TABLE I

| Sulfanilamide[1] N⁴-substituent | N¹-substituent | Formula | M. p., °C., uncor. | Nitrogen, % Calcd. | Found |
|---|---|---|---|---|---|
| α-Furoyl | None | $C_{11}H_{10}N_2O_4S$[a] | 273.5 | 10.52 | 10.69 |
| α-Furoyl | Phenyl | $C_{17}H_{14}N_2O_4S$[a] | 243.5–44 | 8.18 | 8.41 |
| α-Furoyl | (4-Nitro)-phenyl | $C_{17}H_{13}N_3O_6S$[a] | 259 | 10.85 | 11.09 |
| α-Furoyl | (4-Amino)-phenyl | $C_{17}H_{15}N_3O_4S$[b] | 238–38.5 | 11.76 | 11.89 |
| α-Furoyl | 2-Pyridyl | $C_{16}H_{13}N_3O_4S$[c] | 242 | 12.23 | 12.30 |
| α-Thenoyl | None | $C_{11}H_{10}N_2O_3S_2$[d] | 278–78.5 | 9.93 | 10.12 |
| α-Thenoyl | Phenyl | $C_{17}H_{14}N_2O_3S_2$[e] | 228–30 | 7.82 | 7.90 |
| α-Thenoyl | (4-Nitro)-phenyl | $C_{17}H_{13}N_3O_5S_2$[f] | 261–62.5 | 10.42 | 10.70 |
| α-Thenoyl | (4-Amino)-phenyl | $C_{17}H_{15}N_3O_3S_2$[f] | 267.2 | 11.26 | 11.43 |
| α-Thenoyl | 2-Pyridyl | $C_{16}H_{13}N_3O_3S_2$[d] | 257–58 | 11.70 | 12.13 |
| Nicotinyl | None | $C_{12}H_{11}N_3O_3S$[10,d] | 250 | 15.16 | 14.64 |
| Nicotinyl | Phenyl | $C_{18}H_{15}N_3O_3S$[b] | 222.8 | 11.90 | 11.81 |
| Nicotinyl | (4-Nitro)-phenyl | $C_{18}H_{14}N_4O_5S$[a] | 267–69 | 14.06 | 14.04 |
| Nicotinyl | (4-Amino)-phenyl | $C_{18}H_{16}N_4O_3S$[a] | 227 | 15.22 | 15.70 |
| Nicotinyl | 2-Pyridyl | $C_{17}H_{14}N_4O_3S$[11,d] | 265–66 | 15.82 | 16.72 |
| *n*-Caproyl | None | $C_{12}H_{18}N_2O_3S$[6,9,b] | 205 | 10.37 | 10.46 |
| *n*-Caproyl | Phenyl | $C_{18}H_{22}N_2O_3S$[g] | 190–90.5 | 8.09 | 8.24 |
| *n*-Caproyl | (4-Nitro)-phenyl | $C_{18}H_{21}N_3O_5S$[e] | 225 | 10.73 | 10.89 |
| *n*-Caproyl | (4-Amino)-phenyl | $C_{18}H_{23}N_3O_3S$[e] | 197.5–98 | 11.62 | 11.76 |
| *n*-Caproyl | 2-Pyridyl | $C_{17}H_{21}N_3O_3S$[g] | 200–01 | 12.10 | 12.25 |

[a] From acetone–petroleum ether. [b] From 95% EtOH. [c] From dioxane. [d] Washed with acetone. [e] From dilute alcohol. [f] From aqueous acetone.

ide and 100 cc. of 28% ammonium hydroxide. This solution was quickly added to a vigorously stirred suspension of ferrous hydroxide prepared by adding 70 cc. of 10% sodium hydroxide to 20 g. of ferrous sulfate in 50 cc. of water. Stirring was continued for one-half hour. The reaction mixture was filtered, the residue washed with a little hot water and the combined filtrates chilled. The amino compound, after precipitation from the cold filtrate with glacial acetic acid, was collected, washed with water and air-dried; yield, 3.7 g. Crystallization from aqueous acetone, with the use of a little decolorizing charcoal, gave 2.5 g. of light straw colored crystals, m. p. 266–267°.


## Summary

The preparation and properties of fifteen N⁴-heteroöyl- and five N⁴-*n*-caproyl-N¹-substituted sulfanilamides have been described. With the exceptions noted, preliminary biologic tests indicate that, as a class, these derivatives are much inferior to sulfanilamide and the N¹-substituted sulfanilamides as antistreptococcal agents. Their activity against pneumococci is even less.


KALAMAZOO, MICHIGAN RECEIVED APRIL 1, 1940

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

# Sulfanilamide Compounds. IV. N⁴-Aryl- and N⁴-Arylidine-N¹-substituted Sulfanilamides

BY H. G. KOLLOFF AND JAMES H. HUNTER

Among the rapidly increasing number of sulfanilamide derivatives and related compounds, N⁴-benzylsulfanilamide[1] (Septazine, Proseptazine)[2] is one of the few to have attained a meritorious status in this new class of chemotherapeutic agents.

The preparation of a short series of N⁴-aryl-N¹-substituted sulfanilamides was considered pertinent in view of the favorable properties reported for N⁴-benzylsulfanilamide.[3,4] We have had a two-fold purpose in the study of this type of derivative: first, in ascertaining their antibacterial effectiveness in relation to sulfanilamide and certain N¹-substituted sulfanilamides and, second, in comparing the activity of these N⁴-benzyl compounds with the corresponding N⁴-benzylidine derivatives, *i. e.*, in studying the effect of reducing the anil linkage and thereby stabilizing the molecule.

As a supplement to our previous work,[5] we are

(1) Nomenclature of Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2217 (1938).

(2) The reader is referred to the following books for the historical, experimental and clinical aspects of N⁴-benzylsulfanilamide: Mellon, Gross and Cooper, "Sulfanilamide Therapy of Bacterial Infections," C. C. Thomas, Springfield, Ill., Baltimore, Md., 1938. Long and Bliss, "The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds," The Macmillan Company, New York, N. Y., 1939.

(3) Whitby, *Lancet*, **I**, 1517 (1937).

(4) Molitor and Robinson, *J. Pharmacol.*, **65**, 405 (1939).

(5) Kolloff and Hunter, THIS JOURNAL, **62**, 158 (1940).

TABLE I

$N^4$-ARYL-$N^1$-SUBSTITUTED SULFANILAMIDES

| Number | Substituted sulfanilamide | Formula | M. p., °C. (uncor.) | Nitrogen, % Calcd. | Found |
|---|---|---|---|---|---|
| I | $N^4$-Benzyl- | $C_{13}H_{14}N_2O_2S$[7,8][a] | 174.5–175.8 | 10.69 | 10.69 |
| II | $N^4$-(4-Methoxy)-benzyl- | $C_{14}H_{16}N_2O_3S$[a] | 177–178 | 9.59 | 9.68 |
| III | $N^4$-Benzyl-$N^1$-phenyl- | $C_{19}H_{18}N_2O_2S$[a] | 177.5–178.1 | 8.28 | 8.48 |
| IV | $N^4$-(4-Methoxy)-benzyl-$N^1$-phenyl- | $C_{20}H_{20}N_2O_3S$[a] | 162–162.4 | 7.62 | 7.85 |
| V | $N^4$-(4-Methoxy)-benzyl-$N^1$-(2-pyridyl)- | $C_{19}H_{19}N_3O_3S$[b] | 216.5–217.5 | 11.38 | 11.90 |
| VI | $N^4$-Acetyl-$N^1$-[4-(benzyl)-amino]-phenyl- | $C_{21}H_{21}N_3O_3S$[a] | 182–182.5 | 10.63 | 10.41 |
| VII | $N^4$-Acetyl-$N^1$-[4-(4-methoxybenzyl)-amino]-phenyl- | $C_{22}H_{23}N_3O_4S$[a] | 208–208.5 | 9.88 | 9.92 |
| VIII | $N^1$-[4-(Benzyl)-amino]-phenyl- | $C_{19}H_{19}N_3O_2S$[c] | 175–175.5 | 11.90 | 12.18 |
| IX | $N^1$-[4-(4-Methoxy-benzyl)-amino]-phenyl- | $C_{20}H_{21}N_3O_3S$[c] | 157–157.5 | 10.97 | 10.47 |
| X | $N^4$-(4-Methoxy)-benzyl-$N^1$-[4-(4-methoxy-benzyl)-amino]-phenyl- | $C_{28}H_{29}N_3O_4S$[c] | 184–185 | 8.34 | 8.53 |

[a] From dilute alcohol. [b] From dilute acetic acid. [c] From 95% alcohol.

TABLE II

$N^4$-ARYLIDINE-$N^1$-SUBSTITUTED SULFANILAMIDES

| Number | Substituted sulfanilamide | Formula | M. p., °C. (uncor.) | Nitrogen, % Calcd. | Found |
|---|---|---|---|---|---|
| 1 | $N^4$-Benzylidine-$N^1$-(2-carboxy)-phenyl- | $C_{20}H_{16}N_2O_4S$[a] | 226–226.5 | 7.37 | 7.59 |
| 2 | $N^4$-(4-Methoxy)-benzylidine-$N^1$-(2-carboxy)-phenyl- | $C_{21}H_{18}N_2O_5S$[b] | 233–233.5 | 6.83 | 7.04 |
| 3 | $N^4$-(4-Dimethylamino)-benzylidine-$N^1$-(2-carboxy)-phenyl- | $C_{22}H_{21}N_3O_4S$[c] | 247–248 | 9.93 | 9.51 |
| 4 | $N^4$-Cinnamylidine- | $C_{16}H_{14}N_2O_2S$[e,g] | 214 | 9.80 | 10.00 |
| 5 | $N^4$-Cinnamylidine-$N^1$-(2-pyridyl)- | $C_{20}H_{17}N_3O_2S$[d,f] | 215–217.5 | 11.58 | 11.75 |
| 6 | $N^4$-(4-Nitro)-benzylidine- | $C_{13}H_{11}N_3O_4S$[e] | 187.5–188 | 13.76 | 14.30 |
| 7 | $N^4$-(4-Nitro)-benzylidine-$N^1$-phenyl- | $C_{19}H_{15}N_3O_4S$[d] | 196–197 | 11.02 | 11.07 |
| 8 | $N^4$-(4-Nitro)-benzylidine-$N^1$-(4-nitro)-phenyl- | $C_{19}H_{14}N_4O_6S$[e] | 201.5–202 | 13.15 | 13.45 |
| 9 | $N^4$-(4-Nitro)-benzylidine-$N^1$-(2-pyridyl)- | $C_{18}H_{14}N_4O_4S$[c] | 245–246.2 | 14.66 | 14.90 |
| 10 | $N^4$-(2-Nitro)-benzylidine-$N^1$-(2-pyridyl)- | $C_{18}H_{14}N_4O_4S$[c] | 193–194 | 14.66 | 14.90 |
| 11 | $N^4$-(3-Hydroxy)-benzylidine-$N^1$-(2-pyridyl)- | $C_{18}H_{15}N_3O_3S$[c] | 242–243.5 | 11.89 | 11.72 |

[a] Washed with ether and acetone. [b] Washed with ether. [c] Washed with acetone. [d] From xylene. [e] From absolute alcohol. [f] Scudi, Ratish and Bullowa, THIS JOURNAL, **61**, 2554 (1939). [g] Gray, Buttle and Stephenson, *Biochem. J.*, **31**, 724 (1937).

including a number of $N^4$-arylidine-$N^1$-substituted sulfanilamides. In view of the high antistreptococcal activity displayed by several of these, we feel them worthy of record.

$N^4$-Benzylsulfanilamide was first reported by Goissedet, Despois, Gailliot and Mayer,[6] and in 1938 a general method for the preparation of this type of derivative was reported by Goissedet and Despois.[7] They described two alternative preparatory procedures, namely, condensation of a benzyl halide with sulfanilamide in the presence of a weak base or hydrogenation of a benzylidine sulfanilamide in the presence of active nickel.

Essentially, we have used the latter procedure for preparing the compounds given in Table I. Reduction was generally complete within an hour, and the yields were moderately good. Compounds VIII and IX were obtained by hydrolysis of the $N^4$-acetyl derivatives. These $N^4$-arylsulfanilamides, in contrast to the $N^4$-arylidine compounds, are stable, more soluble, easily purified, and their melting points lower.

The arylidine derivatives recorded in Table II were prepared by condensation of the aldehyde with the sulfanilamide in the absence of a solvent according to the general method previously described.[5] In some cases, compound 8 for instance, the reaction temperature was lowered from 140–150° to about 130°.

The biologic evaluation of the derivatives herein reported is at present incomplete[8]; however, the activity of those which have been tested appears to be relatively slight. According to our preliminary tests, compound I has only about two-thirds of the antistreptococcal activity of sulfanilamide; under the same conditions, compound II has a relative activity of approximately one-half. The activity of compound IV was found to be only one-fifth of that of $N^1$-phenyl-

(6) Goissedet, Despois, Gailliot and Mayer, *Compt. rend. soc. biol.*, **121**, 1082 (1936).

(7) Goissedet and Despois, U. S. Patent 2,111,768.

(8) We wish to express our appreciation to Dr. F. A. Eberly and Mr. E. A. Gibson for performing the biologic tests.

sulfanilamide or one-tenth of that of sulfanilamide. For the corresponding $N^4$-arylidine derivatives the values are decidedly higher.[5] Thus, on the basis of these few compounds, indications are that the activity of not only the $N^1$-substituted sulfanilamides is lowered by introduction of the benzyl group, but also that, in comparison to the $N^4$-arylidine-$N^1$-substituted sulfanilamides, activity is considerably diminished. This evidence suggests the possibility that the activity of the arylidine derivatives may be due to an *in vivo* rupture of the unstable anil linkage, with subsequent liberation of the active sulfanilamide moiety. Of the $N^4$-arylidine derivatives, recorded in Table II, whose relative antistreptococcal activity has been determined,[8] compounds 4, 9 and 10 were found to be equivalent to sulfanilamide, while compound 5 possessed a relative activity of about 86%.

## Experimental

**$N^4$ - (4 - Methoxybenzyl) - $N^1$ - phenylsulfanilamide.**—Three and sixty-six hundredths grams (0.01 mole) of $N^4$-(4-methoxy)-benzylidine-$N^1$-phenylsulfanilamide[5] was dissolved in 100 cc. of dioxane (Eastman Kodak Co. "Histological"), 5.8 g. of Raney nickel[9] added, and the mixture hydrogenated at approximately three atmospheres of hydrogen. The mixture was filtered, concentrated to about 40 cc., and diluted with 100 cc. of water. The white precipitate was collected, washed with water and air-dried; yield 3.7 g., m. p. 154–55° (uncor.). Repeated crystallization from dilute alcohol gave a pure white product melting at 162–162.4° (uncor.).

**$N^4$ - Acetyl - $N^1$ - [4 - (benzyl) - amino] - phenylsulfanilamide.**—Three and ninety-five hundredths grams (0.01 mole) of $N^4$-acetyl-$N^1$-[4-(benzylidine)-amino]-phenylsulfanilamide was dissolved in 100 cc. of warm dioxane (Eastman Kodak Co. "Histological"), a small amount (about 2 g.) of Raney nickel[9] added and the mixture hydrogenated at 47–56° and approximately three atmospheres of hydrogen. The reaction mixture was filtered, concentrated to about one-half its volume and diluted with 200 cc. of water. The precipitate was collected, washed with water and air-dried; yield 2.7 g. After several crystallizations from dilute alcohol, white needles melting at 182–82.5° (uncor.) were obtained.

**$N^1$ - [4 - (Benzyl) - amino] - phenylsulfanilamide.**—Five and five-tenths grams (0.0139 mole) of $N^4$-acetyl-$N^1$-[4-(benzyl)-amino]-phenylsulfanilamide was gently refluxed for two hours with 50 cc. of 5% sodium hydroxide. The alkaline solution was cooled, diluted with a little water, and acidified to litmus with dilute acetic acid. After cooling, the white precipitate was collected, washed with water and dried in air; yield 5.1 g. Several crystallizations from 95% alcohol, using a little decolorizing charcoal, gave white needles, melting at 174–175° (uncor.).

(9) Covert and Adkins, THIS JOURNAL, **54**, 4116 (1932).

## Summary

A brief series of $N^4$-aryl-$N^1$-substituted sulfanilamides and a heterogeneous group of $N^4$-arylidine-$N^1$-substituted sulfanilamides are reported. Preliminary biologic tests on a limited number of the $N^4$-aryl derivatives indicate that their antistreptococcal activity is much lower than that of sulfanilamide and certain $N^1$-substituted sulfanilamides. Moreover, their activity is considerably inferior to that of the corresponding $N^4$-arylidine derivatives. Of the new $N^4$-arylidine compounds tested, several showed an antistreptococcal activity equivalent to sulfanilamide.

KALAMAZOO, MICHIGAN RECEIVED APRIL 29, 1940

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[COMMUNICATION NO. 760 FROM THE KODAK RESEARCH LABORATORIES]

# Surface Conditions of Silver Halides and the Rate of Reaction. II. Reduction of Nucleated Silver Chloride

BY T. H. JAMES

The reduction of precipitated silver chloride by hydroxylamine appears to result from the direct attack of the reducing agent upon the solid silver halide.[1] Reaction apparently starts at discrete points on the silver chloride surface and continues at the silver–silver chloride interface, but the auto-accelerating nature of the reaction curve made unsatisfactory any attempt at a detailed analysis of the data previously available. It was not certain whether the number of reaction centers depends solely upon the previous history of the precipitate or varies with the reaction conditions. In order to clear up this point, and to obtain a more detailed mechanism of reaction, kinetic and microscopic studies of the reduction of nucleated silver chloride precipitates have been made.

The materials and general procedure employed have already been outlined. Several procedures

(1) T. H. James, THIS JOURNAL, **62**, 536 (1940).