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4-Amino-6-(trichloroethenyl)-1,3-benzenedisulfonamide, a New, Potent Fasciolicide[1]

Helmut Mrozik,* Richard J. Bochis, Philip Eskola, Alexander Matzuk, Frank S. Waksmunski, Leonard E. Olen, George Schwartzkopf, Jr., Alex Grodski, Bruce O. Linn, Aino Lusi, Mu T. Wu, Clifford H. Shunk, Louis H. Peterson, John D. Milkowski, Dale R. Hoff, Peter Kulsa,

Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065

Dan A. Ostlind, William C. Campbell, Russell F. Riek,

Merck Institute for Therapeutic Research, Rahway, New Jersey 07065

and Robert E. Harmon

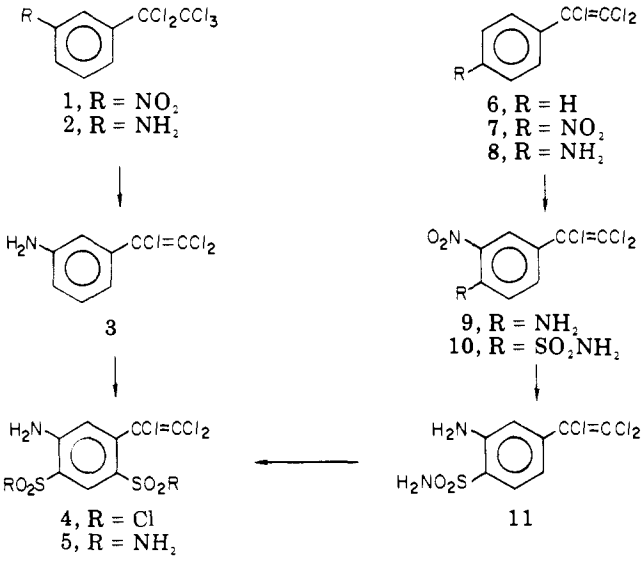
Western Michigan University, Kalamazoo, Michigan 49001. *Received March 14, 1977*

The synthesis and fasciolicidal activity of 4-amino-6-(trichloroethenyl)-1,3-benzenedisulfonamide are reported. A single dose of 15 mg/kg was effective in removing over 90% of immature *Fasciola hepatica* from sheep (6 weeks after infection) and calves (8 weeks after infection). A 2.5 mg/kg dose removed over 90% of mature (16 weeks old) liver fluke from sheep. Single oral doses up to 400 mg/kg were tolerated by sheep without gross toxic symptoms.

The recent discovery of fasciolicidal activities for certain 3,5-disubstituted sulfanilamides and benzenemonosulfonamides[2] prompted the evaluation of related sulfonamides[3] for anthelmintic effects. Activity against mature *Fasciola hepatica* in rats was observed with 4-amino-6-(pentafluoroethyl)-1,3-benzenedisulfonamide[4] after one oral dose of 100 mg/kg. This activity was confirmed against immature, 6-weeks-old liver fluke infections in sheep with a single dose of 100 mg/kg. Extensive structural modifications[5] of this lead culminated in the discovery of 4-amino-6-(trichloroethenyl)-1,3-benzenedisulfonamide (**5**) as a highly active and well-tolerated fasciolicide.[1]

Chemistry. The 3-(trichloroethenyl)aniline (**3**) required as starting material was obtained by reduction of 3-(pentachloroethyl)aniline[6] (**2**) with zinc in ethanol or by reduction of 3-(pentachloroethyl)nitrobenzene[6] (**1**) with iron in aqueous ethanol containing a catalytic amount of hydrochloric acid. Compound **3** was described[6] as a reduction product of 3-(trichloroethenyl)nitrobenzene, which had been obtained by nitration of phenyltrichloroethylene (**6**) with HNO_3–H_2SO_4. In our hands, however, this procedure furnished after purification by chromatography on silica gel a 57% yield of the isomeric 4-(trichloroethenyl)nitrobenzene (**7**),[10] readily identified by the presence of two AB doublets in the NMR spectrum. This gave on reduction 4-(trichloroethenyl)aniline (**8**) whose NMR spectrum again was in agreement with the proposed para substitution. It was also converted to the disulfonamide **5** by a lengthy route through the monosulfonamide **11**. However, bischlorosulfonation of 3-(trichloroethenyl)aniline (**3**), followed by reaction of the disulfonyl chloride **4** with ammonia, gave the desired disulfonamide **5** in 33% yield.

Biological Data. In preliminary tests with rats previously infected with *F. hepatica* metacercariae,[7] more than 90% of flukes were eliminated with a single oral dose of 3.1 mg/kg. The minimal effective level of rafoxanide[8] used as a standard in the same test is also 3.1 mg/kg. A single oral dose of 15 mg/kg eliminated over 90% of *F. hepatica* 6 weeks of age from sheep or 8 weeks of age from calves, while a 2.5 mg/kg dose was 90% effective against mature (16 weeks old) infection in sheep.[9] No gross toxic reactions could be observed in one sheep each after a single



oral dose of 200 and 400 mg/kg.[1]

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained from a Nujol mull with a Perkin-Elmer 137 IR spectrometer and UV spectra in MeOH with a Cary 118 UV spectrometer. Varian T-60, T-60A, and HA100 NMR spectrometers, an LKB Model 9000 mass spectrometer, and Varian Aerograph Series 1200 vapor-phase chromatographs with columns packed with 3–5% SE-30 on 100/120 Varaport were used. Silica gel GF plates (Analtech or E. Merck) were applied for analytical and preparative TLC with C_6H_6 and C_6H_6–EtOAc solvent systems, and UV fluorescence and iodine served to visualize the spots. Elemental analyses were obtained by the staff of the microanalytical laboratory of Merck and are within ±0.4% of calculated values.

3-(Trichloroethenyl)aniline (3). A. From 3-(Pentachloroethyl)nitrobenzene (1). A boiling solution of 3-(pentachloroethyl)nitrobenzene (**1**) (3.23 g, 0.01 mol) in aqueous EtOH (50% *v/v*, 100 mL) was stirred vigorously with iron powder (6.14 g, 0.11 mol) for 90 min, while 2.0 N HCl in 50% aqueous EtOH (1.3 mL, 0.0026 mol) was added in small portions. The hot solution was filtered through Supercel, which was washed well with hot 50% aqueous EtOH. The filtrate was neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. After drying ($MgSO_4$) and evaporation of the solvent 1.76 g (79%) of **3** was obtained as a yellow oil: MS *m/e* 221 (Cl_3, M^+), 186 (Cl_2, M – Cl), and 151 (Cl_1, M – Cl_2). It was characterized as the *N*-acetyl derivative: mp 115–117 °C (MeOH–H_2O); NMR ($CDCl_3$) δ 7.0–6.0 (m, 4 H, meta-substituted benzene). Anal. ($C_{10}H_8Cl_3NO$) C, H, N, Cl.

B. From 3-(Pentachloroethyl)aniline (2). 3-(Pentachloroethyl)aniline (**2**) (340 g, 1.16 mol) was added during 45 min to a mixture of zinc dust (550 g, 8.4 mol) in absolute EtOH which was stirred vigorously under reflux. Stirring and boiling was continued for 30 min before the reaction mixture was filtered hot and concentrated in vacuo to 1.5 L, when a further precipitate had appeared. It was cooled by addition of ice, made slightly basic with NaOH (33% aqueous solution), and filtered, and the filtrate was extracted with $HCCl_3$. Further concentration in vacuo gave 221 g (86%) of crude **3**, as an oil, identical with the product obtained by route A in TLC, GC, IR, and NMR.

4-Amino-6-(trichloroethenyl)-1,3-benzenedisulfonyl Chloride (4). A mixture of 4-amino-6-(trichloroethenyl)-1,3-benzenedisulfonamide (**5**) (5.0 g, 0.013 mol) and chlorosulfonic acid (15 mL, excess) was heated with stirring at 100 °C for 3 h. After cooling to 25 °C, it was poured onto ice water, filtered, and dried in vacuo at 25 °C. Crystallization from CH_2Cl_2–hexane gave 2.98 g of **4**: mp 157–159 °C; NMR ($CDCl_3$) δ 6.17 (br s, 2 H, NH_2), 6.90 (s, 1 H, C_5-H), 8.58 (s, 1 H, C_3-H). Recrystallization from C_6H_6–hexane gave mp 158–159 °C. Anal. ($C_8H_4Cl_5NO_4S_2$) C, H, N.

4-Amino-6-(trichloroethenyl)-1,3-benzenedisulfonamide (5). A. From 3-(Trichloroethenyl)aniline (3). Chlorosulfonic acid (2218 g, 1255 mL, 19 mol) was stirred at 5–10 °C while 3-(trichloroethenyl)aniline (**3**) (390 g, 1.75 mol) was added during 30 min. The reaction mixture was stirred for 2.5 h at 125–130 °C and then cooled to 20 °C. Thionyl chloride (800 g, 476 mL, 6.7 mol) was added during 15 min, and the mixture was heated for 1.5 h at 80 °C. After being allowed to cool to 20 °C overnight, the reaction mixture was poured onto ice water, which was extracted with CH_2Cl_2. The extracts were dried and concentrated in vacuo to give 640 g of crude 4-amino-6-(trichloroethenyl)-1,3-benzenedisulfonyl chloride (**4**) as a brown foam: NMR ($CDCl_3$) δ 8.57 (s, 1 H, C_2-H) and 6.88 (s, 1 H, C_5-H). This was dissolved in CH_2Cl_2 (1200 mL) and added to liquid NH_3 (3000 mL), which then was allowed to evaporate overnight. The residue was treated with water and concentrated HCl to make it slightly acidic and extracted repeatedly with EtOAc. The extracts were combined and evaporated to give 475 g of crude **4**. This was purified in batches of 200 g by chromatography on a column of 6000 g of silica gel prepared with ether. The ether fractions were concentrated in vacuo to a small volume when **5** crystallized as an etherate: 105 g; mp 100–175 °C. The solvent was removed in high vacuo to give 96 g (34.2%) of **5**, mp 194–203 °C. Anal. ($C_8H_8Cl_3N_3O_4S_2$) C, H, N. Recrystallization from H_2O gave a different crystalline form: mp 203–205 °C; NMR (Me_2SO-d_6) δ 8.2 (s, 1 H, C_3-H), 6.8 (s, 1 H, C_5-H), 7.4 (br s, 4 H, SO_2NH_2), and 6.5 (br s, 2 H, NH_2); UV (MeOH) 325, 267, 227 nm (ε 4530, 17 395, 36 310).

B. From 2-Amino-4-(trichloroethenyl)benzenesulfonamide (11). A solution of 2-amino-4-(trichloroethenyl)-benzenesulfonamide (**11**) (100 mg, 0.33 mmol) in chlorosulfonic acid (1.0 mL) was immersed in an oil bath of 110 °C for 2 h. The mixture was cooled and added to ice water. The brown solid which formed was filtered, washed with water, taken up in EtOAc, washed with water, and concentrated in vacuo to give 120 mg of **4**: brown glass; NMR ($CDCl_3$) δ 6.23 (s, 2 H, NH_2), 6.92 (s, 1 H, C_5-H), 8.60 (s, 1 H, C_2-H). It was redissolved in CH_2Cl_2 (20 mL), treated with NH_3 gas for 15 min, and left for 1 h at 20 °C. Water, EtOAc, and a trace of 2.5 N HCl were added. Evaporation of the EtOAc solution gave 110 mg of crude **5**. Addition of ether gave 65 mg (51%) of the etherate of **5**: mp 115–120/192–193 °C, identical by TLC, IR, NMR, and mass spectrum with **5** prepared by route A.

4-(Trichloroethenyl)nitrobenzene (7). Phenyltrichloroethylene[6] (**6**) (826 g, 4.0 mol) was added to a mixture of concentrated HNO_3 (382 g, 4.25 mol) and concentrated H_2SO_4 (890 g, 9.1 mol) at 10 °C over 1.25 h and stirred at 10 °C for an additional 2 h. The reaction mixture was poured onto ice and extracted with CH_2Cl_2 to give 949 g of crude **7**. This was purified by chromatography on a silica gel column (11.3 kg, Davison Grade 923, 100–200 mesh). The fractions obtained by elution with petroleum benzin (64 L) gave recovered starting material (250 g, 30%); subsequent fractions eluted with benzene (30 L) afforded pure **7** (575 g, 57%, 82% after recovery of starting material): light yellow solid; mp 38–42 °C; NMR ($CDCl_3$) δ 7.66 (d, *J* = 14 Hz, 2 H) and 8.24 (d, *J* = 14 Hz, 2 H); MS *m/e* 251 (Cl_3, M^+), 170 (Cl_2, M – NO_2 and Cl, base peak). Anal. ($C_8H_4Cl_3NO_2$) C, H, N, Cl.

4-(Trichloroethenyl)aniline (8). 4-(Trichloroethenyl)-nitrobenzene (**7**) (287 g, 1.14 mol) was added to a mixture of EtOH (1045 g), concentrated HCl (1045 g, 10.9 mol), and $SnCl_2 \cdot 2H_2O$ (1045 g, 4.6 mol) and stirred at 10 °C. After addition was completed, it was heated in a water bath until the temperature had reached 70 °C, when it was cooled to 40 °C and maintained at that temperature for 4 h. The reaction mixture was poured onto ice and made alkaline with 33% aqueous NaOH. Crystalline product **8** was obtained by extraction with $HCCl_3$ and concentration in vacuo. Recrystallization from ether–petroleum ether gave 146.5 g (59%) of **8**: mp 86–88 °C; NMR ($CDCl_3$) δ 7.21 (d, *J* = 8.5 Hz, 2 H), 6.55 (d, *J* = 8.5 Hz, 2 H), 3.77 (br s, 2 H, NH_2); MS *m/e* 221 (Cl_3, M^+), 186 (Cl_2, -Cl), 151 (Cl_1, -Cl_2, base peak). Anal. ($C_8H_6Cl_3N$) C, H, N.

2-Nitro-4-(trichloroethenyl)aniline (9). 4-(Trichloroethenyl)aniline (**8**) (22.25 g, 0.1 mol) was added in portions to Ac_2O (50 mL) and stirred at 35 °C for 30 min following the addition. Concentrated fuming HNO_3 (sp gr 1.5, 7.4 mL) was added to this slurry during the next 15 min while maintaining the reaction mixture below 35 °C. Shortly before completion of the addition,

the slurry became too thick to stir and additional Ac_2O (50 mL) was added. The mixture was stirred for 3 h at 25 °C when TLC examination showed some starting aniline still present. Additional fuming HNO_3 (0.5 mL) was added and stirring continued for an additional 1 h. The reaction mixture was poured into a vigorously stirred mixture of H_2O (120 mL), EtOH (95 mL), and concentrated HCl (30 mL) and heated under reflux for 70 min, when TLC showed that all acetyl anilide was hydrolyzed. The mixture was allowed to crystallize, aged 1 h in an ice bath, filtered, washed with water, and dried in vacuo at 50 °C to yield 16.7 g (62%) of **9**: mp 146–147 °C; NMR ($CDCl_3$) δ 5.63 (br s, 2 H, NH_2), 6.82 (d, J = 10 Hz, 1 H, C_6-H), 7.48 (q, J = 10, 2 Hz, 1 H, C_5-H), 8.26 (d, J = 2 Hz, 1 H, C_3-H). Recrystallization from C_6H_6–hexane gave pure **9**, mp 147–148 °C. Anal. ($C_8H_5Cl_3N_2O_2$) C, H, N.

2-Nitro-4-(trichloroethenyl)benzenesulfonamide (10). A mixture of 2-nitro-4-(trichloroethenyl)aniline (**9**) (1.02 g, 3.85 mmol), concentrated HCl (7.2 mL), and THF (7.2 mL) was heated for 15 min at 50 °C and then cooled to 5 °C. A solution of $NaNO_2$ (0.34 g, 4.9 mmol) in H_2O (1.2 mL) was added dropwise and the reaction mixture was allowed to stir for an additional 10 min at 5 °C when the excess $NaNO_2$ was destroyed by addition of sulfamic acid. Previously, a saturated solution of SO_2 in AcOH (8.2 mL) was prepared, to which $CuCl_2 \cdot 2H_2O$ (0.20 g, 1.2 mmol) dissolved in H_2O (0.25 mL) was added, and which was cooled to 10 °C, while SO_2 was continuously bubbled into the solution. The diazonium salt solution was added in portions to the AcOH–SO_2–$CuCl_2$ solution with vigorous stirring at 10 °C as rapidly as the gas evolution allowed. After the addition, it was allowed to warm to 25 °C over 30 min and was poured into a water–CH_2Cl_2 mixture. The organic phase was concentrated to 1.2 g of yellow, oily, partly crystalline residue: NMR ($CDCl_3$) δ 8.33 (d, J = 10 Hz, 2 H, C_3-H and C_5-H), 8.38 (d, J = 10 Hz, 1 H, C_6-H). The residue was dissolved in CH_2Cl_2 (20 mL) and NH_3 was bubbled into the solution for 10 min. After an additional 1 h, water (50 mL) and EtOAc (150 mL) were added, it was acidified with dilute HCl, and the organic layer was worked up to yield 1.0 g (79%) of **10**: NMR (CD_3COCD_3) δ 7.03 (br s, 2 H, SO_2NH_2), 8.22 (m, 3 H, aromatic). Recrystallization from benzene gave pure **10**, mp 155–156 °C. Anal. ($C_8H_5Cl_3N_2O_4S$) C, H, N.

2-Amino-4-(trichloroethenyl)benzenesulfonamide (11). A mixture of 2-nitro-4-(trichloroethenyl)benzenesulfonamide (**10**) (0.68 g, 2.05 mmol), 50% aqueous EtOH (18 mL), and iron powder (0.68 g, 12.2 mmol) was stirred under reflux, when HCl (0.2 mL of a solution of 5.2 mL of concentrated HCl in 25 mL of 50% aqueous EtOH) was added. Reflux was continued for 45 min. Filtration, neutralization with $NaHCO_3$, and extraction with $HCCl_3$ (70 mL) gave 0.62 g (99%) of **11**, mp 125 °C. Recrystallization from C_6H_6–hexane gave pure **11**: mp 128–129 °C; NMR (Me_2SO-d_6) δ 5.93 (br s, 2 H, NH_2), 6.73 (q, J = 9, 2 Hz, 1 H, C_5-H), 6.97 (d, J = 2 Hz, 1 H), 7.35 (s, 2 H, SO_2NH_2), 7.60 (d, J = 9 Hz, 1 H, C_6-H). Anal. ($C_8H_7Cl_3N_2O_2S$) C, H, N.

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