Application of Mannich Reaction to Sulfones II

Role of Aromatic Aldehydes in Condensation

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Pyridine-2-carboxaldehyde, indole-3-carboxaldehyde, furfural, and *p*-acetylaminobenzaldehyde gave only polymers when subjected to Mannich reaction conditions in the presence of arylsulfonylacetic acids and ammonium acetate or cyclohexylamine. *trans*-Cinnamaldehyde, benzaldehyde, *p*-methoxy-, *p*-chloro-, *p*-isopropyl-, 3,4-methylenedioxy-, and 3,4-dimethoxybenzaldehyde were all successful in the condensation. Only unsaturated sulfones could be isolated when cyclohexylamine was employed as amine component.

IN THE FIRST paper in this series (1) the reactivity of α-hydrogen atoms in various alkyl aryl sulfones was investigated. The products of the condensation, β-aminosulfones, are relatively unstable under the conditions employed in this and other studies (1–3) and decompose rapidly when heated. By-products, *i.e.*, α,β-unsaturated sulfones and alkyl aryl sulfones, are isolable from the reaction mixture. It was the purpose of this research to determine the major pathway leading to the α,β-unsaturated sulfones. Numerous aromatic aldehydes were employed to ascertain any effects attributable to the aldehyde moiety.

The Mannich condensation has been applied successfully to arylsulfonylacetic acids only when aromatic aldehydes and ammonium acetate or primary amines were employed (1–3). Aliphatic aldehydes and/or secondary amines gave only α,β-unsaturated sulfones (2–4).

EXPERIMENTAL

Chemicals for this research were obtained from commercial sources in most cases. *p*-Chloro- and *p*-bromobenzenethiols were obtained from Evans Chemetics, Inc., as was *p*-aminophenylthioacetic acid. Most of the remaining organic chemicals were obtained from Distillation Products Industries, Inc. *p*-Nitrophenylthioacetic acid was provided by the Department of Chemistry, University of Mississippi, University.

p-Methoxybenzenesulfonyl Chloride.—(Not in tables).—According to the method of Morgan and Cretcher (5), 350 Gm. of anisole and 760 Gm. of chlorosulfonic acid in 1300 ml. of chloroform gave a 53.0% yield of crystals (from hexane) melting at 39.0-40.0° [literature, 40–42° (5)].

p-Methoxybenzenethiol.—(Not in tables).—Utilizing the method of Backer and Kramer (6), 350 Gm. of *p*-methoxybenzenesulfonyl chloride, 1700 ml. of concentrated hydrochloric acid, and 750 Gm. of tin gave a white oil, b.p. 85°/5 mm., in 53.5% yield.

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p-Substituted Phenylthioacetic Acids.—(Table I).—For the preparation of the phenylthioacetic acids required in this study, the procedure of Uyeda (7) was modified and adapted as follows: a mixture of 1 mole of the appropriate benzenethiol and 1 mole of sodium hydroxide in 250 ml. of water was added to a mixture of 1 mole of chloroacetic acid and 1 mole of sodium bicarbonate in 2.5 L. of water. The resultant solution was heated on a steam bath or at reflux for 1–3 hr. After cooling, a portion of the product (as the sodium salt), contaminated with water-insoluble by-products, usually precipitated. The solution was filtered, the filtrate treated with charcoal, and refiltered. The resultant filtrate was acidified with dilute sulfuric acid and the flocculent white precipitate collected on a Büchner funnel. A second crop was obtained by dissolving the residue (from filtering the original reaction mixture) in 1–3 L. of water (some insoluble material was present), treating with charcoal, and refiltering. Acidification of the resultant filtrate with dilute sulfuric acid and collection of the precipitate on a Büchner funnel gave the second crop of product. The combined crops were purified by suspending the solid material in 1–3 L. of water, neutralizing (dilute NaOH solution), and treating with charcoal. The charcoal-treated solution was stirred for 30 min. and the charcoal removed by filtration. Acidification of the filtrate with dilute sulfuric acid gave a white precipitate, which then was collected on a Büchner funnel. Analytical purity was achieved after two such treatments, followed by one or more recrystallizations from hot water.

For example, *p*-chlorophenylthioacetic acid was prepared in the above manner in 78.5% yield; m.p. 105.5–106.0°. *p*-Methoxyphenylthioacetic acid, prepared from *p*-methoxybenzenethiol, was obtained in 63.0% yield, m.p. 72.0–73.0°. Data for other *p*-substituted phenylthioacetic acids are given in Table I.

N-p-Acetylaminophenylthioacetic Acid.—(Table I, Compound *2*).—A modification of the procedure of Herbst and Shemin (8) was used for this preparation. Thus, 91.6 Gm. of *p*-aminophenylthioacetic acid (0.488 mole, 97.7% purity) in 200 ml. of water and a total of 110 ml. (1.17 moles) of acetic anhydride added in four to ten equal portions 10–15 min. apart gave 77.0–79.0% yields of product, melting at 152.5–154.0°. Addition of acetic anhydride in a single portion, as called for by Herbst and Shemin (8), gave only a 54.9% yield. After stirring for 1.5 hr., the product was collected on a Büchner funnel, dissolved in dilute sodium bicarbonate or

TABLE I.—MISCELLANEOUS COMPOUNDS

Compd.	Name	Yield, %	Formula	M.p., °C.[a]	Anal.[b] C Found	C Calcd.	H Found	H Calcd.	S Found	S Calcd.
1	*p*-Bromophenylthioacetic acid[c]	79.0	$C_8H_7BrSO_2$	115.0–116.0	38.89	38.88	2.75	2.86	12.75	12.97
2	*p*-Acetylaminophenylthioacetic acid[c]	79.0	$C_{10}H_{11}NSO_3$	152.5–154.0	53.23	53.30	5.13	4.92	14.40	14.23
3	*p*-Nitrophenylthioacetic acid[c,d]	[d]	$C_8H_7NSO_4$	155.5–156.0[g]	45.26	45.06	3.52	3.31	15.30	15.04
4	*p*-Bromobenzenesulfonylacetic acid[e]	79.0	$C_8H_7BrSO_4$	144.5–146.0	34.60	34.42	2.60	2.52	11.49	11.49
5	*p*-Acetylaminobenzenesulfonylacetic acid[e]	72.0	$C_{10}H_{11}NSO_5$	195.5–197.0[h]	46.84	46.67	4.46	4.31	12.50	12.46
6	*p*-Nitrobenzenesulfinylacetic acid[e]	77.9	$C_8H_7NSO_5$	173.5–174.5[i]	42.06	41.92	3.26	3.08	14.01	13.99
7	Cyclohexylammonium *p*-nitrobenzenesulfinylacetate[e]	39.0–44.6	$C_{14}H_{20}N_2SO_5$	153.5–154.5	51.32	51.20	6.08	6.14	10.11	9.76
8	*p*-Chlorobenzenesulfonylmethane[f]	50.6	$C_7H_7ClSO_2$	96.5–97.5	44.26	44.10	3.44	3.70	17.30	16.82
9	*p*-Bromobenzenesulfonylmethane[f]	39.3	$C_7H_7BrSO_2$	103.0–103.5	35.93	35.76	2.90	3.00	13.91	13.64

[a] All melting points are uncorrected and were obtained using a Fisher-Johns melting point apparatus. [b] Microanalytical data for compound 4 provided by A. Bernhardt of Mülheim (Ruhr), West Germany. All other microanalytical data were provided by Weiler and Strauss, Oxford, England. [c] Recrystallized from water. [d] This compound was provided by the Department of Chemistry, University of Mississippi. Neither yield nor data on the method of preparation are available. [e] Recrystallized from 2-propanol. [f] Recrystallized from 95% ethanol. [g] Lit. m.p., 149–151° (22) and 156.7° (23). [h] Lit. m.p., 215–216° (24). [i] Lit. m.p., 177.0–177.5° (22).

sodium hydroxide solution, and treated with charcoal. After stirring for 30 min., the mixture was filtered. Acidification of the filtrate gave a flocculent off-white precipitate which was collected on a Büchner funnel and purified as outlined in the previous procedure.

After standing for 12 hr. in basic solution in the presence of charcoal, the compound acquires a pink color which cannot be discharged by charcoal treatment. Data for this compound are given in Table I.

p-Substituted Benzenesulfonylacetic Acids.—(Table I).—*p*-Substituted benzenesulfonylacetic acids were obtained by oxidation of the corresponding *p*-substituted phenylthioacetic acids with hydrogen peroxide (9). Thus, 0.1 mole of the appropriate phenylthioacetic acid was suspended in 50 ml. of glacial acetic acid and 50 ml. of acetic anhydride and chilled in an ice bath. Hydrogen peroxide (27 ml. 30% solution) was added and the mixture stirred for 1 hr. at 0°. The ice then was allowed to melt and the mixture permitted to stand for 24–48 hr. at room temperature. Heating at 50° for 0.5 hr. completed the reaction. The solvent was removed *in vacuo* at room temperature and the residue dissolved in 5% sodium hydroxide solution. The resultant solution was stirred with charcoal for 30 min., filtered, and acidified with dilute sulfuric acid. The flocculent precipitate was collected on a Büchner funnel and purified in the same manner as the substituted phenylthioacetic acids.

Thus, *p*-chlorobenzenesulfonylacetic acid was obtained in the above manner in 73.5% yield. *p*-Nitrophenylthioacetic acid gave only the sulfinyl derivative (77.9% yield, m.p. 173.5–174.5°) by this procedure. *p*-Methoxybenzenesulfonylacetic acid could not be rendered analytically pure, although derivatives are described in Table III. Data for other *p*-substituted benzenesulfonylacetic acids are given in Table I.

Sulfone Mannich Bases.—(Table II).—Sulfone Mannich bases were prepared according to the procedure of Balasubramanian and Baliah (2). Arylsulfonylacetic acids (0.02–0.04 mole) were combined with equivalent amounts of aromatic aldehydes and cyclohexylamine or ammonium acetate in 4–8 ml. of glacial acetic acid and refluxed 5–15 min. or until vigorous evolution of carbon dioxide ceased. The cooled mixture was extracted with 50–100 ml. of anhydrous ether, and the ether extract was treated with anhydrous hydrogen chloride. In most cases a precipitate formed before this treatment. Analyses of the purified precipitates indicated that they were unsaturated sulfones. (See the procedure following.) The hydrochlorides of the Mannich bases were collected on a Büchner funnel and purified from ethanol or *n*-propanol. No products resulted in the hexylamine series, nor were the condensations successful when heterocyclic aldehydes, such as indole-3-carboxaldehyde, furfural, and pyridine-2-carboxaldehyde, were employed. Treatment with excess hydrogen chloride resulted in darkening and in conversion of the Mannich base hydrochlorides to unsaturated sulfones. Yields, physical properties, and analyses are recorded in Table II.

α,β-Unsaturated Sulfones.—(Table III).—The filtrates which resulted from the isolation of the hydrochloride salts (described above) were evaporated, and several milliliters of 95% alcohol were added. In many cases a precipitate was noted at this point; but in some cases it was necessary to decolorize the mixture at the boiling point with charcoal, filter while hot, and cool before crystals could be obtained. The crystalline products were collected on a Büchner funnel, decolorized with charcoal, and precipitated by cooling the alcoholic solution. The relevant data for these compounds are given in Table III.

RESULTS AND DISCUSSION

Preparation of most of the compounds in Table I proceeded smoothly. In the oxidation of *p*-substituted phenylthioacetic acids, the product always contained traces of benzenethiol or other malodorous compounds. Disproportionation of the intermediate sulfoxides in the acid media could produce benzenethiol and glyoxylic acid as minor by-products of the oxidation. Similar reactions have been reported (10–12).

In all the Mannich condensations attempted, only aldehyde polymers could be obtained when *p*-acetylaminobenzaldehyde, furfural, indole-3-carboxaldehyde, or pyridine-2-carboxaldehyde were employed. Only α,β-unsaturated sulfones could be obtained when cyclohexylamine was employed as the amine, along with *trans*-cinnamaldehyde (Table III, compound *6*), benzaldehyde (Table III, compound *5*), *p*-chloro- (Table III, compound *7*), *p*-methoxy- (Table III, compound *3*), or 3,4-methylenedioxybenzaldehyde (Table III, compound *2*) as the aldehyde component. Ammonium acetate in combination with benzaldehyde or *p*-chlorobenzaldehyde and *p*-acetylaminobenzenesulfonylacetic acid gave only unsaturated sulfones (Table III, compound *12*; Table III, compound *13*).

Combinations which gave both α,β-unsaturated sulfones and Mannich bases include *p*-bromobenzenesulfonylacetic acid, ammonium acetate, and *p*-isopropyl- (Table II, compound *1*), *p*-methoxy- (Table II, compound *3*; Table III, compound *9*), or 3,4-methylenedioxybenzaldehyde (Table II, compound *2*; Table III, compound *8*). Additional combinations which provided Mannich bases and α,β-unsaturated sulfones were reported previously (1). *p*-Nitrobenzenesulfinylacetic acid (Table I, compound *6*), provided only cyclohexylammonium *p*-nitrobenzenesulfinylacetate (Table I, compound *7*) when subjected to the Mannich procedure. Mannich bases, isolated as the hydrochloride salts, are reported in Table II. The by-products, methyl aryl sulfones and α,β-unsaturated sulfones, are reported in Tables I and III, respectively.

Primary aliphatic amines which have been successful in giving rise to isolable Mannich bases include ammonium acetate (1–3), methylamine (2), ethylamine (2), allylamine (2), butylamine (2), octylamine (2), and benzylamine (1,2). Primary aliphatic amines unsuccessful in giving rise to isolable Mannich bases include benzhydrylamine and cyclohexylamine, both used in this study. Steric hindrance probably accounts for the failure of the two latter amines to provide sulfone Mannich bases.

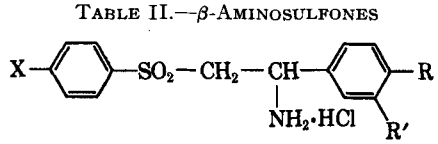
Four courses leading to α,β-unsaturated sulfones as by-products may be postulated. These are: (*a*) reversal of the Mannich reaction, followed by direct combination of the resultant alkyl aryl sulfone and the aldehyde under the conditions of the reaction; (*b*) breakdown of the postulated intermediate, 3-amino-3-aryl-2-arylsulfonylpropionic acid, zwitterion form, according to the concerted decarboxylation-amine elimination mechanism of Chodroff and Whitmore (4); (*c*) deamination of the hydrochloride or acetate salt of the expected Mannich bases; or (*d*) direct condensation of the aldehyde and the arylsulfonylacetic acid with accompanying decarboxylation.

Relevant to the first postulate, there is no doubt that the Mannich reaction might be reversible (13), but only alkyl aryl sulfones could result. Simple decarboxylation of the arylsulfonylacetic acids also can account for the presence of these same sulfones. The alkyl aryl sulfones are almost entirely devoid of ability to react with aromatic aldehydes (14), however, and this pathway may be classified as improbable.

In a given series of reactions, the concerted mechanism of Chodroff and Whitmore (4) [see (*b*) above] alone cannot account for the Mannich bases isolated. A competitive process involving only decarboxylation of the zwitterion intermediate would be required in order to provide the Mannich bases isolated. The yields of Mannich base and α,β-unsaturated sulfone from such competitive processes should be random. Results reported in this manuscript and elsewhere (1–3, 15) indicate that with longer reaction time the yield of Mannich base decreases, while the yield of α,β-unsaturated sulfone increases. These data indicate that at least part of the total yield of α,β-unsaturated sulfone must be formed from the Mannich base, which no longer possesses a carboxyl group and not from the postulated zwitterion intermediate.

The relative contributions of the pathways listed as (*c*) and (*d*) above cannot be resolved completely from existing data. Optimum yields of Mannich bases appear within 5–15 min., while yields of α,β-unsaturated sulfones approach a maximum after 25–30 min. As previously pointed out, at least part of the α,β-unsaturated sulfone, particularly that portion formed after the yield of Mannich base reaches a maximum, probably arises by means of an E-2 elimination of amine from the acetate salt of the

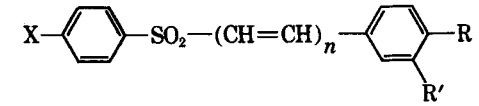
TABLE II.—β-AMINOSULFONES



Compd.	X	R	R'	Yield, %	Formula	M.p., °C.[a]	Anal.[b] C Found	C Calcd.	H Found	H Calcd.	S Found	S Calcd.
1	Br	$(CH_3)_2CH$—	H	18.8	$C_{17}H_{21}ClBrNSO_2$	220.0–221.0[c]	48.73	48.75	4.71	5.02	8.02	7.66
2	Br	—O—CH_2—O—		17.4	$C_{16}H_{15}ClBrNSO_4$	215.5–217.5[c]	42.97	42.82	3.30	3.59	7.64	7.62
3	Br	CH_3O—	H	14.6	$C_{16}H_{17}ClBrNSO_3$	204.5–207.0[c]	44.08	44.29	4.12	4.21	8.11	7.88

[a] Uncorrected melting points were obtained on a Fisher-Johns melting point apparatus. [b] Compounds were analyzed by Weiler and Strauss, Oxford, England. [c] Recrystallized from 2-propanol–petroleum ether (60–110° boiling range) mixture (1:4 ratio by volume).

TABLE III.—α,β-UNSATURATED SULFONES



Compd.	X	n	R	R'	Yield, %	Formula	M.p., °C.[a]	Anal.[b] C Found	C Calcd.	H Found	H Calcd.	S Found	S Calcd.
1	Cl	1	Cl	H	30.2	$C_{14}H_{10}Cl_2SO_2$	163.0–164.0[c]	53.68	53.69	3.01	3.22	10.21	10.24
2	Cl	1	—O—CH_2—O—		20.9	$C_{15}H_{11}ClSO_4$	147.0–147.5[d]	55.93	55.82	3.70	3.43	9.86	9.93
3	Cl	1	CH_3O—	H	19.0	$C_{15}H_{13}ClSO_3$	142.5–143.5[d]	58.47	58.33	4.35	4.24	10.28	10.38
4	Cl	1	CH_3O—	CH_3O—	10.2	$C_{16}H_{15}ClSO_4$	144.0–146.0[e]	56.53	56.72	4.64	4.46	9.40	9.46
5	Br	1	H	H	22.3	$C_{14}H_{11}BrSO_2$	103.5–104.5[f]	52.15	52.03	3.49	3.43	9.91	9.93
6	Br	2	H	H	14.3	$C_{16}H_{13}BrSO_2$	170.0–171.5[f]	54.92	55.02	3.71	3.75	...	...
7	Br	1	Cl	H	17.6	$C_{14}H_{10}ClBrSO_2$	185.0–187.0[f]	47.19	47.01	2.78	2.82	8.95	8.96
8	Br	1	—O—CH_2—O—		30.3	$C_{15}H_{11}BrSO_4$	167.0–167.5[c]	49.14	49.06	2.86	3.02	9.07	8.73
9	Br	1	CH_3O—	H	22.7	$C_{15}H_{13}BrSO_3$	149.0–150.0[e]	51.24	51.00	3.51	3.71	9.34	9.08
10	Br	1	CH_3O—	CH_3O—	7.1	$C_{15}H_{15}BrSO_4$	142.5–144.0[e]	50.09	50.14	3.85	3.95	8.25	8.37
11	CH_3O	1	Cl	H	15.8	$C_{15}H_{13}ClSO_3$	136.5–137.5[d]	58.26	58.33	4.61	4.24	10.45	10.39
12	$CH_3CO\cdot NH$—	1	H	H	14.1	$C_{16}H_{15}NSO_3$	172.5–173.5[e]	63.46	63.77	4.75	5.02	10.68	10.64
13	$CH_3CO\cdot NH$—	1	Cl	H	16.9	$C_{16}H_{14}ClNS_2O_3\cdot{}^1/_2H_2O$	191.5–192.5[d]	55.80	55.73	4.40	4.39	9.36	9.30

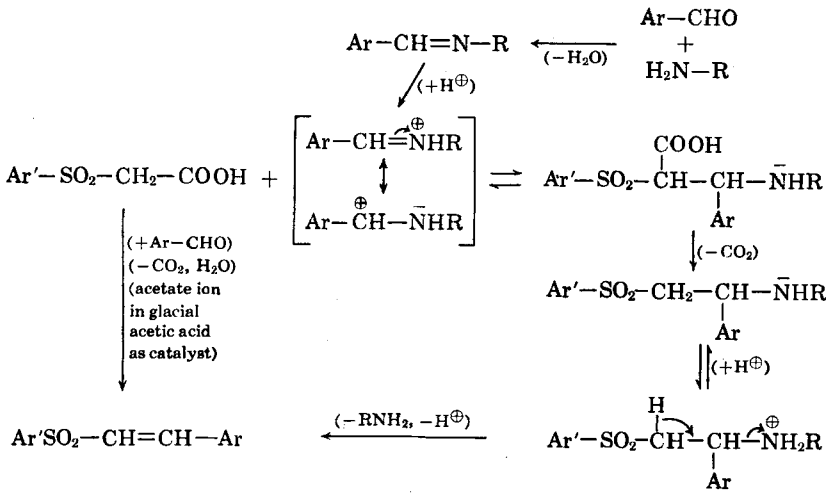
[a] Uncorrected melting points were taken on a Fisher-Johns melting point apparatus. [b] Microanalytical data on compounds *4*, *8*, and *10* were provided by A. Bernhardt, Mülheim (Ruhr), West Germany. The remaining data were provided by Weiler and Strauss, Oxford, England. [c] Recrystallized from ethanol. [d] Recrystallized from 2-propanol. [e] Recrystallized from 95% ethanol. [f] Recrystallized from methanol.

Mannich base. Support of this conclusion is given by Balasubramanian and Baliah (2), who reported complete conversion of 2-amino-2-phenyl-1-ethyl *p*-tolyl sulfone into 1-phenyl-2-*p*-toluenesulfonylethene on refluxing the former in glacial acetic acid for 30 min.

The formation of Mannich base and α,β-unsaturated sulfone when aromatic aldehyde and primary amine or ammonium acetate are used is in contrast to the isolation of only α,β-unsaturated sulfones when aliphatic aldehyde and primary amine or ammonium acetate are employed (2, 4). No noticeable effect on the stability of the Mannich bases should be produced by such a substitution. However, there is a great difference between the ability of aliphatic and aromatic aldehydes to function effectively in an aldol-type reaction. The evidence appears to indicate that an aldol-type process occurs to the complete exclusion of a Mannich condensation in combinations involving aliphatic aldehydes. If this is a correct conclusion, formation of α,β-unsaturated sulfones in condensations involving aromatic aldehydes probably occurs by means of an aldol-type condensation of relatively similar rate to the Mannich condensation during the early stages of the process, with amine elimination becoming more important in the later stages of the reaction. In both processes, the acetate anion acts as a strong base. Its base strength in glacial acetic acid is comparable to the base strength of the hydroxide ion in aqueous solution.

Some α,β-unsaturated sulfone may arise during isolation. For example, 2-*p*-bromobenzenesulfonyl-1-(3,4-methylenedioxyphenyl)-1-ethylamine hydrochloride (Table II, compound *2*) turned dark brown during hydrochlorination and gave a mixture of brown-colored needle clusters in a field of pale yellow powder on recrystallization. After subsequent mechanical separation, purification, and analysis, the brown-colored needles were identified as 1-(*p*-bromobenzenesulfonyl)-2-(3,4-methylenedioxyphenyl)ethene (Table III, compound *8*) and the yellow powder as the desired Mannich base hydrochloride (Table II, compound *2*). Both were colorless when pure. The coloration was probably due to a phenolic breakdown product, since all alkoxy-substituted derivatives assumed this coloration. A subsequent experiment, in which excessive hydrochlorination was employed deliberately, resulted in such extensive contamination of 2-(*p*-bromobenzenesulfonyl)-1-(*p*-chlorophenyl)ethylamine hydrochloride (not reported) by its unsaturated sulfone by-product, 1-*p*-(bromobenzenesulfonyl)-2-(*p*-chlorophenyl)ethene (Table III, compound *7*), that purification was rendered difficult. Mechanical separation, purification, and analysis confirmed these results.

The role of the amine also requires some clarification. Balasurbramanian and Baliah (2) reported the isolation of only α,β-unsaturated sulfones when secondary amines were employed. A proposal for the mechanism of the Mannich reaction was published by Hellmann and Opitz (17) and later by Cummings and Shelton (18). Both groups agreed that an initial condensation between the aldehyde and amine occurs, producing an aminomethanol. Acid retards this condensation. Once formed, however, this intermediate may be protonated, with subsequent expulsion of a molecule of water and



Scheme I

formation of a resonant carbonium-immonium ion. The latter then reacts with a carbanic center developed on the active hydrogen component of the reaction, thus producing the normal product of the reaction. The failure of secondary amines in the condensation may be due to unfavorable competition of the amine with the aryl-sulfonylacetic acid for the aldehyde as a result of steric factors. Furthermore, the use of aromatic aldehydes may lead to Schiff bases rather than to the postulated aminomethanols, since the former are more stable than the latter under the conditions of the reaction (17, 19–21). This conclusion may be supported by the work of Balasubramanian and Baliah (16), who reported that acetaldehyde-ammonia and ω-benzenesulfonylaceophenone gave only 2,4-bis(benzenesulfonyl) - 1,5 - diphenyl - 3 - methyl - 1,5 - pentanedione. The order of addition may also account for this product (17, 21).

The conclusions drawn in this study are presented in the form of a tentative mechanism proposal (Scheme I). Kinetic studies on the formation of the unsaturated sulfone are being planned and will be the subject of a future study.

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