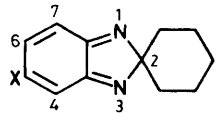
2*H*-Benzimidazoles (Isobenzimidazoles). Part 2.† Synthesis and Reactions of 5-Azido-2*H*-benzimidazole-2-spirocyclohexane

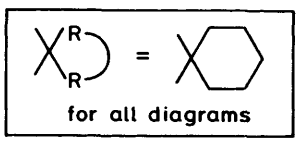
Hans Suschitzky *
The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT, U.K.
Walter Kramer, Richard Neidlein,* and Helmut Uhl
Pharmazeutisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 364, D-6900 Heidelberg, F.R.G.

A practicable synthesis of the title compound from 5-phenylsulphonyl-2*H*-benzimidazole and sodium azide is described. The 5-azido-2*H*-benzimidazole undergoes photolysis in the presence of various secondary aliphatic amines to give the corresponding 4-amino-5-dialkylamino-2*H*-benzimidazoles. By contrast thermal decomposition of the azide with exclusion of light led, in the presence of secondary amines, to 5-amino-6-dialkylamino-2*H*-benzimidazoles, but with thiols the corresponding 5-amino-4-thio-2*H*-benzimidazoles were obtained. A mechanism to account for the formation of these derivatives is proposed and conversions of some of the products into other heterocycles are described. Selective ^{13}C-{^1H} n.O.e. difference spectroscopy was applied for a structural assignment.

The results reported here stem from our continuing interest in the photolysis and thermolysis of organic azides in the presence of nucleophiles.[2] Since we found[1] that 2*H*-benzimidazole behaves like stable benzoquinone di-imine, its 5-azido derivative (**1**; X = N_3) could be obtained as expected from the chloro compound (**1**; X = Cl) and sodium azide in DMSO in *ca.* 60% yield. This is by analogy with the well documented[3] reaction of



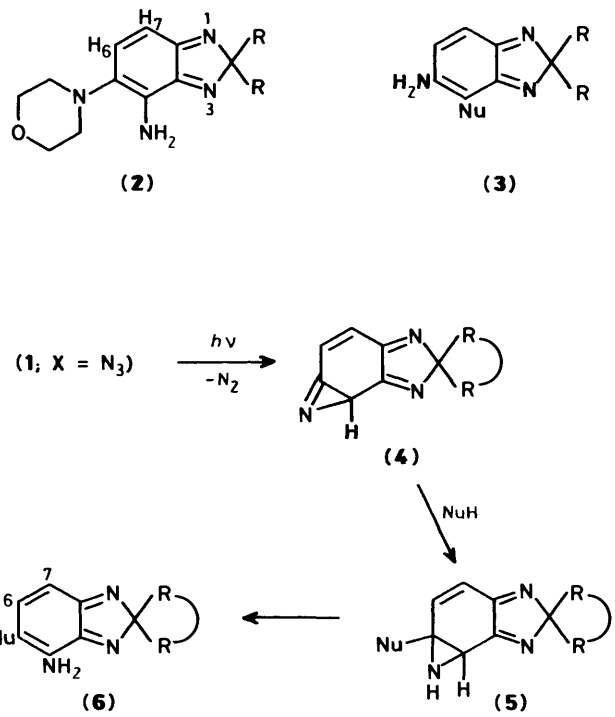
(**1**)



chloroquinones with sodium azide to give azidoquinones. However, a comparison of the ^{13}C n.m.r. spectrum of the starting material with that of the crude reaction product showed the reaction to be incomplete with *ca.* 40% of the starting material remaining. This assessment was based on comparison of the C-4 azide peak (**1**; X = N_3) with that of the corresponding peak in the chloro compound (**1**; X = Cl) which appeared at 109.6 and 123.7 p.p.m. respectively. The reason for the unsatisfactory azide yield lies in the fact that 5-chloro-2*H*-benzimidazole does not undergo exclusive ipso substitution with nucleophiles.

In view of the incomplete displacement of the chlorine atom in (**1**; X = Cl), other leaving groups were considered. For instance substitution of alkyl- or aryl-sulphones by nucleophiles has been successfully exploited especially in π-deficient heterocyclic systems.[4] 2-Azidopyrimidine for instance is conveniently prepared from the 2-methylsulphonyl derivative and sodium azide.[5] In fact sulphones have been observed to be superior to chlorine as leaving groups in some cases.[6] We found that, when the readily available[1] 5-phenylsulphonyl-2*H*-benzimidazole (**1**; X = SO_2Ph) was made to react with sodium azide in DMSO at ambient temperature, 5-azido-2*H*-benzimidazole (**1**; X = N_3) was obtained in 90% yield within 30 min.

Photoreactions of 5-*Azido*-2H-*benzimidazole* (**1**; X = N_3).—(a) *With secondary amines.* Irradiation of the azide (**1**; X = N_3) in dry THF in the presence of an excess of morpholine until



Scheme 1.

evolution of nitrogen ceased (*ca.* 1 h) gave, after chromatographic purification (Al_2O_3), an orange crystalline solid which, according to analytical data, was an aminomorpholino-2*H*-benzimidazole. The ^1H n.m.r. spectrum (*cf.* Table 1) corresponded clearly to a 4,5-disubstituted 2*H*-benzimidazole. These data did not, however, allow a distinction to be made between the two possible isomers (**2**) and (**3**) (Nu = morpholino). The differential diagnosis followed from irradiation of the α-methylene protons of the morpholine, which resulted in enhancement of the doublet at δ 7.05 [6-H, *cf.* (**2**)] apart from the expected intensity rise of the methylene protons adjacent to oxygen. Moreover, irradiation of the amino group did not affect the intensity of either doublet (6-

† Part 1[1] appeared under the general Series title 'Isobenzimidazoles (2*H*-Benzimidazoles).'

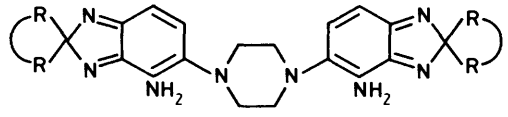
Table 1. 4,5-Diamino-2*H*-benzimidazoles from photolysis of the azide (**1**; X = N_3) and secondary amines

Compound (**6**) Nu	Yield (%)	M.p. (°C)	Found (%) required C	H	N	Formula	δ(CDCl$_3$; 90 MHz)/p.p.m. 6-H	7-H	$J_{6\,7}$ (Hz)	NH_2	c.-hexyl and Nu
Morpholino*	61.7	196	67.2 (67.1)	7.7 (7.8)	19.1 (19.5)	$C_{16}H_{22}N_4O$	7.05	6.63	9.75	4.59	2.04—1.30, 3.83 (4 H, m), 2.87 (4 H, m)
Piperidino	66.8	135	72.1 (71.8)	8.6 (8.5)	19.7 (19.7)	$C_{17}H_{24}N_4$	7.05	6.60	9.9	4.49	2.0—1.30 (16 H, m), 2.8 (4 H, m)
N-Me-piperazino*	68.3	185	68.3 (68.2)	8.4 (8.4)	23.3 (23.3)	$C_{17}H_{25}N_5$	7.06	6.63	9.8	4.53	1.96—1.53 (10 H, m), 2.91 (4 H, 2-CH_2), 2.57 (4 H, m, 2-CH_2), 2.36 (Me, s)
Et_2N	74.8	92	70.2 (70.6)	8.7 (8.9)	20.7 (20.6)	$C_{16}H_{24}N_4$	6.97	6.60	9.6	4.68	2.1—1.5 (10 H, m), 2.88 (4 H, q, 2-CH_2), 1.03 (6 H, t, 2 Me)
Pr^i_2N	54.8	107	72.1 (72.0)	9.4 (9.4)	18.3 (18.7)	$C_{18}H_{28}N_4$	6.92	6.52	9.9	4.77	2.04—1.26 (10 H, m), 3.41 (2 H, 2-CH), 1.07 (12 H, d, 4 Me)
PrNMe	51.1	67	70.2 (70.6)	8.8 (8.9)	20.3 (20.6)	$C_{16}H_{24}N_4$	6.94	6.53	9.72	4.50	1.86—1.18 (12 H, m), 2.50 (3 H, s, Me), 0.82 (3 H, t, Me)
N-Me-anilino	46.7	145	74.4 (74.5)	7.3 (7.2)	18.1 (18.3)	$C_{19}H_{22}N_4$	6.90—6.57[a] (5 H, m, 3 ArH)			4.47	1.96—1.66 (10 H, m), 3.17 (3 H, s, Me)
Compound (**7**)	32.9	225	69.3 (69.4)	7.5 (7.5)	22.7 (23.1)	$C_{28}H_{36}N_8$	7.10	6.65	9.9	4.6	2.04—1.26 (20 H, m), 3.02 (8 H, s, 4-CH_2)

* ^{1}H N.m.r. at 250 MHz.

[a] 6-H and 7-H buried in ArH.

H, 7-H). The mechanism leading to the product (**2**) involves a nitrogen shift (nitrogen walk) from position 5→4 as the 4-amino group in the product obviously originated from the 5-azido substituent. The photolysis of this vinyl azide (**1**; X = N_3) occurs, we believe, in a manner analogous to that of the well documented aryl azides[2] as shown in Scheme 1. The azirine (**4**) which arises when a photolytically induced singlet nitrene (RN:) is converted into an aziridine (**5**) by addition of the nucleophile. Ring opening of the strained ring (**5**) leads to the product (**6**) in which the amino group is derived from one of the nitrogen atoms. Photolysis of the azide (**1**; X = N_3) in the presence of various other secondary amines gave the corresponding 4,5-diamino-2*H*-benzimidazoles listed in Table 1. Piperazine led to a bis-2*H*-benzimidazole (**7**). Chemical shifts of the 4-amino group and

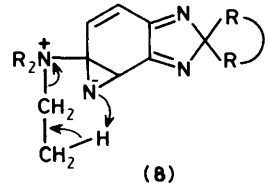


(**7**)

the 6-H and 7-H protons as well as the 6,7-H coupling constant are practically independent of the nature of the secondary amine in position 5. The mass spectra of these 2*H*-benzimidazoles show, in every case, a molecular ion and, apart from a characteristic fragmentation of the dialkylamino moiety, a loss of 43 corresponding to a $[C_3H_7]^+$ fragment of the cyclohexyl ring.

(b) *With primary amines.* Photolysis of the 5-azido-2*H*-benzimidazole (**1**; X = N_3) in the presence of primary aliphatic or aromatic amines under the above conditions led to unidentifiable products.

(c) *With tertiary amines.* Photolysis with tertiary amines (*N*-ethylmorpholine and triethylamine) gave products corresponding to a reaction with secondary amines, *i.e.* (**6**; Nu =



(**8**)

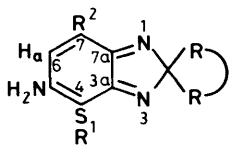
morpholino or Et_2N respectively). This could be due to elimination of ethylene from the intermediate alkylammonium structure (**8**) as shown for the reaction with triethylamine.

(d) *With sulphur nucleophiles.* Photoreaction of (**1**; X = N_3) with an excess of butanethiol under the usual conditions gave only 5-amino-4,7-dibutylthio-2*H*-benzimidazole (**9**; R^1 = Bu, R^2 = BuS) which was identical with the product obtained from the dark reaction (*cf.* below). The rate of the 1,4-Michael addition of the strongly nucleophilic thiol to the undecomposed azide (**1**; X = N_3) appears to compete successfully with that of the azide photolysis. The outcome of the reaction is thus due to a non-photolytic pathway (*cf.* below).

Dark Reactions of 5-*Azido*-2H-*benzimidazole* (**1**; X = N_3).—(a) *With sulphur nucleophiles.* In a typical reaction butanethiol in benzene was made to react at room temperature with 5-azido-2*H*-benzimidazole for 22 h in the dark. The main product (51.6%) was identified as 5-amino-4-butylthio-2*H*-benzimidazole (**9**; R^1 = Bu, R^2 = H) (*cf.* n.m.r. in Table 2). The i.r. spectrum (KBr) showed peaks characteristic of an amino group ($\nu_{max.}$ = 3 430 and 3 280 cm^{-1}). In addition a broad peak appeared at 3 100 cm^{-1} characteristic also of all other amino thio derivatives (**9**; *cf.* below). We ascribe this band to an NH group at position 3 arising from a tautomeric equilibrium (**9**) ⇌ (**10**). The spectral data do not distinguish between (**9**; R^1 = Bu, R^2 = H) and its isomer 4-amino-5-butyl-2*H*-benzimidazole in which the substituents occupy reverse positions. However, a distinct intensity increase of the doublet at δ 6.76 (**9**; H_a) on irradiation of the amino group is only

Table 2. Products from dark reactions of 5-azido-2*H*-benzimidazole with thiols (**1**)—(**5**) and secondary amines (**6**)—(**8**)

Compound (**9**)	Yield (%)	M.p. (°C)	Found (%) (Required) C	H	N	Formula	δ($CDCl_3$; 250 MHz) p.p.m.
1; R^1 = BuS, R^2 = H	51.6	151	66.3 (66.4)	8.0 (8.0)	14.6 (14.6)	$C_{16}H_{23}N_3S$	7.19 (1 H, d, *J* 9.76 Hz), 6.75 (1 H, α, *J* 9.76 Hz), 5.09 (2 H, s, NH_2), 2.81 (2 H, t, CH_2), 2.01—1.28 (14 H, m, 2 CH_2 and C_6H_{10}), 0.85 (3 H, t, Me)
R^1 = R^2 = BuS	8.3	117	63.5 (63.6)	8.2 (8.3)	11.4 (11.1)	$C_{20}H_{31}N_3S_2$	6.33 (1 H, s), 5.12 (2 H, s, NH_2), 2.93 (2 H, t, CH), 2.75 (2 H, t, CH_2), 1.94—1.34 (18 H, m, C_6H_{10} +4 CH_2), 0.95 (3 H, t, Me), 0.84 (3 H, t, Me)
2; R^1 = PrS, R^2 = H	48.4	173	65.4 (65.4)	7.6 (7.7)	15.1 (15.3)	$C_{15}H_{21}N_3S$	7.18 (1 H, d, *J* 9.58 Hz), 6.76 (1 H, d, *J* 9.63), 5.12 (2 H, s, NH_2), 2.78 (2 H, t, CH_2), 2.08—1.28 (12 H, m, C_6H_{10} +CH_2), 0.95 (3 H, t, CH_2)
R^1 = R^2 = PrS	13.0	155	61.8 (61.9)	7.9 (7.8)	11.7 (12.0)	$C_{18}H_{27}N_3S_2$	6.31 (1 H, s), 5.09 (2 H, s, NH_2), 2.94 (2 H, t, CH_2), 2.74 (2 H, t, CH_2), 1.94—1.48 (14 H, m, C_6H_{10} +2 CH_2), 1.09 (3 H, t, Me), 0.94 (3 H, t, Me)
3; R^1 = Pr^{i}S, R^2 = H	53.6	207	65.0 (65.4)	7.7 (7.7)	15.0 (15.3)	$C_{15}H_{21}N_3S$	7.19 (1 H, d, *J* 9.65 Hz), 6.82 (1 H, d, *J* 9.76 Hz), 5.33 (2 H, s, NH_2), 3.47 (1 H, pent. CH), 2.11—1.43 (10 H, m, C_6H_{10}), 1.23 (6 H, d, 2 Me)
R^1 = R^2 = Pr^{i}S	9.8	164	61.5 (61.9)	7.7 (7.8)	11.9 (12.0)	$C_{18}H_{27}N_3S_2$	6.28 (1 H, s), 5.02 (2 H, s, NH_2), 3.14 (1 H, pent. CH), 2.05—1.45 (10 H, m, C_6H_{10}), 1.14 (6 H, d, 2 Me), 0.98 (6 H, d, 2 Me)
4; R_2 = R^1 = Bu^{t}S, R^2 = H	66.3	217	66.5 (66.4)	8.0 (8.0)	14.5 (14.5)	$C_{16}H_{23}N_3S$	7.22 (1 H, d, *J* = 9.6), 6.82 (1 H, d, *J* 9.6 Hz), 5.37 (2 H, s, NH_2) 2.08—1.45 (10 H, m, C_6H_{10}), 1.35 (9 H, s, CMe_3)
5; R^1 = $PhCH_2S$, R^2 = H	45.7	194	70.7 (70.6)	6.6 (6.6)	13.0 (13.0)	$C_{19}H_{21}N_3S$	7.18—7.06 (6 H, m, C_6H_5 +CH), 6.60 (1 H, d, *J* 9.60 Hz), 4.75 (2 H, s, NH_2), 3.97 (2 H, s, CH_2), 2.02—1.73 (10 H, m, C_6H_{10})
R^1 = R^2 = $PhCH_2S$	19.1	145	70.5 (70.1)	6.2 (6.1)	9.0 (9.4)	$C_{26}H_{27}N_3S_2$	7.36—7.04 (10 H, m, 2-Ph), 6.24 (1 H, s), 4.73 (2 H, s, NH_2), 4.19 (2 H, s, CH_2), 3.91 (2 H, s, CH_2), 1.96—1.46 (10 H, m, C_6H_{10})
6; R^1 = PhS, R^2 = H	48.2	218	70.4 (70.0)	6.3 (6.2)	13.5 (13.6)	$C_{18}H_{19}N_3S$	7.37—7.11 (6 H, m, Ph +CH), 6.82 (1 H, d, *J* 9.7 Hz), 5.20 (2 H, s, NH_2), 1.4—1.52 (10 H, m, C_6H_{10})
Compound (**13**)							
7; R^2 = $[CH_2]_2O[CH_2]_2$	72.5	218	70.6 (70.1)	8.0 (7.7)	17.2 (17.2)	$C_{16}H_{22}N_4O$· 0.5 C_6H_6	7.27 (3 H, s, 0.5 C_6H_6), 6.63 (1 H, s), 6.18 (1 H, s), 4.62 (2 H, s, NH_2) 3.86 (4 H, m, 2 CH_2), 3.01 (4 H, m, 2 CH_2), 1.95—1.55 (10 H, m, C_6H_{10})
8; R^2 = $[CH_2]_5$	79.4	230	71.9 (71.8)	8.3 (8.5)	19.7 (19.7)	$C_{17}H_{24}N_4$	6.58 (1 H, s), 6.11 (1 H, s), 4.64 (2 H, s, NH_2), 2.92 (4 H, m, 2 CH_2), 1.93—1.57 (16 H, m, C_6H_{10} and C_3H_6)
9; R^2 = $[CH_2]_2N(Me)[CH_2]_2$	70.9	225	70.7 (71.0)	8.8 (8.3)	21.0 (20.7)	$C_{17}H_{25}N_5$· 0.5 C_6H_6	7.27 (3 H, s, 0.5 C_6H_6), 6.64 (1 H, s), 6.13 (1 H, s), 4.61 (2 H, s, NH_2), 3.03 (4 H, m, 2 CH_2), 2.59 (4 H, m, 2 CH_2), 2.37 (3 H, s, Me), 1.93—1.48 (10 H, m, C_6H_{10})



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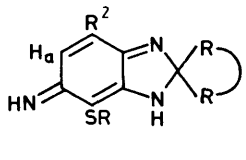

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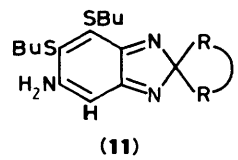
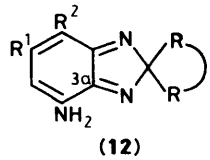


(**11**)



(**12**)

compatible with the isomer (**9**; R^1 = Bu, R^2 = H). In a further and complementary experiment irradiation at H_a [*cf.* (**9**)] caused enhancement of the peaks due to 7-H and the NH_2 group (**9**; R^2 = H).

The minor product (8.3%) proved to be 5-amino-4,7-dibutylthio-2*H*-benzimidazole (**9**; R^1 = Bu, R^2 = SBu). The spectral and analytical data (*cf.* Table 2, No. 1) satisfy, however, three possible structures, namely (**9**; R^1 = Bu, R^2 = SBu), (**11**), and (**12**) (R^1 = R^2 = SBu). Irradiation at δ 6.33 (=C*H*) caused enhancement of the amino signal as well as in the lower field triplet (δ 2.93, $SCH_2CH_2CH_2CH_3$) which, in turn, on irradiation, produced an intensity change in the ring proton signal (δ 6.33, 1 H). These data exclude structure (**11**) from consideration as the unsubstituted ring position in this compound is not adjacent to a butylthio group. Since ^{1}H n.m.r. could not distinguish between the alternatives (**9**; R^1 = Bu, R^2 = SBu) and (**12**; R^1 = R^2 = SBu) we turned for elucidation of the structure to ^{13}C {^{1}H-selective} n.O.e. difference spectroscopy [7] (*cf.* Figure). Single frequency ^{1}H pre-irradiation at the ring proton (δ 6.33) resulted in a clear n.O.e. in the ^{13}C n.m.r. spectrum of the non-protonated carbons at δ 152.6 and 139. Since structure (**11**) can be discounted, the signals must be due to the quaternary carbons in =CNH_2 and in one of the =C*S*Bu moieties. It is reasonable to assume that, owing to the charge distribution in an enamine ($NH_2C{=}C \longleftrightarrow \overset{+}{N}H_2{=}C{=}\bar{C}$), the quaternary carbon in one of the =CSBu structures should be shielded in (**9**) (*cf.* position 4) which is indeed the case (δ 92.7). Furthermore, a negative n.O.e. is observed for the α-carbon in the C(7)-S$CH_2CH_2CH_2CH_3$ side-chain (δ 30.6) which is an indirect effect due to dipole–dipole interaction between the 6-H and the C(7)-S$CH_2CH_2CH_2CH_3$ protons.[8] Selective ^{13}C{^{1}H}

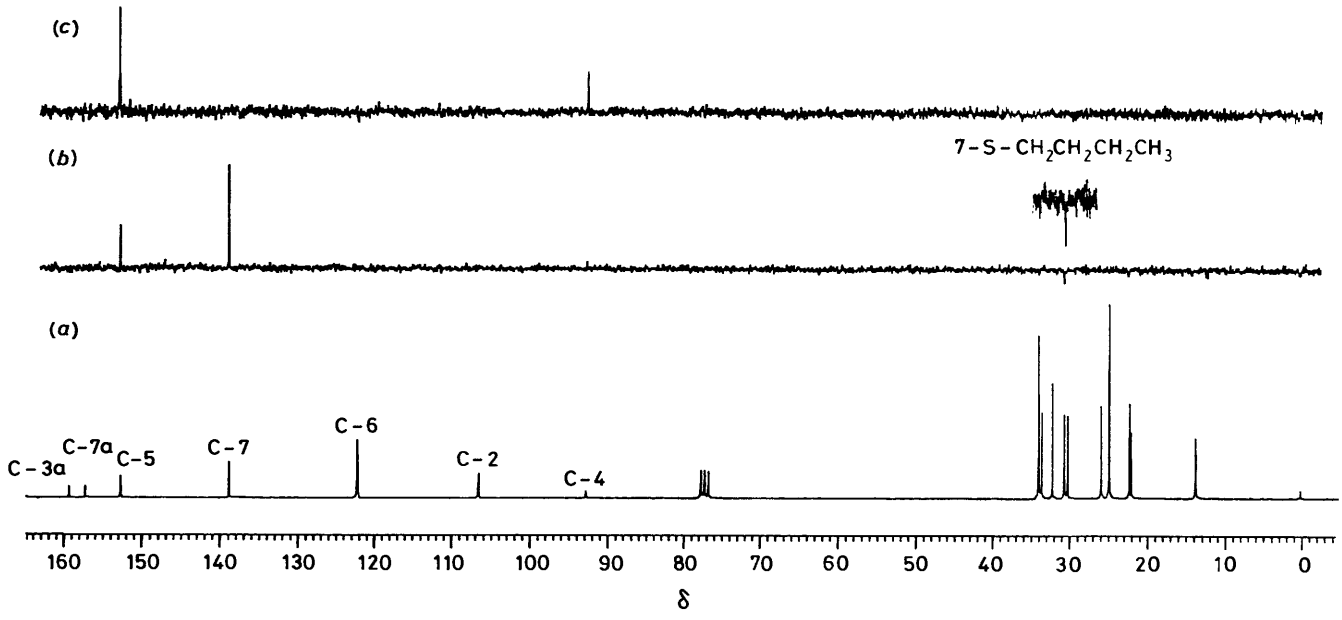
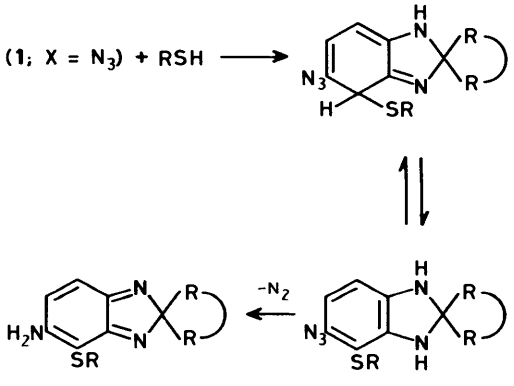
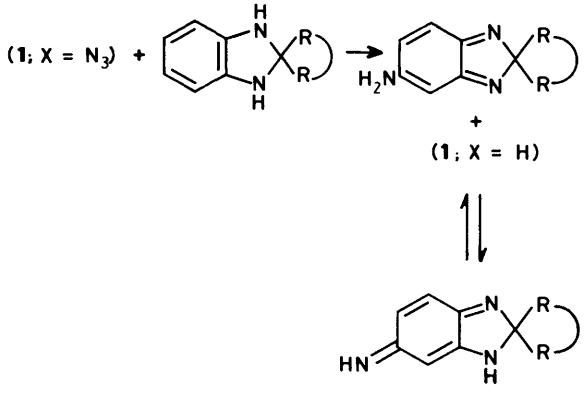


Figure. ^{13}C N.m.r. spectra (62.89 MHz Bruker WM 250), in $CDCl_3$ for compound (**9**): (a) proton noise-decoupled spectrum; $^{13}C\{^1H\}$-n.O.e.-difference spectra obtained by selective low-power pre-irradiation of (b) 6-H and (c) 5-NH_2

low-power decoupling of C(7)-S$CH_2CH_2CH_2CH_3$ (lower field triplet at δ 2.93) confirms the assignment of δ 30.6. Structure (**12**) can now be discounted since the enamine effect associated with charge density on its β-carbon would result in an upfield shift of the CH signal (*ca.* 85—100 p.p.m.)[9] which is not observed (CH at δ 122). Further evidence in support of structure (**9**) came from an irradiation of the amino group which produced an n.O.e. in the ^{13}C spectrum at δ 152.6 and 93.8, both signals attributable to the non-proton bearing ring carbons =CNH_2 and =CSBu respectively. The products from other thiols are listed in Table 2. The reaction with thiophenol (Table 2, No. 6) was carried out in hexane, as it was too vigorous in benzene, the solvent chosen in all other cases (Schemes 1—5). The various thiol substituents have little influence on the chemical shifts or fragmentation pattern in the m.s. of the rest of the molecule. The mechanism of the dark reaction is noteworthy, as the presence of a thiol causes reduction of the azido-2*H*-benzimidazole (**1**; X = N_3) to an amine. We ascribe this to an intra- or inter-molecular redox process of the dihydro intermediate arising from the addition of the thiol as set out in Scheme 2. The alternative route in which the azide is thermolysed to a nitrene which forms the amine as triplet product prior to the thiol addition can be discounted as the azido-2*H*-benzimidazole proved stable when kept under the reaction conditions for several days. The possiblity that the thiol reduces the azide can also be refuted on grounds of stoicheiometry, since the yield of amine far exceeds the amount of thiol employed. Further support for the proposed redox mechanism proceeding intermolecularly came from the following observation: an equimolar benzene solution of the azide (**1**; X = N_3) and the dihydrobenzimidazole liberated a vigorous stream of nitrogen and a dark-red precipitate of amino-2*H*-benzimidazole separated in practically quantitative yield (Scheme 3). A corresponding quantity of 2*H*-benzimidazole (**1**; X = H) was also formed. Structure assignment as the 5-amino derivative (**1**; X = NH_2) followed from its ^1H n.m.r. and i.r. spectra ($\nu_{max.}$ 3 350 and 3 160 cm^{-1}) which indicated a tautomeric mixture (*cf.* Scheme 3).

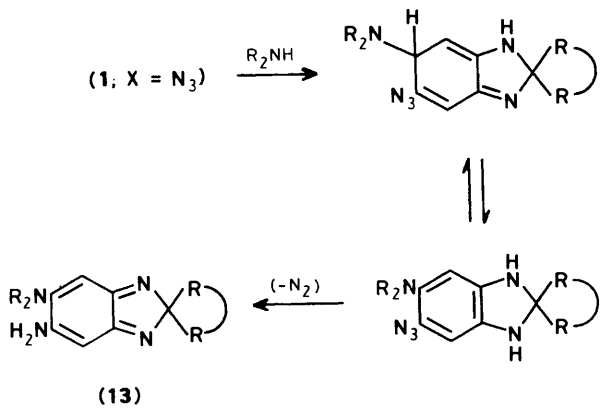


Scheme 2.



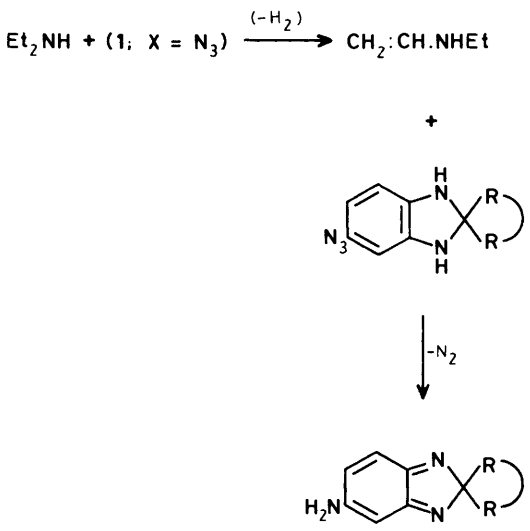
Scheme 3.

(b) *With secondary amines* (cf. *Table* 2). When morpholine was made to react with the azide (**1**; X = N_3) in benzene for 20 h with exclusion of light at room temperature, the 5-amino-6-morpholino derivative [**13**; R_2 = $(CH_2)_2O(CH_2)_2$; 72.5%]



Scheme 4.

was obtained as the only product. Analogous products were obtained from piperidine and *N*-methylpiperazine [**13**; R_2 = $(CH_2)_5$ and $(CH_2)_2NMe(CH_2)_2$ respectively]. The dark reaction with secondary amines follows in principle the same mechanism as with the thiols, except that the first step involves a 1,4- (*cf.* Scheme 4) and not 1,6-addition as in the latter (*cf.* Scheme 2). We ascribe this difference to the acidity of the thiols leading to incipient protonation of the azide and formation of the conjugate acid ($RNH\overset{+}{N}_2$). As with other electron-withdrawing groups[1] (SO_2Ar, NO_2, $Me\overset{+}{O}=$) the incoming nucleophile becomes subject to 1,6-addition. An unexpected result occurred when diethylamine was made to react with the azide (**1**; X = N_3) in equimolar proportions. The only isolable product was the 5-amino-2*H*-benzimidazole (**1**; X = NH_2). When, however, a large excess of the diethylamine was employed the expected 5-amino-6-diethylamino derivative (**13**; R_2 = Et_2) was obtained. This unusual result may be due to dehydrogenation of the diethylamine to an unstable ethylvinylamine[10] (CH_2:CHNHEt) with conversion of the reduced 5-azidobenzimidazole into the 5-amino compound (**1**; X = NH_2) (Scheme 5). We have previously[1] observed an analogous formation of a vinylamine as an intermediate product with a 2*H*-benzimidazole (**1**; X = SO_2Ar). In the present case, however, no cognate derivative was isolated and the reason why only diethylamine amongst the secondary amines should suffer

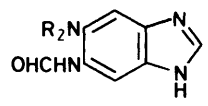


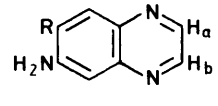
Scheme 5.

dehydrogenation is not clear at present. The amino-2*H*-benzimidazole itself (**1**; X = NH_2), however, reacted smoothly with diethylamine to give the expected product (**13**; R_2 = Et_2).

(c) *With triphenylphosphine in benzene or* THF, *in light or in the dark.* The reaction of the azide was exothermic with strong nitrogen evolution depositing within minutes the yellow phosphinimine (**1**; X = N:PPh_3), a typical Staudinger product.[11]

Heterocycles from Substituted 2H-*Benzimidazoles.*—The conversion of substituted 2*H*-benzimidazoles into heterocycles by reductive ring-opening with sodium dithionite to give the corresponding *o*-phenylenediamine followed by conventional cyclisations proved as successful as previously reported.[1] Thus treatment of the 5-amino-6-morpholino-2*H*-benzimidazole [**13**; R^2 = $(CH)_2O(CH_2)_2$; *cf.* Table 2; No. 7] with sodium dithionite in aqueous methanol gave an unstable tetra-amine which on formylation cyclised to the benzimidazole [**14**; R_2 = $(CH_2)_2$-$O(CH_2)_2$]. Reaction of the above crude tetra-amine with glyoxal gave the quinoxaline (**15**; R = morpholino). Its ^1H n.m.r. spectrum showed the expected features except for the two doublets at δ 8.55 and 8.46 with an unexpectedly low coupling constant of J_{H_a,H_b} 2 Hz [*cf.* (**15**)]. An analogous low coupling value has, however, been reported[12] for the *ortho*-protons in the pyrazine moiety of pteridines (*J* 1.7 Hz) and is generally ascribed to the influence of the adjacent electronegative


(14)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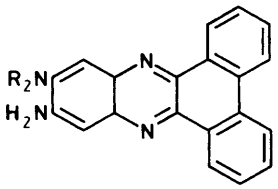
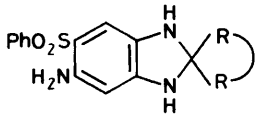

(16)


(17)

nitrogens. Condensation of the intermediate tetra-amine with phenanthroquinone furnished the 11,12-aminomorpholinophenazine [**16**; R_2 = $(CH_2)_2O(CH_2)_2$]. The 6-amino-7-phenylsulphonylquinoxaline (**15**; R = SO_2Ph) was prepared by treating the 5-amino derivative (**1**; X = NH_2) with sodium benzenesulphinate in acetic acid to give the stable dihydrobenzimidazole (**17**). Its reaction with hot aqueous glyoxal gave the above intensely fluorescent quinoxaline. Characteristically its *ortho*-protons [H_a, H_b *cf.* (**15**)] at δ 8.79 and 8.66 showed a low coupling constant (*J* 1.78 Hz).

Experimental

I.r. spectra were measured on a Perkin-Elmer 325 spectrometer, ^1H n.m.r. spectra with a Bruker HX-90E (90 MHz, W.M.-250 MHz) and ^{13}C with a Bruker (62.89 MHz) and δ values are quoted relative to TMS. The conditions for carrying out the selective $^{13}C\{^1H\}$ n.O.e. difference spectroscopy were as previously reported[13] by us. M.p.s. were measured on a Reichert melting-point microscope and are uncorrected. For column chromatography alumina Type H (Merck) or silica gel 60 (63—200 μm) (Merck) was employed. Mass spectra were obtained on a Varian MAT-311-A. U.v. spectra were measured on a Carl Zeiss DMR 4 spectrometer. Light petroleum refers to the fraction of b.p. 60—80 °C. If not otherwise stated all ^1H

n.m.r. spectra are given for 90 MHz. Irradiations were performed under nitrogen with a 125 W medium-pressure mercury lamp (Hanau 254 nm, T.Q. 150) placed inside a water-cooled immersion well.

5-Azido-2H-benzimidazole (**1**; X = N_3).—(*a*) Sodium azide (6 g, 92.3 mmol) was added to a solution of 5-phenylsulphonyl-2*H*-benzimidazole (10 g, 30.6 mmol) in DMSO (50 ml) and the mixture stirred at room temperature in the dark for 0.5 h. The reaction mixture was poured onto ice (400 g) and saturated brine (600 ml), and the organic matter extracted (4 × 150 ml diethyl ether). The extracts were dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Chromatography (Al_2O_3, dichloromethane) gave the azide (**1**; X = N_3) (90%), m.p. 60 °C (lit.[1] m.p. 54—55 °C); $\nu_{max.}$(KBr) 2 125 cm^{-1} (N_3); δ($CDCl_3$; 250 MHz) 7.27 (dd, 1 H, 7-H, $J_{5,7}$ 9.75, $J_{4,7}$ 1.03 Hz), 6.68 (dd, 1 H, 4-H, $J_{4,6}$ 2.15, $J_{4,7}$ 0.95 Hz), 6.67 (dd, 1 H, 6-H, $J_{6,7}$ 9.75, $J_{4,6}$ 2.13 Hz), and 1.99—1.64 (m, 10 H, C_6H_{10}); *m/z* 227 (M^+); $\lambda_{max.}$(MeOH) 375 (log ε 3.47), 285 (3.77), and 245 nm (4.17).

(*b*) A sample of (**1**; X = N_3) of inferior purity was obtained from 5-chloro-2*H*-benzimidazole and sodium azide in DMSO as previously described.[1]

Reactions of 5-Azido-2H-benzimidazole (**1**; X = N_3).—(a) *With triphenylphosphine.* Triphenylphosphine (0.925 g, 3.52 mmol) was added with stirring to a solution of the azide (0.8 g, 3.52 mmol) in benzene (5 ml) or THF (10 ml). Precipitation of a solid was made complete by addition of light petroleum (b.p. 40—60 °C). Recrystallisation of the product (benzene–hexane) gave yellow crystals of 1,1,1-*triphenyl*-2-(2′*H*-*benzimidazole*-2′-*spirocyclohexan*-5′-yl)*phosphinimine* (**1**; X = N=PPh_3) (1.42 g, 87.4%), m.p. 175 °C; δ($CDCl_3$; 250 MHz) 7.79—7.71 (m, 6 H ArH), 7.56—7.44 (m, 9 H, ArH), 7.04 (m, 2 H), 5.81 (m, 1 H), and 1.85—1.55 (m, 10 H, C_6H_{10}); *m/z* 461 (M^+) (Found: C, 77.85; H, 6.1; N, 8.75. $C_{30}H_{28}N_3P$ requires C, 78.1; H, 6.1; N, 9.1%). The course of the reaction was unaffected by light.

(b) *Photolysis in presence of amines* (cf. *Table* 1). In a representative procedure the azide (**1**; X = N_3) (0.68 g, 3 mmol) and freshly distilled morpholine (6.0 ml, 70 mmol) dissolved in THF (80 ml) were irradiated until N_2 evolution had ceased (*ca.* 1 h). The solvent was distilled off and the residue chromatographed (Al_2O_3, dichloromethane) to yield red 4-*amino*-5-*morpholino*-2H-*benzimidazole*-2-*spirocyclohexane* (**2**) (61.7%), m.p. 196 °C; $\lambda_{max.}$(log ε, MeOH) 465 (3.47), 285 (3.59), and 228 (4.38) nm; $\nu_{max.}$(KBr) 3 420 and 3 320 (NH_2); *m/z* 286 (M^+). Under the above conditions primary amines ($PhNH_2$, $BuNH_2$) gave intractable tars, while tertiary amines (*N*-ethylmorpholine and triethylamine) gave the products arising from secondary amines (**6**; Nu = morpholino or Et_2NH; *ca.* 25%).

(c) *Dark reaction in presence of thiols* (cf. *Table* 2). In a typical experiment the azide (**1**; X = N_3) (0.8 g, 3.52 mmol) and butanethiol (0.4 ml, 3.72 mmol) were dissolved in benzene (5 ml) and stirred for 22 h at ambient temperature with exclusion of light. Work-up as in (b) and chromatography (Al_2O_3, CH_2Cl_2–ethyl acetate, 9:1) gave as second fraction the orange 5-*amino*-4-*butylthio*-2H-*benzimidazole* (**9**: R^1 = SBu, R^2 = H) (51.6%), m.p. 151 °C; $\lambda_{max.}$(MeOH) 450 (log ε 3.68), 270 (4.07), and 228 (4.42) nm; $\nu_{max.}$(KBr) 3 430, 3 280, and 3 105 cm^{-1}; *m/z* 289 (M^+). The first fraction yielded the dark-red 4,7-dibutylthiol compound (**9**; R^1 = Bu, R^2 = SBu) (8.3%), m.p. 117 °C; $\lambda_{max.}$(MeOH) 475 (log ε 3.71), 335 (3.88), 250 (4.17), and 230 nm (4.35); $\nu_{max.}$(KBr) 3 475 and 3 270 cm^{-1}. Also in the other examples given in Table 2 (Nos. 2, 3, and 5) the first chromatographic fraction was the dithio compound (**9**; R^2 = SR), and the second band the monothio compound (**9**; R^2 = H).

(d) *Dark reaction in presence of secondary amines* (cf. *Table* 2). A typical preparation was carried out by stirring a benzene solution (12 ml) of the azido compound (3.2 g, 14.08 mmol) and morpholine (1.24 ml, 14.2 mmol) for 17 h with exclusion of light. The precipitate was collected and recrystallised from benzene–hexane to yield the 5-*amino*-6-*morpholino*-2H-*benzimidazole* [**13**; R_2 = $(CH_2)_2O(CH_2)_2$] as yellow crystals (3.31 g, 72.5%), m.p. 218 °C; $\lambda_{max.}$(MeOH) 345 (log ε 4.10), 255 (4.09), and 220 (4.49) nm; $\nu_{max.}$(KBr) 3 440 and 3 100 cm^{-1}; *m/z* 286 (M^+).

Reaction of the azide under similar conditions with diethylamine gave only 5-amino-2*H*-benzimidazole (**1**; X = NH_2) while with an excess (10×) of diethylamine the 5-amino-6-diethylamino derivative (**13**; R_2 = Et_2) was obtained identical with an authentic sample [for data of (**1**; X = NH_2) *cf.* below].

5-Amino-2H-benzimidazole (**1**; X = NH_2).—A solution of 2,3-dihydrobenzimidazole-2-spirocyclohexane (4 g, 21.25 mmol) and 5-azido-2*H*-benzimidazole-2-spirocyclohexane (3.35 g, 14.8 mmol) in toluene (280 ml) (*cf.* Scheme 3), was stirred at room temperature with or without exclusion of light for 3 h to give slow separation of a red solid. The solvent volume was concentrated to 2/3 under reduced pressure after which the solid was filtered off and recrystallised (toluene–hexane) to yield carmine crystals of 5-*amino*-2H-*benzimidazole*-2-*spirocyclohexane* (2.75 g, 92.3%), m.p. 190 °C; $\lambda_{max.}$(CH_2Cl_2) 410 (log ε 3.58), 260 (3.92), and 230 (4.26) nm; $\nu_{max.}$(KBr) 3 350 and 3 160 cm^{-1} (NH_2, NH); δ($CDCl_3$; 250 MHz) 7.17 (dd, 1 H, 7-H, $J_{6,7}$ 9.68 Hz, $J_{4,7}$ 0.8 Hz), 6.64 (dd, 1 H, 6-H, $J_{6,7}$ 9.71, $J_{4,6}$ 2.15 Hz), 6.08 (dd, 1 H, 4-H, $J_{4,6}$ 2.12, $J_{4,7}$ 0.8 Hz), 4.35 (s, 2 H, NH_2, D_2O exch.), and 2.05—162 (m, 10 H, C_6H_{10}); *m/z* 201 (M^+) (Found: C, 71.9; H, 7.5; N, 20.3. $C_{12}H_{15}N_3$ requires C, 71.6; H, 7.5; N, 20.8%). The filtrate gave, on evaporation, 2*H*-benzimidazole (**1**; X = H).

(a) *Reaction with diethylamine.* The amine (**1**; X = NH_2) (1 g, 4.99 mmol), diethylamine (5 ml, 48 mmol), and sufficient ethanol to obtain a solution were stirred with activated MnO_2 (5 g) for 24 h. The MnO_2 was filtered off and the solvent and excess of diethylamine were distilled off. Chromatography of the residue (Al_2O_3, ethyl acetate–CH_2Cl_2–EtOH, 7:2:1) gave 5-*amino*-6-*diethylamino*-2H-*benzimidazole*-2-*spirocyclohexane* (**13**; R_2 = Et_2) (63.3%), m.p. 195 °C; $\lambda_{max.}$(MeOH) 360 (log ε 4.12), 260 (4.03), and 220 nm (4.50); $\nu_{max.}$ 3 430, 3 300, and 3 110 cm^{-1} (NH_2, NH); δ($CDCl_3$; 250 MHz) 6.67 (s, 1 H), 6.11 (s, 1 H), 4.78 (s, 2 H, NH_2), 3.06 (q, 4 H, 2 CH_2), 1.95—1.53 (m, 10 H, C_6H_{10}), and 1.09 (t, 6 H, 2 Me); *m/z* 272 (M^+) (Found: C, 70.6; H, 9.05; N, 20.6. $C_{16}H_{24}N_4$ requires C, 70.55; H, 8.9; N, 20.6%).

(b) *Reaction with sodium benzenesulphinate.* Sodium benzenesulphinate (3 g, 18.27 mmol) in water (10 ml) was added to a solution of the amino compound (**1**; X = NH_2) (1.5 g, 7.48 mmol) in acetone (150 ml) and acetic acid (0.43 ml, 7.51 mmol) in one portion. The reaction mixture was stirred for 4 h in the dark. The volume of the mixture was reduced to 30 ml by distillation and the precipitate, after collection, recrystallised (toluene) to give 5-*amino*-2,3-*dihydro*-6-*phenylsulphonylbenzimidazole*-2-*spirocyclohexane* (**17**) (87.5%), m.p. 155 °C; $\nu_{max.}$(KBr) 3 470, 3 370, and 3 080 cm^{-1} (NH_2); δ($CDCl_3$; 250 MHz) 7.89 (m, 2 H, ArH), 7.47 (m, 3 H, ArH), 6.90 (s, 1 H), 5.71 (s, 1 H), 4.83 (s, 3 H, NH_2 and NH), 4.42 (s, 1 H, NH), and 1.69—1.43 (m, 10 H, C_6H_{10}); *m/z* 343 (M^+) (Found: C, 63.1; H, 6.1; N, 12.1. $C_{18}H_{21}N_3O_2S$ requires C, 62.95; H, 6.2; N, 12.2%).

Heterocycles from 2H-*Benzimidazoles.*—(a) *Quinoxalines.* The 5-amino-6-phenylsulphonyldihydrobenzimidazole (**17**) (1 g, 2.91 mmol) was hydrolysed as a suspension in methanol–water (1:1; 50 ml) at 60 °C for 20 min to the corresponding *o*-phenylenediamine. Aqueous glyoxal (2.25 ml, 40%) and sodium hydrogen sulphite (2.62 g) dissolved in water (12.5 ml) were added all at once. The reaction mixture was kept on a hot water-bath for 5 min and then allowed to cool to room temperature. The product was extracted with ether (3 × 100 ml), the extract

evaporated, and the residue chromatographed (Al_2O_3, ethyl acetate) to give the yellow *6-amino-7-phenylsulphonylquinoxaline* (**15**; R = SO_2Ph) (54.8%), m.p. 156 °C; $\nu_{max.}$(KBr) 3 460 and 3 370 cm^{-1} (NH_2); δ([$^2H_6$] DMSO; 250 MHz) 8.79 (d, 1 H, J_{H_a,H_b} 1.78 Hz), 8.66 (d, 1 H, J_{H_a,H_b} 1.78 Hz), 8.56 (s, 1 H, 8-H), 8.10 (m, 2 H, ArH), 7.59 (m, 3 H, ArH), 7.25 (s, 1 H, 5-H), and 6.52 (s, 2 H, NH_2); *m/z* 286 (M^+) (Found: C, 58.8; H, 3.9; N, 14.6. $C_{14}H_{11}N_3O_2S$ requires C, 58.9; H, 4.0; N, 14.7%). A solution of 5-amino-6-morpholino-2*H*-benzimidazole (1.63 g, 5.69 mmol, *cf.* Table 2, No. 7) in methanol–water (1:1; 60 ml) was reduced in an ice-bath by addition of sodium dithionite (25 g, 143.6 mmol) with vigorous stirring for 1 h. Extraction of the mixture with dichloromethane (4 × 100 ml) and evaporation under reduced pressure of the combined organic extracts left a brown crystalline solid. This was treated immediately with an aqueous solution of glyoxal (40%; 2.25 ml) and water (12.5 ml) and sodium hydrogen sulphite as described for the above preparation except for the final extraction which was with dichloromethane (5 × 100 ml). The *6-amino-7-morpholinoquinoxaline* (**15**; R = morpholino) was obtained as yellow crystals (toluene–hexane) (56.5%), m.p. 170 °C; $\lambda_{max.}$(MeOH) 395 (log ε 3.74), 2.90 (3.88), 270 (4.36), and 250 nm (4.54); $\nu_{max.}$(KBr) 3 450, 3 300, and 3 200 cm^{-1} (NH_2); δ([$^2H_6$] DMSO; 250 MHz) 8.55 (d, 1 H, $J_{2,3}$ 2.0 Hz), 8.46 (d, 1 H, $J_{2,3}$ 2.0 Hz), 7.37 (s, 1 H), 3.10 (s, 1 H), 5.79 (s, 2 H, NH_2), 3.84 (m, 4 H, 2 CH_2), and 2.99 (m, 4 H, 2 CH_2); *m/z* 230 (M^+) (Found: C, 62.7; H, 6.7; N, 24.3. $C_{12}H_{14}N_4O$ requires C, 62.6; H, 6.1; N, 24.3%).

(b) *Phenazine* (**16**). Reduction of the 5-amino-6-morpholino-2*H*-benzimidazole (1.4 g, 4.89 mmol) with $Na_2S_2O_4$ (30 g) was carried out as above. Addition to a suspension of the residue in ethanol (15 ml) of 9,10-phenanthraquinone (1.1 g, 5.28 mmol) dissolved in hot acetic acid gave a yellow precipitate which was purified (SiO_2, CH_2Cl_2–ethyl acetate, 9.5:0.5) to give *11-amino-12-morpholinodibenzo*[a, c]*phenazine* (**16**) (36.6%), m.p. 300 °C; $\lambda_{max.}$(MeOH) 440 (log ε 4.21), 405 (4.10), 325 (4.57), 280 (4.52), 255 (4.57), and 235 nm (4.57); $\nu_{max.}$ 3 420, 3 300, and 3 080 cm^{-1} (NH_2); *m/z* 380 (M^+); δ($CDCl_3$; 250 MHz), 9.52 (m, 1 H), 9.36 (m, 1 H), 8.63 (m, 2 H), 7.79 (m, 5 H), 6.44 (s, 2 H, NH_2), 5.62 (s, 1 H), 3.79 (m, 4 H, 2 CH_2), and 3.04 (m, 4 H, 2 CH_2) (Found: C, 75.8; H, 5.3; N, 14.7. $C_{24}H_{20}N_4O$ requires C, 75.8; H, 5.3; N, 14.7%).

(c) *Benzimidazole* (**14**; R^2 = $[CH_2]_2O[CH_2]_2$). An aqueous methanolic solution (50 ml; MeOH:H_2O, 1:1) of 5-amino-6-morpholino-2*H*-benzimidazole (Table 2, No. 7; 1.0 g, 3.49 mmol) was kept in an ice-bath, mixed with sodium dithionite (15 g, 86.15 mmol), and vigorously agitated for 1 h. The reaction mixture was allowed to reach ambient temperature and then extracted with dichloromethane (3 × 50 ml). The combined extracts were washed (water, 30 ml), dried ($MgSO_4$), and finally concentrated to 5 ml. Addition of light petroleum produced a brown precipitate which was separated and immediately treated with formic acid for 1 h under reflux. Addition of water (30 ml) followed by adjustment of the pH (9—10) with Na_2CO_3 gave a precipitate which on chromatography (Al_2O_3, ethyl acetate) furnished *6-formamido-5-morpholinobenzimidazole* (**14**; R^2 = $[CH_2]_2O[CH_2]_2$), (47.7%), m.p. 215 °C; $\nu_{max.}$ 3 440 (NH) and 1 670 cm^{-1} (CO); *m/z* 246 (M^+); δ([$^2H_6$] DMSO; 250 MHz) 9.48 (s, 1 H, NH), 8.49 (s, 1 H, 7-H), 8.45 (d, CHO, $J_{8,9}$ 1.85 Hz), 8.15 (s, 1 H, 2-H), 7.46 (s, 1 H, 4-H), 3.84 (m, 4 H, 2 CH_2), 3.4 (s, 1 H, N*H*CHO), and 2.82 (m, 4 H, 2 CH_2) (Found: C, 58.4; H, 5.7; N, 22.3. $C_{12}H_{14}N_4O_2$ requires C, 58.5; H, 5.7; N, 22.75%).

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