Reactions of Fatty Acids with Amines. Part 2.† Sequential Thermal Reactions of Stearic (Octadecanoic) Acid with Some 1,2- and 1,3-Aminoalcohols and Bis-amines

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Thermal reactions of stearic (octadecanoic) acid with 2-aminoethanol and 3-aminopropanol in a heavy hydrocarbon oil as solvent involved (i) salt formation, (ii) stearoylation of the amino-nitrogen, and (iii) a stearoyl transfer between two molecules of the stearamidoalcohol to give the amido-ester. Each successive step took place at a higher temperature. The reaction of the stearamidoalcohols with thionyl chloride involved N $\rightleftharpoons$ O stearoyl rearrangements, and did not yield stable cyclised products. Thermal reactions of stearic acid with some propane-1,3-diamine and with bis-(2-hydroxyethyl)amine gave diamides and amidoesters.

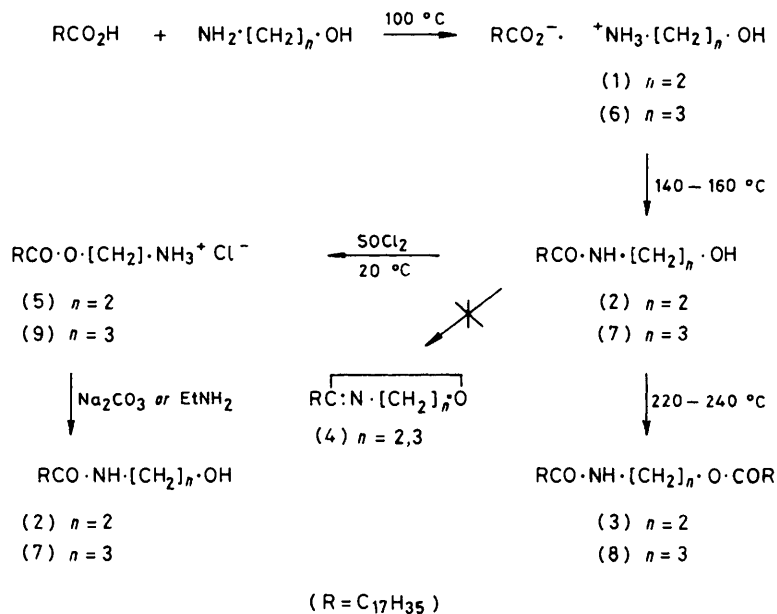THE reactions of carboxylic acids with substituted 2-aminoalcohols [1] have provided routes to 2-alkyl-Δ^2-oxazolines *via* dehydrative cyclisation of intermediate 2-amidoalcohol derivatives,[2] either thermally or with dehydrating reagents such as thionyl chloride.[3,4] While

† Part I, ref. 5.

[1] H. Wenker, *J. Amer. Chem. Soc.*, 1935, **57**, 1079.
[2] For reviews see (a) J. A. Frump, *Chem. Rev.*, 1971, **71**, 483; (b) R. H. Wiley and L. L. Bennet, *Chem. Rev.*, 1949, **44**, 447.
[3] M. Bergmann and E. Brand, *Ber.*, 1923, **53B**, 1280.
[4] M. T. Leffler and R. Adams, *J. Amer. Chem. Soc.*, 1937, **59**, 2252.

the thermal route to Δ^2-oxazolines from aliphatic carboxylic acids and 2-aminoalcohols has been effective for 4- or 5-substituted derivatives, the reaction has not proved satisfactory for 4,5-unsubstituted Δ^2-oxazolines particularly with long-chain fatty acids.[2a] The general comparison of the routes to Δ^2-oxazolines with the routes to Δ^2-imidazolines using 1,2-diamines [5] drew our attention to unusual failure of 2-aminoethanol in attempted

water (nos 5, and 7—9 in the Table). Since water is generated in the overall thermal reaction of stearic acid with 2-aminoethanol, the path to the ester (3) is favoured. The erratic results (nos 2 and 3 in the Table) observed in undried TVO are undoubtedly due to the presence of varying traces of water in the solvent. Lengthening the methylene chain of the aminoalcohol did not alter the course of the reaction and similar reactions were

$$RCO_2H \quad + \quad NH_2 \cdot [CH_2]_n \cdot OH \quad \xrightarrow{100\ °C} \quad RCO_2^- \cdot \ {}^+NH_3 \cdot [CH_2]_n \cdot OH$$

(1) $n = 2$
(6) $n = 3$

$$\Big\downarrow 140 - 160\ °C$$

$$RCO \cdot O \cdot [CH_2] \cdot NH_3^+\ Cl^- \quad \xleftarrow[20\ °C]{SOCl_2} \quad RCO \cdot NH \cdot [CH_2]_n \cdot OH$$

(5) $n = 2$ (2) $n = 2$
(9) $n = 3$ (7) $n = 3$

$$\Big\downarrow Na_2CO_3\ or\ EtNH_2 \qquad R\overset{|}{C}\!:\!N \cdot [CH_2]_{\overset{|}{n}}O \qquad \Big\downarrow 220 - 240\ °C$$

(4) $n = 2,3$

$$RCO \cdot NH \cdot [CH_2]_n \cdot OH \qquad\qquad RCO \cdot NH \cdot [CH_2]_n \cdot O \cdot COR$$

(2) $n = 2$ (3) $n = 2$
(7) $n = 3$ (8) $n = 3$

$$(\ R = C_{17}H_{35}\ )$$

Scheme

thermal cyclisations to oxazolines.[2a] The nature of the thermal reaction has not been reported and previous interest has centred mainly on using dehydrating agents to achieve cyclisation.

RESULTS AND DISCUSSION

2-Aminoethanol and 3-Aminopropanol.—When equimolar quantities of stearic (octadecanoic) acid and 2-aminoethanol were heated to 140—160 °C in the heavy hydrocarbon solvent, tractor vapourising oil (TVO), the stearamido-derivative (2) was formed in 90% yield. A precursory ammonium salt (detected by i.r. spectroscopy, $\nu_{max.}$ 2 100—2 200 cm^{-1}) formed initially as the temperature was raised (see Scheme). When the reaction was allowed to proceed at 220—240 °C for periods varying from 3 h to 3 days, the ester (3) was obtained in 89—92% yields. No trace of the oxazoline (4) ($n = 2$) was encountered. Separate heating of compound (2) in TVO at 220—240 °C, gave compound (3) in erratic yields (nos 2 and 3 in Table). The influences of a number of variables on this reaction are given in the Table (see Experimental section). Compound (2) was converted into the ester (3) by heat alone but the reaction was considerably enhanced by the presence of

[5] R. N. Butler, C. B. O'Regan, and P. Moynihan, *J.C.S. Perkin I*, 1976, 386.

observed between stearic acid and 3-aminopropanol to give compounds (6)—(8).

The conversion of compound (2) into (3) could involve

Heating of 2-stearamidoethanol at 210—230 °C

| | Conditions | | Products (%) | |
No.	time (h)	solvent/additive	(2) [b]	(3)
1	3	Neat	70	20
2	3	TVO (undried)	93	
3	3	TVO (undried)	42	41
4	2.5	TVO (dry)	92	
5	18	TVO (dry)	68.5	20.6
6	3.5	TVO/HCl	<1 [c]	40
7	18	TVO/H₂O [a]		93
8	16	TVO/H₂O [a]		92
9	3.5	TVO/H₂O [a]	56	39
10	4	TVO/NH₂C₂H₄OH [a]	95	
11	6	TVO/(NH₂CH₂)₂ [a]	89	
12	4	TVO/EtNH₂ [a]	88	

[a] One molar proportion. [b] Recovered unchanged. [c] One molar quantity of HCl (aqueous, 36%) was used. Stearic acid (40%) was also recovered from this reaction.
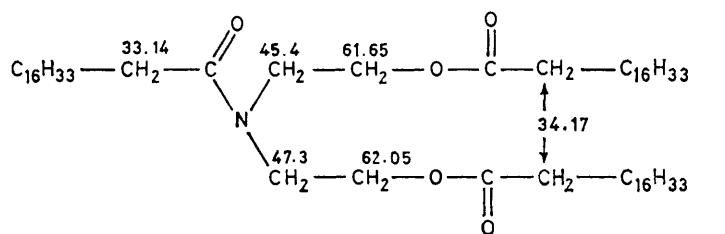
a partial cleavage to free stearic acid which might then esterify with a parent molecule of the stearamidoalcohol (2). Thus, when compound (2) was heated separately with stearic acid in TVO at 220—240 °C, a 91% yield of the ester (3) was obtained. However, this does not appear to be the route to the amido-ester (3) since free stearic acid could not be trapped from the thermal
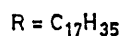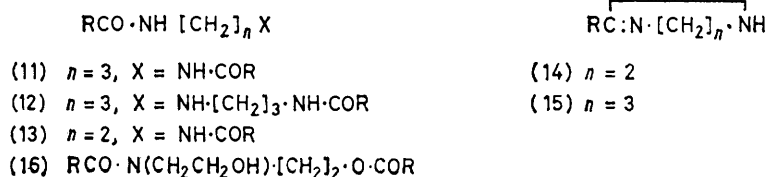
reaction. When compound (2) was heated in TVO containing water together with either ethane-1,2-diamine or ethylamine, no trace of the readily formed [5] stearamido-derivatives of these amines was detected and, in fact, the conversion of compound (2) into the ester (3) was inhibited (nos 10—12 in the Table). This also occurred when 2-aminoethanol was added and when an excess of 2-aminoethanol was used in the direct reaction with stearic acid (2 : 1 molar ratio); the amide (2) only being formed even after prolonged heating at 210—230 °C. That the amido-ester (3) was not formed in the presence of these amines was further confirmed by control reactions in which the ester (3) was heated separately with 1 mol equiv. of the amine. High yields of the amidoalcohol (2) were not encountered in these reactions. When the amine was 2-aminoethanol, the ester was recovered and either no reaction occurred or, more likely, the ester was aminolysed to 2 mol equiv. of the amidoalcohol (2) which subsequently re-esterified. When the amine used was ethane-1,2-diamine, the

limiting the yields of (3). However, we did not detect any 2-aminoethanol in the system but small quantities of gums were sometimes encountered. The high yields of compound (3) suggest that 2-aminoethanol may have evaporated as it was gradually generated at the high temperatures. Inhibition of the reaction by an added excess of aminoethanol would then be expected because of its influence on the equilibrium. However, the effect of the other amines is not as readily explained. The reaction could, alternatively, involve a more complex thermal fragmentation type process which is generally inhibited by basic amines. The presence of hydro-chloric acid did not enhance the yield of ester (3) but led to considerable decomposition to stearic acid (no. 6 vs 9, in the Table). Under such acidic conditions free stearic acid could be involved.

Rearrangements.—Thionyl chloride has proved a useful reagent for the cyclisation of amidoalcohols of type (2) to oxazolines (4) ($n = 2$).[3,4,6] Treatment of compound (2) with thionyl chloride at ambient temperatures, gave

$$C_{16}H_{33}-CH_2-\overset{33.14}{C}\overset{O}{\underset{N}{\parallel}}\overset{45.4}{CH_2}-\overset{61.65}{CH_2}-O-\overset{O}{\underset{\parallel}{C}}-CH_2-C_{16}H_{33}$$

$$\overset{47.3}{CH_2}-\overset{62.05}{CH_2}-O-\overset{}{\underset{\parallel}{C}}-CH_2-C_{16}H_{33}$$

(10)

RCO·NH [CH₂]ₙ X

(11) $n = 3$, X = NH·COR
(12) $n = 3$, X = NH·[CH₂]₃·NH·COR
(13) $n = 2$, X = NH·COR
(16) RCO·N(CH₂CH₂OH)·[CH₂]₂·O·COR

RC:N·[CH₂]ₙ·NH

(14) $n = 2$
(15) $n = 3$

R = C₁₇H₃₅

product was a complicated mixture containing compounds (13) and (14) together with the amidoalcohol (2) and the ester (3). In this case aminolysis of the ester probably occurred giving compound (2) and RCONH-[CH₂]₂NH₂, the latter of which was partitioned between cyclisation to compound (14) and a further aminolysis to give the diamide (13). Hence, the thermal conversion of compound (2) into (3) does not involve a direct cleavage of the amide but rather appears to involve an N→O acyl transfer between two molecules of compound (2). The mechanism of this reaction * requires further study. It may be a thermally favoured alcoholysis in which case 2-aminoethanol should be generated and expected to display a subsequent inhibiting effect

the rearranged ester amine hydrochloride (5) (38—42%) together with starting material and an oxazoline was not encountered. An attempt to free the amine from the salt (5) led to the reverse rearrangement. Thus treatment of compound (5) with weak bases gave the amido-alcohol (2) in yields of 89—93%. Proton removal from the amine lone-pair in compound (5) is, apparently, accompanied by a rapid preferential 1,4 O→N stearoyl migration in the ester amine. Rearrangements of this type have been observed previously with other systems,[4,7-9] and have been regarded as involving cyclisation to oxazolines, which undergo rapid ring cleavage. Interestingly, when the methylene chain was lengthened so as to require a 1,5 O→N stearoyl migration

* We acknowledge helpful comments concerning this by a referee.

[6] Y. Ishii, M. Mase, and A. Kaneshiro, *Yukaguku*, 1958, **7**, 70 (*Chem. Abs.*, 1961, **55**, 5993b).

[7] M. Bergmann and A. Miekeley, *Z. Physiol. Chem.*, 1924, **140**, 128.
[8] F. Bettzieche, *Z. Physiol. Chem.*, 1925, **146**, 227.
[9] W. Krabbe, W. Eisenlohr, and H. Schone, *Ber.* 1940, **73B**, 656.

involving a six-membered transition state or a dihydro-1,3-oxazine intermediate (4; $n = 3$), a similar sequence of rearrangements (7)→(9)→(7) (see Scheme), was also observed.

Bis-(2-hydroxyethyl)amine.—When stearic acid (2 mol equiv.) was heated with bis-(2-hydroxyethyl)amine (1 mol equiv.) in TVO at temperatures up to 200 °C, the amido-di-ester (10) was obtained in 96% yield. The compound (10) showed restricted rotation about the amide C–N bond (relevant ^{13}C shifts in p.p.m. from SiMe4, shown). The sequential nature of this reaction was not readily detectable since both amide and ester

Commercial samples of stearic acid (Aldrich; 95%) and the amines were thoroughly purified by recrystallisations (stearic acid had m.p. 70—71 °C) and distillation before use. Reaction mixtures were heated under a condenser fitted with a calibrated Dean–Stark-type water trap. Temperatures were measured directly with a thermometer embedded in the reaction mixture. For the reactions, (2) —→ (3) and (7) —→ (8), which are, in effect, disproportionations, the percent yields are calculated so that the yield is 100% when 2 mol. equiv. of substrate gives 1 mol. equiv. of product.

(i) *Thermal Reaction of Stearic Acid with 2-Aminoethanol and 3-Aminopropanol.*—A mixture of stearic acid (28.4 g),
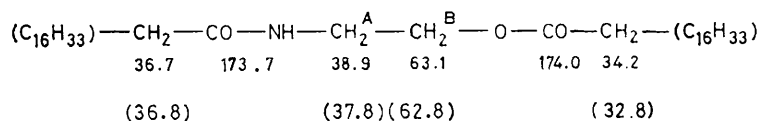
$$(C_{16}H_{33})—CH_2—CO—NH—CH_2^A—CH_2^B—O—CO—CH_2—(C_{16}H_{33})$$

36.7   173.7   38.9   63.1   174.0   34.2

(36.8)   (37.8)(62.8)   (32.8)

FIGURE   Observed and calculated (in parenthesis) [13]C n.m.r. chemical shifts (p.p.m. from SiMe4) for compound (3).

i.r. bands began to appear simultaneously in the heated mixtures. However, at temperatures between 100—150 °C using equimolar ratios of reactants, the main product was the amido-mono-ester (16) (90%). This, when heated separately with stearic acid at 180 °C, gave compound (10) in high yield (85%). When a 2 : 1 molar excess of amine was used, mixtures of compound (16) (40%) with reactants were encountered and precursors were not detected.

Propane-1,3-Diamine and Bis-(3-aminopropyl)amine.—Heating of stearic acid with propane-1,3-diamine or bis-(3-aminopropyl)amine using either 1 : 1 or 2 : 1 acid : amine molar ratios in TVO at 180—190 °C gave high yields of the bis-amides (11) and (12) respectively. These amides were thermally stable and cyclisations to tetrahydropyrimidines were not observed at temperatures up to 250 °C. The absence of stearoylation of the secondary NH moiety of compound (12) (*cf.* ref. 5) which readily occurred with compound (10), is also of interest. We have pointed out previously [5] the difficulty of direct thermal cyclisation of bis-amides. For example, heating of compound (13) at 240—250 °C for 3 days gave only 17% of the imidazoline [5] (14) while in the present work we failed to encounter compound (15) on heating of compound (11). We have now found that phenyl-phosphorodiamidate (PPDA) has a strong catalytic effect on some of these cyclisations. Direct heating of compound (13) with 2 mol. equiv. of PPDA at 240—250 °C for 7 min gave a 90% yield of the cyclised product (14). The usefulness of PPDA for such cyclisations is being examined.

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 or 457 spectrophotometer. [1]H and [13]C n.m.r. spectra, in CDCl3 were measured at probe temperatures on JEOL JNM-100 and FX-60 spectrometers. Because of paucity of [13]C n.m.r. data on fatty acid amides data are given in detail [compound (10) and Figure].

2-aminoethanol (6.1 g) and TVO (15 ml) was heated to 150—160 °C for 4 h and then cooled. The resulting solid on recrystallisation from aqueous alcohol yielded successive crops (89—92% yields) of 2-stearamidoethanol (2), m.p. 100—102 °C (Found: C, 73.6; H, 12.5; N, 4.3. $C_{20}H_{41}$-NO_2 requires C, 73.4; H, 12.5; N, 4.3%); $\nu_{max.}$ 3 300 (NH) and 1 640 cm^{-1} (C=O); τ(CDCl3) 7.80 (t, J 8 Hz, CH2CO), 6.61 (q, J 5 Hz, NH–CH2), 6.26 (t, J 5 Hz, CH2–OH), 4.05 (br, NH). When the reaction mixture was heated at 210—220 °C for 6 h and cooled, fractional crystallisation of the solid product from ethanol gave 2-stearamidoethyl-stearate (3) (89%), m.p. 92—94 °C (Found: C, 76.6; H, 12.8; N, 2.7. $C_{38}H_{75}NO_3$ requires C, 76.9; H, 12.6; N, 2.4%); $\nu_{max.}$ 3 300 (NH), 1 735 (ester C=O), 1 640 (amide C=O), and 1 170 cm.$^{-1}$ (ester C–O–C); τ(CDCl3) 7.87 (overlapping ts, J 7 Hz, CH2C=O), 6.58 (q, J 5 Hz, CH2A), 5.94 (t, J 5 Hz, CH2B), ^{13}C, see Figure; CH_2CO shifts were calculated [2,10] by replacing the terminal Me group of n-decane by CONR2 and CO2R groups; C^A and C^B shifts were calculated by replacing the terminal Me groups of n-butane with CONR2 and OCOR groups.[10]

Similar thermal reactions of stearic acid with 3-amino-propanol gave compound (7) (91%), m.p. 98—99 °C (Found: C, 74.2; H, 12.7; N, 4.35. $C_{21}H_{43}NO_2$ requires C, 73.9; H, 12.6; N, 4.1%), $\nu_{max.}$ 3 300 (NH) and 1 640 cm^{-1} (C=O); τ 7.74 (t, J 8 Hz, CH2·CO), 6.48 (q, J 5 Hz, (NH–CH2), 6.28 (t, J 6 Hz, CH2–OH), and 4.0 (br, NH); and compound (8) (92%), m.p. 82—83 °C (Found: C, 76.9; H, 12.7; N, 2.6. $C_{39}H_{77}NO_3$ requires C, 77.1; H, 12.7; N, 2.3%), $\nu_{max.}$ 3 300 (NH), 1 735 (ester C=O), 1 640 (amide C=O), and 1 170 cm^{-1} (ester C–O–C); τ 7.64—7.88 (overlapping t, CH2·CO), 6.62 (q, J 5 Hz, NH–CH2), 5.80 (t, J 6 Hz, CH2·OCO), and 4.20 (br, NH). When compound (7) was heated separately at 210—230 °C in TVO containing water (1 mol equiv.), compound (8) was readily obtained.

Reactions of 2-Stearamidoethanol.—(a) *Thermal.* The results of a series of these reactions are summarised in the Table. The following is a typical example. A mixture of compound (2) (3 g), TVO (3 g), and water (200 mg) was heated at 220—230 °C for 16 h, cooled, and the residue taken up in hot ethanol. Fractional evaporation of the ethanolic solution gave successive crops of the ester (3) (92% overall).

[10] G. C. Levy and G. L. Nelson, ' Carbon-13 Nuclear Magnetic Resonance for Organic Chemists', Wiley, London, 1972, pp. 40, 47.

No starting amide was encountered. A similar reaction for a shorter period (3.5 h), gave the ester (3) (39%) and the amide (2) (56%), separated by fractional crystallisation from chloroform in which compound (2) is less soluble.

With thionyl chloride. A solution of compound (2) (2.0 g) in thionyl chloride (4.0 g) was stirred at ambient temperatures for 2 h. The thionyl chloride was evaporated off under reduced pressure at 20° °C and starting amide (2) (52.5%) was removed from the solid residue by repeated extractions with boiling ether. The ether-insoluble white solid was 2-*aminoethylstearate hydrochloride* (5), m.p. 121—123 °C (42%) (Found: C, 65.95; H, 11.75; N, 3.8. $C_{20}H_{42}ClNO_2$ requires C, 66.0; H, 11.55; N, 3.85%), $v_{max.}$ 2 040 (NH_3^+), 1 740 (ester C=O), and 1 170 cm^{-1} (ester C–O–C).

When a mixture of compound (5) (which was insoluble in cold aqueous or organic solvents), 50% aqueous ethanol, and 1 mol. equiv. of either sodium carbonate or ethylamine was warmed to 50—60 °C until a clear solution resulted, compound (2) (identified by mixture m.p. and i.r. spectra with an authentic sample) separated on cooling in yields of 90—95%. Similar reactions involving compound (9), m.p. 107—109 °C (Found: C, 67.0; H, 11.8; N, 3.55. $C_{21}H_{44}ClNO_2$ requires C, 66.75; H, 11.65; N, 3.7%), $v_{max.}$ 2 040 (NH_3^+), 1 740 (ester C=O), and 1 165 cm^{-1} (ester C–O–C), were observed when compound (7) was treated with thionyl chloride.

Stearic Acid with Bis-(2-hydroxyethyl)amine.—A mixture of stearic acid (14.2 g), bis-(2-hydroxyethyl)amine (2.62 g), and TVO (5 g), when heated at 200 °C for 7 h, gave compound (10) (96%), m.p. 72—74 °C (Found: C, 77.05; H, 12.6; N, 1.6. $C_{58}H_{113}NO_5$ requires C, 77.1; H, 12.5; N, 1.55%), $v_{max.}$ 1 735 (ester C=O), and 1 630 cm^{-1} (amide C=O), no NH bands; τ(CDCl$_3$) 7.56—7.80 (overlapping ts, 6 H, CH$_2$–CO), 6.28—6.48 (m, 4 H, N–CH$_2$), and 5.78 (br, t, 4 H, CH$_2$–O·CO); ^{13}C, *cf.* structure (10), also 173.5 (C=O), stearyl chain at 31.95, 29.7, 24.9, 25.35, 22.7, and 14.1 p.p.m. When this reaction was carried out using an equimolar ratio of reactants for periods of 14—20 h at reflux temperatures in solvents such as xylene and ligroin compound (16), m.p. 72—73 °C (from ethanol), (90%)

separated (Found: C, 75.45; H, 12.55; N, 2.15. C_{40}-$H_{79}NO_4$ requires C, 75.35; H, 12.4; N, 2.2%), $v_{max.}$ 3 400br (OH), 1 730 (ester C=O), and 1 630 cm^{-1} (amide C=O); τ(CDCl$_3$) 7.60—7.80 (overlapping ts, 4 H, CH$_2$CO), 6.44 (ts, 4 H two N–CH$_2$), 6.28 (t, *J* 6 Hz, 2 H, CH$_2$OH), and 5.84 (t, *J* 6 Hz, 2 H, CH$_2$–O–CO). Separate heating of equimolar quantities of compound (16) and stearic acid in TVO at 180 °C for 7.5 h gave the di-ester (10) (85%).

Stearic Acid with Propane-1,3-diamines.—Heating of equimolar quantities of stearic acid with propane-1,3-diamine in TVO at 180—190 °C for 5 h gave NN′-*distearoyl-propane-1,3-diamine* (11) (92%), m.p. 133—135 °C (from alcohol) (Found: C, 77.4; H, 12.8; N, 4.55. $C_{39}H_{78}N_2O_2$ requires C, 77.2; H, 12.9; N, 4.6%), $v_{max.}$ 3 300 (NH stretch), 1 640 (C=O), and 1 550 cm^{-1} (NH bend); τ 7.80 (t, *J* 8 Hz, CH$_2$·CO) and 6.72 (q, *J* 5 Hz, NH·CH$_2$). A similar reaction with bis-(3-aminopropyl)amine gave *bis-*(3-*stearamidopropyl)amine* (12) (88%), m.p. 115—117 °C (Found: C, 76.15; H, 13.0; N, 6.3. $C_{40}H_{81}N_3O_2$ requires C, 76.0; H, 12.8; N, 6.3%), $v_{max.}$ 3 300 (NH stretch), 1 640 (C=O), and 1 550 cm^{-1} (NH bend); τ 7.76 (t, *J* 8 Hz, CH$_2$·CO), 7.28 (t, *J* 7 Hz, CH$_2$–NH–CH$_2$), 6.56 (q, *J* 5 Hz, CONH*CH*$_2$), and 3.60 (br, NH).

When compounds (11) and (12) were heated at 230 °C for periods of 30—65 h, they were recovered in over 90% and cyclisation was not detected.

Cyclisation with Phenylphosphordiamidate (PPDA).—A mixture of compound (13) (2.4 g) and PPDA (1.36 g) was heated at 240—250 °C for 7 min, cooled and boiled in n-butylamine (40 ml). Solid material was removed and when the solution was cooled the imidazoline (14) [5] (1.1 g, 90%) separated in two crops. Fractional evaporation of the butylamine solution yielded crops of *N*-stearoylbutylamine (84%). No reaction was observed when compound (13) was boiled in butylamine without PPDA treatment.