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Some Branched-chain Analogues of Analgesically Active 1-(2-Aminoethyl)-2-benzylbenzimidazole Derivatives

By A. F. Casy and J. Wright

The synthesis of some 1-(2-aminopropyl)-2-benzyl(and 4-ethoxybenzyl)benzimidazoles is reported. A p.m.r. study of the alkylation of 2-benzylbenzimidazole with 2-chloro-1-dimethylaminopropane shows that reactions of this type represent a practicable route to 1-(2-aminopropyl)benzimidazoles, since the 1-(2-amino-1-methylethyl)-isomer forms only a small percentage of the reaction product.

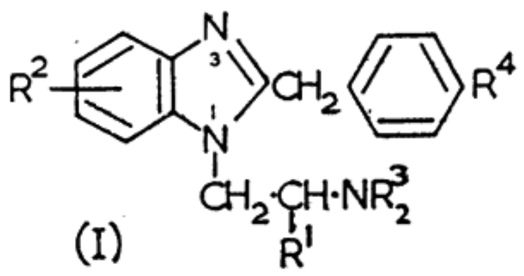
A NEW class of potent analgesics (I) related to 2-benzylbenzimidazole, was described in 1957.[1] In an attempt to delineate structural features common to active 2-benzylbenzimidazole derivatives and to diphenylpropylamine analgesics, such as methadone (II; R = Me), the proposal was made that N-1 of the benzimidazole derivatives (I) was equivalent to the CPh_2 quaternary carbon atom of the diphenylpropylamines, and that the 2-aminoethyl substituents linked to N-1 of (I) and CPh_2 of (II) were also equivalent.[2] Since branching of the 2-aminoethyl substituent enhances analgesic activity in diphenylpropylamine derivatives,* a test of the latter of the above proposals would be to examine the effect of chain branching upon the analgesic activities of the benzimidazole derivatives (I; R^1 = H).

* *E.g.*, methadone (II; R = Me), ED_{50} 1·6 mg./kg.; normethadone (II; R = H), ED_{50} 2·5 mg./kg. (in mice; hot-plate test).[2]

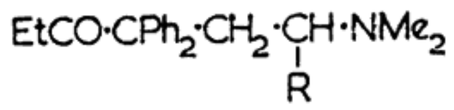
[1] A. Hunger, J. Kebrle, A. Rossi, and K. Hoffmann, *Experientia*, 1957, **13**, 400; F. Gross and H. Turrian, *ibid.*, p. 401.

[2] A. H. Beckett and A. F. Casy, *Prog. Medicin. Chem.*, 1965, **4**, 171.

In this Paper the synthesis of some branched-chain derivatives (I; R^1 = Me) is described.



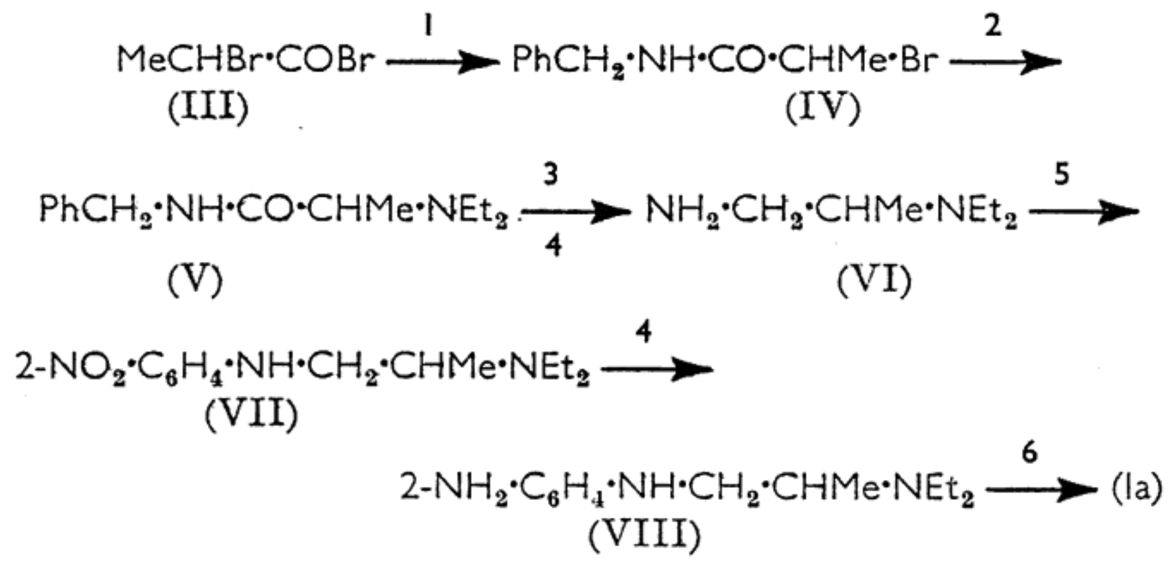
(I)



(II)

a: R^1 = Me, R^2 = H, R^3 = Et, R^4 = OEt
b: R^1 = Me, R^2 = H, R^3 = Me, R^4 = OEt

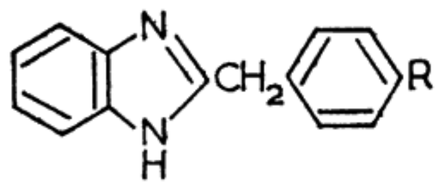
1-(2-Diethylaminopropyl)-2-(4-ethoxybenzyl)benzimidazole (Ia) was obtained by condensing the imine ethyl ether hydrochloride (reagent 6 in Scheme) with the substituted *o*-phenylenediamine (VIII), obtained from the acid bromide of α-bromopropionic acid as outlined in the Scheme. The diamine (VIII) rapidly



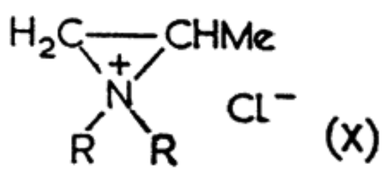
Reagents: 1, $PhCH_2{\cdot}NH_2$; 2, Et_2NH; 3, $LiAlH_4$; 4, Pd–C/H_2; 5, *o*-$Cl{\cdot}C_6H_4{\cdot}NO_2$; 6, 4-$EtO{\cdot}C_6H_4{\cdot}CH_2{\cdot}C(OEt){:}NH_2^+Cl^-$

darkened on exposure to air, so it was freshly prepared for the cyclisation (VIII) to (Ia). 4-Ethoxybenzyl cyanide, the precursor of reagent 6 was obtained by treating the chloromethylation prduct of phenetole with sodium cyanide;[3] in our hands, the cyanide was obtained in low yield when acetone was used as reaction solvent (a yield of 84% has been claimed [3]), and an improved yield resulted when dimethyl sulphoxide was solvent (cf. ref. 4). The structure of the product (a solid, previously reported as a liquid [3]) was confirmed by p.m.r. spectroscopy (its aromatic proton signal was a typical A_2B_2 quartet). 1-Amino-2-diethylamino-propane (VI), an intermediate in the reaction sequence, was prepared more directly by treating 2-chloro-1-diethylaminopropane with potassium phthalimide and cleaving the resultant phthalimido-derivative with hydrazine hydrate. A molecular rearrangement must occur during this reaction, since the product, obtained in 40% yield, was identical with the diamine (VI) made by the previous, unambiguous, method; the isomeric diamine, 2-amino-1-diethylaminopropane, was not detected (cf. the following, analogous, reactions).

Because the route outlined in the Scheme for the synthesis of 1-(2-dialkylaminopropyl)benzimidazole derivatives was lengthy and gave low overall yields, an alternative procedure was investigated, involving alkylation of the 2-benzylbenzimidazole derivatives (IX) with a 2-chloro-1-dialkylaminopropane or the 1-chloro-2-dialkylamino-isomer. Reactions of this type probably



(IX)



(X)

proceed through ions such as (X), and hence may result in binary isomeric mixtures since such intermediates may open in either of two ways.* However, when the sodium salt of the 2-benzylbenzimidazole (IX; R = OEt) was treated with 2-chloro-1-diethylaminopropane, the 1-(2-diethylaminopropyl)benzimidazole (Ia), identical with the product of unambiguous synthesis, was the only material isolated.

To determine whether alkylations of this type generally lead to 1-(2-aminopropyl)- rather than 1-(2-amino-1-methylethyl)-benzimidazole derivatives, a study was made of the alkylation of 2-benzylbenzimidazole (IX; R = H) with 2-chloro-1-dimethylaminopropane, the reaction, in this case, being readily amenable to investigation by p.m.r. spectroscopy (see Table). The p.m.r. spectrum of the total basic product indicated it to be a mixture of the isomers (XI; $R^1 = R^3$ = Me, $R^2 = R^4$ = H) and (XI; $R^2 = R^3$ = Me, $R^1 = R^4$ = H), since dimethylamino and secondary methyl signals were displayed in duplicate, of 11 and 30 cycles separation, respectively (see Table, no. 1). However, one isomer showed a marked preponderance, the isomeric ratio being assessed as approximately 7 : 1 from integral data (average of several results). Although the isomers could not be separated by fractional distillation (Table, no. 2), fractional crystallisation of the corresponding di-hydrochlorides gave a pure sample of the major isomer in high yield (Table, nos. 3 and 4), while the mother-liquors contained increased proportions of the minor isomer (Table, no. 6). P.m.r. evidence for assigning the second structure to the major product and the first structure to the minor isomer is as follows.

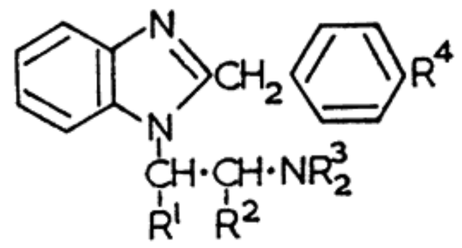
(1) When the side-chain nitrogen atom is protonated,† the secondary methyl signal of the major isomer moves downfield by 12 cycles; in contrast, the secondary methyl chemical shift of the minor isomer has the same value in both the base and mono-hydrochloride (solvent $CDCl_3$ in all cases) (Table, nos. 6 and 7). These results support the 2-aminopropyl structure for the major and the 2-amino-1-methylethyl structure for the minor isomer, since the increase in electronegativity of the side-chain nitrogen atom that results upon proton

* *E.g.*, the alkylation of diphenylacetonitrile with 1-chloro-2-dimethylaminopropane (or isomer) gives approximately equal amounts of 3-dimethylamino-1,1-diphenylbutyl cyanide and 3-dimethylamino-2-methyl-1,1-diphenylpropyl cyanide.[5]

† This atom, rather than the heterocyclic nitrogen atom, must be the site of protonation in the mono-hydrochlorides (Table, no. 7) because the pK_a' values of the two basic centres differ so widely in derivatives of this type [*e.g.*, (I; $R^1 = R^2 = R^4$ = H, R^3 = Me), pK_a' 6·49 (initial), 4·12 (second), in ethanol–water (1 : 1)] (unpublished results).

[3] E. Profft and R. Drux, *J. prakt. Chem.*, 1956, **3**, 274.
[4] L. Friedmann and H. Schechter, *J. Org. Chem.*, 1960, **25**, 877.
[5] E. M. Schultz and J. M. Sprague, *J. Amer. Chem. Soc.*, 1948, **70**, 48.

P.m.r. characteristics of some 1-(2-aminoethyl)-2-benzylbenzimidazoles (XI)



(XI)

No.	Sample	R^1	R^2	R^3	R^4	Solvent	P.m.r. characteristics [a] Aryl	CH_2Ar [b]	NR_2^3	OCH_2Me [c]	sec.Me [d]
1	Total base mixture (undistilled)	H Me	Me H	Me Me	H H	$CDCl_3$	464, 437, 435 [e]	260	133·5 [b] (N*Me*) 122 [b] integral [f] 8 : 1	—	49 (*J* 7) 78·5 (*J* 7) integral [g] 6 : 1
2	Total base mixture (distilled)	H Me	Me H	Me Me	H H	$CDCl_3$	468, 436 [e]	261	135 [b] (N*Me*) 123 [b] integral [f] 6 : 1	—	50 (*J* 7) 80 (*J* 7) integral [g] 9 : 1
3	Pure base from di-hydrochloride	H	Me	Me	H	$CDCl_3$	467, 439	262·5	135 [b] (N*Me*)	—	49·5 (*J* 7)
4	Di-hydrochloride (pure)	H	Me	Me	H	D_2O	492, 478 [e]	314	207·5 [b] (N*Me*)	—	104 (*J* 6·5)
5	Mono-hydrochloride (trace of minor isomer)	H Me	Me H	Me Me	H H	D_2O	480, 462 [e]	279	193 [b] (N*Me*) 182·5 [b]	—	79 (*J* 7) 100 (*J* 7)
6	Base from mother-liquors enriched in minor isomer	H Me	Me H	Me Me	H H	$CDCl_3$	464, 436 [e]	261	135 [b] (N*Me*) 123 [b] integral [f] 1 : 1	—	49 (*J* 7) 80 (*J* 7) integral [g] 4 : 5
7	Mono-hydrochloride of sample no. 6	H Me	Me H	Me Me	H H	$CDCl_3$	475, 442	271·5	163 [b] (N*Me*) 145·5 [b]	—	61 (*J* 6·5) 80 (*J* 6·5)
8	Mono-hydrochloride of sample no. 6	H Me	Me H	Me Me	H H	D_2O	483, 457 [e]	285	193 [b] (N*Me*) 181 [b]	—	78 (*J* 6·5) 101 (*J* 6·5)
9	Base from pure di-hydrochloride (unambiguous synthesis)	H	Me	Et	OEt	$CDCl_3$ $CDCl_3$ $CF_3{\cdot}CO_2H$	468, 438 [e] 435, 426, 414, 405 [h] 470, 441 [e] 438, 428, 414, 405 [h]	258·5 260	55·5 [c] (*J* 7) (NCH_2Me) 65 [c] (*J* 7)	81 (*J* 7) 81 (*J* 7)	52 (*J* 7) 54 (*J* 7)
10	Total base from alkylation synthesis	H	Me	Et	OEt	$CDCl_3$	468, 439 [e] 436, 427·5, 415, 406 [h]	258	56·5 [c] (*J* 7) (NCH_2Me)	82 (*J* 7)	53 (*J* 7)
11	Pure mono-hydrochloride	H	Me	Me	OEt	D_2O	471 [e] 456, 447, 431·5, 422·5 [h]	281	192·5 [b] (N*Me*)	85 (*J* 7)	81 (*J* 7)

[a] Chemical shifts and coupling constants in c./sec. from tetramethylsilane (60 Mc.). [b] Singlet. [c] Triplet. [d] Doublet. [e] Main peak(s) of multiplet. [f] Ratio of lower to higher field signal. [g] Ratio of higher to lower field signal. [h] Peaks of A_2B_2 quartet.

uptake would be expected to have a greater deshielding influence on a methyl group two bonds removed (as in the former structure) than on one three bonds removed from the protonated electronegative centre (as in the latter structure). Comparisons made between bases in $CDCl_3$ and mono-hydrochlorides in D_2O similarly show greater secondary methyl (base/salt) downfield shifts in the case of the major isomer (major 29 c./sec., minor 21 c./sec.; Table, nos. 6 and 8). Here, however, other effects (*e.g.*, solvation differences in $CDCl_3$ and D_2O for the two isomers), as well as electronegativity increases, may influence the observed secondary methyl resonance positions.

(2) The fact that the secondary methyl signal of the minor isomer occurs at a lower field than that of the major form is also in accord with the above assignments. While the secondary methyl groups of both isomers are two bonds removed from an electronegative nitrogen atom, that of the 1-(1-methylethyl)-derivative is subject to an additional deshielding influence, in that it falls well within the paramagnetic shielding zone of the aromatic benzimidazole nucleus (evidence from models).

(3) The chemical shift of the secondary methyl signal of the major isomer (49 c./sec.) is very close to that of 2-methyl in the benzimidazole (Ia) (52 c./sec.) of unambiguous structure. [In the p.m.r. spectrum of the latter compound, the 2-methyl doublet and *N*-ethyl methyl ($N-CH_2Me$) triplet overlap; the two signals may be differentiated, however, from the relative peak heights of the resultant unsymmetrical triplet and from downfield shifts induced on the addition of trifluoroacetic acid (Table, no. 9).]

This study establishes the alkylation of 2-benzylbenzimidazole derivatives (IX) with 1-amino-2-chloropropanes to be a practicable route to 1-(2-aminopropyl)-benzimidazoles (I). The small yield of the 1-(1-methylethyl) isomer which results from this reaction is probably a result of steric factors favouring ethyleneimonium ion (X) opening at CH_2 rather than CHMe, the minor isomer being a highly crowded molecule as a result of interaction between methyl attached to C-1 of the 1-ethyl side-chain and the C-7 aromatic hydrogen atom. The destabilising nature of this interaction is emphasised by the fact that attempts to prepare a hindered derivative of the same type (namely 2-benzyl-1-s-butylbenzimidazole), by reaction between s-butyl bromide and the sodio-derivative of 2-benzylbenzimidazole, failed.

Alkylation of 2-4′-ethoxybenzylbenzimidazole (IX; R = OEt) with 2-chloro-1-dimethylaminopropane gave the 1-(2-dimethylaminopropyl) derivative (Ib), its structure being assigned on the basis of the above study and upon the near-identity of the chemical shifts of the dimethylamino and secondary methyl p.m.r. signals of the product and the corresponding signals of the 2-aminopropyl derivative (XI; $R^2 = R^3 = Me$, $R^1 = R^4 = H$) (Table, nos. 5 and 11). The pharmacology of the described derivatives (I; $R^1 = Me$), together with unbranched analogues (I; $R^1 = H$), will be reported elsewhere.

EXPERIMENTAL

1-(2-*Diethylaminopropylamino*)-2-*nitrobenzene* (VII).—Benzylamine (25 g.) in ether (20 ml.) was added to an ice-cooled, stirred solution of α-bromopropionyl bromide (30 g.) in ether (200 ml.) during 1 hr., and the mixture then stirred at 20° for 4 hr. The benzylammonium bromide which separated was removed by filtration, and the filtrate washed with dilute hydrochloric acid, dried (Na_2SO_4), and evaporated to give N-*benzyl*-α-*bromopropionamide* (IV) (20 g.), m. p. 85° (from ether) (Found: C, 49·4; H, 5·2; N, 5·8. $C_{10}H_{12}BrNO$ requires C, 49·6; H, 5·0; N, 5·8%). The bromo-amide (IV) (10 g.) was added to diethylamine (15·6 g.) in benzene (200 ml.) during 1 hr., and the mixture was heated under reflux for 12 hr. and filtered to remove the precipitated diethylammonium bromide. The filtrate was washed with dilute hydrochloric acid, dried (Na_2SO_4), evaporated, and the residue distilled, to give *N*-benzyl-α-diethylaminopropionamide (9·5 g.), b. p. 120°/0·02 mm. It gave a *picrate*, m. p. 145° (from ethanol) (Found: C, 51·8; H, 5·6; N, 15·4. $C_{20}H_{25}N_5O_8$ requires C, 51·8; H, 5·4; N, 15·1%). The amino-amide (V) (9·25 g.), in ether (50 ml.), was added to a stirred suspension of lithium aluminium hydride (3 g.) in ether (250 ml.). The mixture was heated under reflux for 12 hr., cooled, and decomposed with water (8·4 ml.) followed by dilute sodium hydroxide (8·4 ml.). The ether phase was filtered, dried, and evaporated, and the residue distilled, to give 1-benzylamino-2-diethylaminopropane (3 g.), b. p. 83—85°/0·02 mm. A mixture of the benzylamino-diamine (5 g.), in ethanol (150 ml.), and palladium–charcoal (0·5 g.; 10%) was shaken with hydrogen at room temperature and pressure. When absorption of gas had ceased, the mixture was filtered and the filtrate evaporated and distilled, to give 1-amino-2-diethylaminopropane (VI) (2·5 g.), b. p. 40°/20 mm. (Found: Equiv., 66. Calc. for $C_7H_{18}N_2$: Equiv., 65). It gave a *picrate*, m. p. 120—122° (from ethanol) (Found: C, 43·55; H, 6·2. $C_{13}H_{21}N_5O_7$ requires C, 43·45; H, 5·85%). The diamine (VI) was also obtained as follows. A mixture of 2-chloro-1-diethylaminopropane (93 g.; freshly liberated from the corresponding hydrochloride) and potassium phthalimide (100 g.) in ethanol (100 ml.) was heated under reflux for 24 hr. Potassium chloride was removed by filtration and the filtrate was treated with hydrazine hydrate (30 g.) and heated under reflux for 30 min. The solvent was evaporated under reduced pressure and the residue treated with 5N-hydrochloric acid (200 ml.) and filtered. The filtrate was concentrated under reduced pressure, and the residual hydrochloride made basic with methanolic sodium hydroxide; the product (after removal of methanol) was fractionally distilled, to give 1-amino-2-diethylaminopropane (30 g.), b. p. 40°/20 mm., and 2-chloro-1-diethylaminopropane (20 g.), b. p. 60°/20 mm. The diamine was identical with previously prepared material (i.r. spectrum and picrate).

o-Chloronitrobenzene (5 g.) was added during 30 min. to 1-amino-2-diethylaminopropane (8 g.) maintained at 140°. The mixture was then heated under reflux for 4 hr., cooled, made alkaline with aqueous ammonia, and extracted with ether. The dried extract was evaporated, and the residue crystallised from ethanol to give 1-(2-*diethylaminopropylamino*)-2-*nitrobenzene* (4 g.), m. p. 30° (Found: C, 62·35; H, 8·2; N, 16·8%; Equiv., 252. $C_{13}H_{21}N_3O_2$ requires C, 62·2; H, 8·35; N, 16·7%; Equiv., 251).

1-(2-*Diethylaminopropyl*)-2-(4-*ethoxybenzyl*)*benzimidazole* (Ia).—An ice-cooled mixture of 4-ethoxybenzyl cyanide (2 g.), ethanol (1 ml.), and chloroform (20 ml.) was saturated with hydrogen chloride and left overnight at room temperature. The mixture was evaporated under reduced pressure and the residual imino-ether hydrochloride dissolved in chloroform (20 ml.). A mixture of 1-(2-diethylaminopropylamino)-2-nitrobenzene (4 g.) in ethanol (75 ml.) and palladium–charcoal (0·5 g.; 10%) was shaken with hydrogen at room temperature and pressure until the theoretical volume of hydrogen had been absorbed. The product was filtered and the filtrate evaporated, to give impure 2-(2-diethylaminopropylamino)aniline (VIII) as a pale yellow oil which rapidly darkened on exposure to air. This product was added to the imino-ether in chloroform (see above), and the mixture heated under reflux for 12 hr. and then made alkaline with aqueous ammonia. The organic phase was dried (Na_2SO_4) and evaporated, to give impure 1-(2-diethylaminopropyl)-2-(4-ethoxybenzyl)benzimidazole (1 g.). It gave a *di-hydrochloride* (1·2 g.), m. p. 147—149° (from ethanol–ether) (Found: C, 58·4; H, 7·85; Cl, 14·45; N, 8·9%; Equiv., 245. $C_{23}H_{33}Cl_2N_3O,2H_2O$ requires C, 58·2; H, 7·8; Cl, 14·9; N, 8·9%; Equiv., 237), $\nu_{max.}$ 3400 cm.$^{-1}$ (H_2O). 4-Ethoxybenzyl cyanide, used in the above synthesis, was prepared as follows. 4-Ethoxybenzyl chloride [3] (50 g.) was added to a cooled, stirred suspension of sodium cyanide (15 g.) in dimethyl sulphoxide (100 ml.) during 20 min. The mixture was stirred for a further 1 hr., filtered, and evaporated under reduced pressure. The residue, in ether, was washed with dilute hydrochloric acid, and the ether dried ($MgSO_4$), and evaporated. The residue was distilled, to give 4-ethoxybenzyl chloride (9 g.), b. p. 120°/12 mm., and 4-ethoxybenzyl cyanide (30 g.), b. p. 140°/12 mm., m. p. 40° (from chloroform) (Found: C, 74·4; H, 6·8; N, 8·7. Calc. for $C_{10}H_{11}NO$: C, 74·5; H, 6·8; N, 8·7%). P.m.r. characteristics in CCl_4: 434, 426, 412, 404 c./sec. (A_2B_2 quartet, 4 aryl protons); 237 c./sec. (quartet, $J = 7$, OCH_2Me); 212 c./sec. (singlet, CH_2CN); 82 c./sec. (triplet, $J = 7$, OCH_2Me). The cyanide was obtained in very low yield (1 g. from 50 g. of 4-ethoxybenzyl chloride) when acetone was used as reaction solvent.

Alkylation of 2-*Benzylbenzimidazole* (IX; R = H) *with* 2-*Chloro*-1-*dimethylaminopropane*.—Sodamide (1·3 g.) was added to a stirred suspension of 2-benzylbenzimidazole [6] (6·2 g.) in dioxan (55 ml.), and the mixture heated under reflux for 24 hr. 2-Chloro-1-dimethylaminopropane (4·4 g.), freshly liberated from the hydrochloride and distilled, was added to the product, cooled to 60°, and the mixture maintained at this temperature for 16 hr., and then filtered. The filtrate was concentrated under reduced pressure,

[6] A. Hunger, J. Kebrle, A. Rossi, and K. Hoffmann, *Helv. Chim. Acta*, 1960, **43**, 800.

and the residue that remained was dissolved in concentrated hydrochloric acid, extracted twice with ether, made alkaline with aqueous ammonia, and extracted with chloroform. The chloroform was dried ($MgSO_4$) and evaporated, to give a residue (total base of Table, no. 1) which distilled at 224°/0·5 mm. (distilled base of Table, no. 2). The distillate, with an excess of ethanolic hydrogen chloride, gave 2-*benzyl*-1-(2-*dimethylaminopropyl*)*benzimidazole dihydrochloride* (5 g.), m. p. 215—220° (decomp.) (from ethanol) (Found: C, 62·25; H, 6·9; N, 11·5. $C_{19}H_{25}Cl_2N_3$ requires C, 62·3; H, 6·8; N, 11·5%). A *mono-hydrochloride*, m. p. 191—193° (Found: C, 69·3; H, 7·3; N, 12·9. $C_{19}H_{24}ClN_3$ requires C, 69·3; H, 7·3; N, 12·8%), was also prepared (see Table nos. 4 and 5, for p.m.r. characteristics of these salts). The mother-liquors remaining after several crops of the di-hydrochloride had been separated were evaporated, and the residue (isolated as the free base) examined by p.m.r. spectroscopy (Table no. 6). This base was treated with 1 mol. of ethanolic hydrogen chloride, evaporated, and residual mono-hydrochloride mixture (dried in a desiccator) also examined by p.m.r. spectrosopy (Table nos. 7 and 8).

2-(4-*Ethoxybenzyl*)*benzimidazole* (IX; R = OEt).—4-Ethoxybenzyl cyanide (20 g.) was converted into the corresponding imino-ether hydrochloride, as described above, and the product dissolved in a solution of *o*-phenylenediamine (16 g.) in chloroform (50 ml.). The mixture was heated under reflux for 24 hr. and then made alkaline with aqueous ammonia. The chloroform was separated, washed with water, dried ($MgSO_4$), and evaporated, to give the *product* (15 g.), m. p. 190—192° (from ethanol) (Found: C, 76·1; H, 6·35; N, 11·1%; Equiv., 254. $C_{16}H_{16}N_2O$ requires C, 76·2; H, 6·35; N, 11·1%; Equiv., 252).

Alkylation of 2-(4-*Ethoxybenzyl*)*benzimidazole with* 1-*Amino*-2-*chloropropanes*.—Reaction between sodamide, 2-(4-ethoxybenzyl)benzimidazole (12·4 g.), and 2-chloro-1-diethylaminopropane [7] (9 g.), by the method described for the alkylation of 2-benzylbenzimidazole with 2-chloro-1-dimethylaminopropane, gave 1-(2-diethylaminopropyl)-2-(4-ethoxybenzyl)benzimidazole (Ia) (15 g.), which formed a dihydrochloride, m. p. and mixed m. p. 147—149°. Its i.r. and p.m.r. spectra were identical with those of the sample prepared by the unambiguous route. Alkylation of 2-(4-ethoxybenzyl)benzimidazole (8 g.) with 2-chloro-1-dimethylaminopropane (6 g.) gave 1-(2-*dimethylaminopropyl*)-2-(4-*ethoxybenzyl*)*benzimidazole* (Ib), isolated as a *mono-hydrochloride* (9 g.), m. p. 146—148° (from ethanol–ether) (Found: C, 62·25; H, 7·6; N, 10·0. $C_{21}H_{28}ClN_3O,2H_2O$ requires C, 61·55; H, 7·8; N, 10·25%), $\nu_{max.}$ 3400 cm.$^{-1}$ (H_2O).

The p.m.r. spectra were recorded on a Varian A-60 instrument with tetramethylsilane as internal standard; we thank Miss J. Lovenack, School of Pharmacy, University of London, for carrying out these measurements, and Dr. H. Keberle for advice in synthesising the diamine (VI).

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