $C_{10}H_{11}N_3O_2Cl_2$ requires C, 43.48; H, 3.99; N, 15.21; Cl, 25.72%). Mass spectrum: m/z 241 (0.4), 239 (M^+, 1), 204 (4), 190 (1), 177 (10), 160 (5), 147 (3), 131 (23), 116 (3), 103 (7), 90 (10), 76 (7), 63 (24), 52 (12%). ^1H n.m.r. (CD_3OD): δ 2.41 (p, 2H, J_{av} = 7.4, $CH_2\mathbf{CH_2}CH_2Cl$), 3.28 (t, 2H, J = 7.6, $\mathbf{CH_2}CH_2CH_2Cl$), 3.68 (t, 2H, J = 6.4, CH_2Cl), 7.37 (t, 1H, J = 8.1, H-6), 8.03 (dd, 1H, J = 8, J = 0.9, H-5), 8.11 (dd, 1H, J = 8.2, J = 0.9, H-7).

*2-(3-Chloropropyl)-4-nitrobenzimidazole (**6c**)*

2-(3-Chloropropyl)-4-nitrobenzimidazole hydrochloride (0.0315 g) in ethanol was passed through a short column (about 1 cm) of silica gel with ethyl acetate as eluent; evaporation of the eluent gave the free base as colourless crystals (0.0223, 89%); m.p. 125-126°. (Found: C, 49.88; H, 4.32; N, 17.09; Cl, 14.98%. $C_{10}H_{10}N_3O_2Cl$ requires C, 50.12; H, 4.21; N, 17.53; Cl, 14.79%). Mass spectrum: m/z 241 (0.5), 239 (M^+, 2), 204 (4), 177 (100), 158 (6), 131 (21), 103 (6), 90 (8), 76 (6), 63 (18). ^1H n.m.r. ($CDCl_3$): δ 2.44 (p, 2H,

J_{av} = 6.8, $CH_2\mathbf{CH_2}CH_2Cl$), 3.25 (t, 2H, J = 7.3, $\mathbf{CH_2}CH_2CH_2Cl$), 3.72 (t, 2H, J = 6.1, CH_2Cl), 7.36 (t, 1H, J = 8.1, H-6), 8.06 (d, 1H, J = 7.9, H-7), 8.14 (d, 1H, J = 8.2, H-5).

2-(3-Chloropropyl)-4-aminobenzimidazole Dihydrochloride (6d.2HCl)

2-(3-chloropropyl)-4-nitrobenzimidazole hydrochloride (0.2763 g, 1 mmol.) in dry ethanol (20 mL) was hydrogenated at atmospheric pressure over 10% palladium-on charcoal (0.1007 g). After filtration, concentrated hydrochloric acid (5 mL) was added and the solution evaporated; the residue on recrystallization from ethanol-ether gave colourless crystals (0.2458 g, 87%); m.p. 173-174°. (Found: C, 42.75; H, 4.99; N, 14.70; Cl, 37.61%. $C_{10}H_{14}N_3Cl_3$ requires C, 42.50; H, 4.99; N, 14.87; Cl, 37.64%). Mass spectrum: m/z 211 (5), 210 (2), 209 (M^+, 16), 173 (100), 147 (99), 133 (4), 118 (7), 105 (13), 91 (7), 86 (25), 73 (24), 65 (12), 52 (17%). ^{1}H n.m.r. (CD_3OD): δ 2.34 (p, 2H, J_{av} = 7.8, $CH_2\mathbf{CH_2}CH_2Cl$), 3.35 (t [partly obscured], 1.4H, J = 8, $\mathbf{CH_2}CH_2CH_2Cl$), 3.71 (t, 2H, J = 6.2, CH_2Cl), 6.69 (dd, 1H, J = 7.8, J = 0.9, H-5), 6.92 (d, 1H, J= 8, H-7), 7.16 (t, 1H, J = 7.9, H-6). ^{1}H n.m.r. (d^6-DMSO): δ 2.48 (p, 2H, J_{av} = 7.6, $CH_2\mathbf{CH_2}CH_2Cl$), 3.23 (t, 2H, J = 8, $\mathbf{CH_2}CH_2CH_2Cl$), 3.57 (bs, 2H, NH_2), 3.82 (t, 2H, J = 6.2, CH_2Cl), 6.64 (d, 1H, J = 7.7, H-5), 6.86 (d, 1H, J = 7.6, H-7), 7.18 (t, 1H, J_{av} = 7.7, H-6).

2-(4-Chlorobutyl)-4-methylbenzimidazole Hydrochloride (7b.HCl)

To 4-(4-methyl-2-benzimidazolyl)-1-butanol (0.1515 g, 0.75 mmol.) was added thionyl chloride (~2 mL) and the solution warmed at 80° for one hour. Excess thionyl chloride was then removed by evaporation and four successive co-distillations with toluene on a rotary evaporator. The product on recrystallization from ethanol-toluene gave colourless crystals (0.1883 g, 97%); m.p. 179-180°. (Found: C, 55.85; H, 6.54; N, 10.76; Cl, 27.34%. $C_{12}H_{16}N_2Cl_2$ requires C, 55.60; H, 6.18; N, 10.81; Cl, 27.41%). Mass spectrum: m/z 224 (6), 223 (3), 222 (M^+, 19), 187 (78), 173 (12), 159 (100), 146 (51), 131 (9), 117 (6), 104 (12), 91 (15), 85 (5), 77 (31), 65 (16), 51 (26%). ^{1}H n.m.r. (CD_3OD): δ 1.91 (p, 2H, J_{av} = 7.6, $CH_2\mathbf{CH_2}CH_2CH_2Cl$), 2.12 (p, 2H, J_{av} = 7.6, $CH_2CH_2\mathbf{CH_2}CH_2Cl$), 2.65 (s, 3H, CH_3), 3.25 (t, 2H, J = 7.6, $\mathbf{CH_2}CH_2CH_2CH_2Cl$), 3.68 (t, 2H, J = 6.7, CH_2Cl), 7.37 (d, 1H, 7.2, H-5), 7.48 (t, 1H, J_{av} = 7.4, H-6), 7.58 (d, 1H, J = 7.2, H-7).

2-(4-Chlorobutyl)-4-nitrobenzimidazole Hydrochloride (7c.HCl)

To 4-(4-nitro-2-benzimidazolyl)-1-butanol (0.2354 g, 1 mmol.) was added thionyl chloride (~3 mL) and the mixture warmed at 80° for one hour. The excess thionyl chloride was then removed by evaporation and four successive co-distillation with toluene on a rotary evaporator. The product on recrystallization from ethanol-toluene gave almost colourless crystals (0.2672 g, 92%); m.p. 192-194°. (Found: C, 46.06; H, 4.16; N, 14.31; Cl, 24.53%. $C_{11}H_{13}N_3O_2Cl_2$ requires C, 45.53; H, 4.48; N, 14.48; Cl, 24.48%). Mass spectrum: m/z 255 (3), 254 (1), 253 (M^+, 11), 218 (77), 190 (100), 177 (23), 158 (12), 144 (24), 130 (33), 117 (12), 103 (14), 90 (26), 76 (17), 63 (48), 54 (32%). ^{1}H n.m.r. (d^6-DMSO): δ 1.83 (p, 2H, J_{av} = 7.2, $CH_2\mathbf{CH_2}CH_2CH_2Cl$), 2.01 (p, 2H, J_{av} = 7.4, $CH_2CH_2\mathbf{CH_2}CH_2Cl$), 3.19 (t, 2H, J = 7.4, $\mathbf{CH_2}CH_2CH_2CH_2Cl$), 3.72 (t, 2H, J = 6.4, CH_2Cl), 7.64 (t, 1H, J_{av} = 8.2, H-6), 8.21 (dd, 1H, J = 8.3, J = 1.1, H-5), 8.32 (dd, 1H, J = 8.3, J = 1, H-7).

2-(4-Chlorobutyl)-4-aminobenzimidazole Dihydrochloride (7d.2HCl)

2-(4-chlorobutyl)-4-nitrobenzimidazole hydrochloride (0.2903 g, 1 mmol.) in dry ethanol (20 mL) was hydrogenated (1 atm) over 10% Pd/C catalyst (0.1005 g). After filtration, concentrated hydrochloric acid (5 mL) was added and the solution evaporated. The residue, on recrystallization from ethanol-ether, gave colourless crystals (0.2402 g, 81%); m.p.122-123°. (Found: C, 44.43; H, 5.60; N, 14.03; Cl, 35.73%. $C_{11}H_{16}N_3Cl_3$ requires C, 44.54; H, 5.44; N, 14.17; Cl, 35.86%). Mass spectrum: m/z 225 (3), 224 (2), 223 (M^+, 10), 187 (100), 172 (4), 160 (21), 146 (15), 131 (3), 118 (4), 105 (8), 92 (6), 78 (9), 63 (6), 52 (14%). ^1H n.m.r. (d^6-DMSO): δ 1.81 (p, 2H, J_{av} = 7.4, $CH_2\mathbf{CH_2}CH_2CH_2Cl$), 2.03 (p, 2H, J_{av} = 7.4, $CH_2CH_2\mathbf{CH_2}CH_2Cl$), 3.14 (t, 2H, J = 7.5, $\mathbf{CH_2}CH_2CH_2CH_2Cl$), 3.71 ((t, 2H, J = 6.5, CH_2Cl), 5.92 (vbs, 2H, NH_2), 6.68 (d, 1H, J = 8.2, H-5), 6.89 (d, 1H, J = 7.8, H-7), 7.20 (t, 1H, J_{av} = 7.9, H-6).

(2-Benzimidazolyl)methanol Hydrochloride

A solution of (2-benzimidazolyl)methanol (0.74 g, 0.005 mole), prepared according to the literature procedure[20], in methanol (5 mL) and conc. hydrochloric acid (~2 mL) was evaporated. The residue, on recrystallization from methanol - light petroleum gave colourless crystals (0.88 g, 95%); m. p. 222-224°. (Found: C, 52.32; H, 4.86; N, 15.15; Cl, 19.39%. $C_8H_9N_3OCl$ requires C, 52.04; H, 4.91; N, 15.17; Cl, 19.20%)

(4-Methyl-2-benzimidazolyl)methanol

A mixture of 2,3-diaminotoluene (0.6103 g, 5 mmol.) and 70% glycollic acid (10 mL) was heated under reflux overnight at 160° under nitrogen. After cooling, the mixture was made alkaline with saturated sodium carbonate solution and the product was extracted with ethyl acetate (4×30 mL). The residue, after evaporation of the dried extract, was purified by radial chromatography (SiO_2, 5% ethanolic ethyl acetate). The unreacted diamine eluted first and then the product, which, on evaporation of the solvent, was obtained as colourless crystals (0.6728 g, 83%); m.p. 196-197°. (Found: C, 66.34; H, 6.45; N, 17.00%. $C_9H_{10}N_2O$ requires C, 66.65; H, 6.22; N, 17.27%). Mass spectrum: m/z 163 (11), 162 (M+, 100), 161 (28), 144 (95), 133 (36), 117 (15), 104 (34), 90 (10), 77 (44), 66 (34), 51 (33%). ^1H n.m.r. (CD_3OD): δ 2.65 (s, 3H, CH_3), 4.85 (s, 2H, CH_2), 7.02 (d, 1H, J = 8, H-5), 7.11 (t, 1H, J = 8, H-6), 7.32 (d, 1H, J = 8, H-7).

(4-Methyl-2-benzimidazolyl)methanol Hydrochloride

A solution of (4-methyl-2-benzimidazolyl)methanol (0.081 g) in methanol (5 mL) and conc. hydrochloric acid (~2 mL) was evaporated. The residue, on recrystallization from methanol - light petroleum gave colourless crystals (0.093 g, 94%); m.p. 246-247°. (Found: C, 55.12; H, 5.32; N, 13.88%. $C_9H_{11}N_2OCl$ requires C, 54.41; H, 5.54; N, 14.11%).

3-(2-Benzimidazolyl)propanol Hydrochloride

A solution of 3-(2-benzimidazolyl)propanol (0.88 g, 0.005 mole), prepared according to the literature procedure[20], in methanol (5 mL) and conc. hydrochloric acid (~2 mL) was evaporated. The residue was recrystallised from methanol - light petroleum giving colourless crystals (0.97 g, 92%); m.p. 155-156°. (Found: C, 56.45; H, 6.27; N, 132.05%. $C_{10}H_{13}N_2OCl$ requires C, 56.47; H, 6.16; N, 13.17%)

*(2-Benzimidazolyl)methyl Chloroacetate Hydrochloride (**8a**.HCl)*

A solution of (2-benzimidazolyl)methanol hydrochloride (0.3692 g) in chloroacetyl chloride (2 mL) was heated under reflux for one hour at 130°. After cooling, on addition of dry toluene (40 mL) the product crystallized. Recrystallization from ethanol-toluene gave colourless crystals (0.4855 g, 93%); m.p. 195-196°. (Found: C, 46.28; H, 3.89; N, 10.73; Cl, 27.10%. $C_{10}H_{10}N_2O_2Cl_2$ requires C, 45.98; H, 3.83; N, 10.73; Cl, 27.20%). Mass spectrum: m/z 226 (3), 225 (1), 224 (M^+, 11), 189 (1), 147 (100), 131 (30), 119 (14), 103 (15), 91 (28), 77 (53), 65 (13), 59 (93%). ^{1}H n.m.r. (CD_3OD): δ 4.41 (s, 2H, CH_2Cl), 5.69 (s, 2H, CH_2O), 7.63 (2H, AA'**BB**', J_{ortho} = 8.0, J_{meta} = 1.0, J_{para} = 0.6, H-5, H-6), 7.81 (2H, **AA**'BB', J_{ortho} = 8.0, J_{meta} = 1.0, J_{para} = 0.6, H-4, H-7).

*(4-Methyl-2-benzimidazolyl)methyl Chloroacetate Hydrochloride (**8b**.HCl)*

(4-Methyl-2-benzimidazolyl)methanol hydrochloride (0.2973 g) and chloroacetyl chloride (2 mL) were heated under reflux for one hour at 130°. The product was isolated by evaporation in vacuum and recrystallised from ethanol - toluene as colourless crystals (0.4962 g, 90%); m.p. 195-196°. Mass spectrum: m/z 240 (4), 239 (2), 238 (M^+, 15), 161 (100), 144 (41), 133 (9), 117 (8), 104 (12), 91 (10), 77 (23), 65 (7%). ^{1}H n.m.r. (CD_3OD): δ 2.65 (s, 3H, CH_3), 4.41 (s, 2H, CH_2Cl), 5.70 (s, 2H, CH_2O), 7.43 (dd, 1H, J = 7.4, J = 0.85, H-5), 7.52 (t, 1H, J_{av} = 7.8, H-6), 7.62 (dd, 1H, J = 8, J= 0.4, H-7).

*3-(2-Benzimidazolyl)propyl Chloroacetate Hydrochloride (**9a**.HCl)*

3-(2-Benzimidazolyl)propanol hydrochloride (0.4252 g, 2 mmol.) and chloroacetyl chloride (2 mL) were heated under reflux for one hour at 130°. The product was isolated by evaporation in vacuum and recrystallised from ethanol - toluene as colourless crystals (0.5318 g, 92%); m.p.140-141°. (Found; C, 49.52; H, 4.66; N, 9.39; Cl, 24.57%. $C_{12}H_{14}N_2O_2Cl_2$ requires C, 49.84; H, 4.88; N, 9.69; Cl, 24.52%). Mass spectrum: m/z 254 (2), 253 (2), 252 (M^+, 7), 175 (17), 159 (15), 145 (40), 132 (100), 118 (4), 104 (3), 92 (8), 77 (14), 63 (8), 51 (10%). ^{1}H n.m.r. (CD_3OD): δ 2.32 (p, 2H, J_{av} = 6, $CH_2\mathbf{CH_2}CH_2$), 3.29 (cxm, $\mathbf{CH_2}CH_2CH_2O$ [overlapped by CD_2H of CD_3OD]), 4.05 (s, 2H, CH_2Cl), 4.33 (t, 2H, J = 6, CH_2O), 7.58 (2H, AA'**BB**', J_{ortho} = 8.0, J_{meta} = 1.0, J_{para} = 0.6, H-5, H-6), 7.75 (2H, **AA**'BB', J_{ortho} = 8.0, J_{meta} = 1.0, J_{para} = 0.6, H-4, H-7). ^{1}H n.m.r. (CD_3COOD): δ 2.39 (p, 2H, J_{av} = 6.3, $CH_2\mathbf{CH_2}CH_2$), 3.45 (t, 2H, J = 7.6, $\mathbf{CH_2}CH_2CH_2O$), 4.09 (s, 2H, CH_2Cl), 4.32 (t, 2H, J = 5.8, CH_2O), 7.52 (cxm, 2H, H-5, H-6), 7.81 (cxm, 2H, H-4, H-7).

Intramolecular Cyclizations:

General Intramolecular Alkylation and Isolation Procedure:

The relevant 2-(ω-chloroalkyl)benzimidazole hydrochloride salt (0.5-1.0 mmol.) was dissolved in dry ethanol or dimethylformamide (10-20 mL) to give an about 0.05 M solution in a stoppered flask kept at 30±0.1° in a constant temperature bath. Following dissolution, 2.05 equivalents of sodium hydride (55.0% dispersed in oil) was added, the flask flushed with dry nitrogen and then kept overnight at 30±0.1°. Then after removal of the solvent by evaporation using a rotary evaporator, 20-30 mL water was added to the residue and the mixture exhaustively and quantitatively extracted with chloroform (aq. phase checked by u.v.). The chloroform extract was dried over anhydrous sodium sulphate. The residue obtained after evaporation of the dried organic layer

was analysed by t.l.c. and ^{1}H n.m.r. spectroscopy. The isomeric components were separated by preparative t.l.c. and characterized by m.p., microanalysis, mass spectrometry (EI, 70 eV), and ^{1}H n.m.r. spectroscopy. Comparison of these physical and spectral properties with related isomeric benzimidazoles[1-3,20,21,23] was used to confirm structural assignments.

Quantitative Spectroscopic Analyses

The relative proportions of the two isomers in the crude product mixtures were estimated by computer generated listing of the integral intensities (p.F.t. ^{1}H n.m.r. spectroscopy, Varian XL-200E and Varian GEMINI-300) of the *N*-methylene signals (in some cases signals other than *N*-CH_2 signals were used). Care was taken to obtain good quantitative spectra[34] by using: adequate delay times between pulses (>5 × max. T_1, generally 30 - 40 sec); a maximal Fourier number for good digital resolution of peaks; adequate sweep widths to avoid fold-back; a large number of transients to optimize the signal / noise; appropriate zero point filling; and *consistent*, wide integration extension on *both* sides of each appropriate isomer signal.

Duplicate alkylation reactions of similar scale were performed and analysed similarly with the results averaged. Estimated uncertainty of these analyses is ±1%, with reproducability of alkylation product ratios generally ±0.5%.

Intramolecular Alkylation of 2-(3-Chloropropyl)-4-methylbenzimidazole (6b)

(a) **In ethanol.** Standard alkylation and isolation procedures were followed using 2-(3-chloropropyl)-4-methylbenzimidazole hydrochloride (0.1227 g, 0.5 mmol.) and sodium hydride (0.0463 g, 55.0% in oil, 1.06 mmol.) in dry ethanol (10 mL). The crude mixture (0.0945 g) contained the two isomeric products in unequal amounts (t.l.c. and ^{1}H n.m.r.) with no residual, uncyclized parent heterocycle. ^{1}H n.m.r.: δ 2.54 (s, CH_3 [N^3]), 2.64 (s, CH_3 [N^1]), 2.67 (m, $2CH_2$ [N^1 and N^3], $NCH_2\mathbf{CH_2}CH_2C$), 3.03 (m, $2CH_2$ [N^1 and N^3], $NCH_2CH_2\mathbf{CH_2}C$), 4.07 (t, *N*-CH_2 [N^1]), 4.31 (t, *N*-CH_2 [N^3]), 6.91-7.52 (ArH). The two *N*-methylene triplets were integrated (extending 20 Hz on each side from the centre of the triplets) giving a 5-methyl-2,3-dihydro-*1H*-pyrrolo[1,2-a]benzimidazole (N^1) : 8-methyl-2,3-dihydro-*1H*-pyrrolo[1,2-a]benzimidazole (N^3) ratio of 34.4±1.0 : 65.6±1.0%. (duplicate run = 34.2±1.0 : 65.8±1.0%)

(b) **In dimethylformamide**. Standard alkylation and isolation procedures were followed using 2-(3-chloropropyl)-4-methylbenzimidazole hydrochloride (0.1226 g, 0.5 mmol.) and sodium hydride (0.0471 g, 55.0% in oil, 1.06 mmol) in dry dimethylformamide (10 mL). T.l.c. and ^{1}H n.m.r. spectroscopy indicated the crude mixture contained the two isomeric products and no residual uncyclized parent heterocycle. The isomeric proportions were determined by quantitative ^{1}H n.m.r. spectroscopy, as in the above section (a). The N1:N3 alkylation ratio = 36.3±1.0 : 63.7±1.0% (duplicate run = 36.6±1.0 : 63.4±1.0%).

*Separation of 5- and 8-Methyl-2,3-dihydro-*1H*-pyrrolo[1,2-a]benzimidazoles (**12b, 10b**)*

The above mixture (0.0205 g) of two isomers was separated by preparative t.l.c. (20×20×0.1 cm, SiO_2, 5% ethanolic ethyl acetate). The minor isomer, 5-methyl-2,3-dihydro-*1H*-pyrrolo[1,2-a]benzimidazole (**12b**, higher R_f), was obtained on evaporation of the solvent as colourless crystals (0.0063 g); m.p.130-131°. (Found: C, 76.65; H, 7.10; N, 16.12%. $C_{11}H_{12}N_2$ requires C, 76.71; H, 7.02; N, 16.27%). Mass spectrum: m/z 173 (11), 172 (M^+, 100), 171 (53), 157 (2), 144 (25), 131 (2), 116 (5), 104 (5), 91 (6), 86 (14), 77 (14),

65 (9), 51 (15%). ^{1}H N.m.r.: δ 2.64 (m, 7H, CH_3, $NCH_2\mathbf{C}\mathbf{H_2}CH_2C$), 3.05 (t, 2H, J = 7.8, $NCH_2CH_2\mathbf{CH_2}C$), 4.04 (t, 2H, J = 7, *N*-CH_2), 7.03 (bd, 1H, H-5), 7.10 (m, 2H, H-6, H-7).

The major isomer, 8-methyl-2,3-dihydro-*1H*-pyrrolo[1,2-a]benzimidazole (**10b**, lower R_f), was obtained on evaporation of the solvent as colourless crystals (0.0113 g); m.p. 155-156°. (Found: C, 76.93; H, 7.26; N, 16.03%. $C_{11}H_{12}N_2$ requires C, 76.71; H, 7.02; N, 16.27%). Mass spectrum: m/z 173 (11), 172 (M^+, 100), 171 (67), 157 (2), 144 (12), 131 (2), 116 (7), 104 (6), 89 (10), 85 (7), 77 (14), 65 (10), 51 (17%). ^{1}H N.m.r.: δ 2.53 (s, 3H, CH_3), 2.61 (p, 2H, J_{av} = 7.3, $NCH_2\mathbf{C}\mathbf{H_2}CH_2C$), 2.96 (t, 2H, J = 7.6, $NCH_2CH_2\mathbf{CH_2}C$), 4.21 (t, 2H, J = 7, *N*-CH_2), 6.91 (d, 1H, J = 7.4, H-5), 7.07 (t, 1H, J_{av} = 7.6, H-6), 7.49 (d, 1H, J = 8, H-7).

*Intramolecular Alkylation of 2-(4-Chlorobutyl)-4-methylbenzimidazole (**7b**)*

Standard alkylation and isolation procedures were followed using 2-(4-chlorobutyl)-4-methylbenzimidazole hydrochloride (0.1259 g, 0.5 mmol.) and sodium hydride (0.0458 g, 55.0% in oil, 1.05 mmol.) in dry ethanol (10 mL). The crude mixture contained the two isomeric products in unequal amounts (t.l.c. and ^{1}H n.m.r.) with no residual, uncyclized parent heterocycle. ^{1}H N.m.r.: δ 1.88-2.17 (cxm, $4CH_2$ [N^1 and N^3], $NCH_2\mathbf{CH_2CH_2}CH_2C$), 2.64 (s, CH_3 [N^1]), 2.67 (s, CH_3 [N^3]), 3.07 (q, $2CH_2$ [N^1 and N^3], $NCH_2CH_2CH_2\mathbf{CH_2}C$), 4.02 (t, *N*-$CH_2$ [N^1]), 4.41 (t, *N*-CH_2 [N^3]), 6.84-7.53 (ArH). The two *N*-methylene triplets were integrated (extending 30 Hz on each side from the centre of the triplets) giving a. 6-methyl-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (N^1) : 9-methyl-1,2,3,4-dihydropyrido-[1,2-a]benzimidazole (N^3) ratio of 44.8±1.0 : 55.2±1.0 % (duplicate run = 44.7±1.0 : 55.3 ±1.0 %).

*Separation of 6- and 9-Methyl-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazoles (**13b**, **11b**)*

The above mixture (0.0214 g) of two isomers were separated by preparative t.l.c. (20×20×0.1 cm SiO_2, 5% ethanol / ethyl acetate). The minor isomer, 6-methyl-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (**13b**, higher R_f), was obtained on evaporation of the solvent as colourless gum, which slowly crystallized, (0.0084 g); m.p. 85-86°. (Found: mol wt 186.1157. $C_{12}H_{14}N_2$ requires mol wt 186.1157). Mass spectrum: m/z 187 (12), 186 (M^+, 100), 185 (35), 171 (7), 158 (23), 145 (9), 131 (10), 117 (5), 104 (10), 89 (18), 77 (32), 65 (30), 51 (45%). ^{1}H N.m.r.: δ 2.04 (cxm, 2H, $NCH_2CH_2\mathbf{CH_2}CH_2C$), 2.12 (cxm, 2H, $NCH_2\mathbf{CH_2}CH_2CH_2C$), 2.66 (s, 3H, CH_3), 3.13 (t, 2H, J = 6.4, $NCH_2CH_2CH_2\mathbf{CH_2}C$), 4.08 (t, 2H, J = 6.1, *N*-CH_2), 7.06 (m, 1H, H-5), 7.14 (m, 2H, H-6, H-7).

The major isomer, 9-methyl-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (**11b**, lower R_f), was obtained on evaporation of the solvent as colourless gum, which slowly crystallized, (0.0098 g); m.p. 100-101°. (Found: mol wt 186.1157. $C_{12}H_{14}N_2$ requires mol wt 186.1157). Mass spectrum: m/z 188 (1), 187 (14), 186 (M^+, 100), 185 (33), 171 (6), 158 (22), 145 (5), 131 (8), 116 (6), 104 (6), 89 (12), 77 (16), 65 (14), 51 (20%). ^{1}H n.m.r.: δ (dp, 2H, J_{av} = 6.3, $NCH_2CH_2\mathbf{CH_2}CH_2C$), 2.11 (dp, 2H, J_{av} = 6.1, $NCH_2\mathbf{CH_2}CH_2CH_2C$), 2.71 (s, 3H, CH_3), 3,09 (t, 2H, J = 6.5, $NCH_2CH_2CH_2\mathbf{CH_2}C$), 4.47 (t, 2H, J = 6.2, *N*-CH_2), 6.92 (d, 1H, J = 7.1, H-5), 7.09 (t, 1H, J_{av} = 7.6, H-6), 7.51 (d, 1H, J = 8.2, H-7).

Intramolecular Alkylation of 2-(3-Chloropropyl)-4-nitrobenzimidazole (6c)

(a) **In ethanol**. Standard alkylation and isolation procedures were followed using 2-(chloropropyl)-4-nitrobenzimidazole hydrochloride (0.1882 g, 0.5 mmol.) and sodium hydride (0.0453, 55.0% in oil, 1.04 mmol) in dry ethanol (10 mL). The crude mixture (0.1104 g) contained the two isomeric products in unequal amounts (t.l.c. and ^{1}H n.m.r.) with no residual, uncyclized parent heterocycle. ^{1}H n.m.r.: δ 2.73 (p, $NCH_2\mathbf{CH_2}CH_2C$ [N^3]), 2.84 (q, $NCH_2\mathbf{CH_2}CH_2C$ [N^1]), 3.14 (t, $NCH_2CH_2\mathbf{CH_2}C$ [N^3]), 3.24 (t, $NCH_2CH_2\mathbf{CH_2}C$ [N^1]), 4.24 (t, *N*-CH_2 [N^1]), 4.66 (t, *N*-CH_2 [N^3]), 7.25-8.15 (ArH). The two *N*-methylene triplets were integrated (extending 30 Hz on each side from the centre of the triplets) giving a 5-nitro-2,3-dihydro-*1H*-pyrrolo[1,2-a]benzimidazole (N^1) : 8-nitro-2,3-dihydro-*1H*-pyrrolo[1,2-a]benzimidazole (N^3) ratio of 10.3±1.0 : 89.7±1.0% (duplicate run = 10.2±1.0 : 89.8±1.0%).

(b) **In dimethylformamide**. Standard alkylation and isolation procedures were followed by taking 2-(3-chloropropyl)-4-nitrobenzimidazole hydrochloride (0.1881 g, 0.5 mmol.) and sodium hydride (0.0459 g, 55.0% in oil, 1.05 mmol.) in dry dimethylformamide (10 mL). The N^1:N^3 alkylation ratio was found = 10.5±1.0 : 89.5±1.0% (duplicate run = 10.7±1.0 : 89.3±1.0%).

*Separation of 5- and 8-Nitro-2,3-dihydro-*1H*-pyrrolo[1,2-a]benzimidazoles (12c, 10c)*

The above mixture (0.0586 g) was separated by sequential radial (SiO_2, ethyl acetate) and preparative t.l. chromatography (20×20×0.1 cm SiO_2, 5% ethanol / ethyl acetate). The higher R_f band yielded the major isomer, 8-nitro-2,3-dihydro-1H-pyrrolo[1,2-a]benzimidazole (**10c**), obtained as pale yellow crystals (0.0458 g); m.p. 130-131°. (Found: mol wt 203.0696. $C_{10}H_9N_3O_2$ requires mol wt 203.0695). Mass spectrum: m/z 204 (7), 203 (M^+, 63), 186 (77), 173 (6), 157 (36), 156 (100), 145 (18), 129 (67), 116 (16), 102 (62), 89 (19), 75 (52), 63 (59), 51 (61%). ^{1}H N.m.r.: δ 2.72 (p, 2H, J_{av} = 7.5, $NCH_2\mathbf{CH_2}CH_2C$), 3.14 (t, 2H, J = 7.8, $NCH_2CH_2\mathbf{CH_2}C$), 4.66 (t, 2H, J = 7.2, *N*-CH_2), 7.28 (t, 1H, J = 8.1, H-6), 7.98 (d, 1H, J = 7.7, H-5), 8.07 (d, 1H, J = 8.2, H-7).

The minor isomer, 5-nitro-2,3-dihydro-1H-pyrrolo[1,2-a]benzimidazole (**12c**), was isolated from the lower band as pale yellow crystals (0.0049 g); m.p. 165-166°. (Found: mol wt 203.0696. $C_{10}H_9N_3O_2$ requires mol wt 203.0695). Mass spectrum: m/z 204 (2), 203 (M^+, 21), 186 (28), 177 (5), 156 (35), 149 (31), 129 (23), 102 (24), 90 (8), 85 (15), 76 (23), 71 (52), 57 (100%). ^{1}H N.m.r.: δ 2.82 (p, 2H, J_{av} = 7.6, $NCH_2\mathbf{CH_2}CH_2C$), 3.24 (t, 2H, J = 7.7, $NCH_2CH_2\mathbf{CH_2}C$), 4.24 (t, 2H, J = 7.1, *N*-CH_2), 7.31 (t, 1H, J = 8, H-6), 7.62 (dd, 1H, J = 7.2, J = 1.1, H-5), 8.13 (dd, 1H, J = 8.2, J = 1.1, H-7).

Intramolecular Alkylation of 2-(4-Chlorobutyl)-4-nitrobenzimidazole (7c)

Standard alkylation and isolation procedures were followed using 2-(4-chlorobutyl)-4-nitrobenzimidazole hydrochloride (0.1452 g, 0.5 mmol.) and sodium hydride (0.0453 g, 55.0% in oil, 1.04 mmol.) in dry ethanol (10 mL). The crude mixture (0.1097 g) contained the two isomeric products in unequal amounts (t.l.c. and ^{1}H n.m.r.) with no residual, uncyclized parent heterocycle. ^{1}H N.m.r.: δ 1.98-2.26 (cxm, $NCH_2\mathbf{CH_2CH_2}CH_2C$ [N^1 and N^3]), 3.18 (t, $NCH_2CH_2CH_2\mathbf{CH_2}C$ [N^3]), 3.24 (t, $NCH_2CH_2CH_2\mathbf{CH_2}C$ [N^1]), 4.18 (t, *N*-CH_2 [N^1]), 4.31 (t, *N*-CH_2 [N^3]), 7.25-8.15 (ArH). The two *N*-methylene triplets were integrated (extending 12 Hz on each side from the centre of the triplets) giving a 6-nitro-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (N^1) : 9-nitro-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (N^3) ratio = 48.0±1.0 : 52.0±1.0% (duplicate run = 47.8±1.0 : 52.2±1.0%).

*Separation of 6- and 9-Nitro-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazoles (**13c, 11c**)*

The above mixture (0.0206 g) of two isomers were separated by preparative t.l.c. (20×20×0.2 cm SiO_2, 4:1 ethyl acetate / light petroleum). The minor isomer, 6-nitro-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (**13c**, lower R_f), was obtained on evaporation of the solvent as pale yellow crystals (0.0083 g); m.p. 150-152°. (Found: mol wt 217.0852. $C_{11}H_{11}N_3O_2$ requires mol wt 217.0851). Mass spectrum: m/z 219 (1), 218 (4), 217 (M^+, 36), 201 (2), 190 (13), 187 (65), 177 (14), 159 (38), 144 (15), 130 (28), 116 (27), 103 (29), 90 (37), 76 (75), 63 (100), 55 (94%). ^{1}H N.m.r.: δ 2.09 (cxm, 2H, $NCH_2CH_2\mathbf{CH_2}CH_2C$), 2.19 (cxm, 2H, $NCH_2\mathbf{CH_2}CH_2CH_2C$), 3.23 (t, 2H, J = 6.5, $NCH_2CH_2CH_2\mathbf{CH_2}C$), 4.18 (t, 2H, J = 6.1, *N*-CH_2), 7.29 (t, 1H, J_{av} = 8, H-6), 7.61 (dd, 1H, J = 8.2, J = 1.1, H-5), 8.11 (dd, 1H, J = 8.2, J = 1.1, H-7).

The major isomer, 9-nitro-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (**11c**, higher R_f), was obtained on evaporation of the solvent as a pale yellow gum, which slowly crystallized to pale yellow crystals (0.0094 g); m.p. 96-97°. (Found: mol wt 217.0852. $C_{11}H_{11}N_3O_2$ requires mol wt 217.0851). Mass spectrum: m/z 218 (6), 217 (M^+, 45), 200 (44), 170 (100), 161 (24), 156 (10), 143 (24), 129 (28), 116 (25), 102 (32), 90 (33), 75 (44), 63 (60), 55 (70%). ^{1}H N.m.r.: δ 2.08 (cxm, 4H, $NCH_2\mathbf{CH_2CH_2}CH_2C$), 3.18 (t, 2H, J = 6.3, $NCH_2CH_2CH_2\mathbf{CH_2}C$), 4.31 (t, 2H, J = 5.9, *N*-CH_2), 7.28 (t, 1H, J_{av} = 8, H-6), 7.84 (d, 1H, J = 8.2, H-5), 7.93 (d, 1H, J = 7.7, H-7).

*Intramolecular Alkylation of 2-(3-Chloropropyl)-4-aminobenzimidazole (**6d**)*

(a) **In ethanol**. Standard alkylation and isolation procedures were followed using 2-(3-chloropropyl)-4-aminobenzimidazole dihydrochloride (0.1415 g, 0.5 mmol.) and sodium hydride (0.0664 g, 1.52 mmol.) in dry ethanol (10 mL). The crude mixture (0.0905 g) contained the two isomeric products in unequal amounts (t.l.c. and ^{1}H n.m.r.) with no residual, uncyclized parent heterocycle. ^{1}H n.m.r. (CD_3OD): δ 2.65 (cxm, $NCH_2\mathbf{CH_2}CH_2C$ [N^1 and N^3]), 2.95 (cxm, $NCH_2CH_2\mathbf{CH_2}C$ [N^1 and N^3]), 4.02 (t, *N*-CH_2 [N^1]), 4.36 (t, *N*-CH_2 [N^3]), 6.48-7.02 (ArH). The two *N*-methylene triplets were integrated (extending 24 Hz on each side from the centre of the triplets) giving a 5-Amino-2,3-dihydro-1H-pyrrolo[1,2-a]benzimidazole (N^1) : 8-amino-2,3-dihydro-1H-pyrrolo[1,2-a]benzimidazole (N^3) ratio = 56.4±1.0 : 43.6±1.0% (duplicate run = 56.3±1.0 : 43.7±1.0%).

(b) **In dimethylformamide**. Standard alkylation and isolation procedures were followed using 2-(3-chloropropyl)-4-aminobenzimidazole dihydrochloride (0.1413 g, 0.5 mmol.) and sodium hydride (0.0661 g, 1.51 mmol.) in dry dimethylformamide (10 mL). The crude mixture (0.0897 g) contained the two isomeric products in unequal amounts (t.l.c. and ^{1}H n.m.r.) with no residual, uncyclized parent heterocycle. The N^1:N^3 alkylation ratio was found = 56.8±1.0 : 43.2±1.0% (duplicate run = 57.0±1.0 : 43.0±1.0%).

*Separation of 5- and 8-Amino-2,3-dihydro-*1H*-pyrrolo[1,2-a]benzimidazoles (**12d, 10d**)*

The above mixture (0.0226 g) of two isomers were separated by preparative t.l.c. (20×20×0.2 cm, SiO_2, 10% ethanol / ethyl acetate). The major isomer, 5-amino-2,3-dihydro-*1H*-pyrrolo[1,2-a]benzimidazole (**12d**, higher R_f), was obtained on evaporation of the solvent as pale brown crystals (0.0103 g); m.p. 176-177°. (Found: mol wt 173.0952. $C_{10}H_{11}N_3$ requires mol wt 173.0953). Mass spectrum: m/z 174 (12), 173 (M^+, 100), 172 (29), 158 (1), 144 (17), 132 (1), 118 (7), 105 (8), 91 (10), 86 (12), 78 (11), 52 (17%). ^{1}H N.m.r.: δ 2.74 (p, 2H, J_{av} = 7.3, $NCH_2\mathbf{CH_2}CH_2C$), 3.08 (t, 2H, J = 7.5, $NCH_2CH_2\mathbf{CH_2}C$), 4.10 (t, 2H, J = 7, *N*-CH_2), 6.54 (d, 1H, J = 7.7, H-5), 6.73 (d, 1H, J = 8.1, H-7), 7.04 (t, 1H, J = 7.7, H-6).

The minor isomer, 8-amino-2,3-dihydro-*1H*-pyrrolo[1,2-a]benzimidazole (**10d**, lower R_f), was obtained on evaporation of the solvent as pale brown crystals (0.0088 g); m.p.195-196°. (Found: mol wt 173.0952. $C_{10}H_{11}N_3$ requires mol wt 173.0953). Mass spectrum: m/z 174 (7), 173 (M^+, 63), 172 (21), 158 (2), 144 (12), 129 (1), 117 (5), 105 (5), 91 (25), 78 (7), 65 (11), 60 (100%). ^{1}H N.m.r.: δ 2.74 (p, 2H, J_{av} = 7.2, $NCH_2\mathbf{CH_2}CH_2C$), 3.05 (t, 2H, J = 7.2, $NCH_2CH_2\mathbf{CH_2}C$), 4.42 (t, 2H, J = 7, *N*-CH_2), 6.54 (d, 1H, J = 7.2, H-5), 7.03 (t, 1H, J_{av} = 7.9, H-6), 7.21 (d, 1H, J = 8.1, H-7).

Intramolecular Alkylation of 2-(4-Chlorobutyl)-4-aminobenzimidazole (7d)

Standard alkylation and isolation procedures were followed using 2-(4-chlorobutyl)-4-aminobenzimidazole dihydrochloride (0.1484 g, 0.5 mmol.) and sodium hydride (0.0667 g, 55.0% in oil, 1.53 mmol) in dry ethanol (10 mL). The crude mixture (0.1075 g) contained the two isomeric products in unequal amounts (t.l.c. and ^{1}H n.m.r.) with no residual, uncyclized parent heterocycle. ^{1}H N.m.r.: δ 2.04 (cxm, $NCH_2CH_2\mathbf{CH_2}CH_2C$ [N^1 and N^3]), 2.11 (cxm, $NCH_2\mathbf{CH_2}CH_2CH_2C$ [N^1 and N^3]), 3.08 (m, $NCH_2CH_2CH_2\mathbf{CH_2}C$ [N^1 and N^3]), 4.05 (t, *N*-CH_2 [N^1]), 4.28 (bs, NH_2), 4.54 (t, *N*-CH_2 [N^3]), 6.48-7.21 (ArH). To remove the NH_2 signal in the ^{1}H n.m.r. spectrum, a drop of D_2O was added to the $CDCl_3$ solution of the crude mixture and then the two *N*-methylene triplets were integrated (extending 26 Hz on each side from the centre of the triplets) giving a 6-amino-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (N^1) : 9-amino-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (N^3) ratio = 71.6±1.0 : 28.4±1.0% (duplicate run = 71.7±1.0 : 28.3±1.0%).

Separation of 6- and 9-Amino-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazoles (13d, 11d)

The above mixture (0.0318 g) of two isomers were separated by preparative t.l.c. (20×20×0.2 cm SiO_2, 10% ethanol / ethyl acetate). The major isomer, 6-amino-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (**13d**, higher R_f), was obtained on evaporation of the solvent as pale brown gum, which slowly crystallized (0.0203 g); m.p. 150-151 °. (Found: mol wt 187.1109. $C_{11}H_{13}N_3$ requires mol wt 187.1109). Mass spectrum: m/z 188 (14), 187 (M^+, 100), 186 (21), 172 (3), 159 (23), 149 (21), 131 (5), 117 (5), 105 (10), 91 (11), 85 (17), 78 (13), 71 (42), 65 (18), 57 (77%). ^{1}H N.m.r.: δ 2.03 (cxm, 2H, $NCH_2CH_2\mathbf{CH_2}CH_2C$), 2.11 (cxm, 2H, $NCH_2\mathbf{CH_2}CH_2CH_2C$), 3.08 (t, 2H, J = 6.4, $NCH_2CH_2CH_2\mathbf{CH_2}C$), 4.04 (t, 2H, J = 6, *N*-CH_2), 6.53 (dd, 1H, J = 7.7, J = 1.1, H-5), 6.71 (dd, 1H, J = 7.3, J = 1.1, H-7), 7.03 (t, 1H, J_{av} = 7.8, H-6).

The minor isomer, 9-amino-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (**11d**, lower R_f), was obtained on evaporation of the solvent as pale brown crystals (0.0073 g); m.p. 163-164°. (Found: mol wt 187.1109. $C_{11}H_{13}N_3$ requires mol wt 187.1109). Mass spectrum: m/z 188 (15), 187 (M^+, 100), 186 (22), 172 (3), 159 (21), 146 (6), 131 (4), 117 (4), 105 (8), 91 (15), 78 (12), 65 (15), 52 (17%). ^{1}H N.m.r.: δ 1.99 (cxm, 2H, $NCH_2CH_2\mathbf{CH_2}CH_2C$), 2.12 (cxm, 2H, $NCH_2\mathbf{CH_2}CH_2CH_2C$), 3.09 (t, 2H, J = 6.5, $NCH_2CH_2CH_2\mathbf{CH_2}C$), 4.56 (t, 2H, J = 6.1, *N*-CH_2), 6.51 (d, 1H, J = 7.8, H-5), 7.01 (t, 1H, J_{av} = 7.8, H-6), 7.19 (d, 1H, J = 8, H-7).

Dimerization of (2-Benzimidazolyl)methyl Chloroacetate

The standard alkylation procedure was followed using (2-benzimidazolyl)methyl chloroacetate hydrochloride (0.1311 g, 0.5 mmol.), sodium hydride (0.0461 g, 55.0% in oil, 1.05 mmol.) in dry dimethylformamide (10 mL). The residue, on evaporation of dimethylformamide, was not soluble in chloroform

or water. This insoluble white powder (0.0813 g), which decomposes on heating, was identified as a symmetric dimer by mass spectroscopic and ^{1}H n.m.r. analysis. (Found: mol wt 376.1171. $C_{20}H_{16}N_4O_4$ requires mol wt 376.1172). Mass spectrum: m/z 377 (5), 376 (M^+, 25), 287 (17), 274 (14), 260 (4), 188 (14), 169 (10), 157 (20), 144 (49), 132 (22), 117 (40), 100 (39), 85 (45), 77 (62), 58 (92%). ^{1}H n.m.r. (CF_3COOD): δ 5.25 (s, 2H, *N*-CH_2), 5.65 (s, 2H, CCH_2O), 7.50 (cxm, 4H, H-4, H-5, H-6, H-7).

Dimerization of (2-Benzimidazolyl)propyl Chloroacetate

Standard alkylation procedures were followed using (2-benzimidazolyl)propyl chloroacetate hydrochloride (0.1447 g, 0.5 mmol.) and sodium hydride (0.0458 g, 55.0% in oil, 1.05 mmol.) in dry dimethylformamide (10 mL). The residue, on evaporation of dimethylformamide, was not soluble in chloroform or water. This insoluble white powder (0.1035 g), which decomposes on heating, was identified as a symmetrical dimer by mass spectrometry and n.m.r. analysis. (Found: mol wt 432.1796. $C_{24}H_{24}N_4O_4$ requires mol wt 432.1798). Mass spectrum: m/z 434 (1), 433 (8), 432 (M^+, 30), 388 (4), 217 (21), 191 (10), 171 (85), 157 (51), 146 (44), 131 (24), 117 (17), 103 (22), 90 (16), 77 (100), 63 (22), 51 (73%). ^{1}H n.m.r. (CF_3COOD): δ 2.14 (bs, 2H, $CH_2\mathbf{CH_2}CH_2$), 3.14 (t, 2H, J = 7.2, $\mathbf{CH_2}CH_2CH_2O$), 4.19 (t, 2H, J = 6, CH_2O), 5.14 (s, *N*-CH_2), 7.38 (cxm, 3H, ArH), 7.47 (cxm, 1H, ArH).

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