cumstances in which Tswett column separation is the method of choice, and it is hoped shortly to report further on some of these.

Since small amounts of pure acids can readily be obtained from mixtures by this method it may be expected that the Tswett column separation technique would find application in conjunction with an isotope dilution method such as that of Rittenberg, *et al.*,[13] if it were to be shown that fatty acids with abnormal isotope contents are inseparable from their normal analogs in these columns.

(13) D. Rittenberg and G. L. Foster, *J. Biol. Chem.*, **133**, 737 (1940).

I am indebted to Professor R. J. Anderson who provided some of the materials used in this work and who gave advice and criticism during its progress, and to the National Tuberculosis Association which furnished funds in aid of this work.

Summary

A method has been described and illustrated for separating mixtures of higher fatty acids by Tswett adsorption analysis on a column of adsorbent carbon.

NEW HAVEN, CONN. RECEIVED MAY 14, 1941

[CONTRIBUTION FROM THE DERMATOLOGICAL RESEARCH LABORATORIES DIVISION OF ABBOTT LABORATORIES]

N¹-Heterocyclic Sulfanilamide Derivatives*

BY G. W. RAIZISS, L. W. CLEMENCE AND M. FREIFELDER

The replacement of an amide hydrogen in sulfanilamide by a benzene nucleus did not produce compounds showing therapeutic activity in pneumococcus infections. However, replacement by a heterocyclic nucleus containing nitrogen such as in sulfapyridine,[1] or containing nitrogen and sulfur as in sulfathiazole,[2] resulted in high therapeutic activity.[3] A nucleus containing two nitrogens, such as pyrimidine, also was found to promote activity.[4]

It appeared of interest to us to prepare derivatives with nuclei containing two or three nitrogens; five-membered rings containing two nitrogens such as pyrazole and hydantoin; six-membered rings containing nitrogen and sulfur in comparison with thiazole and thiazoline, which are both five-membered rings (the latter described in this paper); and also compounds with both benzene and heterocyclic rings containing nitrogen and sulfur. The compounds were prepared in the usual way by the condensation of *p*-acetaminobenzene sulfonyl chloride with the heterocyclic amine. The acetylsulfanilyl derivatives thus formed were hydrolyzed to give the sulfanilylamino heterocycle. The various intermediate amines were prepared by methods described in the literature.

The therapeutic activity of these compounds as determined in preliminary experiments in lower animals infected with pneumococcus type II proved to be generally low except sulfapyrazine (XIV),[5] sulfahydantoin (XV) and sulfathiazoline (XVI).[6] The last-named product proved to be particularly interesting both on account of low toxocity and high therapeutic effect. For these experiments mice were infected intraperitoneally with 2 to 20 minimum lethal doses of type II pneumococcus of which the average minimum lethal dose was 0.5 cc. of 1:10,000,000 dilution of broth culture. The drugs were given by mouth in a dose of 10 mg. Mice were treated immediately after infection, 3 times daily for five days, twice on the sixth day, and once on the seventh—a maximum of 18 treatments.[7]

Experimental

The N¹-substituted sulfanilamides were prepared in the usual manner by the condensation of *p*-acetylaminobenzenesulfonyl chloride and the corresponding heterocyclic amine in pyridine; however, in some cases an additional solvent such as acetone was added to promote solution (I, X, XI, XII, XIII, XVI). In several cases, also, the pyridine was replaced by using sodium bicarbonate in acetone–aqueous solution (II, III, VI, VIII). The crude acetylsulfanilyl derivatives were precipitated by the addition

* This paper was presented before the Division of Medicinal Chemistry of the American Chemical Society in St. Louis, April, 1941.

(1) Whitby, *Lancet*, **1**, 1210 (1938).

(2) Fosbinder and Walter, THIS JOURNAL, **61**, 2032 (1939).

(3) Reinhold, Flippin and Schwartz, *Am. Jour. Med. Sci.*, **199**, 393 (1940).

(4) Roblin, Williams, Winnek and English, THIS JOURNAL, **62**, 2002 (1940).

(5) After this paper was submitted for publication, Joiner and Spoerri, THIS JOURNAL, **63**, 1929 (1941), described the preparation of 3-sulfanilamino-2,5-dimethylpyrazine.

(6) During the completion of this paper, Sprague and Kissinger, *ibid.*, **63**, 578 (1941), described the preparation of this compound, 2-sulfanilylaminothiazoline.

(7) We are indebted to Dr. M. Severac and Mr. J. Moetsch for their coöperation in conducting the animal experiments.

TABLE I

No.	Compound	Formula	M. p., °C., uncor.	Ref. to intermediate	N analyses, % Found	Calcd.
I	5 - Sulfanilylamino - 2 - methoxypyridine	$NH_2C_6H_4SO_2NHC_5H_3NOCH_3$	178	a	14.84	15.06
II	2 - Sulfanilylamino - 6 - piperidylpyridine	$NH_2C_6H_4SO_2NHC_5H_3NN(CH_2)_5$	185	b	17.24	16.86
III	N - Sulfanilyl - 1,2,3,4 - tetrahydroquinoline	$NH_2C_6H_4SO_2NC_9H_{10}$	125	c	9.37	9.68
IV	7 - Sulfanilylamino - 2 - hydroxy-3,4-dihydroquinoxaline	$NH_2C_6H_4SO_2NHC_8H_7ON_2$	188	d	17.34	17.61
V	2 - Sulfanilylamino - 5,6 - diphenyl-1,3,4-triazine	$NH_2C_6H_4SO_2NHC_3N_3(C_6H_5)_2$	189 (f)	e	S, 7.24	7.90
VI	2 - Sulfanilylamino - 5,6 - dihydro-1,3,4-thiazine	$NH_2C_6H_4SO_2NHC_4H_6NS$	88	g	15.37	15.49
VII	2 - Sulfanilylamino - 5 - bromo-5,6-dihydro-1,3,4-thiazine	$NH_2C_6H_4SO_2NHC_4H_5NSBr$	100	h	12.10	12.00
VIII	Sodium salt of 3-sulfanilylamino-5-methyltriazole	$NH_2C_6H_4SO_2NC_2HN_3CH_3Na$	(i)	j	S, 11.56	11.63
IX	4-Sulfanilylamino-pyrazole	$NH_2C_6H_4SO_2NHC_3H_3N_2$	185	k	S, 13.55	13.44
X	4 - Sulfanilylamino - 3,5 - dimethylpyrazole	$NH_2C_6H_4SO_2NHC_3HN_2(CH_3)_2$	233	l	21.74	21.05
XI	2-Sulfanilylaminobenzimidazole	$NH_2C_6H_4SO_2NHCN_2HC_6H_4$	211–212	m	18.93	19.44
XII	2-Sulfanilylaminophenothiazine	$NH_2C_6H_4SO_2NHC_{12}H_8NS$	above 315	n	10.96	11.36
XIII	4 - Sulfanilylamino - 3,5 - diphenylpyrrole	$NH_2C_6H_4SO_2NHC_4H_2N(C_6H_5)_2$	178–180	p	10.45	10.71
XIV	2-Sulfanilylaminopyrazine	$NH_2C_6H_4SO_2NHC_4H_3N_2$	253	q	22.31	22.40
XV	5-Sulfanilylaminohydantoin	$NH_2C_6H_4SO_2NHC_3H_3O_2N_2$	122 (d)	r	20.19	20.74
XVI	2-Sulfanilylaminothiazoline	$NH_2C_6H_4SO_2NHC_3H_4NS$	209–210	s	15.88	16.34

[a] Binz and von Schickh, U. S. Patent 2,145,579. [b] Dow Chemical Co. [c] Eastman Kodak Co. [d] Waldman, *J. prakt. Chem.*, [2] **91**, 193 (1915). [e] Thiele and Behan, *Ann.*, **302**, 309 (1898). [f] With preliminary softening. [g] Gabriel and Lauer, *Ber.*, **23**, 94 (1890). [h] Dixon, *J. Chem. Soc.*, **69**, 22 (1896). [i] Did not melt below 300°. [j] Thiele and Heidenreich, *Ber.*, **26**, 2599 (1893). [k] 4-Nitropyrazole prepared according to Hill and Torrey, *Am. Chem.* **22**, 105 (1899), and reduced according to Knorr, *Ber.*, **37**, 3520 (1904). [l] Morgan and Ackerman, *J. Chem. Soc.*, **123**, 1311 (1923). [m] Eastman Kodak Company. [n] Bernthsen, *Ann.*, **230**, 101 (1885). [p] Gabriel, *Ber.*, **41**, 1138 (1908). [q] Hall and Spoerri, THIS JOURNAL, **62**, 664 (1940). [r] Biltz and Giesler, *Ber.*, **46**, 3423 (1913). [s] Gabriel, *ibid.*, **22**, 1140 (1889).

of about five volumes of water, and were hydrolyzed by refluxing for one hour with ten volumes of 1 *N* sodium hydroxide solution, except in case of III, VII, X and XVI, 10% hydrochloric acid was substituted for the sodium hydroxide. The hydrolyzed solutions, after cooling, were neutralized, whereupon the crude amino compounds precipitated. These were recrystallized from water and in a few instances the more difficultly soluble compounds were recrystallized from 50% alcohol. Compound VIII, which was decomposed both by alkaline and acid hydrolysis, was refluxed with an equivalent of sodium methoxide in alcohol and on cooling separated as the sodium salt.

With the exception of this salt, the compounds were rather difficultly soluble in water. They were soluble in dilute sodium hydroxide solution, except III; compounds I, II, VI, VII, IX, X, XI, XII, XIV, XV and XVI were soluble in dilute hydrochloric acid; compounds III, IV, V and XIII were soluble in concentrated hydrochloric acid.

Acknowledgment.—We gratefully acknowledge the assistance of Dr. Wm. Sidon and Mr. Harry Sobel in the preparation of the intermediates.

Summary

1. The preparation of a number of N^1-heterocyclic sulfanilamides is described. Among these are ring structures containing from one to three nitrogen atoms and also some with nitrogen and sulfur.

2. The therapeutic activity in experimental type II pneumococcic infection in preliminary studies proved to be low for some of the compounds.

3. Three of the products, sulfapyrazine (XIV), sulfahydantoin (XV) and sulfathiazoline (XVI) are therapeutically promising.

PHILADELPHIA, PA. RECEIVED JULY 5, 1941