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ONE STEP SYNTHESIS OF ANILINO ALKYL-N-SUBSTITUTED PHTHALIMIDES RELATED TO BENZOISOQUINOLINE-1,3-DIONES (1)

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Abstract

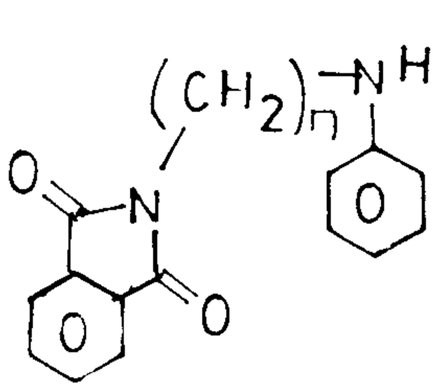
A facile one step synthesis of anilino alkyl-N-substituted phthalimide **I** is reported. The following compounds belonging to this series were made:

1. (anilino-N-ethyl) phthalimide **8**
2. (3, 4, 5-trimethoxy anilino-N-ethyl) phthalimide **6**
3. (3, 4, 5-trimethoxy anilino-N-propyl) phthalimide **7**
4. N-(ethyl phthalimido-p-amino benzoyl) glutamic acid diethyl ester **10**
5. N-(propyl phthalimido-p-amino benzoyl) glutamic acid diethyl ester **11**

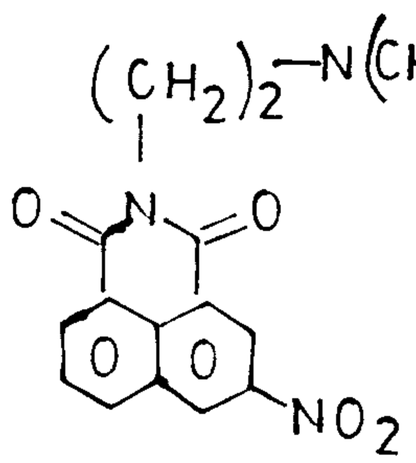
Introduction

Phthalimides are useful precursors for amine synthesis [2, 3] e. g. alkyl diamines (of varying chain lengths used as metal chelating agents and amino acids from α-halo esters). Phthalimides **1** (n = 2,3) were synthesized in a one step process using N-halo alkyl phthalimides and the corresponding anilines.

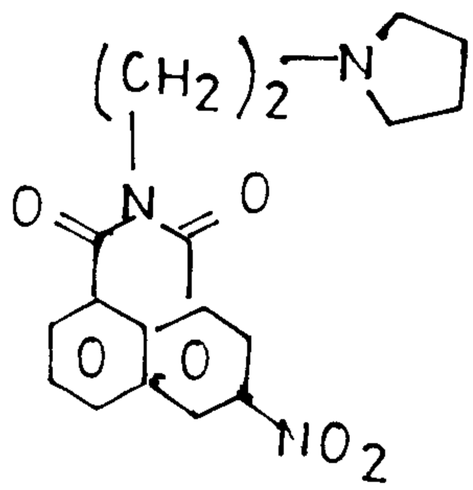
Naphthalimides **II** and **III** are known [4, 5]. They have shown antiviral activity. Phthalimides **1** are analogs of **II** and **III** with the imide ring compressed from 6 to 5 members and a reduction in the number of the aromatic rings. The compound **III** can be seen as being formed from **II** by bridging the N, N-dimethyl groups into a pyrrolidine ring, whereas in **1** the external nitrogen has been substituted by a benzene ring. The novel system **1** may therefore demonstrate similar biological behaviour as **II** or **III** on the basis of their structural resemblance.



1



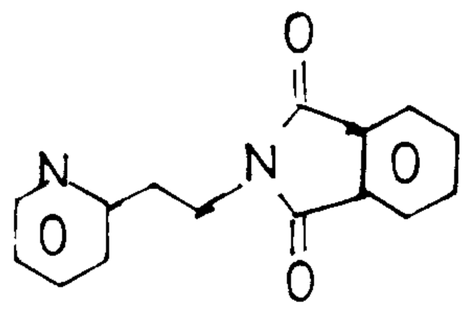
II (M421)



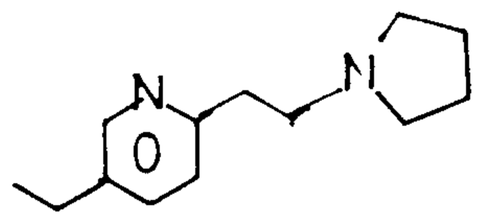
III (M12210)

Keywords: Substituted phthalimides; Phthalimides

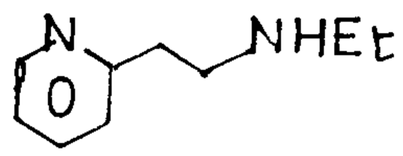
Phthalimides **1** can also be related to N-2(2-pyridyl ethyl) phthalimides **IV** a medicinal agent used in the treatment of severe menstrual conditions and headaches in women [6].



IV



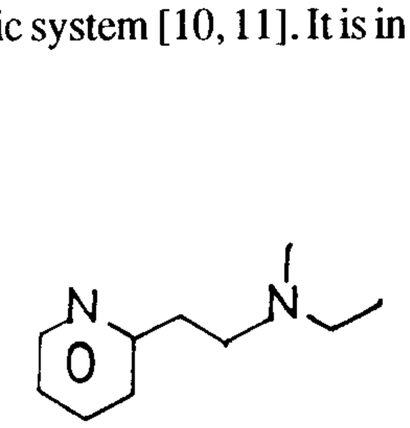
V



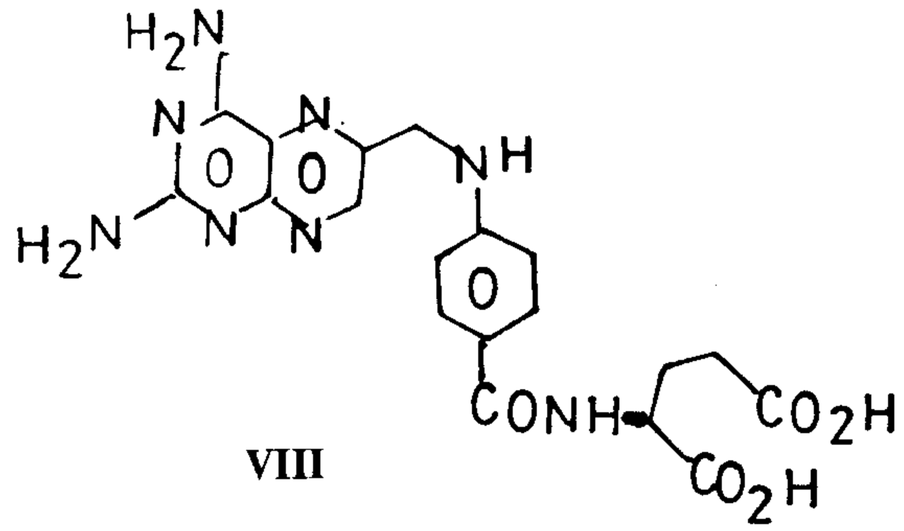
VI

It is also interesting to further relate **1** to **V** (antihistaminic activity) [7]; **VI** and **VII** (adrenergic blocking properties). Compound **VI** completely reverses epinephrine response at one tenth the toxic dose [3, 9].

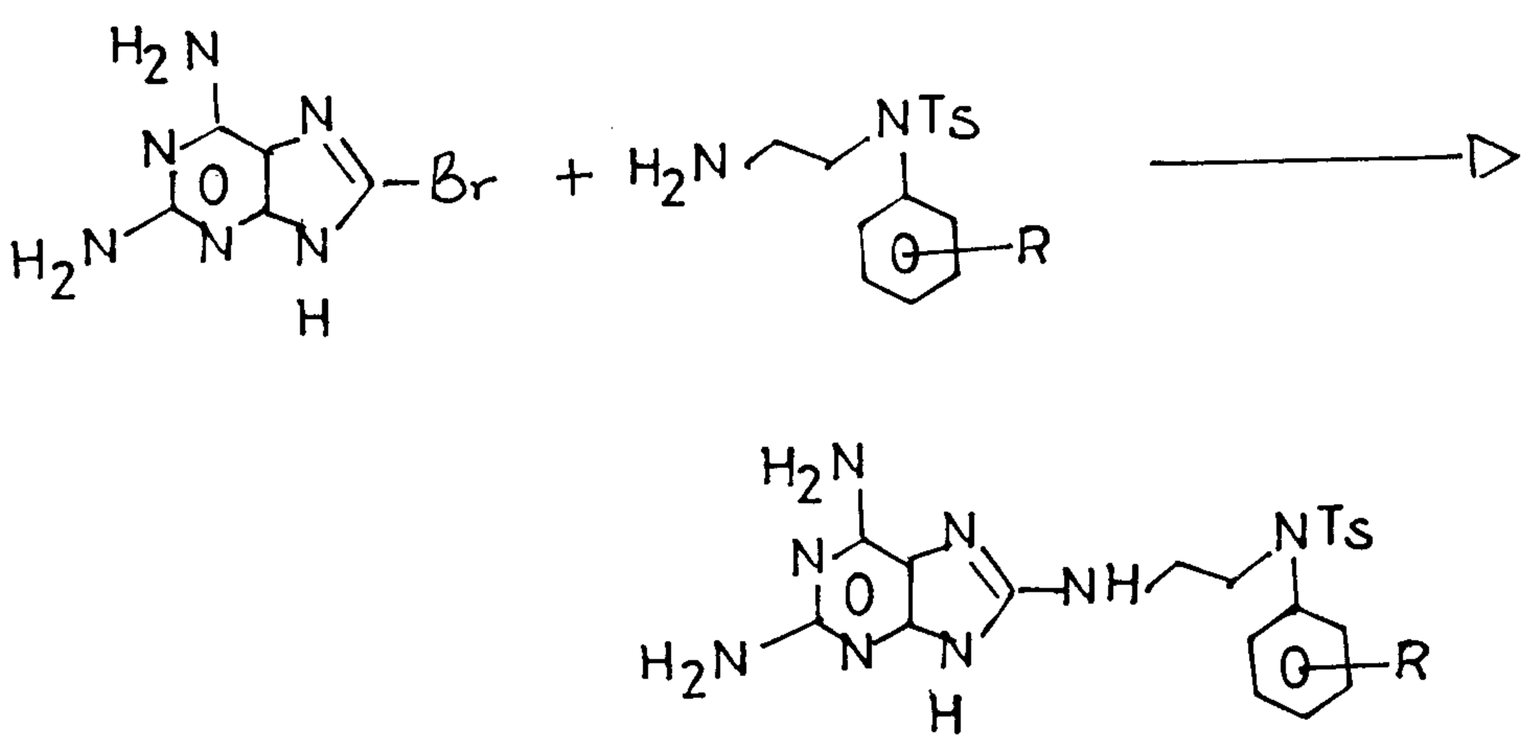
Gray and coworkers have shown that hypotensive activity is obtained for diamines separated by 2 or 3 methylene bridges and particularly so when one of the nitrogens is part of a cyclic system [10, 11]. It is in the hope that, with good pharmacology, **1** will turn up as belonging to any of the categories described in this text, that their syntheses are reported. These novel phthalimides **1** can have good synthetic applications. In this regard, N-phenylalkalene diamines (from hydrazinolysis of **1**) can act as purine delivering agents and analogs of methotrecate **VIII** (an anti-cancer agent) can be produced (Equ. 1) [12].



VII



VIII



Equ. 1

Experimental Section

Chemistry

The syntheses of the traget compounds were achieved by either of two methods (scheme: 1 [13-17]). In scheme 1, substituted anilines (solids) were co-melted with bromoalkyl phthalimide and a few drops of triethylamine were added to the melt (this was further treated until a syrupy reaction mixture was obtained). The products obtained analysed adequately as expected [15, 16, 17].

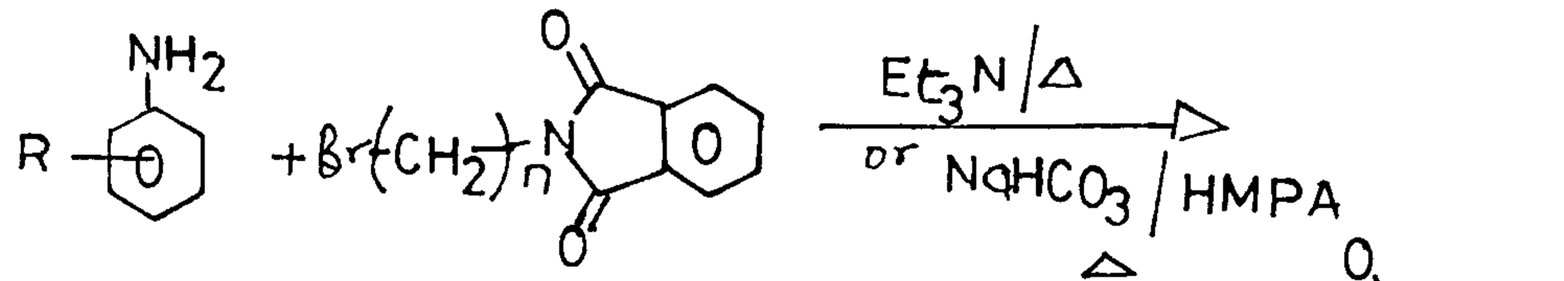
In the second method (scheme 1), the same reagents were taken in hexamethyl phospharamide (HMPA) containing anhydrous sodium bicarbonate ($NaHCO_3$) and moderately heated. The products were obtained in reasonable yield. [13, 14].

Results and Discussion

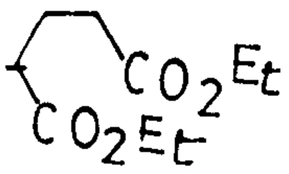
Several literature reports in which a simple fusion of aromatic amines with alkyl halides succeeds in alkylating the amino nitrogen have appeared [15, 16, 17]. In the present investigations, by utilizing haloalhylphthalimides (of varying chain lengths) as the alkylating agents, (scheme 1) comparatively higher yields of products have been obtained (as in Table 1.) by a co-melting method accelerated by a few drops of a base (triethyl amine). The reaction (fusion type C as in the table) was fast (less than 5 minutes) and products were easily recovered from the reaction mixture. However, the reaction was handicapped because it is limited to small scale operations. The syrupy nature of the reaction mixture prevented effective stirring and made it difficult to monitor the progress of reaction on TLC, and proper heat distribution in the reacting system was impaired.

The later use of HMPA (hexamethylphospharamide) as the solvent system afforded a better alternative for a large scale process on account of the homogenous nature of the reacting system [14, 15]. However, the same factors that limited the yield were operative. These were factors arising from:

Scheme 1



1. R = 3, 4, 5 – OMe

2. R = p –CONH 

3. R = H

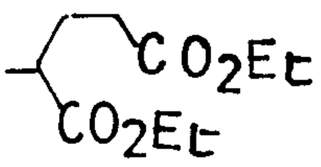
4. n = 2
5. n = 3

R = 3, 4, 5 – OMe

6. n = 2.
7. n = 3.

R = H

8. n = 2
9. n = 3

R = P-CONH 

10. n = 2
11. n = 3

Table 1. Elemental Analysis

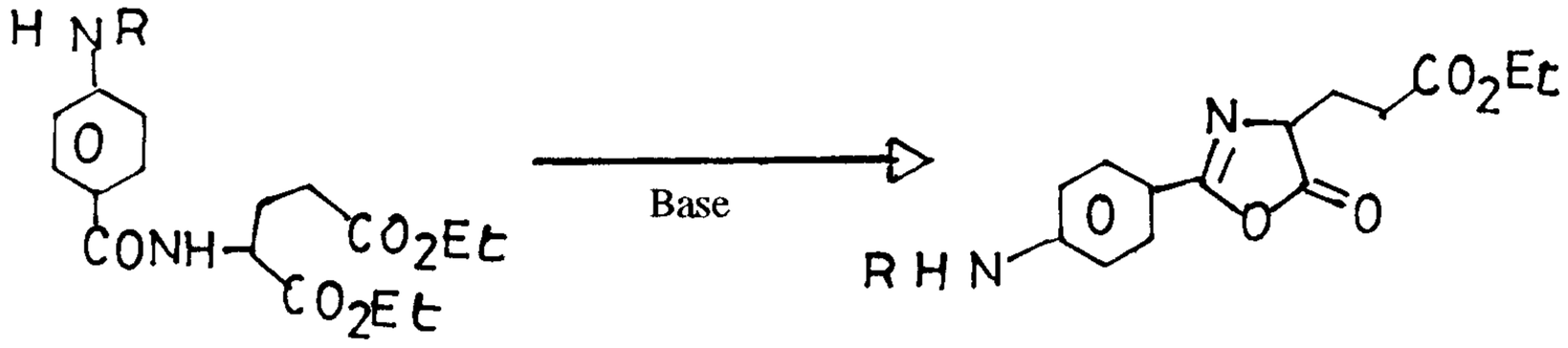
Compound No.	RF	MP	% Yield		C	H	N	Mol. Formula
8	0.62[a]	171° - 173°	28.00°	Calc.	67.60	5.63	9.86	$C_{16}H_{14}O_2N_2.H_2O$
			38.50[d]	Found	67.99	4.79	9.01	
6	0.69[a]	144° - 146°	42.40[c]	Calc.	64.05	5.62	7.86	$C_{19}H_{20}N_2O_5$
				Found	63.90	5.68	7.83	
7	0.91[b]	147° - 150°	52.14[c]	Calc.	64.80	5.90	7.56	$C_{20}H_{22}N_2O_5$
			61.15[d]	Found	64.98	6.02	7.47	
10	0.37[a]	130° - 133°	7.50°	Calc.	63.03	5.95	8.48	$C_{26}H_{29}O_7N_3$
			—	Found	62.86	5.95	8.46	
11	0.84[b]	119° - 121°	90.60[c]	Calc.	63.35	6.09	8.25	$C_{27}H_{31}O_7N_3$
				Found	63.43	6.16	7.99	

a = 10% acetone / chloroform
b = 40% acetone / chloroform
c = Co-melting of reactants + Et_3N
d = Reaction in HMPA / $NaHCO_3$ system

(I) Competition between N-alkylation and N, N-dialkylation (the latter being preferred on the basis of increased nucleophilicity of the initially alkylated nitrogen).
(II) Steric factors probably presented by the alkyl chain length (better yields obtained for n = 3 than n = 2).

The HMPA reaction system could be monitored easily by TLC and effective control exercised over N-monoalkylation versus N, N-dialkylation. It was easily adapted to large scale production of materials.
It is important to note the following:
(a) HMPA solvates ions well and enhances the reactivity of these ions.
(b) It is a high boiling solvent which needs to be stripped off at low pressures and low temperatures to prevent pyrolysis of useful products at elevated temperatures. The use of Kugelrohr distillation equipment, in stripping off HMPA, resolved this problem and ensured the integrity of the products. The work-up procedure was simple and traces of contaminative HMPA were removed by filtering the product through a short column of silica gel contained in a sintered glass funnel.

The particularly low yield of **10** made by the co-melting methodology under triethylamine could be accounted for by side reactions e.g. the possibility of forming an azlactone e. g.:



Materials and Methods

The melting points were obtained with a Mel-Temp apparatus. 'HNMR spectra were run on Varian A-60 spectrometers and d-values (in ppm) are reported downfield from TMS internal standard. Deutero-chloroform was used as the 'HNMR solvent unless otherwise stated. Infrared spectra were obtained on a Nicolet Model 700 FT-IR interferometer and absorption frequencies are reported in cm^{-1}. Atlantic Microlabs, Inc., Atlanta, Georgia, supplied the elemental analyses.

1. Anilino-N-ethyl phthalimide, 8
Method A

Aniline **3** (0.01 mole, 1 g) was mixed with 2-bromo ethyl phthalimide (2.24 g, 0.01 mole) in a 100 ml round bottom flask carrying a reflux water condenser. This set up was heated until the 2-bromo-ethylphthalimide formed a solution in aniline. Triethylamine (2.9 ml) was added to this solution and stirred for 5 to 10 minutes till the reaction became very syrupy. The work-up consisted of taking the syrupy reaction mixture in ethyl acetate. The filtrate was evaporated to dryness and the yellowish oil that was obtained from this was subjected to column chromatography using silica gel. A white crystalline solid (0.127 g) was obtained from the first fraction that came off the column. This solid proved difficult to identify on the basis of 'HNMR and was not investigated further. However, a yellowish oil (one spot on TCL Rf 0.62 – 10% acetone/ chloroform) was obtained from the second fraction from the column and weighed 0.78 g (30. 00%). The elemental analysis was in good agreement with that obtained from **Method B** i. e. the HMPA/ $NaHCO_3$ reaction system.

Analysis calculated for $C_{16}H_{14}O_2N_2.\ H_2O$
Calculated C 67.60 H 5.63 N 9.86
Found **C 67.56 H 5.08 N 9.46**
M. P. 171° - 172°
Rf = 0.62 (10% acetone/ chloroform)
IR (cm^{-1}) **KBr** 3412 3050 3022
2949 2880 1758 1706
1600 1501 1400 1338 1160 823 750
'HNMR 7.85 – 7.60 4H (m) 7.25 – 6.45
5H (m) 4.05 – 3.45 5H (m).

1. Anilino-N-ethyl phthalimide, 8
Method B

Aniline **3** (0.49 ml, 0.46 g, 0.005 mole) was taken in anhydrous HMPA (5 ml) containing dry sodium bicarbonate (1.26 g, 0.015 mole) in a 25 ml round bottom flask. To this flask, 2-bromoethylphthalimide **4** (1.32 g, 0.005 mole) was added. A reflux water condenser carrying a calcium chloride tube was attached to the flask which was then heated to 120° - 130°. The reaction was stirred as heating continued for an overnight period. The progress of the reaction was monitored on TLC (10% acetone/ chloroform). The TLC showed one spot (product) on the plate at the end of the reaction. The work-up was conducted as follows:

(a) The reaction mixture was filtered so as to remove solid inorganic products.
(b) The solvent (HMPA) from the filtrate was stripped off by Kugelrohr distillation using a vacuum pump (full vacuum).
(c) The solid residue left was washed several times with diethyl ether and the ether washings were combined.
(d) The combined ether extract was evaporated to dryness leaving a residue. This residue was subjected to recrystallization in water and acetone mixture to yield 0.50 g (dry weight) of product (yield 38.5%).

M. P. 171° – 173°
R_f 0.62 (10% acetone/ chloroform)
IR (cm^{-1}) **KBr** 3408 (–NH) 3061 3023 2955 2884
1769, 1706 (C=0) 1600 1508 1402 1339 1163 1120
873 753
'HNMR 7.85 – 7.60 4H (m), 7.25 – 6.45
5H (m); 4.05 – 3.45 5H (m)
Analysis calculated for $C_{16}H_{14}O_2N_2.\ H_{20}$
Calculated C 67.60 H 5.63 N 9.86
Found C 67.99 H 5.69 N 9.84

2. N-(3,4,5-Trimethoxyanilino ethyl) phthalimide 6
Method A

3, 4, 5-Trimethoxy-aniline **1** (1 g, 0.0054 mole) was taken in 10 ml of hexamethylphosphoramide (HMPA) and heated with 2-bromo-ethylphthalimide **4** (1.4 g, 0.0054 mole) to a temperature of about 125° – 130°.

$NaHCO_3$ (sodium bicarbonate, 0.9 g, 0.0108 mole) was added to the reaction system. On monitoring the reaction (10% acetone/ chloroform) by TLC, two spots were seen, one at the origin and the other, faster moving and yellowish, at the end of the reaction. The reaction solvent (HMPA) was taken off by Kugelrohr distillation. The residue was washed several times with diethyl ether and the ether washings pooled and evaporated to dryness. The solid left was further dissolved in chloroform and allowed to go through a short column of silica gel contained in a sintered glass funnel. The filtrate was evapo-

rated to dryness and the yellowish solid left was recrystallized with acetone/ water 3:1 V/V to give a yellowish solid that melted at 132° – 134° and weighed 0.938 g (44.02%). It showed an R_f of 0.69 (10% acetone/ chloroform).

Analysis calculated for $C_{19}H_{20}N_2O_5$
Calculated C 64.05; H 5.62; N 7.86
Found C 63.90 H 5.68 N 7.83.

2. Method B

3,4,5- imethoxy aniline **1** (1 g, 0.0054 mole) was co-melted with 2-bromoethyl phthalimide **4** (1.39 g. 0.0054 mole) at 120° – 125°, in a dry round bottom (100 ml) flask. As soon as the solids were completely melted, triethylamine (1.5 ml) was rapidly injected into the melt and vigorously stirred. Stirring was continued until the syrupy nature of the reaction mixture prevented any further movement of the stirrer.

Triethylamine was observed to be refluxing during the stirring. At the end of the reaction, the syrupy reaction mixture was taken in ethylacetate and filtered. The filtrate was evaporated to dryness and the crude oily residue was recrystallized from a solvent mixture of acetone and water (2:1) to yield 0.823 g of **6** in analytically pure form (yield 42.4%).

MP 132° – 134°
R_f = 0.69 (10% acetone/ chloroform)
IR (cm^{-1} **KBr** 3401 (–NH) 2992, 2943 2844 ($–CH_2$)
1773, (C=0) 1710, 1611, 1513, 1470, 1231, 1125, 963, 872, 724.
'HNMR 7.6 – 7.2 (4H d. J = 3Hz)
6.25 (2H, S) 3.85 (H, S) 3.68 (6H, S), 3.80 (2H, tt, J = 3Hz) 3.65 (2H, tt, J = 3Hz) 2.45 (3H, S).

3. N-(3,4,5-Trimethoxyanilino-propyl) phthalimide, 7
Method A

3,4,5-trimethoxy aniline **1** (0.67 g 0.0037 mole) was mixed with 3-bromopropyl phthalimide **2** (1 g, 0.0037 mole) and melted in the same way as those described before. To this melt, two equivalents of triethylamine (1. 03 ml) was added and on work up (in ethylacetate) a yellow solid product weighing 0.72 g (52.14% and melting at 147° – 150°) was obtained. This compound showed an R_f of 0.91 (40% acetone/ chloroform). Its 'HNMR was consistent with the expected structure.

R_f = 0.91 (40% acetone/ chloroform)
MP = 147° – 150°
IR (cm^{-1} **KBr** 3450 (NH) wo13 2971 2943 2933 2865 ($–CH_2–$) 1766 1710 (C = 0 amide), 1597 1513 1456 1189 1125 1041 (–OMe) 949 815 780
'HNMR 7.80 (4H, m) 5.80 (2H, S)
3.85 (3H, S), 3.80 (6H, S)
4.0 – 1.8 (6H tt, J = $3H_z$)
2.45 (1H, S)
Analysis calculated for $C_{20}H_{22}N_2O_5$
Calculated C 64.80, H 5.90, N 7.56
Found C 64.98, 6.02, N 7.47

Method B 7

3,4,5-Trimethoxy aniline **1** (1.69 g, 0.009 mole) was reacted with 3-bromopropyl phthalimide **5** (2.5 g, 0.009 mole) in 20 ml of HMPA under heat (120° – 125°) in the presence of sodium bicarbonate (0.78 g, 0.009 mole). TLC (10% acetone/ chloroform) showed three spots, one at the origin and two others as faster moving up the TLC plate. One of the faster moving spots proved to be unreacted 3,4,5-trimethoxy aniline (by comparison with a side spot of starting 3,4,5-trimethoxyanilino). However, the reaction went to completion with the disappearance of any trace of 3,4,5-trimethoxy aniline in the reaction medium (as evidenced by TLC). The work-up of the reaction was done following the sequence as for anilino-N-ethylphathalimide **8**. Water and acetone mixture (2:1) was used for recrystallization and a dry weight of 2.12 g of yellow solid (analytically pure, yield = 61. 15%) was obtained from the reaction.

R_f = 0.91 (40% acetone/ chloroform)
MP = 147° – 150°.

4. N-Ethyl phathalimido-p-aminobenzoyl glutamic acid diethyl ester 10

P-aminobenzoyl glutamic acid diethyl ester **2** (1 g, 0.002 mole) was reacted with 2-bromoethyl phthalimide **4** (0.76 g, 0.003 mole) in the presence of two equivalents of triethylamine (TEA) following the same fusion method as that described for N–(3,4,5-trimethoxyanilino ethyl) phthalimide **6**. The product recovered weighed 0.115 g (i. e. 7.5% yield).

R_f = 0.37 (10% acetone/ chloroform).
M_p = 130° – 133°
IR (cm^{-1} **KBr** 3408 (–NH) 2985 2943 ($–CH_2–$) 1731, 710 (C = 0 amide) 1632, 1611 1534 1506 1400 1301 1189 1104 1020 970 836 766 717.
'HNMR 7.80 (4H, m) 7.61-6.63 (4H, dd. J= $2H_z$) 6.85 (1H, dd, J= $2H_z$), 4.6 (1H. m) 4.20 – 4.00 (5H, m), 4.20 –

3.40 (4H, q, J = $2H_z$) 2.35 – 2.05 (4H, m) 1.45 – 1.05 (6H, t, J = $2H_z$).

Analysis calculated for $C_{26}H_{29}O_7N_3$
Calculated C 63.03, H 5.85, N 8.48
Found C 62.86, H 5.95, N 8.46.

5. N-(Propylphathalimido-p-aminobenzoyl) glutamic acid diethyl ester 11

P-aminobenzoyl glutamic acid diethyl ester **2** (0.6 g, 0.002 mole) was fused with 3-bromoprophyl phthalimide **5** (0.5 g, 0.002 mole) following the procedures described for the N-ethyl phthalimido relatives **10** or **6** and using two equivalents of triethylamine. On work-up and recrystallization (10% acetone/chloroform) 0.86 g of expected product was obtained (yield 90.6%).

R_f = 0.84 (40% acetone/methylene chloride)
M. P. = 119° – 121°
IR (cm^{-1}) **KBr** 3408, 3309 (–NH), 2985, 2936, 2872, 2844, (–CH_2–) 1745, 1731, 1703 (C = 0 amide) 1611, 1576, 1541 1513 1403 1400 1363, 1189, 1104, 1034 893 829 773 724
'HNMR 7.80 (4H, m), 7.60 – 6.60 (4H, dd, J = $4H_z$) 6.90 (1H, d). 4.70 (1H, q, J = $4H_z$), 4.40 (4H, q J = $2H_z$) 3.90 – 3.10 (4H, tt, J = $3H_z$), 2.70 – 2.30 (5H, m), 2.20 – 1.90 (2H, q, J = $3H_z$)
1.50 – 1.15 (6H, tt, J = $2H_z$).
Analysis calculated for $C_{27}H_{31}O_7N_3$
Calculated C 63.35, H 6.09, N 8.25
Found C 63.43, H 6.16, N 7.99

Method B

P-aminobenzoyl glutamate **2** (3 g, 0.0112 mole) was reacted with 3-bromoprophyl phthalimde **5** in dry HMPA (containing 0.76 g of sodium bicarbonate under heat 120° – 125°) following the same procedure as for N–(3, 4, 5-trimethoxy anilino) propylphthalimide **7**. The reaction was also similarly worked up and 2.046 g of expected product was obtained after recrystallization and drying (oven 80°), yield **35.9%** .

R_f = 0.84 (40% acetone/ methylene chloride)
MP = 119° – 121°

Acknowledgements

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