N,N'-Ethylenediyl-*Bis*-Alkanamides: Differential Scanning Calorimetry Studies

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ABSTRACT: Some longer-chain *bis*-alkanamides of ethylenediamine have been synthesized and crystallized for use as potential standards for the measurement of decomposition of aminophylline suppositories. The thermal properties of the compounds have been investigated by differential scanning calorimetry (DSC). Each of the compounds was found to give two endotherms. The endotherms at the higher temperature corresponded to the melting temperatures. However, over the homologous series, the upper endotherm demonstrated paradoxical behavior in that the temperature decreased as the length of the alkanoyl chain, and hence the relative molecular mass, increased. The endotherm at the lower temperature could not be attributed to any visible change in the physical or microscopic state of the crystals. It behaved more as expected from the thermal properties of other fatty acid derivatives, such as the esters, mono-, di-, and triglycerides, in that the temperature increased as the alkanoyl chainlength increased. Cooling the compounds to 25°C after this first DSC run and then reheating under the same conditions showed that the upper endotherm remained the same but that a number of new endotherms replaced the lower endotherm. The endotherms found during this repeat run had lower enthalpies per gram than were obtained from the freshly crystallized materials. A possible structure for the crystals is presented. A model is proposed with hydrogen bonding and van der Waals bonding between adjacent molecules where differential breaking of these bonds causes the two initial endotherms.
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KEY WORDS: Differential scanning calorimetry, *N,N'*-ethylenediyl-*bis*-alkanamides, thermal properties.

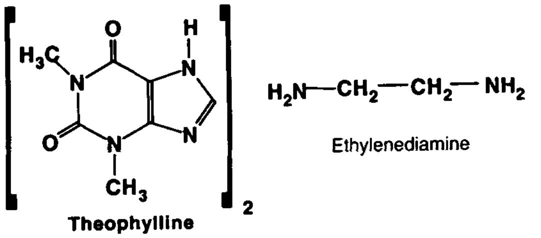

FIG. 1. The structure of theophylline (left) and ethylenediamine (EDA) (right), which are present in a ratio of 2 (theophylline):1 (EDA) in aminophylline (Ref. 1). The presence of EDA is intended to increase water solubility, and, therefore, the rate of absorption of theophylline from medicinal formulations.

Pryce-Jones *et al.* (1) investigated the behavior of aged aminophylline suppositories under differential scanning calorimetry (DSC). It had previously been reported that aged aminophylline suppositories contained *bis*-amide decomposition products (2–6). The structures of theophylline and ethylenediamine (EDA) and the composition of aminophylline are shown in Figure 1. Pryce-Jones *et al.* (7) and de Blaey and Rutten-Kingma (3) showed that there was considerable reduction in the release of theophylline from aged aminophylline suppositories and that aging corresponded to an increase in the melting temperatures of the suppositories. None of the reports (2–6) had attempted to quantify the amount of decomposition products and relate them to the deterioration in the product. Pryce-Jones and McGuffie (8), Grant *et al.* (9) and Pryce-Jones *et al.* (1,10,11) investigated various methods including assay of EDA, and DSC, gas–liquid chromatography (GLC) and GLC/mass spectrometry (MS) of decomposition products, to quantitate deterioration of the product during its storage life.

When Pryce-Jones *et al.* (1,10) compared the DSC behavior of aged aminophylline suppositories with those of freshly made suppositories, they found that the thermograms showed some changes. Firstly, the endotherm, due to the boiling point of EDA, had disappeared, and secondly, two new peaks had appeared at approximately 95 and 110°C. After extracting the remaining triglycerides and recrystallizing the residue, Pryce-Jones *et al.* (1,10) obtained a material that gave two endotherms at approximately 96 and 146°C in the DSC. The proposed reaction sequence for the aminolysis of triglyceride suppository bases by EDA to form *N,N'*-ethylenediyl-*bis*-alkanamides and mixtures of mono-, di-, and triglycerides is shown in Scheme 1 (1). In suppository bases, the fatty acid residues range between 10 and 18 carbons and all alkyl chains are saturated. Assuming that the earlier work was reasonable evidence that *N,N'*-ethylenediyl-*bis*-alkanamides were formed (2–6,11), Pryce-Jones *et al.* (1) made symmetrical *N,N'*-ethylenediyl-*bis*-hexadecanamide in an attempt to use it as a standard with which to compare the enthalpies of the endotherms of the aged suppositories. However, although the material contained two endotherms at approximately 117 and

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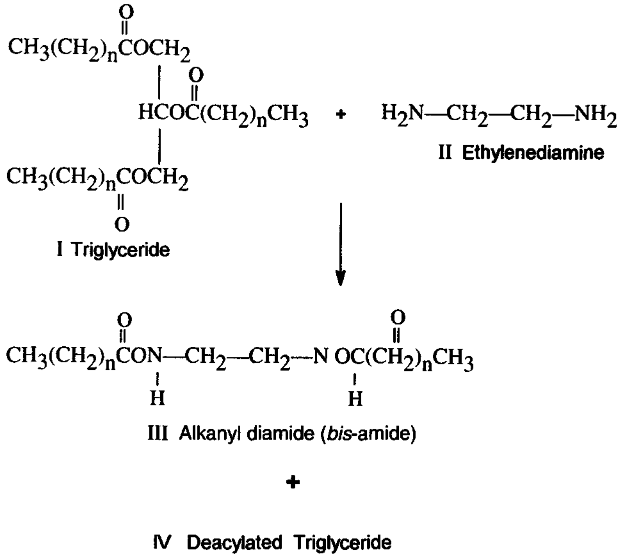

SCHEME 1

149°C, it was clearly not the same as the recrystallized material from the aged suppositories. Furthermore, when the synthetic material was mixed with fresh suppository base, the positions of the peaks changed to approximately 118 and 133°C, again not identical with that of the aged aminophylline suppositories. Similar symmetrical *bis*-alkanamides of EDA had previously been reported (12,13), and it was thought that one of these might be a suitable standard. However, the original authors had reported unusual melting temperatures for the materials they had synthesized. As the carbon chain of the fatty acids increased, there appeared to be a decrease in the melting temperatures. Neither author commented that this might be an unusual phenomenon. It is well established that the most usual relationship between melting temperature and relative molecular mass of fatty acid derivatives is that the melting temperature increases with an increase in the relative molecular mass (RMM) (12–14).

The objectives of the current research were to investigate (i) the DSC properties of a range of long-chain alkanoyl ($n > 9$) symmetrical *N,N′*-ethylenediyl-*bis*-alkanamides to try to identify one compound that has endotherms at approximately 96 and 146°C, which might be used as a standard material against which to measure the appearance of breakdown products in aged aminophylline suppositories; (ii) whether the compounds changed their properties on subsequent heating, as might have happened in studying the aged suppositories, or if they were polymorphic; (iii) the possibility that the symmetrical *N,N′*-ethylenediyl-*bis*-alkanamides have thermal properties that do not conform to those expected of other derivatives of the same fatty acids; and (iv) to try to draw some conclusions about the crystal structures of the compounds studied.

EXPERIMENTAL PROCEDURES

All solvents used were either analytical reagent-grade (Merck Ltd., Lutterworth, Leicestershire, United Kingdom) or puriss (Aldrich Chemical Company, Poole, Dorset, United Kingdom) Fatty acid chlorides were obtained from either Fluka Chemicals Ltd. (Glossop, Derbyshire, United Kingdom), Aldrich Chemical Company (Poole, Dorset, United Kingdom), or Lancaster Synthesis (Morecambe, Lancashire, United Kingdom).

Preparation of N,N′*-ethylenediyl-*bis*-alkanamides.* Samples of each of six homogeneous synthetic *N,N′*-ethylenediyl-*bis*-alkanamides (alkanoyl chains C_9 to C_{20} and C_{22}) were prepared by cautiously adding a solution of the appropriate alkanoyl chloride in acetonitrile or benzene to EDA (hydrate) (in the same solvent) in a 2:1 molar ratio (this reaction can be vigorous with the shorter-chain acid chlorides). The white flocculent precipitate, which formed immediately, was filtered off and dried in a vacuum oven at 105°C. The white to off-white amorphous powder residue, which for the higher RMM compounds was only poorly soluble in most solvents, was found to dissolve at low concentrations in hot $CHCl_3$/MeOH (50:50), $CHCl_3$/dimethylformamide (50:50), pentylethanoate, ethylbutanoate, or benzene. Higher concentrations were achieved in hot methoxyethanol or butan-1-ol, butan-2-ol, or 2-methyl-2-propanol. Butan-1-ol was used to recrystallize the products. A low concentration of water (less than 5%) helped form clear solutions in the hot solvents during the first crystallization, but was not needed on subsequent recrystallizations. The crystallized products were dried in air.

Analytical procedures. H, Cl, and N microanalysis was carried out on the pure *bis*-amides and the materials extracted from the suppositories. High-field ^1H nuclear magnetic resonance (NMR) spectra were obtained on a Bruker (Coventry, West Midlands, United Kingdom) AMX-400 spectrometer at 400 MHz. About 50 mg of the sample was dissolved in 0.5 cm^3 deuterochloroform at 323 K (15).

Melting temperatures. Melting temperatures were determined on a Linkam TH600 hot stage with a PR600 controller (Linkam, Epsom, Surrey, United Kingdom) fitted to an Olympus Vannox microscope, Olympus Optical Co. (London, United Kingdom) (10).

DSC. A Du Pont Instruments Model 9900 thermal analyzer and a DuPont Instruments Model 910 differential scanning calorimeter (DuPont de Nemours SA, Stevenage, Herts., United Kingdom) were used to investigate thermal properties of EDA, suppository bases, synthetic *bis*-amides, and decomposition products extracted from aged/heated aminophylline and EDA suppositories (1,9). Sample weights of between 5 and 9 mg were placed in sealed metal pans and tested against similar sealed reference pans containing alumina (Al_2O_3). The test runs were all carried out at a heating rate of 10°C/min. After heating the samples in the DSC, the pans were cooled and some time later (approximately 24 h) resubjected to a second DSC analysis.

RESULTS

The twice-recrystallized materials were all white in color. All crystals were small and approximately isodiametric plates that were very thin. These materials were all bulky and of low density.

The NMR results and elemental analysis of the synthesized compounds confirmed the results reported by Eccleston *et al.* (15). The melting temperatures of the thirteen *N,N'*-ethylenediyl-*bis*-alkanamides that were synthesized were the same by DSC and hot-stage microscopy and are shown in column 3 of Table 1. Figure 2 shows the stacked DSC thermograms for the *N,N'*-ethylenediyl-*bis*-alkanamides with odd numbers of carbon atoms in the alkanoyl chains. Figure 3 shows the same data for the compounds with even numbers of carbon atoms in the alkanoyl chains. For compounds containing 20 to 40 carbon atoms (total), there were two endotherms, one between 97 and 123°C, and a second one between 145 and 167°C. For the two longer compounds, 42 and 46 carbon atoms, (Fig. 4), there were three and five endotherms, respectively. The temperatures of each of the endotherms are shown in Table 1, together with their enthalpies.

A graph of the temperature of each of the two endotherms (and two main endotherms for the 42 and 46 carbon compounds) against total carbon number in the molecule is shown in Figure 4. The upper graph line in Figure 4, representing the melting endotherm, shows an irregular downward trend with an increase in relative molecular mass. The lower graph line curve for the lower endotherm in Figure 4, however, shows the opposite, i.e., an irregular increase in the temperature that corresponds to an increase in relative molecular mass.

Figure 5 shows the same results as Figure 4, but the data have been separated into Figure 5A, which shows the graph for the compounds containing odd numbers of carbon atoms in the alkanoyl chains, and Figure 5B, which shows the graph for the compounds containing even numbers of carbon atoms.

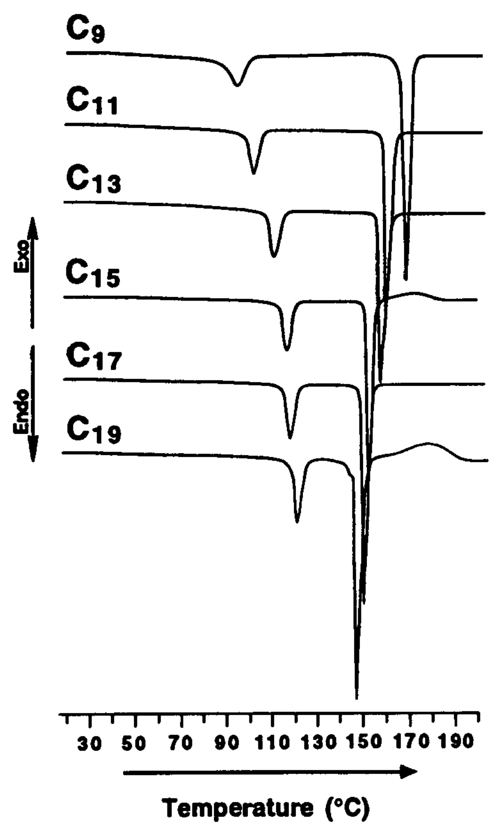

FIG. 2. Superimposed differential scanning calorimetry thermograms of the symmetrical ethylenediyl-*bis*-alkanamides with odd-carbon alkanoyl chains. These were obtained by heating compounds that had been crystallized from butan-1-ol and then dried in air. Exo, exotherm; Endo, endotherm.

TABLE 1
Temperatures and Enthalpies of Both Endotherms Given by Homogeneous Long-Chain Freshly Crystallized Alkanamides of Ethylenediamine on Their First Differential Scanning Calorimogram[a]

	First endotherm		Second endotherm	
N,N'-ethylenediyl-*bis*-alkanamides	Temperature °C	Enthalpy J/g	Temperature °C[b]	Enthalpy J/g
Nonamide	97.6	50.2	166.3	135.4
Decanamide	98.2	47.8	163.8	115.2
Undecanamide	106.4	36.5	160.8	107.9
Dodecanamide	106.2	50.0	157.8	136.5
Tridecanamide	114.0	43.8	158.0	43.8
Tetradecanamide	114.1	68.4	154.2	158.9
Pentadecanamide	121.1	41.3	154.3	121.1
Hexadecanamide	116.5	33.7	150.6	88.4
Heptadecanamide	119.9	54.8	149.9	151.4
Octadecanamide	121.5	44.7	149.6	120.2
Nonadecanamide	122.3	49.3	147.5	137.7
Docosanamide	122.6	58.0	143.4	114.7
Eicosanamide	127.3	52.3	145.3	113.1

[a] The second endotherm corresponds to the melting temperature found by hot-stage microscopy.
[b] Also the melting temperature.

The second DSC thermograms (reruns of samples from Figs. 2 and 3) are shown in Figures 6 and 7. They show that, for most of the samples, there were more phase transitions than originally present. The only one with fewer phase transitions was the *bis*-docosanamide. The thermograms showed different numbers of phase changes. The maximum number of such events was six, while most compounds showed four, and a smaller number showed five and three. Most of the phase changes were endotherms; however, in the thermograms of the first eight compounds (C_{20} to C_{34}) there was a small exotherm. The phase changes were arbitrarily assigned code letters, starting at the highest temperature, which was designated A, and then B, C, D, E, and F with each successive reduction in temperature as shown in Figures 8 and 9. The respective temperatures for the position of each thermal event are given in Table 2. The melting temperatures of the largest endotherm for each compound had not changed substantially from that in the first DSC of the unheated crystalline material as seen from comparing the upper line of Figures 8 and 9 with those of Figure 5.

DISCUSSION

When a fresh sample of a long chain symmetrical *bis*-alkanamide of EDA was heated at room temperature for the first

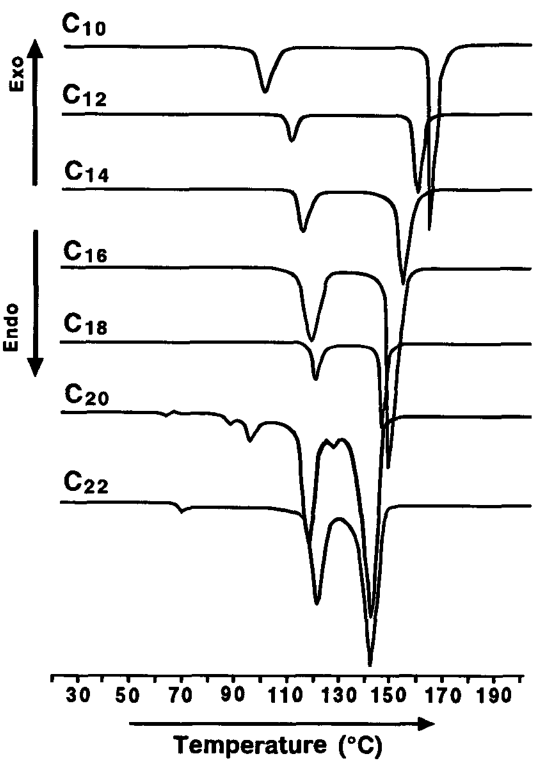

FIG. 3. Superimposed differential scanning calorimetry thermograms of the symmetrical ethylenediyl-*bis*-alkanamides with even-carbon alkanoyl chains. These were obtained by heating compounds that had been crystallized from butan-1-ol and then dried in air. See Figure 2 for abbreviated words.

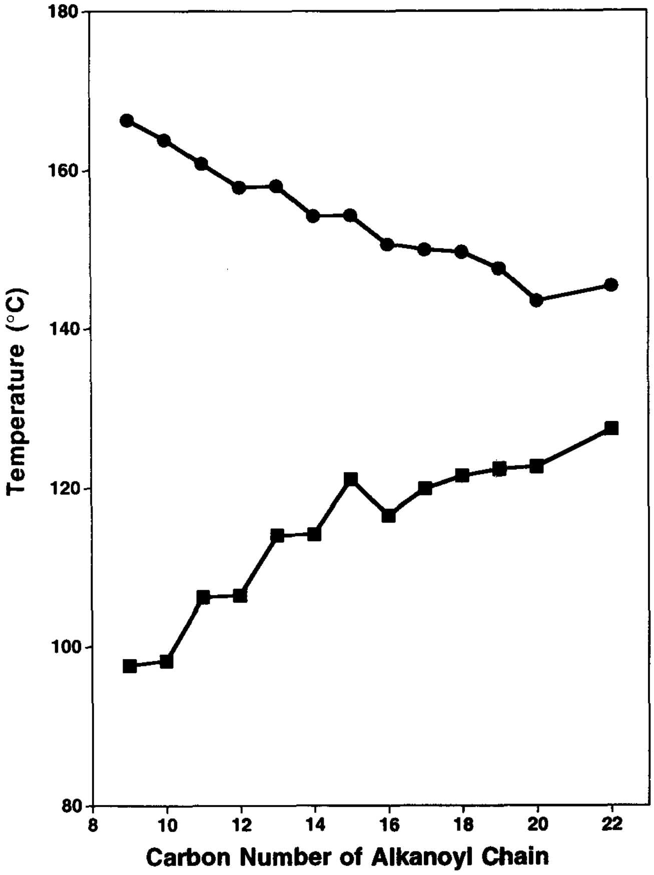

FIG. 4. Graph of the endotherm temperatures plotted against alkanoyl carbon number for all odd- and even-carbon ethylenediyl-*bis*-alkanamides. The upper graph line (●) shows the plot for the second endotherm (identified as the melting temperature) and the lower graph line (■) shows the plot for the first endotherm.

time, two endotherms were observed in each thermogram. The second endotherm found in each thermogram was identical to the melting temperature observed by hot-stage microscopy. It was concluded that these endotherms are due to melting of the compounds. The symmetrical *bis*-alkanamides all gave different thermograms after being heated to 200°C, cooled, and then heated again. This is an indication that they may be polymorphic; although, in most cases, the final melting temperatures (second runs) varied by less than 1°C from the melting temperatures found during the first runs. It was concluded that, while several of the compounds had melting temperatures close to 146°C, none of them produced a lower endotherm near enough to 96°C to allow it to be used as an external standard against which to measure the amount of diamide by DSC.

When the melting temperatures of the odd-carbon compounds were plotted against carbon number, there was a smooth and almost predictable curve (Figs. 4 and 5A), and the same feature was seen in the graph of the even-carbon molecules only (Fig. 5B). However, when plotted together (Fig. 4), a "saw-toothed" appearance was seen on a part of the graph, i.e., the graph demonstrated a high and low alternation of melting points, resulting in a stepwise progression. This is characteristic of fatty acids and some of their other derivatives (16–19). Larsson (16,20) and Malkin (19) have explained this as being due to the odd- and even-carbon alkyl chains having their terminal methyl groups on opposite sides of the molecules, which prevents the odd-carbon chains from packing close to their neighbors, thus reducing the energy required to disrupt the crystal structure and thereby lowering the melting points below those expected. A paradoxical observation in this study was that the odd-number carbon chain *bis*-alkanamides had the higher melting temperatures, whereas in the curves published by Malkin (19) and Larsson (20) it was shown that the even-carbon molecules have higher melting temperatures for most fatty acids and their glyceride esters.

The melting points (second endotherms in Table 1) of the long-chain symmetrical *bis*-alkanamides of EDA decreased from 166.3°C (C_9 alkanoyl) to 143.4°C (C_{20} alkanoyl) as the carbon chainlength and the RMM increased. This was another paradoxical observation that would not be expected from the melting points of the saturated straight-chain fatty acids (17), fatty acid methyl esters (18), fatty acid esters of glycerol (19), fatty acid amines (21), and most of their other derivatives, which all increase with increasing chainlength. However, similar depressions of melting temperatures with increasing carbon number have been reported for the 2-alkyl-

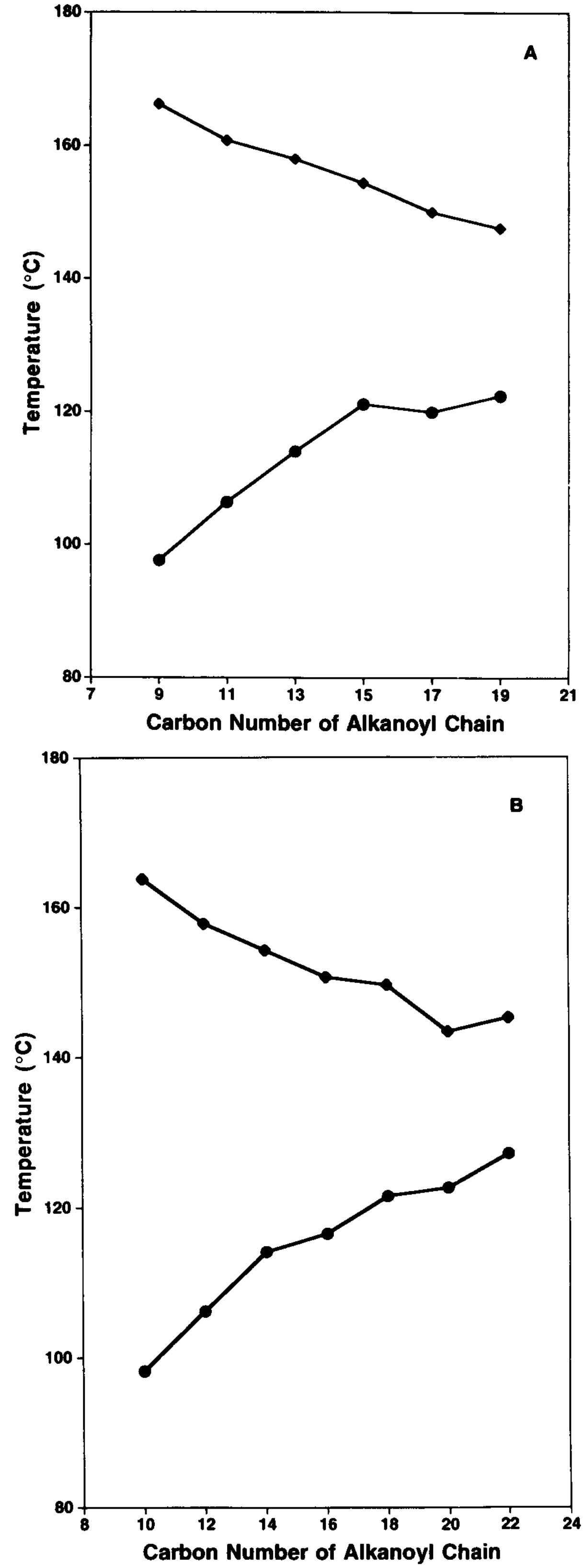

FIG 5. (A) Graphs of the endotherm temperatures plotted against alkanoyl carbon number. The graph plots the endotherms for the odd-carbon ethylenediyl-*bis*-alkanamides. (B) Graphs of the endotherm temperatures plotted against alkanoyl carbon number. The graph plots the endotherms for the even-carbon ethylenediyl-*bis*-alkanamides: —●—, first endotherm; —◆—, second endotherm.

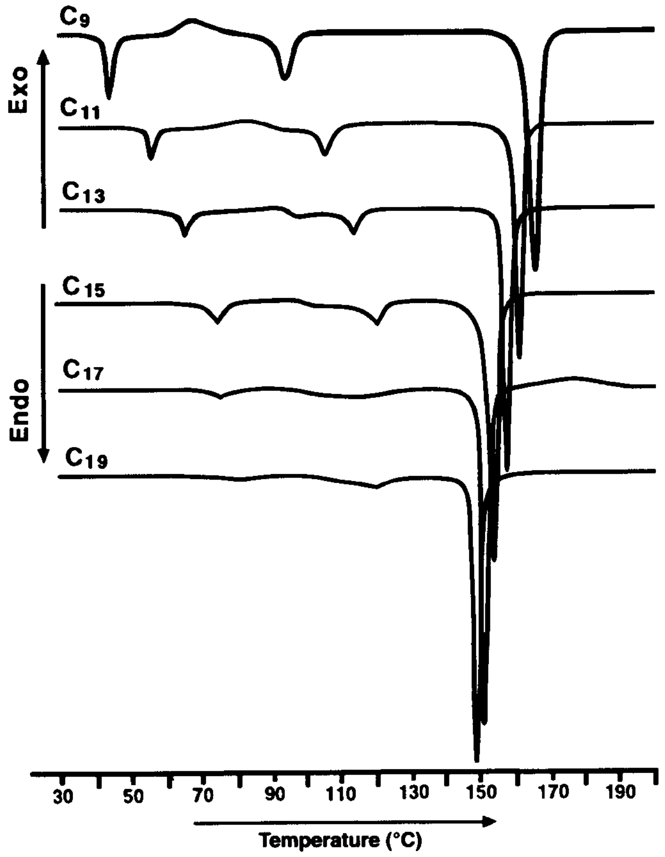

FIG. 6. Repeat differential scanning calorimetry thermograms of the symmetrical ethylenediyl-*bis*-alkanamides with odd-carbon alkanoyl chains. These thermograms were obtained from the samples, whose endotherms are shown in Figure 2, after they had been cooled to 25°C and then reheated in the same pan under the same conditions.

benzimidazoles (22) and the *bis*-amides of 4,4′-diaminodiphenylmethane (23).

The first (lower) endotherms from each first DSC run could not be attributed to any visible physical changes. However, its temperature increased as the chainlength increased. This is in keeping with most observations made on fatty acids and their derivatives (16–21,24,25). This endotherm may represent a phase change, which in turn might indicate that the compounds are liquid crystals (10).

Apart from those at the melting temperatures, the endotherms seen in the second DSC runs were different from, and more numerous than, those of the first runs. They were so numerous in some samples that it would be difficult to speculate on their origins without further structural data. The last endotherm, indicated by "A," had a similar temperature to the original melting temperature (recrystallized from butan-1-ol) and to the second endotherm found during heating of the freshly crystallized material. The small differences found between the upper endotherm temperatures from both the first and second DSC runs may be due to experimental error or they may be due to the materials having crystallized in different polymorphic forms. It is not possible to draw definite conclusions without further investigations. During the

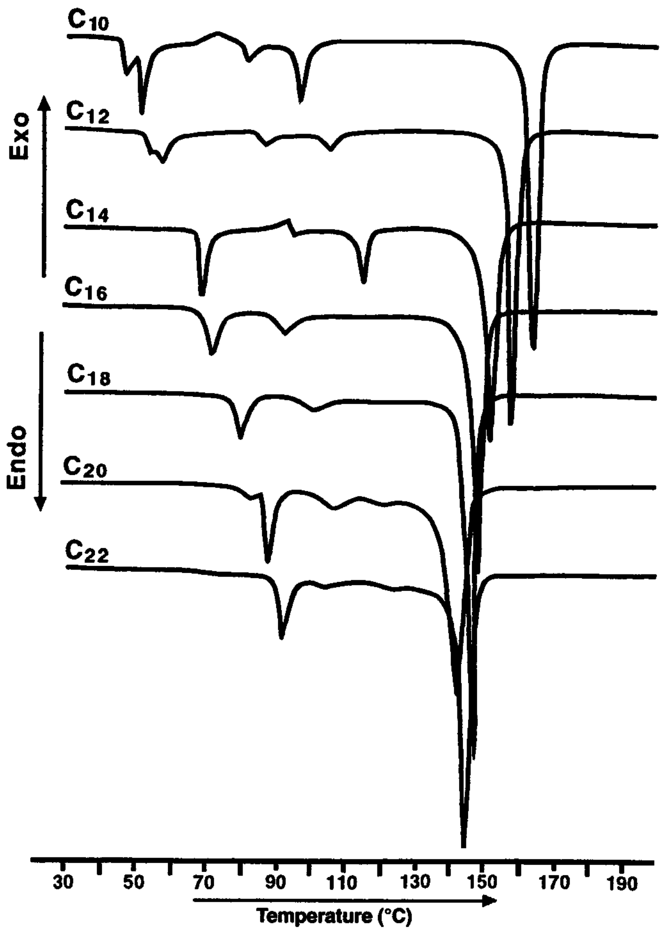

FIG. 7. Repeat differential scanning calorimetry thermograms of the symmetrical ethylenediyl-*bis*-alkanamides with even-carbon alkanoyl chains. These thermograms were obtained from the samples, whose endotherms are shown in Figure 3, after they had been cooled to 25°C and then reheated in the same pan under the same conditions.

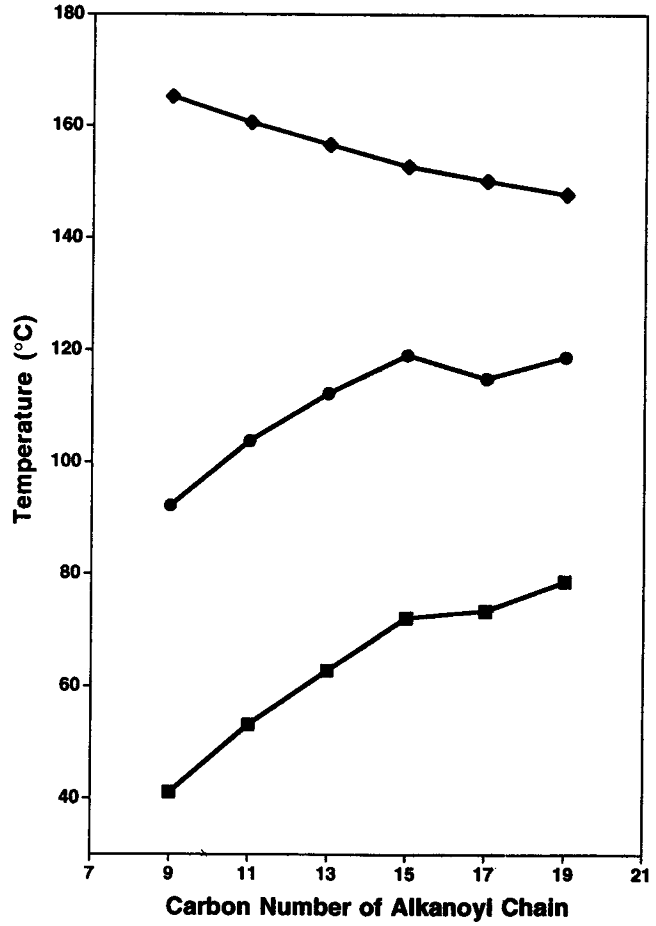

FIG. 8. Graphs of the endotherm temperatures plotted against alkanoyl carbon number for the odd-carbon ethylenediyl-*bis*-alkanamides (from Fig. 6 and Table 2). The temperatures of the endotherms A, —♦—; B, —●—; and E, —■— are shown plotted against alkanoyl carbon number.

second run, the endotherms B, C, E, and F were all considerably smaller than the endotherm marked "A" and the lower endotherm from the first heating. The only clear conclusion that can be drawn from these second runs is that the crystalline structure of the compounds subjected to melting and solidification is quite different from, and possibly more complex, than that existing in the material crystallized from butan-1-ol. Although it would not necessarily indicate that the materials formed by crystallization and fusion are polymorphic forms, it seems possible that phase changes occurred that represent rearrangements of the individual molecules in the crystals.

Tucker (12), Takase (13), and Agre *et al.* (14) all reported the synthesis of some of these and the shorter-chain (C_1–C_8 alkanoyl) symmetrical *bis*-alkanamides of EDA. The melting temperatures they found were the same (within acceptable experimental variation) as those reported here, although none of the authors commented upon the fact that, unexpectedly, the melting temperatures rose to a peak at 191°C for the C_4 acid and then decreased gradually.

Many fatty acids and their derivatives form long straight molecules in the crystalline state (16,19,20,26–28). Observation of the chemical structure of the compounds shows that it is possible to consider the crystals as being formed by hydrogen bonding between the carbonyl oxygen atoms and the hydrogen atoms attached to the amide nitrogen atoms, as well as by van der Waals bonding between the alkyl chains (Fig. 10), which shows that the molecules can be represented with linear structures. The amide bonds are planar with the hydrogen atom on the nitrogen on the opposite side of the bond to the adjacent carbonyl oxygen (also planar). These two groups will always be arranged so that the proton on the nitrogen will be on the opposite side of the molecule to the carbonyl oxygen. It can also be seen from this diagram that, in this arrangement, the two carbonyl oxygens will be on opposite sides of the molecule, as will the two nitrogen protons. When lined up side by side, it is possible that the adjacent molecules form hydrogen bonds from the proton on the amide nitrogen of one molecule to the carbonyl oxygen of the next molecule. The other amide bond of the molecule is arranged the other way around, so that the carbonyl oxygen and the nitrogen proton again form a hydrogen bond. The same process

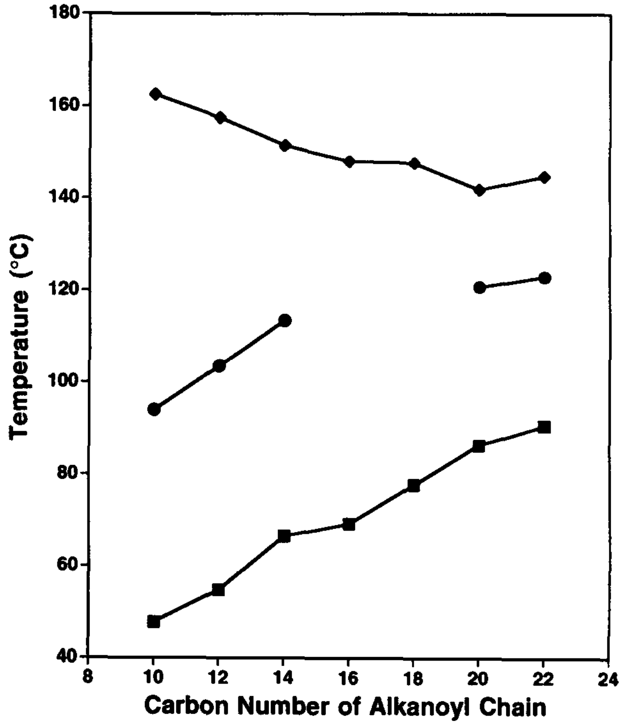

FIG 9. Graphs of the endotherm temperatures plotted against alkanoyl carbon number for the even-carbon ethylenediyl-*bis*-alkanamides (from Fig. 7 and Table 2). The temperatures of the endotherms A, —◆—; B, —●—; and E, —■— are shown plotted against alkanoyl carbon number.

TABLE 2
Temperatures and Enthalpies of Both Endotherms Given by Homogeneous Long-Chain Alkanamides of Ethylenediamine After Cooling from Their First Differential Scanning Calorimogram and Reheating Under the Same Conditions[a]

Ethylenediyl-*bis*-alkanamides	Endotherm temperature (°C)					
	A[b]	B	C	D	E	F
Nonamide	165.2	92.2	—	65.6X	41.1	—
Decanamide	162.5	93.9	78.3	69.2X	47.8	43.5
Undecanamide	160.6	103.8	91.3	79.6X	53.2	—
Dodecanamide	157.5	103.5	84.7	80.1X	54.8	52.4
Tridecanamide	156.6	112.32	94.98	90.4X	62.9	—
Tetradecanamide	151.4	113.3	93.53	90.6X	66.5	—
Pentadecanamide	152.7	119.0	99.18	94.7X	72.2	—
Hexadecanamide	148.0	—	91.2	—	69.2	—
Heptadecanamide	150.2	114.9	101.1	—	73.4	—
Octadecanamide	147.7	—	98.9	—	77.7	—
Nonadecanamide	147.8	118.8	106.5	—	78.7	—
Docosanamide	141.9	120.7	105.1	—	86.3	81.4
Eicosanamide	144.8	122.9	—	—	90.5	—

[a] The endotherm "A" is similar to the original melting temperature found by hot-stage microscopy and the value found on the first differential scanning calorimetry run. X, Indicates that the peak is an exotherm; —, indicates that there was no equivalent peak observed.
[b] Also the melting temperature.

can happen on the other side of the molecule, resulting in a highly ordered crystal, which is effectively two-dimensional. This representation shows that each molecule would be slightly longitudinally displaced from its neighbors, giving

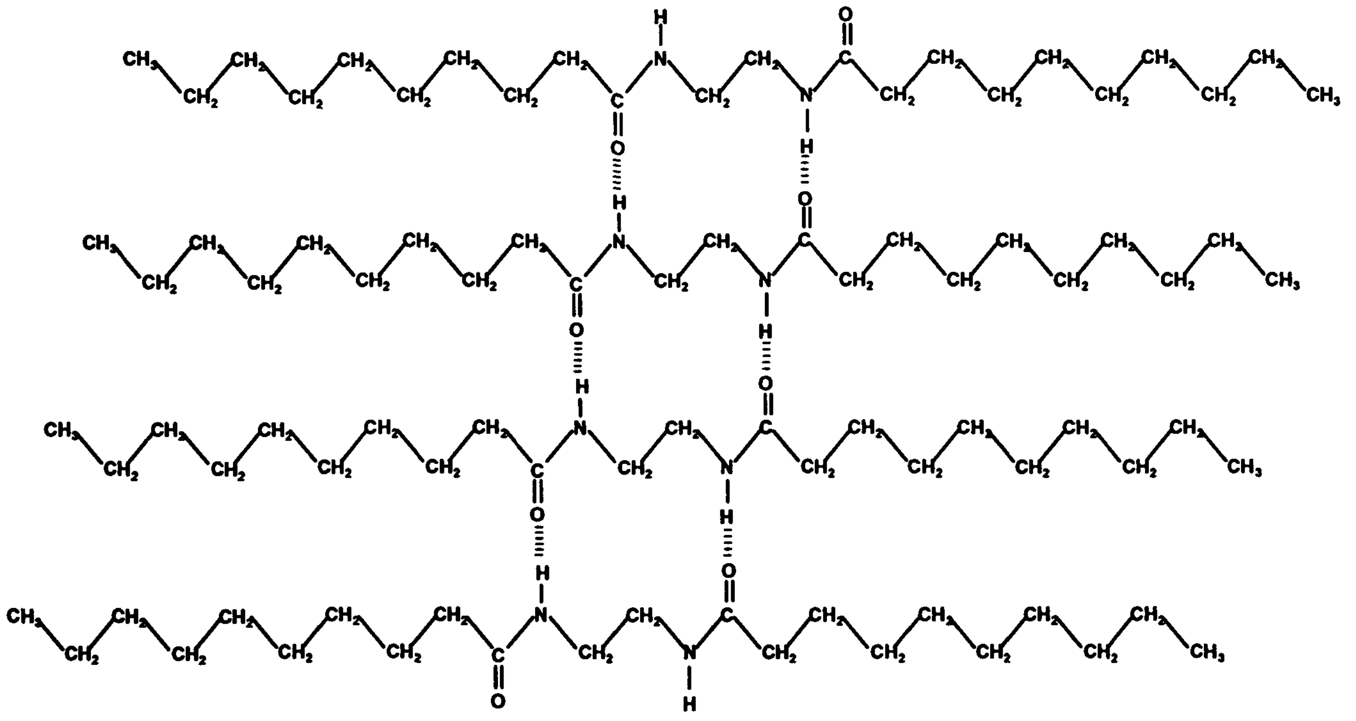

FIG. 10. Representation of a possible configuration of the *N,N'*-ethylenediyl-*bis*-alkanamides in crystals, showing the adjacent chains laterally displaced. This is envisaged as being due to the hydrogen bonding between the carbonyl oxygen atoms on one molecule and the amide hydrogens on the adjacent molecule and *vice versa*. Only the structure of the *bis*-decanamide is shown.

rise to an angle of tilt with respect to the plane of the end methyl groups. The result would be a thin layer of molecules with essentially two dimensions. Such a structure might explain the thin and fragile plates that the crystals formed.

We concluded that the two endotherms observed during this study were due to the binding of the two different parts of each molecule. One endotherm might be due to the loosening of the van der Waals bonds between alkyl chains and the other to breaking of the hydrogen bonds between the adjacent amide bonds. It could be inferred further that the lower temperature endotherm was due to loosening of the van der Waals bonds between the alkyl chains, leading to them becoming "liquid" as suggested by Skoulios and Luzzati (29) for the sodium salts of fatty acids. This would be consistent with the increase in the temperature of the lower endotherm parallel with the increase in alkyl chainlength. This would then suggest that the melting temperature is dependent mainly on the intermolecular hydrogen bonding between the adjacent amide bonds as also suggested by Skoulios and Luzzati (29).

The temperature required to disrupt the hydrogen bonds might be expected to remain constant because both the configuration of the two amide bonds and the distance between them remain constant. However, the decrease in melting temperature with increasing alkyl chainlength might be explained if this increase in size of the latter were to lower the binding constants of the hydrogen bonds. This would be expected to reduce the energy required to disrupt the crystal structure and lower the melting points. This apparently increasing influence of the carbon number of the alkyl chains over the hydrogen bonding was also cited by von Sydow (28) to explain the properties of different crystalline polymorphs of a homologous series of saturated fatty acids.

Timms (30) has suggested that, as the chainlength of monoglycerides shortens, the end groups start to interact more, resulting in more order and therefore more heat required to melt them. He further suggested that, as the chainlength increases, there is less interaction between the methyl end groups, resulting in less order, so that they are in a "more expanded state." He concludes that ". . . in the process of melting, energy is required only to separate the methylene groups, energy is released in converting the end groups from the solid to the liquid state." A mechanism such as this could be the explanation for the temperatures of the *N,N′*-ethylenediyl-*bis*-alkanamides decreasing with increasing molecular weight.

Larsson (16) and Malkin (19) have argued, convincingly, that the alternation of melting temperatures, in crystalline fatty acids, esters, and glycerides, is an indication of the molecules being arranged at an angle to the planes of their methyl end groups. This would imply that the same phenomenon occurs in the *N,N′*-ethylenediyl-*bis*-alkanamides. There is evidence (14,16,24,27,29) that molecules with long hydrocarbon chains are arranged with most of the chains parallel to one another. This complies well with the model described above and in Figure 10. If Larsson (16) and Malkin (19) are right, this and the opposite-side methyl end groups of odd- and even-chain molecules could explain why the melting temperatures alternate between consecutive molecules in the homologous series. The model described above and in Figure 10 could also explain why the melting temperatures are much higher than in the triglycerides, for example. It does not explain, however, why, in the alternation of the melting temperatures of all various derivatives of fatty acids mentioned above (14–19), the even-carbon molecules have the higher melting points while in the *N,N′*-ethylenediyl-*bis*-alkanamides, reported here, it is the odd-carbon molecules that melt at the higher temperatures.

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