Synthesis and Characterization of a Series of 1,*x*-bis-(4-Oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)alkanes.

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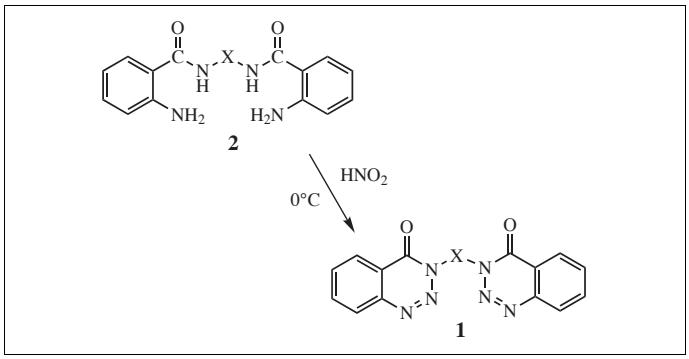

Reaction of isatoic anhydride with an alkanediamine in DMF solution under mild conditions affords excellent yields of the 1,*x*-bis-{(2-aminobenzoyl-)amino}alkanes (**2a-k**), which have been characterized by IR and NMR spectroscopy, high resolution mass spectrometry and elemental analysis. Diazotization of the bis-{(2-aminobenzoyl-)-amino}alkanes in aqueous solution gives high yields of the 1,*x*-bis-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)alkanes (**1a-k**), whch have also been characterized by IR and NMR spectroscopy, high resolution mass spectrometry and elemental analysis. The alkanediamines employed are as follows: ethylene diamine, 1,3-propanediamine, 1,2-propanediamine, 2-methyl-1,2-propanediamine, 2,2-dimethyl-1,3-propanediamine, 2-hydroxy-1,3-propanediamine, 1,4-diaminobutane, 1,5-diaminopentane, 1,3-diaminopentane (*DYTEK® EP diamine*), 1,6-diaminohexane and 1,7-diaminoheptane. The alternative method of synthesis of the bis-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)alkanes (**1**) *via* the diazonium salt from methyl anthranilate was explored.

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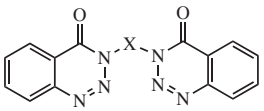
Introduction.

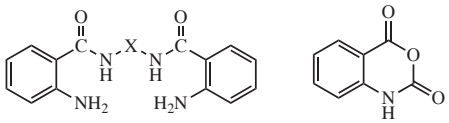
This paper reports the synthesis and characterization of a series of new bis-benzo-1,2,3-triazin-3-yl)alkanes illustrated by structure **1 (a-k)**. The prime method of synthesis is *via* diazotization of the bis-anthranilamide (**2**), which in turn is obtained by the reaction of isatoic anhydride (**3**) with the appropriate alkanediamine. Simple benzotriazinone derivatives of type **4** have been synthesized by several methods. A convenient one-pot method is to prepare the diazonium salt **5** from methyl anthranilate, and to react the diazonium salt with an excess of the alkyl amine (RNH_2) to give the linear 1-aryl-3-methyltriazene (**6**). These triazenes undergo facile cyclization to afford the 3-alkyl-4-oxo-3,4-dihydro-1,2,3-benzotriazine (**4**) [1]. An alternative general method is to react isatoic anhydride (**3**) with the alkyl amine to give the anthranilamide (**7**) [2]; diazotization of the anthranilamides affords the benzotriazinone **4**.

The use of isatoic anhydride (**3**) in *o*-aminobenzoylation reactions has been studied for many years. The first attempt at reaction of **3** with ammonia was reported by Kolbe [3], who expected to produce the ammonium salt of anthranilic acid; instead, the actual product was determined to be anthranilamide (**7**, R = H). Subsequently, Staiger *et al* [4] investigated the reaction of **3** with a wide

Scheme 1



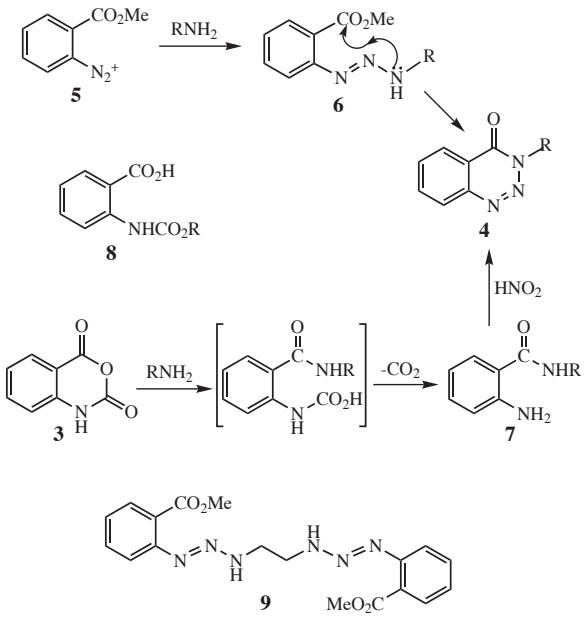
1 a) X =CH_2CH_2
b) X = $CH_2CH_2CH_2$
c) X = $(CH_2)_4$
d) X = $(CH_2)_5$
e) X = $(CH_2)_6$
f) X = $(CH_2)_7$
g) X = $CH_2CH(CH_3)$
h) X = $CH_2C(CH_3)_2$
i) X = $CH_2C(CH_3)_2CH_2$
j) X = $CH_2CH_2CH(CH_2CH_3)$
k) X = $CH_2CH(OH)CH_2$



2 **3**

variety of nucleophiles and developed the synthesis of esters, diesters, thioesters, amides and ureas. The addition of 4-dimethylaminopyridine (DMAP) as a catalyst can improve the efficiency of the *o*-aminobenzoylation [5], which can also be affected *via* active esters of anthranilic acid [6]. These reactions of isatoic anhydride are frequently carried out under conditions of base catalysis; in the absence of a base catalyst, the ring opening reaction affords different products such as the isatoic esters (**8**) from reaction with alcohols [7].

Scheme 2



The products of a ring-opening reaction of isatoic anhydride are often useful in themselves as precursors of other heterocyclic molecules. Thus, isatoic anhydride has been used for the synthesis of quinazolinediones [8], benzoxazinediones [9], the benzodiazaphosphorin ring system [10], dihydrobenzoxadiazoninediones [11], imino-indolinones [12], the benzopyrano[3,2-*c*]quinoline ring system [13] and quinolines [14]. These and other aspects of the chemistry of isatoic anhydride have been reviewed [15].

A simple extension of the methyl anthranilate synthesis (*i.e.* **5** → **6** → **4**) [1] is to use ethylenediamine as the primary amine. This approach was used by van Heyningen [1] to synthesize the bis-benzotriazinone (**1a**), the prototype molecule of the series described in this paper. The objective of the present work was to build on the previous work in order to synthesize a series of bis-benzotriazinones with different spacer groups between the heterocyclic rings. The alternative method to use an extension of the anthranilamide synthesis from isatoic anhydride (*i.e.* **3** → **7**) with ethylenediamine as the nucleophile, in a 1:2 ratio, has also been explored.

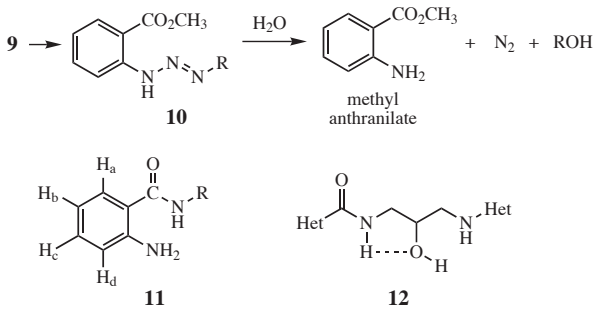
Results and Discussion.

The initial approach to the synthesis of the bis-benzotriazinones (**1**) was to adopt the method of van Heyningen [1]. The diazonium salt (**5**) was reacted with ethylene diamine to afford a moderate yield of the bis-benzotriazinylethane (**1a**). Presumably, the initially formed bis-triazene (**9**) undergoes spontaneous cyclization at both ends to afford **1a**. The product of this reaction had all of the physical characteristics of **1a** described in the literature. The melting point is within a few degrees of the literature value, and the IR spectrum has a carbonyl band at 1679 cm^{-1}, which is typical for a 3-alkylbenzotriazinone [16]. The NMR spectrum of **1a** is straightforward; the methylene protons of the two-carbon spacer appear as a four-proton singlet at δ 5.02 and the aromatic protons appear as an 8-proton multiplet in the range 7.60-8.40 ppm.

Attempts to reproduce the synthesis of **1a** by this method, and to extend the method to reaction with other alkanediamines, proved to be unfruitful. Instead of a clean solid product, we obtained oils of various textures from gummy to clear red oil. The IR spectra of these oils showed clearly that the major component of the oil was methyl anthranilate, either unreacted or regenerated. These observations are in fact consistent with the report of van Heyningen [1], who found that reaction of **5** with ethylene diamine gave a 60% yield of methyl anthranilate with only 11% yield of the sought after product **1a**. Evidently, our initial success with a 42% yield of **1a** was purely serendipitous.

Van Heyningen explained the formation of methyl anthranilate by suggesting that the intermediate **9** tautomerizes to the intermediate 1-alkyl-3-aryltriazene (**10**) and the latter is cleaved by a nucleophile such as water to give the anthranilate.

Scheme 3



These observations suggested that the methyl anthranilate approach is not appropriate as an entry into

the series of compounds of structure **1**, so we turned our attention fully to the isatoic anhydride method.

Isatoic anhydride was reacted with ethylene diamine (½ equivalent) in dimethylformamide at 50 °C. Evolution of a gas, presumably carbon dioxide, from the reaction mixture indicated that a reaction was proceeding and the cessation of gas evolution was taken as a sign that the reaction was complete. Pouring the reaction mixture into a large volume of cold water, followed by adjustment of the pH of the mixture to 9, afforded a solid product, which after washing and drying, was recrystallised from a mixture of ethanol and dimethylsulfoxide to afford an excellent yield of the 1,2-bis-{(2-aminobenzoyl)amino}-ethane (**2a**). The product was identified by IR and NMR spectroscopy and by elemental analysis. The IR spectrum displays a carbonyl band at 1628 cm^{-1}, a singlet amide NH band at 3283 $cm^{-1}$and the symmetric/asymmetric NH_2 bands at 3369 and 3475 cm^{-1} The NH proton is seen at 8.29 ppm in the NMR spectrum and the NH_2 protons resonate at 6.39 ppm. The methylene protons of the spacer group appear as a 4-proton singlet at 3.33 ppm and the four different aromatic protons of each ring are fully resolved in the 60 MHz spectrum.

Extension of the reaction of isatoic anhydride to those with other alkanediamines proved to be a general method for the synthesis of the series of 1,2-bis-{(2-aminobenzoyl)amino}alkanes (**2a-k**) in high yields ranging from 80-95% with only one exception, **2k**. All products in this series are crystalline solids with the exception of **2h**, which was repeatedly obtained as an oil. The products were identified by IR and NMR spectroscopy in all cases, and either by elemental analysis or by high resolution mass spectrometry. HR-MS was preferred in those cases where the molecular ion was observed under EI conditions; more costly elemental analysis was employed in the case of **2a** where the molecular ion was not observable under EI conditions. The IR spectra of the bis-anthranilamides displayed the amide carbonyl band in the range 1622-1687 cm^{-1}; the NH group of the amide side chain gives a single band in the range 3156-3303 cm^{-1}, whereas the NH_2 group gives two bands, the symmetric and asymmetric vibrations, in the ranges 3292-3379 and 3417-3481cm^{-1} In the case of the unsymmetrically substituted 1,3-bis-{(2-aminobenzoyl)amino}-pentane **(2j)**, the subtly different carbonyl groups are resolved at 1623 and 1639 cm^{-1}, the amide NH groups are resolved at 3232 and 3340 cm^{-1} and three of the four NH_2 bands are resolved at 3372, 3442 and 3467 cm^{-1}.

NMR spectra of **2a-**k were recorded in d_6-DMSO initially at 60MHz for convenience using the in-house spectrometer at Saint Mary's University. For several of the bis-anthranilamides, namely **2a**, **2b**, **2h** and **2i**, the resolution of the 60MHz instrument was more than adequate for characterization. The other members of the series were characterized by 500MHz NMR analysis, which provided the resolution necessary for characterization of these compounds. In most of the compounds of series **2** a broad 4-proton signal at *ca*. 6.3 ppm originated from the equivalent NH_2 groups; only in one case, that of **2h**, which was recorded in $CDCl_3$, did the NH_2 resonance diverge from this value and was observed at 5.12 ppm. The amide NH protons resonate at lower field, *ca*. 8.1-8.3 ppm, and in most cases the signal is resolved as a triplet due to coupling with the adjacent methylene group. These generalizations apply to the compounds of series **2** with a symmetrical carbon spacer, *i.e*. **2a-f**, **2i** and **2k**.

Compound **2g** is derived from 1,2-diaminopropane; the spacer is like that in **2a**, but with a methyl branch at one end. This branching point creates considerable asymmetry in the molecule. The amide NH protons have different chemical shift, 7.98 and 8.27 ppm, and different multiplicity, *i.e*. doublet and triplet respectively, because of the different number of neighbouring hydrogens. The NH_2 groups are also distinct at 6.31 and 6.32 ppm, both being 2-proton broad singlets. Similar observations are made in the spectrum of **2j**, derived from 1,3-pentanediamine. The non-equivalent NH protons occur at 7.91 (doublet) and 8.11 (triplet) ppm and the NH_2 protons occur as broad singlets at 6.27 and 6.34 ppm.

The difference between compounds of series **2** with symmetrical and unsymmetrical spacers is also evident in the aromatic region of the proton spectra. The aromatic signals of the symmetrical series is typified by compound **2c**, derived from 1,4-diaminobutane. The two benzene rings are equivalent; thus, there are four resolved chemical shifts in the aromatic frequency range from H_a, H_b, H_c and H_d (see structure **11**). In most cases the multiplicity is fully resolved in the 500MHz spectrum. A signal at 7.46 ppm, assigned to H_a, is a doublet of doublets due to vicinal coupling to H_b and long range w-coupling to H_c. H_b is seen as a doublet of triplets at 7.11 ppm due to vicinal coupling to H_a and H_c and long range coupling to H_d. Similarly, H_c is a doublet of triplets at 6.49 ppm, and H_d is a doublet of doublets at 6.67 ppm. In the compound with an unsymmetrical spacer group, **2j**, the aromatic rings are subtly different and the 500MHZ spectrum is almost completely resolved, showing seven distinct aromatic chemical shifts with the multiplicity almost completely resolved. H_a and $H_{a'}$ are resolved at 7.45 and 7.51 ppm; H_b and $H_{b'}$ are resolved at 7.12 and 7.13 ppm; H_c and $H_{c'}$ are resolved at 6.50 and 6.52 ppm, whereas H_d and $H_{d'}$ are coincidental at 6.68 ppm.

The proton signals of the spacer groups in the symmetrical molecules of series **2** are consistent with the structures assigned. The straight chain spacers in compounds **2a-f** give rise to signals with appropriate

chemical shifts and multiplicities; the symmetry of these molecules is evident in the equivalence of methylene groups. However, multiplicity is not always resolved; in compound **2e** the methylene signals at 1.34, 1.52 and 3.21ppm are all quite broad signals with hardly any fine structure evident, whereas **2f** has a very well resolved set of signals from the seven-carbon spacer. The symmetry of compound **2i**, and the absence of vicinal coupling in the spacer, is also reflected in the simplicity of the spectrum. The absence of vicinal coupling in the spacer of compound **2h** is also evident in the simplicity of the spectrum. On the other hand, the spectrum of the seemingly symmetrical compound **2k** is a little different. The hydroxyl group proton shows up at 5.03 ppm as a predictable doublet due to coupling with the lone tertiary hydrogen, which itself resonates at 3.77 ppm as a sextet. However, the two methylene groups do not appear to be equivalent, showing up as two 2-proton quintets at 3.24 and 3.31 ppm. A possible explanation for this non-equivalence could be the presence of a strong hydrogen bond between NH and O (see structure **12**) in solution which would create the apparent asymmetry.

Nevertheless, the most interesting of these spacer group NMR are those of the unsymmetrical spacers, which contain a stereo center as in compounds **2g** and **2j**. In addition to the non-equivalence of the NH, NH_2 and aromatic groups in these molecules discussed previously, the pattern of signals from the spacer protons is complex and informative. In **2g**, the stereo centre at C2 creates a diastereotopic methylene group at C1. The C3 methyl group is a normal doublet at 1.15 ppm due to vicinal coupling with the adjacent tertiary hydrogen, which itself is a 7-line multiplet at 4.19 ppm. The diastereotopic protons of the C1 methylene group give rise to a doublet of triplets at 3.35 ppm. But, the most complex of all is the proton spectrum of the 1,3-pentanediamine derivative **2j**. The methyl group at C5 of the spacer is a normal 3-proton triplet at 0.87 ppm, but the diastereotopic methylene group adjacent to it at 1.55 ppm is a 2-proton multiplet, with 12 lines resolved. The diastereotopic protons of the C2 methylene group are well resolved as two 1-proton multiplets with 9 lines each at 1.68 and 1.77 ppm. Similarly, the diastereotopic protons of the C1 methylene group are well resolved as two 1-proton multiplets with 6 lines each at 3.16 and 3.34 ppm. The latter multiplet is partially obscured by the water peak at 3.31 ppm. Lastly, the tertiary proton at C3 is found at 3.91 ppm as a 1-proton multiplet.

Selected compounds in the series **2a-k** were analyzed by ^{13}C NMR spectroscopy. In general the amide carbonyl carbon is observed at *ca*. 169 ppm and the methylene carbon adjacent to the amide nitrogen is observed at *ca*. 39 ppm. Other carbon atoms of the spacer group are observed in expected positions. In the symmetric compounds, the six non-equivalent aromatic carbon atoms are observed at *ca*. 114.5, 115, 116, 128, 131, and 149 ppm. In the unsymmetrical compounds, **2g** and **2j**, the non-equivalent carbonyl carbon atoms are resolved, at 168.26 and 169.51 in **2g**, and at 168.65 and 168.83 in **2j**. In **2g**, ten of the aromatic carbons are fully resolved; only the 149.45 carbons are not resolved. In **2j**, all twelve of the aromatic carbon atoms of the non-equivalent benzene rings are resolved. Also in **2j**, the five non-equivalent carbon atoms of the alkane spacer are resolved.

The conversion of the bis-{(2-aminobenzoyl)-amino}alkanes (**2**) to the bis-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)alkanes (**1**) proceeded smoothly in yields ranging from 35-79%. The bis-amide (**2**) was diazotized with 2 equivalents of nitrous acid at low temperature and all of the bis-benzotriazinones (**1**) were obtained as stable solids, which recrystallized from ethanol or DMSO or a mixture of the two. The IR spectra of the bis-benzotriazinones (**1**) are devoid of NH bands and display a single carbonyl band in the range 1675-1697 cm^{-1}. Only the butanediamine derived product (**1c**) displayed two distinct carbonyl bands at 1673 and 1694 cm^{-1}, which could be attributed to symmetric and asymmetric vibrations. The OH group of compound **1k** gives rise to a broad band at 3328 cm^{-1} The ^{1}H NMR spectra of the bis-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)alkanes (**1**) clearly display two sets of signals, those from the aromatic protons and those arising from the protons of the alkane spacer groups. As in the case of the bis-{(2-aminobenzoyl-)amino}alkanes, the compounds of series **1** can be divided into a group with a symmetrical spacer moiety and a group with an unsymmetrical spacer. In those compounds with a symmetrical spacer group, the four protons of each equivalent benzene ring are resolved (at 500MHz) with multiplicity of either a doublet of triplets or a doublet of doublets; in some cases the latter is only resolved as a doublet.

The eight non-equivalent aromatic protons in the 500MHz spectrum of **1j**, which has an unsymmetrical spacer group, are all fully resolved with the predicted multiplicity. The proton signals of the spacer group in **1j** are incredibly complex due to the presence of a stereo center, but can be interpreted to a certain level. The terminal methyl group (C5) is a triplet, as expected, at 0.81 ppm. The diastereotopic protons of the C4 methylene group are resolved as a one hydrogen ten-line multiplet at 1.80-1.85 ppm and a second one-hydrogen ten-line multiplet at 1.89-1.95 ppm. The methine proton at C3 gives rise to a septet at 4.71 ppm, and the diastereotopic protons of the C2 methylene group give rise to two 14-line multiplets at 2.33-2.39 and 2.48-2.53 ppm, each integrating for one hydrogen. Finally, the

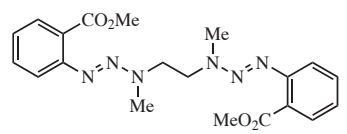
diastereotopic protons of the methylene group at C1 are observed as two one-proton multiplets at 3.99 and 4.08 ppm. The ^{13}C NMR spectrum of compound **1j** also shows the effect of the unsymmetrical spacer group; there are two carbonyl carbon signals at 155.3 and 155.7 ppm, the five unique carbon atoms of the spacer group are clearly observed and eleven of the twelve unique aromatic carbon atoms are resolved.

The protons of the spacer groups in the compounds of series **1** with symmetrical spacers give rise to signals in the NMR spectra that are consistent with the structures, as illustrated by the spectrum of **1e**, derived from 1,6-diaminohexane. The symmetry of the 6-carbon spacer is manifested by a 4-proton quintet at 1.51 ppm (methylene groups at C3 and C4), a 4-proton quintet at 1.95 ppm (methylene groups at C2 and C5) and a 4-proton triplet at 4.48 ppm (methylene groups at C1 and C6). The carbon atoms of this spacer group are seen at 26.23(C3/C4), 28.73(C2/C5) and 49.70(C1/C6). In general, the carbonyl carbon in compounds of series **1** is found at *ca.* 155.5. The aromatic carbon atoms of the symmetrical compounds in series **1** are observed at *ca.* 119.8, 125.1, 128.3, 132.2, 134.5 and 144.3 ppm.

Conclusion.

The results reported in this paper clearly show that the bis-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)alkanes (1) can be synthesized and characterized. These compounds are stable, crystalline solids. This study complements the on-going work in this laboratory, which is primarily directed at the synthesis of bis-triazenes [17]. The "triazene", *e.g.* **10**, is the non-cyclic, or open-chain, equivalent of the heterocyclic "triazine". Among the several types of bis-triazene that we have synthesized recently [18,19], one group stands out as being relevant to the bis-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)alkanes (**1**) reported here. That group is the series of 1,2-bis-(1-aryl-3-methyltriazen-3-yl)ethanes (Ar-N=N-NMe-CH_2CH_2-NMe-N=N-Ar) previously reported [20]; of particular relevance is the compound of that series derived from methyl anthranilate, which is the bis-triazene (**13**) shown in Scheme 4. Compound **13** is the closest thing to an acyclic analogue of the prototype compound **1a**, so it would seem appropriate to compare their characteristics; **13** is a relatively low melting solid, soluble in non-polar solvents, in contrast to **1a**. The carbonyl bands are found at 1710 cm^{-1} in **13** and at 1679 cm^{-1} in **1a**, which is predictable since **1a** is an amide and **13** is an ester. The chemical shifts of the protons of the two-carbon spacer are significantly different, 5.02 ppm in **1a** and 4.08 ppm in **13**.

Scheme 4



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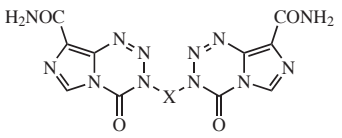

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A further development of this project will be to compare the solid state structures of the compounds of type **1** with the structures of compounds of type **13**, which have already been studied [21]. Compounds of type **13** showed significant divergence in the preferred solid-state conformation, either the folded *gauche* conformation or the extended *staggered* conformation, dependent on the nature of the substituent group in the aryl ring. It will be of interest to see if the length of the polymethylene spacer group in **1** influences the conformation of the molecule in the solid state. At a certain point, it would be expected that the molecule of **1** could assume a folded conformation held in place by π—π stacking between the phenyl rings.

Finally it should be noted that Stevens *et al* synthesized a series of bis(imidazotetrazinones) (**14**) [22] by interaction of 5-diazoimidazole-4-carboxamide and a series of diisocyanates. These bis(imidazotetrazinones) are related in structure to the antitumour agent temozolomide [23], but the presence of the polymethylene spacer does not substantially affect the antitumour activity relative to the unlinked imidazotetrazine.

EXPERIMENTAL

All reagents were reagent grade materials purchased from Sigma-Aldrich Canada Ltd and were used without further purification. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using Nujol mulls with a Bruker Vector 22 spectrometer. ^1H and ^{13}C NMR spectra were obtained with either (i) the Bruker 500MHz spectrometer at the Atlantic Regional Magnetic Resonance Center at Dalhousie University, or (ii) the ANASAZI 60MHz EFT spectrometer at SMU. Chemical shifts were recorded in solution in $CDCl_3$ or d_6-DMSO (as specified) at 20 °C, and are relative to TMS as internal standard. The peak multiplicities are abbreviated as follows: s(singlet), d(doublet), t(triplet, q(quartet), dd(doublet of doublets), dt(doublet of triplets), dq(doublet of quartets), m(multiplet), br(broad). Elemental Analyses were performed by the Canadian Microanalytical Service Ltd., Delta, B.C. High resolution mass spectral data (EI) were obtained with the CEC 21-110B mass spectrometer at Dalhousie University in Halifax. The standard deviation of mass measurement is +/- 0.0008amu, which is an average of 3.6 ppm over the mass range 100 to 300 amu.

Synthesis of the 1,*x*-bis-{(2-aminobenzoyl-)amino}alkanes (**2a-k**).

General Procedure.

Isatoic anhydride (8.20 g, 0.05 mol) was dissolved in dimethylformamide ("DMF") (25.0 mL) and the solution was warmed to 50°C in a water bath. The appropriate alkane-diamine (0.025 mol) was dissolved in DMF (10.0 mL) and this solution was added slowly to the warm isatoic anhydride solution over a period of one hour. The reaction was then allowed to run for approximately 3.5 h until carbon dioxide evolution had ceased. The reaction mixture was then poured into cold water (400.0 mL) creating a slurry, which was basified to pH 9 with concentrated potassium hydroxide solution. The product was then filtered by suction filtration, washed with water, until the wash was caustic free, and dried under suction. Complete drying was achieved in a vacuum dessicator overnight and the product was recrystallized from ethanol or dimethylsulfoxide ("DMSO") to afford the bis-anthranilamides (**2**) as follows:

1,2-Bis-{(2-aminobenzoyl-)amino}ethane (**2a**).

2a: 81%, lustrous cream needles, m.p. 246-247°C (ethanol/ DMSO), IR ν_{max}: 1628, 3283, 3369, 3475 cm^{-1}; ^{1}H nmr (60MHz, DMSO-d_6): δ 3.33(s, 4H), 6.39(4H, br, NH_2), 6.50(2H, m), 6.68(2H, dd, J = 1.3 & 8.2Hz), 7.08(2H, dt, J = 1.4 & 6.7Hz), 7.48 (2H, dd, J = 1.3 & 7.7Hz), 8.29(2H, br, NH)ppm ; Anal. calc'd for $C_{16}H_{18}N_4O_2$: C 64.43, H 6.04, N 18.79; found: C 64.96, H 6.33, N 18.53%.

1,3-Bis-{(2-aminobenzoyl-)amino}propane (**2b**).

2b: 88%, light beige prisms, m.p.170-172°C(ethanol), IR ν_{max}:1622, 3205, 3292, 3417 cm^{-1}; ^{1}H nmr (60MHz, DMSO-d_6): δ 1.76(2H, quintet, J = 6.8Hz), 3.26(4H, t, J = 6.6Hz), 6.39(4H, br, NH_2), 6.52(2H, br), 6.71(2H, dd, J = 1.4 & 7.8Hz), 7.11(2H, dt, J = 1.4 & 6.8Hz), 7.50(2H, dd, J = 1.4 & 7.9Hz) and 8.23(2H, t, J = 6.0Hz, NH)ppm;

HR-MS *m/z* calc'd for $C_{17}H_{20}N_4O_2$. 312.1586 ; found: 312.1587 (EI).

1,4-Bis-{(2-aminobenzoyl-)amino}butane (**2c**).

2c: 84%, beige needles, m.p.199-200°C(ethanol/DMSO), IR ν_{max}: 1628, 3298, 3356, 3471 cm^{-1}; ^{1}H nmr (500MHz, $CDCl_3$): δ 1.54(4H, br t), 3.23(4H, br m, J = 5.7), 6.35(4H, br s, NH_2), 6.49 (2H, dt, J = 1.0 and 7.5Hz), 6.67(2H, dd, J = 0.9 & 7.8Hz), 7.11(2H, dt, J = 1.3 & 7.6Hz), 7.46(2H, dd, J = 1.2 & 7.8Hz), 8.18(2H, t, J = 5.5Hz)ppm.

^{13}C nmr (125.77Hz, $CDCl_3$): δ 26.7, 38.5, 114.5, 115.0, 116.2, 128.0, 131.4, 149.5, 168.8ppm; HR-MS *m/z* calc'd for $C_{18}H_{22}N_4O_2$: 326.1742; found: 326.1744 (EI).

1,5-Bis-{(2-aminobenzoyl-)amino}pentane (**2d**).

2d: 80%, pale yellow rosettes, m.p. 141-142°C (ethanol), IR ν_{max}: 1628, 3298, 3370, 3471 cm^{-1}; ^{1}H nmr (500MHz, $CDCl_3$): δ 1.34(2H, quintet, J = 7.5Hz), 1.53(4H, quintet, J = 7.3Hz), 3.21(4H, q, J = 6.6Hz), 6.34(4H, br s, NH_2), 6.49(2H, dt, J = 0.9 & 7.5Hz), 6.67(2H, dd, J = 0.9 & 7.8Hz), 7.11(2H, dt, J = 1.5 & 7.7Hz), 7.45(2H, dd, J = 1.2 & 7.9Hz), 8.15(2H, t, J = 5.4Hzppm);^{13}C nmr (125.77Hz, $CDCl_3$): δ 24.0, 28.8, 38.7, 114.5, 115.1, 116.2, 128.0, 131.4, 149.4, 168.7ppm; HR-MS *m/z* calc'd for $C_{19}H_{24}N_4O_2$: 340.1899; found: 340.1906 (EI).

1,6-Bis-{(2-aminobenzoyl-)amino}hexane (**2e**).

2e: 84%, pale yellow prisms, m.p. 176-177°C (ethanol), IR ν_{max}: 1642, 3288, 3365, 3481 cm^{-1}; ^{1}H nmr (500MHz, DMSO-d_6): δ 1.34(4H, br), 1.52(4H,br), 3.21(4H, br), 6.34(4H, br, NH_2), 6.51(2H, m), 6.68(2H, m), 7.13(2H,m), 7.46(2H,br), 8.16(2H, br, NH)ppm; ^{13}C nmr (125.77Hz, DMSO-d_6): δ 26.8, 29.6, 39.2, 115.0, 115.6, 116.7, 128.5, 131.9, 150.0, 169.7 ppm; HR-MS *m/z* calc'd for $C_{20}H_{26}N_4O_2$: 354.2055; found: 354.2058 (EI).

1,7-Bis-{(2-aminobenzoyl-)amino}heptane (**2f**).

2f: 95%, white needles, m.p. 140-143°C (ethanol), IR ν_{max}: 1624, 3303, 3379, 3470 cm^{-1}; ^{1}H nmr (500MHz, DMSO-d_6): δ 1.32(6H, m), 1.52 (4H, quintet, J = 6.8Hz), 3.20(4H, quartet, J = 6.6Hz), 6.34(4H, br s, NH_2), 6.50(2H, dt, J = 1.2 & 8.0Hz), 6.68(2H, dd, 1.1 & 8.3Hz), 7.12(2H, dt, J = 1.3 & 7.6Hz), 7.45(2H, dd, J = 1.2 & 7.9Hz), 8.16(2H, t, J = 5.5Hz, NH)ppm; ^{13}C nmr (125.77Hz, DMSO-d_6): δ 27.0, 29.1, 29.6, 39.2, 115.0, 115.6, 116.7, 128.5, 131.9, 150.0, 169.2ppm; HR-MS *m/z* calc'd for $C_{21}H_{28}N_4O_2$: 368.2212; found: 368.2210 (EI).

1,2-Bis-{(2-aminobenzoyl-)amino}propane (**2g**).

2g: 83%, white needles, m.p. 178-180°C (ethanol), IR ν_{max}: 1627, 3283, 3363, 3469 cm^{-1}; ^{1}H nmr (500MHz, DMSO-d_6): δ 1.15(3H, d, J = 6.7Hz), 3.35(2H, dt, J = 1.6 & 6.3Hz), 4.19(1H, septet, J = 6.8Hz), 6.31(2H, s, NH_2), 6.32(2H, s, NH_2), 6.50(2H, dq, J = 1.1 & 6.7Hz), 6.67(1H, dd, J = 1.0 & 2.6Hz), 6.68(1H, dd, J = 0.9 & 2.6Hz), 7.12(2H, dt, J = 1.4 & 7.7Hz), 7.45(1H, dd, J = 1.2 & 8.0Hz), 7.48(1H, dd, J = 1.2 & 7.8Hz), 7.98(1H, d, J = 7.9Hz), 8.27(1H, t, J = 5.8Hz)ppm; ^{13}C nmr (125.77Hz, DMSO-d_6): δ 18.0, 30.6, 43.9, 44.9, 114.5, 114.6, 114.9, 115.1, 116.2, 116.2, 128.0, 128.2, 131.5, 131.6, 149.5, 168.5 and 169.3ppm; HR-MS *m/z* calc'd for $C_{17}H_{20}N_4O_2$: 312.1586; found: 312.1590 (EI).

2-Methyl-1,2-bis-{(2-aminobenzoyl-)amino}propane (**2h**).

2h: 95%, oil, IR ν_{max}: 1687, 3156, 3326, 3468 cm^{-1}; ^{1}H nmr (60MHz, $CDCl_3$): δ 1.50(6H, s), 3.30(2H, br), 5.12(4H, br, NH_2), 6.55-7.81 (8H, m), and 8.3(2H, br, NH)ppm; HR-MS *m/z* calc'd for $C_{18}H_{22}N_4O_2$: 326.1742; found: 326.1754 (EI).

2,2-Dimethyl-1,3-bis-{(2-aminobenzoyl-)amino}propane (**2i**).

89%, white prisms, m.p. 204-206°C (ethanol), IR ν_{max}: 1646, 3159(w), 3339, 3477 cm^{-1}; ^{1}H nmr (60MHz, DMSO-d_6): δ 0.91(6H, s), 3.38(4H, s), 6.33(4H, br, NH_2), 6.49(2H, br d, J = 8.2Hz), 6.72(2H, br d, J = 7.1Hz), 7.12(2H, br d, J = 6.8Hz), 7.54(2H, br d, J = 7.8Hz), 8.32(2H, t, J = 5.9Hz, NH)ppm; HR-MS *m/z* calc'd for $C_{19}H_{24}N_4O_2$: 340.1899; found: 340.1893 (EI).

1,3-Bis-{(2-aminobenzoyl-)amino}pentane (**2j**).

2j: 84%, tiny white needles, m.p. 145-146°C(ethanol), IR ν_{max}: 1623, 1639, 3232, 3340, 3372, 3442, 3467 cm^{-1}; ^{1}H nmr (500MHz, $CDCl_3$): δ 0.87(3H, t, J = 7.4Hz), 1.55(2H, m – 12 lines resolved), 1.68(1H, m – 9lines), 1.77(1H, m – 9 lines), 3.16(1H, sextet, J = 6.7Hz), 3.34(1H, m), 3.91(1H, m, 9 lines, J = 4.25Hz), 6.27(2H, br, NH_2), 6.34(2H, br, NH_2), 6.50(1H, dt, J = 0.9 & 7.9Hz), 6.52(1H, dt, J = 0.9 & 8.0Hz), 6.68(2H, dt, J = 0.9 & 7.3Hz), 7.12(1H, dt, J = 1.5 & 7.1Hz), 7.13(1H, dt, J = 1.5 & 7.2Hz), 7.45(1H, dd, J = 1.2 & 8.0Hz), 7.51(1H, dd, J = 1.3 & 7.9Hz), 7.91(1H, d, J = 8.7), and 8.11(1H, t, J = 5.4Hz)ppm; ^{13}C nmr (125.77Hz, $CDCl_3$): δ 10.6, 27.1, 34.1, 36.5, 48.1, 114.5,

114.5, 115.0, 115.5, 116.1, 116.2, 127.9, 128.1, 131.4, 131.4, 149.3, 149.5, 168.7, and 168.8 ppm. HR-MS *m/z* calc'd for $C_{19}H_{24}N_4O_2$: 340.1899; found: 340.1893 (EI).

2-hydroxy-1,3-bis-{(2-aminobenzoyl-)amino}propane (**2k**).

2k: 38%, small white prisms, m.p. 183-185°C (ethanol), IR ν_{max}: 1625, 3195 (OH, br), 3287, 3344, 3459 cm^{-1}; ^1H nmr (500MHz, $CDCl_3$): δ 3.24(2H, quintet, J = 6.4Hz), 3.31(2H, quintet, J = 6.2Hz), 3.77(1H, sextet, J = 4.6Hz), 5.03(1H, d, J = 5.0Hz, OH), 6.35(4H, br, NH_2), 6.51(2H, dt, J = 0.9 & 7.5Hz), 6.69(2H, dd, J = 0.9 & 7.8Hz), 7.13(2H, dt, 1.4 & 7.7Hz), 7.50(2H, dd, J = 1.0 & 8.0Hz) and 8.15(2H, t, J = 5.8Hz, NH) ppm; ^{13}C nmr (125.77Hz, $CDCl_3$): δ 43.2, 68.6, 114.6, 114.8, 116.3, 128.0, 131.6, 149.5 and 169.1 ppm; HR-MS *m/z* calc'd for $C_{17}H_{20}N_4O_3$: 328.1535; found: 328.1548 (EI).

Synthesis of the 1,*x*-bis-(4-Oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)alkanes (**1 a-k**).

General Procedure.

The bis-anthranilamide (**2**) (0.01 mol) was dissolved in 3 *M* hydrochloric acid (25.0 mL) and cooled in an ice/salt bath to 0 °C. The solution was diazotized with sodium nitrite (1.72 g) in water (6.0 mL) keeping the temperature around 0 °C. The mixture was stirred in the cold for 2.0 h. At this point, any insoluble material was removed by cold vacuum filtration, and the filtrate was then treated with saturated sodium bicarbonate solution to precipitate the product, which was separated by vacuum filtration, dried and recrystallised from ethanol or DMSO to afford the bis-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)alkanes (**1a-k**) as follows:

1,2-Bis-(4-Oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)ethane (**1a**).

1a: 70%, pale yellow needles, m.p. 217-219 °C (DMSO) {lit. m.p. [1] 213-215°C}, IR ν_{max}: 1679 cm^{-1}; ^1H nmr (60MHz, $CDCl_3$): δ 5.02(4H, s), 7.60-8.40(8H, m) ppm; HR-MS *m/z* calc'd for $C_{16}H_{12}N_6O_2$: 320.1021; found: 320.1023 (EI).

1,3-Bis-(4-Oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)propane (**1b**).

1b: 35%, fine white needles, m.p. 188-189 °C (ethanol), IR ν_{max}: 1683 cm^{-1}; ^1H nmr (60MHz, $CDCl_3$): δ 2.56(2H, quintet, J = 6.9Hz), 4.65(4H, t, J = 7.2Hz), 7.28-8.30(8H, m)ppm.

Anal. Calcd. for $C_{17}H_{14}N_6O_2$: C 61.08, H 4.19, N 25.15. Found: C 60.80, H 4.16, N 25.36 %.

1,4-bis-(4-Oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)butane (**1c**).

1c: 48%, feathery white needles, m.p. 225-228°C (DMSO), IR ν_{max}: 1694, 1673 cm^{-1}; ^1H nmr (500MHz, $CDCl_3$): δ 1.86(4H, m), 4.11(4H, br t, J = 5.9Hz), 7.01(2H, dt, J = 0.8 & 6.8Hz), 7.14(2H, dt, J = 1.2 & 6.8Hz), 7.32(2H, d, J = 7.3Hz), and 7.50(2H, dd, J = 0.7 & 7.2Hz)ppm; ^{13}C nmr (125.77Hz, $CDCl_3$): δ 26.1, 49.2, 119.8, 125.1, 128.3, 132.4, 134.8, 144.3 and 155.5 ppm.

Anal. Calcd. for $C_{18}H_{16}N_6O_2$: H 4.60, N 24.14. Found: H 4.31, N 23.91 %.

1,5-Bis-(4-Oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)pentane (**1d**).

1d: 73%, white needles, m.p. 193-195°C (ethanol/DMSO), IR ν_{max}: 1675 cm^{-1};
^1H nmr (60MHz, $CDCl_3$): δ 1.71(2H, m), 2.05(4H, m), 4.50(4H, t, J = 6.0Hz), 7.71-8.40(8H, m) ppm.

Anal. Calcd. for $C_{19}H_{18}N_6O_2$: C 62.97, H 5.01, N 23.19: Found: C 62.99, H 5.01, N 23.25

1,6-Bis-(4-Oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)hexane (**1e**).

1e: 66%, white needles, m.p. 186-187°C (DMSO), IR ν_{max}: 1681 cm^{-1}; ^1H nmr (500MHz, $CDCl_3$): δ 1.51(4H, quintet, J = 5.5Hz), 1.95(4H, quintet, J = 7.5Hz), 4.48(4H, t, J = 7.5Hz), 7.79(2H, dt, J = 1.0 & 8.1Hz), 7.94(2H, dt, J = 1.4 & 8.4Hz), 8.14(2H, d, J= 8.1Hz), 8.34(2H, d, J = 0.9 & 8.0Hz) ppm; ^{13}C nmr (125.77Hz, $CDCl_3$): δ 26.2, 28.7, 49.7, 119.8, 125.1, 128.2, 132.2, 134.7, 144.3, 155.5 ppm;:HR-MS *m/z* calc'd for $C_{20}H_{20}N_6O_2$: 376.1647; found: 376.1632 (EI).

1,7-Bis-(4-Oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)heptane (**1f**).

1f: 64%, white needles, m.p. 144-146°C (ethanol), IR ν_{max}: 1697 cm^{-1}; ^1H nmr (500MHz, $CDCl_3$): δ 1.45(6H, m), 1.93(4H, quintet, J = 7.5Hz), 4.47(4H, t, J = 7.5Hz), 7.79(2H,dt, J = 1.1 & 7.7Hz), 7.94(2H, dt, J = 1.3 & 7.8Hz), 8.14(2H, d, J = 8.1Hz), 8.35(2H, dd, J = 0.9 & 7.9Hz) ppm; ^{13}C nmr (125.77Hz, $CDCl_3$): δ 26.5, 28.7, 28.8, 49.8, 119.8, 125.1, 128.2, 132.2, 134.6, 144.3 and 155.5 ppm; HR-MS *m/z* calc'd for $C_{21}H_{22}N_6O_2$: 390.1804; found: 390.1805 (EI).

1,2-Bis-(4-Oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)propane (**1g**).

1g: 61 %, white needles, m.p. 133-134°C (ethanol), IR ν_{max}: 1679.5 cm^{-1};
^1H nmr (60MHz, $CDCl_3$): δ 1.81(3H, d, J = 7.0Hz), 5.01(2H, d, J = 6.2Hz), 5.82(1H, m, J = 6.4Hz), 7.29-8.27(8H, m) ppm; HR-MS *m/z* calc'd for $C_{17}H_{14}N_6O_2$: 334.1178; found: 334.1181 (EI).

2-Methyl-1,2-bis-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)-propane (**1h**).

1h: 79%, white needles, m.p. 159-160°C (ethanol), IR ν_{max}: 1681.5 cm^{-1};
^1H nmr (60MHz, $CDCl_3$): δ 1.95(6H, s), 5.32(2H, s), 7.68-8.40(8H, m) ppm.
Anal. Calcd. for $C_{18}H_{16}N_6O_2$: C 62.07, H 4.60, N 24.14. Found: C 62.34, H 4.71, N 24.46%.

2,2-Dimethyl-1,3-bis-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)propane (**1i**).

1i: 66%, fine white powder, m.p. 180-182°C (ethanol), IR ν_{max}: 1687 cm^{-1}; ^1H nmr (60MHz, $CDCl_3$): δ 1.16(6H, s), 4.62(4H,s), 7.76-8.40(8H, m) ppm; HR-MS *m/z* calc'd for $C_{19}H_{18}N_6O_2$: 362.1491; found: 362.1495 (EI).

1,3-bis-(4-Oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)pentane (**1j**).

1j: 55%, thick white needles, m.p. 101-103°C (ethanol), IR ν_{max}: 1687.5 cm^{-1};
^1H nmr (500MHz, $CDCl_3$): δ 0.81(3H, t, J = 7.5Hz), 1.80-1.85(1H, m – 10lines), 1.89-1.95(1H, m – 10 lines resolved), 2.33-2.39(1H, m – 14 lines resolved), 2.48-2.53(1H, m – 14 lines resolved), 3.99(1H, m – 7 lines), 4.08(1H, quintet, J = 6.3Hz), 4.71(1H, septet, J = 4.2Hz), 6.99(1H, dt, J = 0.9 & 8.1Hz), 7.01(1H, dt, J = 0.9 & 8.1Hz), 7.11(1H, dt, J = 1.5 & 7.5Hz), 7.13(1H, dt, J = 1.5 & 7.5Hz), 7.27(1H, d, J = 7.5Hz), 7.30(1H, d, J = 7.5Hz), 7.43(1H, dd, J = 1.5& 7.4Hz), and 7.49(1H, dd, J = 1.5 & 7.4Hz) ppm;

^{13}C nmr (125.77Hz, $CDCl_3$): δ 28.2, 40.8, 44.4, 54.9, 62.2, 129.0, 129.2, 133.1, 133.3, 135.4, 135.5, 138.4, 140.2, 140.2, 146.8, 147.1, 155.3 and 155.7 ppm.

Anal. Calcd. for $C_{19}H_{18}N_6O_2$: H 5.01, N 23.19. Found: H 4.94, N 22.78%.

2-Hydroxy-1,3-bis-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)-propane (**1k**).

48%, fine burgundy powder, m.p. 213-217°C (ethanol), IR ν_{max}: 1681, 3328(br) cm^{-1};

^{1}H nmr (500MHz, $CDCl_3$): δ 3.72(1H, d, J = 5.1Hz, OH), 4.71-4.79(5H, m), 7.83(2H, dt, J = 0.9 & 7.5Hz), 7.97(2H, dt, J = 1.4 & 7.7Hz), 8.18(2H, d, J = 8.1Hz) and 8.36(2H, dd, J = 0.9 & 8.0Hz)ppm; ^{13}C nmr (125.77Hz, $CDCl_3$): δ 53.7, 69.6, 119.6, 125.2, 128.5, 132.7, 135.2, 144.12 and 156.6 ppm.

Anal. Calcd. for $C_{17}H_{14}N_6O_3$: C 58.28, H 4.03, N 23.99. Found: C 58.51, H 4.07, N 24.05%.

1,2-Bis-(4-Oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)ethane (**1a**).

Alternate Method.

Methyl anthranilate (1.51 g, 0.01 mol) was dissolved in 3 *M* hydrochloric acid (12.0 mL) and cooled to between 0-5 °C. The cold solution was diazotized with a solution of sodium nitrite (0.75 g) in water (3.0 mL) and then stirred for 0.5 h. in the cold. Ethylenediamine (0.307 g, 0.005 mol) dissolved in water (2.0 mL) was added slowly to the cold diazonium salt solution with stirring and cooling. The mixture was then neutralized with saturated sodium bicarbonate solution (15.5 mL), whereupon a precipitate was formed. The solid was isolated by suction filtration, dried overnight and then recrystallised from ethanol to afford the pure 1,2-bis-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)ethane (**1a**), 42.5% yield, m.p. 218-220 °C {lit. m.p. [1] 213-215 °C};

IR ν_{max}: 1679cm^{-1}; ^{1}H nmr (60MHz, $CDCl_3$): δ 5.02(4H, s), 7.62-8.40(8H, m). This product was identical in all respects (IR, NMR, m.p.) with the product of diazotization of 1,2-bis-{(2-aminobenzoyl-)amino}ethane **(2a)** described above.

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