1,2- and 1,3-Diamine Exchange between Substituted 4,5-Dihydroimidazoles and 1,4,5,6-Tetrahydropyrimidines: Routes to Benzimidazoles, Dihydroimidazoles, and Tetrahydropyrimidines

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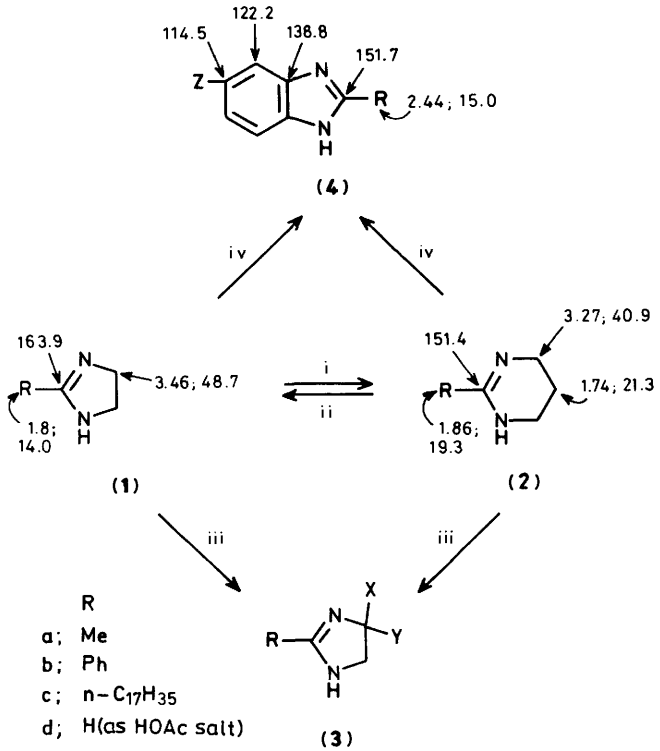
A range of 2-substituted 4,5-dihydroimidazoles and 2-substituted 1,4,5,6-tetrahydropyrimidines when heated with an excess of substituted ethane-1,2-diamines, *o*-phenylenediamines, and propane-1,3-diamine underwent diamine exchange to give 2-substituted heterocycles derived from the solvent diamine. The reaction was an equilibrium process favouring six-membered rings. The synthetic scope is amplified by the ready aromatisation of these partially reduced heterocycles.

Recently we reported[1] a useful rapid cyclisation of fatty 1,2-diamides to fatty substituted 4,5-dihydroimidazoles (**1c**) with phenylphosphorodiamidate. In the course of that work we briefly noted that fatty dihydroimidazoles (**1**) could be converted reversibly into the corresponding tetrahydropyrimidines (**2**) by simply being heated with a large excess of propane-1,3-diamine. This facile exchange of the diamine between the rings is a particularly useful synthetic technique the significance of which is magnified by the combination of the economic significance[2,3] of those types of ring systems and the difficulties of their synthesis often involving prolonged high-temperature cyclisations of diamides.[4–7] Herein we report an exploration of the scope of the reaction and extend it beyond the fatty derivatives.

The exchange of 1,2- and 1,3-diamines between the 4,5-dihydroimidazoles (**1**) and the tetrahydropyrimidines (**2**), on heating in an excess of the incoming diamine, readily occurred



Scheme 1. *Reagents:* i, $NH_2(CH_2)_3NH_2$; ii, $NH_2(CH_2)_2NH_2$; iii, $NH_2CH_2CXY\text{-}NH_2$; iv, 4-Z-substituted *o*-phenylenediamine ^1H and ^{13}C n.m.r. shifts are shown for the **a** series (Z = H)

Table.

Reaction No.	Substrate	Reagent	X, Y	Product	M.p. (°C)	Yield (%)
1	(**1a**)	i	—	(**2a**)	73—74[a]	98
2	(**1a**)	iii	H, Me	(**3a**)	oil	82
3	(**1a**)	iii	Me, Me	(**3a**)	oil	86
4	(**1a**)	iv	(Z = H)	(**4a**)	175—176[b]	75
5	(**1a**)	iv	(Z = Me)	(**4a**)	200[c]	81
6	(**1b**)	i	—	(**2b**)	83—85[d]	85
7	(**1b**)	iii	H, Me	(**3b**)	<25[e]	61
8	(**1b**)	iv	(Z = H)	(**4b**)	292—294[f]	20
9	(**1c**)	i	—	(**2c**)	73—75[g]	98
10	(**1c**)	iii	H, Me	(**3c**)	63[h]	97
11	(**1c**)	iv	(Z = H)	(**4c**)	88—90[i]	70
12	(**1c**)	iv	(Z = Me)	(**4c**)	65[i]	63
13	(**1d**)	i	—	(**2d**)	64—66[j]	72
14	(**2d**)	ii	—	(**1d**)	—[k]	76
15	(**2a**)	ii	—	(**1a**)	93—95[l]	99

[a] Purified by distillation under reduced pressure. [b] From chloroform. [c] From water. [d] From toluene. [e] Oily solid. [f] From aqueous ethanol. [g] From light petroleum (b.p. 60—80 °C). [h] Washed with Et_2O. [i] From ethanol. [j] From ethyl acetate. [k] Yellow oil which hardened to a glass. [l] From benzene.

for a number of 2-substituents R, including aryl groups, low alkyl groups, and the formyl derivative, R = H (Scheme 1) (Table 1). Since the formyl derivatives (R = H) are highly sensitive to atmospheric moisture the exchange reactions were carried out on their acetates (**1d**) and (**2d**). The exchange was also successful with some non-active substituents, X and Y, on the diamine thus allowing easy synthesis of 4- and 5-substituted 4,5-dihydroimidazoles. For substituted aliphatic diamines, which are liquids, the incoming diamine (required in excess) was used as the solvent to prepare the substrates (**3**) from either (**1**) or (**2**) (Scheme 1). Aromatic 1,2-diamines are solids but the reaction was usefully extended into this series to give substituted benzimidazoles using benzylamine as solvent. Thus heating of 2-methyl-4,5-dihydroimidazole (**1a**) with *o*-phenylenediamine (2.05 mol) in benzylamine gave 2-methylbenzimidazole (**4a**; Z = H) in good yields (Table, entry 4). The upper limit of the 1,*n*-diamine which could be exchanged in this general manner was 1,3- and the reaction failed for 1,4- and 1,6-diamines which would have given rings with more than six atoms. The expected product from the reaction of the substrates (**1**) with butane-1,4-diamine would be 4,5,6,7-tetrahydro-2-methyl-1,3-diazepine which has been reported[8] from the reaction of butane-1,4-diamine with acetamidine hydrochloride. We prepared this compound[8] for comparison

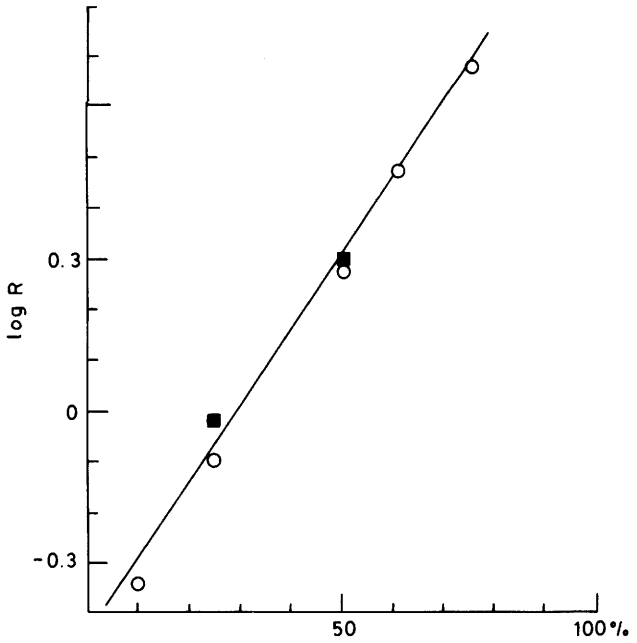


Figure. Plot of the log of the ratio (*R*) (see Experimental section) against the % of reagent i in mixtures of reagents i and ii (see caption to Scheme 1); ⊙ for substrate (**1a**), ■ for substrate (**2a**)

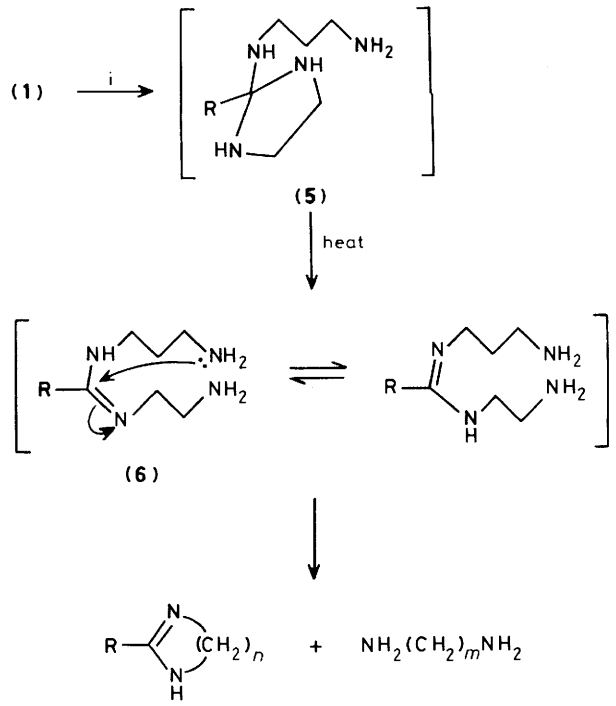
purposes but it was not detected even in small amounts from the reactions of butane-1,4-diamine with either of the substrates (**1**) or (**2**).

When mixtures of 1,2- and 1,3-diamines were used as solvents in the exchange reaction the products were mixtures of dihydroimidazoles and tetrahydropyrimidines the composition of which showed a statistical relationship to the relative proportions of the diamines used (Figure), thus indicating an equilibrium exchange process. The same equilibrium distribution was arrived at by starting from either the dihydroimidazoles (**1**) or the tetrahydropyrimidines (**2**). The preferred product was the six-membered ring for all mixtures and with a 1:1 mixture of propane-1,3-diamine and ethane-1,2-diamine the ratio of (**2a**) to (**1a**) in the products was 1.9:1. This is consistent with a mechanism in which the cyclisation step involves an internal nucleophilic exo-trigonal cyclisation of an amidine species (**6**) (Scheme 2), itself being formed by nucleophilic addition to the substrate. A further addition of diamine to the amidine (**6**) may give rise to an intermediate requiring an exo-tet cyclisation with displacement of a diamine molecule but since ring formation by intramolecular *n*-exo-tet displacement is well known to favour five-membered rings[9] it is unlikely to be occurring in these exchange reactions.

The synthetic value of the exchange reactions is further amplified by the ready aromatisation of the compounds (**1**)—(**3**) by oxidation with reagents such as manganese dioxide and lead oxide. Thus the reaction can be used to provide routes to a wide range of substituted imidazoles and pyrimidines as well as their reduced derivatives.

Experimental

M.p.s were measured on an electrothermal apparatus. N.m.r. spectra were measured on JEOL JNM-GX-270 and MH-100 instruments with tetramethylsilane as internal reference and deuteriochloroform or hexadeuteriodimethyl sulphoxide as solvents. I.r. spectra were measured for mulls on a Perkin-Elmer 930G machine. 2-Substituted dihydroimidazole substrates (**1a**—**d**) were prepared by literature procedures.[1,5,10,11] All the compounds gave satisfactory C, H, N microanalyses and these



Scheme 2.

are provided as supplementary material [SUP No. 56727 (4 pp.)].*

Diamine Exchange Reactions.—The following are typical examples:

(*i*) A solution of 2-methyl-4,5-dihydroimidazole (**1a**) (1.00 g, 11.8 mmol) in 1,3-diaminopropane (10 cm^3) was heated under reflux for 30 min, cooled, and the excess diamine was removed under reduced pressure and the residue purified by distillation to give a clear liquid which solidified to white crystals of 2-methyl-1,4,5,6-tetrahydropyrimidine (**2a**) (98%), m.p. 72—74 °C (lit.,[12] m.p. 75 °C). The reaction when carried out with the hydrochloride of compound (**1a**) gave the hydrochloride of compound (**2a**) (81%), m.p. 132 °C.

(*ii*) A solution of 2-phenyl-4,5-dihydroimidazole (**1b**) (300 mg) and *o*-phenylenediamine (1.4 g) in benzylamine (5 cm^3) was stirred under reflux for 36 h and then evaporated under reduced pressure. The residue was dissolved in warm dry benzene (20 cm^3) and fractional evaporation gave successive crops of 2-phenylbenzimidazole (**4b**) (20%), m.p. 292—294 °C (lit.,[13] m.p. 293 °C).

A similar reaction for 16 h with the substrate (**1a**) gave the product (**4a**) in 75% yield, m.p. 175—176 °C (lit.,[13] m.p. 176—177 °C).

(*iii*) A solution of the acetic acid salt of 4,5-dihydro-2-imidazoline (**1d**) (850 mg) in propane-1,3-diamine (10 cm^3) was heated under reflux for 2 h. It was then cooled and the diamine solvent removed under reduced pressure to leave a residue which was crystallised at −15 °C from propan-2-ol–ethyl acetate (9:1, v/v) to give the acetic acid salt of 1,4,5,6-tetrahydropyrimidine (**2d**) (72%), m.p. 64—66 °C (lit.,[11] m.p. 62—66 °C).

When compound (**2d**) was similarly treated with ethane-1,2-diamine removal of the solvent gave an oil which changed to a

* For details of the Supplementary publications scheme see Instructions for Authors (1989), *J. Chem. Soc., Perkin Trans. 1*, 1989, issue 1.

glass (**1d**) on cooling. Similar treatment of the series (**2**) gave the corresponding compounds (**1**) or (**3**) in high yields.

(*iv*) A mixture of 2-heptadecyl-4,5-dihydroimidazole (**1c**) (400 mg, 0.97 mmol), 3,4-diaminotoluene (1 g), and benzylamine (5 cm^3) was heated under reflux for 30 h, cooled, evaporated under reduced pressure. The residue was leached with water and insoluble 2-heptadecyl-5-methylbenzimidazole (**4c**; Z = Me), m.p. 65 °C (from ethanol) (63%) was collected.

Competitive Reactions.—Solutions of 2-methyl-4,5-dihydroimidazole (**1a**) (300 mg, 3.5 mmol) in mixtures of propane-1,3-diamine and ethane-1,2-diamine (total mol content, 142 mmol) were heated under reflux under standardized conditions. The liquid solution was allowed to cool and homogeneous samples were removed, dissolved in $CDCl_3$ and analysed by 270 MHz n.m.r. (using the dihydroimidazole ^1H signal at δ 3.46 and the tetrahydropyridine signal at δ 3.27) to determine the ratio of compounds (**2a**):(**1a**). For the following solvent compositions (propane-1,3-diamine–ethane-1,2-diamine), 10:90; 25:75; 50:50; 60:40; 75:25; the product ratio (**2a**):(**1a**) (*R*) was, respectively, 0.45; 0.80; 1.9; 3.0; 4.8. For initial solutions of 2-methyl-1,4,5,6-tetrahydropyrimidine (**2a**) in diamine mixtures 25:75 and 50:50 the product ratio (*R*) was 0.95 and 1.95 respectively (data for Figure).

Aromatization.—The following is a typical example.

A solution of compound (**1a**) (200 mg) in dry benzene or toluene (20 cm^3) was treated with active manganese dioxide (800 mg) and the mixture heated under reflux for 1.5 h, cooled, and filtered through Celite to remove solid material. Evaporation of the solution gave 2-methylimidazole, m.p. 142—143 °C (94%) (lit.,[14] m.p. 143—145 °C).

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