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## Itaconic Acid Derivatives Of Sulfanilamide and Sulfone

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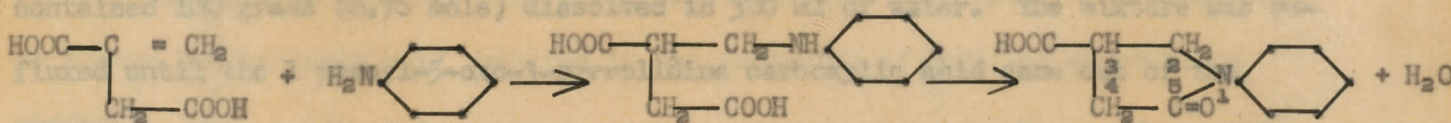
ITACONIC ACID DERIVATIVES OF SULFANILAMIDE AND SULFONE

By Malcolm J. Thompson

Part I.--Itaconic acid derivatives of Sulfanilamide involving 1(p-Chloro sulfonyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid with primary amines.

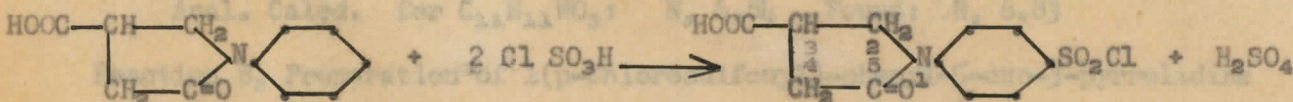
In this investigation thirty-eight itaconic acid derivatives of sulfanilamide, 1(p-Sulfamyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid were synthesized. Before this problem could be brought to a successful conclusion, two essential compounds were initially prepared. The first, 1 phenyl-5-oxo-3-pyrrolidine carboxylic acid, was formed by the interaction of aniline and itaconic acid, the second by condensation of 1 phenyl-5-oxo-3-pyrrolidine carboxylic acid with chlorosulfonic acid to give 1(p-Chlorosulfonyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid.

This interaction of aniline with methylene succinic acid (itaconic acid) to give 1 phenyl-5-oxo-3-pyrrolidine carboxylic acid had previously been studied and reported.<sup>2</sup> The probable mechanism for this reaction is:<sup>1</sup>



and will be referred to as carboxy pyrrolidination.

It has been shown that chlorosulfonation of 1 phenyl-5-oxo-3-pyrrolidine carboxylic acid yields chiefly 1(p-Chlorosulfonyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid at 60-65° C.



1. Nomenclature; Chemical Abstracts, 44, 1950.
2. (a) Gottlieb, Ann., 77, P. 264, 1851; (b) Michael and Palmer, Am. Chem. J., 9, P. 199, 1887; (c) Scharfenberg, Ann., 254, P. 149, 1889; (d) Anschutz and Reuter, Ann., 254, P. 129, 1889; (e) Paytash, Gathe and Sparrow, J. Am. Chem. Soc., 72, P. 1415, 1950.



between 65-70° C until the evolution of HCl had ceased (15-20 minutes). The syrupy liquid was cooled to room temperature, and poured slowly with stirring into large excess of crushed ice in order to precipitate the 1-(p-Chlorosulfonyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid. It was filtered by suction and washed thoroughly with cold water. The crude yield was 45-50 grams (76-85%). Melting point of purified compound was 164-166° C (from benzene).

Anal. Calcd. for  $C_{11}H_{10}ClNO_5S$ : N, 4.60 Found: N, 4.58

Reaction C, Preparation of 1-(p-Sulfamyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid derivatives. Ten grams of crude 1-(p-Chlorosulfonyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid was condensed with primary and secondary amines (mole ratio of 1-1.5) by bringing about the reactions in an alkaline medium (sodium bicarbonate) or acetone. At room temperature the reactions were brought about in an alkaline medium from a few hours to standing overnight; Whereas in acetone the time varied from one quarter hour to three hours. The crude compounds produced were usually gummy products, but upon successive recrystallizations from water, dilute alcohol or dilute hydrochloric acid resulted in the formation of purified crystalline products.

1-(p-Sulfonyl)-phenyl-5-oxo-3-pyrrolidine Carboxylic Acid derivatives		
	R <sub>1</sub> Methyl	Methylamine
	R <sub>1</sub> Methyl, R <sub>2</sub> Methyl	Dimethylamine
	R <sub>1</sub> Ethyl	Ethylamine
	R <sub>1</sub> Ethyl, R <sub>2</sub> Methyl	Methylamine
	R <sub>1</sub> Isopropyl	Isopropylamine
	R <sub>1</sub> 3-Methoxypropyl	3-Methoxypropylamine
	R <sub>1</sub> 3-Isopropoxypropyl	3-Isopropoxypropylamine
	R <sub>1</sub> n-Butyl	n-Butylamine
	R <sub>1</sub> n-Butyl, R <sub>2</sub> n-Butyl	n-Butylamine
	R <sub>1</sub> Cyclohexyl	Cyclohexylamine
	R <sub>1</sub> 2,4,4,4-Tetraethyl-2-pentanone	2,4,4,4-Tetraethyl-2-pentanone
	R <sub>1</sub> 3,5,5-Trimethylhexyl	3,5,5-Trimethylhexylamine
	R <sub>1</sub> Carboxymethyl	Aminoacetic Acid
	R <sub>1</sub> Phenyl	Aniline
	R <sub>1</sub> Phenyl, R <sub>2</sub> Methyl	Methylamine
	R <sub>1</sub> 2-Chlorophenyl	o-Chloroaniline

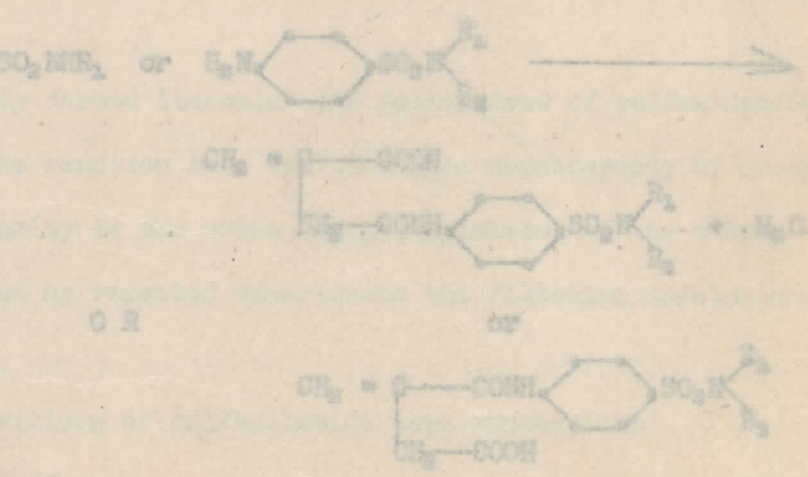
TABLE I<sup>a</sup>

		Yield <sup>d</sup> %	M. p. <sup>c</sup>	Calcd. Found <sup>b</sup>	Neut. Equiv. Found	Mol. Cal. Found <sup>c</sup>
1-(p-Sulfamyl phenyl)-5-oxo-3-Pyrrolidine Carboxylic Acid derivative						
Methylamine	R <sub>1</sub> Methyl	49	204-206	9.38 9.44	305	298 297
Dimethylamine	R <sub>1</sub> Methyl R <sub>2</sub> Methyl	70	220-223 237-239	8.96 8.97	307	312 -
Ethylamine	R <sub>1</sub> Ethyl	46	198-199	8.96 8.99	314	312 317
Diethylamine	R <sub>1</sub> Ethyl R <sub>2</sub> Ethyl	51	152-153	8.23 8.27	336	340 340
Isopropylamine	R <sub>1</sub> Isopropyl	81	190-191	8.55 8.55	330	326 -
3 Methoxypropylamine	R <sub>1</sub> 3 Methoxypropyl	37	104-106	7.82 7.84	390	356 -
3 Isopropoxypropylamine	R <sub>1</sub> 3 Isopropoxypropyl	60	105-107	7.21 7.27	382	385 381
n-Butylamine	R <sub>1</sub> n-Butyl	51	168-169	8.23 8.23	343	340 340
Di n-Butylamine	R <sub>1</sub> n-Butyl R <sub>2</sub> n-Butyl	48	74-76	7.06 7.04	396	396 -
Cyclohexylamine	R <sub>1</sub> Cyclohexyl	83	174-175	7.64 7.60	369	366 367
2,4,4, Trimethyl-2-Amino Pentane	R <sub>1</sub> 2,4,4, Trimethyl-2-Pentyl	75	185-186	7.06 7.03	394	396 394
3,5,5, Trimethyl hexylamine	R <sub>1</sub> 3,5,5, Trimethylhexyl	35	156-157	6.82 6.88	409	410 403
Aminoacetic Acid	R <sub>1</sub> Carboxymethyl	35	190-192	8.18 8.24	172	342 -
Aniline	R <sub>1</sub> Phenyl	67	192-193	7.77 7.78	359	360 -
Ethylaniline	R <sub>1</sub> Phenyl R <sub>2</sub> Ethyl	72	188-189	7.21 7.18	388	388 -
o-Chloroaniline	R <sub>1</sub> 2 Chlorophenyl	57	166-168	7.09 7.09	-	395 390

m-Chloroaniline	R <sub>1</sub> 3 Chlorophenyl	85	209-210	7.09	7.08	-	395	400
2,4-Dichloroaniline	R <sub>1</sub> 2,4-Dichlorophenyl	75	210-211	6.52	6.52	-	429	428
2,5-Dichloroaniline	R <sub>1</sub> 2,5-Dichlorophenyl	65	104-106	6.52	6.52	-	429	433
o-Nitroaniline	R <sub>1</sub> 2 Nitrophenyl	30	189-191	10.37	10.18	402	405	400
m-Nitroaniline	R <sub>1</sub> 3 Nitrophenyl	85	233-235	10.37	10.20	400	405	406
p-Nitroaniline	R <sub>1</sub> 4 Nitrophenyl	60	220-226d	10.37	10.18	400	405	413
o-Toluidine	R <sub>1</sub> 2 Tolyl	65	160-161	7.48	7.49	378	374	-
m-Toluidine	R <sub>1</sub> 3 Tolyl	68	178-179	7.48	7.57	378	374	379
p-Toluidine	R <sub>1</sub> 4 Tolyl	41	150-151	7.48	7.49	375	374	374
m-Nitro-p-Toluidine	R <sub>1</sub> 3 Nitro 4 Tolly	30	156-157	10.25	10.17	413	419	-
Benzylamine	R <sub>1</sub> Benzyl	47	194-195	7.48	7.44	379	374	366
B-Phenylethylamine	R <sub>1</sub> B-Phenylethyl	92	187-188	7.21	7.24	395	388	387
o-Anisidine	R <sub>1</sub> 2 Methoxyphenyl	77	182-183	7.17	7.25	391	390	390
p-Chloroanisidine	R <sub>1</sub> 2 Methoxy 5 Chlorophenyl	86	188-189	6.59	6.54	439	425	420
2,5 Dimethoxyaniline	R <sub>1</sub> 2,5 Dimethoxyphenyl	90	157-158	6.61	6.63	428	420	416
2,5 Diethoxyaniline	R <sub>1</sub> 2,5 Diethoxyaniline	49	159-160	6.24	6.26	456	448	445
B-3,4 Dimethoxyphenyl ethylamine	R <sub>1</sub> B-3,4 Dimethoxyphenylethyl	68	111-115	6.24	6.19	449	448	-
o-Aminodiphenyl	R <sub>1</sub> 2 Diphenyl	50	199-200	6.41	6.39	437	437	445
p-Aminodiphenyl	R <sub>1</sub> 4 Diphenyl	75	214-215	6.41	6.41	437	437	433
p-Phenylenediamine	R <sub>1</sub> 1-p-(p-Sulfamyl phenyl)Phenyl 5-oxo-3-Pyrrolidyl Carboxylic Acid	80	280d	8.70	8.61	326	643	-

Benzidine	80	315-320d	7.80	7.83	355	719	-
R <sub>1</sub> 1-p-(p-Sulfamyl diphenyl)Phenyl 5-oxo-3-Pyrrolidyl Carboxylic Acid	75	252-254	12.06	12.20	460	464	451
p-Aminoazobenzene	-	192-193	6.82	6.82	426	410	408
1-Naphthylamine	-	-	-	-	-	-	-
R <sub>1</sub> Azobenzene	-	-	-	-	-	-	-
R <sub>1</sub> 1-Naphthyl	-	-	-	-	-	-	-

(a) The following derivatives could not be confirmed either because of the lack of sufficient analytical data or unsuccessful synthesis: R<sub>1</sub> 4-Chlorophenyl, R<sub>1</sub> 4-Methoxyphenyl, R<sub>1</sub> 2-Pyridyl, R<sub>1</sub> Primidyl, and R<sub>1</sub> 2-Thiazolyl, R<sub>1</sub> 2-Thiophenyl. (b) Gunning, Arnold, and Dyer, Modified Kjeldahl Method. H. C. Sherman, Methods of Organic Analysis, The Macmillan Company, New York, New York, P. 291. Nitro and azo compounds were first reduced with Salicylic Acid and Sodium Thiosulphate. (c) Rast Camphor Method. (d) Yields based on two or more recrystallizations.



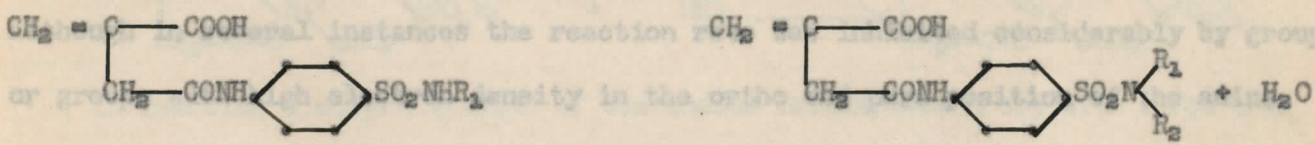
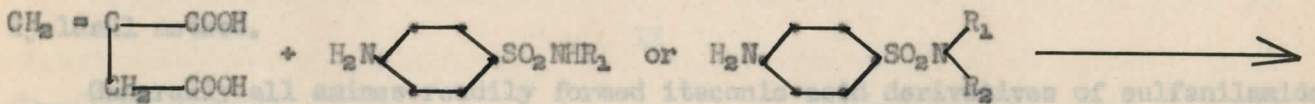
All itaconic acid derivatives of sulfanilamides produced are classified as strong acids. Prior to this investigation only two itaconic acid derivatives of sulfanilamide had been reported. 2e realization equivalents of derivatives with SO<sub>2</sub>NHR<sub>2</sub> group did not correspond with their values when phenolphthalein (pH range 8.3-10) was used and 1(p-Sulfamyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid. These were made by the fusion of Sulfaguanidine and Sulfanilamide with itaconic acid respectively.

Although simultaneously with this investigation further attempts were made to prepare 1(p-Sulfamyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid derivatives by indicator accurate results were obtained. 4 was observed that phenol red gave an end point change at pH of 7.45 in potentiometric titration the end points were reached proceed as expected. Instead the reaction favored formation of N<sup>4</sup> Itaconyl acid between a pH of 6 and 7. Compounds with the (SO<sub>2</sub>NHR<sub>2</sub>) group gave no indication of abnormal neutralization equivalents.

From the above observations it was concluded that (SO<sub>2</sub>NHR<sub>2</sub>) group was affected by fusion with itaconic acid. Only eleven of fifty fusion gave the desired 1(p-Sulfamyl phenyl)-5-oxo-3-pyrrolidine carboxylic acid derivatives. Forty gave N<sup>4</sup> Itaconyl acid sulfanilamides.

Carboxy pyrrolidination was not favored in the fusion of itaconic acid and sulfanilamides under similar circumstances as were aniline and itaconic acid. The in the ring of R enhanced the hydrogen activity of the (SO<sub>2</sub>NHR<sub>2</sub>) group. Similar derivatives empirical formulas, neutralization equivalents and nitrogen analyses were produced when R contained two or more phenyl radicals.

All derivatives formed were stable to hydrochloric acid and sodium hydroxide acid derivatives. hydrolysis. No difficulty was experienced in the determination of nitrogen by the



From the results established by repeated experiments the following conclusions were formulated:

1. Itaconic acid derivatives of sulfanilamide were synthesized readily by this method.

4. A paper by Paytash, Thompson, and Fykes, has been accepted by the J. Am. Chem. Soc. for publication.

ascribed to electronic and steric hindrance of the amine.



All itaconic acid derivatives of sulfanilamide produced are classified as strong acids. Neutralization equivalents of derivatives with  $\text{SO}_2\text{NHR}_1$  group did not correspond with their values when phenolphthalein (pH range 8.3-10) was used as the indicator, but fairly accurate results were obtained by potentiometric titration.

Further investigation showed that when phenol red was used as end point indicator accurate results were obtained. It was observed that phenol red gave an end point change at pH of 7.4; in potentiometric titration the end points were reached between a pH of 6 and 7. Compounds with the  $(\text{SO}_2\text{N}^{\text{R}_1})^{\text{R}_2}$  group gave no indication of abnormal neutralization equivalents.

From the above observations it was concluded that  $(\text{SO}_2\text{NHR}_1)$  group was affected by 0.1 N sodium hydroxide above a pH of 8, causing activity of the hydrogen ion of the  $(\text{SO}_2\text{NHR}_1)$  group.

It was also observed that  $(\text{SO}_2\text{NHR}_1)$  group with a halogen or halogens anywhere in the ring of R enhanced the hydrogen activity of the  $(\text{SO}_2\text{NHR}_1)$  group. Similar results were produced when R contained two or more phenyl radicals.

All derivatives formed were stable to hydrochloric acid and sodium hydroxide hydrolysis. No difficulty was experienced in the determination of nitrogen by the Kjeldahl method.

Generally all amines readily formed itaconic acid derivatives of sulfanilamide although in several instances the reaction rate was inhibited considerably by group or groups with high electron density in the ortho and para position of the amine.

From the results established by repeated experiments the following conclusions were formulated:

1. Itaconic acid derivatives of sulfanilamide were synthesized readily by this method.
2. Difficulty in obtaining several derivatives immediately were ascribed to electronic and steric hindrance of the amine.

3. Thirty-eight new compounds were formed.

4. 1(p-Sulfamyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid

derivatives were not favored by fusion of itaconic acid and

sulfanilamide derivatives, instead N<sup>a</sup> Itaconyl acid

sulfanilamide derivatives were the principle products.

5. Primary itaconic acid derivatives of sulfanilamide gave

unusual hydrogen activity at a pH of 8.0 or higher.

Part II.--Itaconic acid derivatives of p amino phenyl sulfone. 1(p-R<sub>1</sub>

Sulfonyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid was prepared successfully by

the condensation of 1(p-Sodium sulfinate)-phenyl-5-oxo-3-pyrrolidine sodium carboxylate

with various alkyl and aryl halides. The free acid was subsequently produced upon

acidification.

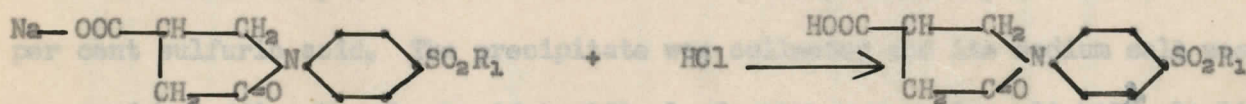
Section B, Preparation of 1(p-Sulfonyl)-phenyl-5-oxo-3-pyrrolidine



A

B

II



In reaction I esterification of the sodium carboxylate group with alkyl and aryl halides was shown to take place, but by limiting the time of reaction to a

minimum, and using only a slight excess of the halides, compound A was formed in

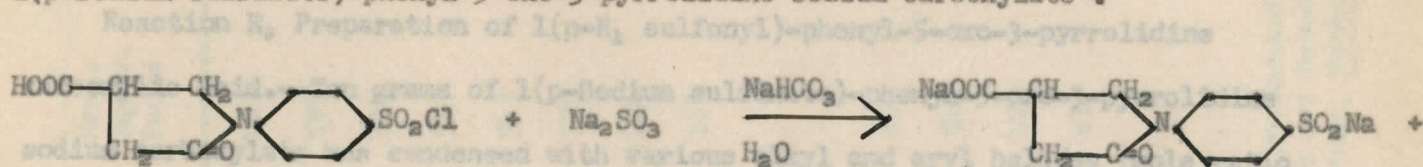
predominating yields. Hydrolysis of B with dilute sodium hydroxide produced

compound A.

5. 1(p-Chloro sulfonyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid with anhydrous

6. Formation of 1(p-Sodium sulfinate)-phenyl-5-oxo-3-pyrrolidine sodium carboxylate was favored above 15° C.

Anal. Calcd. for  $C_{11}H_{11}NO_3S$ : N, 5.20 Found: N, 5.19  
 sodium sulfite in an aqueous solution kept alkaline with sodium bicarbonate yielded  
 1(p-Sodium sulfinato)-phenyl-5-oxo-3-pyrrolidine sodium carboxylate .



$\text{NaCl} + \text{NaHSO}_4$

Fifteen of twenty compounds investigated gave the desired compounds 1(p-R<sub>1</sub> sulfonyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acids. They are listed in table II with their corresponding analytical data. Five derivatives could not be confirmed either because of inadequate analytical data or unsuccessful synthesis.

### Experimental

Reaction D, Preparation of 1(p-Sodium sulfinato)-phenyl-5-oxo-3-pyrrolidine sodium carboxylate.--Fifty grams of (0.17 mole) of crude 1(p-Chloro sulfonyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid, as prepared in Reaction B, was added at intervals with constant stirring to 300 ml of water which contained 30 grams (0.24 mole) of sodium sulfite. The temperature was kept below 15° C. The reaction mixture was kept slightly alkaline by addition of sodium bicarbonate.

After the solution had been stirred for two hours, Norite was added and the solution filtered by suction. The filtrate was then carefully acidified with 60 per cent sulfuric acid. The precipitate was collected and its sodium salt was prepared by adding the free acid to 300 ml of water and making slightly alkaline to litmus with sodium bicarbonate. This filtrate was evaporated to dryness at 75° C.

The yield of the free acid produced was 30-35 grams (66-77 per cent of the theoretical amount based on the sulfonyl chloride used). The purified acid compound melted at 175°-180° C.

5. Gilman and Blatt; Organic Synthesis, I, 1948.

6. Formation of 1(p-Sodium sulfinato)-phenyl-5-oxo-3-pyrrolidine sodium carboxylate was favored above 15° C.

Anal. Calcd. for  $C_{11}H_{11}NO_5S$ : N, 5.20 Found: N, 5.19

N.E. 134.6 N.E. 135

Reaction E, Preparation of 1(p-R<sub>1</sub> sulfonyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid.--Ten grams of 1(p-Sodium sulfinate)-phenyl-5-oxo-3-pyrrolidine sodium carboxylate was condensed with various alkyl and aryl halides (mole ratio of 1-1) by bringing about the reactions in 75 ml. of 50% aqueous alcoholic solutions. The mixtures were allowed to reflux from four to eight hours. The mixtures remained alkaline throughout the reaction. Norite was added and solutions poured into 200-300 ml of cold water. Acidification of the filtrates with dilute hydrochloric usually produced the desired derivatives. Final recrystallization was done either from water, dilute alcohol, or hydrochloric acid.

TABLE II

1(p-R<sub>1</sub> Sulfonyl)phenyl-5-oxo-3-pyrrolidine Carboxylic acid derivative

Halide Used	Yield (%)	mp (°C)
Ethyl Iodide	70	70
Methyl Bromide	62	62
n-Propyl Iodide	75	75
n-Butyl Bromide	80	80
n-Octyl Iodide	67	67
Allyl Chloride	50	50
Chloroacetic Acid	49	49
3-Chloropropionic Acid	55	55
3-Chloropropionitrile	55	55
Chloroethyl Acetate	35	35
Chloro Ethyl Acetate	37	37
Benzyl Chloride	85	85
p-Nitro Benzylchloride	83	83
Phenacyl bromide	40	40
1 Chloro, 2,4 dinitrobenzene	55	55

(a) The following derivatives were not confirmed either because of insufficient yield or because of low melting point: (1) p-Toluenesulfonyl, (2) p-Toluenesulfonyl, (3) p-Toluenesulfonyl, (4) p-Toluenesulfonyl, (5) p-Toluenesulfonyl, (6) p-Toluenesulfonyl, (7) p-Toluenesulfonyl, (8) p-Toluenesulfonyl, (9) p-Toluenesulfonyl, (10) p-Toluenesulfonyl, (11) p-Toluenesulfonyl, (12) p-Toluenesulfonyl, (13) p-Toluenesulfonyl, (14) p-Toluenesulfonyl, (15) p-Toluenesulfonyl, (16) p-Toluenesulfonyl, (17) p-Toluenesulfonyl, (18) p-Toluenesulfonyl, (19) p-Toluenesulfonyl, (20) p-Toluenesulfonyl, (21) p-Toluenesulfonyl, (22) p-Toluenesulfonyl, (23) p-Toluenesulfonyl, (24) p-Toluenesulfonyl, (25) p-Toluenesulfonyl, (26) p-Toluenesulfonyl, (27) p-Toluenesulfonyl, (28) p-Toluenesulfonyl, (29) p-Toluenesulfonyl, (30) p-Toluenesulfonyl, (31) p-Toluenesulfonyl, (32) p-Toluenesulfonyl, (33) p-Toluenesulfonyl, (34) p-Toluenesulfonyl, (35) p-Toluenesulfonyl, (36) p-Toluenesulfonyl, (37) p-Toluenesulfonyl, (38) p-Toluenesulfonyl, (39) p-Toluenesulfonyl, (40) p-Toluenesulfonyl, (41) p-Toluenesulfonyl, (42) p-Toluenesulfonyl, (43) p-Toluenesulfonyl, (44) p-Toluenesulfonyl, (45) p-Toluenesulfonyl, (46) p-Toluenesulfonyl, (47) p-Toluenesulfonyl, (48) p-Toluenesulfonyl, (49) p-Toluenesulfonyl, (50) p-Toluenesulfonyl, (51) p-Toluenesulfonyl, (52) p-Toluenesulfonyl, (53) p-Toluenesulfonyl, (54) p-Toluenesulfonyl, (55) p-Toluenesulfonyl, (56) p-Toluenesulfonyl, (57) p-Toluenesulfonyl, (58) p-Toluenesulfonyl, (59) p-Toluenesulfonyl, (60) p-Toluenesulfonyl, (61) p-Toluenesulfonyl, (62) p-Toluenesulfonyl, (63) p-Toluenesulfonyl, (64) p-Toluenesulfonyl, (65) p-Toluenesulfonyl, (66) p-Toluenesulfonyl, (67) p-Toluenesulfonyl, (68) p-Toluenesulfonyl, (69) p-Toluenesulfonyl, (70) p-Toluenesulfonyl, (71) p-Toluenesulfonyl, (72) p-Toluenesulfonyl, (73) p-Toluenesulfonyl, (74) p-Toluenesulfonyl, (75) p-Toluenesulfonyl, (76) p-Toluenesulfonyl, (77) p-Toluenesulfonyl, (78) p-Toluenesulfonyl, (79) p-Toluenesulfonyl, (80) p-Toluenesulfonyl, (81) p-Toluenesulfonyl, (82) p-Toluenesulfonyl, (83) p-Toluenesulfonyl, (84) p-Toluenesulfonyl, (85) p-Toluenesulfonyl, (86) p-Toluenesulfonyl, (87) p-Toluenesulfonyl, (88) p-Toluenesulfonyl, (89) p-Toluenesulfonyl, (90) p-Toluenesulfonyl, (91) p-Toluenesulfonyl, (92) p-Toluenesulfonyl, (93) p-Toluenesulfonyl, (94) p-Toluenesulfonyl, (95) p-Toluenesulfonyl, (96) p-Toluenesulfonyl, (97) p-Toluenesulfonyl, (98) p-Toluenesulfonyl, (99) p-Toluenesulfonyl, (100) p-Toluenesulfonyl.

TABLE II<sup>a</sup>

Organic Analysis. The Macmillan Company, New York, New York, 1932. <sup>b</sup> Nitro compound. <sup>c</sup> Neut. Equiv. Found. Mol. Wt. Cal. Found

Halide Used	1(p-R <sub>1</sub> Sulfonyl)phenyl-5-oxo-3-pyrrolidine Carboxylic Acid derivative	Yield %	M. p. C	Calcd. N %	Found	Neut. Equiv. Found	Mol. Wt. Cal. Found
Methyl Iodide	R <sub>1</sub> Methyl	70	209-210	4.94	4.94	283	283
Ethyl Bromide	R <sub>1</sub> Ethyl	62	240-242	4.70	4.64	298	297
n-Propyl Iodide	R <sub>1</sub> Propyl	75	205-206	4.50 4.60	4.54	306	311
n-Butyl Bromide	R <sub>1</sub> Butyl	80	167-168	4.31 4.44	4.40	313	315 325
n-Amyl Iodide	R <sub>1</sub> n-Pentyl	63	159-160	4.12	4.05	343	339
Allyl Chloride	R <sub>1</sub> Allyl	50	196-198	4.52	4.50	308	309
Chloroacetic Acid	R <sub>1</sub> Carboxymethyl	49	203-205	4.25	4.27	164	327
B-Chloropropionic Acid	R <sub>1</sub> Carboxylethyl	55	213-215	4.10	4.06	168	341
B-Chloropropionitrile	R <sub>1</sub> Ethyl nitrile <sup>d</sup>	85	195-197	8.68	8.64	322	322
Chloromethyl Acetate	R <sub>1</sub> Carboethoxy methyl <sup>d</sup>	35	138-140	4.10	4.16	350	341
Chloro Ethyl Acetate	R <sub>1</sub> Carboethoxy methyl <sup>d</sup>	37	216-218	3.94	3.94	350	355
Benzyl Chloride	R <sub>1</sub> Benzyl <sup>d</sup>	85	227-229	3.90	3.88	344	359
p-Nitro Benzylchloride	R <sub>1</sub> 4,Nitro Benzyl <sup>d</sup>	80	236-238	6.92	7.00	402	404
Phenacyl bromide	R <sub>1</sub> Benzoyl methyl <sup>d</sup>	40	202-203	3.23 3.17	3.15	430	432
1 Chloro, 2,4 dinitrobenzene	R <sub>1</sub> 2,4, Dinitro Phenyl	55	145-147	9.63	9.60	435	435

(a) The following derivatives were not confirmed either because of insufficient analytical data or unsuccessful synthesis: R<sub>1</sub> Isopropyl, R<sub>1</sub> Tert-butyl, R<sub>1</sub> Phenyl, R<sub>1</sub> Carboethoxy and R<sub>1</sub> Amino Phenyl. (b) Yields are based on two or more recrystallizations. (c) Gunning, Arnold, and Dyer Modified Kjeldahl Method. H. C. Sherman, Methods of

Prior to this investigation no itaconic acid derivatives of p-amine phenyl sulfone had been reported. Although simultaneously with this investigation it was shown that similar derivatives could be produced by the reaction of itaconic acid with p-amine phenyl alkyl and aryl sulfones. Two such derivatives were prepared, 1-(benzyl sulfonyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid and 1-(p-ethyl sulfonyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid. Although the reaction again failed to give itaconic acid derivatives as reported in Part I. Further work is still in progress on this particular problem.

All itaconic acid derivatives of p-amine phenyl sulfone are classified as itaconic acids. Their neutralization equivalents were in accordance with their theoretical values except in some cases where 0.1 N sodium hydroxide decomposed the compound. For example 1-(p-ethyl sulfonyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid hydrolyzed instantaneously to 1-(p-carboxy ethyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid thus its neutralization equivalent value was reduced to half of its theoretical value. Several derivatives were susceptible to acid or alkaline hydrolysis. This instability was attributed to the original nature of the halide and not to the acid formed.

Difficulty was experienced in the determination of nitrogen by the Kjeldahl method. Generally all alkyl halides readily formed itaconic acid derivatives of p-amine phenyl sulfone, although the secondary halides which were experimented with did not react. Only one tertiary alkyl halide activity was investigated and a mixture of compounds resulted. Aryl halides containing one or more nitro groups ortho or para to the halogen were sufficiently reactive to give fair yields of itaconic acid derivatives.

From this investigation of itaconic acid derivatives of p-amine phenyl

Organic Analysis. The Macmillan Company, New York, 1931, P. 291. Nitro compounds were first reduced with Salicylic Acid and Sodium Thiosulphate. (d) Easily decomposed by acid or base hydrolysis.

Prior to this investigation no itaconic acid derivatives of p-amino phenyl sulfone had been reported. Although simultaneously with this investigation it was shown that similar derivatives could be produced by the fusion of itaconic acid with p-amino phenyl alkyl and aryl sulfones. Two such derivatives were prepared, 1(p-Benzyl sulfonyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid and 1(p-Methyl sulfonyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid. Although the reaction again favored N<sup>4</sup> Itaconyl acid derivatives as reported in Part I. Further work is still in progress on this particular problem.

All itaconic acid derivatives of p-amino phenyl sulfone are classified as strong acids. Their neutralization equivalents were in accordance with their theoretical values except in remote cases where 0.1 N sodium hydroxide decomposed the compound. For example 1(p-Ethyl nitrile sulfonyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid hydrolyzed instantaneously to 1(p-Carboxy ethyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid thus its neutralization equivalent value was nearly equalled to half of its theoretical value. Hydroxide was ascribed to the

Several derivatives were susceptible to acid or alkaline hydrolysis. This instability was attributed to the original nature of the halide and not to the sulfone formed.

No difficulty was experienced in the determination of nitrogen by the Kjeldahl method.

Generally all alkyl halides readily formed itaconic acid derivatives of p-amino phenyl sulfone, although the secondary halides which were experimented with did not react. Only one tertiary alkyl halide activity was investigated and a mixture of compounds resulted. Aryl halides containing one or more nitro groups ortho or para to the halogen were sufficiently reactive to give fair yields of sulfones.

From this investigation of itaconic acid derivatives of p-amino phenyl

sulfone the following conclusions were formulated: Research Corporation for their Research: 1. Itaconic acid derivatives of p-amino phenyl sulfone were synthesized readily with primary alkyl halides by the method for their general employment, of amines and halides:

2. Due to decrease reactivity of the halogens of secondary halides, they did not react. HOOKER ELECTRO CHEMICAL COMPANY
3. Aryl halides required activating groups in the ortho or para position before they reacted. AL COMPANY
4. Fifteen new compounds were formed. DIVISION
5. 1(p-R<sub>1</sub> sulfonyl)-phenyl-5-oxo-3-pyrrolidine carboxylic acid derivatives were not favored by fusion of itaconic acid and p-amino phenyl sulfone derivatives, instead N<sup>4</sup> Itaconyl acid derivatives were the principles products.
6. The instability of several derivatives toward dilute hydrochloric acid or dilute sodium hydroxide was ascribed to the instability of the parent halide toward these compounds.



This author wishes to express his gratitude to Research Corporation for their Research Fellowship in support of this investigation, to Professor Peter L. Paytash for his assistance and suggestions, and to the following Chemical Companies for their generous supply of amines and halides:

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Malcolm J. Thompson

On February 13, 1927 in Baldwin, Louisiana, I was born to Eugene Johnson and Alfred Thompson. Nine days later the sacrament of Baptism was administered to me at the Sacred Heart Church of Baldwin.

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After celebrating my sixth birthday, I attended Baldwin Public School, from which I was graduated seven years later.

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During this first year of attending at Xavier my financial resources were such that to realize my ambition I was forced to work at night. Indeed this was not an ideal situation, but my desire for advanced formal education was greater than the hardships encountered by me during this period.

At the conclusion of my freshman year, I willingly responded to the call of my country and entered the service of the United States Army. My principle assignment in the army was performed in doing occupational duty in Japan.

Malcolm J. Thompson

On February 15, 1927 in Baldwin, Louisiana, I was born to Beneva Johnson and Alfred Thompson. Nine days later the sacrament of baptism was administered to me at the Sacred Heart Church of Baldwin.

After celebrating my sixth birthday, I entered Baldwin Public School, from which I was graduated seven years later.

During my elementary education I received the formal instructions in the basic principles of my religion and received the sacraments of penance, Holy Eucharist and Confirmation.

In September of 1940 I entered the Godman Junior High School in my native city. As a result of my high scholastic standing I was tendered a scholarship to a senior high school of my selection.

Intrigued by the possibilities of realizing my ambition in a large accredited preparatory school, I elected to leave Baldwin and enrolled as a science major at Xavier University Preparatory School of New Orleans, Louisiana.

Four years of undaunted enthusiasm and hard work rewarded me with a graduation certificate in June of 1944.

Cognizant of the inadequacy of my meager knowledge in my chosen field of study, I sought the higher fields of learning by enrolling in the College of Science at Xavier University in September 1944.

During this first year of matriculating at Xavier my financial resources were such that to realize my ambition I was forced to work at night. Indeed this was not an ideal situation, but my desire for advanced formal education was greater than the hardships encountered by me during this period.

At the conclusion of my freshman year, I willingly responded to the call of my country and entered the service of the United States Army. My principle assignment in the army was performed in doing occupational duty in Japan.

This brief period I considered extremely valuable to the attitude and disposition of my future hopes and desires. I feel that the experience and education derived from this assignment rendered me more mature of mind and more determined to realize my ambition. As a result, immediately after having received my honorable discharge papers from the Armed Forces in the spring of 1947, I returned directly to Xavier University to continue my studies that I had put aside two years previously.

Re-entering Xavier University I pursued the science course, majoring in Chemistry and minoring in Mathematics. The great love developed within me for the field of my choice was rewarded with the reception of a Bachelor of Science Degree in my chosen field in May 1950.

Upon my graduation I received a Research-fellowship in chemistry and immediately started to pursue graduate study leading to a Master of Science Degree in Organic Chemistry. I was also appointed a part-time laboratory assistant in Organic and Physical Chemistry.

The research work prerequisite for a Master's Degree was done in the field of Itaconic Acid Derivatives of Sulfanilamide and p-Amino Phenyl Sulfone. An excerpt from the field in which I have specialized has been accepted for publication in the near future by the Journal of the American Chemical Society.

My graduate work will have been completed in May of 1952. It is my fond hope that I may be graciously honored as the recipient of a Master of Science Degree at the forthcoming commencement exercise to be held at Xavier University in June, 1952.