Rapid Synthesis and Interconversions of Fatty 4,5-Dihydroimidazoles and Fatty 1,4,5,6-Tetrahydropyrimidines. Thermal Cyclizations of Fatty Amides Involving Phenyl Phosphorodiamidate

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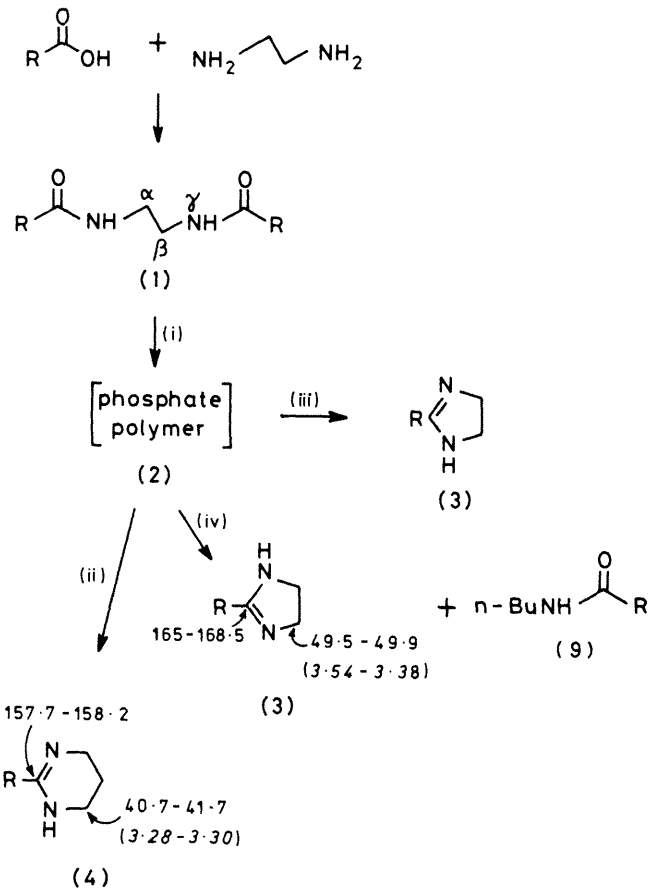
Brief heating of ethane-1,2- and propane-1,3-bis-fatty amides at 235—250 °C with phenyl phosphorodiamidate gave routes to high yields of 2-fatty alkyl-4,5-dihydroimidazoles and 1,4,5,6-tetrahydropyrimidines. Ready interconversions of fatty dihydroimidazoles and tetrahydropyrimidines, involving diamine exchange with solvent, were observed on brief heating of these materials in ethylenediamine and trimethylenediamine as solvents.

Fatty 4,5-dihydroimidazoles and 1,4,5,6-tetrahydropyrimidines are used widely as surface-active compounds such as emulsifiers and adhesive agents.[1] Their industrial synthesis is often difficult and requires prolonged thermal reactions of 1,2- and 1,3-diamines with carboxylic acids.[2-4] The expensive prolonged high-temperature steps arise because of the formation of ethane-1,2-diamides (1) and propane-1,3-diamides (8) which cyclise with difficulty.[5,6] For example, heating 1,2-bis(stearamido)ethane (1a) at 240—250 °C for 3 d gave only a 17% yield of 2-heptadecyl-4,5-dihydroimidazole (3a).[5] Catalysts such as hydrochloric acid,[7] metal chlorides,[8,9] and phosphorus pentaoxide [10] have been employed to improve these cyclizations but reaction times were still lengthy. An alternative approach was to avoid the formation of bis-amides from the diamine, since monoacyl 1,2- and 1,3-diamines generally cyclise readily on heating. However, in thermal reactions of polyamines with carboxylic acids the amidation of each of the primary amino functions occurs equally rapidly [5,6] and a satisfactory route to heterocycles involving monoamide formation requires a large excess of diamine [11] which is inherently inefficient and magnifies the problems of isolation and purification. In this work we report [12] a new, rapid cyclization of fatty amides involving phenyl phosphorodiamidate (PPDA), $PhOP(=O)(NH_2)_2$, which gives high-yield routes to saturated and unsaturated fatty dihydroimidazoles and tetrahydropyrimidines with reaction times of the order of *ten minutes*. The most ubiquitous natural fatty chains were included in the substrates used to establish the generality of the process.

Results and Discussion

Phenyl phosphorodiamidate (PPDA) is structurally related to adenosine-5'-phosphoroamidate which is a potentially active aminating species in enzymatic transaminations. Some useful direct aminations of six-membered amidoheterocycles, [-C(=O)NH-] to the corresponding amino derivatives [-C(NH$_2$)=N-] have been reported with this reagent.[13-15] These reactions are complicated and a number of mechanistic pathways have been proposed.[15,16] In the present work mixtures of a range of diamides (1) (Scheme 1) and PPDA (2 mol equiv.) were rapidly raised to the temperature range 235—250 °C by placing the flask in a preheated isomantle. The mixture melted at 220 °C and thereafter a vigorous reaction gave off phenol and ammonia vapours. After 5—8 min the mixture was cooled to 85—90 °C and leached for about 5 min with boiling n-butylamine after which insoluble polyphosphates were removed. On being cooled the butylamine solution deposited the dihydroimidazoles (3) (Table 1) in high yield. Fractional evaporation of the butylamine solutions gave the n-butyl amides of the fatty acids (80—95%). The reaction



Scheme 1. R = fatty chain. ^{13}C (and ^1H) N.m.r. shifts shown. *Reagents and conditions:* (i) PPDA, 235—250 °C; (ii) $H_2N[CH_2]_3NH_2$; (iii) $H_2N[CH_2]_2NH_2$; (iv) Bu^nNH_2

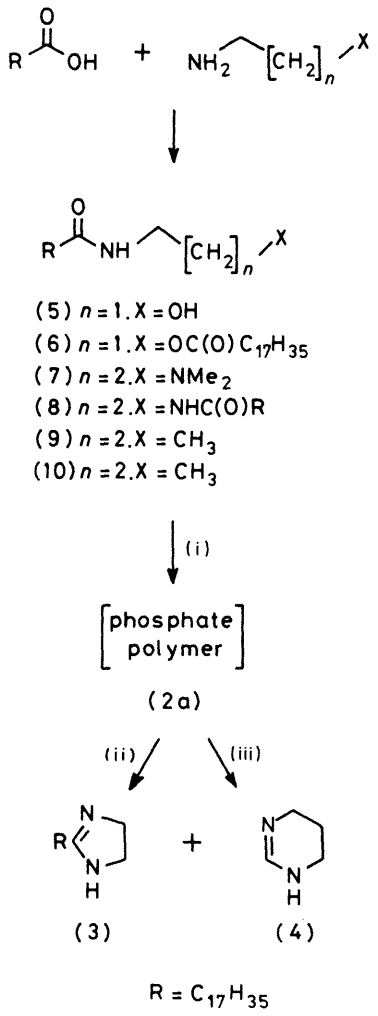
worked best with saturated fatty chains but it was also successful with a *cis*- or *trans*-double bond in the fatty chain (Table 1). When the initial product (2) from the thermal reaction was treated with ethylenediamine the dihydroimidazoles (3) were again obtained and, when the initial product (2) was leached with trimethylenediamine, fatty tetrahydropyrimidines (4) (Scheme 1) (Table 1) were obtained.

The initial product mass (2) (Scheme 1) which was the precursor to the fatty heterocycles was polymeric and sticky-viscous in character. I.r. and ^1H and ^{13}C N.m.r. spectra showed the presence of fatty chains, phenol rings, and phos-

Table 1. Synthesis of fatty heterocycles from fatty amides with PPDA

			Dihydroimidazole (3) [a]		Tetrahydropyrimidine (4) [b]	
Suffix letter	Fatty acid	R	Yield (%)	M.p. (°C)	Yield (%)	M.p. [b.p.] (°C)
(a)	Stearic	n-$C_{17}H_{35}$	91	94—95	80	74—75
(b)	Palmitic	n-$C_{15}H_{31}$	92	92—93	50	68
(c)	Myristic	n-$C_{13}H_{27}$	86	88—89	54	59—60
(d)	Lauric	n-$C_{11}H_{23}$	80	82—83	*c*	45
(e)	Capric	n-C_9H_{19}	81	74—75	*c*	19—20
(f)	Oleic	9-*cis*-$C_{17}H_{33}$	55	64	*c*	[228 °C at 4.5 mmHg]
(g)	Elaidic	9-*trans*-$C_{17}H_{33}$	66	74	*c*	38

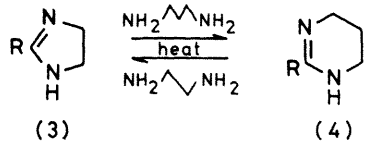
[a] Reaction product mixture leached with n-butylamine or ethylenediamine. [b] Product mixture leached with trimethylenediamine. [c] Spectral analysis indicated a high-yield conversion (≥90%). Low-melting products failed to separate clearly from the solvent and, owing to interference by side-products, recoverable yields were low.



Scheme 2. *Reagents and conditions:* (i) PPDA, 235—250 °C; (ii) for (7)—(9): $H_2N[CH_2]_2NH_2$, heat; for (5), (6): Bu^nNH_2, heat; (iii) $H_2N[CH_2]_3NH_2$

phorus–nitrogen bonds. Careful chromatographic analysis showed that the free heterocycles were not present in the product mass (2) prior to it being heated with butylamine. This polymeric mass appeared to contain highly labile fatty acyl and fatty amidino moieties which are probably the true precursors to the fatty heterocycles. The formation of the dihydroimidazoles involves cleavage of the β–γ (C–N) bond in the substrates (1) in the high-temperature reaction. Identical

Table 2. Diamine exchange between fatty heterocycles



(3) (4)

Yield (%)	R	Yield (%)
92	n-$C_{17}H_{35}$	90
94	9-*cis*-$C_{17}H_{33}$	92
89	9-*trans*-$C_{17}H_{33}$	94
90	n-$C_{15}H_{31}$	95
89	n-$C_{13}H_{27}$	95
90	n-$C_{11}H_{23}$	95
89	n-C_9H_{19}	97

reactions were observed when this bond was a C–O bond. Thus, treatment of the substrates (5) and (6) with PPDA gave a polymeric mass which, when leached with butylamine, gave high yields of the imidazoline (3a) [as well as *N*-butylstearamide from compound (6), Scheme 2]. These results support a cleavage of the β–γ bond and suggest that one of the nitrogens of the dihydroimidazole moiety came from the PPDA since the substrates (5) and (6) have only one nitrogen atom. When the β–γ bond of the amide was a C–C bond, as in the substrates (7)—(9), the reaction was somewhat different and extraction of the initial product mass with butylamine gave only intractable resins. However, extraction of this initial product mass (2a) (Scheme 2) with ethylenediamine and trimethylenediamine gave the products (3a) and (4a), respectively, in high yields (86—92%) hence suggesting that the diamines had reacted with a labile fatty acyl or amidine moiety in the polymer. The lability of these fatty acyl moieties is illustrated by the fact that, on being briefly heated with butylamine (b.p. 77.8 °C), the residue gave not only the compounds (3) but also high yields of *N*-butylstearamide. The formation of fatty amides from fatty acids and amines normally requires prolonged heating at temperatures >100 °C. Transamination of the amido group to an amidino moiety would be an acyclic analogue of the transaminations of cyclic amides previously reported with PPDA.[12,15] More detailed knowledge of the nature of the sticky-viscous polymers (2) will require extensive further studies.

The scope of these new synthetic routes to fatty heterocycles was extended by a useful and experimentally simple interconversion of the fatty dihydroimidazolines (3) and tetrahydropyrimidines (4). When the compounds (3) were heated under reflux for *ca.* 10 min with trimethylenediamine as solvent they were converted in high yields into the tetrahydropyrimidines (4) (Table 2). Similar treatment of the

compounds (4) in ethylenediamine as solvent gave a high-yield conversion into the dihydroimidazoles (3) (Table 2). Hence, in each case, a rapid diamine exchange with the solvent occurred. This ready interconversion of dihydroimidazole and tetrahydropyrimidine rings expands the synthetic value of the PPDA process which provides an effective route to fatty dihydroimidazoles, since these in turn can be easily converted into fatty tetrahydropyrimidines. For example, in the case of low-melting fatty 1,4,5,6-tetrahydropyrimidines (4) (Table 1) it was difficult to obtain high yields of pure samples from the PPDA mixture because of the higher solubility of the products and interference by side-products in fractional distillations. The best route to these low-melting tetrahydropyrimidines was *via* the corresponding dihydroimidazoles (3) which could be converted almost quantitatively into the tetrahydropyrimidines (Table 2).

Experimental

M.p.s were measured with an Electrothermal apparatus. I.r. spectra were measured for either films or mulls with a Perkin-Elmer 377 spectrophotometer. ^1H and ^{13}C N.m.r. spectra were measured for solutions in $CDCl_3$ with Me_4Si as internal reference on JEOL JNM-100 and CFT-20 spectrometers. Commercial samples of saturated fatty acids were thoroughly purified by recrystallization before use (stearic acid had m.p. 69—71 °C). Oleic acid (M. & B.) was purified by distillation (b.p. 205 °C at 4 mmHg) and pure elaidic acid [m.p. 43—44 °C (lit.,[17] 44 °C)] was obtained by isomerization [17,18] of oleic acid. The series of fatty amides (1a—g) and (5)—(9) (Table 3) was obtained by heating the carboxylic acid with the appropriate amine using procedures previously described.[5,6]

(i) *Reactions involving Phenyl Phosphorodiamidate* (PPDA). —The following are typical examples: (a) A mixture of 1,2-bis(stearamido)ethane (1a) (2.96 g, 0.005 mol) and PPDA (1.72 g, 0.01 mol) was rapidly raised to 220—240 °C by placing the flask in a preheated isomantle. The temperature was monitored directly with a thermometer embedded in the mixture. Above 220 °C, after the mixture had melted, a vigorous reaction gave off ammonia and phenol vapours and a white solid began to separate. After 8 min the reaction had subsided and on being allowed to cool a white viscous mass formed [the polymeric product (2)]. This was treated by either of the following procedures. (i) The mixture was heated under reflux in n-butylamine (25 ml) for 5—10 min and insoluble polyphosphates were removed from the warm solution. When the butylamine solution was slowly cooled it gave successive crops of 2-heptadecyl-4,5-dihydroimidazole (3a) (91%) (Table 1), m.p. 94—95 °C (from chloroform) (Found: C, 78.1; H, 13.2; N, 9.2. Calc. for $C_{20}H_{40}N_2$: C, 77.9; H, 13.1; N, 9.1%); $\nu_{max.}$ 3 200 (NH) and 1 610 cm^{-1} (C=N); δ_C 2.2 (t, *J* 8 Hz, CH_2C=N) and 3.54 (s, NCH_2CH_2N); δ_C 49.9 (NCH_2CH_2N) and 168.5 p.p.m. [C(NH)=N]. Evaporation of the n-butylamine solution to half volume gave n-butylstearamide, m.p. 85—87 °C (86%). (ii) The mixture was heated at 80 °C in ethylenediamine for 20 min and, after insoluble polyphosphates were removed from the warm solution, was cooled to give compound (3a) (88%). (iii) The mixture was treated with trimethylenediamine (5 ml), heated briefly (10 min) under reflux, cooled, and extracted with diethyl ether (70 ml) to give 2-heptadecyl-1,4,5,6-tetrahydropyrimidine (4a), m.p. 74—75 °C (from light petroleum b.p. 60—80 °C) (80%) in successive crops from the ethereal solution (Found: C, 78.7; H, 13.2; N, 8.7. $C_{21}H_{42}N_2$ requires C, 78.2; H, 13.1; N, 8.7%); $\nu_{max.}$ 3 150—3 200br (NH) and 1 632 cm^{-1} (C=N); δ_H 1.60—1.84 (m, CCH_2C), 2.08 (t, *J* 8 Hz, CH_2C=N), and 3.3 (t, *J* 5 Hz, CH_2N); δ_C 41.58 (NCH_2) and 158.15 p.p.m. (C=N) {we have previously [5] listed an analysis of carbon shifts of the fatty chain system $CH_3CH_2CH_2CH_2[CH_2CH_2]_nCH_2CH_2CH_2C$=O(N)}. When the reactions with PPDA were carried out using PPDA : amide ratios of 1.5 : 1 and 1 : 1 similar products were encountered along with the expected quantity of starting substrate recovered based on a 2 mol PPDA stoicheiometry.

(b) Treatment of the amides (5) and (6) with PPDA (2 mol equiv.) followed by work-up with $BuNH_2$ gave the dihydroimidazole (3a) (85—90%). Similar treatment of compounds (7)—(9) gave only viscous intractable products. However, with all the compounds (5)—(9) work-up of the initial viscous mass with ethylediamine gave the fatty dihydroimidazole (3a) and work-up using trimethylenediamine as above gave compound (4a) in yields >85%.

(ii) *Interconversions of Fatty Dihydroimidazoles and Tetrahydropyrimidines.*—The following is the general procedure: a

Table 3. Analytical data for fatty amides and heterocycles

Compd.	M.p. [b.p.] (°C)	Found (%) (Required) C	H	N	Formula
(1b)	152—153	76.3 (76.1	12.7 12.7	5.5 5.2)	$C_{34}H_{68}N_2O_2$
(1c)	155—157	74.8 (75.0	12.8 12.5	5.9 5.8)	$C_{30}H_{60}N_2O_2$
(1d)	160—162	73.35 (73.6	12.4 12.25	6.7 6.6)	$C_{26}H_{52}N_2O_2$
(1e)	165—167	71.6 (71.95	12.3 12.6	7.6 7.6)	$C_{22}H_{44}N_2O_2$
(1f)	115—116	77.9 (77.5	12.5 12.3	5.0 4.75)	$C_{38}H_{72}N_2O_2$
(1g)	130—131	77.6 (77.5	12.5 12.3	5.1 4.75)	$C_{38}H_{72}N_2O_2$
(3b)	92—93	76.9 (77.1	13.0 12.8	10.2 10.0)	$C_{18}H_{36}N_2$
(3c)	88—89	75.9 (76.2	12.5 12.7	11.0 11.1)	$C_{16}H_{32}N_2$
(3d)	82—83	74.8 (75.0	12.7 12.5	12.3 12.5)	$C_{14}H_{28}N_2$
(3e)	74—75	73.3 (73.5	12.0 12.2	14.4 14.3)	$C_{12}H_{24}N_2$
(3f)	64	78.7 (78.35	12.5 12.5	9.3 9.15)	$C_{20}H_{38}N_2$
(3g)	74	78.1 (78.35	12.7 12.5	9.4 9.15)	$C_{20}H_{38}N_2$
(4b)	68	77.2 (77.5	13.3 13.0	9.6 9.5)	$C_{19}H_{38}N_2$
(4c)	59—60	76.3 (76.6	13.1 12.9	10.4 10.5)	$C_{17}H_{34}N_2$
(4d)	45	75.2 (75.5	12.8 12.7	11.8 11.8)	$C_{15}H_{30}N_2$
(4e)	19—20	74.0 (74.3	12.4 12.4	13.0 13.3)	$C_{13}H_{26}N_2$
(4f)	[228 at 4 mmHg]	78.3 (78.65	12.3 12.6	8.5 8.75)	$C_{21}H_{40}N_2$
(4g)	38	78.2 (78.65	12.4 12.6	8.4 8.75)	$C_{21}H_{40}N_2$
(5)	100—102	73.6 (73.4	12.5 12.5	4.3 4.3)	$C_{20}H_{41}NO_2$
(6)	92—94	76.6 (76.9	12.8 12.6	2.7 2.4)	$C_{38}H_{75}NO_3$
(7)	65—67	75.2 (75.0	13.0 13.0	7.6 7.6)	$C_{23}H_{48}N_2O$
(8)	133—135	77.4 (77.2	12.8 12.9	4.55 4.6)	$C_{39}H_{78}N_2O_2$
(9)	85—87	77.6 (77.9	13.0 13.3	4.0 4.1)	$C_{22}H_{45}NO$

sample of a compound (3) (1 g) in trimethylenediamine (10 ml) or compound (4) (1 g) in ethylenediamine (10 ml) was heated under reflux for 10 min and cooled whereupon the product heterocycle derived from the solvent separated in high yield (Table 2). The products were washed with cold diethyl ether (30 ml) and acetone (30 ml). When the m.p. of the product was low the diamine was distilled off under reduced pressure.

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