[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, XAVIER UNIVERSITY]

Itaconic Acid Derivatives of 4-Aminophenyl (Alkyl or Aryl) Sulfone

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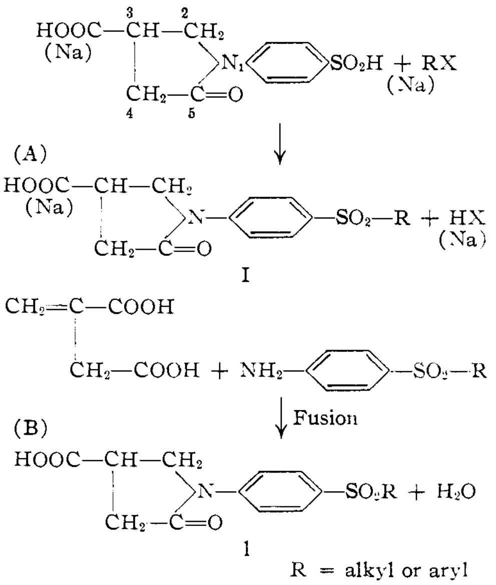
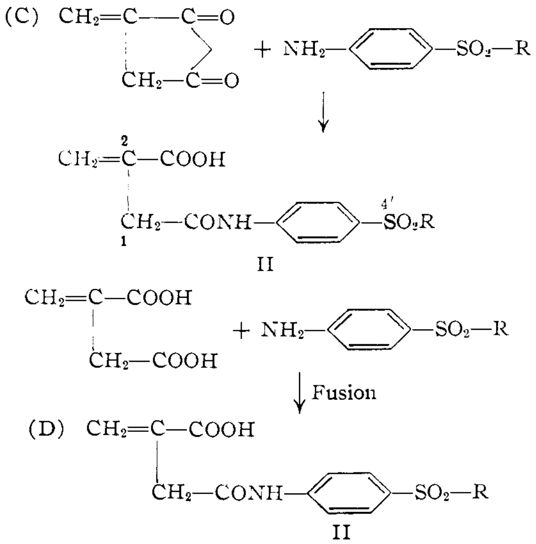
Itaconic acid can condense with 4-aminophenyl (alkyl or aryl) sulfones in two different ways to form 1-[(*p*-alkyl or aryl sulfonyl)-phenyl]-5-oxo-3-pyrrolidinecarboxylic and 2-methylene-4′-(alkyl or aryl sulfonyl)-succinanilic acids. Both types were synthesized by an alternate method.

Reactions involving the condensation of itaconic acid with sulfanilamide to form 1-[(*p*-alkyl or aryl sulfamyl)-phenyl]-pyrrolidinecarboxylic and 2-methylene-4′-(alkyl or aryl sulfamyl)-succinanilic acids[3] were previously reported.[4]

This investigation is a continuation of that problem as applied to 4-aminophenyl (alkyl or aryl) sulfone. Nineteen such compounds were prepared and used to form 1-[(*p*-alkyl or aryl sulfonyl)-phenyl]-5-oxo-3-pyrrolidinecarboxylic (I) and 2-methylene-4′-(alkyl or aryl sulfonyl)-succinanilic (II) acid derivatives. Derivatives I were prepared according to method (A) by condensing the sodium salt of 1-[(*p*-sulfino)-phenyl]-5-oxo-3-pyrrolidinecarboxylic acid (III) with various alkyl or aryl halides and by an alternate (B) the fusion of itaconic acid with 4-aminophenyl (alkyl or aryl) sulfones.



Derivatives II were prepared with method (C) by condensing itaconic anhydride and 4-aminophenyl (alkyl or aryl) sulfones using acetone or methyl ethyl ketone as solvent. An alternate method (D), fusion of itaconic acid with 4-aminophenyl (alkyl or aryl) sulfones, produced in poor yields derivatives II. Their properties are given in Table II.



Experimental

Preparation of 4-Aminophenyl (Alkyl or Aryl) Sulfones.—The 4-aminophenyl (alkyl or aryl) sulfones used in this investigation was synthesized according to methods found in the literature and verified for their authenticity by melting points. They are given as (alkyl or aryl): methyl, ethyl, propyl, butyl, amyl, isoamyl, hexyl, cyanoethyl, carboxymethyl, carbethoxymethyl, benzyl, 4-nitrobenzyl, 4-nitrophenyl, 2,4-dinitrophenyl and 4-aminophenyl.[5]

Alkyl and Aryl Halides.[6]—The following halides were used: methyl iodide, ethyl bromide, propyl iodide, butyl bromide, amyl iodide, isoamyl iodide, hexyl iodide, allyl chloride, chloroacetic acid, β-chloropropionic acid, β-chloropropionitrile, chloroethyl acetate, butyl chloroacetate, 2-bromoethylcyclohexane, benzyl chloride, 4-nitrobenzyl chloride, 2-bromoethylbenzene, phenacyl bromide, 1-chloro-4-nitrobenzene and 1-chloro-2,4-dinitrobenzene.

Preparation of the Sodium Salt of 1-[(*p*-Sulfino)-phenyl]-5-oxo-3-pyrrolidinecarboxylic Acid (III).—Compound III was prepared by treating fifty grams (0.17 mole) of crude 1-[(*p*-chlorosulfonyl)-phenyl]-5-oxo-3-pyrrolidinecarboxylic acid[4] (IV) with 30 g. (0.24 mole) of anhydrous sodium sulfite in aqueous solution maintained alkaline with sodium bicarbonate. The free acid was obtained from III by treating the sodium salt with dilute hydrochloric acid. The yield of acid was 35 g. or 77% with melting point of 175–180°. *Anal.* Calcd. for $C_{11}H_{11}NO_5S$: N, 5.20. Found: N, 5.19.

Method (A) Preparation of 1-[(*p*-Alkyl or Aryl Sulfonyl)-phenyl]-5-oxo-3-pyrrolidinecarboxylic Acid (I). Procedure.—Ten grams of III was condensed with various alkyl or aryl halides (mole ratio 1–1) in 75 ml. of 50% aqueous alcohol with refluxing (1–8 hours).[7]

The reaction was maintained alkaline with solid sodium bicarbonate. Compound I was isolated by acidifying with

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[2] Rev. Mother Catherine Drexel Fellowship.

[3] Nomenclature of *Chemical Abstracts*. Referred to as N4-itaconyl acid sulfanilamides in original publication below.

[4] P. L. Paytash, M. J. Thompson and M. E. Fykes, THIS JOURNAL, **74**, 4549 (1952).

[5] Prepared by reduction of 4-aminophenyl-4-nitrophenylsulfone.

[6] We wish to express our gratitude to the following companies for their generous supply of intermediate chemical compounds: Dow Chemical Company, American Cyanamid Company, Monsanto Chemical Company, Carbide and Carbon Chemicals Corporation, Hooker Electrochemical Company and Shell Development Company.

[7] Time varied with reactivity of halide.

dilute hydrochloric acid. Recrystallization was done from water or dilute alcohol (see Table I).

Method (B) **Preparation of 1-[(*p*-Alkyl or Aryl Sulfonyl)-phenyl]-5-oxo-3-pyrrolidinecarboxylic Acid. (I) Procedure.**—Two-hundredths of a mole of 4-aminophenyl (alkyl or aryl) sulfone was added to 5 g. (0.04 mole) of itaconic acid[8] and heated in oil-bath for 15 minutes at 180°. The hot reaction mixture was poured into cold water to precipitate I along with 2-methylene-4′-(alkyl or aryl sulfonyl) succinanilic acid (II). By acid hydrolysis II was separated from I, the latter being stable under these conditions. Product I was recrystallized from water or dilute alcohol (see Table I).

TABLE I

1-[(*p*-Alkyl or aryl sulfonyl)-phenyl]-5-oxo-3-pyrrolidine-carboxylic acid	Yield, %[b] Method[e, i] A	Yield, %[b] Method[e, i] B[d]	M.p.,[a] °C.	N, % Calcd.	N, % Found	Neut. equiv. found[i]	Mol. wt. calcd.
Methyl	70	15	209–210	4.94	4.94	283	283
Ethyl	62	13	240–242	4.70	4.64	298	297
Propyl	75	16	205–206	4.50	4.54	306	311
Butyl	80	13	167–168	4.31	4.29	313	325
Amyl	63	20	159–160	4.12	4.05	343	339
Isoamyl	59	20	173–175	4.12	4.09	341	339
Hexyl	40	17	154–155	3.96	3.98	350	353
Allyl	50	..	196–198	4.52	4.50	308	309
Carboxy-methyl	49	..	203–205	4.27	4.27	164	327
Carboxy-ethyl	55	..	213–215[h]	4.10	4.06	168	341
Cyanoethyl[f]	85	..	195–197	8.68	8.64	..	322
Carbethoxy-methyl[c]	37	..	216–218[g]	3.94	3.94	350	355
Cyclohex-ylethyl	50	..	167–168	3.70	3.70	382	379
Benzyl	85	13	227–229	3.90	3.88	344	359
4-Nitro-benzyl	80	11	236–238	6.92	7.00	402	404
Phenethyl	60	..	185–187	3.75	3.74	370	373
4-Nitro-phenyl	..	14	215–216	7.17	7.14	..	390
2,4-Dinitro-phenyl	55	15	145–147	9.63	9.60	..	435
1-Phenyl-5-oxo-3-carboxypyr-rolidyl	..	10	297–300[j] d.	5.92	6.01	..	472

[a] Melting points are uncorrected and were determined with a Fisher–Johns heating block. [b] Two or more recrystallizations. [c] Readily hydrolyzed to carboxymethyl group. [d] Poor yields were due to decomposition and formation of 2-methylene-4′-(alkyl or aryl sulfonyl)-succinanilic acid. [e] Compound (A) and (B) when mixed gave no depression of melting point. [f] Formed by allowing potassium salt of III to react with β-chloropropionitrile at 44° for 48 hours. [g] Purified by dissolving in sodium bicarbonate solution and precipitating with dilute hydrochloric acid. [h] Melting point of 222–224° was also observed. [i] Blank spaces indicate failure to corroborate. [j] Washing crude products with acetone before recrystallizing gave a better product.

Method (C) Preparation of 2-Methylene-4′-(alkyl or Aryl Sulfonyl)-succinanilic Acid (II). Procedure.—Three grams (0.029 mole) of itaconic anhydride[9] was condensed with (0.019 mole) of 4-aminophenyl (alkyl or aryl) sulfone (mole ratio 1.5–1.0)[10] by using 15.0 ml. of acetone or methyl ethyl ketone as solvent and refluxing over a water-bath from 30 to 45 minutes. Compound II was isolated by pouring the reaction mixture into cold water and purified by dissolving in sodium bicarbonate solution, treating with charcoal and reprecipitating with dilute hydrochloric acid. Further purification was attained by recrystallizing from dilute alcohol (see Table II).

Method (D). Preparation of 2-Methylene-4′-(alkyl or Aryl Sulfonyl)-succinanilic Acid (II). Procedure.—Five grams (0.04 mole) of itaconic acid (50-ml. erlenmeyer flask) was heated to a molten state in an oil-bath (180°). To this was added in one portion (0.026 mole) of 4-aminophenyl (alkyl or aryl) sulfone (mole ratio 1.5–1.0).[10] The reaction was maintained under these conditions for about two minutes and then poured into cold water to precipitate II. Purification of II was done as in method (C) (see Table II).

TABLE II

2-Methylene-4′-(alkyl or aryl sulfonyl)-succinanilic acid[f]	Yield, %[b] Method[c, e] C	Yield, %[b] Method[c, e] D	M.p.,[a] °C.	N, % Calcd.	N, % Found	Neut. equiv. found[e]	Mol. wt. calcd.
Methyl	54	14	191–192[g]	4.94	4.92	282	283
Ethyl	53	13	161–162	4.70	4.70	298	283
Propyl	56	14	141–142	4.50	4.50	309	311
Butyl	55	16	146–147	4.31	4.28	323	325
Amyl	49	19	144–146	4.12	4.10	340	339
Isoamyl	53	20	157–158	4.12	4.02	342	339
Hexyl	55	15	143–144	3.96	4.04	355	353
Carboxy-methyl	30	..	197–199	4.27	4.20	159	325
Cyanoethyl	59	..	196–197	8.68	8.67	..	322
Carbethoxy-methyl	62	..	179–180	3.94	4.01	360	355
Benzyl	39	12	180–181	3.90	3.94	358	359
Phenacyl	45	10	190–192	3.62	3.66	384	387
4-Nitrophenyl	43	9	201–202	7.17	7.15	385	390
2,4-Dinitro-phenyl	20	7	195–197	9.63	9.69	..	435
4′,4‴-Sulfonyl bis-(2-methylenesuccin-anilic acid)[d]	35	..	196–198	5.95	6.00	..	472

[a] Melting points are uncorrected and were determined with a Fisher–Johns heating block. [b] Two or more recrystallizations. [c] Compound (C) and (D) when mixed gave no depressions of melting point. [d] Name of compound according to nomenclature of *Chemical Abstracts*. [e] Blank spaces indicate failure to corroborate. [f] Readily hydrolyzed with dilute hydrochloric acid to give itaconic acid and original 4-aminophenyl (alkyl or aryl) sulfone. [g] Melting point of 186–187° was also observed.

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[8] Supplied by Pfizer Company.

[9] Prepared by dehydrating itaconic acid with acetyl chloride, melting point, 62–64°.

[10] Mole ratio (2.5–1.0) was used with 4,4-diaminodiphenyl sulfone.