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The Reaction of Phthalic Anhydride with Diethylenetriamine and Triethylenetetramine. A Literature Correction

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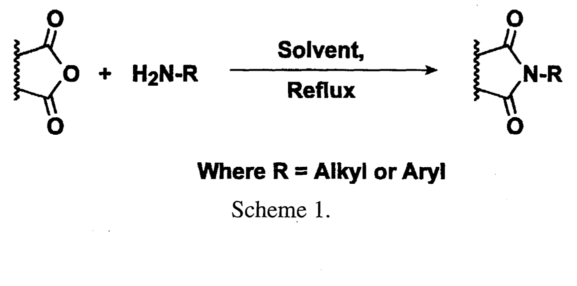
A report that phthalic anhydride reacts with diethylenetriamine in acetic acid to form hydrogen phthalate salt of bis-(2-phthalimidoethyl)amine predominantly was reinvestigated. The major product that we obtained was bis(2-phthalimidoethyl)amine, some amide, and very little of the salt. With linear triethylenetetramine, we did not obtain *N*,*N*′-bis(2-phthalimidoethyl)ethylenediamine, nor the rearranged tris(2-phthalimidoethyl)amine or 1,4-bis(2-phthalimidoethyl)piperazine reported. A novel amide — 2-{*N*-2-phthalimidoethyl-*N*-[2-(2-phthalimidoethyl)aminoethyl]carbamoyl}benzoic acid — was formed as the major product instead. The products reported in the literature are attributed to branched and cyclic amines in their triethylenetetramine, and not to rearrangement reactions. Such possibility is supported by analysis of triethylenetetramine from the same supplier (ca. 65% linear), and our failure to duplicate the results with an authentic triethylenetetramine. Several reported compounds were prepared from pure amines, with no evidence of isomerization.

There is a continuing need and interest in the synthesis of imide derivatives.[1,2] Despite the wide applicability of imides in synthetic and polymer chemistry, available routes for their synthesis are limited.[1] Among them, the dehydrative condensation of anhydride and an amine at elevated temperature (neat or in azeotroping solvents),[2] and cyclization of amic acid in the presence of acidic reagents are the typical methods.[3] Our interest is in the reaction of anhydrides with polyethylenepolyamines, including diethylenetriamine (DETA) and triethylenetetramine (TETA) (Scheme 1).

Barrett et al. have recently reported unusual major products from the reaction of phthalic anhydride with polyethylenepolyamines in acetic acid.[4] The reaction with DETA produced a π–π stabilized complex (**2**) between diphthalimidodiethylamine and phthalic acid, while TETA produced the rearranged products **5** and **6**, respectively. The products were characterized by ^{1}H and ^{13}C NMR and X-ray crystallography. We have studied the reactions of alkylsuccinic anhydrides with polyethylenepolyamines to produce bissuccinimides for use as lubricating oil additives, and agree that Barrett's results are unusual. In our work with xylene as the azeotroping solvent, only the expected bissuccinimides were formed. Therefore, we chose to repeat the reaction of phthalic anhydride with DETA and authentic TETA (98.3% linear, GC) to confirm the products and/or rearrangements.



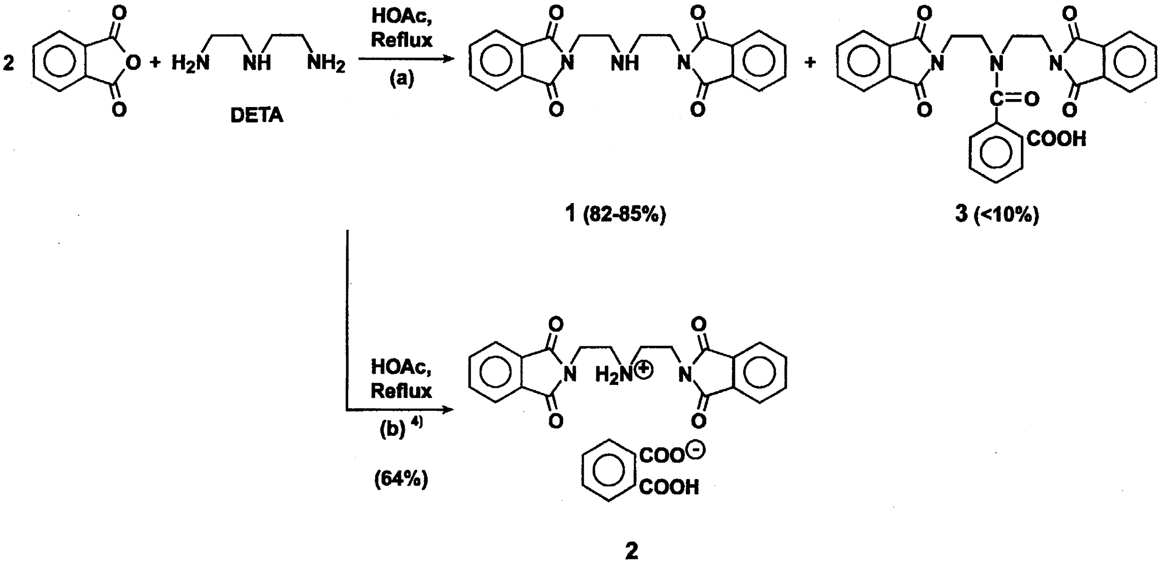
Scheme 1.

Results and Discussion

Reaction with DETA. Ng et al. obtained **1** from the reaction of phthalic anhydride with DETA in refluxing acetic acid (mp 182—183 °C; 78%, incorrect MW used and yield) (Scheme 2).[5] Barrett et al.,[4] on repeating Ng's work, obtained salt **2** instead (mp 176—177 °C; 64%, incorrect MW used and yield). The previously unrecognized product was attributed by Barrett et al. to the use of acetic acid. They further argued that **2** could have easily been mistaken for **1** since Ng's analysis was limited, and that **1** and **2** would have served equally well for their application. Since the melting points of **1** and **2** are similar, we chose to resolve the apparent discrepancy in product identification.

After a mixture of phthalic anhydride and DETA [CMR (anhydride/amine) = 2.0] was refluxed in acetic acid for 1 h and the acetic acid was stripped under vacuum, the oil was allowed to stand for 2 weeks until crystallization occurred. Recrystallization from ethanol afforded **1** (82%). Similarly, **1** (86%) was isolated when the solution after reflux was left standing at room temperature (1 week) prior to work-up. Repeating the reaction, and working up the product mixture within a day or two, afforded **1** in lower yield (ca. 40—50%). The filtrate contained noncrystallized **1**, some amide **3**, but no spectral evidence was found for the hydrogen phthalate salt **2** (NMR).[4] At a CMR = 2.2, the actual ratio used in earlier work,[4,5] product **1** crystallized from ethanol (48%), and the filtrate on standing overnight deposited a small crop which had the required elemental analysis and NMR spectra for **2** (2%).

The hydrogen phthalate salt **2** was also prepared in a stoi-



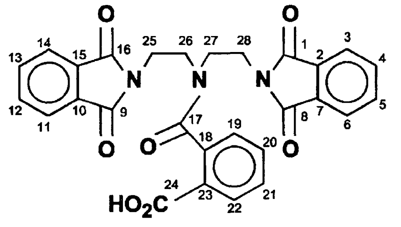
Scheme 2.

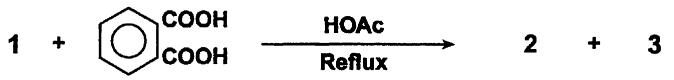
chiometric reaction of **1** with phthalic acid by refluxing in acetic acid (30 min, salt **2** ca. 40%; amide **3** ca. 60%, NMR) (Scheme 3). Continued reaction and work-up led to isolation of pure **3** (2 h, 80%). The structure of **3** was assigned based upon ^{15}N NMR and 2D NMR analysis (HETCOR) (see Table 1). The ^{1}H NMR spectrum of the methylene region of **3** ($\delta = 3.4$—3.9) (32 °C) contained peaks that appeared to be involved in a dynamic exchange process (Fig. 1). This may be due to hindered rotation about the carbon–amide bond. At the fast exchange limit (72 °C) four distinct triplets were observed that are assigned to the four distinct pairs of methylene hydrogens in structure **3**. At the slow exchange limit

Table 1. NMR Spectral Correlations for Amide 3

Carbon chem shift[a]	Carbon type[b]	Proton chem shift[c]	Assignment[d]
170.58	1C		C_{24}
167.87	2C		C_1, C_8
167.32	2C		C_9, C_{16}
166.32	1C		C_{17}
137.76	1C		C_{18}
134.35	4CH	7.80, t, 4H	C_4, C_5, C_{12}, C_{13}
132.17	1CH	7.30, t, 1H	C_{20}
131.63	2C		C_2, C_7, (C_{10}, C_{15})
131.44	2C		C_{10}, C_{15}, (C_2, C_7)
130.13	1CH	7.90, d, 1H	C_{22}
128.69	1CH	7.50, t, 1H	C_{21}
127.80	1C		C_{23}
126.22	1CH	6.96, d, 1H	C_{19}
122.94	4CH	7.38, d, 4H	C_3, C_6, C_{11}, C_{14}
45.95	$1CH_2$	3.37, t, 2H	C_{26} (C_{27})
42.20	$1CH_2$	3.77, br s, 2H	C_{27} (C_{26})
34.90	$1CH_2$	3.68, t, 2H	C_{25} (C_{28})
34.60	$1CH_2$	3.93, br s, 2H	C_{28} (C_{25})

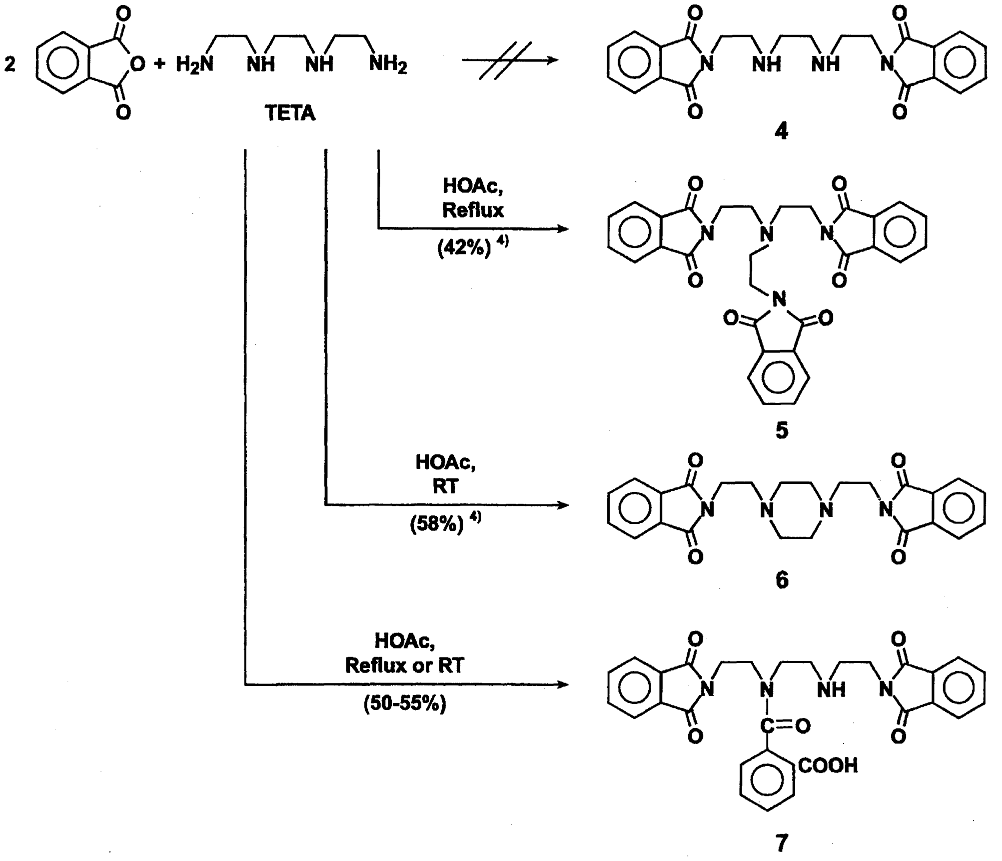
a) ppm downfield from TMS internal std. b) Obtained from DEPT and APT Expts. c) Obtained from HETCOR Expts. d) Advanced Chemistry Development Inc. Program (ACD/Labs, Toronto, Canada) was used for some assignments.





	2	3	
0.5 h	40%	60%	(NMR)
2 h	–	100	(80% Recovered)
or RT, 48 h	–	100	(69%)

Scheme 3.



Scheme 4.

(−26 °C) a more complex spectrum appeared that has not been completely assigned.

Reaction with TETA. Barrett et al.[4] were the first to react phthalic anhydride with TETA in the acetic acid system.[6] The isolated products **5** and **6** are those expected from tris(2-aminoethyl)amine and 1,4-bis(2-aminoethyl)piperazine, respectively, amines known to be present in technical TETA (Scheme 4).[7] We have independently prepared compounds **5** and **6**, and found the spectral data and mp's to be in agreement with the literature.[4] No spectral evidence was found for any rearrangements in these runs. To eliminate the complication of products resulting from isomeric amines in TETA, a linear TETA was used.

Reacting phthalic anhydride with TETA·xH$_2$O (CMR = 2.0) in acetic acid at room temperature or reflux, and varying the addition order of reactants and solvent concentration, had no major effect on the reaction; the same amide **7** was isolated predominantly in each run (ca. 50—55%), and no bisphthalimide **4**. While formation of **7** was anticipated from a stoichiometric CMR = 3.0, its formation at CMR = 2.0 was unexpected. At this time it is unclear what factors are driving this reaction at lower CMR. No pertinent peaks for products **5** and **6** were found in the filtrate by NMR.[4] The structure of **7** was based on ^{15}N NMR analysis, and the similarity of ^{1}H and ^{13}C NMR spectra to that of **3**. More specifically, the proton spectrum was solvent dependent, and possessed the diagnostic ring protons for the 2-carboxybenzoyl group, and a broad, poorly resolved, ethylene proton region at $\delta = 3.4$—4.7. With the use of trifluoroacetic acid (TFA) cosolvent, the methylene region became narrower ($\delta = 3.3$—4.2), and developed some fine structure. We suspect that amide **7** may be present in the zwitterion form in the absence of TFA, which also accounts for its low solubility in some solvents.

While the reaction of phthalic anhydride with TETA did not produce linear **4** in acetic acid, the latter was synthesized via a thermal reaction of neat phthalimide with TETA

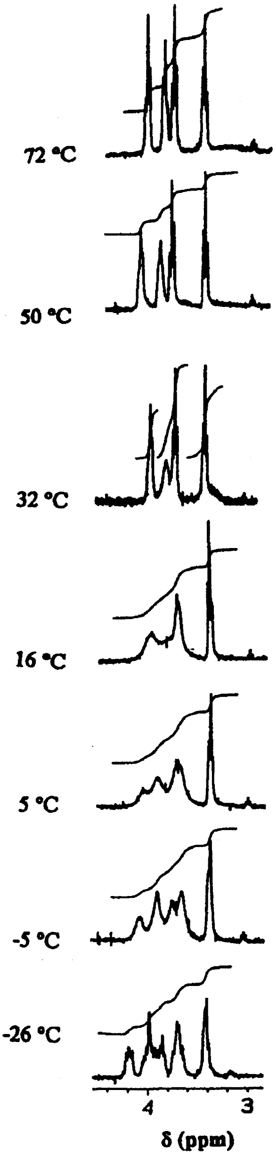


Fig. 1. Temperature Dependence of Methylene Proton Resonance (300 MHz) of **3** in Chloroform-*d* (+CF_3COOH)

at 200—210 °C (37%). With the optimization of reaction parameters (temperature, reaction time, mode of addition and CMR) the yield could be improved.

Finally, we have no satisfactory explanation why DETA in acetic acid produced **1** and little **3**, while TETA gave **7** and none of **4**. A possible rationale may involve steric and statistical considerations. A single secondary-N in DETA was assumed to be hindered leading mostly to reaction at the primary-N. In TETA, the two secondary-N's have fewer steric restictions, and they compete more favorably with the primary-N's. The refluxing acetic acid temperature may be too low to cause transformation of amide **7** into **4**. With higher boiling solvents — xylenes, propionic, and valeric acids — amide **7** was either insoluble, or it failed to rearrange into **4**.

Conclusion. In the reaction of phthalic anhydride with DETA, only a low yield of hydrogen phthalate salt **2** was isolated. The predominant product was clearly the anticipated **1**, along with some **3**. In the case of linear TETA, the predominant product was amide **7**. The products reported in the literature probably resulted from TETA isomers, and not from ethylene group migrations. This is consistent with our analysis of TETA (Fisher)[4] (ca. 65% linear), and our failure to reproduce the published results with an authentic TETA. Compounds **5** and **6** were prepared from the corresponding amines, with no evidence of rearrangement to other isomers.

Experimental

General Procedures. All melting points were obtained by DSC. ^{1}H NMR, ^{13}C NMR, and ^{15}N NMR spectra were recorded on Varian Gemini-300 spectrometer, operating at 300, 75, and 30 MHz, respectively. ^{13}C and ^{15}N NMR spectra required 0.05 M (M = mol dm^{-3}) $Cr(acac)_3$ relaxation reagent for quantitation. The chemical shifts are expressed in δ values relative to Me_4Si (0.00, ^{1}H and ^{13}C) and $HCONH_2$ (0.0, ^{15}H). GC/MS data were acquired on a Hewlett Packard 5970 spectrometer. Infrared spectra were recorded as KBr pellets on a Nicolet 510 FTIR spectrometer. Microanalyses were obtained using a Carlo Erba Analyzer. All starting materials were obtained from Aldrich, Fisher, or Dow.

Bis(2-phthalimidoethyl)amine (1). A mixture of phthalic anhydride (16.1 g, 109 mmol) and DETA (5.6 g, 54 mmol) in acetic acid (53 g) was refluxed for 1 h. After stripping in vacuo to remove acetic acid, the pale yellow oil was allowed to stand for 2 weeks (r.t.) until crystallization occurred. The product was ground to a fine powder, triturated twice with hot ethanol, filtered, and dried (P_2O_5, vacuo) to afford 16.1 g (82%) of pure **1**; white solid; mp 180 °C (lit,[5] mp 182—183 °C; lit,[8] mp 183 °C; lit,[9] mp 178—180 °C); ^{1}H NMR ($CDCl_3$) $\delta = 1.46$ (br s, 1H, NH, D_2O exchanges), 2.95 (t, 4H, CH_2), 3.77 (t, 4H, CH_2), 7.68 (m, 4H, ring), 7.72 (m, 4H, ring); ^{13}C NMR ($CDCl_3$) $\delta = 37.33$, 46.98, 122.96, 131.92, 133.67, 168.22; ^{15}N NMR ($CDCl_3$) $\delta = -214$ (imide), -344 (=NH); IR (KBr) ν_{max} 1713 (s), 1777 (w) cm^{-1}. Found: C, 66.26; H, 4.58; N, 11.26%. Calcd for $C_{20}H_{17}N_3O_4$: C, 66.10; H, 4.72; N, 11.56%. No diagnostic peaks were observed in the NMR spectrum of the filtrate for the phthalate salt **2**.

Bis(2-phthalimidoethyl)ammonium Hydrogen Phthalate (2). To a solution of DETA (5.15 g, 50 mmol) in acetic acid (80 g) was added phthalic anhydride (16.6 g, 112 mmol) and the mixture was refluxed for 1 h. After rotoevaporation in vacuo to remove acetic acid the product was recrystallized from ethanol. The first two crops (7.5 g and 1.4 g) were pure **1**. After standing overnight, a third crop was recovered from the filtrate and identified as **2** (0.32 g, 2%): white solid; mp 173 °C (lit,[4] mp 176—177 °C); ^{1}H NMR (DMSO-d_6) $\delta = 3.19$ (t, 4H, CH_2), 3.82 (t, 4H, CH_2), 7.51 (q, 2H, ring), 7.87 (m, 8H, ring), 8.07 (q, 2H, ring);[4] IR (KBr) ν_{max} 1708 (s), 1717 (s), 1776 (w) cm^{-1}. Found: C, 63.60; H, 4.51; N, 7.73%. Calcd for $C_{28}H_{23}N_3O_8$: C, 63.52; H, 4.35; N, 7.94%. The mother liquor contained additional **1** (major) and little salt **2** which failed to crystallize out.

2[*N*,*N*-Bis(2-phthalimidoethyl)carbamoyl]benzoic Acid (3). A mixture of **1** (2.0 g, 5.5 mmol) and phthalic acid (0.92 g, 5.5 mmol) in acetic acid (20 g) was refluxed for 2 h. After rotoevaporation of acetic acid in vacuo, the oil was recrystallized twice from EtOH to give pure **3** (2.24 g, 80%): white solid; mp 225 °C; ^{15}N NMR (DMSO-d_6) $\delta = -221$ (imide), -222 (imide), -264 (amide); IR (KBr) ν_{max} 1774 (m, imide), 1720 (s, imide), 1711 (s, COOH), 1647 (s, amide) cm^{-1}; ^{1}H and ^{13}C NMR spectra are listed in Table 1. Found: C, 65.81; H, 4.20; N, 8.11%. Calcd for $C_{28}H_{21}N_3O_7$: C, 65.75; H, 4.14; N, 8.22%.

***N*,*N*-Bis(2-phthalimidoethyl)ethylenediamine (4).** A mixture of phthalimide (14.7 g, 100 mmol) and TETA·$x\mathrm{H_2O}$ (7.3 g, 50 mmol) was heated to 200—210 °C in ca. 20 min, and held there, while stirring, for ca. 20 min under $\mathrm{N_2}$blanket. On reaching 160 °C the mixture became fluid, and foaming was observed initially. The product mixture (ammonia odor) was cooled, triturated with ethanol, and filtered to give crude **4** (6.1 g, 37%). After dissolving in hot 2-propanol and filtering, pure **4** crystallized from solution: white solid; mp 151 °C; IR (KBr) ν_{max} 1709 (s, imide), 1769 (wk, imide) cm^{-1}; ^{1}H NMR ($\mathrm{CDCl_3}$) $\delta = 1.53$ (br s, 2H, NH, exchanges with $\mathrm{D_2O}$), 2.73 (s, 4H, $\mathrm{CH_2}$), 2.89 (t, 4H, $\mathrm{CH_2}$), 3.77 (t, 4H, $\mathrm{CH_2}$), 7.70 (m, 4H, ring), 7.83 (m, 4H, ring); ^{13}C NMR ($\mathrm{CDCl_3}$) δ=37.73, 47.60, 48.62, 123.17, 132.04, 133.94, 168.39; ^{15}N NMR ($\mathrm{CDCl_3}$) $\delta = -225$ (imide), -355 (=NH). Found: C, 65.00; H, 5.41; N, 13.61%. Calcd for $\mathrm{C_{22}H_{22}N_4O_4}$: C, 65.01; H, 5.46; N, 13.79%.

Tris(2-phthalimidoethyl)amine (5). A mixture of tris(2-aminoethyl)amine (2.5 g, 17 mmol) and phthalic anhydride (7.6 g, 51 mmol) was refluxed in acetic acid as above to afford **5** (5.2 g, 57%): pale yellow solid; mp 192 °C (EtOH) (lit,[4] mp 183 °C); ^{1}H NMR ($\mathrm{CDCl_3}$) $\delta = 2.90$ (t, 6H, $\mathrm{CH_2}$), 3.74 (t, 6H, $\mathrm{CH_2}$), 7.69 (s, 12H, ring);[4] ^{13}C NMR ($\mathrm{CDCl_3}$) δ=35.32, 51.50, 122.94, 132.00, 133.68, 167.99;[4] ^{15}N NMR ($\mathrm{CDCl_3}$) $\delta = -225$ (imide), -355 (=N–); IR (KBr) ν_{max} 1712 (s), 1771 (w) cm^{-1}. Found: C, 67.18; H, 4.67; N, 10.70%. Calcd for $\mathrm{C_{30}H_{24}N_4O_6}$: C, 67.15; H, 4.51; N, 10.44%.

1,4-Bis(2-phthalimidoethyl)piperazine (6). A mixture of 1,4-bis(2-aminoethyl)piperazine (1.5 g, 87 mmol) and phthalic anhydride (2.6 g, 176 mmol) was heated at reflux in acetic acid as above to afford **6** (3.0 g, 80%): off-white powder (EtOH); mp 253 °C (lit,[4] mp 256 °C); ^{1}H NMR ($\mathrm{CDCl_3}$) $\delta = 2.50$ (s, 8H, $\mathrm{CH_2}$), 2.60 (t, 4H, $\mathrm{CH_2}$), 3.80 (t, 4H, $\mathrm{CH_2}$), 7.70 (m, 4H, ring), 7.82 (m, 4H, ring);[4] ^{13}C NMR ($\mathrm{CDCl_3}$) δ=35.18, 52.88, 55.58, 123.19, 132.16, 133.91, 168.27;[4] ^{15}N NMR ($\mathrm{CDCl_3}$) $\delta = -226$ (imide), -343 (=N–); IR (KBr) ν_{max} 1770 (s), 1770 (w) cm^{-1}.

2{*N*-(2-Phthalimidoethyl)-*N*-[2-(2-phthalimidoethyl)aminoethyl]carbamoyl}Benzoic Acid (7). A mixture of TETA·$x\mathrm{H_2O}$ (7.3 g, 50 mmol) and phthalic anhydride (14.8 g, 100 mmol) in acetic acid (60 g) was refluxed for 2 h. After rotoevaporation of acetic acid, the product solidified on standing overnight. After two triturations with hot ethanol, filtering, and drying, pure **7** was recovered (10.1 g, 55%): white solid; mp 227 °C; ^{15}N NMR ($\mathrm{CF_3COOD/DMSO}$-d_6) $\delta = -224$ (imide), -255 (amide), -337 (NH); ^{1}H NMR ($\mathrm{CDCl_3+CF_3COOD}$) $\delta = 3.47$ (s, 2H, $\mathrm{CH_2}$), 3.71 (m, 7H, $\mathrm{CH_2}$), 4.13 (t, 2H, $\mathrm{CH_2}$), 4.61 (br t, 1H, $\mathrm{CH_2}$), 7.01 (d, 1H, ring/amide), 7.44 (t, 1H, ring/amide), 7.57 (t, 1H, ring/amide), 7.70—7.77 (m, 2H, ring), 7.77—7.82 (m, 2H, ring), 7.48 (m, 4H, ring), 8.11 (d, 1H, ring/amide), 8.60 (br s, COOH); ^{13}C NMR ($\mathrm{CDCl_2+CF_3COOD}$) δ=24.27, 35.13, 41.40, 46.54, 47.25, 136.20, 134.85, 134.36, 133.40, 131.77, 131.69, 129.89, 126.74, 126.40, 123.71, 123.52, 167.8 (amide), 168.0 (imide), 168.6 (imide), 175.0 (COOH); IR (KBr) ν_{max} 1775 (w), 1724 (s), 1712 (s) 1631 (s), 1595 (w) cm^{-1}. Found: C, 67.00; H, 5.05; N, 10.31%. Calcd for $\mathrm{C_{30}H_{26}N_4O_6}$: C, 66.90; H, 4.87; N, 10.40%. Amide **7**, mp 226 °C, was also isolated from technical grade TETA reaction (CMR = 2.0, 40% based on linear TETA content). Its filtrate contained a complex mixture of products from other TETA isomers which failed to crystallize, and the NMR spectra were too complex to decipher.

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7) The linear TETA (Aldrich) was in the form of the hydrate, mp 45—48 °C; purity by GC, 98.3%. The TETA from Fisher showed four isomers in order of their emergence off the GC column: tris(2-aminoethyl)amine (6.8%), MS (70 eV EI) *m*/*z* (rel intensity) 146 (M$^+$; 0), 116 (23), 99 (20), 87 (10), 73 (13), 56 (16), 44 (100);[10] TETA (65.1%), MS *m*/*z* (rel intensity) 146 (M$^+$; 0), 116 (11), 99 (9), 73 (40), 56 (19), 44 (100), 41 (14);[10] 1,4-bis(2-aminoethyl)piperazine (13.4%), MS *m*/*z* (rel intensity) 172 (M$^+$; 0), 142 (71), 125 (18), 113 (14), 98 (100), 97 (98), 82 (15), 70 (46), 56 (54), 44 (85), 42 (86);[10] and *N*-(2-piperazinylethyl)ethylenediamine (14.7%), MS *m*/*z* (rel intensity) 172 (M$^+$; 0), 142 (6), 112 (14), 99 (100), 70 (47), 56 (86), 44 (70), 42 (31).[10] Since 1995, 97% linear TETA (GC) has been also available from Fluka.

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