1,2,4-Benzothiadiazine 1,1-Dioxides by Acetylene Dicarboxylate Additions

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Previous publications from these laboratories have demonstrated interesting physiological activity in the unique heterocyclic products obtained from the condensation of difunctional nucleophiles and dimethyl acetylenedicarboxylate (I), (1,2,3,4). From *o*-substituted benzamides and (I) excellent yields of fumarate adducts were obtained and these could be ring-closed (see Scheme I) to six-membered systems (T = S, O, or NH) or alternatively in one case, to seven-membered systems (T = NH) (5).

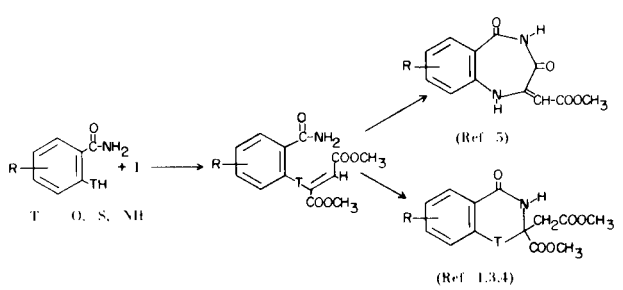
By analogy to the results obtained from *o*-aminobenzamide and (I) (4,5), the two potential heterocyclic classes which might be expected from *o*-aminobenzenesulfonamides and (I) would be the 1,2,4-benzothiadiazine 1,1-dioxides (IV) or the 1,2,5-benzothiadiazepine 1,1-dioxides (V and VI) (see Scheme II), both of which have considerable precedent as pharmacologically active classes (6,7).

We have found that the exclusive cyclization products of the 1:1 adducts of *o*-aminobenzenesulfonamides (II) and (I), are the 1,2,4-benzothiadiazine 1,1-dioxides (IV) and that several members of this class displayed antihypertensive or central nervous system depressant activity.

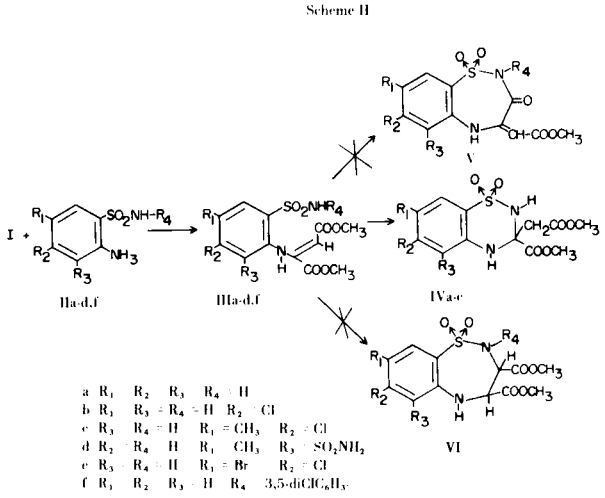
The condensation of equimolar quantities of the *o*-aminobenzenesulfonamides and dimethyl acetylenedicarboxylate (I) in anhydrous methanol was mildly exothermic and after a two hour reflux period returned 60 to 90% yields of 1:1 adducts. Such adducts clearly involved the aryl amine addition to the triple bond since benzenesulfonamide was inert to reaction with (I) while aniline adducts of (I) are well known (8,10).

Furthermore, all of the adducts possessed a single vinyl

Scheme I



Scheme II



proton resonance at δ 5.75 to 5.84 ppm which corresponded well with the analogous fumarate-enamine adducts of *o*-aminobenzamide and (I) which displayed vinyl resonances at δ 5.42 to 5.67 ppm (5). Additional support for the stereospecifically transoid nature of the N-H to alkyne addition was provided by the appearance in the infrared spectra of the adducts (III) of low frequency ester absorptions at 1690 ± 4 cm^{-1}. These Iwanami has ascribed to intramolecular N-H to carbonyl hydrogen bonding in a six-membered chelate-like structure possible only for fumarates (11).

The 2,6-disulfonamide-4-methylaniline (IId) did not yield a detectable adduct under the standard reaction conditions of two hours of reflux in methanol and this result probably reflects the greater steric hindrance at the amino nitrogen. Heating the mixture at reflux for 22 hours gave a 21% yield of the 5-sulfonamido-7-methyl-1,2,4-benzothiadiazine 1,1-dioxide (IVd). Analysis of the mother liquors by nmr revealed no trace of the presumed adduct precursor (IIId) but only the 1:1 adduct of methanol and (I) known to be generated by prolonged contact of these components in the presence of an amine base (12). In at least one other related case (13) involving acetylenedicarboxylate condensations, cyclized product formation ensued without the detectable presence of an intermediate adduct.

Table I

o-Aminobenzenesulfonamide Adducts of Dimethyl Acetylenedicarboxylate

Compound	M.p., °C	Yield %	Formula	Analysis % Calcd. C	H	N	Found C	H	N
IIIa	135.5-136.5°	69	$C_{12}H_{14}N_2O_6S$	45.86	4.49	8.91	46.01	4.50	9.10
IIIb	165.5-167.5°	72	$C_{12}H_{13}ClN_2O_6S$	41.33	3.76	8.03	41.13	3.83	8.08
IIIc	150-152°	89	$C_{13}H_{15}ClN_2O_6S$	43.03	4.17	7.72	43.34	4.15	7.45
IIIf	159.5-161.0°	62	$C_{18}H_{16}Cl_2N_2O_6S$	47.07	3.51	6.10	47.01	3.40	6.00

Table II

1,2,4-Benzothiadiazine 1,1-Dioxides

Compound	M.p., °C	Yield %	Formula	Analysis % Calcd. C	H	N	Found C	H	N
IVa	110-111	74	$C_{12}H_{14}N_2O_6S$	45.86	4.49	8.91	46.04	4.30	8.68
IVb	68-71	85	$C_{12}H_{13}ClN_2O_6S$	41.33	3.76	8.03	41.59	3.49	8.01
IVc	156-157	89	$C_{13}H_{15}ClN_2O_6S$	43.03	4.17	7.72	42.93	4;30	7.62
IVd	221-222	21 (a)	$C_{13}H_{17}N_3O_8S$	38.33	4.21	10.31	38.23	4.02	10.22
IVe	161-162	56 (b)	$C_{12}H_{12}BrClN_2O_6S$	33.70	2.83	6.55	33.85	2.82	6.68

(a) Prepared directly from **IId** without isolation of adduct. (b) Prepared by bromination of **IVb**.

The action of sodium methoxide in methanol converted the isolated fumarate adducts into 1,2,4-benzothiadiazine 1,1-dioxides (IV) in 74 to 89% yields. The six-membered system was easily distinguished from other structural possibilities (V and VI) by combustion analyses, by the double absorption bands for the two saturated ester carbonyls between 1730 and 1760 cm^{-1} and by the resonance for the pendant exocyclic methylene group at δ 3.19 to 3.26 ppm. In closely related quinazolinones derived from *o*-aminobenzamides and (I), this methylene absorption appeared at δ 3.17 to 3.41 ppm (5). The predominant mass spectral fragments of P-59 ($COOCH_3$) and P-73 (CH_2COOCH_3) also confirmed the presence of the two ester side chains (4).

The adduct of the *N*-arylsulfonamide (IIIf) invariably fragmented to its precursors (IIf) and (I) on treatment with sodium methoxide in xylene, benzene or methanol or with sodium hydride in tetrahydrofuran. In addition, the adduct (IIIf) could be recovered unchanged from three hours of fusion at 170°. The *N*-substituted sulfonamido nitrogen may be too sterically hindered to cyclize to the acrylate side chain and a reverse Michael reaction predominates.

The 1,2,4-benzothiadiazine (IVe) was prepared by controlled bromination of (IVb) and not by ring closure of an adduct. The site of bromine incorporation was established as C-7 since the nmr spectrum of the product IVe revealed two non-coupled, *i.e.*, *para*, protons for C-5 and C-8.

Although the series of benzothiadiazines prepared for biological evaluation is somewhat limited, it appears that chlorination of the heterocyclic ring contributes to CNS depression and that a free sulfonamido group is needed for anti-hypertensive potency.

Compounds IVa-e were evaluated at 300 and 100 mg./kg. in the standard neuropharmacological mouse profile (9). With IVb and IVc there was marked depression, abnormal gait, and reduction of spontaneous motor activity at 300 mg./kg. which persisted, although attenuated, at 100 mg./kg. Very modest depression was observed with IVe at 300 mg./kg. With rats showing artificial hypertension induced by administration of desoxycorticosterone acetate and salt, only IVd displayed any lowering of the systolic blood pressure at 100 mg./kg. p.o. in the standard assay (14). With IVd, the pre-dose systolic blood pressure of the rats was 192 ± 6.1 mm Hg and this fell to 173 ± 8.9 mm Hg at 4 hours and to 184 ± 4.4 mm Hg at 24 hour post dosing.

EXPERIMENTAL

Melting points are uncorrected. Pmr spectra were obtained on a Perkin Elmer Hitachi R20A Spectrometer and infrared spectra

were obtained as hydrocarbon mulls on a Perkin Elmer Model 257 Spectrometer. Elemental analyses were provided by Dr. George I. Robertson, Jr., Florham Park, N. J.

Preparation of the *o*-Aminobenzenesulfonamides.

Two members of this class, IIa and IIb, were provided by Wateree Chemical Company and IIc was prepared as described in the literature (15).

4-Methyl-2,6-disulfonamidoaniline (IId).

Finely powdered sodium 6-amino-*m*-toluenesulfonate (50.0 g., 24.0 mmoles) was added to 100 ml. of chlorosulfonic acid, heated on a steam bath for 1 hour, cooled, treated to the dropwise addition of 50 ml. of thionyl chloride, and heated again for an additional 2 hours. The greenish-yellow disulfonyl chloride which formed when the reaction mixture was cautiously poured over chopped ice was filtered, washed with water, dissolved in benzene, dried over magnesium sulfate, and crystallized upon evaporation of the solution as yellow microcrystals of m.p. 82-84° (49 g., 67%). The disulfonamide (IId) was prepared by vigorous agitation of 45.5 g. (15 mmoles) of the 4-methyl-2,6-dichlorosulfonylaniline with 125 ml. of 8 *M* aqueous ammonium hydroxide for 12 hours. The precipitated product was collected, washed with 50 ml. of cold water and with 30 ml. of benzene, recrystallized from water and dried to provide 29.8 g. (75%, from the disulfonyl chloride) of analytically pure material, m.p. 244-245°.

Anal. Calcd. for $C_7H_{11}N_3O_4S_2$: C, 31.69; H, 4.18; N, 15.84. Found: C, 31.99; H, 4.38; N, 15.82.

N-(3,5-Dichlorophenyl)-2-nitrobenzenesulfonamide.

Equimolar quantities (10 mmoles) of 3,5-dichloroaniline and 2-nitrobenzenesulfonyl chloride were mixed in 60 ml. of anhydrous pyridine and after the initially exothermic reaction had terminated the solution was refluxed for 4 hours. Evaporation of the solvent gave a crude crystalline mass which was washed with 100 ml. of cold dichloromethane; and 50 ml. of cold 10% aqueous hydrochloric acid, and then taken up in 200 ml. of 5% aqueous sodium hydroxide. Acidification with glacial acetic acid precipitated the sulfonamide which was recrystallized from benzene (sparingly soluble) to yield 40%, m.p. 196-197°, of the product.

Anal. Calcd. for $C_{12}H_8Cl_2N_2O_4S$: C, 41.51; H, 2.32; N, 8.07. Found: C, 41.60; H, 2.27; N, 7.99.

N-(3,5-Dichlorophenyl)-2-aminobenzenesulfonamide (IIf).

A solution prepared from 22 g. of stannous chloride dihydrate, 36 ml. concentrated hydrochloric acid, 72 ml. of 95% ethanol, and 12.8 g. (36.8 mmoles) of *N*-(3,5-dichlorophenyl)-2-nitrobenzenesulfonamide was refluxed with stirring for 1 hour, cooled and filtered. The solid was taken up in hot 1:1 ethanol:water, decolorized with charcoal, concentrated, and chilled to precipitate 10.0 g. (85%) of IIf, m.p. 158-159°.

Anal. Calcd. for $C_{12}H_{10}Cl_2N_2O_2S$: C, 45.44; H, 3.18; N, 8.83. Found: C, 45.36; H, 3.13; N, 8.88.

Preparation of the Sulfonamidoaniline Adducts (IIIa-c and IIIf).

To a solution of the *o*-aminobenzenesulfonamide, IIa-c and IIf, in anhydrous methanol (30 to 40 mmoles/100 ml. of methanol) was added an equimolar quantity of dimethyl acetylenedicarboxylate. After the initial heat evolution had ceased, the contents of the flask were refluxed with stirring for 2 hours, chilled to ice-bath temperatures, and filtered to remove the precipitated product. Additional crystal crops were obtained by evaporation of the mother liquors under reduced pressure. Analytical samples were obtained by 2 recrystallizations from methanol (see Table I). Adduct IIId could not be isolated.

Preparation of the 1,2,4-Benzothiadiazine 1,1-Dioxides (IVa-c).

A refluxing methanol solution of the initial adduct (IIIa-c) containing 10 mmoles per each 50 ml. of anhydrous methanol was treated with 0.1 g. of powdered sodium methoxide and the reflux continued for an additional 2 hours. Product isolation was effected by concentration *in vacuo* to one-third of the original volume and chilling in an ice-salt bath to precipitate the cyclized material. Recrystallization from methanol invariably gave 1:1 methanol solvates (by nmr and combustion analysis) of the desired products which could be obtained free of entrapped solvent by prolonged drying under vacuum or recrystallization from benzene (see Table II). The adduct IIIf could not be cyclized either by the above procedure or with sodium hydride as the basic catalyst. Nearly quantitative scissions of the pendant side chain resulted with recovery of the sulfonamide, IIf. Heating IIIf at its melting point for 3 hours returned the material unchanged.

3-Carbomethoxy-3-carbomethoxymethyl-5-sulfonamido-7-methyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide (IVd).

Equimolar (19 mmoles) amounts of I and IId were mixed and refluxed in 50 ml. of methanol for 22 hours. The methanol was evaporated and the oily residue induced to crystallize by trituration with cold chloroform. The crystals, which were shown by nmr analysis to be a 4:1 ratio of IId and IVd, were purified by 3 successive recrystallizations from methanol to yield 1.55 g., 21%, of IVd, m.p. 221-222°; ir (hydrocarbon mull): 3380, 3310, 3280, 3210 (N-H), and 1745 cm^{-1} (br, C=O); nmr (DMSO-d_6): δ 2.27 (s, 3, CH_3), 3.26 (s, 2, CH_2), 3.61 (s, 3, OCH_3), 3.65 (s, 3, OCH_3), 7.45 (br s, 1, N-H), 7.60 (br s, 2, SO_2NH_2), 8.87 (br s, 1, N-H), 7.59 (d, 1, Ar-*H*, J_m = 2 Hz), and 7.76 ppm (d, 1, Ar-*H*, J_m = 2 Hz).

Evaporation of the mother liquors gave an oily residue which was shown by nmr and ir spectral comparison with an authentic sample (12) to be a mixture of dimethyl methoxyfumarate and dimethyl methoxymaleate.

Synthesis of 7-Bromo-6-chloro-3-carbomethoxy-3-carbomethoxymethyl-3,4-dihydro-1,2,4-benzothiazine 1,1-Dioxide (IVe).

A 5% solution of bromine/carbon tetrachloride was added dropwise to a well-stirred refluxing methanol solution of IVb (10 mmoles in 100 ml. of methanol) until the characteristic bromine color persisted. Evaporation *in vacuo* of the solvents yielded an off-white solid which was recrystallized from benzene to yield 56% of IVf, m.p. 161-162°; ir (hydrocarbon mull): 3345, 3220 cm^{-1} (N-H), and 1755, 1728 cm^{-1} (C=O); nmr (deuteriochloroform) δ 3.24 (s, 2, $-CH_2-$), 3.77 (s, 3, OCH_3), 3.86 (s, 3, OCH_3), 5.95 (s, 1, N-*H*), 6.37 (s, 1, N-*H*), 6.93 (s, 1, Ar-H_5) and 7.77 ppm (s, 1, Ar-H_8).

Anal. Calcd. for $C_{12}H_{12}BrClN_2O_6S$: C, 33.70; H, 2.83; N, 6.55. Found: C, 33.85; H, 2.82; N, 6.68.

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