DERIVATIVES OF SULFONAMIDE

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CHAPTER I

INTRODUCTION

The discovery by Rich and Fellis that sulfanilamide has an inhibitory effect upon the development of tuberculosis in guinea pigs aroused considerable interest in the use of sulfonamides, sulfones, and related compounds in the chemotherapy of tuberculosis in man. A major problem in the use of each of these compounds was the fact that in order to be effective it had to be administered in such large doses that it proved to be fatally toxic to many of the test animals.

Shortly after the publication of the reports of Rich and Fellis, Smith and co-workers in the Division of Physiology of the National Institute of Health undertook a survey of various sulfonamides and sulfones hoping to discover a compound which would be effective in the treatment of tuberculosis and at the same time have the freedom from toxicity which curtailed the use of sulfanilamide. In the course of the survey, Smith tested twenty-five or more compounds and found that although sulfonamides possess little

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2 M. I. Smith, New York State Journal of Medicine, 45, 1665 (1945).
anti-tubercular activity, sulfones seemed to offer some possibilities. 4,4'-diaminodiphenyl sulfone, first used by Buttle and his associates, showed the greatest activity as an anti-tubercular agent. However, this compound was far too toxic for practical use. Among the other compounds examined in this survey and found to offer considerable promise in the treatment of tuberculosis was Promizole. It has the structure:

Lehman prepared a series of compounds for testing as anti-tuberculans. Among them was the following substance:

Gregory and Wiggins, in their attempt to find less toxic compounds for the use as anti-bacterial agents and for possible use

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as anti-tuberculars, prepared 4-acetamideophenyl 6-methylpyridaz-3-yl sulfone, with the structure:

They too were working from the basic structure of 4,4'-diaminodiphenyl sulfone and found in their series of compounds that if both the phenyl groups were replaced by heterocyclic rings, all bacterial action was destroyed.

The essential structure of sulfonamides may be defined as a free amine group in the para position to a sulfonic acid or other acid group. The conversion of the sulfonic acid to an amide enhances the activity, particularly when the amide group is derived from a suitable heterocyclic compound. The compound 4-acetamideophenyl 6-methylpyridaz-3-yl sulfone differs from the common sulfonamides in that the sulfonic acid instead of being converted to a simple amide is connected to the nitrogen in the heterocyclic ring. Very few references are found to this type of structure and usually they are incidental to other problems.

It was surmized that there should be a definite relationship between the heterocycles, piperidine and 1,2,3,4-tetrahydroquinolines, and the pyrimidine and pyrazine

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residues used by Gregory and Wiggins. Therefore a series of sulfones were synthesized having this type of S-N bonding with substituted piperidines and 1,2,3,4-tetrahydroquinolines. These compounds have the following structure:

\[
\text{H}_2\text{N} - \begin{array}{c}
\text{S}\text{O} \\
\text{N} \\
\text{R}
\end{array} - \begin{array}{c}
\text{N} \\
\text{R}
\end{array}
\]

\[
\begin{array}{c}
\text{R} = \text{CH}_3 \\
\text{C}_5\text{H}_{11} \\
\text{C}_6\text{H}_{13} \\
\text{C}_8\text{H}_{17} \\
\text{C}_9\text{H}_{19}
\end{array}
\]

\[
\text{H}_2\text{N} - \begin{array}{c}
\text{S}\text{O} \\
\text{N}
\end{array} - \begin{array}{c}
\text{N} \\
\text{R}
\end{array}
\]

\[
\begin{array}{c}
\text{R} = \text{CH}_3 \text{ (in 6,7,8 positions)}
\end{array}
\]

The compounds in this series are currently being tested for anti-tubercular activity by Parke, Davis and Company.
CHAPTER II

EXPERIMENTAL PROCEDURE

4-Nitrobenzenesulfonyl Chloride 9

A 1000-ml., three-necked flask fitted with mechanical stirrer and condenser was charged with 100 g. (0.325 mole) of 4,4'-dinitrophenyl disulfide, 10 500 ml. of conc. hydrochloric acid, and 100 ml. of conc. nitric acid. Chlorine gas was passed into the mixture at the rate of two bubbles per second. The material was warmed to 70° during this time. The disulfide melted and the heating and stirring was continued for one hour.

The solid sulfonyl chloride was separated by decantation, washed with two 1500-ml. portions of water and allowed to solidify. The water was drained away from the solid. The residue was dissolved in 70 ml. of glacial acetic acid at 50-60° and filtered. The filtrate was stirred while chilling. The solid was removed and titurated with 500 ml. of water and filtered on a Buchner funnel. This procedure was then repeated. The sulfonyl chloride was added to 1-1.

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9 This compound was prepared in a manner analogous to that of o-nitrobenzenesulfonyl chloride; A. H. Blatt, Organic Synthesis, Collective Vol. II, p. 471.

of cold water containing 10 ml. of ammonium hydroxide. The 
crystals were collected at once on a filter and washed with 
200 ml. of water and air dried; m. p. 67°


Platinum Oxide (Adam Catalyst)

The platinum oxide catalyst for use in the low-pressure, 
low-temperature hydrogenations was prepared according to 
directions given in Organic Synthesis. ¹¹

Three and five-tenths grams of chloroplatinic acid 
(5%/solution) and 50 g. C. P. sodium nitrate were evaporated 
to dryness and then heated to 500° until the evolution of 
NO₂ ceased. The residual brown powder was then filtered, 
washed with 1%/ sodium nitrate solution and dried in a 
vacuum dessicator. About 1.5 g. of platinum oxide were 
obtained.

1-(4-Acetylaminobenzensulfonyl)-4-methylpiperidine

A one-neck, ground-glass reaction flask was charged with 
6.93 g. (0.03 mole) of 4-acetylaminobenzensulfonyl chloride 
dissolved in 50 ml. of dioxane. To this mixture was added 
2.97 g. (0.03 mole) of 4-methylpiperidine dissolved in 25 ml.

of dioxane. To this mixture was added 1.2 g. (0.03 mole) of sodium hydroxide dissolved in a few ml. of water. The reaction flask was fitted with a heating mantle and refluxed slowly for two to four hours.

At the end of this time the hot reaction mixture was filtered and decolorizing carbon added. This mixture was heated for about ten minutes. The decolorizing carbon was removed by filtration and the filtrate made turbid with water at about 70°. The mixture was allowed to cool and placed in refrigerator for twenty-four hours.

The fine white crystals were filtered and recrystallized from dioxane; m. p. 142°, yield 89%.


1-(4-Acetylamino benzene sulfonyl)-4-(1-amyl)piperidine

The same procedure was used for this and the following compounds as was used in the preparation of 1-(4-acetylamino benzene sulfonyl)-4-methylpiperidine. A 94% yield of fine needles was obtained, m. p. 157-158°.

**Anal.** Calcd. for C₁₆H₂₈N₂O₅S: N, 8.03. Found: N, 8.2.

1-(4-Acetylamino benzene sulfonyl)-4-(1-hexyl)piperidine

M. p. 149-150°. Yield, 87%.

**Anal.** Calcd. for C₁₉H₃₉N₂O₅S: N, 7.6. Found: N, 7.93.
l-(4-Acetylaminobenzenesulfonyl)-4-(1-ethyl)piperidine

M. p. 150-152°. Yield, 91%/.

Anal. Calcd. for C_{21}H_{34}N_{2}O_{3}S: N, 7.16. Found: N, 7.58.

l-(4-Acetylaminobenzenesulfonyl)-4-(1-nonyl)piperidine

M. p. 150-152°. Yield, 93%/.

Anal. Calcd. for C_{22}H_{36}N_{2}O_{3}S: N, 6.9. Found: N, 7.2.

l-(4-Nitrobenzenesulfonyl)-4-(1-amy1)piperidine

![Chemical Structure]

A one-neck, ground-glass reaction flask was charged with 2.21 g. (0.01 mole) of 4-nitrobenzenesulfonyl chloride and 1.54 g. (0.01 mole) of 4-(1-amy1)piperidine dissolved in 50 ml. dioxane. The flask was fitted with a heating mantle and refluxed for two hours.

The mixture was filtered, allowed to cool and neutralized with 5%/ sodium bicarbonate solution. The mixture was re-heated with decolorizing carbon to about 70°. The decolorizing carbon was then filtered, and the mixture made turbid with water at about 70°. This solution was allowed to cool and placed in refrigerator for twenty-four hours. The white crystals were filtered and recrystallized from dioxane; m. p. 210-212°. A yield of 83%/ was obtained.

Anal. Calcd. for C_{16}H_{24}N_{2}O_{4}S: N, 8.25. Found: N, 8.1.
1-(4-Nitrobenzenesulfonyl)-4-(1-hexyl)piperidine

The same procedure was used for this and the following compounds as was used in the preparation of 1-(4-nitrobenzenesulfonyl)-4-(1-amyl)piperidine. This product melted at 133-134°. A yield of 75% was obtained.

Anal. Calcd. for NC_{17}H_{28}N_{3}O_{4}S: N, 7.93. Found: N, 7.8.

1-(4-Nitrobenzenesulfonyl)-4-(1-ethyl)piperidine

M. p. 123-124°. Yield, 72%.

Anal. Calcd. for C_{19}H_{26}N_{3}O_{4}S: N, 7.35. Found: N, 7.3.

1-(4-Nitrobenzenesulfonyl)-4-(1-nonyl)piperidine

M. p. 129-130°. Yield, 88%.

Anal. Calcd. for C_{20}H_{32}N_{3}O_{4}S: N, 7.2. Found: N, 7.08.

1-(4-Aminebenzenesulfonyl)-4-(1-amyl)piperidine

Method I. Hydrolysis of the Acetyl Amino Derivative

A one-neck, ground-glass reaction flask was charged with 3.49 g. (0.01 mole) of 1-(4-acetylaminobenzenesulfonyl)-4-(1-amyl)piperidine and 100 ml. of 10% hydrochloric acid in 50-50 dioxane and water solution. The mixture was refluxed for four hours. The hot mixture was filtered and crystallized from the water and dioxane; m. p. 148-149°. A yield of 90% was obtained.

Anal. Calcd. for C_{16}H_{28}N_{3}O_{2}S: N, 9.1. Found: N, 9.3.
Method II. Reduction of the Nitro Derivative

A one-neck flask was charged with 0.1 ml. of acetic acid, 100 ml. of a 50-50 water-dioxane solution, 15 g. iron powder, and 5 g. of 1-(4-nitrobenzenesulfonyl)-4-(1-amyl)piperidine, and refluxed for eight hours. At the end of this time the black liquid was filtered hot. The filtrate was concentrated by evaporation to 60 ml. The mixture was allowed to cool and white, fine crystals were obtained. Further separation of the free amine from the nitro compound was obtained by precipitation from strong hydrochloric acid solution to remove the nitro compound. The hydrochloride salt was neutralized with sodium bicarbonate. The free amine precipitated during this reaction; m. p. 148-150°. The yield was less than 10°/o.

1-(4-Aminobenzenesulfonyl)-4-methylpiperidine

The same two procedures were used on this and the following compounds as in the preparation of 1-(4-aminobenzene- sulfonyl)-4-(1-amyl)piperidine, except the nitro compound corresponding to this compound was not prepared for reduction. M. p. 107-109°. Yield, 70°/o.

Anal. Calcd. for C_{12}H_{18}N_{2}O_{2}S: N, 11.0. Found: N, 11.12.

1-(4-Aminobenzenesulfonyl)-4-(1-hexyl)piperidine


Anal. Calcd. for C_{17}H_{26}N_{2}O_{2}S: N, 8.7. Found: N, 8.9.
1-(4-Aminobenzenesulfenyl)-4-(1-ethyl)piperidine
Method I. M. p. 112-114°. Yield, 90%. 
Method II. M. p. 112-114°. Yield, less than 10%. 

1-(4-Aminobenzenesulfenyl)-4-(1-nonyl)piperidine
Method I. M. p. 122-125°. Yield, 89%. 
Method II. M. p. 122-125°. Yield, less than 10%. 

1-(4-Acetylaminobenzenesulfenyl)-1,2,3,4-tetrahydroisoquinoline

\[
\begin{align*}
\text{H}_3\text{C}-\text{C}^\equiv\text{N} & \quad \text{S} - \text{N} \to \text{SO} \quad \text{N}\text{C}_4\text{H}_8
\end{align*}
\]

A one-neck reaction flask was charged with 2.31 g. (0.01 mole) of 4-acetylaminobenzenesulfenyl chloride and 1.33 g. (0.01 mole) of 1,2,3,4-tetrahydroisoquinoline dissolved in 50 ml. acetone. The flask was fitted with a heating mantle and the mixture was refluxed for ten hours.

The reaction mixture was filtered while hot and decolorizing carbon added at the boiling temperature. The carbon was filtered and the hot filtrate was made turbid with water when cooled in the refrigerator for twenty-four hours. A 74% yield of fine white crystals were obtained; m. p. 179°.

1-(4-Acetylamino)benzenesulfonyl)-6-methyl-1,2,3,4-tetrahydrolequinoline

This and the following compounds were prepared by the
same procedure as was used for preparation of 1-(4-acetylamino)benzenesulfonyl)-1,2,3,4-tetrahydroleisoquinoline. This
procedure gave a 28\% yield of desired product which melted
at 192-193°.

Anal. Calcd. for C_{18}H_{20}N_{2}O_{2}S: N, 6.2. Found: N, 8.34.

1-(4-Acetylamino)benzenesulfonyl)-7-methyl-1,2,3,4-tetrahydrolequinoline

M. p. 143-144°. Yield, 42\%.

Anal. Calcd. for C_{18}H_{20}N_{2}O_{2}S: N, 6.2. Found: N, 8.11.

1-(4-Acetylamino)benzenesulfonyl)-8-methyl-1,2,3,4-tetrahydrolequinoline

M. p. 97-99°. Yield, 32\%.

Anal. Calcd. for C_{18}H_{20}N_{2}O_{2}S: N, 6.2. Found: N, 8.36.

1-(4-Nitrobenzenesulfonyl)-6-methyl-1,2,3,4-tetrahydrolequinoline

A one-neck reaction flask was charged with 2.21 g.
(0.01 mole) of 4-nitrobenzenesulfonyl chloride and 1.47 g.
(0.01 mole) of 6-methyl-1,2,3,4-tetrahydrolequinoline dissolved
in 50 ml. of acetone. The flask was fitted with a heating mantle and refluxed for two hours. At the end of this period the hot mixture was filtered and the filtrate was treated with decolorizing carbon. The carbon was filtered and this filtrate made turbid with water at about 50°. The mixture was allowed to cool and placed in the refrigerator for twenty-four hours.

Fine crystals were filtered and recrystallized from acetone and water; m. p. 135-136°; yield, 50%/.

**Anal.** Calcd. for C_{16}H_{16}N_{2}O_{4}S: N, 8.4. Found: N, 8.3.

1-(4-Nitrobenzenesulfonyl)-7-methyl-1,2,3,4-tetrahydroquinoline

The preparation of this and the following compound is by the same method as that used for the preparation of 1-(4-nitrobenzenesulfonyl)-6-methyl-1,2,3,4-tetrahydroquinoline. A 41%/ yield was obtained; m. p. 130°.

**Anal.** Calcd. for C_{16}H_{16}N_{2}O_{4}S: N, 8.4. Found: N, 8.5.

1-(4-Nitrobenzenesulfonyl)-8-methyl-1,2,3,4-tetrahydroquinoline

This material melted at 145-147° and was obtained in a 26%/ yield.

**Anal.** Calcd. for C_{16}H_{16}N_{2}O_{4}S: N, 8.6. Found: N, 8.4.
Aminoquinoline Derivatives

These compounds were prepared by the same two methods as used for the amino piperidines.

1-(4-Aminobenzenesulfonyl)-6-methyl-1,2,3,4-tetrahydroquinoline

Method I. M. p. 176-177°; yield, 32°/o.
Method II. The yield was less than 10°/o.

1-(4-Aminobenzenesulfonyl)-7-methyl-1,2,3,4-tetrahydroquinoline

Method I. M. p. 110°; yield, 41°/o.
Method II. The yield was less than 10°/o.

1-(4-Aminobenzenesulfonyl)-8-methyl-1,2,3,4-tetrahydroquinoline

Method I. M. p. 114°; yield, 32°/o.
Method II. Yield, less than 10°/o.

1-(4-Aminobenzenesulfonyl)-1,2,5,4-tetrahydropyridinequinoline

Method I. M. p. 184°; yield, 52°/o.
Method II. Yield, 21°/o.
CHAPTER III

DISCUSSION

There were two apparent routes through which the desired compounds could be synthesized. One method was the preparation of the respective pyridinium compounds, followed by the catalytic hydrogenation of the pyridinium ring. This procedure has been utilized in synthesizing N-phenacylpiperidinium compounds. The second method was the hydrogenation of the pyridines to the respective piperidines followed by the direct coupling of these amines with the sulfonyl chlorides. The disadvantages of this method were the difficulties of hydrogenation and separation of the unhydrogenated product. This separation could be carried out either by the Hinsberg method or fractional distillation. These handicaps were overcome by the availability of the piperidines from other research being conducted in these laboratories through a permanent fractional distillation set-up. The reactivity of the sulfonyl chlorides also favored this reaction. Therefore the first method was not applied as the object was to

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13 Hinsberg, Ber., 23, 2963 (1890).
prepare these compounds and the route was not considered as important.

All the reactions with the piperidines proceeded as expected with near quantitative yields in most cases, considering the recovery of the starting material from the original reaction mixture. In most cases no additional recovery was attempted after the initial precipitation since the conversions were high.

All attempts to obtain coupling with 2-alkylpiperidines failed. Vigorous, anhydrous reaction conditions followed by careful concentration of the residue by evaporation failed to give anything other than varying degrees of polymerization or degeneration. No attempt was made to identify this sticky residue.

The preparation of the derivatives containing the various hydrogenated methylquinolines was not so easily accomplished due to the tendency of the derivatives to become oils during precipitation. This handicap was overcome in some cases only by carefully concentrating the reaction mixture during the precipitation. After the original precipitation, recrystallization was accomplished from dioxane, alcohol or acetone with ease. The yields of the quinoline derivatives were lowered considerably by the additional handling necessary. It is surmised that the preparation of the quinolinium salts and subsequent hydrogenation may be an alternate to this problem.
The nitro compounds were reduced to the corresponding amines by the method of Waldron and Reid\(^{14}\) without undue difficulty.

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