[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & CO.]

Some Chemotherapeutically Active Sulfones.[1] III. Azido Substituted Sulfones

BY C. K. BANKS AND O. M. GRUHZIT

The activity of 4,4′-diaminodiphenylsulfone against β-hemolytic streptococcal infections in mice has resulted in the preparation of innumerable sulfone derivatives of varying types. A survey of variously substituted sulfones[2] indicated that derivatives easily hydrolyzed to the parent 4,4′-diaminodiphenylsulfone, such as the di-dextrose bisulfite (Promin) and the di-formaldehyde sulfoxylate (Diamidin, Diasone), retained the same type of therapeutic activities as the parent sulfone. When groups which would hydrolyze only with difficulty were substituted on the amine groups, the activity was generally retained when one amino group remained unsubstituted, but was lost if both amine groups were substituted.

It was thought of interest to prepare related compounds in which the character of the amino group was completely changed. The triazo group was chosen since it resembles the amino group in some respects but also has some greatly different reaction properties. 4,4′-bis-Triazo-, 4-amino-4′-triazo, 4-succinylamino-4′-triazo- and 2-sulfamyl-4,4′-bis-triazodiphenylsulfone were prepared by variations in standard procedures. Both hydroxylamine and hydrazine were investigated as reactants with diazonium salts and hydrazine was found to be superior for these preparations. While the compounds generally separated from the reaction mixtures in better than 99% purities, special recrystallization techniques were necessary to remove traces of diazotizable amines. All of the compounds had very sharp explosion points when pure.

Experimental[3]

4,4′-*bis*-Triazodiphenylsulfone.—4,4′-Diaminodiphenylsulfone (25 g.) was worked into a paste with 60 g. of concentrated sulfuric acid and then poured over 100 g. of ice. The resulting suspension was cooled in an ice-bath and diazotized by the slow addition of 14 g. of sodium nitrite in 100 ml. of water. When the diazotization was nearly completed, the nitrite was added dropwise, testing the diazonium solution after each drop until an excess was indicated by starch-potassium iodide strips. A coupling solution of 100 g. of sodium acetate, 20 ml. of 85% hydrazine hydrate, 100 g. of ice and 200 ml. of water was prepared and placed in a 4-liter beaker. The diazonium solution was added all at one time with vigorous stirring, resulting in violent foaming which required octyl alcohol to prevent overflow.[4] After four hours, the yellow product was filtered off and dissolved in 600 ml. of acetone. The acetone solution was treated with two types of charcoal (Darco G 60 and Norite) and then diluted with 2 liters of water. The resulting precipitate was recrystallized from glacial acetic acid and then dissolved in a minimum of acetone, charcoaled and the solution filtered directly into a large volume of air-free water. The acetone recrystallization was repeated until no diazotizable amine was present. The product was filtered off and dried *in vacuo* over phosphorus pentoxide; yield 70%, nearly white, explosion point 156–157°.

Anal. Calcd. for $C_{12}H_8N_6O_2S$: N, 28.02. Found: N, 27.94.

4-Amino-4′-triazodiphenylsulfone.—4-Acetoamino-4′-aminodiphenylsulfone (60 g.) was suspended in 100 ml. of water, 50 ml. of concentrated hydrochloric acid added and 100 g. of ice. The hydrochloride salt precipitated and was diazotized slowly with 14 g. of sodium nitrite in 100 ml. of water using the same precautions as above to avoid an excess. The diazonium solution was added all at once to a solution of 100 g. of sodium acetate and 25 ml. of 85% hydrazine hydrate in 200 ml. of water and 200 g. of ice. The crude product was filtered off and hydrolyzed by refluxing in 300 ml. of 3 *N* hydrochloric acid until solution occurred. The solution was cooled and neutralized with ammonia to precipitate a nearly white product which was purified further by recrystallization from 70% alcohol; yield 40%, white, m. p. 130–131°, explodes immediately after melting.

Anal. Calcd. for $C_{12}H_{10}N_4O_2S$: N, 20.44. Found: N, 20.49.

4-Succinylamino-4′-triazodiphenylsulfone.—4-Amino-4′-succinylaminodiphenylsulfone (7 g.) was diazotized in 60 ml. of water and 4 ml. of concentrated sulfuric acid with 1.4 g. of sodium nitrite. The coupling was performed with a solution of 10 g. of sodium acetate, 2 ml. of 85% hydrazine hydrate, 50 ml. of water and 100 g. of ice. After coupling was completed, the solution was made alkaline to phenolphthalein paper, filtered and acidified. The product was recrystallized from 70% acetone until no diazotizable amine was found; yield 60%, white, explosion point 182–185°.

Anal. Calcd. for $C_{16}H_{14}N_4O_5S$: N, 14.92. Found: N, 14.95.

2-Sulfamyl-4,4′-*bis*-triazodiphenylsulfone.—4,4′-Diamino-2-sulfamyldiphenylsulfone (18.2 g.) was diazotized in 50 ml. of water, 50 ml. of concentrated hydrochloric acid and 100 g. of ice as in the other preparations. Coupling was performed with 50 g. of sodium acetate, 15 ml. of 85% hydrazine hydrate and 100 g. of ice in 100 ml. of water. Recrystallized from 70% acetic acid, then repeatedly from an acetone–alcohol–water (40–40–20) until no diazotizable amine test was obtained; yield 50%, nearly white, explosion point 176–178°. *Anal.* Calcd. for $C_{12}H_9N_7O_4S_2$: N, 25.88. Found: N, 25.42.

Chemotherapy

The chemotherapeutic activity of the triazosulfones was determined in albino mice injected intraperitoneally with about 5,000–10,000 lethal doses of β *Streptococcus hemolyticus* or about 750 lethal doses of pneumococcus Type I cultures, as based on the titration for virulence at the time of the tests. A "lethal dose" of either culture resulted in the death of all control animals in thirty-six hours. Treatment of the pneumococcus-infected mice was begun immediately following inoculation, and in one to one and one-half hours after *Streptococcus hemolyticus* inoculation. The mice were treated orally by cannula twice daily for three days when infected with pneumococci and

(1) Parts I and II, Bambas, THIS JOURNAL, **67**, 668, 671 (1945).

(2) B. F. Tullar and C. K. Banks, presented before the Division of Medicinal Chemistry of the American Chemical Society Division, Cincinnati meeting, April, 1941.

(3) Analytical determinations by Frances C. Hummel.

(4) Slow addition of the diazonium solution resulted in the formation of tars.

TABLE I

Compound	LD_{50}-oral[a] mg./mouse	Chemotherapy: β-Strep. hemolyt. salivarius[b] M. E. D.[d] × days mg./M./day	% Survival 14 days	Pneumococcus[c] mg./M./day × 3 days	% Survival 7 days
4,4′-Diaminodiphenylsulfone	12.6	0.25	80	2.5	80
disodium didextrosesulfonate[e]	130	2.8	90	10.0	56
disodium diformaldehydesulfoxylate[f]	250	10.0	90	..	..
4,4′-bis-Triazodiphenylsulfone	250	0.5	83	20.0	13
4-Amino-4′-triazodiphenylsulfone	21.4	0.5	90	5.0	12
2-Sulfamyl-4,4′-bis-triazodiphenylsulfone	>500	2.5	83	20.0	0

[a] Calcd. by the method of Dragstedt, *J. Pharmacol.*, **32**, 217 (1927–1928). [b] Lancefield's Group A, 01625. [c] Type I, 02444. [d] M. E. D. = minimal effective dose permitting survival of 80 to 90% of mice. [e] Promin. [f] Diamidin, Diasone.

once daily for three days when infected with streptococci. The animals were observed for twenty-eight days; however, the comparison of compounds was made on the basis of fourteen and seven day survival rates, respectively. Except for 4,4′-diaminodiphenylsulfone, the results tabulated in Table I are based on one or two routine tests for each compound, using ten to fifteen animals per dose level. Diaminodiphenylsulfone was used as a reference standard in all tests and the values given are the statistical average of all tests. Only those minimal doses which achieved comparable therapy are reported. The oral LD_{50} in mice was also determined for each compound.

The activities of the triazo compounds against mouse streptotoccal infections resembled those of the analogous aminosulfones but the pneumococcal activities were much less. 4,4′-bis-Triazodiphenylsulfone was of greatest interest. The acute toxicity of the triazo compound given orally in mice was much less than that of the analogous amino compound, yet the minimal dose of triazosulfone to achieve comparable therapy was only twice that required for the aminosulfone. Furthermore, no free or hydrolyzable amine could be detected in the blood of mice given up to 10 mg./mouse of 4,4′-bis-triazodiphenylsulfone orally, while the minimum oral therapeutic dose of 4,4′-diaminodiphenylsulfone (0.25 mg./mouse) gave demonstrable blood levels, indicating that conversion of any triazo group to amino *in vivo* was of a very low order.

Summary

1. Four new triazodiphenylsulfones are described. These compounds had antistreptococcal activity in mice comparable to that of the corresponding aminodiphenylsulfones.

2. 4,4′-bis-Triazodiphenylsulfone, although absorbed orally in sufficient amounts to achieve demonstrable antistreptococcal activity, was not converted *in vivo* to an amino compound in detectable amounts. It is possible that the activity of this compound functions through a different mechanism than that common to sulfa drugs in general.

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Reactions of Atoms and Free Radicals in Solution. XIII. The Reactions of Diacetyl Peroxide with Aliphatic Ketones. A New Synthesis of 1,4-Diketones

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Attention has been called[1] to the fact that the free primary or secondary alkyl radicals (formed by the decomposition of the diacyl peroxides of low molecular weight) remove hydrogen atoms from solvents to form new free radicals. The relations between the structure and the properties of the new free radicals thus formed are of considerable interest. A good deal of information regarding the behavior of the free radicals formed by the removal of hydrogen atoms from acids,[1] esters,[2] nitriles,[3] acid halides,[2] alkylbenzenes and ring-substituted alkylbenzenes[4] has already been recorded. The present paper deals with the reactions of the free radicals formed by the removal of hydrogen atoms from aliphatic and aryl-substituted aliphatic ketones.

(1) Kharasch and Gladstone, THIS JOURNAL, **65**, 15 (1943).
(2) Kharasch, Jensen and Urry, *J. Org. Chem.*, **10**, 386 (1945).
(3) Kharasch, Smith and Urry, unpublished work.
(4) Kharasch, McBay and Urry, *J. Org. Chem.*, **10**, 401 (1945).

Discussion

The products and the yields of such products obtained by the decomposition of diacetyl peroxide in aliphatic ketones, can be best explained by assuming that the free methyl radical, formed by the decomposition of the diacetyl peroxide, abstracts an *alpha* hydrogen atom from the ketone molecule, and that the new free radical, thus formed, dimerizes.

(1) $RR'CHCOCHRR' + H_3C\cdot \longrightarrow RR'COCHRR'$
(A) (B)