thiophene-free benzene, and anhydrous aluminum chloride (30.5 g.; 0.23 mole) added in one portion with continuous stirring and cooling. The temperature of the reaction mixture was now raised slowly to 45° during thirty minutes and maintained at 45° for thirty minutes.

After cooling the reaction mixture in an ice-bath, 100 g. of chopped ice was added slowly, followed by 20 cc. of concentrated hydrochloric acid and enough water to bring the final volume to about 250 ml. The excess benzene was then removed by steam distillation. The colorless reaction product was filtered, washed with cold water, dissolved in 75 ml. of aqueous sodium carbonate solution (10%) and the solution boiled during three hours. After filtering, the solution was rendered acid to congo red by addition of concentrated hydrochloric acid (10 ml.) and the resulting colorless precipitate was filtered off, and washed with cold water. The yield of dry, crude 3-benzoyl-norcamphane-2-carboxylic acid was 20.3 g. (87% of theoretical), m. p. 150–158°.

The compound is soluble in benzene, ether, glacial acetic acid, hot ethyl acetate, acetone or chloroform. It is insoluble in water or petroleum ether.

A portion (12 g.) of the acid was recrystallized by dissolving in 300 ml. of hot, dry benzene and adding 50 ml. of petroleum ether to the warm solution. On cooling, a crystalline precipitate was obtained which, after filtering and drying, weighed 6.7 g. and had m. p. 170–173°. The filtrate was evaporated until the volume was about 50 ml., whereupon an equal volume of petroleum ether was added, resulting in a second crop of crystalline product (5.2 g.) having m. p. 170–171°.

*Anal.* Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60; neut. equiv., 244.2. Found: C, 74.12; H, 6.84; neut. equiv., 247.0.

**Attempted Cyclization of VI to the Substituted Anthraquinone.**—A small portion of the acid (VI) was dissolved in 1 ml. of concentrated sulfuric acid and heated on the steam-bath during forty-five minutes. On pouring the resulting yellow-colored solution into 10 ml. of water, a colorless precipitate was formed. It was filtered off and washed free of acid. On examining the product for the presence of the quinone structure, the tests were negative, indicating that cyclization to the substituted anthraquinone had not occurred.

## Summary

1. *cis*-3,6-Endomethylene-hexahydrophthalic anhydride (II) has been prepared by direct catalytic hydrogenation (under high pressure) of *cis*-3,6-endomethylene-$\Delta^4$-tetrahydrophthalic anhydride (I).

2. A number of new alkyl esters, imides, amides and ammonium salts of the two acids corresponding are described.

3. The synthesis of 3-benzoyl-norcamphane-2-carboxylic acid (VI) by a Friedel–Crafts reaction is given.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MERCK & CO., INC.]

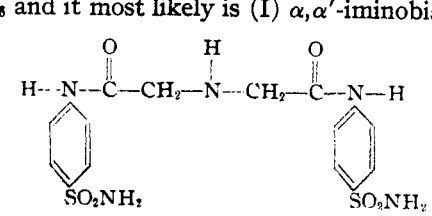
# N⁴-Substituted Sulfonamides

BY JACOB FINKELSTEIN*

In 1938, Fourneau and co-workers[1] showed the formyl and acetyl sulfanilamides were considerably less active than sulfanilamide against streptococcal infections. However, in a rather thorough study of the effect of various acyl groups on the activity of sulfanilamide, Miller, Rock and Moore[2] found that the caproyl derivative was as effective as the parent drug and yet, less toxic. During that time, we have prepared several N⁴-substituted derivatives of the several widely used sulfa drugs. Among these compounds are several already recorded in the literature. However, they are included in this report because the work has been extended to include their action against other pathogenic organisms and to present a more complete basis for comparison with related substances.

The chloroacetyl compounds were prepared by two methods. In one, the required chloroacetyl chloride was added dropwise to an ice-cooled suspension of the drug in an inert solvent, and in the other, the chloroacetyl chloride was added to an aqueous solution of the sulfa drug in dilute sodium hydroxide. The aminoacetyl compounds were obtained by dissolving the chloroacetyl derivatives in aqueous ammonia, warming at 40° for twenty-four to forty-eight hours, followed by evaporation of the solvent. These compounds were difficult to purify because of their unfavorable solubility properties.

The preparation of N⁴-aminoacetylsulfanilamide was reported by Pollak, *et al.*,[3] who recorded a melting point of 259°, whereas our product melted at 216–218°. Therefore, we repeated their work using liquid ammonia in place of aqueous ammonia, and obtained a product which melted at 256–258°. The analysis of this compound indicated the empirical formula $C_{16}H_{19}N_5S_2O_6$ and it most likely is (I) $\alpha,\alpha'$-iminobis-(N⁴-



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acetylsulfanilamide), which the above authors erroneously reported as glycyl sulfanilamide, in spite of the fact that their recorded analytical values agree with those of the desired compound.

The substances here discussed were tested at the Merck Institute for Therapeutic Research by

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(1) Fourneau, *Compt. rend. soc. biol.*, **122**, 258 (1938).

(2) Miller, Rock and Moore, THIS JOURNAL, **61**, 1198 (1939).

(3) Pollak, *et al.*, *Monatsh.*, **58**, 118 (1931).

TABLE I

| Compound | From | M. p., °C. | Empirical formula | Calcd., % C | Calcd., % H | Calcd., % N | Found, %[e] C | Found, %[e] H | Found, %[e] N |
|---|---|---|---|---|---|---|---|---|---|
| $N^4$-Chloroacetylsulfanilamide[a] | Water | 211–213 | $C_8H_9N_2SO_3Cl$ | 38.64 | 3.64 | 11.26 | 38.62 | 3.38 | 11.02 |
| 2-($N^4$-Chloroacetylsulfanilamido)-pyridine | Dioxane | 192–193 | $C_{13}H_{12}N_4SO_3Cl$ | 47.94 | 3.71 | 12.90 | 47.93 | 3.86 | 13.07 |
| 2-($N^4$-Chloroacetylsulfanilamido)-thiazole | Abs. alc. | 205–206 | $C_{11}H_{10}N_4S_2O_3Cl$ | 39.83 | 3.04 | 12.66 | 39.82 | 3.14 | 12.46 |
| 2-($N^4$-Chloroacetylsulfanilamido)-4-methylthiazole | Abs. alc. | 231–232 | $C_{12}H_{12}N_4S_2O_3Cl$ | 41.69 | 3.50 | 12.15 | 42.38 | 3.76 | 11.72 |
| 2-($N^4$-Chloroacetylsulfanilamido)-pyrimidine | Abs. alc. | 208–210 | $C_{12}H_{11}N_5SO_3Cl$ | 44.12 | 3.40 | 17.14 | 44.36 | 3.66 | 17.36 |
| $N^4$-Aminoacetylsulfanilamide[a] | Water | 216–218 | $C_8H_{11}N_3SO_3$ | 41.93 | 4.84 | 18.33 | 41.95 | 5.03 | 18.57 |
| 2-($N^4$-Aminoacetylsulfanilamido)-pyridine | Water | 220–221 | $C_{13}H_{14}N_4SO_3$ | 50.98 | 4.53 | 18.29 | 50.70 | 4.76 | 17.97 |
| 2-($N^4$-Aminoacetylsulfanilamido)-thiazole | Water | 215–216 | $C_{11}H_{13}N_4S_2O_3$ | 42.31 | 3.88 | 17.94 | 41.87 | 3.88 | 17.34 |
| 2-($N^4$-Aminoacetylsulfanilamido)-4-methylthiazole | Abs. alc.[b] | 205–206 | $C_{12}H_{14}N_4S_2O_3$ | 44.18 | 4.23 | 17.17 | 43.75 | 4.36 | 16.78 |
| 2-($N^4$-Aminoacetylsulfanilamido)-pyrimidine | Water | 238–240 | $C_{12}H_{13}N_5SO_3$ | 46.91 | 4.24 | 22.79 | 47.04 | 4.27 | 22.57 |
| $\alpha,\alpha'$-Iminobis-($N^4$-acetylsulfanilamide)[c] | Water | 260 | $C_{16}H_{19}N_5S_2O_6$ | 43.54 | 4.34 | 15.86 | 43.62 | 4.37 | 15.33 |
| 2-($N^4$-Caproylsulfanilamido)-pyridine[d] | Abs. alc. | 193–194 | $C_{17}H_{21}N_3SO_3$ | 58.78 | 6.10 | 12.09 | 58.31 | 5.96 | 12.25 |
| 2-($N^4$-Caproylsulfanilamido)-thiazole[d] | Aq. alc. | 193–195 | $C_{15}H_{19}N_3S_2O_3$ | 50.99 | 5.42 | 11.89 | 51.16 | 5.42 | 12.20 |
| 2-($N^4$-Caproylsulfanilamido)-pyrimidine | Abs. alc. | 214–215 | $C_{16}H_{20}N_4SO_3$ | 55.17 | 5.79 | 16.08 | 55.26 | 5.86 | 16.37 |

[a] Mietzach, *et al.*, U. S. P. 2,289,029; July 7, 1942. [b] After six recrystallizations. [c] Pollak, *et al.*[3] [d] Raiziss, *et al.*, *J. Lab. Clin. Med.*, **27**, 1276 (1942). [e] All recorded analyses were performed by Messrs. Hayman, Reiss, Clark and Boos.

Dr. A. O. Seeler and Dr. Harry Robinson against malaria and pathogenic organisms.

Dr. Robinson reported that "preliminary toxicity experiments in mice suggest that the acute oral toxicity of these derivatives is similar to that of sulfadiazine, sulfapyridine, and sulfathiazole. This apparent low acute toxicity may be due in part to the poor absorption from the gastrointestinal tract. Efficacy experiments in mice indicate that these compounds afford good protection against severe experimental infections produced by the intraperitoneal injection of *Streptococcus hemolyticus, Staphylococcus aureus, Diplococcus pneumonia* Type I and *Salmonella schottmülleri*. However, more accurate evaluations will be based upon blood level determinations."

These compounds were tested for activity against the schizonts of *Plasmodium lophurae* in Pekin ducklings. Fifty-gram ducklings were inoculated intravenously with 2,000,000 parasitized erythrocytes. Administration of the drugs was begun on the day of inoculation and was continued for six days. In order to maintain a reasonably constant blood level, the drugs were mixed into the diet in such fashion that the birds would consume their daily dose throughout the twenty-four hours. The relative activity was estimated by comparing the effects on the parasite count when the drugs were given at the same dose levels. Since the number of ducks receiving each drug was small and blood level determinations were not performed, a precise quantitative comparison cannot be made. In no case, however, was the derivative more active than the parent substance on a weight basis. The caproyl compounds all showed about the same activity as the parent sulfonamides and the chloracetyl derivatives seemed uniformly less active.

The solubility determinations of the compounds were performed by Mr. Walter A. Bastedo, Jr., of these Laboratories. All derivatives are soluble in 100 ml. of water at 37° to the extent of less than four-tenths of mg. except glycylsulfanilamide (157 mg./100 ml.) and glycylsulfathiazole (0.7 mg./100 ml.).

**Acknowledgments.**—The author wishes to acknowledge his indebtedness to Drs. R. T. Major and K. Folkers for their advice and interest, and to express his appreciation to Dr. A. O. Seeler and Dr. Harry Robinson of the Merck Institute for Therapeutic Research for their evaluation of the products as therapeutic agents.

## Experimental

### Preparation of $N^4$-Chloroacetyl Derivative

**Method I.**—To a well-stirred solution of 24.9 g. of sulfapyridine in 80 cc. of 1.25 *N* sodium hydroxide, 18 g. of chloroacetyl chloride was added slowly and dropwise. There was only a slight rise in temperature. One hour after the addition was completed, the white insoluble product was filtered and washed with water. After several recrystallizations from dioxane, the pure product was obtained.

**Method II.**—To a well-stirred suspension of 10 g. of sulfadiazine in 3.2 g. of dry pyridine and 60 cc. of dry chloroform cooled in an ice-salt mixture, 4.6 g. of chloroacetyl chloride was added slowly and dropwise. The reaction mixture was kept at room temperature for some time and the insoluble product filtered. It was stirred for a short time with 40 cc. of 2.5 *N* hydrochloric acid, collected by filtration and, after washing with water, recrystallized from boiling absolute alcohol.

### Preparation of $N^4$-Aminoacetyl Derivatives

The preparation of the glycyl derivatives may be illustrated as follows. A solution of 50 g. of $N^4$-(chloroacetyl)-sulfanilamide was prepared by adding small amounts to 600 cc. of concentrated aqueous ammonia with stirring. The solution was placed in a pressure bottle and heated in a water-bath at 40° for two days. The solution was filtered from a small amount of insoluble material and evaporated in a shallow dish until a colorless, crystalline product separated. After three recrystallizations from water, there was obtained pure $N^4$-aminoacetylsulfanilamide.

The caproyl derivatives of sulfapyridine, sulfathiazole and sulfadiazine were prepared according to the method of Miller, Rock and Moore.[2]

## Summary

A series of chloroacetyl and aminoacetyl derivatives of sulfonamides has been prepared for study as agents to combat infectious organisms. Many of these drugs were found to be very effective against such organisms as streptococcus, pneumococcus (type I), *Staphylococcus aureus* and *Salmonella schottmülleri*.

RAHWAY, N. J. RECEIVED SEPTEMBER 24, 1943