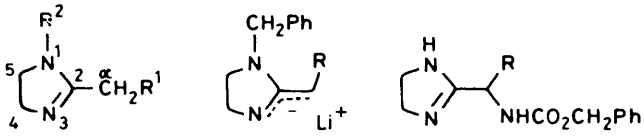
Dihydroimidazoles in Synthesis: *C*-Alkylation of 1-Benzyl-2-(α-lithioalkyl)-4,5-dihydroimidazoles and a Synthesis of Alkanoic Acids

Michael W. Anderson and Raymond C. F. Jones *
Department of Chemistry, The University, Nottingham NG7 2RD
John Saunders
I.C.I. Ltd., Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire SK10 4TG

1-Benzyl-2-alkyl-4,5-dihydroimidazoles have been (laterally) metallated and *C*-alkylated by reaction with alkyl halides and an epoxide; intramolecular *C*-alkylation has led to a tetrahydro-5*H*-pyrrolo-[1,2-*a*]imidazole. Hydrolysis of the 4,5-dihydroimidazoles to produce alkanoic acids completes a homologation sequence.

The use of heterocyclic systems as vehicles for the transfer of functionalised carbon atoms and for the formation of carbon–carbon bonds is a well-established part of modern methodology.[1] In Nature it is a cyclic amidine, a 4,5-dihydroimidazole, that is involved in the transfer of functionalised carbon at various oxidation levels through the tetrahydrofolate coenzymes such as N^5,N^{10}-methenyltetrahydrofolate.[2] We have sought to develop synthetic methods patterned on the biological processes involving dihydroimidazoles, and to this end have been exploring the chemistry of dihydroimidazoles (**1**).[3] A further factor in this programme is the well-established pharmaceutical importance of dihydroimidazoles, especially in the cardiovascular area.[4] We now detail the preparation and *C*-alkylation of 2-(α-lithioalkyl)-4,5-dihydroimidazoles (**2**), and the conversion of the products into alkanoic acids.[5]



(**1**) (**2**) (**3**)

(**4**) (**5**)

a; R = Me
b; R = Et
c; R = $(CH)_2Me$
d; R = $(CH_2)_4Me$
e; R = $(CH_2)_8Me$
f; R = CH_2CHMe_2
g; R = $(CH_2)_2CH{=}CMe_2$
h; R = $(CH_2)_2Ph$
i; R = $CHMe(CH_2)_7Me$
j; R = $CH[(CH_2)_3Me](CH_2)_7Me$
k; R = $CH(CHMe_2)(CH_2)_7Me$
l; R = $CH(CH_2Ph)(CH_2)_7Me$
m; R = $(CH_2)_2CHOHMe$

Results and Discussion

Although the labile nature of the α-hydrogen atoms in (**1**) can be recognised in some earlier reports,[6] *e.g.* the racemisation and exchange of α-hydrogen for deuterium in the dihydroimidazoles (**3**),[6a] α-metallation has not been reported. As a substrate for our studies we chose 1-benzyl-2-methyl-4,5-dihydroimidazole (**4a**), easily and efficiently prepared from *N*-benzylethanediamine and ethyl acetimidate hydrochloride.[3c] The benzyl masking group at N-1 was designed to allow removal at a later stage. Treatment of (**4a**) with D_2O in tetrahydrofuran (THF) at 20 °C confirmed the lability of the methyl protons, as rapid deuterium incorporation was observed, with consequent decrease in the signal at δ 2.0 in the ^1H n.m.r. spectrum. Lithiation was easily achieved using butyl-lithium in THF at −78 °C, and the formation of (**2**; R = H) was marked by the development of a pale orange to red colouration. *C*-Alkylation of the lithiodihydroimidazole was carried out by addition of an alkyl halide (1 mol equiv.) at −78 °C, allowing the mixture to warm to 20 °C and maintaining it at that temperature until reaction was complete. Aqueous work-up and distillation afforded the 1-benzyl-2-alkyl-4,5-dihydroimidazoles (**4b**—**h**) in good yields (Table, entries 1—9). The observed differences in reactivity between alkyl halides are as expected. When an excess of alkyl halide is employed, the expected *N*-alkylation accompanies *C*-alkylation; for example use of iodomethane (3 mol equiv.) led to separation of the solid quaternary salt (**5**).

Metallation of a methylene rather than a methyl group to afford (**2**; R ≠ H), and the potential for two successive *C*-alkylations of the 2-methyl compound (**4a**), was demonstrated by a series of experiments using 1-benzyl-2-nonyl-4,5-dihydroimidazole (**4e**). Lithiation and treatment with an alkyl halide as before, with work-up after 2 h at 20 °C, led to mixtures shown (g.l.c.) to consist of recovered (**4e**) and new products, identified after distillation as the desired *C*-alkylated materials, (**4i**—**l**) (Table, entries 10—13); reaction times were not further optimised and the yields are estimated from g.l.c. Two successive *C*-alkylations of the 2-methyldihydroimidazole (**4a**) in 'one-pot', using iodomethane followed by 1-iodo-octane or *vice versa* as the electrophiles, did indeed afford a product containing predominantly the dialkylated compound (**4i**) along with unchanged (**4a**) and mono-*C*-alkylated products.

The lithiodihydroimidazole (**2**; R = H) also reacts with 2-methyloxirane to produce the hydroxy adduct (**4m**) (Table, entry 14), along with some unchanged (**4a**) (separated by column chromatography) even after an extended reaction time. 2-Phenyloxirane produces the two possible hydroxy adducts but these have not been fully characterised, whilst 2-propyl- and 2-pentyl-oxiranes led to recovery of (**4a**) and extensive polymerisation of the epoxides.

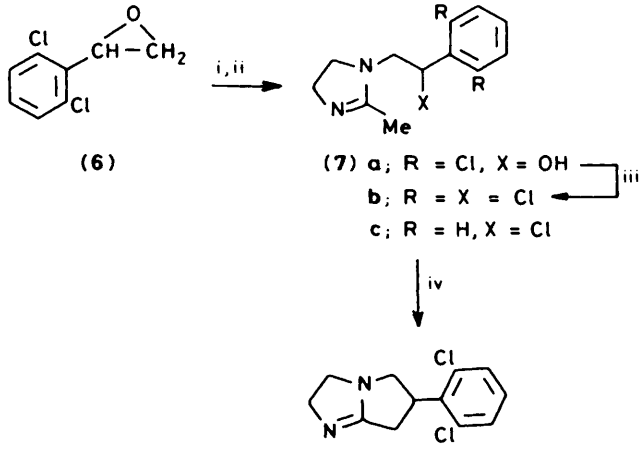
We have applied our *C*-alkylation methodology to the

Table. *C*-Alkylation of lithiodihydroimidazoles

Entry	Substrate	Electrophile	Product	Reaction t at 20 °C	Yield (%)
1	(**4a**)	MeI	(**4b**)	2 h	85
2	(**4a**)	EtI	(**4c**)	2 h	89
3	(**4a**)	BuI	(**4d**)	2 h	82
4	(**4a**)	BuBr	(**4d**)	5 h	79
5	(**4a**)	$Me(CH_2)_7I$	(**4e**)	4 h	88
6	(**4a**)	Pr^iI	(**4f**)	4 h	88
7	(**4a**)	$Me_2C{=}CHCH_2Br$	(**4g**)	2 h	84
8	(**4a**)	$PhCH_2Br$	(**4h**)	4 h	78
9	(**4a**)	$c\text{-}C_6H_{11}I$		2 h	0
10	(**4e**)	MeI	(**4i**)	2 h	68[a]
11	(**4e**)	BuI	(**4j**)	2 h	82[a]
12	(**4e**)	Pr^iI	(**4k**)	2 h	84[a]
13	(**4e**)	$PhCH_2Br$	(**4l**)	2 h	56[a]
14	(**4a**)	MeCHCH$_2$O	(**4m**)	18 h	53[b]

[a] Estimated from g.l.c. [b] Some unchanged (**4a**) recovered (see Experimental section).

synthesis of a pharmacologically interesting bicyclic dihydroimidazole (Scheme). 2-(2,6-Dichlorophenyl)oxirane (**6**) was



Scheme. *Reagents*: i, $H_2N(CH_2)_2NH_2$; ii, $MeC(OEt){=}\overset{+}{N}H_2C\bar{l}$; iii, $SOCl_2$; iv, $LiNPr^i_2$

treated successively with 1,2-diaminoethane and ethyl acetimidate hydrochloride to give the dihydroimidazole (**7a**). Reaction of the chloride (**7b**) [prepared from (**7a**) with thionyl chloride] with lithium di-isopropylamide in THF (−60 to −10 °C) afforded the tetrahydro-5*H*-pyrrolo[1,2-*a*] imidazole (**8**) *via* intramolecular *C*-alkylation. Use of butyl-lithium as base also led to (**8**), but in this case some elimination to produce the *N*([2-(2,6-dichlorophenyl)ethenyl]dihydroimidazole was observed. [Compound (**8**) has been reported to be a centrally acting antihypertensive agent.[7]] A similar cyclisation of the unsubstituted phenyl analogue (**7c**) was not successful, giving instead mainly the product of β-elimination; the difference in behaviour of (**7b**) and (**7c**) is possibly attributable to conformational differences.

The potential of dihydroimidazoles as precursors of alkanoic acids, and hence formal completion of a homologation with 1-benzyl-2-methyl-4,5-dihydroimidazole (**4a**) to provide a two-carbon unit, was demonstrated by the production of hexanoic and decanoic acids from the 2-pentyl and 2-nonyl compounds, (**4d**) and (**4e**), respectively, upon hydrolysis with 66% sulphuric acid. A rather more mild alternative procedure applied to (**4e**) involved first basic attack (0.0375M-sodium hydroxide in ethanol[8]) to give *N*-(2-benzylaminoethyl)decylamide [$PhCH_2NH(CH_2)_2NHCO(CH_2)_8Me$], followed by acidic hydrolysis with 6M hydrochloric acid. Dihydroimidazoles (**4d**) and (**4e**) were stable to dilute (2M) hydrochloric acid and were hydrolysed only slowly by 6M hydrochloric acid at 100 °C;[9] this resistance to acidic hydrolysis has been noted elsewhere[6c,8,10] and attack on a diprotonated species has been shown to be the rate-determining step.[10b,11]

Finally, removal of the masking benzyl group at N-1 could be efficiently achieved by sodium–ammonia reduction; the 2-nonyl compound (**4e**), for example, afforded 2-nonyl-4,5-dihydroimidazole (**1**; $R^1 = (CH_2)_8Me$, $R^2 = H$) in good yield.*

Experimental

General directions are as in our earlier publication,[3c] with the following addition. G.l.c. was performed using a Pye Unicam 104 instrument with a 5 ft glass column packed with 10% Carbowax 20M (5% potassium hydroxide washed), oven temperature 250—255 °C.

C-Alkylation of Lithiodihydroimidazoles: 1-*Benzyl-2-ethyl-4,5-dihydroimidazole* (**4b**).—To 1-benzyl-2-methyl-4,5-dihydroimidazole (**4a**)[3c] (1.85 g, 10.6 mmol) in dry THF (15 ml) stirred at −78 °C under nitrogen was added butyl-lithium (1.23 M solution in hexane; 9.5 ml, 11.7 mmol). After 1 h iodomethane (1.66 g, 11.7 mmol) was added dropwise, the temperature being maintained at −78 °C; the mixture was then allowed to warm to 20 °C over 1 h and then stirred for a further 2 h at 20 °C. The solution was then concentrated under reduced pressure and the residue partitioned between chloroform (50 ml) and ice–water (50 ml). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give a residue that was subjected to Kugelrohr distillation (oven temperature 110—115 °C) at 0.1 mmHg to afford the *title compound* (**4b**) (1.7 g, 85%) as a colourless oil (Found: M^+, 188.1315. $C_{12}H_{16}N_2$ requires *M*, 188.1313); $\nu_{max.}$(film) 2 900, 1 610, and 1 500 cm^{-1}; δ 1.3 (3 H, t, Me), 2.3 (2 H, q, CH_2Me), 3.1—3.8 (4 H, 2t, NCH_2CH_2N), 4.3 (2 H, s, CH_2Ph), and 7.25 (5 H, s, Ph); *m/z* 188 (M^+), 187, 133, 120, 106, and 91 (100%). For compound (**4b**) and the other simple 2-alkyl-1-benzyl-4,5-dihydroimidazoles (**4c**—**l**) described below it did not prove possible, despite repeated distillations and attempts at salt formation (and presumably because of their hygroscopic nature), to obtain satisfactory combustion analyses. The purity of these materials was, however, confirmed by g.l.c. examination (see general directions) when only one peak was observed.

The dihydroimidazoles (**4c**—**h**) were prepared as above from (**4a**) and the appropriate alkyl halide (Table, entries 2—8). Reaction times at 20 °C and yields are also given in the Table, whilst distillation (oven temperature and pressure) and spectroscopic data were as follows:

1-*Benzyl-2-propyl-4,5-dihydroimidazole* (**4c**). 120—124 °C at 0.1 mmHg (Found: M^+, 202.1491. $C_{13}H_{18}N_2$ requires *M*, 202.1469); $\nu_{max.}$(film) 2 900, 2 800, 1 610, 1 500, and 1 450 cm^{-1}; δ 1.1 (3 H, t, Me), 1.5—1.9 (2 H, m, CH_2Me), 2.3 (2 H, t, CH_2), 3.1—3.8 (4 H, 2t, NCH_2CH_2N), 4.3 (2 H, s, CH_2Ph), and 7.25 (5 H, s, Ph); *m/z* 202 (M^+), 201, 188, 187, 174, 173, 148, and 91 (100%).

* Experiments with silyl masking functions at N-1 did not prove useful; the 1-trimethylsilyl-2-methyl compound (**1**; $R^1 = H$, $R^2 = SiMe_3$) was too moisture sensitive for our purposes, and whilst the more stable 1-t-butyldimethylsilyl derivative (**1**; $R^1 = H$, $R^2 = SiMe_2Bu^t$) did undergo α-lithiation and *C*-alkylation, yields were only moderate and non-reproducible.

1-*Benzyl*-2-*pentyl*-4,5-*dihydroimidazole* (**4d**). 126—130 °C at 0.1 mmHg (Found: M^+, 230.1797. $C_{15}H_{22}N_2$ requires M, 230.1782); $\nu_{max.}$(film) 2 900, 2 850, 1 610, 1 500, and 1 460 cm^{-1}; δ 0.9 (3 H, t, Me), 1.5 (4 H, m, 2 × CH_2), 1.8 (2 H, m, CH_2), 2.3 (2 H, t, CH_2), 3.1—3.9 (4 H, 2t, NCH_2CH_2N), 4.3 (2 H, s, CH_2Ph), and 7.25 (5 H, s, Ph); *m/z* 230 (M^+), 187, 174, 173, and 91 (100%).

1-*Benzyl*-2-*nonyl*-4,5-*dihydroimidazole* (**4e**). 162—166 °C at 0.2 mmHg (Found: M^+, 286.2411. $C_{19}H_{30}N_2$ requires M, 286.2408); $\nu_{max.}$(film) 2 900, 2 850, 1 610, 1 500, and 1 460 cm^{-1}; δ 0.9 (3 H, t, Me), 1.2 (12 H, br s, 6 × CH_2), 1.7 (2 H, m, CH_2), 2.3 (2 H, t, CH_2), 3.1—3.9 (4 H, 2t, NCH_2CH_2N), 4.3 (2 H, s, CH_2Ph), and 7.25 (5 H, s, Ph); *m/z* 286 (M^+), 174, 173, 133, 120, and 91 (100%).

1-*Benzyl*-2-*isobutyl*-4,5-*dihydroimidazole* (**4f**). 155—160 °C at 0.4 mmHg (Found: M^+, 217.1719. $C_{14}H_{21}N_2$ requires M, 217.1704); $\nu_{max.}$(film) 2 900, 2 850, 1 610, 1 500, and 1 460 cm^{-1}; δ 1.0 (6 H, d, $CHMe_2$), 2.1—2.2 (3 H, br s and m, CH_2 and CH), 3.1—3.9 (4 H, 2t, NCH_2CH_2N), 4.3 (2 H, s, CH_2Ph), and 7.25 (5 H, s, Ph); *m/z* 217 (M^+), 216, 201, 174, 173, and 91 (100%).

1-*Benzyl*-2-(4-*methylpent*-3-*enyl*)-4,5-*dihydroimidazole* (**4g**). 60—65 °C at 0.05 mmHg (Found: M^+, 242.1799. $C_{16}H_{22}N_2$ requires M, 242.1788); $\nu_{max.}$(film) 2 900, 2 820, 1 610, 1 500, and 1 450 cm^{-1}; δ 1.6 and 1.7 (each 3 H, s, Me), 2.4 (4 H, br s, CH_2CH_2), 3.1—3.9 (4 H, 2t, NCH_2CH_2N), 4.3 (2 H, s, CH_2Ph), 5.2 (1 H, br t, CH), and 7.25 (5 H, s, Ph); *m/z* 242 (M^+), 188, 174, 173, 120, and 91 (100%).

1-*Benzyl*-2-*phenethyl*-4,5-*dihydroimidazole* (**4h**). 70—75 °C at 0.05 mmHg (Found: M^+, 264.1618. $C_{17}H_{18}N_2$ requires M, 264.1626); $\nu_{max.}$(film) 3 000, 2 900, 2 810, 1 610, 1 500, and 1 420 cm^{-1}; δ 2.5—3.2 (4 H, m, CH_2CH_2), 3.2—3.8 (4 H, 2t, NCH_2CH_2N), 4.2 (2 H, s, CH_2Ph), and 7.25 (10 H, s, 2 × Ph); *m/z* 264 (M^+), 263, 120, and 91 (100%).

1-*Benzyl*-2-*ethyl*-3-*methyl*-4,5-*dihydroimidazolium Iodide* (**5**).—This compound was prepared from 1-benzyl-2-methyl-4,5-dihydroimidazole (**4a**) by the method described above for the preparation of (**4b**), but using an excess of iodomethane (3 mol equiv.). After the mixture had been stirred at 20 °C for 18 h, the solid was filtered off, washed with ether, and dried to afford the 4,5-*dihydroimidazolium salt* (**5**) (88%) as a yellow solid, m.p. 83—85 °C (from aqueous ethanol) (Found: C, 42.35; H, 6.15; N, 7.6%. $C_{13}H_{19}N_2I{\cdot}2H_2O$ requires C, 42.65; H, 6.35; N, 7.65%); $\nu_{max.}$(Nujol) 3 400br (H_2O) and 1 615 cm^{-1}; δ[$(CD_3)_2SO$] 1.13 (3 H, t, $MeCH_2$), 2.84 (2 H, q, CH_2Me), 3.2 (3 H, s, MeN), 3.3—3.4 (br, H_2O), 3.7—3.9 (4 H, m, NCH_2CH_2N), 4.84 (2 H, s, CH_2Ph), and 7.52 (5 H, s, Ph).

C-Alkylation of 1-*Benzyl*-2-*nonyl*-4,5-*dihydroimidazole* (**4e**).—The alkylation was performed by the method described above for the preparation of (**4b**), from (**4e**) and the appropriate alkyl halide (Table, entries 10—13). After 2 h at 20 °C the reaction mixture was worked up to afford a pale yellow oil (85—95%) shown by g.l.c. to contain the starting 4,5-dihydroimidazole (**4e**) and a new material, a sample of which was obtained on Kugelrohr distillation (oven temperature 180—200 °C) at 0.2 mmHg and shown to be the desired dihydroimidazoles (**4i**—**l**). The yields estimated from g.l.c. are given in the Table whilst the spectroscopic data were as follows.

1-*Benzyl*-2-(1-*methylnonyl*)-4,5-*dihydroimidazole* (**4i**). (Found: M^+, 300.2572. $C_{20}H_{32}N_2$ requires M, 300.2565); $\nu_{max.}$(film) 2 950, 2 900, 2 850, 1 610, 1 495, 1 460, and 1 450 cm^{-1}; δ 0.9 (3 H, t, $MeCH_2$) 1.2—1.4 [15 H, br s, $(CH_2)_6$ and $MeCH$], 1.7 (2 H, m, CH_2CH), 2.55 (1 H, m, CH), 3.3—3.9 (4 H, 2t, NCH_2CH_2N), 4.44 (2 H, s, CH_2Ph), and 7.3 (5 H, m, Ph); *m/z* 300 (M^+), 174, 120, and 91 (100%).

1-*Benzyl*-2-(1-*butylnonyl*)-4,5-*dihydroimidazole* (**4j**) (Found: M^+, 342.3021. $C_{23}H_{38}N_2$ requires M, 342.3034); $\nu_{max.}$(film) 2 940, 2 860, 1 610, 1 500, and 1 450 cm^{-1}; δ 0.9 (6 H, br t, 2 × Me), 1.25 [16 H, br s, $(CH_2)_6$ and $(CH_2)_2$], 1.6 (4 H, m, 2 × CH_2CH), 2.35 (1 H, m, CH), 3.1—3.8 (4 H, 2t, NCH_2CH_2N), 4.25 (2 H, s, CH_2Ph), and 7.2 (5 H, s, Ph); *m/z* 342 (M^+), 286, 285, 187, 174, and 91 (100%).

1-*Benzyl*-2-(1-*propan*-2-*ylnonyl*)-4,5-*dihydroimidazole* (**4k**) (Found: M^+, 328.2888. $C_{22}H_{36}N_2$ requires M, 328.2878); $\nu_{max.}$(film) 2 950, 2 925, 1 610, 1 500, 1 460, and 1 450 cm^{-1}; δ 0.9 (9 H, m, Me_2CH and $MeCH_2$), 1.25 [12 H, br s, $(CH_2)_6$], 1.6 (2 H, m, CH_2CH), 1.9—2.3 (2 H, m, 2 × CH), 3.0—3.8 (4 H, 2t, NCH_2CH_2N), 4.22 (2 H, s, CH_2Ph), and 7.2 (5 H, s, Ph); *m/z* 328 (M^+), 285, 216, 215, 201, 187, 174, and 91 (100%).

1-*Benzyl*-2-(1-*benzylnonyl*)-4,5-*dihydroimidazole* (**4l**) (Found: M^+, 376.2891. $C_{26}H_{36}N_2$ requires M, 376.2878); $\nu_{max.}$(film) 3 000, 2 950, 2 900, 2 850, 1 610, 1 490, and 1 450 cm^{-1}; δ 0.86 (3 H, t, Me), 1.25 [12 H, br s, $(CH_2)_6$], 1.65 (2 H, m, CH_2CH), 2.6 (1 H, m, CH), 2.8—3.2 (4 H, m, NCH_2CH_2N and $PhCH_2CH$), 3.6—4.2 (4 H, m, NCH_2CH_2N and $PhCH_2N$), and 7.15 (10 H, br s, 2 × Ph); *m/z* 376 (M^+), 285, 264 (100%), 263, 197, 173, and 91.

1-*Benzyl*-2-(3-*hydroxybutyl*)-4,5-*dihydroimidazole* (**4m**) (*with J. Schofield*).—This compound was prepared according to the method described above for the preparation of (**4b**), from (**4a**) (1 g, 5.75 mmol) and 2-methyloxirane. After 20 h at 20 °C the reaction mixture was worked-up to afford a residue that was chromatographed on a column of silica gel (Merck Kieselgel 60 Art. 7734; 130 g), eluting with chloroform–2-aminopropane [95:5 (v/v)], to afford initially some unchanged (**4a**) (71 mg, 7%), followed by some mixed fraction (125 mg), and then pure *title compound* (**4m**) (702 mg, 53%) as a viscous oil (Found: C, 69.25; H, 9.2; N, 11.55%; M^+, 232.1571. $C_{14}H_{20}N_2O{\cdot}0.5H_2O$ requires C, 69.7; H, 8.75; N, 11.6%; M, 232.1575); $\nu_{max.}$(film) 3 200v br, 2 950, 2 900, 1 600, 1 490, and 1 450 cm^{-1}; δ 1.2 (3 H, d, *J* 7 Hz, Me), 1.83 (2 H, q, *J* 6 Hz, CH_2CH_2CH), 2.5 (2 H, br t, CH_2CH_2CH), 3.15—3.4 (2 H, m, NCH_2CH_2N), 3.6—4.0 (3 H, m, NCH_2CH_2N and CHOH), 4.35 (2 H, s, CH_2Ph), 5.15 (1 H, br s, OH), and 7.35 (5 H, m, Ph); *m/z* 232 (M^+), 231, 217, 215, 188, 187, 174 (100%), 173 (92), and 91 (99).

2-(2,6-*Dichlorophenyl*)*oxirane* (**6**).—Trimethylsulphoxonium iodide (144 g, 0.65 mol) was added to a stirred suspension of sodium hydride (80% w/w; 19.8 g, 0.66 mol) in dry dimethyl sulphoxide (375 ml) under an atmosphere of nitrogen with cooling to maintain a temperature of 20 °C. After 2 h, 2,6-dichlorobenzaldehyde (105 g, 0.6 mol) in dry dimethyl sulphoxide (800 ml) was added over 20 min at 20 °C. The mixture was stirred for a further 30 min and then poured onto ice–water (2 l) and extracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated to leave a residue that was distilled at reduced pressure to afford 2-(2,6-dichlorophenyl)oxirane (**6**) (57 g, 50%), b.p. 74—80 °C at 0.15 mmHg, m.p. 50—52 °C; $\nu_{max.}$ 1 590 and 1 570 cm^{-1}; δ 2.8—3.3 (2 H, m, CH_2), 3.85 (1 H, m, CH), and 7.07 (3 H, m, ArH); *m/z* 192, 190, and 188 (M^+), 162, 160, 158, 125, and 123.

1-[2-(2,6-*Dichlorophenyl*)-2-*hydroxyethyl*]-2-*methyl*-4,5-*dihydroimidazole* (**7a**).—A mechanically stirred mixture of the foregoing oxirane (**6**) (56.7 g, 0.3 mol) and ethane-1,2-diamine (180 g) was heated at 90 °C for 18 h and then evaporated. The residue in dry ethanol (300 ml) was treated with ethyl acetimidate hydrochloride (37.1 g, 0.3 mol) and the mixture heated under reflux for 2.5 h. After evaporation of the ethanol the residue was triturated with dry ether (3 × 100 ml) and the remaining solid recrystallised from propan-2-ol to afford the *title compound* (**7a**) as the *hydrochloride salt* (55 g, 59%), m.p. 221—222 °C (Found: C, 46.5; H, 5.0; N, 8.7. $C_{12}H_{15}Cl_3N_2O$ requires C, 46.5; H, 4.8; N, 9.0%); $\nu_{max.}$ 3 150, 1 615, and 1 595

cm^{-1}; δ[$(CD_3)_2SO$] 2.24 (3 H, s, Me), 3.2—4.1 (6 H, m, CH_2N and NCH_2CH_2N), 5.44—5.72 (1 H, dd, *J* 11 and 5.5 Hz, C*H*OH), 6.1—6.9 (2 H, br, OH and NH), and 7.41 (3 H, m, ArH): *m/z* 276, 274, and 272 (M^+ − HCl).

1-[2-*Chloro*-2-(2,6-*dichlorophenyl*)*ethyl*]-2-*methyl*-4,5-*dihydroimidazole* (**7b**).—The foregoing hydroxyethyl-4,5-dihydroimidazole (**7a**) as the hydrochloride salt (15 g, 0.048 mol) and thionyl chloride (75 ml) were were kept at 20 °C for 18 h. The residue after exhaustive evaporation of the thionyl chloride was triturated with ether and the remaining oil crystallised from propan-2-ol to give the *title compound* (**7b**) as the *hydrochloride salt* (10.7 g, 67%), m.p. 161 °C (Found: C, 43.5; H, 4.6; N, 8.0. $C_{12}H_{14}Cl_4N_2$ requires C, 43.8; H, 4.3; N, 8.5%); $\nu_{max.}$ 3 390, 3 320, 3 160, 1 620, and 1 605 cm^{-1}; δ[$(CD_3)_2SO$] 2.42 (3 H, s, Me), 4.05 (4 H, br s, NCH_2CH_2N), 4.35 (2 H, m, CH_2N), 5.95—6.19 (1 H, dd, *J* 8.5 and 6 Hz, CHCl), and 7.5 (3 H, s, ArH); *m/z* 296, 294, 292, and 290 (M^+ − HCl).

6-(2,6-*Dichlorophenyl*)-2,3,6,7-*tetrahydro*-5H-*pyrrolo*[1,2-a]-*imidazole* (**8**).—Butyl-lithium (1.6 M solution in hexane; 7.15 ml, 11.4 mmol) was added to di-isopropylamine (1.52 ml; redistilled) in dry THF (15 ml) at −40 °C under an atmosphere of nitrogen . After 20 min the mixture was cooled to −60 °C and the foregoing chloroethyl-4,5-dihydroimidazole (**7b**) as the free base (2.91 g, 10 mmol; prepared from the hydrochloride by treatment with 3M aqueous sodium hydroxide) in THF (10 ml) was added. The mixture was allowed to warm to −10 °C and after 2 h was poured onto ice (200 g). Ether extraction followed by evaporation of the dried ($MgSO_4$) organic extracts gave an oil that was immediately treated with an excess of a saturated solution of oxalic acid in ether. The solid was collected and recrystallised from ethanol–ethyl acetate to afford the *title compound* (**8**) as the *oxalate salt* (1.42 g, 41%), m.p. 199—200 °C from ethanol (Found: C, 48.7; H, 4.2; N, 8.3. $C_{14}H_{14}Cl_2N_2O_4$ requires C, 48.7; H, 4.1; N, 8.1%); $\nu_{max.}$ 3 300—2 200br, 1 750, 1 665, 1 640, and 1 595 cm^{-1}; δ(CF_3CO_2D) 3.26 (2 H, d, *J* 9 Hz, CH_2), 4.0 (4 H, m, NCH_2CH_2N), 4.42 (2 H, m, CH_2N), 5.34 (1 H, m, CH), 7.36 (3 H, m, ArH), and 7.74 (1 H, br s, NH); *m/z* 258, 256, and 254 (M^+ − $C_2H_2O_4$).

Acidic Hydrolysis of 1-*Benzyl*-2-*nonyl*-4,5-*dihydroimidazole* (**4e**): *Decanoic Acid.*—1-Benzyl-2-nonyl-4,5-dihydroimidazole (**4e**) (1.67 g, 5.84 mmol) was heated in sulphuric acid [66% (w/w); 50 ml] under gentle reflux for 2 h. The cooled solution was poured into water (100 ml) and extracted with ether (2 × 50 ml), and the combined ether extracts were dried ($MgSO_4$) and evaporated to afford decanoic acid (0.65 g, 65%), m.p. 30—32 °C (lit.,[12] 31.5 °C), identical with an authentic sample.

Acidic hydrolysis of 1-benzyl-2-pentyl-4,5-dihydroimidazole (**4d**) was performed as above to afford hexanoic acid (71%), identical with an authentic sample.

Basic Hydrolysis of 1-*Benzyl*-2-*nonyl*-4,5-*dihydroimidazole* (**4e**): N-(2-*Benzylaminoethyl*)*decylamide.*—1-Benzyl-2-nonyl-4,5-dihydroimidazole (**4e**) (1.5 g, 5.24 mmol) was taken up in a solution of sodium hydroxide in 95% ethanol (0.0375M; 100 ml) and the mixture heated under gentle reflux for 2 h. The cooled solution was evaporated at reduced pressure, the residue partitioned between water (100 ml) and ether (100 ml), and the dried ($MgSO_4$) organic extract evaporated to afford *N*-(2-benzylaminoethyl)decylamide as a colourless oil (1.45 g, 91%) that was homogeneous by t.l.c., gave a negative fluram test,[13] and was used without further purification; $\nu_{max.}$(film) 3 250, 3 000, 2 900, 1 640, 1 550, 1 500, and 1 460 cm^{-1}; δ 0.85 (3 H, t, Me), 1.25 [12 H, br s, $(CH_2)_6$], 1.6 (2 H, m, CH_2CH_2CO), 1.75 (1 H, s, NH), 2.16 (2 H, t, *J* 7.5 Hz, CH_2CO), 2.73 (3 H, t, *J* 6 Hz, NCH_2CH_2NHCO), 3.32 (2 H, q, *J* 6 Hz, NCH_2CH_2NHCO), 3.72 (2 H, s, CH_2Ph), 6.3 (1 H, br s, CONH), and 7.25 (5 H, s, Ph); *m/z* 304 (M^+), 251, 210, 133, 120, 106, and 91 (100%).

Acidic Hydrolysis of N-(2-*Benzylaminoethyl*)*decylamide.*—The foregoing amide (0.88 g, 2.89 mmol) was heated in hydrochloric acid (6M; 100 ml) under reflux for 3 h. The cooled solution was extracted with ether (2 × 50 ml), and the combined ether extracts were dried ($MgSO_4$) and evaporated to afford decanoic acid (0.33 g, 66%), identical with an authentic sample.

2-*Nonyl*-4,5-*dihydroimidazole.*—To 1-benzyl-2-nonyl-4,5-dihydroimidazole (**4e**) (5 g, 17.5 mmol) in dry ethanol (20 ml) and liquid ammonia (100 ml) was added sodium (1.6 g, 69.5 mmol) in portions over a period of 20 min. The liquid ammonia was allowed to evaporate and the residue was diluted with water (100 ml) and stirred at 25 °C for 2 h. The resulting solid was filtered off, and the filtrate extracted with chloroform (3 × 50 ml). The organic extracts were dried ($MgSO_4$) and concentrated to leave a solid residue (2 g) that was combined with the filtered solid and recrystallised from light petroleum (b.p. 40—60 °C) to afford 2-nonyl-4,5-dihydroimidazole (2.65 g, 77%) as white prisms, m.p. 68—69 °C (lit.,[25] 71 °C) (Found: M^+ 196.1932. Calc. for $C_{12}H_{24}N_2$: *M* 196.1939); δ 0.9 (3 H, br t, Me), 1.3 [12 H, br s, $(CH_2)_6$], 1.6 (2 H, m, CH_2), 2.22 (2 H, t, CH_2), 3.59 (4 H, s, NCH_2CH_2N), and 4.7 (1 H, br s, NH); *m/z* 196 (M^+), 195, 167, 153, 139, 125, 111, 97, and 84 (100%).

Acknowledgements

We thank I.C.I. Ltd. (Pharmaceuticals Division) and the S.E.R.C. for a CASE studentship (to M. W. A.).

References

1 See for example, A. I. Meyers, 'Heterocycles in Organic Synthesis,' Wiley, New York, 1974.
2 S. J. Benkovic and W. P. Bullard in 'Progress in Bio-organic Chemistry,' eds. E. T. Kaiser and F. J. Kézdy, Wiley-Interscience, New York, 1973, vol. 2, p. 133.
3 (*a*) M. W. Anderson, R. C. F. Jones, and J. Saunders, *Tetrahedron Lett.*, 1981, **22**, 261; (*b*) *J. Chem. Soc., Chem. Commun.*, 1982, 282; (*c*) M. W. Anderson, M. J. Begley, R. C. F. Jones, and J. Saunders, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2599; (*d*) see also, H. Bieräugel, R. Plemp, H. C. Hiemstra, and U. K. Pandit, *Tetrahedron*, 1983, **39**, 3971.
4 See for example, R. J. Grout in 'The Chemistry of Amidines and Imidates,' ed. S. Patai, Wiley, London, 1975, p. 255.
5 For a preliminary account of part of this work, see ref. 3*a*. For related studies on other monocyclic five-membered heterocycles see ref. 1, p. 201; A. I. Meyers and E. D. Mihelich, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 270; A. I. Meyers *et al.*, *J. Org. Chem.*, 1975, **40**, 2021, 2025; T. Okutome, Y. Sakurai, M. Kurumi, H. Kawamura, S. Sato, and K. Yamaguchi, *Chem. Pharm. Bull.*, 1975, **23**, 48; B. H. Lipshutz and R. W. Hungate, *J. Org. Chem.*, 1981, **46**, 1410; H. H. Wasserman, R. J. Gambale, and M. J. Pulwer, *Tetrahedron Lett.*, 1981, **22**, 1737; J. Crousier and J. Metzger, *Bull. Soc. Chim. Fr.*, 1967, 4134; L. J. Altman and S. L. Richheimer, *Tetrahedron Lett.*, 1971, 4709; A. I. Meyers and G. N. Knaus, *J. Am. Chem. Soc.*, 1973, **95**, 3408; B. Iddon and B. L. Lim, *J. Chem. Soc., Perkin Trans. 1*, 1983, 271.
6 (*a*) K. Yonetani, Y. Hirotsu, and T. Shiba, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 3302; (*b*) S. Shibata, H. Matsushita, K. Kato, M. Noguchi, M. Saburi, and S. Yoshikawa, *ibid.*, 1979, **52**, 2938; (*c*) T. Shiba, K. Sawada, and Y. Hirotsu, *Heterocycles*, 1978, **10**, 133; (*d*) J. W. McFarland, L. H. Conover, H. L. Howes, J. E. Lynch, D. R. Chisholm, W. C. Austin, R. L. Cornwell, J. C. Danilewicz, W. Courtney, and D. H. Morgan, *J. Med. Chem.*, 1969, **12**, 1066.
7 D. P. Clough, R. Hatton, S. J. Pettinger, G. M. R. Samuels, and A. Shaw, *Br. J. Pharmacol.*, 1978, **62**, 385.
8 B. G. Harnsberger and J. L. Riebsomer, *J. Heterocycl. Chem.*, 1964, **1**, 188.

9 Hydrolysis of dihydroimidazoles by concentrated hydrochloric acid at 175 °C for 12 h has been observed: W. L. Hawkins and B. S. Biggs, *J. Am. Chem. Soc.*, 1949, **71**, 2530.
10 (*a*) R. B. Martin and A. Parcell, *J. Am. Chem. Soc.*, 1961, **83**, 4830; (*b*) P. Haake, and J. W. Watson, *J. Org. Chem.*, 1970, **35**, 4063.
11 S. Limatibul and J. W. Watson, *J. Org. Chem.*, 1971, **36**, 3803.
12 'Handbook of Tables for Organic Compound Identification,' 3rd edn., CRC Press, Cleveland, 1967, p. 193.
13 M. Weigele, S. L. DeBernado, J. P. Tengi, and W. Leimgruber, *J. Am. Chem. Soc.*, 1972, **94**, 5927.

Received 10*th September* 1984; *Paper* 4/1549