[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Sulfanilamide Compounds. III. N^4-Heteroöyl Derivatives of N^1-Substituted Sulfanilamides

BY H. G. KOLLOFF AND JAMES H. HUNTER

In the course of the development of the chemotherapy of sulfanilamide, its derivatives and related compounds, the N^4-acyl type of derivatives[1] has received the attention of several investigators.[2-9] However, of the N^4-acyl derivatives which have been reported, only two[10,11] have been mentioned in which the acid radical was of a heterocyclic character.

In continuance of our studies[12] of derivatives of certain N^1-substituted sulfanilamides, the preparation and biologic evaluation of a number of N^4-heteroöyl derivatives of these N^1-substituted sulfanilamides was undertaken with the view of determining whether or not the introduction of a heterocyclic acid group would result in the diminution of activity generally observed in the N^4-acyl, -aracyl and -aroyl substituents. Toward the completion of our study of this series, Miller, Rock and Moore[9] reported N^4-*n*-caproyl sulfanilamide to be equally efficacious as sulfanilamide in the treatment of experimental β-hemolytic streptococcic infection of mice. On the basis of their report, we have included several N^4-*n*-caproyl-N^1-substituted sulfanilamides in this communication for comparative study.

Sulfanilamide, sulfapyridine, N^1-phenylsulfanilamide and N^1-(4-nitro)-phenylsulfanilamide were obtained as previously described.[12] *n*-Caproyl chloride was prepared from the acid and thionyl chloride; nicotinyl chloride, in the form of its hydrochloride, and α-thenoyl chloride[13] in a similar fashion from nicotinic and α-thiophene carboxylic acid[14]; α-furoyl chloride was obtained from Eastman Kodak Company. Except for the N^1-(4-amino)-phenyl derivatives, the compounds recorded in Table I were prepared in excellent (65% to practically quantitative) yields by condensing the sulfonamide compound, dissolved in pyridine, with 10% excess of the requisite acid chloride. The N^1-(4-amino)-phenyl derivatives were prepared from the corresponding nitro compound by reduction with alkaline ferrous sulfate.[15] The N^4-heteroöyl and N^4-*n*-caproyl derivatives are stable, high melting compounds, somewhat sparingly soluble in water and organic solvents, soluble in caustic alkali.

Based on preliminary pharmacologic data,[16] the antistreptococcal and antipneumococcal activity of the majority of the heteroöyl derivatives is, as compared to the N^1-substituted sulfanilamides, greatly diminished. One compound, however, N^4-α-furoyl-N^1-(2-pyridyl)-sulfanilamide, showed an antistreptococcal activity only slightly lower than sulfanilamide. Of the N^4-*n*-caproyl derivatives tested, all were found to be approximately equivalent to sulfanilamide in antistreptococcal activity; against pneumococci their activity was very slight.

The toxicity of all the compounds tested was found to be considerably lower than that of sulfanilamide and the N^1-substituted sulfanilamides.

Experimental

N^4-α-Thenoyl-N^1-(4-nitro)-phenylsulfanilamide.—Eleven and seventy-two hundredths grams (0.04 mole) of pure N^1-(4-nitro)-phenylsulfanilamide was dissolved in 50 cc. of anhydrous pyridine. While the solution was stirred mechanically, 6.45 g. (0.044 mole) of α-thenoyl-chloride was slowly added dropwise. After all the acid chloride had been added, the reaction mixture was heated, with continuous stirring, on a steam-bath for forty-five minutes. The mixture was then cooled under the tap, diluted with 200 cc. of water, acidified to litmus with hydrochloric acid and chilled in a refrigerator overnight. The yellow solid was collected, washed with water, and air dried; yield, 16.3 g. Repeated crystallization from aqueous acetone gave faintly yellow crystals, m. p. 261–262.5°.

N^4-α-Thenoyl-N^1-(4-amino)-phenylsulfanilamide.—Four and three hundredths grams (0.01 mole) of N^4-α-thenoyl-N^1-(4-nitro)-phenylsulfanilamide was dissolved in a warm mixture of 100 cc. of 2.5% sodium hydrox-

(1) Nomenclature of Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2217 (1938).
(2) Buttle, Gray and Stephenson, *Lancet*, **I**, 1296 (1936).
(3) Rosenthal, *Pub. Health Reports*, **52**, 48 (1937).
(4) Trefouel, Nitti and Bovet, *Ann. Inst. Pasteur*, **58**, 30 (1937).
(5) I. G. F., British Patent 470,461, *C. A.*, **32**, 597 (1938).
(6) I. G. F., French Patent 820,546, *ibid.*, **32**, 2958 (1938).
(7) Adams, Long and Johanson, THIS JOURNAL, **61**, 2342 (1939).
(8) Adams, Long and Jeanes, *ibid.*, **61**, 2346 (1939).
(9) Miller, Rock and Moore, *ibid.*, **61**, 2950 (1939).
(10) Daniels, U. S. Patent 2,192,828.
(11) Stuart, U. S. Patent 2,186,773.
(12) Kolloff and Hunter, THIS JOURNAL, **62**, 158 (1940).
(13) Jones and Hurd, *ibid.*, **43**, 2444 (1921).
(14) Schlenk and Ochs, *Ber.*, **48**, 679 (1915).
(15) Webster and Powers, THIS JOURNAL, **60**, 1553 (1938).
(16) We are indebted to Dr. F. A. Eberly and Mr. E. A. Gibson for conducting the biologic testing.

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	$C_{18}H_{22}N_2O_3S$[e]	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	$C_{17}H_{21}N_3O_3S$[e]	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

[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).