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SULFONES. IV. α,β-UNSATURATED 4-AMINOPHENYL SULFONES

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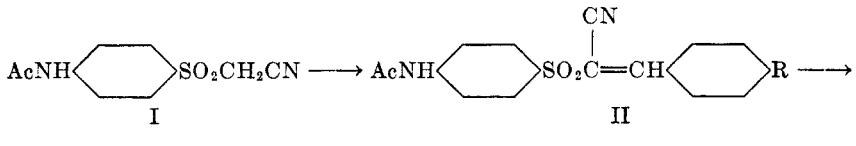
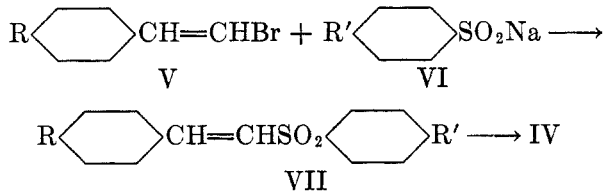
α,β-Unsaturated ketones have been shown by Geiger and Conn (1) to have antibiotic activity, attributed to the ease with which the double bond added thiols. Since the sulfone group can also activate a double bond towards addition of thiols (2), it seemed of interest to synthesize some α,β-unsaturated sulfones in order to examine their possible chemotherapeutic activity.[1]

Condensation of benzaldehyde, 4-acetaminobenzaldehyde or 4-hydroxybenzaldehyde with 4-acetaminobenzenesulfonylacetonitrile (I)[2] led to the unsaturated



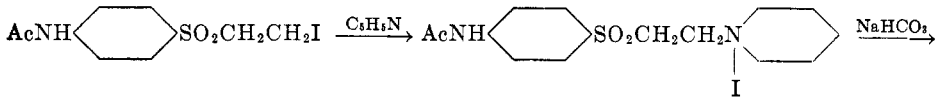
sulfones, II. Short acid hydrolysis removed the acetyl group with the formation of III, but extended hydrolysis to remove the cyano group to form IV led to regeneration of the aldehyde by cleavage.

Compounds of type IV were successfully synthesized by the condensation of β-bromostyrene or 4-nitro-β-bromostyrene (V) with sodium benzenesulfinate or sodium 4-acetaminobenzenesulfinate (VI), forming VII, followed by reduction and/or hydrolysis.

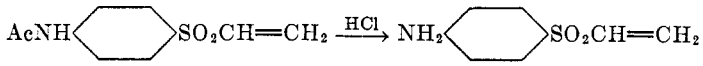


[1] The biological studies will be reported elsewhere. [2] This method is a modification of that used by Tröger and Prochnow (3) for the condensation of phenylsulfonylacetonitrile with aromatic aldehydes. 4-Acetaminophenylsulfonylacetamide, 4-acetaminophenylsulfonylacetic acid or its ethyl ester would not condense with benzaldehyde under a variety of conditions. However, salicylaldehyde readily condensed with ethyl 4-acetaminophenylsulfonylacetate in the presence of piperidine to form 3-(*p*-acetaminophenylsulfonyl)coumarin in excellent yield. Methyl β-(carbomethoxymethylsulfonyl)propionate reacted in the same manner. A similar condensation between ethyl phenylsulfonylacetate and salicylaldehyde has been described by Tröger and Lux (4).

When 4-acetaminophenyl β-iodoethyl sulfone (VIII) (5) was refluxed in pyridine, a pyridinium iodide (IX) formed. Stirred with aqueous sodium bicarbonate, the pyridinium iodide eliminated pyridine to yield 4-acetaminophenyl



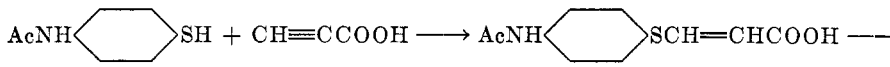
VIII IX



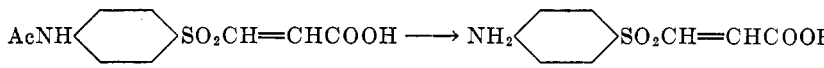
X XI

vinyl sulfone (X). Short acid hydrolysis gave the desired unsaturated sulfone XI.

Although 4-acetaminobenzenesulfinic acid did not add to propiolic acid in basic solution, 4-acetaminothiophenol (XII) rapidly reacted to give XIII in excellent yield. The thio acid, XIII, was smoothly oxidized with hydrogen peroxide to the sulfonylacrylic acid, XIV, which was hydrolyzed to the amino acid, XV. Since the benzylamide of XV was also desired it was obtained from the benzylamide of β-(4-acetaminophenylthio)acrylic acid (XIII) by oxidation, then short acid hydrolysis.



XII XIII



XIV XV

4-Acetaminothiophenol also added to the triple bond of acetylene dicarboxylic acid or its ethyl ester. Saponification of the ester gave an acid, lower-melting, but isomeric to that obtained by direct addition of the thiophenol to acetylene dicarboxylic acid. The lower-melting acid is assumed to be 4-acetaminophenylthiomaleic acid and the higher-melting acid the corresponding derivative of fumaric acid. Neither thioacid nor the ester yielded an isolatable sulfone on oxidation with hydrogen peroxide under conditions which smoothly oxidized β-(4-acetaminophenylthio)acrylic acid (XIII) to its sulfone, XIV.

Acknowledgment. The authors wish to thank Mr. Louis Brancone and his staff for the microanalyses.

EXPERIMENTAL

4-Acetaminophenylsulfonylacetonitrile (I). A mixture of 52 g. of 4-acetaminobenzenesulfinic acid, 250 cc. of alcohol, 60 cc. of water, and 18 cc. of concentrated ammonia water was heated to boiling to complete solution. After the addition of 15.6 cc. of chloroacetonitrile, the solution was refluxed for fifteen hours during which part of the product separated. The cooled mixture was filtered and the product washed with alcohol, then water; yield, 41.5 g. (67%), m.p. 265–267°. The average yield was 62% in six runs.

Walker (6) recorded the m.p. 263–264° and yield of 92% for this compound using the sodium salt in 75% alcohol. We were not able to isolate any of the product by this procedure.

Ethyl 4-acetaminophenylsulfonylacetate. A mixture of 20 g. of 4-acetaminobenzenesulfinic acid, 100 cc. of alcohol, 13 cc. of ethyl chloroacetate, and a solution of 4 g. of reagent sodium hydroxide in 4 cc. of water was refluxed for two hours, then diluted to turbidity with water and cooled in an ice-bath; yield, 20.5 g. (72%), m.p. 122–125°. Recrystallization from dilute alcohol gave white crystals, m.p. 124–125°.

Anal. Calc'd for $C_{12}H_{15}NO_5S$: C, 50.5; H, 5.3; N, 4.9.
Found: C, 50.1; H, 5.3; N, 5.2.

Goldberg and Besley (7) have described a less convenient procedure for preparing this compound. They employed the anhydrous sodium sulfinate in xylene and obtained a yield of 70%, m.p. 122–124°.

4-Acetaminophenylsulfonylacetic acid. To a mixture of 35 g. of 4-acetaminobenzensulfinic acid, 19 g. of chloroacetic acid, and 150 cc. of water was added cautiously 20.2 g. of anhydrous sodium carbonate. After being heated on the steam-bath for three hours, the solution was cooled and acidified; yield, 42.7 g. (95%), m.p. 214–216° dec. Recrystallization of a sample from water gave white crystals, m.p. 215–216° dec.

Anal. Calc'd for $C_{10}H_{11}NO_5S$: N, 5.4. Found: N, 5.6.

Goldberg and Besley (7) obtained a yield of 53%, m.p. 206–208°d., with the use of sodium hydroxide as the base for condensation, whereas Walker (6) employed the less convenient sodium 4-acetaminobenzenesulfinate and obtained an 80% yield, m.p. 216–217°d.

α-(4-Acetaminophenylsulfonyl)cinnamonitrile (II, R = H). A mixture of 7.5 g. of 4-acetaminophenylsulfonylacetonitrile, 3.3 cc. of benzaldehyde, 150 cc. of alcohol, 70 cc. of water, and 0.75 cc. of piperidine was heated on the steam-bath until solution took place, then it was allowed to stand one hour. Dilution with water gave 7.4 g. (73%) of white crystals, m.p. 189°. Recrystallization from dilute alcohol raised the m.p. to 193°.

Anal. Calc'd for $C_{17}H_{14}N_2O_3S$: C, 62.6; H, 4.3; N, 8.6.
Found: C, 62.7; H, 4.7; N 8.7.

Similarly, *4-acetamino-α-(4-acetaminophenylsulfonyl)cinnamonitrile* (II, R = AcNH) was prepared in 57% yield from 4-acetaminobenzaldehyde (8); white crystals from dilute alcohol, m.p. 266–267°.

Anal. Calc'd for $C_{19}H_{17}N_3O_4S$: C, 59.6; H, 4.5; N, 11.0.
Found: C, 59.3; H, 4.2; N, 10.8.

Also, *4-hydroxy-α-(4-acetaminophenylsulfonyl)cinnamonitrile* (II, R = OH) was prepared in 82% yield, m.p. 247–255°. Recrystallization from dilute alcohol raised the m.p. to 276–277°.

Anal. Calc'd for $C_{17}H_{14}N_2O_4S$: C, 59.7; H, 4.1.
Found: C, 60.0; H, 4.5.

α-(4-Aminophenylsulfonyl)cinnamonitrile (III, R = H). A mixture of 30 g. of α-(4-acetaminophenylsulfonyl)cinnamonitrile (II, R = H), 90 cc. of water, 150 cc. of acetic acid, and 60 cc. of concentrated sulfuric acid was refluxed for twenty minutes, then cooled and poured into ice and excess ammonia. The crude product was recrystallized from 50% alcohol; yield, 22 g. (85%), m.p. 145–147°. Further recrystallization raised the m.p. to 146–147°.

Anal. Calc'd for $C_{15}H_{12}N_2O_2S$: C, 63.3; H, 4.3; N, 9.9.
Found: C, 63.4; H, 4.9; N, 9.6.

4-Amino-α-(4-aminophenylsulfonyl)cinnamonitrile (III, R = NH_2). From 35 g. of II (R = AcNH), 105 cc. of water, 175 cc. of acetic acid, and 70 cc. of concentrated sulfuric acid was obtained 23.2 g. (85%) of crude product, m.p. 198–201°, as in the preceding experiment. Recrystallization by solution in a mixture of alcohol and acetone, then dilution with water raised the m.p. to 206–207°.

Anal. Calc'd for $C_{15}H_{13}N_3O_2S$: N, 14.0. Found: N, 13.8.

4-Hydroxy-α-(4-aminophenylsulfonyl)cinnamonitrile (III, R = OH). A mixture of 30 g. of II (R = OH), 90 cc. of water, 150 cc. of acetic acid, and 60 cc. of conc'd sulfuric acid was refluxed exactly five minutes. The cooled solution was poured on excess ice and 400 cc.

of 28% ammonia water. The mixture was acidified with acetic acid, the product collected and washed with water. Recrystallization from dilute alcohol gave 20.5 g. (81%) of solid, m.p. 200–203°. Further recrystallization from dilute alcohol raised the m.p. to 203–205°.

Anal. Calc'd for $C_{15}H_{12}N_2O_3S$: C, 60.0; H, 4.0; N, 9.3.
Found: C, 60.4; H, 4.0; N, 9.6.

A longer reflux period led to mixtures.

Methyl β-(carbomethoxymethylsulfonyl)propionate. To a stirred solution of 95 g. of methyl β-(carbomethoxymethylthio)propionate, prepared in 97% yield according to a procedure described for the corresponding ethyl ester (9), in 500 cc. of acetic acid was added dropwise a solution of 230 g. of potassium permanganate in 2300 cc. of water over a period of thirty minutes maintaining the temperature just below 50° by adequate cooling. The manganese dioxide was dissolved by the addition of sodium bisulfite. The oil was removed by two extractions with ethyl acetate. Washed with aqueous sodium bicarbonate and water, the combined extracts were evaporated to dryness *in vacuo*. The residual oil solidified on standing, m.p. 53–57°; yield, 93.6 g. (85%). Recrystallization from heptane-benzene gave white crystals, m.p. 55–56°.

Anal. Calc'd for $C_7H_{12}O_6S$: C, 37.5; H, 5.4.
Found: C, 38.2; H, 5.8.

3-(β-Carbomethoxyethylsulfonyl)coumarin. To a mixture of 10 g. of methyl β-(carbomethoxymethylsulfonyl)propionate and 5.3 cc. of salicylaldehyde cooled to 0° in an ice-salt bath was added 0.5 cc. of piperidine. After five hours at 3°, the solid was triturated with alcohol; yield, 11.5 g. (87%), m.p. 153–156°. Recrystallization from alcohol raised the m.p. to 154–155°.

Anal. Calc'd for $C_{13}H_{12}O_6S$: C, 52.7; H, 4.1.
Found: C, 52.9; H, 3.7.

Attempts to convert this compound to 2-hydroxy-ω-(β-carboxyethylsulfonyl)styrene according to the procedure used by Tröger and Bolte (10) for a similar compound were unsuccessful

3-(β-Carboxyethylsulfonyl)coumarin. To a solution of 12 g. of the above ester in 25 cc. of acetic acid was added 120 cc. of 50% sulfuric acid. After being heated on the steam-bath for thirty minutes during which time part of the product separated, the mixture was diluted with ice and water; yield, 10.7 g. (94%) of white crystals, m.p. 195–196°. Recrystallization from methanol did not change the m.p.

Anal. Calc'd for $C_{12}H_{10}O_6S$: C, 51.1; H, 3.5.
Found: C, 51.6; H, 3.3.

Similarly, *3-(β-carbomethoxyethylsulfonyl)-7-hydroxycoumarin* was prepared from 2,4-dihydroxybenzaldehyde in 15% yield, m.p. 210–212°. Hydrolysis gave 3-(β-carboxyethylsulfonyl)-7-hydroxycoumarin in 79% yield, m.p. 243–245°d. Recrystallization from dilute alcohol raised the m.p. to 246–247°d.

Anal. Calc'd for $C_{12}H_{10}O_7S$: C, 48.3; H, 3.4.
Found: C, 48.7; H, 3.9.

3-(4-Acetaminophenylsulfonyl)coumarin. A hot solution of 5.8 g. of ethyl 4-acetaminophenylsulfonylacetate and 2.6 cc. of salicylaldehyde in 25 cc. of absolute alcohol was cooled to 25° and treated with 0.6 cc. of piperidine. In a few minutes a solid began to separate. After one hour the solid was washed with alcohol; yield, 7.5 g. (100%), m.p. 270–276°. Recrystallization from pyridine raised the m.p. to 275–277°.

Anal. Calc'd for $C_{17}H_{13}NO_5S$: C, 59.5; H, 3.8; N, 4.1.
Found: C, 59.7; H, 4.5; N, 4.6.

3-(4-Aminophenylsulfonyl)coumarin. A mixture of 24 g. of the preceding acetyl derivative, 120 cc. of acetic acid, and 120 cc. of 50% sulfuric acid was heated on the steam-bath for fifty minutes during which time solution took place and a solid separated. The mixture was poured on ice and 480 cc. of 28% ammonia water. After digestion on the steam-bath for thirty minutes, the mixture was cooled, the product was collected and washed with water;

yield, 19.5 g. (93%), m.p. 203–205°. Recrystallization from dilute acetone raised the m.p. to 208–210°.

Anal. Calc'd for $C_{15}H_{11}NO_4S$: N, 4.6. Found: N, 4.4.

4-Acetaminophenyl ω-styryl sulfone. A mixture of 50 g. of 4-acetaminobenzenesulfinic acid, 49 g. of ω-bromostyrene, 150 cc. of Methyl Cellosolve, 50 cc. of water, 2.5 g. of sodium iodide, and 14 g. of anhydrous sodium carbonate was refluxed for thirty hours, then diluted with several volumes of water and extracted twice with ethyl acetate. Dried with magnesium sulfate, the combined extracts were evaporated to dryness *in vacuo*. The residue was crystallized from benzene-heptane; yield, 33 g., m.p. 140–158°. Recrystallization from dilute alcohol gave 23.5 g. (31%) of product, m.p. 162–165°. Further recrystallization from dilute alcohol raised the m.p. to 168–170°.

Anal. Calc'd for $C_{16}H_{15}NO_3S$: C, 63.8; H, 5.0; N, 4.7.
Found: C, 63.7; H, 5.8; N, 4.70.

4-Nitro-ω-styryl 4'-acetaminophenyl sulfone. A mixture of 29.5 g. of a crude mixture of *cis* and *trans* isomers of 4-nitro-ω-bromostyrene (11), 27 g. of 4-acetaminobenzenesulfinic acid, 195 cc. of alcohol, 52 cc. of water, and 7.7 g. of anhydrous sodium carbonate was refluxed 25 hours. The mixture was cooled, the product was collected, and washed well with alcohol; yield, 11.4 g. (24%), m.p. 243–246°. For analysis a sample was recrystallized from Methyl Cellosolve-water, m.p. 244–245°.

Anal. Calc'd for $C_{16}H_{14}N_2O_5S$: N, 7.8. Found: N, 8.0.

4-Nitro-ω-styryl phenyl sulfone was obtained in a similar manner using 55 g. of crude 4-nitro-ω-bromostyrene and 20 g. of sodium benzenesulfinate; yield, 17%, m.p. 158–161°. Recrystallization from 1:1 alcohol-Methyl Cellosolve narrowed the m.p. to 158–160°.

Anal. Calc'd for $C_{14}H_{11}NO_4S$: C, 58.2; H, 3.8; N, 4.8.
Found: C, 57.7; H, 4.6; N, 5.0.

4-Amino-ω-styryl 4'-acetaminophenyl sulfone. A mixture of 41 g. of 4-nitro-ω-styryl 4'-acetaminophenyl sulfone, 82 g. of iron powder, 1 l. of alcohol, 165 cc. of water, and 8 cc. of concentrated hydrochloric acid was refluxed with stirring for three hours. The hot mixture was filtered through Celite, the filtrate was evaporated to dryness *in vacuo*, and the residue crystallized from dilute alcohol; yield, 30 g. (80%), m.p. 160–165°. Further recrystallization from ethyl acetate-heptane raised the m.p. to 173–175°.

Anal. Calc'd for $C_{16}H_{16}N_2O_3S$: C, 60.7; H, 5.1; N, 8.9.
Found: C, 60.7; H, 5.2; N, 8.8.

4-Amino-ω-styryl phenyl sulfone hydrochloride was prepared in the same way from 4-nitro-ω-styryl phenyl sulfone except that the product was isolated as the hydrochloride from 6 *N* hydrochloric acid in 25% yield, m.p. 220° dec.

Anal. Calc'd for $C_{14}H_{14}ClNO_2S$: N, 4.7. Found: N, 4.9.

ω-Styryl 4-aminophenyl sulfone. A mixture of 38.5 g. of 4-acetaminophenyl ω-styryl sulfone, 117 cc. of water, 78 cc. of concentrated sulfuric acid, and 195 cc. of acetic acid was refluxed for twenty minutes, then cooled and poured into ice and 600 cc. of 28% ammonia water. The crude product (32 g., m.p. 147–150°) was recrystallized from alcohol; yield, 26 g. (79%), m.p. 158–160°.

Anal. Calc'd for $C_{14}H_{13}NO_2S$: C, 64.8; H, 5.0; N, 5.4.
Found: C, 65.0; H, 5.3; N, 5.2.

Similarly, hydrolysis of 4-aminostyryl 4'-acetaminophenyl sulfone gave *4-aminostyryl 4'-aminophenyl sulfone* in 61% yield, m.p. 155–158°. Recrystallization from dilute alcohol raised the m.p. to 160–161°.

Anal. Calc'd for $C_{14}H_{14}N_2O_2S$: C, 61.4; H, 5.2; N, 10.2.
Found: C, 61.1; H, 5.1; N, 10.5.

4-Acetaminophenyl vinyl sulfone (X). A solution of 172.5 g. of 4-acetaminophenyl β-iodoethyl sulfone (VIII) (5) in 530 cc. of reagent pyridine was refluxed for three hours, then evaporated to dryness *in vacuo*. The residue was dissolved in hot water, filtered from a little insoluble material, then cooled in an ice-bath. The pyridinium iodide (IX) was washed with ice water; yield, 193 g. (88%), m.p. 108–110°.

A mixture of 100 g. of the pyridinium iodide (IX), 2 l. of 8% sodium bicarbonate, and 1 l. of ethyl acetate was stirred for fifteen hours. The aqueous layer was separated and extracted once more with ethyl acetate. Dried with magnesium sulfate, the combined extracts were evaporated to dryness *in vacuo*. Trituration of the residue with water gave 35.5 g. (71%) of product, m.p. 120–122°. Recrystallization from ethyl acetate-benzene-petroleum ether raised the m.p. to 122–123°.

Anal. Calc'd for $C_{10}H_{11}NO_3S$: C, 53.3; H, 4.9; N, 6.2.
Found: C, 53.1; H, 5.1; N, 6.3.

4-Aminophenyl vinyl sulfone (XI) *hydrochloride*. A mixture of 35.5 g. of 4-acetaminophenyl vinyl sulfone (X) and 355 cc. of 6 *N* hydrochloric acid was refluxed for twenty minutes. The solution was evaporated to dryness *in vacuo*. The residual hydrochloride, obtained in quantitative yield, m.p. 211–213°, was recrystallized from methanol-ethyl acetate, m.p. 212–213°.

Anal. Calc'd for $C_8H_{10}ClNO_2S$: C, 43.8; H, 4.6; N, 6.4.
Found: C, 43.8; H, 5.2; N, 6.6.

β-(4-Acetaminophenylthio)acrylic acid (XIII). To a suspension of 40 g. of 4-acetaminothiophenol (12) in 150 cc. of alcohol was added successively 20 g. of propiolic acid (13), 20 cc. of concentrated ammonium hydroxide, and 20 cc. of water. The mixture was heated on the steam-bath for five minutes, then diluted with several volumes of water and cooled. Some insoluble material was removed and the filtrate acidified; yield, 46 g. (82%), m.p. 198–202°d. Recrystallization from alcohol gave white crystals, m.p. 210–212°dec.

Anal. Calc'd for $C_{11}H_{11}NO_3S$: C, 55.7; H, 4.7; N, 5.9.
Found: C, 55.8; H, 4.6; N, 5.9.

β-(4-Acetaminophenylthio)-N-benzylacrylamide. To a suspension of 46 g. of the above acid (XIII) in 100 cc. of reagent ether containing 0.5 cc. of pyridine was added 92 cc. of thionyl chloride. The mixture was shaken for fifteen minutes during which time most of the acid dissolved and the acid chloride separated. The solid was washed with dry ether. The solvent-wet acid chloride was covered with 460 cc. of acetone and treated dropwise with stirring with 92 cc. of benzylamine in 100 cc. of acetone over a period of fifteen minutes, the temperature being maintained at 20–25° by ice-cooling. After being stirred for five minutes more, the mixture was diluted with dilute hydrochloric acid. The product was washed with water; yield, 46.5 g. (74%), m.p. 213–216°, suitable for the next step. Recrystallization from Methyl Cellosolve gave white crystals, m.p. 229–230°.

Anal. Calc'd for $C_{18}H_{18}N_2O_2S$: N, 8.6. Found: N, 8.6.

The *anilide* was prepared in the same way and formed white crystals from dilute alcohol, m.p. 228–230°.

Anal. Calc'd for $C_{17}H_{16}N_2O_2S$: N, 9.0. Found: N, 9.2.

β-(4-Acetaminophenylsulfonyl)acrylic acid (XIV). A mixture of 41.5 g. of β-(4-acetaminophenylthio)acrylic acid (XIII), 540 cc. of acetic acid, and 96 cc. of 30% hydrogen peroxide was heated in a bath at 50° for three hours. The solution was evaporated to dryness *in vacuo* and the residue triturated with water. The hydrated solid was washed with water, and dissolved in ethyl acetate. The ethyl acetate solution, dried with magnesium sulfate, was diluted to turbidity with petroleum ether; yield, 28.6 g. (61%), m.p. 172–175°. For analysis a sample was twice recrystallized from ethyl acetate by the addition of sufficient acetone at the b.p. to cause solution, followed by concentration and cooling; white crystals, m.p. 174–176°.

Anal. Calc'd for $C_{11}H_{11}NO_5S$: N, 5.2. Found: N, 5.0.

The corresponding *benzylamide* was prepared in 87% yield, m.p. 174–177°, by oxidation in the same manner except that the residue remaining after evaporation of the reaction mixture was crystallized from dilute alcohol. Recrystallization from alcohol gave white crystals, m.p. 185–186°.

Anal. Calc'd for $C_{18}H_{18}N_2O_4S$: C, 60.4; H, 5.1; N, 7.8.
Found: C, 60.5; H, 5.7; N, 7.6.

β-(4-Aminophenylsulfonyl)acrylic acid (XV) *hydrochloride*. A solution of 2.0 g. of β-(4-

acetaminophenylsulfonyl)acrylic acid (XIV) and 20 cc. of 6 *N* hydrochloric acid was refluxed for five minutes when the product separated. The hydrochloride was washed with alcohol; yield, 1.0 g. (51%), m.p. 232–233°d. Recrystallization by solution in water and addition of an equal volume of concentrated hydrochloric acid gave white crystals of the same m.p.

Anal. Calc'd for $C_9H_{10}ClNO_4S$: C, 41.1; H, 3.8; N, 5.3.
Found: C, 41.0; H, 3.6; N, 5.4.

β-(4-Aminophenylsulfonyl)-N-benzylacrylamide and hydrochloride. A mixture of 10 g. of β-(4-acetaminophenylsulfonyl)-N-benzylacrylamide and 100 cc. of 6 *N* hydrochloric acid was refluxed for twenty minutes during which solution took place and the hydrochloride separated. The hydrochloride was washed with acetone; yield, 7 g. (82%), m.p. 200–204°d.

A hot filtered solution of a sample of the hydrochloride in 1 *N* hydrochloric acid was poured into excess dilute ammonia. The free base was recrystallized from acetone-water; white crystals, m.p. 213–215°.

Anal. Calc'd for $C_{16}H_{16}N_2O_3S$: C, 60.8; H, 5.1; N, 8.9.
Found: C, 60.8; H, 5.2; N, 8.7.

Ethyl (4-Acetaminophenylthio)maleate. To a mixture of 13 g. of 4-acetaminothiophenol (12) and 14.5 g. of ethyl acetylenedicarboxylate was added 65 cc. of alcohol. An exothermic reaction took place. The mixture was heated on the steam-bath until solution was complete, then it was diluted with water until the product began to separate. The mixture was cooled in an ice-bath, filtered, and the product washed with dilute alcohol; yield, 20 g. (80%), m.p. 128–133°. Recrystallization from alcohol gave yellow crystals, m.p. 140–141°.

Anal. Calc'd for $C_{16}H_{19}NO_5S$: C, 56.9; H, 5.7; N, 4.2.
Found: C, 57.0; H, 5.8; N, 4.2.

Attempts to oxidize the thio ether to the sulfone were unsuccessful; (a) chromic acid in acetic acid or (b) hydrogen peroxide in alcohol gave starting material and (c) hydrogen peroxide in acetic acid gave no identifiable product.

(4-Acetaminophenylthio)maleic acid. To a solution of 2.1 g. of sodium hydroxide in 75 cc. of 3-A alcohol[3] was added 5 g. of the preceding ester. The solution was refluxed for one hour during which a sodium salt separated. This salt was washed with 3-A alcohol, and dissolved in water. The solution was acidified with hydrochloric acid, saturated with salt, and extracted with ethyl acetate. The combined extracts, dried with magnesium sulfate, were evaporated to dryness *in vacuo*. The oily residue was crystallized from ethyl acetate-benzene; yield, 2.8 g. (67%), m.p. 145–146°dec. Recrystallization from the same solvents raised the m.p. to 150–152° dec.

Anal. Calc'd for $C_{12}H_{11}NO_5S$: N, 5.0. Found: N, 5.4.

(4-Acetylaminophenylthio)fumaric acid. To a solution of 2.5 g. of potassium hydrogen acetylenedicarboxylate in 20 cc. of water and 1.1 cc. of concentrated ammonium hydroxide was added 2.7 g. of 4-acetaminothiophenol, 10 cc. of alcohol, and 0.1 cc. of piperidine. The mixture was refluxed for fifteen minutes. Most of the alcohol was removed *in vacuo*, the remainder of the solution was diluted with water and acidified. The aqueous solution containing suspended oil was shaken with ethyl acetate and the insoluble material removed. The ethyl acetate layer was evaporated to dryness *in vacuo*. The gummy residue, covered with ethyl acetate-benzene, gradually solidified; yield, 2.7 g. (59%), m.p. 198–200°dec.

Recrystallization from acetone-petroleum ether raised the m.p. to 205–207°dec.

Anal. Calc'd for $C_{12}H_{11}NO_5S$: C, 51.3; H, 3.9; N, 5.0.
Found: C, 51.5; H, 4.2; N, 5.6.

SUMMARY

Twelve α,β-unsaturated sulfones, ten of which contain the 4-aminophenyl radical, have been synthesized for chemotherapeutic testing.

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[3] Denatured ethyl alcohol.

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