STRUCTURE AND CHEMOTHERAPEUTIC ACTIVITIES OF SULFANILAMIDE DERIVATIVES[1]

E. H. NORTHEY

Calco Chemical Division, American Cyanamid Company, Bound Brook, New Jersey

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CONTENTS

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A. Introduction

The discovery of the antistreptococcic activity of azo dyes derived from sulfanilamide in the laboratories of the I. G. by Mietzsch, Klarer, and Domagk, coupled with the later work at the Pasteur Institute by the Tréfouëls, Nitti, and Bovet, which showed that the activity resided in the sulfanilamide part of the molecule, is beyond doubt the greatest contribution to chemotherapy yet made. It surpasses Ehrlich's discoveries, which were limited to the field of trypanosome diseases, since it has already led

to cures of most of the common infectious diseases of bacterial origin. The discovery stimulated intensive work on sulfanilamide derivatives and allied compounds by almost every large pharmaceutical concern and medical institution in the world.

The frenzied research of the past five years has resulted in the synthesis and disclosure of about thirteen hundred new compounds derived from the parent sulfanilamide. When allied compounds and undisclosed sulfanilamide derivatives are added to these, it is probable that more than three thousand new compounds are available for chemotherapeutic study. Almost every class of sulfanilamide derivative has now been explored. Inevitably, there has been an enormous duplication in synthesis, so that often four or more groups have synthesized the same compound, independently, and within a few days or weeks of each other.

While sulfanilamide derivatives have been well explored from the chemical side, the bacteriological and pharmacological studies have been superficial and wholly inadequate. Obvious reasons for this are that pharmacologists have had a great amount of work in widening the field of usefulness of sulfanilamide and its commercial derivatives, in investigating the numerous toxic reactions, and in laying a foundation of test methods. Each new derivative calls for several weeks' work at a cost of many experimental animals before even a preliminary estimation of its therapeutic value against a single disease can be given. When this is multiplied by the number of diseases now known to be susceptible to treatment by this group of drugs, it will be appreciated that each pharmaceutical chemist should be backed by a staff of at least ten bacteriologists and pharmacologists if they are to keep pace with synthesis in this field. Unhappily the ratio is apt to be the reverse!

Marshall (128) has recently summarized experimental infections treated by the new chemotherapy as follows: "The therapeutic effect of sulfanilamide (or allied compounds) is excellent in experimental mouse infections due to the β-hemolytic streptococcus, meningococcus, and pneumococcus. It is still good, but less satisfactory in mouse infections produced by strains of gonococcus and staphylococcus; Proteus, colon, typhoid, and paratyphoid organisms; the Sonne strain of the dysentery bacillus; a strain of Listerella; Hemophilus influenzae, the Welch bacillus, and certain members of the Pasteurella group, including the plague bacillus. Prolongation of life, with few or no survivals, is reported for infections produced by strains of Salmonella typhimurium, Friedländer's bacillus; Pasteurella pseudotuberculosis and the anthrax bacillus. A definite inhibitory effect on the development of experimental tuberculosis in the guinea pig and rabbit, an alteration of the natural course of experimental Brucella infections in guinea pigs and Bacterium necrophorum infection in rabbits, and the re-

markable curative effect in certain human urinary tract infections also attest to the widespread antibacterial powers of the sulfonamide group of drugs. In protozoan infections, the only conclusive evidence of effectiveness is that reported for malarial infection of monkeys. In virus infections, the results so far obtained are negative or inconclusive, with the exception of lymphogranuloma venereum and trachoma. In both of these cases, there is some doubt if the infecting agent can be classed as a true virus."

B. Measurement of Chemotherapeutic Activity

For obtaining preliminary data on the activity of a new sulfanilamide derivative, the mouse is used as a test animal almost exclusively. This is because of the ease with which mice can be handled, their low cost, and their susceptibility to infection with many of the bacteria causing human diseases. As yet, there has been no well-standardized technique which has been universally used. As a consequence, the published results of different laboratories testing the same drug have differed widely in their estimations of therapeutic value. Variations in the strain, virulence, or number of infecting organisms, in the size and frequency of dosage, and in the method of administering the drug greatly influence the survival of the mice. There has been great variation also in the length of time allowed before reading survivals and in the manner of expressing results.

Marshall's laboratory (120) has recently established a more nearly quantitative method of evaluation, based on the drug-diet method of dosage worked out by Bieter, Larson, Levine, and Cranston (13).

This method has been summarized by Marshall (128) as follows: "A more or less constant blood concentration of drug during the period of therapy is maintained by using food in which the drug has been incorporated. By treating mice in individual cages, the daily drug intake of each mouse can be determined. Drug diets are so selected that one may expect to obtain with different drug intakes survival percentages greater and less than fifty. The diets are fed for one or more days prior to and for the desired period after infection. Irrespective of the percentage drug in any diet, the average daily drug intakes (per mouse) can be arranged in groups and correlated with percentage survivals. The dosage-survival curve is now computed and the *Median Survival Dose* ($S.D._{50}$) with its standard error obtained. This can be converted into the Median Survival Blood Concentration ($S.B.C._{50}$) by a factor which relates blood concentration to daily drug intake of the drug being tested. By using a standard, one obtains a comparative value for the $S.B.C._{50}$'s which may be nearly absolute, even though the $S.B.C._{50}$'s themselves are variable."

The disadvantages of this method are the large number of individual mouse cages required for any extensive program of testing, and the tedious

weighings and calculations involved. However, the advantages of obtaining reliable results instead of a mass of conflicting and uninterpretable data should far outweigh the extra space and labor required. It is to be hoped that this or a similar method may be universally adopted, so that future publications on chemotherapeutic activities may be of more value than the morass of misinformation now available.

For purposes of correlating chemical constitution with chemotherapeutic effect, much more information is desirable than has been obtained heretofore from ordinary tests in mice. It is highly useful to the chemist in projecting new syntheses to know whether a compound which has failed to protect mice against the infection is inherently inactive, or whether the lack of protection is caused by one or more of the following factors:

(*1*) The drug is rapidly absorbed and eliminated, so that effective blood concentrations are not maintained. This is undoubtedly an important factor with many highly soluble sulfanilamide derivatives; however, it does *not* follow that high water-solubility means that the compound *will* be absorbed and eliminated rapidly.

(*2*) The drug is not absorbed rapidly enough to reach effective blood concentrations. This may be caused by lack of solubility in both water and lipoids, or by other mechanisms.

(*3*) The drug is rapidly conjugated by the animal, and hence does not exist in an active form long enough to exert its chemotherapeutic effect. This is probably a minor factor, although important differences in rate of conjugation have been noted.

(*4*) The drug is toxic to the host.

The chief advantages of expressing results in terms of S.B.C.$_{50}$'s from the chemist's point of view is that, by so doing, factors 1 and 2 are eliminated and he is given a basis for comparison of inherent activities against structural characteristics or other properties of the compounds. Effects of factors 3 and 4 become apparent, also, since blood level studies in control animals will automatically demonstrate conjugation and toxicity. Fortunately, in all cases where the sulfanilamide derivative has a free amino group, or can be converted by reduction or hydrolysis to give a free amino group, blood levels of the drug can readily be determined by the method of Marshall and Cutting (130) or that of Bratton and Marshall (15).

Some further light on whether the compound is inherently active or inactive is obtained by *in vitro* bacteriostatic tests, but too much reliance cannot be placed in the results, since a multitude of factors may affect the results and not all of these are known. Also, the animal body is capable of transforming many compounds which are inactive *in vitro* to active compounds *in vivo*, as witness the original Prontosil.

The preliminary studies in mice tell almost nothing about the complica-

tions which may be encountered in human therapy with the compound, so that, after favorable results have been obtained in mice, it is necessary to conduct very extensive pharmacological and toxicological studies using larger test animals before proceeding to clinical studies. The possible dangers and the means of testing against them have been adequately covered elsewhere (122, 139, 158, 17, 128) and do not concern us here.

It has been the practice to compare the chemotherapeutic activities of new derivatives with the parent sulfanilamide against β-hemolytic streptococci. Lately, this has been broadened to include a comparison with sulfapyridine against pneumococci. However, if the compound is inactive by these tests, its future is apt to be a small niche in Beilstein. This is probably not a just fate, since it is by no means certain that a compound which is inactive against one or two test organisms will be inactive against all other bacteria, or even different strains of the same organism. From the commercial point of view, this is likewise a questionable procedure, since new derivatives to compete successfully with sulfanilamide must offer important advantages. That a derivative will be found which offers such advantages for the treatment of β-hemolytic streptococcic infections appears increasingly unlikely. On the other hand, new derivatives are assured of immediate commercial success if they cure diseases against which sulfanilamide is not particularly effective. The case of sulfapyridine is a pertinent example of this, since it offers little advantage over sulfanilamide against streptococci and is fundamentally a much more expensive compound to produce. It therefore would have had little chance of finding a market, were it not specific for pneumonia.

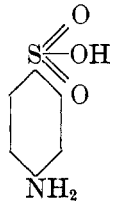
In spite of these objections, the preliminary evaluation of new compounds will continue much as at present, since any other course would soon get out of hand. It is to be hoped, however, that when chemical activity decreases, pharmacologists may make the effort to reëxamine many of the compounds passed over in the first hurried survey. It should be remembered that sulfanilamide was interred in Beilstein over thirty years ago. How many other compounds are awaiting resurrection?

From the foregoing, it will be appreciated that there is comparatively little pharmacological data with which one can correlate the structures of sulfanilamide derivatives. This review has as its main function, therefore, the classification of the known sulfanilamide derivatives according to their chemical structures. Where available, the activity of the derivatives, as compared with sulfanilamide, against β-hemolytic streptococci has been indicated. These results are usually based on preliminary tests in mice and are not particularly trustworthy, as may be gathered from the comments above. As used herein, the signs have the following meaning: +++, slightly superior to sulfanilamide; ++, about equal to sulfanil-

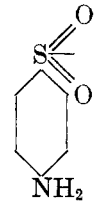
amide; +, moderate activity; ±, very slight or uncertain activity; 0, no activity; −, toxicity (treated animals dead before the controls).

C. Chemical Classification and Nomenclature

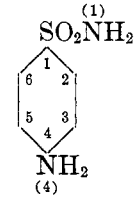
The present paper is strictly limited to derivatives of sulfanilamide. It therefore excludes the therapeutically active diaminodiphenylsulfones and other closely related compounds. The system of listing is based on the nomenclature proposed by the author and coworkers (35), which has been generally accepted in this country. The parent compound is sulfanilic acid (I),



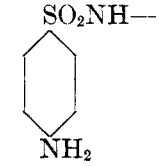
I



II

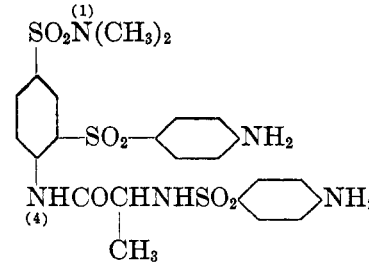


III



IV

which gives rise to the acid radical "sulfanilyl" (II) and to "sulfanilamide" (III), which in turn gives rise to the radical "sulfanilamido" (IV). Simple derivatives are best named as derivatives of sulfanilamide, and to distinguish between the nitrogens, substituents of the amido group are called N^1-substituents, while those of the amino group are N^4-substituents. As an example illustrating the usefulness of the radicals, the compound V may be named N^1,N^1-dimethyl-N^4-(2-sulfanilamidopropionyl)-3-sulfanilylsulfanilamide.



For the purposes of this paper, sulfanilamide derivatives are classified as follows:

I. Nuclear-substituted sulfanilamides.
II. N^1-Substituted sulfanilamides.

III. N^4-Substituted sulfanilamides.
IV. Nuclear,N^1-substituted sulfanilamides.
V. Nuclear,N^4-substituted sulfanilamides.
VI. N^1,N^4-Substituted sulfanilamides.
VII. Nuclear,N^1,N^4-substituted sulfanilamides.
VIII. Salts of sulfanilamide.
IX. Unclassified sulfanilamide derivatives.

Each of the above main divisions is further subdivided into the following:

(A) Inorganic substituents.
(B) Acyclic substituents.
(C) Isocyclic substituents.
(D) Heterocyclic substituents.
(E) Acyl substituents.
(F) Sulfonyl substituents.
(G) Anils (Schiff bases).
(H) Azo derivatives.

Further subdivisions follow the system in Beilstein as closely as practicable.

In the case of multiple substituents, the compound is listed under the substituent having the highest numerical and alphabetical placement above. For example, compound V (above) belongs to division VII (nuclear,N^1,N^4-substituted sulfanilamides). It would be listed under subdivision E (N^4-acyl substituents) and then under N^4-amino-acyclic-acyl substituents, according to carbon content. In a series involving the same N^4-group, it would next be classified according to the N^1-substituents, and finally according to the nuclear substituents.

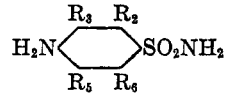
D. Sulfanilamide Derivatives

I. Nuclear-substituted sulfanilamides

Nuclear-substituted sulfanilamides (see table 1) have not been investigated particularly well from either the chemical or the pharmacological side. Two reasons for this are: first, that nuclear substituents are somewhat more difficult to synthesize than are the nitrogen-substituted derivatives, and second, that the simple derivatives so far made have practically no activity. Thus, introduction of a halogen, amino, sulfonamido, methyl, or carboxyl group into the sulfanilamide ring completely destroys the activity. However, the conclusion should not be drawn that *any* substitution of the ring will destroy activity, since 3,5-dimethylsulfanilamide (155) is said to have some activity, as also aniline-3,5-disulfonamide (which, however, is not a sulfanilamide derivative).

TABLE 1

Nuclear-substituted sulfanilamides



R_3	R_2	R_5	R_6	ACTIVITY	REFERENCES
		A. Inorganic substituents			
Cl—	H	H	H		(80)
H	Cl—	H	H		(173)
H	Br—	Br—	H	0	(20, 64)
H	I—	H	H		(167)
H	I—	I—	H		(167)
H	NO_2—	H	H		(55, 97, 181)
H	NO_2—	NO_2—	H	0	(161)
HO—	H	H	H	0	(181)
H	NH_2SO_2—	H	H	0	(55, 86)
H	NH_2SO_2—	NH_2SO_2—	H	0	(20, 125)
H	NH_2—	H	H	0	(61, 86, 181)
NH_2—	H	NH_2SO_2—	H		(125)
		B. Acyclic substituents			
CH_3—	H	H	H	0	(86, 181)
H	CH_3—	H	H	0	(61, 155, 181)
CH_3—	H	CH_3—	H		(80, 84)
CH_3—	H	Cl—	H		(84)
H	CH_3—	CH_3—	H	+	(155)
CH_3—	H	CH_3O—	H		(81, 84)
CH_3—	H	C_2H_5O—	H		(81)
H	CH_3O—	H	H		(173)
CH_3O—	H	H	H		(80)
CH_3O—	H	CH_3O—	H		(84)
H	HOOC—	H	H	0	(57, 95)
HOOC—	H	H	H	0	(95)
		C. Isocyclic substituents			
		None			
		D. Heterocyclic substituents			
		None			

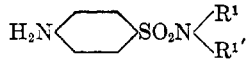
Mention has been made of the anthelmintic activity of 2-methyl-5-methoxysulfanilamide against ascarides (81).

II. N^1-SUBSTITUTED SULFANILAMIDES

This class of sulfanilamide derivatives contains practically all of the therapeutically important new derivatives and has therefore been extensively studied. Because of the number of compounds, the discussion will parallel the chemical subdivisions.

(*A*) *Inorganic substituents*

The derivative of hydroxylamine is claimed to be active, while the derivative of sulfamic acid is inactive. Scarcity of inorganic amino intermediates accounts for the few compounds in this class.



R^1	$R^{1'}$	ACTIVITY	REFERENCES
HO—	H	++	(113)
NaO_3S—	H	0	(121)

(*B*) *Acyclic substituents*

The ready availability of the aliphatic amines, hydroxyamines, and amino acids accounts for the many derivatives in this class (see table 2). In general, the compounds are of low activity. The series of N^1-alkyl- and N^1,N^1-dialkyl-sulfanilamides shows activity almost equal to sulfanilamide for the first two members, but a drop to negligible activity for carbon chains longer than three.

N^1-Hydroxyalkyl- and N^1-carboxyalkyl-sulfanilamides have given variable results in the hands of different investigators. This is probably because of rapid absorption and elimination, so that when compared with sulfanilamide the results are poor if given at the same dosage, and reasonably good if given frequently enough. In spite of the low activities reported in this country for *N*-sulfanilylglycine, it is interesting to note that it has found sale in Sweden under the name Streptasol (5, 51).

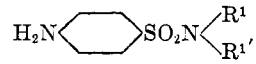
Esterification of N^1-hydroxy- or N^1-carboxy-alkylsulfanilamides destroyed their activity (42).

(*C*) *Isocyclic substituents*

These have been synthesized in great variety, since the intermediates are commercially available from the dye industry, or can readily be made from commercial intermediates. For convenience, this class is further subdivided as follows: (*1*) R = C_nH_{2n-1} to C_nH_{2n-13}; (*2*) oxy and oxo derivatives; (*3*) carboxy derivatives; (*4*) sulfo derivatives; (*5*) amino derivatives; and (*6*) miscellaneous derivatives.

TABLE 2

N^1-Acyclicsulfanilamides



R^1	$R^{1'}$	ACTIVITY	REFERENCES
CH_3—	H	++	(61, 86, 121, 181)
CH_3—	CH_3—	++	(26, 61, 80, 86, 164, 181)
CH_3CH_2—	H	++	(61, 86, 181)
CH_3CH_2—	CH_3CH_2—	++	(61, 70, 86, 181)
$CH_3(CH_2)_2$—	$CH_3(CH_2)_2$—	±	(61, 181)
$(CH_3)_2CH$—	H	±	(61, 181)
$CH_3(CH_2)_3$—	H	±	(61)
$CH_3(CH_2)_3$—	$CH_3(CH_2)_3$—	±	(61)
CH_2=$CHCH_2$—	H	+	(61, 181)
$CH_3(CH_2)_7$—	H	0	(40, 54)
$CH_3(CH_2)_{11}$—	H	0	(40, 54)
$CH_3(CH_2)_{17}$—	H	0	(40, 54)
$CH_3(CH_2)_7CH$=$CH(CH_2)_8$—	H	0	(40, 54)
$HOCH_2$—	H		(193)
$HOCH_2CH_2$—	H	+	(2, 9, 11, 42, 86, 114)
$HOCH_2CH_2$—	CH_3—	0	(40, 121)
$HOCH_2CH_2$—	$HOCH_2CH_2$—	++, +	(2, 42, 87, 121, 100)
$CH_3(CH_2)_{10}COOCH_2CH_2$—	H	0	(40)
$HOCH_2CH_2CH_2$—	H	±	(2, 114)
$CH_3CHOHCH_2$—	H	0, ±	(2, 42, 114)
$(CH_3)_2COHCH_2$—	H	0, ±	(42, 121)
$HOCH_2CH(OH)CH_2$—	H	0	(2, 114)
$CH_3CH(OH)CH_2$—	$CH_3CHOHCH_2$—	±	(42)
$C_2H_5CHOHCH_2$—	H		(114)
$(HOCH_2)(CH_3)_2C$—	H		(40)
$(HOCH_2)_2CH$—	H		(114)
$(HOCH_2)_2(CH_3)C$—	H		(40)
$HOOCCH_2$—	H (Streptasol)	±	(9, 11, 21, 32, 80, 96, 100, 102, 136)
$NaOOCCH_2$—	H	±	(21, 95, 121)
$C_2H_5OOCCH_2$—	H	±	(40)
$HOOC(CH_3)CH$—	H		(136)
$NaOOCCH_2CH_2(HOOC)CH$—	H	±	(21)
$C_4H_9OOCCH_2CH_2CHCOOC_4H_9$	H	0	(40)
$HO_3SCH_2CH_2$—	H		(82)
$H_2O \cdot NaO_3SCH_2CH_2$—	H	0	(121)
$(C_2H_5)_2N(CH_2)_4$—	H		(28, 29, 45)
$CH_3[(C_2H_5)_2N]CHCH_2CH_2$—	H		(28)

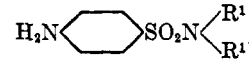
(1) N^1-Isocyclicsulfanilamides: R = C_nH_{2n-1} to C_nH_{2n-13}

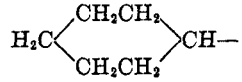
These compounds are summarized in table 3, together with some of their halogen and nitro derivatives.

N^1-Cyclohexylsulfanilamide was found to be inactive, while N^1-phenylsulfanilamide was claimed by Buttle (20) to be as active as sulfanilamide. This claim has been disputed by others, but is historically important in that it may have given impetus to the synthesis of isosteric derivatives in the heterocyclic series leading to the very active derivatives sulfapyridine, sulfathiazole, and sulfadiazine. It is interesting to observe that Gelmo

TABLE 3

N^1-Isocyclicsulfanilamides: R = C_nH_{2n-1} *to* C_nH_{2n-13}



R^1	$R^{1'}$	ACTIVITY	REFERENCES
	H	0	(70, 86)
C_6H_5—	H	+, ++	(20, 66, 102, 163, 181)
C_6H_5—	$HOCH_2CH_2$—	++	(42)
2-ClC_6H_4—	H	0	(42)
4-ClC_6H_4—	H	0	(42)
2-$(NO_2)C_6H_4$—	H		(76)
3-$(NO_2)C_6H_4$—	H		(76, 187)
4-$(NO_2)C_6H_4$—	H	+++, ±	(9, 11, 76, 102, 187)
2,4-$(NO_2)_2C_6H_3$—	H		(48)
2-$(CH_3)C_6H_4$—	H		(66, 91)
3-$(CH_3)C_6H_4$—	H		(66)
4-$(CH_3)C_6H_4$—	H		(66)
$C_6H_5CH_2$—	H	±	(68, 86, 181)
1-$C_{10}H_7$—	H		(66)
2-$C_{10}H_7$—	H		(66)

(66), who first synthesized sulfanilamide, also synthesized N^1-phenylsulfanilamide and its homologs.

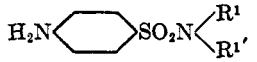
Substitution of chlorine in the phenyl ring destroys activity. N^1-(4-Nitrophenyl)sulfanilamide has been claimed to be more active than sulfanilamide, but also much more toxic. This is contradicted by Kolloff (102), who reports little or no activity for this compound in both streptococcic and pneumococcic infections.

(2) N^1-Isocyclicsulfanilamides: oxy and oxo derivatives (see table 4)

The sulfanilamidophenols as a class have little if any activity against streptococci. Sulfanilamidoguaiacol is also inactive against pneumococci (54).

TABLE 4

N^1-Isocyclicsulfanilamides: oxy and oxo derivatives



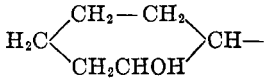
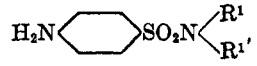
R^1	$R^{1'}$	ACTIVITY	REFERENCES
	H	0	(2)
2-(HO)C_6H_4—	H	−, 0	(42, 121, 187)
3-(HO)C_6H_4—	H	±	(121, 187)
4-(HO)C_6H_4—	H	++, ±	(42, 121, 127, 187)
4-HO-3-(NO_2)C_6H_3—	H	0	(121)
2-(CH_3O)C_6H_4—	H	0	(42, 54)
4-(CH_3O)C_6H_4—	H		(28, 29)
4-(C_2H_5O)C_6H_4—	H	±	(181)
3-CH_3O-4-(HO)C_6H_3—	H	0	(42, 54)
2-CH_3-4-HO-5-[$(CH_3)_2CH$]C_6H_2—	H	0	(42, 54)
4-(CH_3CO)C_6H_4—	H		(197, 145, 158)
4-(CH_3CH_2CO)C_6H_4—	H		(197)
4-(C_6H_5CO)C_6H_4—	H		(197)

TABLE 5

N^1-Isocyclicsulfanilamides: carboxy derivatives



R^1	$R^{1'}$	ACTIVITY	REFERENCES
2-(HOOC)C_6H_4—	H	+++, ±	(35, 54, 91, 100)
2-(NaOOC)C_6H_4—	H	++, 0	(42, 102, 121)
2-(C_2H_5OOC)C_6H_4—	H	0	(42)
3-(HOOC)C_6H_4—	H	+, ±, 0	(35, 91, 102, 121, 100)
4-(HOOC)C_6H_4—	H	+, ++, 0	(9, 11, 35, 54, 100, 102, 121, 165)
4-(NH_2OC)C_6H_4—	H		(107)
2-HOOC-4-ClC_6H_3—	H		(28, 29, 91)
3-(HOOCCH=CH)C_6H_4—	H		(65)
4-(HOOCCH=CH)C_6H_4—	H		(65)
4-HOOC-3-(HO)C_6H_3—	H	0	(42, 91)
4-(HO)$C_6H_4CH_2$(HOOC)CH—	H		(136)

(3) N^1-Isocyclicsulfanilamides: carboxy derivatives (see table 5)

The sulfanilamidobenzoic acids have given variable results with different investigators, probably because of variations in dosage, since these compounds may be absorbed and excreted rapidly. The 2-sulfanilamido-

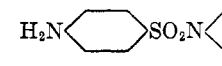
benzoic acid seems slightly more active than the 3- and 4-isomers. All are of low activity against pneumococci (102).

(4) N^1-Isocyclicsulfanilamides: sulfo derivatives (see table 6)

The above remarks on the corresponding carboxy derivatives also apply here. It is difficult to maintain adequate blood levels of sodium N-sul-

TABLE 6

N^1-Isocyclicsulfanilamides: sulfo derivatives



R^1	$R^{1'}$	ACTIVITY	REFERENCES
2-$(HO_3S)C_6H_4$—	H	++, 0	(23, 35, 54)
2-HO_3S-4-FC_6H_3—	H	0	(177)
2-HO_3S-4-ClC_6H_3—	H	0	(177)
3-$(HO_3S)C_6H_4$—	H	+, ±	(35, 54, 91)
3-$(NH_2O_2S)C_6H_4$—	H	++, +	(37, 54)
3-HO_3S-4-FC_6H_3—	H	0	(177)
3-HO_3S-4-ClC_6H_3—	H	0	(177)
4-$(HO_3S)C_6H_4$—	H	±	(35, 65, 91, 100)
4-$(HO_3S)C_6H_4$—	C_2H_5—	0	(42)
4-$(NaO_3S)C_6H_4$—	H	±, 0	(35, 100, 102, 121, 127, 158)
4-HO_3S-2-ClC_6H_3—	H	0	(42)
4-NaO_3S-2,5-$Cl_2C_6H_2$—	H	0	(42)
4-HO_3S-2-$(CH_3)C_6H_3$—	H	+, 0	(35, 91, 121)
5-HO_3S-2-$(CH_3)C_6H_3$—	H		(91)
4-HO_3S-3-$(CH_3)C_6H_3$—	H	0	(35, 91)
2-HO_3S-4-$(CH_3)C_6H_3$—	H	0	(23, 35)
4-HO_3S-2,5-$(CH_3)_2C_6H_2$—	H	0	(35)
1-NaO_3S-5-$C_{10}H_6$—	H	+	(35)
4-NaO_3S-1-$C_{10}H_6$—	H	++, 0	(54, 35, 91)
6-HO_3S-2-$C_{10}H_6$—	H		(35)
3,5-$(HO_3S)_2C_6H_3$—	H	0	(37)
3,6-$(HO_3S)_2$-1-$C_{10}H_5$—	H		(91)
3,8-$(HO_3S)_2$-1-$C_{10}H_5$—	H		(91)
4,8-$(NaO_3S)_2$-1-$C_{10}H_5$—	H	0	(121)
5-NaO_3S-2-$(HO)C_6H_3$—	H	0	(121)
3-HO_3S-4-$(C_2H_5O)C_6H_3$—	H	0	(35)
7-HO_3S-5-HO-2-$C_{10}H_5$—	H		(91)
6-HO_3S-8-HO-2-$C_{10}H_5$—	H		(91)

fanilylsulfanilate. This may partly explain the controversial question of its effectiveness in dog distemper (46, 126). It is reported to be fairly effective in lymphogranuloma venereum infections (73).

Addition of a third group to the N^1-aryl, when this is halogen, alkyl, oxy, or sulfo, destroys the activity.

(5) N^1-Isocyclicsulfanilamides: amino derivatives (see table 7)

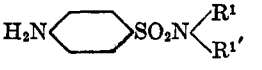
The N^1-aminophenylsulfanilamides have been extensively studied abroad. Whitby (11) reported them to be somewhat inferior to sulfanilamide in antistreptococcic effect, but equal against meningococci and superior against pneumococci. Others have given conflicting evaluations. N^1-(4-Aminophenyl)sulfanilamide as its tartrate was studied clinically in Europe, but withdrawn because it gave a high incidence of peripheral neuritis.

The series of N^1-(4-benzilidineaminophenyl)sulfanilamides (102) is interesting because of the variation in activity with different substituted benzilidine groups. If these anils are hydrolyzed in the body, the resulting activities might be expected to be that of the parent N^1-(4-aminophenyl)sulfanilamide except as modified by rates of absorption and hydrolysis.

The *bis*-sulfanilamidobenzenesulfonic acids and their salts are of passing interest, since they were found to be active when given parenterally but inactive *per os* (35, 54). In spite of high water-solubility, these compounds are not absorbed from the intestinal tract. This is again an illustration of the importance of studying blood levels of the drug in experimental therapy.

(6) N^1-Isocyclicsulfanilamides: miscellaneous derivatives

The three derivatives listed, all arsonic acid derivatives, are apparently inactive against streptococci.



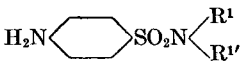
R^1	$R^{1'}$	ACTIVITY	REFERENCES
4-[$(HO)_2OAs$]C_6H_4—	H	0	(178)
4-($NaHO_3As$)C_6H_4—	H	±	(121)
3-[4-[$(HO)_2OAs$]$C_6H_4N{=}N$]-4-$(HO)C_6H_3CH_2(HOOC)CH$—	H		(136)

(*D*) *Heterocyclic substituents*

This class of derivatives is being both extensively and intensively studied. The spectacular success of sulfapyridine against pneumonia has resulted in a gold-rush to the new field and new strikes are being made in quick succession. Two veins of the original lode have been uncovered in sulfathiazole (2-sulfanilamidothiazole) and sulfadiazine (2-sulfanilamidopyrimidine), which may prove to be of equal or greater importance. These

TABLE 7

N^1-Isocyclicsulfanilamides: amino derivatives



R^1	$R^{1'}$	ACTIVITY	REFERENCES
2-$(NH_2)C_6H_4$—	H	±	(76, 121, 187)
3-$(NH_2)C_6H_4$—	H	+	(24, 76, 121, 187, 188)
4-$(NH_2)C_6H_4$—	H	+++, ++, ±	(119, 121, 127, 131, 187, 188)
4-$(CH_3NH)C_6H_4$—	H		(76)
4-$[(CH_3)_2N]C_6H_4$—	H		(65, 76, 84, 131)
4-$[(C_2H_5)_2N]C_6H_4$—	H		(76)
4-$(C_6H_5NH)C_6H_4$—	H		(84)
4-$(C_6H_5CH{=}N)C_6H_4$—	H	+++	(102)
4-$[4'\text{-}(NO_2)C_6H_4CH{=}N]C_6H_4$—	H	+	(102)
4-$[4'\text{-}(CH_3O)C_6H_4CH{=}N]C_6H_4$—	H	++	(102)
4-$[4'\text{-}[(CH_3)_2N]C_6H_4CH{=}N]C_6H_4$—	H	++	(102)
3-CH_3-4-$(NH_2)C_6H_3$—	H		(84)
2-CH_3-5-$(NH_2)C_6H_3$—	H		(76)
5-CH_3-2-$(NH_2)C_6H_3$—	H		(76)
2,3-$(CH_3)_2$-4-$(NH_2)C_6H_2$—	H		(76)
2,4-$(NH_2)_2C_6H_3$—	H		(84)
3,4-$(NH_2)_2C_6H_3$—	H		(131)
4-$[4'\text{-}(NH_2)C_6H_4NH]C_6H_4$—	H		(131)
4-HO-3-$(NH_2)C_6H_3$—	H	0	(121)
3-HO-4-$(NH_2)C_6H_3$—			(84, 131)
2-NH_2-5-$(Na_2O_3S)C_6H_3$—	H	0	(35)
2-$[4'\text{-}(NH_2)C_6H_4SO_2NH]C_6H_4$—	H	0	(42)

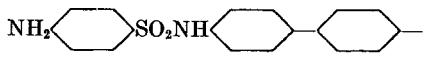
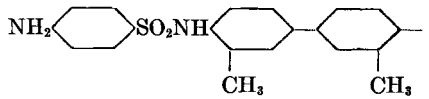
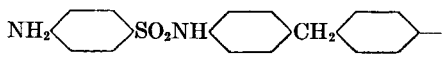
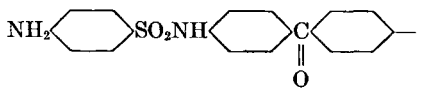
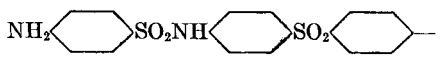
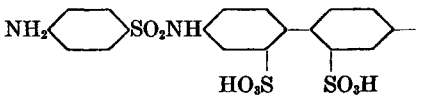
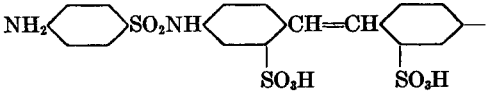
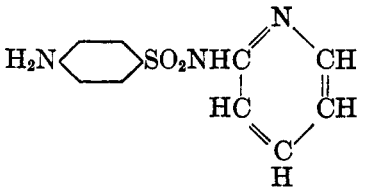
3-[4′-$(NH_2)C_6H_4SO_2NH$]C_6H_4—	H	±	(35, 83)
4-[4′-$(NH_2)C_6H_4SO_2NH$]C_6H_4—	H	++	(35, 76, 83)
3,5-[4′-$(NH_2)C_6H_4SO_2NH]_2C_6H_3$—	H	0	(42)
4-[4′-$(NH_2)C_6H_4SO_2NH$]-2,5-$(CH_3O)_2C_6H_2$—	H		(83)
4-[4′-$(NH_2)C_6H_4SO_2NH$]-2-CH_3-5-$(CH_3O)C_6H_2$—	H		(83)
4-[4′-$(NH_2)C_6H_4SO_2NH$]-1-$C_{10}H_6$—	H		(83)
5-[4′-$(NH_2)C_6H_4SO_2NH$]-1-$C_{10}H_6$—	H		(83)
8-[4′-$(NH_2)C_6H_4SO_2NH$]-1-$C_{10}H_6$—	H		(83)
6-[4′-$(NH_2)C_6H_4SO_2NH$]-2-$C_{10}H_6$—	H		(83)
	H		(83)
	H		(83)
	H		(83)
	H		(83)
	H	±	(19)
2-[4′-$(NH_2)C_6H_4SO_2NH$]-5-$(NaO_3S)C_6H_3$—	H	±	(35)
3-[4′-$(NH_2)C_6H_4SO_2NH$]-4-$(NaO_3S)C_6H_3$—	H	+++, 0	(35, 54)
5-[4′-$(NH_2)C_6H_4SO_2NH$]-2-NaO_3S-4-$(CH_3)C_6H_2$—	H	0	(35)
4-[4′-$(NH_2)C_6H_4SO_2NH$]-2-$(HO_3S)C_6H_3$—	H	+++, 0	(35, 54)

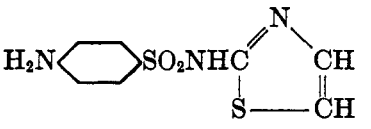
TABLE 7—*Concluded*

R^1	$R^{1'}$	ACTIVITY	REFERENCES
	H	0	(35)
	H	0	(35)
$4\text{-}(NH_2)C_6H_4SO_2NHCH_2CH_2—$	H	0	(40)
$4\text{-}(NH_2)C_6H_4SO_2NHCH_2CH_2—$	$HOCH_2CH_2—$		(40)
$4\text{-}(NH_2)C_6H_4SO_2NHCH_2CH_2—$	$4\text{-}(NH_2)C_6H_4SO_2NHCH_2CH_2—$	0	(40)
$4\text{-}(NH_2)C_6H_4SO_2NHCH_2CHOHCH_2—$	H	±, −	(40, 179)
$2,6\text{-}(HO_3S)_2\text{-}4\text{-}(NH_2)C_6H_2—$	H		(91)
$4\text{-}[4'\text{-}(NH_2)C_6H_4SO_2]C_6H_4—$	H	±	(54, 161)
$4\text{-}[4'\text{-}(4''\text{-}(NH_2)C_6H_4SO_2NH)C_6H_4O]C_6H_4—$	H		(83)
$4\text{-}[4'\text{-}(4''\text{-}(NH_2)C_6H_4SO_2NH)C_6H_4S]C_6H_4—$	H		(83)
$4\text{-}[4'\text{-}(4''\text{-}(NH_2)C_6H_4SO_2NH)C_6H_4SO_2]C_6H_4—$	H		(62, 83)
$4\text{-}[4'\text{-}(4''\text{-}(NH_2)C_6H_4SO_2NH)C_6H_4NH]C_6H_4—$	H		(83)
$4\text{-}[[4\text{-}(4'\text{-}(NH_2)C_6H_4SO_2NH)C_6H_4]_2C(OH)]C_6H_4—$	H	0	(42, 54)

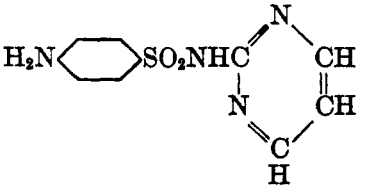
compounds are all isosteric, as may be seen by an inspection of their structural formulas.



Sulfapyridine



Sulfathiazole



Sulfadiazine

The number of compounds so far disclosed is remarkable in view of the difficulties in synthesis, both of the amino heterocycles and of their sulfanilyl derivatives. For convenience, these compounds are further subdivided on the basis of the number of nitrogen, oxygen, or sulfur atoms in the heterocyclic system.

(1) N^1-Heterocyclicsulfanilamides: one oxygen or one sulfur atom in the heterocyclic system (see table 8)

Only two N^1-heterocyclic derivatives containing one oxygen atom in the heterocyclic system have been disclosed, and both are inactive. In these derivatives of mono- and di-furfurylamine the amido group is not attached to the ring but to a side chain, so that these derivatives are not isosteric with sulfapyridine.

(2) N^1-Heterocyclicsulfanilamides: one nitrogen atom in the heterocyclic system

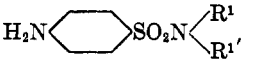
A great many substituted 2- and 3-sulfanilamidopyridines have been made, but of the 4-sulfanilamidopyridines only the parent compound has so far been disclosed (see tables 9, 10, 11). Difficulties in the synthesis of 4-substituted pyridines is the obvious reason.

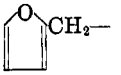
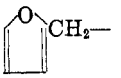
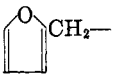
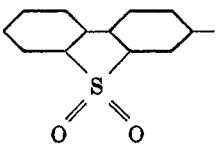
There was no significant difference in activity between 2- and 3-sulfanilamidopyridine on either streptococci or pneumococci (160). Remarkable differences developed in the study of their substitution products, however. In 2-sulfanilamidopyridine, substitution of halogen in the 5-position de-

stroyed the activity, while nitro or amino groups in the 5-position gave slightly enhanced activity against streptococci and slightly less activity against pneumococci. When the positions of the groups were reversed, i.e., substituents introduced in the 2-position in 5-sulfanilamidopyridine, the halogen derivatives were now active and the nitro and amino derivatives inactive! Blood level studies showed no significant differences between active and inactive compounds, so that the difference in activity must be explained by some inherent difference in the compounds themselves.

TABLE 8

N^1-Heterocyclicsulfanilamides: one oxygen or one sulfur atom in the heterocyclic system



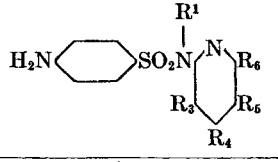
R^1	$R^{1'}$	ACTIVITY	REFERENCES
	H	0	(42, 54)
		0	(40)
$4\text{-}(NH_2)C_6H_4SO_2NH—$			(83)

Theories of the mechanism of the action of sulfanilamide derivatives might well be tested against such pairs of compounds. It is difficult to understand in terms of a postulated *in vivo* oxidation of the amino group to hydroxylamine as the active form, the profound influence of isomerism in an N^1-substituent. One fears that the architecture of new chemotherapeutic agents will continue to be an empirical science for some time to come!

In the sulfanilamidoquinoline series (see tables 12 and 13), few activities have been disclosed. However, there seems to be a marked drop in activity and increase in toxicity as compared with the corresponding sulfanilamidopyridines (54). The corresponding isoquinoline derivative, though inactive, was less toxic.

TABLE 9

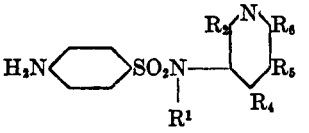
2-Sulfanilamidopyridines



R_1	R_2	R_4	R_5	R_6	ACTIVITY	REFERENCES
					+++, ++	(39, 68, 102, 132, 159, 160, 183, 187, 190)
Na—					+++	(129, 159)
CH_3—						(132)
$C_6H_5CH_2$—						(132)
			Br—		0	(160)
			I—		0	(132, 160)
			NO_2—		+++	(160)
				CH_3—		(132, 183)
	C_2H_5O—				+	(160)
	HOOC—					(132)
			HO_3S—			(132)
			NH_2—		+++	(160)
				NH_2—	+++	(59, 183)
			4-$(NH_2)C_6H_4SO_2NH$—		+	(160)
				4-$(NH_2)C_6H_4SO_2NH$—		(132)

TABLE 10

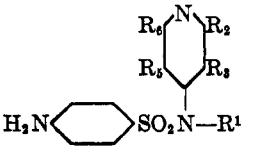
3-Sulfanilamidopyridines



R^1	R_2	R_4	R_5	R_6	ACTIVITY	REFERENCES
					+++	(54, 160, 190)
				Cl—	+++	(160)
				Br—	+++	(160)
				HO—	0	(160)
				C_2H_5O—	+	(160)
				NH_2—	0	(160, 190)

TABLE 11

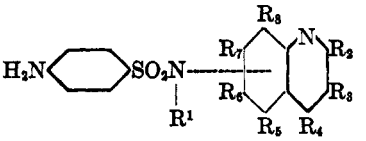
4-Sulfanilamidopyridines



R^1	R_2	R_3	R_5	R_6	ACTIVITY	REFERENCES
						(132, 102)

TABLE 12

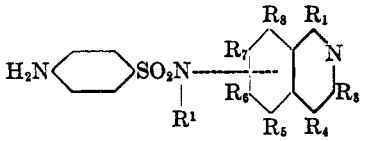
x-Sulfanilamidoquinolines



R^1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	ACTIV-ITY	REFERENCES
	x							±	(42, 54, 132, 183)
		x							(190)
				x					(14, 190)
					x				(14, 132, 190)
						x			(14)
							x	+	(14, 29, 190)
	CH_3—				x				(132)
	C_6H_5—		x						(8)
				x			CH_3O—		(132)
					CH_3O—			+	(29, 45)
	HO—		CH_3—				x		(132)
	C_6H_5—		x		CH_3O—				(8)

TABLE 13

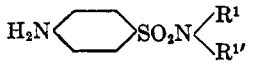
x-Sulfanilamidoisoquinolines

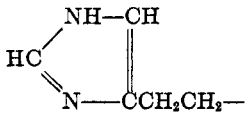
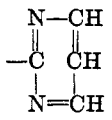
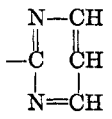
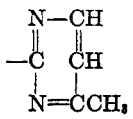
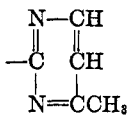
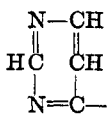
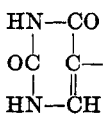
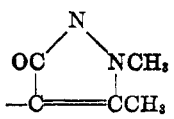


R^1	R_1	R_2	R_4	R_5	R_6	R_7	R_8	ACTIVITY	REFERENCES
	x							0	(42, 54, 132)

TABLE 14

N^1-Heterocyclicsulfanilamides: two or more nitrogen atoms in the heterocyclic system



R^1	$R^{1'}$	ACTIVITY	REFERENCES
	H	0	(42, 54)
	H	+++	(159)
	Na—	+++	(159)
	H	+++	(159)
	Na—	+++	(159)
	H	0	(159)
	H	0	(159)
	H	0	(159)

(3) N^1-Heterocyclicsulfanilamides: two or more nitrogen atoms in the heterocyclic system (see table 14)

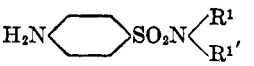
2-Sulfanilamidopyrimidine ("sulfadiazine") (159) has shown several important advantages over sulfapyridine in preliminary studies. It is very readily absorbed, so that adequate blood levels can be maintained at lower dosage levels. Since 2-(N^4-acetylsulfanilamido)pyrimidine is slightly more soluble than 2-sulfanilamidopyrimidine, danger of kidney damage should be less than for sulfapyridine and sulfathiazole, where the reverse solubility relationship holds. Another favorable point is that in 10 per cent aqueous solution the pH of the sodium salt is 9.6 to 9.7, as against pH values of approximately 10 for sodium sulfathiazole and 11 for sodium sulfapyridine.

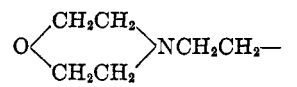
2-Sulfanilamido-4-methylpyrimidine, "sulfamethyldiazine," appears equal to the parent compound in activity on both pneumococci and streptococci. 4-Sulfanilamidopyrimidine is apparently completely inactive, as is 5-sulfanilamidouracil.

While not listed, it might be noted that 5-(*p*-nitrobenzenesulfonyl)tetrazole was synthesized, but could not be reduced to the corresponding 5-sulfanilamidotetrazole without rupture of the tetrazole ring, giving rise to sulfanilylguanidine (159). The nitro group was apparently reduced in the body, since a diazotizable amine could be measured in the blood. The compound was inactive, while the guanidine derivative, which gave more rapid absorption and elimination, showed slight activity. This suggested that the tetrazole ring was not broken down *in vivo* (159).

(4) N^1-Heterocyclicsulfanilamides: one nitrogen atom and one oxygen (or sulfur) atom in the heterocyclic system

Only one derivative of the type containing one nitrogen atom and one sulfur atom in the heterocyclic system has been disclosed and it was found to be inactive; however, the point of attachment was on a side chain rather than to the ring.

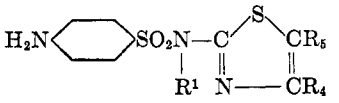


R^1	$R^{1'}$	ACTIVITY	REFERENCE
	H	0	(40)

The sulfanilamidothiazoles have been well explored chemically (see tables 15 and 16). 2-Sulfanilamidothiazole ("sulfathiazole") and 2-sulfanilamido-4-methylthiazole ("sulfamethylthiazole") are very active

TABLE 15

2-Sulfanilamidothiazoles

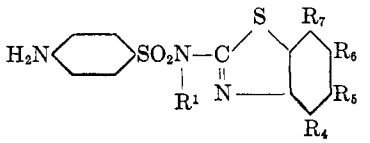


R^1	R_4	R_5	ACTIVITY	REFERENCES
		*	++	(6, 33, 59, 121, 124, 127, 133, 159, 174, 185)
Na—			++	(124, 185)
C_2H_5—				(133)
	CH_3—	†	++	(6, 33, 59, 124, 127, 133, 159, 174, 183)
CH_3—	CH_3—		±	(133, 174)
$C_6H_5CH_2$—	CH_3—			(133)
		CH_3—		(133)
C_2H_5—		CH_3—		(133)
	C_2H_5—			(124)
		C_2H_5—		(133)
	C_6H_5—	‡	+	(6, 133, 174)
	4-(C_6H_5)C_6H_4—		0	(159)
	CH_3—	CH_3—		(133)
	CH_3—	C_6H_5—		(133)
	CH_3—	$HOCH_2CH_2$—		(133)
	CH_3—	HOOC—		(133)
	CH_3—	C_2H_5OOC—	±	(133, 174)

* Sulfathiazole. † Sulfamethylthiazole. ‡ Sulfaphenylthiazole.

TABLE 16

2-Sulfanilamidobenzothiazoles

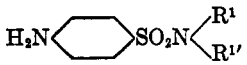


R^1	R_4	R_5	R_6	R_7	ACTIVITY	REFERENCES
					0	(133, 159)
C_2H_5—						(133)
			NO_2—			(133)
			CH_3—			(133)
			C_2H_5O—			(133)
		NH_2—				(133)
		CH_3CONH—				(133)

against both streptococci and pneumococci, and in addition are effective against staphylococci. Sulfathiazole is more regularly absorbed than sulfapyridine and has had wide clinical study against pneumonia and staphylococcal septicemias, with generally favorable results. Sulfamethyl-

TABLE 17

N^1-Heterocyclicsulfanilamides: miscellaneous derivatives



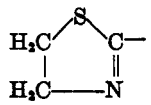
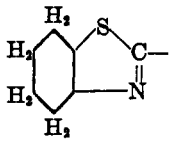
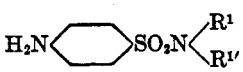
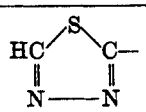
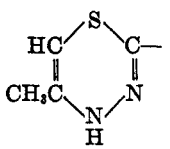
R^1	$R^{1'}$	ACTIVITY	REFERENCES
	H	+	(174)
	H	±	(60, 174)

TABLE 18

N^1-Heterocyclicsulfanilamides: two nitrogen atoms and one sulfur atom in the heterocyclic system



R^1	$R^{1'}$	ACTIVITY	REFERENCES
	H	±	(159)
	H	+	(60)

thiazole was withdrawn from clinical study because about 2 per cent of the patients treated with it developed peripheral neuritis of more or less serious character. Sulfathiazole has not shown this disadvantage, although kidney damage is possible and must be carefully watched for by the clinicians.

Some miscellaneous heterocyclic derivatives containing one nitrogen atom and one sulfur atom in the heterocyclic system are given in table 17.

(5) N^1-Heterocyclicsulfanilamides: two nitrogen atoms and one oxygen (or sulfur) atom in the heterocyclic system (see table 18)

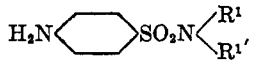
2-Sulfanilamidothiodiazole, while practically inactive against streptococci, was active against pneumococci (159). This is the reverse of usual findings.

(6) N^1-Heterocyclicsulfanilamides: N^1-nitrogen in the heterocyclic system

Not many derivatives have been made of this type, and they appear to be of low activity (see table 19).

(E) Acyl substituents

This series of derivatives has been well explored chemically, with the exception of derivatives of carbonic acid, of which only the guanidine derivative has been described, and it was only slightly active.



R^1	$R^{1'}$	ACTIVITY	REFERENCE
	H	±	(159)

The series of straight-chain acyclic-acyl derivatives is almost complete to eighteen carbon atoms (see table 20). The first member, N^1-acetylsulfanilamide, while only moderately active against streptococci, has been widely sold outside of this country under the name "Albucid" for use in the treatment of gonorrhea. Claims are made that high dosage can be maintained without as much danger of toxic reactions as accompanies the use of sulfanilamide, sulfapyridine, and Uleron.

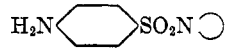
According to Henderson (75), 39 per cent of N^1-acetylsulfanilamide is hydrolyzed in the human body to sulfanilamide and part of this is converted to N^4-acetylsulfanilamide. Examination of the urine shows that of the total urinary sulfanilamides, 61 per cent is unchanged N^1-acetylsulfanilamide, 28.8 per cent N^4-acetylsulfanilamide, and 10.2 per cent sulfanilamide.

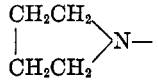
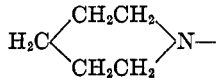
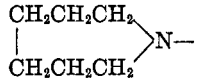
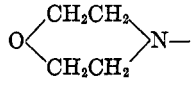
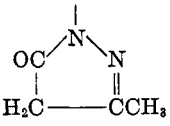
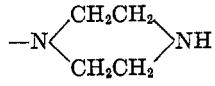
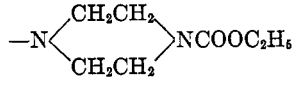
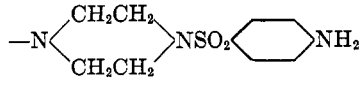
The higher members of the straight-chain series apparently go through peak activity in N^1-butyrylsulfanilamide and N^1-dodecanoylsulfanilamide (55). To obtain adequate absorption of the long-chain compounds, it was found necessary to administer them with oils or fats. Sulfanilamide itself

is also better absorbed when given with oils. When N^1-butyrylsulfanilamide and N^1-dodecanoylsulfanilamide are administered with oil and compared with sulfanilamide in oil for antistreptococcic effect, they are about

TABLE 19

N^1-Heterocyclicsulfanilamides: N^1-nitrogen in the heterocyclic system



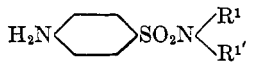
—N◯	ACTIVITY	REFERENCES
		(88)
	±	(68, 70, 86, 87, 88)
	0	(179)
	±	(2, 42, 121)
	+	(159)
	0	(33, 98, 127)
		(98)
		(98)

equal on an equal weight dosage, but definitely superior on an equimolecular dosage. This is of interest, since blood studies indicate that these compounds are largely hydrolyzed to sulfanilamide during some stage of absorption. However, no breakdown could be detected in the intestine.

The marked drop in activity between the straight-chain and branched-chain derivatives, e.g., N^1-butyrylsulfanilamide and N^1-isobutyrylsulfanilamide, is curious if activities can be explained on the basis of hydrolysis to sulfanilamide. More work is evidently needed to settle such questions.

TABLE 20

N^1-Acyclic-acylsulfanilamides



R^1	$R^{1'}$	ACTIVITY	REFERENCES
CH_3CO—	H*	+	(38, 47, 55)
CH_3CO—	Na—		(38)
CH_3CO—	NH_4—		(38)
CH_3CO—	—$NH_2(C_2H_5)_2$		(38)
CH_3CH_2CO—	H	++	(38, 55)
$CH_3(CH_2)_2CO$—	H	+++	(38, 55)
$(CH_3)_2CHCO$—	H	±	(38, 54)
$CH_3(CH_2)_3CO$—	H	++	(42, 55)
$(CH_3)_2CHCH_2CO$—	H	±	(38, 54)
$(C_2H_5)_2CHCO$—	H		(38)
$CH_3(CH_2)_4CO$—	H	+	(38, 55)
$CH_3(CH_2)_5CO$—	H	+	(38, 55)
$CH_3(CH_2)_3CH(C_2H_5)CO$—	H		(38)
$CH_3(CH_2)_6CO$—	H	++	(38, 55)
$CH_3(CH_2)_8CO$—	H	++	(38, 55)
$CH_3(CH_2)_9CO$—	H	++	(38, 55)
$CH_3(CH_2)_{10}CO$—	H	+++	(38, 55)
$CH_3(CH_2)_{10}CO$—	Ag—		(38)
$CH_3(CH_2)_{10}CO$—	$\frac{1}{2}$Hg—		(38)
$CH_3(CH_2)_{10}CO$—	$\frac{1}{2}$Ca—		(38)
$CH_3(CH_2)_{10}CO$—	CH_3—		(38)
$CH_3(CH_2)_{12}CO$—	H	++	(38, 55)
$CH_3(CH_2)_{14}CO$—	H	+	(42, 54)
$CH_3(CH_2)_{16}CO$—	H	+	(38, 55)
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$—	H		(38)

* Albucid.

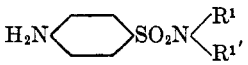
The reported activity of N^1-dodecanoylsulfanilamide (38) against experimental tuberculosis in guinea pigs has not been substantiated by clinical studies.

The N^1-aracylsulfanilamides (see table 21) again show surprising differences in activities.

In the N^1-heterocyclic-acylsulfanilamides (table 22), it is remarkable that N^1-nicotinylsulfanilamide is inactive (54), while N^4-nicotinylsulfanilamide (see III, E (4)) is said to be highly active (43).

TABLE 21

*N*¹-*Isocyclic-acylsulfanilamides*



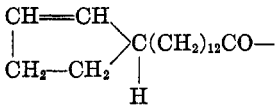
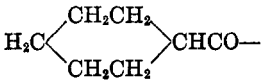
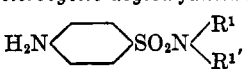
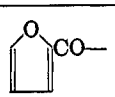
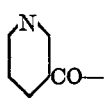
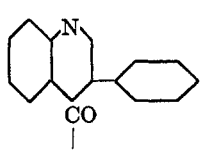
R¹	R¹′	ACTIVITY	REFERENCES
	H	++	(38)
	H	++	(38)
C_6H_5CO—	H		(38, 54)
$C_6H_5CH_2CH_2CO$—	H	++	(38, 54)
C_6H_5CH=$CHCO$—	H	++	(38, 54)
C_6H_5CH=$CHCO$—	Na—	++	(38, 54)
$(C_6H_5)_2CHCO$—	H	±	(38, 54)
4-$(NO_2)C_6H_4CO$—	H	0	(38, 54)
$C_6H_5CH(OH)CO$—	H	0	(38, 54)
2-$(HO)C_6H_4CO$—	H	++	(127)
3-HO-2-$C_{10}H_6CO$—	H		(38)
4-$(HOOC)C_6H_4CO$—	H		(38, 54)
4-$(NH_2)C_6H_4CO$—	H		(38)
4-$(NH_2)C_6H_4SO_2NHCO(CH_2)_8CO$—	H		(38)

TABLE 22

*N*¹-*Heterocyclic-acylsulfanilamides*



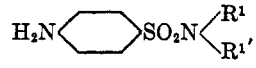
R¹	R¹′	ACTIVITY	REFERENCES
	H	0	(38)
	H	0	(38, 54)
	H	0	(38, 54)

(F) N^1-Sulfonyl substituents

The N^1-acyclicsulfonylsulfanilamides (table 23) appear to be completely inactive, as are the N^1-cycloalkanesulfonylsulfanilamides. Wide discrepancies are shown for activities of disulfanilamide (not to be confused with N^4-sulfanilylsulfanilamide, which was first misnamed disulfanilamide) and its N^1-alkyl derivatives. Free disulfanilamide appears not to be absorbed when given *per os* and first results were reported for parenteral administration. Sodium disulfanilamide, on the other hand, is rapidly absorbed and eliminated. The early reports of effectiveness by Climenko (36) have not been confirmed by Feinstone, using a more vigorous test which tends to favor compounds giving sustained blood levels (54).

TABLE 23

N^1-Alkanesulfonylsulfanilamides



R^1	$R^{1'}$	ACTIVITY	REFERENCES
$CH_3CH_2SO_2$—	H	0	(41)
$CH_3(CH_2)_3SO_2$—	H	0, ±	(41, 174)
$CH_3(CH_2)_3SO_2$—	Na—	0	(42)
$CH_3(CH_2)_4SO_2$—	H	0, ±	(41, 174)
$CH_3(CH_2)_4SO_2$—	Na—	0	(42)
$CH_3(CH_2)_3CH(C_2H_5)CH_2SO_2$—	H		(41)
$CH_3(CH_2)_{11}SO_2$—	H	0	(41)

The reported moderate effectiveness of sodium disulfanilamide in experimental influenza virus infections (36) was not duplicated with sufficient regularity to be significant.

The N^1-isocyclic-sulfonyl derivatives are listed in table 24. No N^1-heterocyclic-sulfonylsulfanilamides have been prepared.

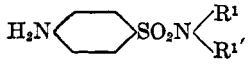
III. N^4-SUBSTITUTED SULFANILAMIDES

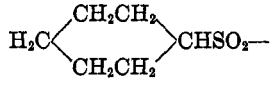
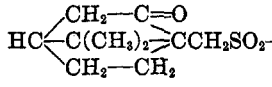
Unless the substituting group in the N^4-position is hydrolyzed, reduced, or otherwise removed *in vivo*, it appears that the derivative will have little, if any, activity. That such processes do occur has been amply demonstrated by the finding of a diazotizable amine in the blood after feeding 4-nitro-, hydroxylamino-, azo-, N^4-acyl-, anil and reduced anil, aldehyde-bisulfite, and aldehyde-sulfoxalate sulfanilamides, and by the isolation of sulfanilamide from the urine of animals so treated. It has not been proved that the activities of these compounds are entirely the

result of cleavage with liberation of sulfanilamide, but there is much which points to such a mechanism. It is quite possible that the superior proper-

TABLE 24

N^1-isocyclic-sulfonylsulfanilamides



R^1	$R^{1'}$	ACTIVITY	REFERENCES
	H	0	(41, 54)
4-$(NO_2)C_6H_4SO_2$—	H		(42)
$C_6H_5CH_2SO_2$—	H	±	(41, 174)
4-$(NO_2)C_6H_4CH_2SO_2$—	H		(42)
4-$(HO)C_6H_4SO_2$	H	±	(42)
	H	0	(41, 54)
4-$(NH_2)C_6H_4SO_2$—	H	+++, +, 0	(22, 36, 54)
4-$(NH_2)C_6H_4SO_2$—	Li—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	Na—	+++, 0	(22, 36, 54)
4-$(NH_2)C_6H_4SO_2$—	½Mg—	++	(22, 36)
4-$(NH_2)C_6H_4SO_2$—	½Ca—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	½Ba—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	½Cu—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	½Ni—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	Ag—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	½Pb—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	½Hg—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	½Zn—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	NH_4—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	$(C_2H_5)_2NH_2$—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	$C_5H_{11}NH_3$—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	$(HOCH_2CH_2)_3NH$—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	CH_3—	+++, 0	(22, 36, 54)
4-$(NH_2)C_6H_4SO_2$—	C_2H_5—	+++, 0	(22, 36, 54)
4-$(NH_2)C_6H_4SO_2$—	$C_{12}H_{23}$—	0	(42, 54)
4-$(NH_2)C_6H_4CH_2SO_2$—	H		(42)

ties claimed for certain derivatives of this type are a result of slow cleavage with prolonged maintenance of therapeutic blood levels of sulfanilamide, or whatever active form may be derived *in vivo* from sulfanilamide.

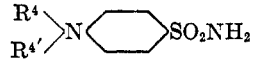
(*A*) *Inorganic substituents*

4-Hydroxylaminobenzenesulfonamide (N^4-hydroxysulfanilamide) (see table 25) was prepared by Mayer and Oechslin (134), who stated that it was one hundred times as active *in vitro* as sulfanilamide and suggested that the activity of sulfanilamide might be the result of an *in vivo* oxidation to the hydroxylamine.

Bratton, White, and Marshall (16) have more fully described the preparation and properties of the compound, and state that it is not more than ten times as active *in vitro*. When injected into dogs, it appeared to be completely converted to sulfanilamide within 5 min.

TABLE 25

Sulfanilamides containing inorganic substituents in the N^4-position



R^4	$R^{4'}$	ACTIVITY	REFERENCES
HO—	H	++, +	(16, 134, 162)
NH_2—	H	0	(20, 134)
H_2O_2P—	H	±	(179)

Much current research on the mechanism of the action of sulfanilamide has centered on this compound. The subject is highly controversial and the author does not feel qualified to review the work critically.

(*B*) *Acyclic substituents*

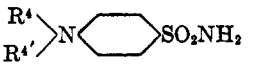
With the exception of the N^4-formaldehyde-bisulfite, N^4-formaldehyde-sulfoxalate, and N^4-glucose-bisulfite derivatives, all of which are probably hydrolyzed to sulfanilamide *in vivo*, these derivatives have little or no activity (see table 26).

(*C*) *Isocyclic substituents*

The only true N^4-arylsulfanilamides were reported without pharmacological data. Most of the other derivatives (see table 27) have been obtained by the reduction of the corresponding anils. With the exception of N^4-(4′-nitrobenzyl)sulfanilamide, these are of relatively low activity and apparently owe their activity to cleavage to sulfanilamide *in vivo* (144). The high activity reported for the 4′-nitrobenzyl derivative is difficult to explain on this basis. Possibly it gives a double action on cleavage, since Rosenthal (197) has reported activity for *p*-nitrotoluene and *p*-nitrobenzoic acid. Further investigations of the products present in the blood stream may shed light on this anomaly and will be awaited with interest.

TABLE 26

N^4-Acyclicsulfanilamides



R^4	$R^{4'}$	ACTIVITY	REFERENCES
CH_3—	H	+	(120)
C_6H_{11}—	H	±	(32)
$HOCH_2CH_2$—	H	±, −	(155, 179)
$HOCH_2(CHOH)_4CH_2$—	H		(52)
$HOOCCH_2$—	H	±	(27, 52, 57, 89, 95, 96, 155, 181)
$HOOCCH_2$—	ON—	±	(57)
NH_2OCCH_2—	H	±	(89, 181, 184)
$C_2H_5OOCCH_2$—	H		(89)
$HOOCCH_2CH_2$—	H	+	(155)
$HOOC(CH_3)CH$—	H		(52)
$HOOCCH_2(HOOC)CH$—	H		(52)
NaO_2SCH_2—	H	++, +	(10, 57, 89, 96, 121, 163)
NaO_3SCH_2—	H	++	(57, 67, 96, 173)
$HOCH_2(CHOH)_4CHSO_3Na$	H	+++	(178)

TABLE 27

N^4-Isocyclicsulfanilamides

R^4	$R^{4'}$	ACTIVITY	REFERENCES
C_6H_5—	H		(90)
$C_6H_5CH_2$—	H*	+	(67, 70, 72, 135, 163, 172, 188)
$4\text{-}(NO_2)C_6H_4CH_2$—	H	+++	(77, 135, 162, 178)
$C_6H_5(CH_2)_3$—	H		(90)
$2\text{-}(HO)C_6H_4CH_2$—	H	±	(67, 90)
$4\text{-}(HO)C_6H_4CH_2$—	H	±	(67, 90)
$2,4\text{-}(HO)_2C_6H_3CH_2$—	H	±	(67)
$2,4,6\text{-}(HO)_3C_6H_2CH_2$—	H	±	(67)
$3\text{-}Cl\text{-}4\text{-}(HOOC)C_6H_3$—	H		(7)
$3\text{-}(NaO_3S)C_6H_4CH_2$—	H		(172)
$C_6H_5(NaO_3S)CH$—	H		(173)
$C_6H_5CH_2(NaO_3S)CH$—	H		(173)
$C_6H_5CH(SO_3Na)CH_2(NaO_3S)CH$—	H†	+	(173, 188)
$4\text{-}(NH_2)C_6H_4CH_2$—	H		(77)
$4\text{-}[(CH_3)_2NH]C_6H_4CH_2$—	H		(77)
C_6H_5NH—	H		(91)
$4\text{-}(NH_2SO_2)C_6H_4NH$—	H	0	(134)

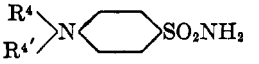
* Septazine. † Soluseptazine.

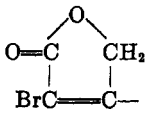
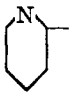
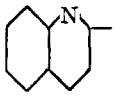
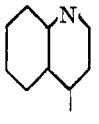
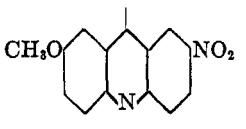
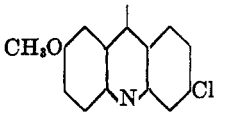
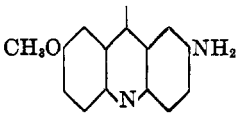
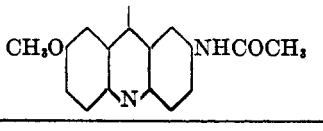
(D) Heterocyclic substituents (see tables 28 and 29)

These compounds appear to be inactive (with the exception of N^4-α-bromotetronylsulfanilamide, which behaves as an N^4-acylsulfanilamide and is probably cleaved *in vivo*). This supports the hypothesis of the

TABLE 28

N^4-Heterocyclicsulfanilamides: N^4-nitrogen not in the heterocyclic system

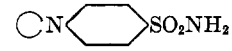


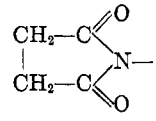
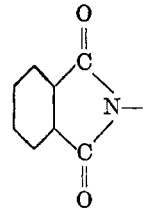
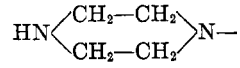
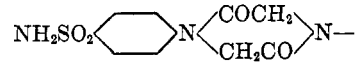
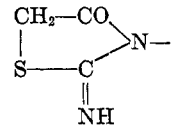
R^4	$R^{4'}$	ACTIVITY	REFERENCES
	H	++	(105)
	H	0	(69)
	H	0	(14, 69)
	H		(8, 14)
	H		(49)
	H		(182)
	H		(49)
	H		(49)

necessity of a potentially free amino group in sulfanilamide derivatives, since the probability of cleavage at such a linkage is remote. The acridine derivatives were synthesized for probable use against malaria, but with what success is not known.

TABLE 29

N^4-Heterocyclicsulfanilamides: N^4-nitrogen in the heterocyclic system



	ACTIVITY	REFERENCES
		(143)
		(60)
		(99)
	0	(1)
	0	(1)

(*E*) *Acyl substituents*

(1) N^4 substituents derived from carbonic acid

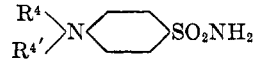
The sulfanilamides containing, in the N^4-position, groups derived from carbonic acid (see table 30) do not appear to be active, with the exception of the guanidine derivative (19), which is said to be equal to sulfanilamide in activity and toxicity. It has not been disclosed whether this compound is cleaved to sulfanilamide on absorption, but it is of interest that it should be active while the corresponding urea derivative is inactive.

(2) N^4-Acyclic-acylsulfanilamides (see table 31)

N^4-Acetylsulfanilamide is the conjugated form of sulfanilamide produced *in vivo* by the administration of sulfanilamide. It has little or no activity. Ockerblad and Carlson (197) have shown that a small amount of sulfanilamide is present in the blood of dogs fed N^4-acetylsulfanilamide, thus indicating that conjugation is a reversible process. Some of the higher straight-chain acyl derivatives show appreciable activity. The activity passes through a maximum for N^4-valeryl- and N^4-caproyl-sulfanilamides (143). This activity is probably the result of hydrolysis to sulfanilamide. As in the N^1-acyl series, the corresponding branched chain

TABLE 30

Sulfanilamides containing N^4 substituents derived from carbonic acid



R^4	$R^{4'}$	ACTIVITY	REFERENCES
C_2H_5OCO—	H	+	(2, 61, 90, 181)
$C_{12}H_{25}OCO$—	H		(123)
$(CH_3)_3N(Cl)CH_2CH_2OCO$—	H		(3)
NH_2CO—	H	0	(34, 90, 100, 112)
$CH_3CONHCO$—	H	0	(34)
4-$(NH_2SO_2)C_6H_4NHCO$—	H	±	(61, 79, 181, 186)
$NH_2C(=NH)$—	H	++	(19)
$NH_2C(=S)$—	H	−	(179)
$CH_2=CHCH_2NHC(=S)$—	H		(65)
4-$(NH_2SO_2)C_6H_4NHC(=S)$—	H		(186)

N^4-acylsulfanilamides are inactive or nearly so. This is remarkable and needs study.

(3) N^4-Isocyclic-acylsulfanilamides (see table 32)

Aside from three inactive derivatives, nothing on the activities of the members of this series has been published. The lack of activity would suggest that experimental animals are unable to hydrolyze aracylamine linkages.

(4) N^4-Heterocyclic-acylsulfanilamides (see table 33)

Three of these derivatives, N^4-(5-pyrrolidone-2-carbonyl)sulfanilamide, N^4-nicotinylsulfanilamide, and the sodium salt of N^4-quinolinylsulfanilamide, are said to be at least as active as sulfanilamide. If the activity is the result of cleavage to sulfanilamide, it remains a mystery why N^4-nicotinylsulfanilamide is cleaved while the isosteric N^4-benzoylsulfanil-

TABLE 31

N^4-Acyclic-acylsulfanilamides

R^4	$R^{4'}$	ACTIVITY	REFERENCES
HCO—	H	+	(61, 181)
CH_3CO—	H	±	(20, 61, 181)
CH_3CO—	HO—	0	(16, 162)
CH_3CO—	CH_3—	±	(76, 181)
CH_3CH_2CO—	H	+	(2, 143)
$CH_3(CH_2)_2CO$—	H	+, ±	(2, 143)
$(CH_3)_2CHCO$—	H	±	(2, 84, 132)
$CH_3(CH_2)_3CO$—	H	++, +	(2, 84, 121, 143)
$(CH_3)_2CHCH_2CO$—	H	±	(84, 143)
$CH_3(CH_2)_4CO$—	H	++	(84, 102, 143)
$(CH_3)_2CHCH_2CH_2CO$—	H	0	(84, 143)
$CH_3(CH_2)_5CO$—	H	±	(84, 143)
$CH_3(CH_2)_6CO$—	H	±	(84, 143)
$CH_3(CH_2)_8CO$—	H		(84)
$CH_3(CH_2)_{10}CO$—	H	0	(84, 143)
$CH_3(CH_2)_{12}CO$—	H		(84)
$CH_3(CH_2)_{14}CO$—	H		(84)
$CH_3(CH_2)_{16}CO$—	H		(84)
$CH_3(CH_2)_{20}CO$—	H		(84)
$CH_3CH{=}CH(CH_2)_7CO$—	H		(84)
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$—	H		(84)
cis-$CH_3(CH_2)_7CH{=}CH(CH_2)_{11}CO$—	H		(84)
$ClCH_2CO$—	H		(90, 94, 154)
$ClCH_2CH_2CO$—	H		(90)
$(C_2H_5)_2C(Br)CO$—	H		(90)
$HOCH_2CO$—	H	0	(90, 121, 123)
CH_3COOCH_2CO—	H	0	(121)
$CH_3CHOHCO$—	H	0, +	(1, 90, 121)
$CH_3(CH_3COO)CHCO$—	H	0	(1)
CH_3OCH_2CO—	H		(90)
CH_3OCH_2CO—	C_6H_5—		(90)
$C_2H_5OCH_2CO$—	H		(90)
$C_4H_9OCH_2CO$—	H		(90)
CH_3COCH_2CO—	H		(90)
$HOOC(CH_2)_2CO$—	H		(24, 111, 143, 153, 165)
$NaOOC(CH_2)_2CO$—	H	0	(121)
$NH_2OC(CH_2)_2CO$—	H	0	(1)
HOOCCH=CHCO—	H		(143)
NaOOCCH=CHCO—	H	0	(121)
NaO_3SCH_2CO—	H	0	(161, 178)
NH_2CH_2CO—	H		(90, 134, 154)
$C_2H_5NHCH_2CO$—	H		(90)
$C_3H_7NHCH_2CO$—	H		(90)
$C_4H_9NHCH_2CO$—	H		(90)
$(C_2H_5)_2NCH_2CO$—	H		(90)
$CH_2{=}CHCH_2NHCH_2CO$—	H		(90)
$C_4H_9NHCH_2CH_2CO$—	H		(90)
$C_4H_9NHC(C_2H_5)_2CO$—	H		(90)

amide, N^4-furoylsulfanilamide, and N^4-thenoylsulfanilamides are not cleaved, but perhaps the latter three owe their lack of activity to lack of absorption.

(F) Sulfonyl substituents (see tables 34, 35, and 36)

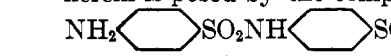
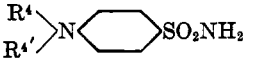
An interesting problem in indexing compounds by the method used herein is posed by the compound designated as N^4-sulfanilylsulfanilamide,  , and its N^1 derivatives. On the basis of activity, the parent compound should probably be called N^1-(4-sulfamylphenyl)sulfanilamide, since it is behaving like an N^1-substituted rather than as an N^4-substituted sulfanilamide. However, the nomenclature is so confused on this compound now that it would be inadvisable to complicate the situation further.

TABLE 32

N^4-Isocyclic-acylsulfanilamides



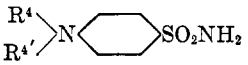
R^4	$R^{4'}$	ACTIVITY	REFERENCES
C_6H_5CO—	H	0	(143)
3-$(NO_2)C_6H_4CO$—	H		(90)
4-$(NO_2)C_6H_4CO$—	H	±	(162)
3,5-$(NO_2)_2C_6H_3CO$—	H		(90)
$C_6H_5CH_2CO$—	H		(84)
C_6H_5CH=$CHCO$—	H		(84)
$C_6H_5CHOHCO$—	H		(117)
$C_6H_5CH(OOCCH_3)CO$—	H		(117)
$C_6H_5OCH_2CH_2CO$—	H		(90)
2-$ClC_6H_4OCH_2CH_2CO$—	H		(90)
2-[$(CH_3)_2CH$]-5-$(CH_3)C_6H_3OCH_2CH_2CO$—	H		(90)
2-$(HOOC)C_6H_4CO$—	H		(165, 179)
2-$(NaOOC)C_6H_4CO$—	H	0	(121)
6-NO_2-2-$(HOOC)C_6H_3CO$—	H		(165)
4,6-$(NO_2)_2$-2-$(HOOC)C_6H_2CO$—	H		(165)
3-$(NH_2)C_6H_4CO$—	H		(90)
3,5-$(NH_2)_2C_6H_3CO$—	H		(90)
1-$(NH_2SO_2)C_6H_4$-4-$NHCOCH_2CO$—	H		(123)
1-$(NHSO_2)C_6H_4$-4-$NHCOC(C_2H_5)_2CO$—	H		(123)

In substantiation of the statement that this is really an N^1-substituted derivative, note that all the N^4-sulfonylsulfanilamides are inactive except where the group is N^4-sulfanilyl or N^4-metanilyl, and the latter has practically no activity, as have most derivatives of *metanilamide*. On the other hand, substituted N^1-phenylsulfanilamides frequently show activity.

Note also that N^3-sulfanilylmetanilamide (correctly classed as an N^1-substituted sulfanilamide; see II (C) (4)) has more activity than N^4-metanilylsulfanilamide. This was predicted before synthesis, since the first com-

TABLE 33

N^4-Heterocyclic-acylsulfanilamides



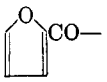
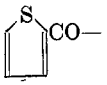
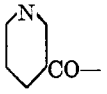
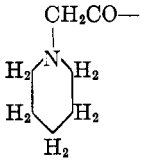
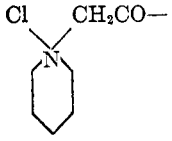
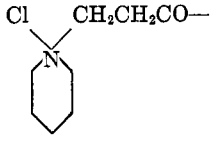
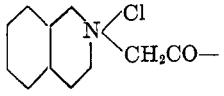
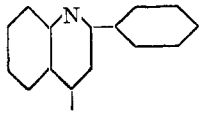
R^4	$R^{4'}$	ACTIVITY	REFERENCES
	H	±	(102)
	H	±	(102)
	H	+++	(43, 102, 157)
	H		(90)
	H		(90)
	H		(90)
	H		(90)
	H		(8)

TABLE 33—*Concluded*

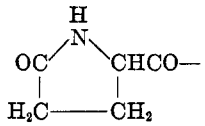
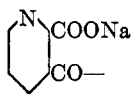
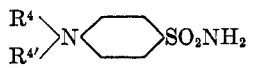
R^4	$R^{4'}$	ACTIVITY	REFERENCES
	H	+++	(70)
	H	++	(78, 165)

TABLE 34

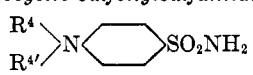
N^4-Acyclicsulfonylsulfanilamides



R^4	$R^{4'}$	ACTIVITY	REFERENCES
CH_3SO_2—	H	0, −	(174, 179)
$C_2H_5SO_2$—	H	0	(174)
$CH_3(CH_2)_3SO_2$—	H	0, −	(174, 179)
$CH_3(CH_2)_4SO_2$—	H	0	(174)
$CH_3(CH_2)_5SO_2$—	H	0	(174)
$CH_3(CH_2)_{11}SO_2$—	H	0	(174)

TABLE 35

N^4-Isocyclic-sulfonylsulfanilamides



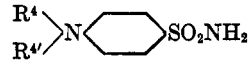
R^4	$R^{4'}$	ACTIVITY	REFERENCES
$C_6H_5SO_2$—	H	0	(174)
3-$(NO_2)C_6H_4SO_2$—	H		(90)
4-$(NO_2)C_6H_4SO_2$—	H		(90)
$C_6H_5OCH_2CH_2SO_2$—	H		(90)
2-CH_3O-5-$(CH_3)C_6H_3OCH_2CH_2CH_2SO_2$—	H		(90)
3,4-$(CH_3O)_2C_6H_3SO_2$—	H		(90)
3-$(HOOC)C_6H_4SO_2$—	H		(165)
3-$(NH_2)C_6H_4SO_2$—	H	±	(37, 90)
4-$(NH_2)C_6H_4SO_2$—	H*	+++, +	(6, 9, 11, 54, 70, 90, 121, 164)
4-[4′-$(NH_2)C_6H_4SO_2NH]C_6H_4SO_2$—	H	++	(9, 11, 37, 90)
4-[4′-$(CH_3CONH)C_6H_4SO_2NH]C_6H_4SO_2$—	H		(9, 37, 90)
4-$[(CH_3)_2N]C_6H_4SO_2$—	H		(90)
4-$(CH_3CONH)C_6H_4SO_2$—	H	±	(90, 131)
$C_6H_5CH_2SO_2$—	H	0	(174)
4-$(NH_2SO_2)C_6H_4NHSO_2$—	H		(186)

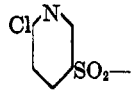
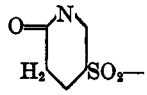
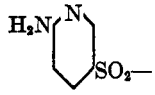
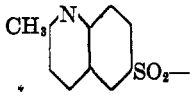
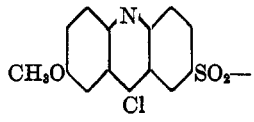
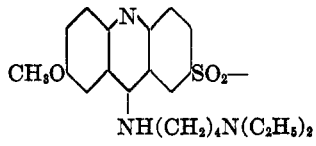
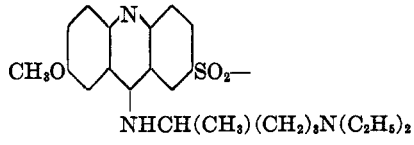
* Diseptyl C, Disulon.

pound is behaving as an N^1-substituted sulfanilamide and the second as an N^1-substituted metanilamide.

TABLE 36

N^4-Heterocyclic-sulfonylsulfanilamides



R^4	$R^{4'}$	ACTIVITY	REFERENCES
	H		(149)
	H		(150)
	H		(149)
	H		(90)
	H		(44)
	H		(44)
	H		(44)

Recent opinions on the effectiveness of N^4-sulfanilylsulfanilamide (54, 121) are that it is much less effective than was first believed against streptococci. It was inactive against pneumococci, but showed some activity against staphylococci.

The drug is used for treatment of gonorrhea, particularly in Europe, but has not gone beyond the clinical stage in this country, probably because of a few cases of peripheral neuritis reported as accompanying its use. The compound is considerably less soluble than sulfanilamide and is not as well absorbed.

(G) *Anils (Schiff bases)*

The anils or Schiff bases derived from sulfanilamide have all been active (see tables 37 and 38). This is almost certain to be the result of break-

TABLE 37

Acyclic anils of sulfanilamide

(a) N^4-Alkylidenesulfanilamides: $R^4{=}N\langle\bigcirc\rangle SO_2NH_2$

R^4	ACTIVITY	REFERENCES
$CH_2{=}$	+	(173, 193)
Sugar derivatives*:		
Xylose		(141)
Glucose	+	(19, 52, 104, 184)
Galactose		(141)
Tetraacetylgalactose		(141)
Lactose		(141)
Mannose		(104)
Arabinose		(104)
Maltose	++	(191)
$HOOCCH{=}$		(26)
$CH_3(HOOC)C{=}$		(26)

(b) N^4-Alkylidene-*bis*-sulfanilamides: $R^4{=}\left(-NH\langle\bigcirc\rangle SO_2NH_2\right)_2$

R^4	ACTIVITY	REFERENCES
$CH_3(CH_2)_6CH{=}$		(50)
$CH_3(CH_2)_7CH{=}$		(50)
$CH_3(CH_2)_8CH{=}$		(50)

* Sugar derivatives are classified here, although they are probably not anils but glucosides (see 104, 141).

down to sulfanilamide on absorption, since the compounds are not especially stable chemically and their more stable reduction products are known to undergo cleavage (144). Small differences in activity may be explained by the results of different observers and of differences in absorption.

Apparent exceptions are cases where the linkage is directly to a heterocyclic ring (see table 39). However, these derivatives are not true anils,

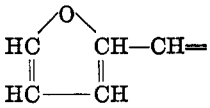
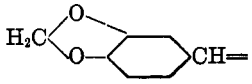
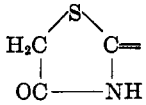
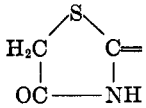
TABLE 38

Isocyclic anils of sulfanilamide: N^4-aralkylidenesulfanilamides

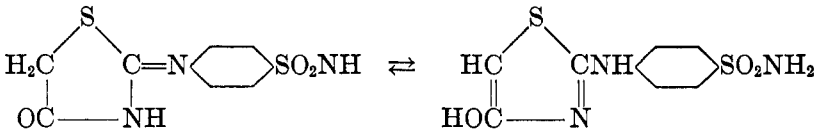
R^4	ACTIVITY	REFERENCES
$C_6H_5CH=$	++	(67, 102, 172)
3-$(NO_2)C_6H_4CH=$	+	(70)
4-$(NO_2)C_6H_4CH=$	++	(26)
6-NO_2-3-$(HO)C_6H_3CH=$	+	(70)
$C_6H_5CH=CHCH=$	+, +++	(70, 102)
$C_6H_5CH=CHCH=$ (·HCl)		(169)
$C_6H_5CH=C(C_5H_{11})CH=$		(123)
2-$(HO)C_6H_4CH=$	++	(67, 155, 172)
4-$(HO)C_6H_4CH=$	+++	(67, 172, 178)
4-$(CH_3O)C_6H_4CH=$	++, +	(70, 101, 102)
4-HO-3-$(CH_3O)C_6H_3CH=$	+	(155)
3,4-$(CH_3O)_2C_6H_3CH=$	+	(70)
3,4-$(C_2H_5O)_2C_6H_3CH=$	+	(70)
2-$(HOOC)C_6H_4CH=$	++	(19)
3-$(HOOC)C_6H_4CH=$		(165)
4-$(CH_3)_2NC_6H_4CH=$	++	(70, 77, 101, 102)
2,4-$(HO)_2C_6H_3CH=$	++, +	(67, 155)
2,4,6-$(HO)_3C_6H_2CH=$	++	(67)

TABLE 39

Heterocyclic anils of sulfanilamide

R^4	ACTIVITY	REFERENCES
	+	(70)
	+	(70)
	0	(121)
	0	(121)

since they might equally well be written in tautomeric form, as in the pair:



Since the reference gave the first formula, the compound has been indexed as an anil. Possibly it might better be classed as an N^4-heterocyclic-sulfanilamide.

(*H*) *Azo derivatives*

While by no means proved, it is nevertheless very likely that the therapeutic properties of the azo dyes derived from sulfanilamide are primarily the therapeutic properties of sulfanilamide itself, which has resulted from cleavage of the azo linkage *in vivo*. The early work of the Trëfouëls, Nitti, and Bovet (180) called attention to the fact that the azo compounds were not active *in vitro*, but showed activity *in vivo* for a wide variety of dyes as long as the sulfanilamide part of the molecule was not varied in structure, but when this was changed by replacing the sulfonamide group, the activity was lost. This indicated to them that sulfanilamide was the active form and led to discovery of its therapeutic properties. Later, Fuller (63) was able to isolate sulfanilamide from the urine of patients treated with Prontosil.

It seems probable that lack of absorption or resistance to cleavage will account for most inactive azo dyes derived from sulfanilamide.

The azo derivatives are taken up in the following order: (*1*) acyclic;

R^4	ACTIVITY	REFERENCE
$CH_3CO(HOOC)CH-$		(148)

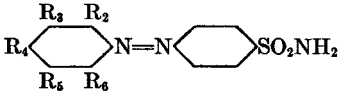
(*2*) isocyclic, including azo derivatives of benzene (table 40), azo derivatives of naphthalene (table 41), and miscellaneous derivatives (table 42); (*3*) heterocyclic, including azo derivatives of pyridine (table 43), azo derivatives of quinoline (table 44), and miscellaneous derivatives (table 45).

IV. NUCLEAR,N^1-SUBSTITUTED SULFANILAMIDES

No pharmacological data are available on these compounds. The compounds that have been synthesized are listed in table 46.

TABLE 40

Azo derivatives of sulfanilamide and benzene

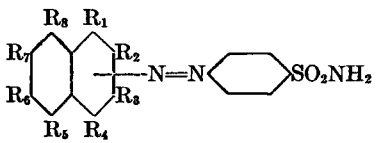


R_2	R_3	R_4	R_5	R_6	ACTIVITY	REFERENCES
						(30, 70, 91, 175)
		HO—			+	(67, 181)
CH_3—		HO—			+	(181)
	CH_3—	HO—			+	(181)
CH_3—		HO—	CH_3—		±	(181)
	CH_3—	HO—	CH_3—		±	(181)
CH_3—(?)	CH_3—(?)	HO—	Cl—(?)			(20, 86)
HO—	CH_3—		CH_3—		±	(181)
CH_3—		HO—	$(CH_3)_2CH$—			(20, 86)
CH_3—		HO—	$CH_3(CH_2)_2$—		±	(181)
HO—		HO—			+++	(67, 102, 181)
CH_3O—		HO—			+	(181)
	CH_3O—	HO—			+	(181)
HO—	$C_5H_{11}S$—		CH_3—		+	(102)
HO—		HO—	C_2H_5—		+	(181)
HO—		HO—	$CH_3(CH_2)_2$—		+	(181)
HO—		HO—	$CH_3(CH_2)_5$—		+	(181)
HO—		HO—		HO—	±	(67, 181)
HO—		HO—		C_2H_5O—	+	(181)
	HOOC—	HO—			+	(67, 102, 108)
	HOOC—	HS—				(67)
		NH_2SO_2—				(167, 175)

HO—			NH_2SO_2—		±	(138)
NH_2—			Cl—			(93)
Cl—		NH_2—				(93)
	Cl—	NH_2—				(93)
		$(CH_3)_2N$—				(68)
NH_2—		NH_2—	(Prontosil)		++	(86)
NH_2—		$(C_2H_5)_2N$—				(86)
$(C_2H_5)_2N$—		$(C_2H_5)_2N$—				(86)
NH_2—		HO—				(87)
HO—		NH_2—				(87)
$HOOCCH_2NH$—		NH_2—				(88)
NaO_3SNH—		HO—				(88)
Cl—		NaO_3SCH_2NH—				(93)
NaO_3SCH_2NH—		NaO_3SCH_2NH—				(88)
NH_2—		NH_2—	HO—			(86)
	HOOC—	NH_2—				(93)
NH_2—		NH_2—	HOOC—			(88)
NH_2—		NH_2—	(Rubiazol)	HOOC—	++	(106)
CH_3CONH—		NH_2—	HOOC—			(88)
NH_2—		NH_2—	HO_3S—			(88)
NH_2—		HO—	HO_3S—			(88)
CH_3CONH—		HO—	HO_3S—			(88)
HO—			$HOOC(NH_2)CH$—		++	(152)
	$(C_2H_5)_2N(CH_2)_3NH$—	HO—			±	(181)
CH_3—		$(NH_2CH_2CHOHCH_2)(C_2H_5)N$—			+	(48)

TABLE 41

Azo derivatives of sulfanilamide and naphthalene



R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	ACTIVITY	REFERENCE
x	HO—								(66, 68)
x	HO—				NO_2—		HO_3S—		(88)
x			NH_2—	NH_2—					(86)
x			HO—	NH_2—					(87)
x	HO—	HOOC—			NH_2—				(88)
x	HO—				NH_2—		HO_3S—		(88)
x	NH_2—			HO—		HO_3S—			(88)
x	CH_3CONH—			HO—		HO_3S—			(88)
x	NH_2CONH—			HO—		HO_3S—			(88)
x	3-$(NH_2)C_6H_4CONH$—			HO—		HO_3S—			(88)
x	$NH_2C(NH)NHC(NH)(NH)$—			HO—		HO_3S—			(88)
x	NH_2OCCH_2NH—			HO—		HO_3S—			(88)
x	CH_3NH—			HO—		HO_3S—			(88)
x	$(C_2H_5)_2N$—			HO—		HO_3S—			(88)
	NH_2—				HO_3S—	x	HO—		(88)
	CH_3CONH—				HO_3S—	x	HO—		(88)
	CH_3CONH—	HO_3S—			HO_3S—	x	HO—*	++	(88)
C_6H_5CONH—			HO_3S—		HO_3S—	x	HO—		(88)

* Neoprontosil.

TABLE 42

Azo derivatives of sulfanilamide and miscellaneous isocyclic compounds

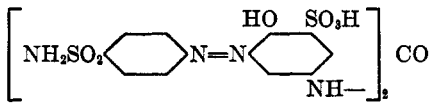
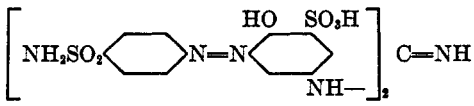
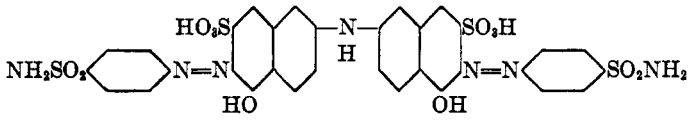
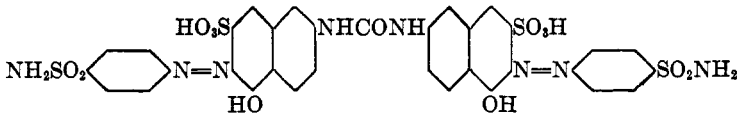
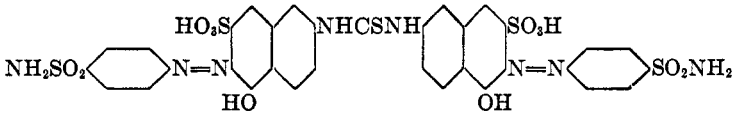
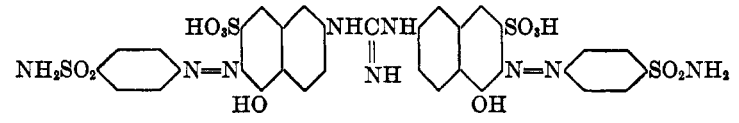
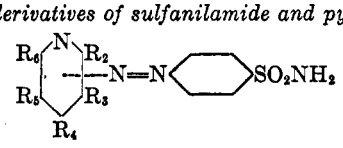
COMPOUND	REFERENCES
	(88)
	(88)
	(88)
	(88)
	(88)
	(88)

TABLE 43

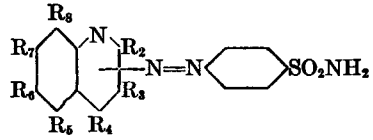
Azo derivatives of sulfanilamide and pyridine



R_2	R_3	R_4	R_5	R_6	ACTIVITY	REFERENCES
HO—			x	CH_3—		(87)
HO—		HO—	x	CH_3—		
NH_2—			x			(87)
NH_2—			x	—NH_2·HCl	+, 0	(33, 59, 60, 87)
HO—			x	—NH_2·HCl		(87)
NH_2—	HO_3S—		x	—NH_2		(88)

TABLE 44

Azo derivatives of sulfanilamide and quinoline



R_2	R_3	R_4	R_5	R_6	R_7	R_8	ACTIVITY	REFERENCES
								(87)
						CH_3—		(87)
			x	HO—				(87)
					HO—			(87)
						HO—		(87, 138)
				Cl—		HO—		(87)
			CH_3—			HO—		(87)
			x	HO—		HO—		(87)
			x		HOOC—	HO—		(88)
			HO_3S—		x	HO—		(88)
			—NH_2·HCl					(87)
			x	—NH_2·HCl				(87)
			x	C_2H_5NH—·HCl				(87)
			x	$(CH_3)_2CH(CH_2)_5NH$—				(87)
			x	$CH_3(CH_2)_{11}NH$—				(87)
			x	$HOOCCH_2NH$—				(88)
			x	NH— $\vert$ CH_2SO_2Na				(88)
			x	NH— $\vert$ CH_2SO_3Na				(88)

					—NH·HCl			(87)
					—C$_2$H$_5$			
					—NH·HCl			(87)
					—C$_4$H$_9$			
			x			—NH$_2$·HCl		(87)
			x	CH$_3$—		—NH$_2$·HCl		(87)
			x	HO—		—NH$_2$·HCl		(87)
			x	CH$_3$O—		—NH$_2$	0	(178)
			x	CH$_3$O—		—NH$_2$·HCl		(87)
HOOC—		HO—		NH$_2$—				(88)

TABLE 45

Azo derivatives of sulfanilamide and miscellaneous heterocyclic compounds

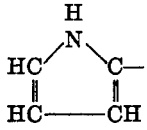
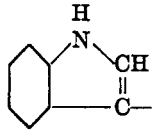
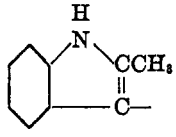
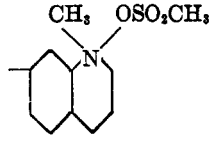
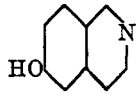
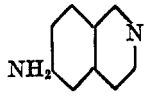
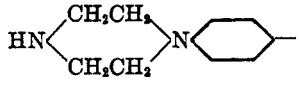
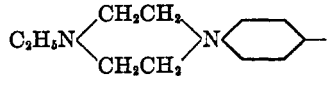
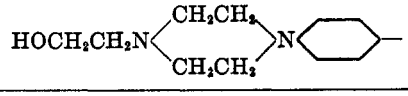
R	ACTIVITY	REFERENCES
	++	(161)
	++	(161)
	0	(161)
	0	(138)
		(87)
		(87)
		(99)
		(99)
		(99)

TABLE 45—*Continued*

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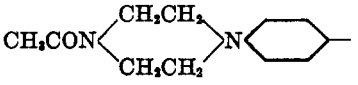
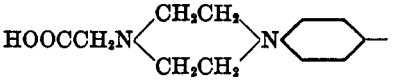
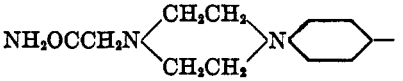
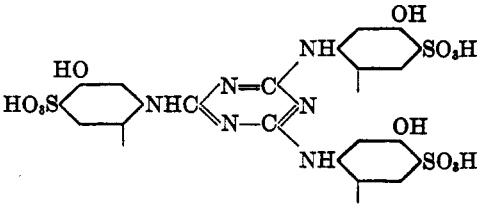
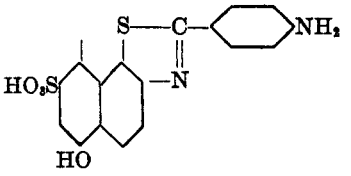
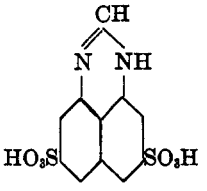
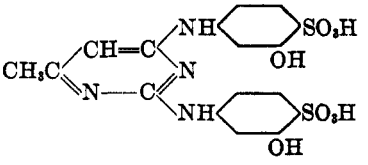
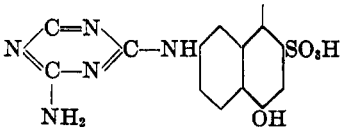
		(99)
		(99)
		(99)
		(88)
		(88)
		(88)
		(88)
		(88)

TABLE 45—*Concluded*

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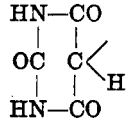
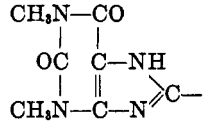
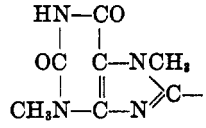
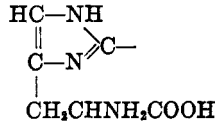
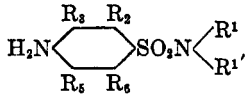
		(148)
	++	(137)
	++	(137)
	++	(152)
Dihydrocupreine	±	(20, 74)
Dihydrocupreidine	±	(20)
Apoquinine	±	(20)
Isoapoquinine	±	(20)
Casein	+	(178)
Antipneumococcus serum		(152)

TABLE 46

Nuclear, N^1-substituted sulfanilamides



R^1	$R^{1'}$	R_2	R_3	R_5	R_6	ACTIVITY	REFERENCE
A. N^1-Inorganic substituents							
No examples							
B. N^1-Acyclic substituents							
CH_3—	H	C_2H_5—	H	H	H		(80)
$HOCH_2CH_2$—	H	H	CH_3O—	H	H		(85)
C. N^1-Isocyclic substituents							
C_6H_5—	H	NH_2—	H	NH_2SO_2—	H		(125)
C_6H_5—	H	NH_2—	H	$C_6H_5NHSO_2$—	H		(125)
C_6H_5—	H	H	$C_6H_5NHSO_2$—	$C_6H_5NHSO_2$—	H		(55)
$(CH_3)_2C_6H_3$—	H	H	Cl—	H	H		(12)
D. N^1-Heterocyclic substituents							
	H	H	NO_2—	H	H		(98)

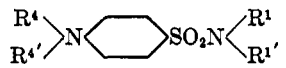
V. NUCLEAR, N^4-SUBSTITUTED SULFANILAMIDES

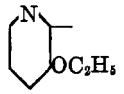
Of the few compounds in this group that have been studied, all have been found inactive (see table 47).

VI. N^1, N^4-SUBSTITUTED SULFANILAMIDES

In these derivatives, the compounds having a potentially free N^4-amino group have activities comparable with the corresponding N^1-substituted sulfanilamide. Where the amino group is blocked by a substituent such as alkyl, aryl, or sulfonyl, the compounds are inactive.

(*A*) *N^4-Inorganic-N^1-substituted sulfanilamides*



R^4	$R^{4'}$	R^1	$R^{1'}$	ACTIVITY	REFERENCE
HO—	H		H		(160)

(*B, C, D*) *N^4-Acyclic-, N^4-isocyclic-, and N^4-heterocyclic-N^1-substituted sulfanilamides*

No data on activity are available for most of the derivatives made (see tables 48, 49, and 50). The formaldehyde-sulfoxalate and formaldehyde-bisulfite derivatives of sulfapyridine and sulfathiazole have the activities of the parent compounds against both streptococci and pneumococci. Undoubtedly, they break down to the parent substances *in vivo*.

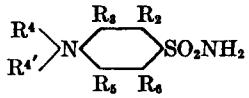
(*E*) *N^4-Acyl-N^1-substituted sulfanilamides*

This very large group of compounds covers practically all the N^1-substituted sulfanilamide derivatives of Class II, because of the fact that the N^4-acetyl derivatives are intermediates in synthesis. Comparatively few N^4-acetyl-N^1-substituted sulfanilamides have been studied, since the early work showed them to be much less active than the deacetylated products.

A number of longer chain N^4-acyl-N^1-substituted sulfanilamides have been made, but these are thought to be intrinsically no more active than the deacylated products. Substantial evidence for this belief is lacking. The proof would involve first the demonstration of free amine *in vivo*, and second, a comparison of S.B.$C._{50}$'s measured against controls in which the blood level distribution was duplicated by administration of the free amine. The results of such experiments will be awaited with interest.

TABLE 47

Nuclear,N⁴-substituted sulfanilamides



R^4	$R^{4'}$	R_2	R_3	R_5	R_6	ACTIVITY	REFERENCES
A. N^4-Inorganic substituents							
None							
B. N^4-Acyclic substituents							
NaO_3SCH_2—	H	H	Cl—	H	H		(173)
NaO_3SCH_2—	H	H	CH_3O—	H	H		(173)
C. N^4-Isocyclic substituents							
C_6H_5—	H	H	NO_2—	H	H		(55)
C_6H_5—	H	H	NH_2SO_2—	H	H		(55)
4-$(CH_3O)C_6H_4$—	H	H	HOOC—	H	H		(7)
D. N^4-Heterocyclic substituents							
None							
E. N^4-Acyl substituents							
(1) N^4-Acetylsulfanilamides with inorganic nuclear substituents							
CH_3CO—	H	Cl—	H	H	H		(181)
CH_3CO—	H	H	Cl—	H	H		(173)

CH_3CO—	H	H	Br—	Br—	H		(167)
CH_3CO—	H	H	I—	H	H		(167)
CH_3CO—	H	H	I—	I—	H		(167)
CH_3CO—	H	H	NO_2—	H	H		(55, 97, 181)
CH_3CO—	H	HO—	H	H	H	0	(181)
CH_3CO—	H	H	CH_3O—	H	H		(173)
CH_3CO—	H	H	NH_2SO_2—	H	H		(55)
CH_3CO—	H	H	NH_2SO_2—	NH_2SO_2—	H		(125)
CH_3CO—	H	H	NH_2—	H	H	0	(86, 181)
CH_3CO—	H	NH_2—	H	NH_2SO_2—	H		(125)

E. N^4-Acyl substituents

(2) N^4-Acetylsulfanilamides with acyclic nuclear substituents

CH_3CO—	H	CH_3—	H	H	H	0	(84, 181)
CH_3CO—	H	H	CH_3—	H	H	0	(61, 84, 181)
CH_3CO—	H	CH_3—	H	Cl—	H		(84)
CH_3CO—	H	CH_3—	H	CH_3—	H		(84)
CH_3CO—	H	CH_3—	H	CH_3O—	H		(84)
CH_3CO—	H	H	CH_3O—	H	H		(173)
CH_3CO—	H	HOOC—	H	H	H	0	(96)
CH_3CO—	H	H	HOOC—	H	H	0	(96)

E. N^4-Acyl substituents

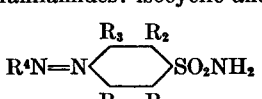
(3) N^4-Acyl substituents derived from carbonic acid

NH_2CO—	H	CH_3—	H	H	H	0	(34)
NH_2CO—	H	H	CH_3—	H	H	0	(34)
$CH_3CONHCO$—	H	CH_3—	H	H	H	0	(34)
$CH_3CONHCO$—	H	H	CH_3—	H	H	0	(34)

TABLE 47—*Concluded*

E. N^4-Acyl substituents

(4) N^4-Acyclic-acylsulfanilamides

R^4	$R^{4'}$	R_2	R_3	R_5	R_6	ACTIVITY	REFERENCES
$ClCH_2CO$—	H	CH_3—	H	C_2H_5O—	H		(90)
$(CH_3)_2CHCH_2CO$—	H	CH_3—	H	Cl—	H		(84)
$(CH_3)_2CHCH_2CO$—	H	CH_3—	H	CH_3O—	H		(25, 84)
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$—	H	CH_3—	H	H	H		(25, 84)
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$—	H	H	CH_3—	H	H		(25, 84)
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$—	H	CH_3—	H	CH_3—	H		(25, 84)
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$—	H	CH_3—	H	CH_3O—	H		(25, 84)
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$—	H	CH_3O—	H	CH_3O—	H		(25, 84)
$C_4H_9NHCH_2CO$—	H	CH_3—	H	C_2H_5O—	H		(90)
F. N^4-Sulfonyl substituents							
$C_6H_5O(CH_2)_3SO_2$—	H	CH_3—	H	CH_3O—	H		(90)
4-$(NH_2)C_6H_4SO_2$—	H	CH_3—	H	CH_3O—	H		(90)
4-$(CH_3CONH)C_6H_4SO_2$—	H	CH_3—	H	CH_3O—	H		(90)
G. N^4-Anils							
None							
H. N^4-Azosulfanilamides: isocyclic and heterocyclic							
							
4-NH_2SO_2-2-IC_6H_3—		H	I—	H	H		(167)

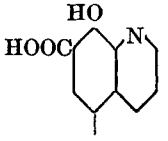
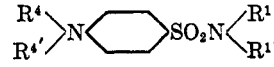
$2,4\text{-}(NH_2)_2C_6H_3$—		H	NH_2SO_2—	H	H		(86)
$2,4\text{-}(NH_2)_2C_6H_3$—		CH_3—	H	H	H		(86, 88)
		H	CH_3—	H	H		(88)

TABLE 48

N^4-Acyclic-N^1-substituted sulfanilamides



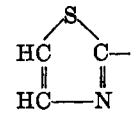
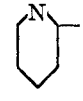
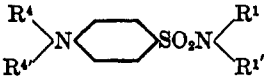
R^4	$R^{4'}$	R^1	$R^{1'}$	ACTIVITY	REFERENCES
CH_3—	H	$CH_3CHOHCH_2$—	H		(2)
CH_3—	CH_3—	C_6H_5—	H		(56)
CH_3—	H	CH_3—	CH_3—		(89)
CH_3—	CH_3—	4-$(HOOC)C_6H_4$—	H		(91)
CH_3—	H	4-$(NH_2)C_6H_4$—	H		(76)
CH_3—	H		H		(132)
CH_3—	CH_3—		H		(132)
CH_3—	CH_3—		CH_3—		(132)
CH_3CH_2—	H	$(CH_3)_2COHCH_2$—	H	0	(2)
NaO_2SCH_2—	H	$CH_3(CH_2)_{10}CO$—	H		(38)
NaO_2SCH_2—	H	NaO_2SCH_2—	H	−	(25, 95)
NaO_2SCH_2—	H		H	++	(96)
NaO_2SCH_2—	H		H	++	(123, 161)
NaO_3SCH_2—	H		H	++	(96)
NaO_3SCH_2—	H	4-$(NH_2SO_2)C_6H_4$—	H	±	(184)
$NaO_3SCH_2CHOHCH_2$—	CH_3—	CH_3—	CH_3—		(89)

Table 51 includes all of the N^4-acetyl-N^1-substituted sulfanilamides, with the latter substituents taken up in the following order: (a) inorganic substituents; (b) acyclic substituents; (c) isocyclic substituents (*1*)

C_nH_{2n-1} to C_nH_{2n-13}, (*2*) oxy or oxo, (*3*) carboxy, (*4*) sulfo, (*5*) amino; (d) heterocyclic substituents; (e) acyl substituents grouped as (*1*) carbonic acid acyl, (*2*) acyclic-acyl, (*3*) isocyclic-acyl, (*4*) heterocyclic-acyl; and (f) sulfonyl substituents. Table 52 contains all of the N^4-acyl-N^1-substituted sulfanilamides in which the group in the N^4-position is an acyl group other than acetyl. These acyl groups are taken up in the following order: (a) acyl groups derived from carbonic acid; (b) acyclic-acyl groups derived from (*1*) monobasic acids and (*2*) dibasic acids; (c) isocyclic-acyl groups; (d) heterocyclic-acyl groups.

TABLE 49

N^4-Isocyclic-N^1-substituted sulfanilamides



R^4	$R^{4'}$	R^1	$R^{1'}$	ACTIVITY	REFERENCES
$C_6H_5CH_2$—	H	$HOCH_2CH_2$—	H	±	(2)
$C_6H_5CH_2$—	H		H		(132)
2,4-$(NO_2)_2C_6H_3$—	H		H		(132)
4-$(CH_3O)C_6H_4CH_2$—	H	C_6H_5—	H	0	(102)

(F) N^4-Sulfonyl-N^1-substituted sulfanilamides (see table 53)

Few derivatives have been studied where the N^4-sulfonyl group is other than N^4-sulfanilyl and in the latter case the compounds are probably behaving as N^1-substituted sulfanilamides (see section III F). Uleron, which has had widespread use (particularly in Germany) for treatment of gonorrhea, has the disadvantage for this use of causing a high incidence of peripheral neuritis when treatment is sufficiently prolonged to be reasonably certain of cure. Its reported effectiveness against staphylococcus infections (48) has not been confirmed by others (140).

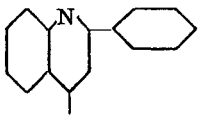
(G) N^4-Anil-N^1-substituted sulfanilamides (see table 54)

The N^4-anils derived from N^1-substituted sulfanilamides retain the activities of the parent compounds in most cases. The high activities claimed for the N^4-*p*-nitrobenzylidine derivatives are noteworthy.

TABLE 50

N^4-Heterocyclic-N^1-substituted sulfanilamides

(1) N^4-Nitrogen not in the heterocyclic system

R^4	$R^{4'}$	R^1	$R^{1'}$	ACTIVITY	REFERENCES
	H	C_6H_5—	C_2H_5—		(8)

(2) N^4-Nitrogen in the heterocyclic system

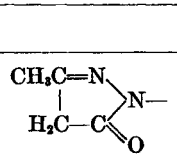
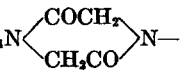
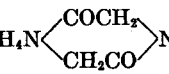
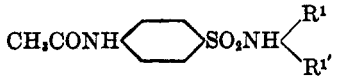
	R^1	$R^{1'}$	ACTIVITY	REFERENCES
	4-(HOOC)C_6H_4—	H		(79)
4-(HOCH$_2$CH$_2$NHSO$_2$)C_6H_4N 	$HOCH_2CH_2$—	H	0	(1)
4-(CH_3CHOHCH$_2$NHSO$_2$)C_6H_4N 	$CH_3CHOHCH_2$—	H	0	(1)

TABLE 51

N^4-Acetyl-N^1-substituted sulfanilamides



R^1	$R^{1'}$	ACTIVITY	REFERENCES
a. N^4-Acetyl-N^1-inorganic sulfanilamides			
HO—	H		(114)
H_2N—	H	–	(179)
b. N^4-Acetyl-N^1-acyclicsulfanilamides			
CH_3—	H	+	(20, 61, 181)
C_2H_5—	H	+	(20, 61, 181)
$CH_3(CH_2)_3$—	H	±	(61, 181)
$(CH_3)_2CHCH_2$—	H	±	(61, 181)
CH_2=CH—CH_2—	H	±	(181)
CH_3—	CH_3—	+	(61, 164, 181)
C_2H_5—	C_2H_5—	+	(61, 70, 181)
$CH_3(CH_2)_2$—	$CH_3(CH_2)_2$—	±	(61, 181)
$HOCH_2CH_2$—	H—	0, ±	(2, 42, 114, 121)
$HOCH_2CH_2$—	CH_3—	0	(42, 121)
$HOCH_2CH_2$—	$HOCH_2CH_2$—	0	(2, 42, 87, 100, 102)
$HOCH_2CH_2CH_2$—	H	0	(2, 85, 114)
$CH_3CHOHCH_2$—	H	±	(2, 42, 114)
$HOCH_2CH(OH)CH_2$—	H	0	(2, 114)
$CH_3CH(OH)CH_2$—	$CH_3CHOHCH_2$—		(42)
$(CH_3)_2COHCH_2$—	H	±	(2)
$C_2H_5CH(OH)CH_2$—	H		(114)
$(HOCH_2)(CH_3)_2C$—	H		(42)
$(HOCH_2)_2CH$—	H		(114)
$(HOCH_2)_3(CH_3)C$—	H		(42)
$HOCH_2(CHOH)_4CH_2$—	CH_3—	0	(2)
$HOOCCH_2$—	H	+	(21, 82, 100, 102)
$NaOOCCH_2$—	H	0	(121)
$C_2H_5OOCCH_2$—	H		(65)
$HOOCCH_2CH_2(HOOC)CH$—	H		(21)
$HOOC(CH_3)CH$—	H		(136)
$NaOOC(CH_3)CH$—	H	0	(121)
$HO_3SCH_2CH_2$—	H		(82)
$(C_2H_5)_2NCH_2CH_2$—	H	0	(121)
$(C_2H_5)_2N(CH_2)_3$—	H	0	(181)
$(C_2H_5)_2N(CH_2)_4$—	H		(28, 29)

TABLE 51—*Continued*

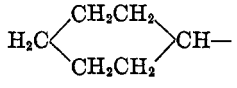
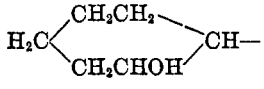
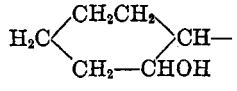
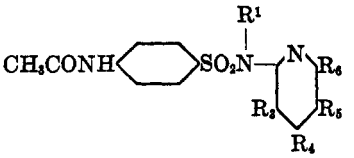
R¹	R¹′	ACTIVITY	REFERENCES
c-1. N^4-Acetyl-N^1-isocyclicsulfanilamides: R = C_nH_{2n-1} to C_nH_{2n-13}			
	H		(70)
	H	0	(121)
C_6H_5—	H	±	(20, 66, 91, 181)
C_6H_5—	$HOCH_2CH_2$—		(42)
2-ClC_6H_4—	H		(42)
4-ClC_6H_4—	H		(42)
2-$(NO_2)C_6H_4$—	H		(100, 187)
3-$(NO_2)C_6H_4$—	H		(187)
4-$(NO_2)C_6H_4$—	H		(9, 76, 187)
2-$(CH_3)C_6H_4$—	H		(66)
3-$(CH_3)C_6H_4$—	H		(66)
4-$(CH_3)C_6H_4$—	H		(91, 66)
$C_6H_5CH_2$—	H	±	(78, 181)
1-$C_{10}H_7$—	H		(66)
2-$C_{10}H_7$—	H		(66)
c-2. N^4-Acetyl-N^1-isocyclicsulfanilamides: oxy or oxo derivatives			
	H	0	(2)
2-$(HO)C_6H_4$—	H	0	(42, 121, 187)
3-$(HO)C_6H_4$—	H	0	(121, 187)
4-$(HO)C_6H_4$—	H	0	(42, 121, 187)
4-HO-2-$(NO_2)C_6H_3$—	H	0	(121)
4-HO-3-$(NO_2)C_6H_3$—	H	0	(121)
2-$(CH_3O)C_6H_4$—	H	0	(42)
3-$(CH_3O)C_6H_4$—	H		
4-$(CH_3O)C_6H_4$—	H		(28, 29)
4-$(HOCH_2)C_6H_4$—	H		(91)
4-$(C_2H_5)C_6H_4$—	H	±	(166, 181)
4-$(HS)C_6H_4$—	H		(91)
5-HS-2-$(CH_3)C_6H_3$—	H		(91)
2-$(OHC)C_6H_4$—	H		(91)
4-$(CH_3CO)C_6H_4$—	H		(197)
4-$(CH_3CH_2CO)C_6H_4$—	H		(197)
4-$(C_6H_5CO)C_6H_4$—	H		(197)

TABLE 51—*Continued*

R^1	$R^{1'}$	ACTIVITY	REFERENCES
c-3. N^4-Acetyl-N^1-isocyclicsulfanilamides: carboxy derivatives			
2-(HOOC)C_6H_4—	H	0	(35, 37, 100, 102, 121)
3-(HOOC)C_6H_4—	H		(35, 91, 100 102)
4-(HOOC)C_6H_4—	H	0	(9, 35, 91, 100, 102, 121)
3-(HOOCCH=CH)C_6H_4—	H		(65)
4-(HOOCCH=CH)C_6H_4—	H		(65)
4-(C_2H_5OOC)C_6H_4—	H		(29, 91)
3-(CN)C_6H_4—	H		(91)
4-(NH_2OC)C_6H_4—	H		(91)
2-CN-4-ClC_6H_3—	H		(91)
4-NO_2-2-(HOOC)C_6H_3—	H		(91)
4-HOOC-3-(HO)C_6H_3—	H		(42, 91)
4-(HO)$C_6H_4CH_2$(HOOC)CH—	H		(136)
c-4. N^4-Acetyl-N^1-isocyclicsulfanilamides: sulfo derivatives			
2-(HO_3S)C_6H_4—	H		(23, 35)
3-(HO_3S)C_6H_4—	H		(35)
4-(HO_3S)C_6H_4—	H		(35, 65, 91, 100, 102)
4-(HO_3S)C_6H_4—	C_2H_5—		(42)
4-(ClO_2S)C_6H_4—	H		(91)
4-($C_6H_5O_3S$)C_6H_4—	H		(91)
2,6-(NO_2)$_2$-4-(HO_3S)C_6H_2—	H		(91)
4-ClO_2S-2-(CH_3)C_6H_3—	H		(91)
4-HO_3S-1-$C_{10}H_6$—	H		(35, 91)
4-NaO_3S-1-$C_{10}H_6$—	H	0	(121)
7-HO_3S-5-HO-2-$C_{10}H_5$—	H		(91)
6-HO_3S-8-HO-2-$C_{10}H_5$—	H		(91)
3,6-(HO_3S)$_2$-1-$C_{10}H_5$—	H		(91)
3,8-(HO_3S)$_2$-1-$C_{10}H_5$—	H		(91)
4,8-(NaO_3S)$_2$-1-$C_{10}H_5$—	H	0	(121)
3,6,8-(NaO_3S)$_3$-1-$C_{10}H_4$—	H	0	(121)
c-5. N^4-Acetyl-N^1-isocyclicsulfanilamides: amino derivatives			
2-(NH_2)C_6H_4—	H	0	(121)
3-(NH_2)C_6H_4—	H	0	(121)
4-(NH_2)C_6H_4—	H	+	(76, 102, 121)
4-(CH_3CONH)C_6H_4—	H		(76, 84, 131)
4-[$CH_3CO(CH_3)N$]C_6H_4—	H		(76)
4-(C_6H_5CH=N)C_6H_4—	H	+	(102)
4-[4′-(NO_2)C_6H_4CH=N]C_6H_4—	H		(102)

TABLE 51—*Continued*

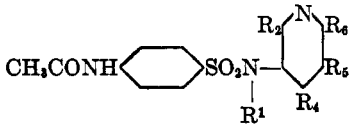
R^1	$R^{1'}$	ACTIVITY	REFERENCES
c-5. N^4-Acetyl-N^1-isocyclicsulfanilamides: amino derivatives—*Continued*			
4-[4′-(CH_3O)$C_6H_4CH{=}N$]C_6H_4—	H	+++	(102)
4-[4′-[(CH_3)$_2N$]$C_6H_4CH{=}N$]C_6H_4—	H	++	(102)
2,4-(CH_3CONH)$_2C_6H_3$—	H		(84)
3,4-(CH_3CONH)$_2C_6H_3$—	H		(131)
4-[4′-(NH_2)C_6H_4NH]C_6H_4—	H		(131)
3-HO-4-(CH_3CONH)C_6H_3—	H		(84, 131)
2-CH_3-5-(CH_3CONH)C_6H_3—	H		(76)
5-CH_3-2-(CH_3CONH)C_6H_3—	H		(76)
3-CH_3-4-(CH_3CONH)C_6H_3—	H		(84)
2,3-(CH_3)$_2$-4-(CH_3CONH)C_6H_2—	H		(76)
4-[(CH_3)$_2N$]C_6H_4—	H		(84)
4-[(C_2H_5)$_2N$]C_6H_4—	H		(76)
4-(C_6H_5NH)C_6H_4—	H		(84)
2,6-(HO_3S)$_2$-4-(NH_2)C_6H_2—	H		(91)
d-1. N^4-Acetyl-N^1-heterocyclicsulfanilamides: one oxygen or sulfur atom in the heterocyclic system			
None			
d-2. N^4-Acetyl-N^1-heterocyclicsulfanilamides: one nitrogen in the heterocyclic system			
(a) 2-(N^4-Acetylsulfanilamido)pyridines			



R^1	R_3	R_4	R_5	R_6	ACTIVITY	REFERENCES
						(39, 68, 129, 132, 159, 183, 189, 190)
Na—						(129)
CH_3—						(132)
$C_6H_5CH_2$—						(132)
			I—			(132)
			NO_2—			(132)
				CH_3—		(132, 183)
	HOOC—		$C_6H_5O_3S$—			(132)
			NH_2—	H		(160)
				NH_2—	+, ++	(33, 59, 60, 183)
				4-(NH_2)-$C_6H_4SO_2NH$—		(132)

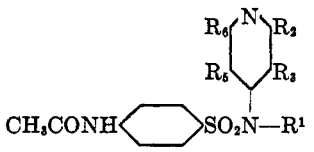
TABLE 51—*Continued*

d-2 (b). 3-(N^4-Acetylsulfanilamido)pyridines



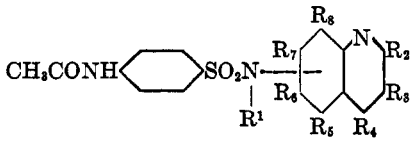
R^1	R_2	R_4	R_5	R_6	ACTIVITY	REFERENCES
						(132, 190)
				CH_3CONH—		(190)

d-2 (c). 4-(N^4-Acetylsulfanilamido)pyridines



R^1	R_2	R_3	R_5	R_6	ACTIVITY	REFERENCE
						(132)

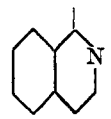
d-2 (d). x-(N^4-Acetylsulfanilamido)quinolines



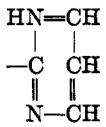
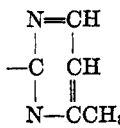
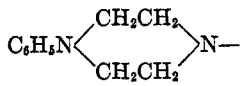
R^1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	ACTIV-ITY	REFERENCES
	x								(132, 183)
		x							(190)
				x					(14, 190)
					x				(14, 132, 190)
						x			(14)
							x		(14, 29, 190)
	CH_3—				x				(132)
	C_6H_5—		x						(8)
				x			CH_3O—		(132)
					CH_3O—		x		(29)
	HO—		CH_3—			x			(132)
	C_6H_5—		x		CH_3O—				(8)

TABLE 51—*Continued*

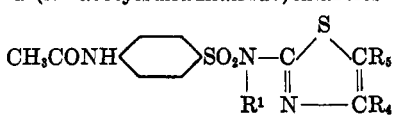
d-2 (e). Miscellaneous N^4-acetyl-N^1-heterocyclicsulfanilamides with one nitrogen atom in the heterocyclic system (general formula as at top of table)

R^1	$R^{1'}$	ACTIVITY	REFERENCE
	H		(132)

d-3. N^4-Acetyl-N^1-heterocyclicsulfanilamides with two or more nitrogen atoms in the heterocyclic system (general formula as at top of table)

R^1	$R^{1'}$	ACTIVITY	REFERENCES
	H		(159)
	H		(159)
	H		(99)

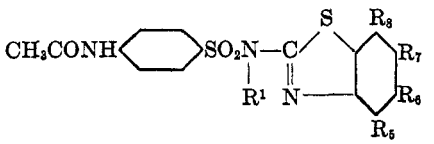
d-4 (a). N^4-Acetyl-N^1-heterocyclicsulfanilamides with one nitrogen atom and one oxygen (or sulfur) atom in the heterocyclic system: 2-(N^4-acetylsulfanilamido)thiazoles



R^1	R_4	R_5	ACTIVITY	REFERENCES
				(59, 124, 133, 159)
	CH_3—			(59, 124, 133, 159, 183)
$C_6H_5CH_2$—	CH_3—			(133)
		CH_3—		(133)
	C_6H_5—			(133)
	CH_3—	C_6H_5—		(133)
	CH_3—	$HOCH_2CH_2$—		(133)
	CH_3—	C_2H_5OOC—		(133)

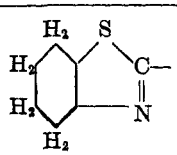
TABLE 51—*Continued*

d-4 (b). 2-(N^4-Acetylsulfanilamido)benzothiazoles



R^1	R_5	R_6	R_7	R_8	ACTIVITY	REFERENCES
						(133)
C_2H_5—						(133)
			NO_2—			(133)
			C_2H_5O—			(133)
		CH_3CONH—				(133)

d-4 (c). Miscellaneous N^4-acetyl-N^1-heterocyclicsulfanilamides with one nitrogen, oxygen, or sulfur atom in the heterocyclic system (general formula as at top of table)

R^1	$R^{1'}$	ACTIVITY	REFERENCE
	H		(60)

d-5. N^4-Acetyl-N^1-heterocyclicsulfanilamides with two nitrogen atoms and one oxygen (or sulfur) atom in the heterocyclic system (general formula as at top of table)

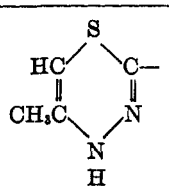
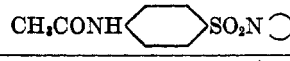
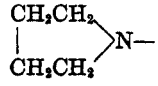
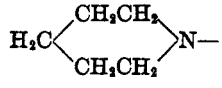
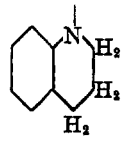
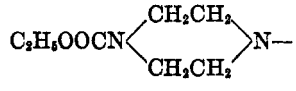
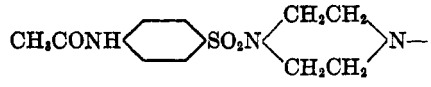
R^1	$R^{1'}$	ACTIVITY	REFERENCE
	H		(60)

TABLE 51—*Continued*

d-6. N^4-Acetyl-N^1-heterocyclicsulfanilamides with the N^1-nitrogen in the heterocyclic system



N◯	ACTIVITY	REFERENCES
		(88)
	0	(68, 70, 86, 87, 88)
	0	(178)
		(98)
		(42, 98)

e. N^4-Acetyl-N^1-acylsulfanilamides (general formula as at top of table)

R^1	$R^{1'}$	ACTIVITY	REFERENCES
e-1. N^4-Acetyl-N^1-inorganicsulfanilamides			
CH_3NHCO—	H	0	(121)
$NH_2C(=NH)$—	H	0	(121)
e-2. N^4-Acetyl-N^1-acyclic-acylsulfanilamides			
CH_3CO—	H		(38, 168)
CH_3CH_2CO—	H		(38)
$(CH_3)_2CHCO$—	H		(38)
$CH_3(CH_2)_2CO$—	H		(38)
$(CH_3)_2CHCH_2CO$—	H		(38)
$(C_2H_5)_2CHCO$—	H		(38)
$CH_3(CH_2)_4CO$—	H		(38)
$CH_3(CH_2)_5CO$—	H		(38)
$CH_3(CH_2)_6CO$—	H		(38)
$CH_3(CH_2)_5CH(C_2H_5)CO$—	H		(38)

TABLE 51—*Concluded*

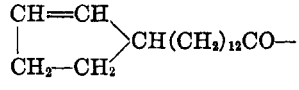
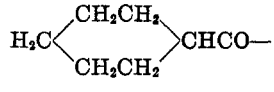
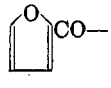
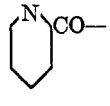
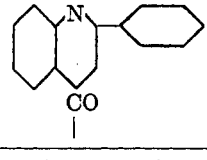
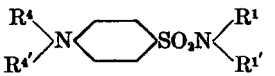
R^1	$R^{1'}$	ACTIVITY	REFERENCES
e-2. N^4-Acetyl-N^1-acyclic-acylsulfanilamides—*Continued*			
$CH_3(CH_2)_3CH(C_2H_5)CO$—	Na—		(38)
$CH_3(CH_2)_3CH(C_2H_5)CO$—	½Mg—		(38)
$CH_3(CH_2)_8CO$—	H		(38)
$CH_3(CH_2)_9CO$—	H		(38)
$CH_3(CH_2)_{10}CO$—	H		(38)
$CH_3(CH_2)_{12}CO$—	H		(38)
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$—	H		(38)
e-3. N^4-Acetyl-N^1-isocyclic-acylsulfanilamides			
	H		(38)
	H		(38)
C_6H_5CO—	H		(38)
$C_6H_5CH_2CH_2CO$—	H		(38)
$C_6H_5CH{=}CHCO$—	H		(38)
$(C_6H_5)_2CHCO$—	H		(38)
4-$(NO_2)C_6H_4CO$—	H		(38)
4-$(HOOC)C_6H_4CO$—	H		(42)
4-$(NH_2)C_6H_4CO$—	H		(38)
e-4. N^4-Acetyl-N^1-heterocyclic-acylsulfanilamides			
	H		(38)
	H		(38, 43)
	H		(38)
n-$C_5H_{11}SO_2$—	H		(174)
4-$(NH_2)C_6H_4SO_2$—	H		(151)
$CH_3CONHC_6H_4SO_2$—	H	±	(19, 36)
$CH_3CONHC_6H_4SO_2$—	CH_3—		(36)
$CH_3CONHC_6H_4SO_2$—	C_2H_5—		(36)

TABLE 52

N^4-Acyl(other than acetyl)-N^1-substituted sulfanilamides



R^4	$R^{4'}$	R^1	$R^{1'}$	ACTIVITY	REFERENCES
a. N^4-Substituents derived from carbonic acid					
C_2H_5OCO—	H	$HOCH_2CH_2$—	H	+	(2)
C_2H_5OCO—	H	$CH_3CHOHCH_2$—	H	±	(2)
C_2H_5OCO—	H	Morpholide		0	(2)
NH_2CO—	H	C_2H_5—	C_2H_5—	0	(34)
CH_2=$CHCH_2NHC(=S)$—	H	CH_3—	CH_3—		(65)
CH_2=$CHCH_2NHC(=S)$—	H	4-$(HO_3S)C_6H_4$—	H		(65)
CH_2=$CHCH_2NHC(=S)$—	H	4-$(NH_2SO_2)C_6H_4$—	H		(65)
b. N^4-Acyclic-acyl: (1) derivatives of monobasic acids					
HCO—	H		H		(123)
CH_3CO—	CH_3—	4-$(NO_2)C_6H_4$—	H		(76)
CH_3CO—	CH_3—	4-CH_3COO-3-$(NO_2)C_6H_3$—	H	0	(121)
CH_3CO—	CH_3—	4-$(CH_3CONH)C_6H_4$—	H		(76)
CH_3CO—	C_2H_5—	$(CH_3)_2C(OH)CH_2$—	H		(2)
$ClCH_2CO$—	H	CH_3—	H		(90)
$ClCH_2CO$—	H	C_2H_5—	C_2H_5—		(90)
$ClCH_2CO$—	H	C_4H_9—	H		(90)
$ClCH_2CO$—	H	C_6H_5—	H		(154)
$ClCH_2CO$—	H	$C_6H_5CH_2$—	H		(90)

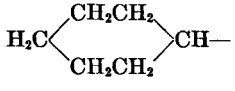
CH_3CH_2CO—	H	$CH_3CHOHCH_2$—	H	±	(2)
CH_3CH_2CO—	H	$(CH_3)_2C(OH)CH_2$—	H	±	(2)
CH_3CH_2CO—	H	4-$(CH_3CONH)C_6H_4$—	H		(76)
CH_3CH_2CO—	H	Morpholide		±	(2)
$CH_3(CH_2)_2CO$—	H	HO—	H	+	(146)
$CH_3(CH_2)_2CO$—	Cl—	Na—	Cl—		(42)
$CH_3(CH_2)_2CO$—	H	$HOCH_2CH_2$—	H	±	(2)
$CH_3(CH_2)_2CO$—	H	$HOCH_2CH_2$—	$HOCH_2CH_2$—	0	(2)
$CH_3(CH_2)_2CO$—	H	$CH_3CHOHCH_2$—	H	0	(2)
$CH_3(CH_2)_2CO$—	H	$(CH_3)_2C(OH)CH_2$—	H	±	(2)
$CH_3(CH_2)_2CO$—	H	Morpholide		±	(2)
$CH_3(CH_2)_2CO$—	H		H		(42)
$(CH_3)_2CHCO$—	H	HO—	H	±	(146)
$(CH_3)_2CHCO$—	H	$HOCH_2CH_2$—	H	+	(2)
$(CH_3)_2CHCO$—	H	$CH_3CHOHCH_2$—	H	±	(2)
$(CH_3)_2CHCO$—	H	$(CH_3)_2C(OH)CH_2$—	H	+	(2)
$(CH_3)_2CHCO$—	H	Morpholide		±, 0	(2, 121)
$CH_3(CH_2)_3CO$—	H	HO—	H	++	(146)
$CH_3(CH_2)_3CO$—	H	$CH_3CHOHCH_2$—	H	±	(2)
$CH_3(CH_2)_3CO$—	H	$(CH_3)_2C(OH)CH_2$—	H	±, 0	(2, 121)
$(CH_3)_2CHCH_2CO$—	H	HO—	H	±	(146)
$(CH_3)_2CHCH_2CO$—	H	$(CH_3)_2C(OH)CH_2$—	H	0	(2)
$(CH_3)_2CHCH_2CO$—	H		H		(84)
$CH_3(CH_2)_4CO$—	H	HO—	H	++	(146)
$CH_3(CH_2)_4CO$—	H	C_6H_5—	H	++	(102)
$CH_3(CH_2)_4CO$—	H	4-$(NO_2)C_6H_4$—	H	++	(102)

TABLE 52—*Continued*

R^4	$R^{4'}$	R^1	$R^{1'}$	ACTIVITY	REFERENCES
$CH_3(CH_2)_4CO$—	H	4-$(NH_2)C_6H_4$—	H	++	(102)
$CH_3(CH_2)_4CO$—	H		H	++	(102)
$CH_3(CH_2)_4CO$—	H		H	++	(174)
$CH_3(CH_2)_4CO$—	H	$CH_3(CH_2)_3SO_2$—	H	±	(174)
$CH_3(CH_2)_4CO$—	H	$CH_3(CH_2)_4SO_2$—	H	±	(174)
$CH_3(CH_2)_4CO$—	H	4-$(NH_2)C_6H_4SO_2$—	H		(42)
$(CH_3)_2CH(CH_2)_2CO$—	H	HO—	H	±	(146)
$(C_2H_5)_2CHCO$—	H		H		(123)
$CH_3(CH_2)_5CO$—	H	HO—	H	++	(146)
$CH_3(CH_2)_6CO$—	H	HO—	H	+	(146)
$CH_3(CH_2)_7CO$—	H	HO—	H	±	(146)
$CH_3(CH_2)_7CO$—	H		H		(42)
$CH_3(CH_2)_{10}CO$—	H	C_4H_9—	H		(84)
$CH_3(CH_2)_{10}CO$—	H	$C_6H_5CH_2$—	H		(84)
$CH_3(CH_2)_{10}CO$—	H	Piperidide			(84)
$CH_3(CH_2)_{10}CO$—	H	$CH_3(CH_2)_{10}CO$—	H	0	(38)

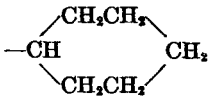
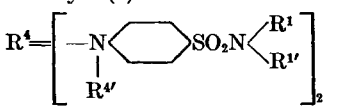
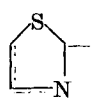
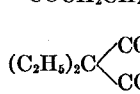
$CH_3(CH_2)_{10}CO$—	H		H	±	(42, 54)
$CH_3(CH_2)_{10}CO$—	H	4-$(NH_2)C_6H_4SO_2$—	H	0	(42)
$HOCH_2CO$—	H		H		(123)
$HOCH_2CO$—	H		H		(123)
CH_3OCH_2CO—	H	$HOCH_2CH_2$—	H	+, 0	(1, 121)
CH_3OCH_2CO—	H	CH_3OCH_2—	H	±	(121)
CH_3OCH_2CO—	H	$CH_3CHOHCH_2$—	H	0	(121)
CH_3COOCH_2CO—	H	$HOCH_2CH_2$—	H	0	(121)
CH_3COOCH_2CO—	H	$CH_3CHOHCH_2$—	H	0	(121)
CH_3COOCH_2CO—	H	$(CH_3)_2C(OH)CH_2$—	H	0	(121)
$C_2H_5OCH_2CO$—	H	CH_3—	CH_3—		(90)
$C_2H_5OCH_2CO$—	H	$C_6H_5CH_2$—	H		(90)
$C_2H_5OCH_2CO$—	H	Piperidide			(90)
$C_2H_5OCH_2CO$—	H		H		(90)
$HOOCCH_2CO$—	H	CH_3—	CH_3—		(89)
$HOOC(C_2H_5)_2CCO$—	H		H		(115)
$HOOC(CH_2)_2CO$—	H	$CH_3CHOHCH_2$—	H	0	(1)

TABLE 52—*Continued*

R^4	$R^{4'}$	R^1	$R^{1'}$	ACTIVITY	REFERENCES
$C_2H_5OOC(CH_2)_2CO$—	H	$CH_3CHOHCH_2$—	H	±	(1)
$CH_3(CH_3COO)CHCO$—	H	$CH_3CHOHCH_2$—	H	0	(1)
$HOCH_2CH_2NHCO(CH_2)_2CO$—	H	$HOCH_2CH_2$—	H	0	(1)
$C_4H_9NHCH_2CO$—	H	C_4H_9—	H		(90)
$C_4H_9NHCH_2CO$—	H	$HOCH_2CH_2$—	H		(90)
$C_4H_9NHCH_2CO$—	H	$C_6H_5CH_2$—	H		(90)
b. N^4-Acyclic-acyl: (2) derivatives of dibasic acids					
					
—$COCH_2CO$—	H	$HOCH_2CH_2$—	H	0	(1)
—$COCH_2CO$—	H	$CH_3CHOHCH_2$—	H	0	(1)
—$COCH_2CO$—	H		H		(123)
—$COCH_2CO$—	H		H		(123)
—$COCH_2CH_2CO$—	H	$HOCH_2CH_2$—	H	0	(1)
—$COCH_2CH_2CO$—	H	$CH_3CHOHCH_2$—	H	0	(1)
—$COCH_2CH_2CH_2CO$—	H	$HOCH_2CH_2$—	H	0	(1)
—$COCH_2CH_2CH_2CO$—	H	$CH_3CHOHCH_2$—	H	0	(1)
	H		H		(123)

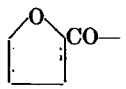
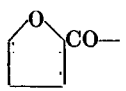
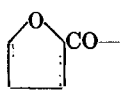
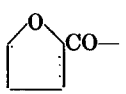
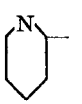
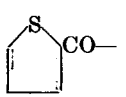
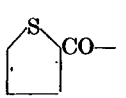
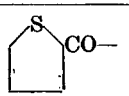
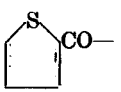
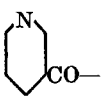
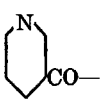
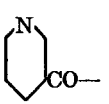
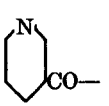
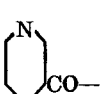
$(C_2H_5)_2C(CO—)(CO—)$	H		H		(123)
c. N^4-Isocyclic-acyl (general formula as at top of table)					
$C_6H_5CO—$	H	$C_6H_5—$	H	0	(143)
$C_6H_5CO—$	H	$3\text{-}(NO_2)C_6H_4—$	H		(76)
$C_6H_5CH{=}CHCO—$	H	$C_2H_5—$	$C_2H_5—$		(84)
d. N^4-Heterocyclic-acyl (general formula as at top of table)					
	H	$C_6H_5—$	H	±	(102)
	H	$4\text{-}(NO_2)C_6H_4—$	H	±	(102)
	H	$4\text{-}(NH_2)C_6H_4—$	H	±	(102)
	H		H	++	(102)
	H	$C_6H_5—$	H	±	(102)
	H	$4\text{-}(NO_2)C_6H_4—$	H	±	(102)

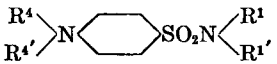
TABLE 52—*Concluded*

R^4	$R^{4'}$	R^1	$R^{1'}$	ACTIVITY	REFERENCES
	H	4-$(NH_2)C_6H_4$—	H	±	(102)
	H		H	±	(102)
	H	C_6H_5—	H		(102)
	H	4-$(NO_2)C_6H_4$—	H	0	(102)
	H	4-$(NH_2)C_6H_4$—	H		(102)
	H		H		(102, 119)
	H		H		(60)

	H		H	(60)
	H	CH_3CO-	H	(43)
	H		H	(43)
	H	CH_3-	H	(90)
	H	C_2H_5-	C_2H_5-	(90)

TABLE 53

N^4-Sulfonyl-N^1-substituted sulfanilamides



R^4	$R^{4'}$	R^1	$R^{1'}$	ACTIVITY	REFERENCES
		1. N^4-Acyclic-sulfonyl			
CH_3SO_2—	H	CH_3—	CH_3—	—	(179)
CH_3SO_2—	H	$HOCH_2CH_2$—	$HOCH_2CH_2$—		(179)
CH_3SO_2—	H	4-$(NH_2SO_2)C_6H_4$—	H		(179)
		2. N^4-Isocyclic-sulfonyl			
$C_6H_5SO_2$—	H	CH_3—	CH_3—		(26)
$C_6H_5SO_2$—	H	C_2H_5—	C_2H_5—		(26)
4-$BrC_6H_4SO_2$—	H	CH_3—	H		(90)
3-$(NO_2)C_6H_4SO_2$—	H	3-$(NO_2)C_6H_4SO_2$—	H		(36)
4-$(NO_2)C_6H_4SO_2$—	H	CH_3—	H		(82)
4-$(NO_2)C_6H_4SO_2$—	H	C_6H_5—	H		(82)
4-$(NO_2)C_6H_4SO_2$—	H	C_4H_9—	H		(82)
4-$(NO_2)C_6H_4SO_2$—	H	CH_3—	CH_3—		(82)
4-$(NO_2)C_6H_4SO_2$—	H	$HOOCCH_2$—	H		(82)
4-$(NO_2)C_6H_4SO_2$—	H	HO_3SCH_2—	H		(82)
4-$(CH_3)C_6H_4SO_2$—	H	$HOCH_2CH_2$—	$HOCH_2CH_2$—	+	(37)
4-$(CH_3)C_6H_4SO_2$—	H	4-[4′-$(CH_3)C_6H_4SO_2NH$]C_6H_4—	H	0	(42)
3-HOOC-4-$ClC_6H_3SO_2$—	H	C_2H_5—	C_2H_5—		(44)
4-$(HOOC)C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)
4-$(ClOC)C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)
4-$(NH_2OC)C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)
4-$(N_3OC)C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)
4-$(NH_2NHOC)C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)

3,4-$(CH_3O)_2C_6H_3SO_2$—	H	CH_3—	H		(90)
3,4-$(CH_3O)_2C_6H_3SO_2$—	H	CH_3—	CH_3—		(90)
3-$(NH_2)C_6H_4SO_2$—	H	3-$(NH_2)C_6H_4SO_2$—	Na—	+	(39)
4-$(NH_2)C_6H_4SO_2$—	H	CH_3—	H	++	(48, 90)
4-$(NH_2)C_6H_4SO_2$—	H	CH_3—	CH_3—*	++, +	(25, 26, 48, 90, 121, 140, 164)
4-$(NH_2)C_6H_4SO_2$—	K—	CH_3—	CH_3—	++	(48)
4-$(NH_2)C_6H_4SO_2$—	Na—	CH_3—	CH_3—	++	(48)
4-$(NH_2)C_6H_4SO_2$—	H	C_2H_5—	H		(90)
4-$(NH_2)C_6H_4SO_2$—	H, Na— or K—	C_2H_5—	C_2H_5—		(25, 26, 90)
4-$(NH_2)C_6H_4SO_2$—	H	C_4H_9—	H		(90)
4-$(NH_2)C_6H_4SO_2$—	H	$HOCH_2CH_2$—	H	++, 0	(9, 11, 37, 54, 90)
4-$(NH_2)C_6H_4SO_2$—	H	$HOCH_2CH_2$—	CH_3—	++	(40)
4-$(NH_2)C_6H_4SO_2$—	H	$HOCH_2CH_2$—	$HOCH_2CH_2$—	+	(39, 90)
4-$(NH_2)C_6H_4SO_2$—	H	$CH_3CHOHCH_2$—	H	+, 0	(2, 39)
4-$(NH_2)C_6H_4SO_2$—	H	$(CH_3)_2C(OH)CH_2$—	H	0, ±	(2, 121)
4-$(NH_2)C_6H_4SO_2$—	H	$HOCH_2CH_2$—	C_6H_5—	++	(39)
4-$(NH_2)C_6H_4SO_2$—	H	$HOOCCH_2$—	H	±	(9, 11, 90)
4-$(NH_2)C_6H_4SO_2$—	H	2-$(HOOC)C_6H_4$—	H	++	(39)
4-$(NH_2)C_6H_4SO_2$—	H	4-$(HOOC)C_6H_4$—	H		(123)
4-$(NH_2)C_6H_4SO_2$—	H	2-$(NaO_3S)C_6H_4$—	H		(23)
4-$(NH_2)C_6H_4SO_2$—	H	4-$(NaO_3S)C_6H_4$—	H	+	(39)
4-$(NH_2)C_6H_4SO_2$—	H	3,6,8-$(HO_3S)_3C_{10}H_4$—	H		(123)
4-$(NH_2)C_6H_4SO_2$—	H	4-[4′-$(NH_2)C_6H_4SO_2NH$]-1-NaO_3S-2-C_6H_3—	H	0	(42)
4-$(NH_2)C_6H_4SO_2$—	H	4-[4′-$(NH_2)C_6H_4SO_2NH$]$C_6H_4SO_2$-$NHCH_2CH_2$—	H	0	(42)
4-$(NH_2)C_6H_4SO_2$—	H	Morpholide		±	(121)
4-$(NH_2)C_6H_4SO_2$—	H	4-$(HO)C_6H_4SO_2$—	H		(42)

*Uleron.

TABLE 53—*Continued*

R^4	$R^{4'}$	R^1	$R^{1'}$	ACTIVITY	REFERENCES
2. N^4-Isocylic-sulfonyl—*Continued*					
4-$(NH_2)C_6H_4SO_2$—	H	4-$(NH_2)C_6H_4SO_2$—	H	+	(39)
4-$(NH_2)C_6H_4SO_2$—	Na—	4-[4′-$(NH_2)C_6H_4SO_2N$(Na)]$C_6H_4SO_2$—	Na—	0	(39)
4-$[(CH_3)_2N]C_6H_4SO_2$—	H	CH_3—	CH_3—	++	(90)
4-$(HO_3SCH_2NH)C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)
4-$(CH_3CONH)C_6H_4SO_2$—	H	CH_3—			(90)
4-$(CH_3CONH)C_6H_4SO_2$—	H	CH_3—	CH_3—		(90, 164)
4-$(CH_3CONH)C_6H_4SO_2$—	H	C_2H_5—	H		(90)
4-$(CH_3CONH)C_6H_4SO_2$—	H	C_2H_5—	C_2H_5—		(90)
4-$(CH_3CONH)C_6H_4SO_2$—	H	C_4H_9—	H		(90)
4-$(CH_3CONH)C_6H_4SO_2$—	H	$HOCH_2CH_2$—	H		(9, 39, 90)
4-$(CH_3CONH)C_6H_4SO_2$—	H	$CH_3CHOHCH_2$—	H	0	(2)
4-$(CH_3CONH)C_6H_4SO_2$—	H	$(CH_3)_2COHCH_2$—	H	0	(2)
4-$(CH_3CONH)C_6H_4SO_2$—	H	$HOOCCH_2$—	H		(9)
4-$(CH_3CONH)C_6H_4SO_2$—	H	Morpholide		0	(121)
4-$(CH_3CONH)C_6H_4SO_2$—	H	C_2H_5OOCN(morpholine)—			(98)
4-$(CH_3CONH)C_6H_4SO_2$—	H	4-$(CH_3CONH)C_6H_4SO_2$—	H		(151)
4-$[CH_3(CH_2)_2CONH]C_6H_4SO_2$—	H	Morpholide		0	(121)
4-$[(CH_3)_2NCH_2CONH]C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)
4-$(C_4H_9NHCH_2CONH)C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)
4-[HOOC(C6)$NHSO_2$(C6)$NHSO_2$(C6)NHCONH]-$C_6H_4SO_2$—	H	4-$(HOOC)C_6H_4$—	H		(123)
4-[4′-$(NH_2)C_6H_4SO_2NH]C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)

4-[4′-(NH_2)$C_6H_4SO_2NH$]$C_6H_4SO_2$—	H	$HOCH_2CH_2$—	H	±	(39)
4-[4′-(NH_2)$C_6H_4SO_2NH$]$C_6H_4SO_2$—	H	$HOCH_2CH_2$—	$HOCH_2CH_2$—	±	(39)
4-[4′-(NH_2)$C_6H_4SO_2NH$]$C_6H_4SO_2$—	H	4-(NaO_3S)C_6H_4—	H	++	(39)
4-[4′-(CH_3CONH)$C_6H_4SO_2NH$]$C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)
4-[4′-(CH_3O)C_6H_4NH]-3-(HOOC)$C_6H_3SO_2$—	H	C_2H_5—	C_2H_5—		(44)

3. N^4-Heterocyclic-sulfonyl

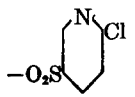
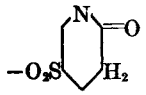
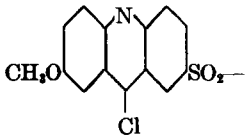
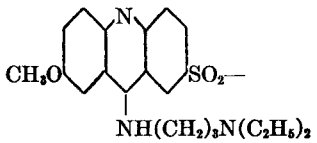
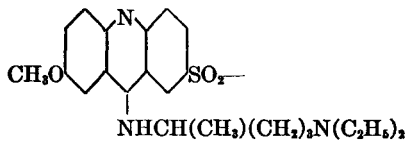
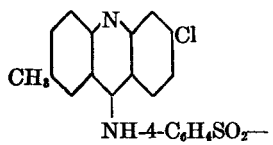
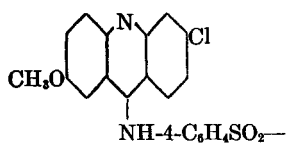
	H		H		(150)
	H		H		(150)
	H	C_2H_5—	C_2H_5—		(44)
	H	C_2H_5—	C_2H_5—		(44)
	H	C_2H_5—	C_2H_5—		(44)

TABLE 53—*Concluded*

R^4	$R^{4'}$	R^1	$R^{1'}$	ACTIVITY	REFERENCES
3. N^4-Heterocyclic-sulfonyl—*Continued*					
	H	C_2H_5—	C_2H_5—		(44)
	H	C_2H_5—	C_2H_5—		(44)
	H	C_2H_5—	C_2H_5—		(44)

It is interesting also that 2-(N^4-benzylidinesulfanilamido)pyridine and 2-(N^4-3-hydroxybenzylidinesulfanilamido)pyridine were rated +++ against streptococci, but only + against pneumococci, whereas the corresponding N^4-(4-methoxybenzylidine) and N^4-(4-dimethylaminobenzylidine) derivatives were rated + against streptococci and + against pneumococci (102). If confirmed by other laboratories, results such as these would refute the argument that the activity of such derivatives can be explained by *in vivo* cleavage to sulfapyridine (which was rated ++ against both organisms), since obviously sulfapyridine, if the active agent, should not give *increased* activity against streptococci and *decreased* activity against pneumococci when administered as compounds which liberate it in the body. It would be interesting to see these results compared in terms of S.B.C.$_{50}$'s.

(*H*) *N^4-Azo-N^1-substituted sulfanilamides*

The N^4-azo-N^1-substituted sulfanilamides are listed in table 55.

VII. NUCLEAR,N^1,N^4-SUBSTITUTED SULFANILAMIDES

These compounds (see table 56) have been synthesized for other purposes usually, and only one has been tested for chemotherapeutic activity. It was inactive, which is not surprising in view of the usual effect of nuclear and N^4-substitution. The series of N^4-arylsulfanilamides was synthesized as intermediates for acridine derivatives of interest against malaria (see section IX).

VIII. SALTS OF SULFANILAMIDE

Sulfanilamide, being an amphoteric substance, forms salts with both strong acids and bases (see table 57). The salts with bases hydrolyze in water to give pH values of 10 to 11, while the salts with acids give values of 2 to 3. The salt with 10-camphorsulfonic acid appears equal to sulfanilamide in effectiveness and has the advantage of being highly soluble so that it can be injected intravenously.

Greater effectiveness is claimed for complex salts of sulfanilamide with the cinchona alkaloids and halogen acids (176).

IX. UNCLASSIFIED SULFANILAMIDE DERIVATIVES

These derivatives are given in tables 58 and 59. In the case of the 2-acridinesulfonamides the numbering system used abroad is as follows:

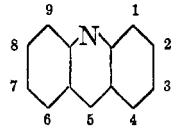
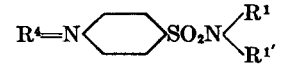


TABLE 54

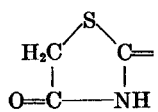
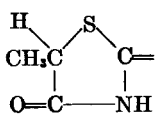
N^4-Anil-N^1-substituted sulfanilamides



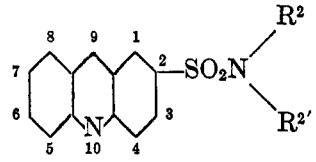
R^4	R^1	$R^{1'}$	ACTIVITY	REFERENCES
	(1) N^4-Acyclic-anil			
Dextrose		H	++	(161)
Galactose		H	+	(161)
	(2) N^4-Isocyclic-anil			
$C_6H_5CH=$	C_6H_5-	H	+, ±	(101, 102)
$C_6H_5CH=$	4-$(NO_2)C_6H_4-$	H	++, +++	(101, 102)
$C_6H_5CH=$		H	++, +++	(101, 102)
$C_6H_5CH=CHCH=$		H	++	(102, 169)
2-$(NO_2)C_6H_4CH=$		H	+++	(102)

4-$(NO_2)C_6H_4CH$=	CH_3—	CH_3—		(90)
4-$(NO_2)C_6H_4CH$=	4-$(NO_2)C_6H_4$—	H	+	(102)
4-$(NO_2)C_6H_4CH$=	$HOOCC_6H_4$—	H		(91)
4-$(NO_2)C_6H_4CH$=	4-[4′-$(NO_2)C_6H_4CH$=N]C_6H_4—	H	±	(102)
4-$(NO_2)C_6H_4CH$=		H	+++	(102)
3-$(HO)C_6H_4CH$=		H	+++	(102)
4-$(CH_3O)C_6H_4CH$=	C_6H_5—	H	+	(101)
4-$(CH_3O)C_6H_4CH$=	4-$(NO_2)C_6H_4$—	H	+	(101)
4-$(CH_3O)C_6H_4CH$=		H	++, +	(101, 102)
4-$(CH_3O)C_6H_4CH$=	4-[4′-$(CH_3O)C_6H_4CH$=N]C_6H_4—	H	++	(102)
4-[$(CH_3)_2N$]C_6H_4CH=	C_6H_5—	H	+	(101)
4-[$(CH_3)_2N$]C_6H_4CH=	4-$(NO_2)C_6H_4$—	H	+	(101)
4-[$(CH_3)_2N$]C_6H_4CH=		H	+	(101)
4-[$(CH_3)_2N$]C_6H_4CH=	4-[4′-[$(CH_3)_2N$]C_6H_4CH=N]C_6H_4—	H	++	(102)

TABLE 54—*Concluded*

R^4	R^1	$R^{1'}$	ACTIVITY	REFERENCES
(3) N^4-Heterocyclic-anil				
	$CH_3CHOHCH_2$—	H	0	(1)
	$CH_3CHOHCH_2$—	H	0	(1)

This numbering has been transcribed to the system used in *Chemical Abstracts* indices



(but not always in *Chemical Abstracts* text!).

E. Summary and General Conclusions on Correlation of Structure and Chemotherapeutic Activity

The following conclusions are based on such scanty and variable pharmacological data that they are of little scientific value. They are given in the hope that they may guide future research to new achievements and that any negative conclusions will not discourage further work in that field.

I. SULFANILAMIDE DERIVATIVES

1. Nuclear-substituted sulfanilamides are usually inactive.

2. N^1-Substitution in sulfanilamide has given the most promising new derivatives.

(*a*) The N^1-acyclic derivatives have not been so active as the parent sulfanilamide.

(*b*) N^1-Arylsulfanilamides are in general not so active as sulfanilamide. Isomerism of substituents on the N^1-aryl nucleus has an important effect on activity.

(*c*) N^1-Heterocyclicsulfanilamides have shown great activity against pneumococci and equal or better activity against streptococci than sulfanilamide. Substituents on the heterocyclic ring modify the activity and position isomerism of such substituents may have a profound influence on the activity, which is difficult to explain in terms of current theories on the mode of action of sulfanilamide and its derivatives.

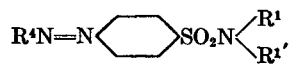
(*d*) Some N^1-acylsulfanilamides show activities somewhat greater than sulfanilamide on an equimolecular dosage. Branched-chain N^1-acylsulfanilamides are much less active than straight-chain derivatives.

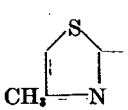
(*e*) N^1-Sulfonylsulfanilamides are generally inactive.

3. An hypothesis which needs verification by extensive pharmacological study is: *Blocking the N^4-nitrogen in sulfanilamide by a group which is not removed in vivo destroys the activity.* Groups which destroy the activity are alkyl, aryl, or sulfonyl. Groups which may be removed or converted *in vivo* to the free amine (or an active substance derived from the free

TABLE 55

N^4-Azo-N^1-substituted sulfanilamides



R^4	R^1	$R^{1'}$	ACTIVITY	REFERENCES
	(1) N^4-Acyclic-azo			
$CH_3CO(HOOC)CH$—	4-$[(CH_3)_2NSO_2]C_6H_4$—	H		(148)
	(2) N^4-Isocyclic-azo			
C_6H_5—	Cl—	Na—		(30, 175)
C_6H_5—	Cl—	Cl—		(30)
C_6H_5—	Br—	Na—		(31)
C_6H_5—	Br—	K—		(31)
C_6H_5—	CH_3—	CH_3—		(91)
C_6H_5—	C_2H_5—	H		(91)
C_6H_5—	4-$(HOOC)C_6H_4$—	H		(91)
C_6H_5—	3-CH_3-4-$(HO_3S)C_6H_3$—	H		(91)
C_6H_5—		H		(133)
2,4-$(HO)_2C_6H_3$—	C_2H_5—	C_2H_5—	+	(181)
4,6-$(HO)_2$-2-$(C_6H_{11})C_6H_2$—	C_2H_5—	C_2H_5—	±	(181)
4-$[Na(Cl)NSO_2]C_6H_4$—	Na—	Cl—		(175)
4-$[(C_2H_5)_2N]C_6H_4$—		H		(132)

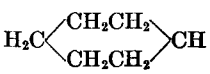
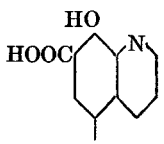
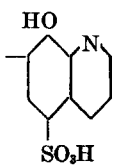
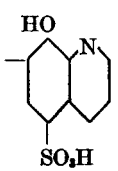
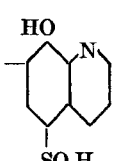
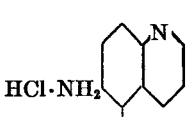
2,4-$(NH_2)_2C_6H_3$—	CH_3—	H		(86)
2,4-$(NH_2)_2C_6H_3$—	C_2H_5—	H		(86)
2,4-$(NH_2)_2C_6H_3$—	CH_3—	CH_3—		(86)
2,4-$(NH_2)_2C_6H_3$—	C_2H_5—	C_2H_5—		(86)
2,4-$(NH_2)_2C_6H_3$—	CH_2OHCH_2—	H		(86)
2,4-$(NH_2)_2C_6H_3$—		H		(86)
2,4-$(NH_2)_2C_6H_3$—	$HOOCCH_2$—	H		(136)
2,4-$(NH_2)_2C_6H_3$—	$HOOC(CH_3)CH$—	H		(136)
2,4-$(NH_2)_2C_6H_3$—	$C_6H_5CH_2$—	H		(68, 86)
2,4-$(NH_2)_2C_6H_3$—		Piperidide		(68, 86)
2,4-$(NH_2)_2C_6H_3$—	4-$(HO)C_6H_4CH_2(HOOC)CH$—	H		(136)
2,4-$(NH_2)_2C_6H_3$—		H		(68)
4-$HOOCCH_2O$-2-$(NH_2)C_6H_3$—	CH_3—	CH_3—		(88)
6-NH_2-1-HO-3-NaO_3S-2-$C_{10}H_4$—		Piperidide		(68)
7-NH_2-1-HO-3-HO_3S-2-$C_{10}H_4$—	$HOOCCH_2$—	H		(136)
7-NH_2-1-HO-3-HO_3S-2-$C_{10}H_4$—	$HOOC(CH_3)CH$—	H		(136)
7-NH_2-1-HO-3-HO_3S-2-$C_{10}H_4$—	4-$(HO)C_6H_4CH_2(HOOC)CH$—	H		(136)
2-$(C_2H_5)_2N$-5-HO-7-$(HO_3S)C_{10}H_4$—	CH_3—	CH_3—		(88)
1-$HOCH_2CH_2NH$-8-HO-3,6-$(HO_3S)_2C_{10}H_3$—	C_2H_5—	C_2H_5—		(88)
1-$HOCH_2CH_2NH$-8-HO-3,6-$(HO_3S)_2C_{10}H_3$—		Piperidide		(88)
1-$HOCH_2CH_2NH$-8-HO-3,6-$(HO_3S)_2C_{10}H_3$—		Pyrrolidide		(88)

TABLE 55—*Concluded*

R^4	R^1	$R^{1'}$	ACTIVITY	REFERENCES
(3) N^4-Heterocyclic-azo				
	C_2H_5—	H		(88)
	CH_3—	CH_3—		(88)
	C_4H_9—	H		(88)
		Piperidide		(88)
	CH_3—	CH_3—		(87)

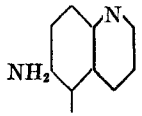
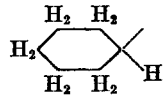
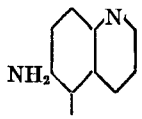
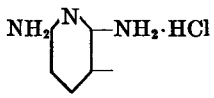
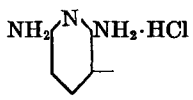
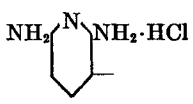
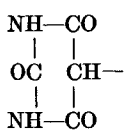
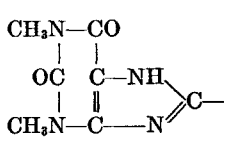
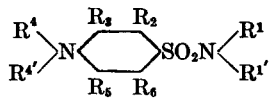
		H		(87)
		Piperidide		(87)
	CH_3—	H		(87)
	CH_3—	CH_3—		(87)
	$HOCH_2CH_2$—	$HOCH_2CH_2$—		(87)
	4-$[(CH_3)_2NSO_2]C_6H_4$—	H		(148)
	4-$[(CH_3)_2NSO_2]C_6H_4$—	H		(137)

TABLE 56

Nuclear, N^1, N^4-substituted sulfanilamides



R^4	$R^{4'}$	R^1	$R^{1'}$	R_2	R_3	R_5	R_6	ACTIVITY	REFERENCES
A. N^4-Inorganic									
None									
B. N^4-Acyclic									
None									
C. N^4-Isocyclic									
C_6H_5—	H	C_6H_5—	H	H	NO_2—	H	H		(55)
C_6H_5—	H	C_6H_5—	H	H	NH_2—	H	H		(55)
C_6H_5—	H	C_6H_5—	H	H	$C_6H_5NHSO_2$—	H	H		(55)
3-$(CH_3)C_6H_4$—	H	CH_3—	CH_3—	H	HOOC—	H	H		(92)
4-$(CH_3)C_6H_4$—	H	CH_3—	CH_3—	H	HOOC—	H	H		(92)
4-$(CH_3O)C_6H_4$—	H	CH_3—	CH_3—	H	HOOC—	H	H		(92)
4-$(CH_3O)C_6H_4$—	H	C_2H_5—	C_2H_5—	H	HOOC—	H	H		(7, 92)
4-$(CH_3O)C_6H_4$—	H	CH_3—	CH_3—	H	Cl—	H	H		(92)
4-$(CH_3O)C_6H_4$—	H	CH_3—	CH_3—	H	CH_2CH_2NHCO— | $N(C_2H_5)_2$	H	H		(92)
4-$(CH_3O)C_6H_4$—	H	C_6H_5—	H	H	HOOC—	H	H		(7)
D. N^4-Heterocyclic									
None									

E. N^4-Acyl									
CH_3CO—	H	$HO(CH_2)_4$—	H	H	CH_3O—	H	H	0	(121)
CH_3CO—	H		H	H	NO_2—	H	H		(98)
NH_2CO—	H	C_2H_5—	C_2H_5—	CH_3—	H	H	H	0	(34)
NH_2CO—	H	C_2H_5—	C_2H_5—	H	CH_3—	H	H	0	(34)
F. N^4-Sulfonyl									
4-$(NO_2)C_6H_4SO_2$—	H	C_2H_5—	C_2H_5—	H	HOOC—	H	H		(87)
4-$(NH_2)C_6H_4SO_2$—	H	CH_3—	CH_3—	H	HOOC—	H	H		(90)
4-$(NH_2)C_6H_4SO_2$—	H	CH_3—	CH_3—	H	NaOOC—	H	H		(90)
4-$(NH_2)C_6H_4SO_2$—	H	CH_3—	CH_3—	H	$(C_2H_5)_2NH\cdot HOOC$—	H	H		(90)
4-$(NH_2)C_6H_4SO_2$—	H	C_2H_5—	C_2H_5—	H	HOOC—	H	H		(90)
4-$(NH_2)C_6H_4SO_2$—	H	C_2H_5—	C_2H_5—	H	NaOOC—	H	H		(90)
4-$(NH_2)C_6H_4SO_2$—	H	C_2H_5—	C_2H_5—	H	$(HOCH_2CH_2)_2NH\cdot HOOC$—	H	H		(90)

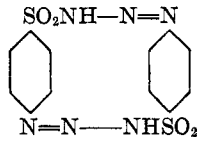
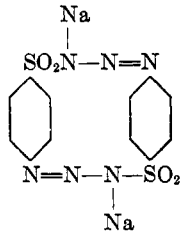
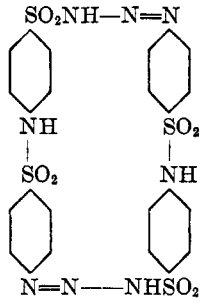
TABLE 57

Salts of sulfanilamide

	SALTS	ACTIVITY	REFERENCES
	A. Salts with acids		
Inorganic acids.....	Hydrochloride	++, +	(67, 86, 121)
	Phosphate		(192)
Acyclic acids.....	Adipate		(61)
Isocyclic acids.....	Camphorate		(50)
	10-Camphorsulfonate	++	(53, 147, 170)
	Benzenesulfonate	++	(53, 170)
	Phenolsulfonate	++	(53, 170)
	Sulfosalicylate	++	(53, 170)
	Salicylate		(192)
	Acetylsalicylate		(192)
	Phenylglycolate		(192)
	Picrate		(168)
Heterocyclic acids...	Quinolinate		(50)
	3-Pyridinesulfonate		(50)
	8-Hydroxyquinolinesulfonate		(192)
	B. Salts with bases		
Inorganic bases.....	Aluminum	+	(71)
	Mercuric Silver		
	Sodium	++	(42, 121)
Acyclic bases.....	None		
Isocyclic bases.....	Phenylmercuric		(110)
	Diphenylmercuric		(110)
Heterocyclic bases...	None		
	C. Mixed salts		
Quinine-sulfanilamide·2HCl		+++	(117, 176)
Quinine-sulfanilamide·2HBr			(118, 176)
Quinine-sulfanilamide·2HI			(118, 176)
Quinidine-sulfanilamide·H_2SO_4			(118, 176)
Quinidine-sulfanilamide·2HCl			(118, 176)
Quinidine-sulfanilamide·2HBr			(118, 176)
Euquinine-sulfanilamide·H_2SO_4			(118, 176)
Euquinine-sulfanilamide·2HCl			(118, 176)
Euquinine-sulfanilamide·2HBr			(118, 176)
Cinchonine-sulfanilamide·H_2SO_4			(118, 176)
Cinchonine-sulfanilamide·2HCl			(118, 176)
Cinchonine-sulfanilamide·2HBr			(118, 176)
Cinchonidine-sulfanilamide·H_2SO_4			(118, 176)
Cinchonidine-sulfanilamide·2HCl			(118, 176)
Cinchonidine-sulfanilamide·2HBr			(118, 176)
Quinine-sulfanilamide-salicylic acid		+++	(117, 176)
Quinine-sulfanilamide·H_2SO_4			(176)
Quinine-sulfanilamide·$1.5H_2SO_4$			(176)
Quinine-sulfanilamide·NH_2SO_3H			(176)
Quinine-sulfanilamide·4-[4′-$(NH_2)C_6H_4SO_2NH$]$C_6H_4SO_3H$			(176)

TABLE 58

Unclassified sulfanilamide derivatives

FORMULA	ACTIVITY	REFERENCES
	+	(115)
	+	(115)
	+	(115)

Various alkali, alkaline-earth, ammonium, and substituted ammonium salts of the above compounds are claimed

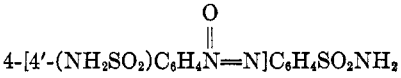
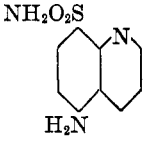
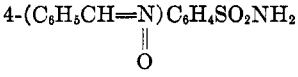
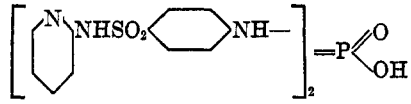
		(16, 134)
		(165)
		(135)

TABLE 58—*Concluded*

FORMULA	ACTIVITY	REFERENCES
4-[4′-$(NO_2)C_6H_4CH{=}N]C_6H_4SO_2NH_2$		(135)
	±	(179)

amine) are anils, certain reduced anils, formaldehyde-bisulfite, and formaldehyde-sulfoxalate derivatives.

4. N^1-Nuclear-, N^4-nuclear-, N^1,N^4-, and N^1,N^4,nuclear-substituted sulfanilamides follow in general the activities to be expected as a result of combining substituents on the basis of paragraphs 1, 2, and 3 above.

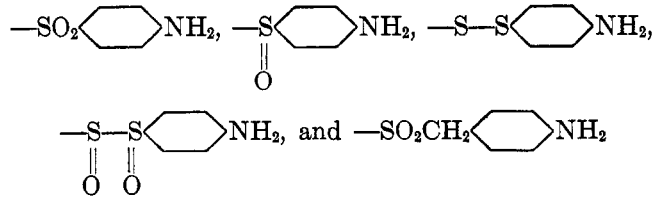
II. ALLIED COMPOUNDS

While not covered by this review, it may be worthwhile to summarize here the results to date on allied compounds. These results are based largely on work by the groups at The Pasteur Institute (61, 180, 181), Wellcome Research Laboratories (18, 19, 20, 69, 70), United States Public Health Service (9, 10, 11, 162, 198), and Rhône-Poulenc (134, 135, 195).

1. Isomers of sulfanilamide (metanilamide and orthanilamide) were inactive. Feinstone (54) has shown that this inactivity is intrinsic and not the result of a lack of adequate blood concentrations. Derivatives of these isomers were also inactive or nearly so.

2. Replacement of the amino group in sulfanilamide by H, —OH, —OR, —COOH, $-SO_2NH_2$, alkyl, or halogen practically destroyed the activity.

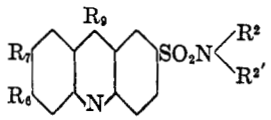
3. Replacement of the sulfonamido group by $-NH_2$, —CN, $-SO_3H$, $-AsO_3H_2$, $-CONH_2$, $-NHCOCH_3$, and $-NO_2$ destroyed the activity. Replacement by $-SO_2H$ retained most of the activity (70). Replacement by



gave compounds of slight activity (62).

TABLE 59

2-Acridinesulfonamides



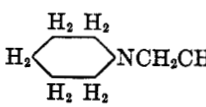
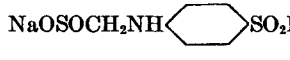
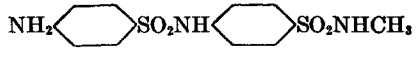
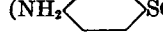
R^2	$R^{2'}$	R_6	R_7	R_9	REFERENCES
			CH_3O—	Cl—	(7)
			CH_3O—	$(C_2H_5)_2N(CH_2)_4NH$—	(7)
			CH_3O—	$(C_2H_5)_2N(CH_2)_3CH(CH_3)NH$—	(7)
CH_3—	CH_3—	CH_3—	H	Cl—	(92)
CH_3—	CH_3—	CH_3—	H	$(C_2H_5)_2NCH_2CHOHCH_2NH$—	(92)
CH_3—	CH_3—	H	CH_3—	Cl—	(92)
CH_3—	CH_3—	H	CH_3—	Br—	(92)
CH_3—	CH_3—	H	CH_3—	NaO_3S—	(92)
CH_3—	CH_3—	H	CH_3—	CH_3O—	(92)
CH_3—	CH_3—	H	CH_3—	C_6H_5O—	(92)
CH_3—	CH_3—	H	CH_3—	4-$(CH_3)C_6H_4S$—	(92)
CH_3—	CH_3—	H	CH_3—	$(C_2H_5)_2N(CH_2)_2S(CH_2)_3NH$—	(92)
CH_3—	CH_3—	H	CH_3—	4-$(NH_2CH_2)C_6H_4NH$—	(92)
CH_3—	CH_3—	H	CH_3—	4-$(CH_3CONHCH_2)C_6H_4NH$—	(92)
CH_3—	CH_3—	H	CH_3—	4-$(HOCH_2CH_2O)C_6H_4NH$—	(92)
CH_3—	CH_3—	H	CH_3—	4-$[(C_2H_5)_2NCH_2CH_2O]C_6H_4NH$—	(92)
CH_3—	CH_3—	H	CH_3—		(92)
CH_3—	CH_3—	H	CH_3O—	Cl—	(92)
CH_3—	CH_3—	H	CH_3O—	$(C_2H_5)_2N(CH_2)_5NH$—	(92)
CH_3—	CH_3—	H	CH_3O—	$(C_2H_5)_2NCH_2CHOHCH_2NH$—	(92)
CH_3—	CH_3—	H	CH_3O—	$(C_2H_5)_2NCH_2CHOHCH_2NHCH_2$-$CH_2NH$—	(92)
C_2H_5—	C_2H_5—	H	CH_3O—	Cl—	(7, 92)
C_2H_5—	C_2H_5—	H	CH_3O—	$(C_2H_5)_2NCH_2CH_2NH$—	(92)
C_2H_5—	C_2H_5—	H	CH_3O—		(92)
C_2H_5—	C_2H_5—	H	CH_3O—	$(C_2H_5)_2NCH_2CHOHCH_2NH$—	(92)
C_2H_5—	C_2H_5—	H	CH_3O—	$(C_2H_5)_2NCH_2CH_2NH$—	(92)
C_2H_5—	C_2H_5—	H	CH_3O—	$(C_2H_5)_2N(CH_2)_4NH$—	(7)
C_2H_5—	C_2H_5—	H	CH_3O—	$(C_2H_5)_2N(CH_2)_3CH(CH_3)NH$—	(7)
C_2H_5—	C_2H_5—	H	CH_3O—	$(C_2H_5)_2NCH_2CHOHCH_2NH$—	(92)
C_6H_5—	H	H	CH_3O—	Cl—	(7)
C_6H_5—	H	H	CH_3O—	$(C_2H_5)_2N(CH_2)_4NH$—	(7)
C_6H_5—	H	H	CH_3O—	$(C_2H_5)_2N(CH_2)_3CH(CH_3)NH$—	(7)

TABLE 60

Trade names of sulfanilamide and derivatives

TRADE NAME	CHEMICAL NAME	FORMULA
Albucid	N^1-Acetylsulfanilamide	$4\text{-}(NH_2)C_6H_4SO_2NHCOCH_3$
Aldanil	Sodium formaldehyde-sulfoxalate derivative of sulfanilamide	
Azosulfamide	See Neoprontosil	
Coccoclase	See Sulfapyridine	
Colsulanyde	Sulfanilamide	
Dagenan	See Sulfapyridine	
Deseptyl	Sulfanilamide	
Diseptal A (DB90)	See Uleron	
Diseptal B (DB87)	N^1-Methyl-N^4-sulfanilylsulfanilamide	
Diseptal C	See Disulon	
Disulon	N^4-Sulfanilylsulfanilamide	
Estreptocida	Sulfanilamide	
Eubasinum	See Sulfapyridine	
Eubasin	See Sulfapyridine	
1162F	Sulfanilamide	
Lysamide	Aluminum sulfanilamide	
Lysococcine	Sulfanilamide	
M & B 693	See Sulfapyridine	

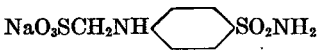
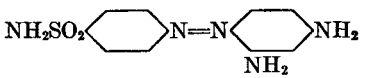
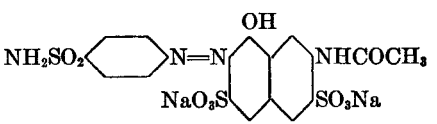
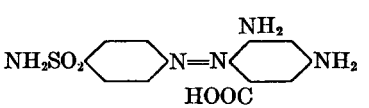
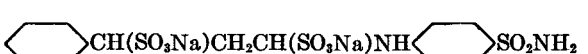
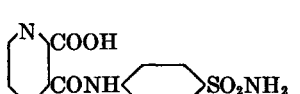
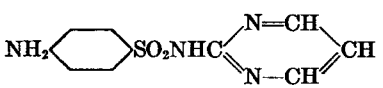
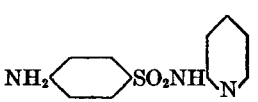
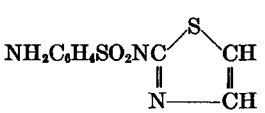
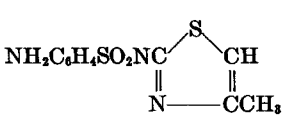
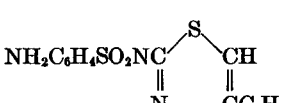
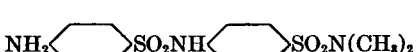
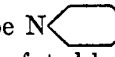
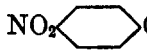
Neoprontosil	See Prontosil Soluble	
Novamide	N^4-(Sodium sulfomethylene) sulfanilamide	
Prontosil	2,4-Diaminoazobenzene-4′-sulfonamide	
Prontosil Album	Sulfanilamide	
Prontosil Flavum	See Prontosil	
Prontosil S(oluble)	Disodium 4-sulfamidophenyl-2-azo-7-acetylamino-1-hydroxynaphthalene-3,6-disulfonate	
Prontylin	Sulfanilamide	
Proseptazine	See Septazine	
Pyriamid	See Sulfapyridine	
Rubiazol	6′-Carboxy-2′,4′-diaminoazobenzene-4-sulfonamide	
Sanamide	Sulfanilamide	
Septazine (Setazine)	N^4-Benzylsulfanilamide	
Septoplex	Sulfanilamide	
Soluseptazine	N^4-(Disodium-α,γ-disulfo-γ-phenylpropyl)sulfanilamide	
Stramide	Sulfanilamide	
Streptal Soluble	N^4-Quinolinylsulfanilamide	
Streptal	Sulfanilamide	

TABLE 60—*Concluded*

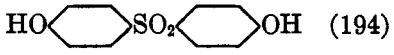
TRADE NAME	CHEMICAL NAME	FORMULA
Streptamid	Sulfanilamide	
Streptasol	*N*-Sulfanilylglycine	$NH_2C_6H_4SO_2NHCH_2COOH$
Streptocide	Sulfanilamide	
Streptocid Album	Sulfanilamide	
Streptocid Rubrum	See Neoprontosil	
Streptozon	See Prontosil	
Streptozon S	See Prontosil Soluble	
Sulfacet	See Albucid	
Sulfadiazine	2-Sulfanilamidopyrimidine	
Sulfamidyl	Sulfanilamide	
Sulfapyridine	2-Sulfanilamidopyridine	
Sulfathiazole	2-Sulfanilamidothiazole	
Sulfamethylthiazole	2-Sulfanilamido-4-methylthiazole	
Sulfaphenylthiazole	2-Sulfanilamido-4-phenylthiazole	
Sulphonamide P	Sulfanilamide	
Uleron (Uliron)	N^1,N^1-Dimethyl-N^4-sulfanilylsulfanilamide	

4. The fundamental unit common to the active compounds has been stated by Fourneau (62) to be  , but the absolute need of both sulfur and nitrogen has been refuted by the finding of slight or moderate activity for the compounds

 (195,198)

 (196)

and

 (194)

However, the latter compound has been called inactive by Buttle (70), so that it is uncertain whether nitrogen can be dispensed with.

F. Appendix A

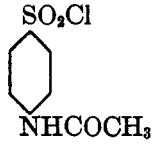
TRADE NAMES OF SULFANILAMIDE AND DERIVATIVES

Table 60 gives the trade names and formulas of sulfanilamide and its derivatives.

G. Appendix B

METHODS FOR SYNTHESIS OF SULFANILAMIDE DERIVATIVES

The common intermediate for almost all sulfanilamide derivatives is *N*-acetylsulfanilyl chloride (ASC):



This is obtained by the sulfonation of acetanilide with a 5-to-1 mole ratio of chlorosulfonic acid.[2] A wet paste of ASC results, which can be used for many purposes without drying or purification. When it is necessary to use purified ASC (as for reaction with expensive aminoheterocycles), it may be air-dried in thin layers on porous plates, or in a vacuum desiccator, and, when dry, recrystallized from a solvent. Benzene and ether, as described in the literature, are poor solvents. Much better results are obtained by using chloroform or ethylene dichloride.

N^4-Acetylsulfanilamide (ASA) is obtained by adding wet ASC to a large excess of 10 to 15 per cent ammonia at 40–50°C. with powerful agitation,

[2] For its preparation see H. Gilman: *Organic Syntheses*, Collective Volume I, p. 8. John Wiley and Sons, Inc., New York (1932).

followed by neutralization of excess ammonia and filtration of the crude ASA. It may be purified by dissolving in warm sodium hydroxide solution, treatment with an activated charcoal, and reprecipitation with acid.

General methods for hydrolysis of N^4-acetylsulfanilamides

Sulfanilamide is obtained from ASA by hydrolysis of the acetyl group with either hydrochloric acid or sodium hydroxide. Contrary to the statement of Gelmo (66), sulfanilamide (and practically all of its N^1-derivatives with the exception of the N^1-acylsulfanilamides) is stable at the sulfonamide linkage to all concentrations of sodium hydroxide at temperatures up to 110°C. On the other hand, many of the N^1-heterocyclic derivatives of sulfanilamide are cleaved at this linkage by boiling hydrochloric acid. Practically all sulfonamide derivatives are cleaved by boiling with 65–70 per cent sulfuric acid. The choice of acid or alkaline hydrolysis is dictated by the nature of the compound. For one which is stable and soluble in acid, the acid hydrolysis is preferred, since it is complete in a few minutes, whereas the alkaline hydrolysis may take several hours.

Acid hydrolysis is generally carried out by boiling the compound with 15 to 20 per cent hydrochloric acid, using about 1.7 moles of the acid per amino equivalent. Hydrolysis is usually complete when the temperature has been at 100°C. for 30 min. The product is then precipitated by neutralization with sodium hydroxide.

Alkaline hydrolysis is preferred for sensitive compounds or compounds which are insoluble in acid. All sulfonamides having a hydrogen remaining on the amido nitrogen form highly water-soluble sodium salts. This is an aid in synthesis, not only in hydrolysis but also in purifications and studies of structure. Alkaline hydrolysis is usually carried out by dissolving the compound in 0.5 to 1.0 molar concentration in water by adding the necessary amount of sodium hydroxide. More sodium hydroxide (1.25 to 1.5 moles per equivalent of acetylamino groups) is then added, and the solution boiled until hydrolysis is complete (2 to 3 hr.), as determined by taking two aliquot samples, making strongly acid with hydrochloric acid, titrating one directly by nitrite (see below) and the other after boiling for 15 min. If the two nitrite values agree, hydrolysis is complete.

Synthesis of N^1-substituted sulfanilamides

If the N^1-substituent is acyclic or isocyclic, the usual method of synthesis is to dissolve or suspend the corresponding amine in water and to add ASC under vigorous agitation while maintaining a pH of 8 to 11 by addition of sodium hydroxide and holding the temperature at 40–50°C. It is

convenient to use a little sodium carbonate as a buffer and indicator (when foaming starts additional sodium hydroxide is needed).

The crude N^4-acetyl-N^1-substituted sulfanilamide is obtained by acidifying and filtering. It may be purified by dissolving in alkaline solution and reprecipitating with acid after treatment with an activated charcoal, or by recrystallization from an organic solvent, of which alcohol is the most generally suitable.

Other methods of synthesis involve dry fusion of ASC with the base, or reaction in a mutual solvent such as acetone or dioxane. Use of pyridine as a solvent has definite advantages with a number of weak bases which do not react well with ASC in its absence. The ASC must be dried for such use, since it hydrolyzes rapidly in the presence of wet pyridine.

The N^4-acetyl group may be hydrolyzed by either of the general methods above, and the resulting N^1-substituted sulfanilamide purified by the same methods as used for the N^4-acetyl derivative. Advantage in purification may occasionally be taken of the ability of the free N^4-amino group to form soluble salts with acids. Since compounds with a free amino group are susceptible to oxidation, it is useful to add a small amount of a reducing agent, such as sodium bisulfite or sodium hydrosulfite, to help prevent such oxidation in the early stages of purification.

For synthesis of N^1-substituted sulfanilamides which are sensitive to hydrolysis by strong acids or bases, it is necessary to start with *p*-nitrobenzenesulfonyl chloride and to react this with the base by any of the above methods. The nitro group is then reduced by neutral iron reduction or catalytic hydrogenation. Unfortunately, there are no very satisfactory methods of preparing *p*-nitrobenzenesulfonyl chloride. The usual synthesis starts with *p*-nitrochlorobenzene, which is reacted with sodium disulfide in alcoholic solution to give 4,4′-dinitrodiphenyl disulfide. This is oxidized to the product with a mixture of nitric and hydrochloric acids or by chlorination in slightly diluted acetic acid. One of the essential points in this synthesis is to prepare pure sodium sulfide, sodium thiosulfate, etc.

Mention should also be made of the procedure of Bell (J. Chem. Soc. **1938,** Trans. 2776) for preparing *p*-nitrobenzenesulfonyl chloride.

Analysis

The diazotization of the amino group in sulfanilamide and its derivatives forms the basis for a volumetric method of assay which is also useful as a control test in following reactions. The method is as follows: Approximately 0.03 mole of the sample is weighed and dissolved (by warming if necessary) in 50 cc. of water and 15 cc. of concentrated hydrochloric acid. The solution is cooled to 15°C. by addition of ice and is then titrated

with $N/10$ sodium nitrite solution (which has been standardized by an identical procedure using pure sulfanilic acid). The nitrite is added under constant agitation until the first *immediate* blue streak is obtained by drawing a stirring rod, wet with the solution, through a smear of starch–iodide paste on filter paper. This end point should be permanent for 2 min.

In cases where the compound is too insoluble to be titrated or where there is an N^4-acyl substituent, it is frequently possible to hydrolyze the sample to sulfanilic acid by boiling with 15 to 20 cc. of 65 per cent sulfuric acid for 30 min., then cooling with ice, adding 5 cc. of concentrated hydrochloric acid, and proceeding with the titration.

The starch–iodide paste may be prepared as follows: Dissolve 2 g. of potassium iodide in 10 cc. of water and add to 285 cc. of boiling water in a flask or beaker heated by an oil bath and mechanically agitated. Add a solution of 5 g. of C.P. zinc chloride in 20 cc. of water to the boiling mixture, then slowly add a suspension of 13 g. of potato starch in 60 cc. of cold water. Again raise to a boil, then allow to cool slowly. Preserve in well-stoppered bottles. The paste should give an *immediate* blue streak when tested with a solution of 1 cc. of $N/10$ sodium nitrite in 1 l. of water and 10 cc. of concentrated hydrochloric acid.

REFERENCES[3]

(1) ADAMS, R., LONG, P. H., AND JEANES, A.: J. Am. Chem. Soc. **61**, 2346 (1939).
(2) ADAMS, R., LONG, P. H., AND JOHANSON, A. J.: J. Am. Chem. Soc. **61**, 2342 (1939).

[3] The following journals have been searched through the date of issue indicated:

JOURNAL	DATE
Berichte der Deutschen Chemischen Gesellschaft	January, 1940
British Chemical Abstracts A, II, III	March, 1940
British Medical Journal	March 23, 1940
Chemical Abstracts, Sections 10, 11, 17	April 20, 1940
Helvetica Chimica Acta	February, 1940
Journal of the American Chemical Society	April, 1940
The Journal of the American Medical Association	March 30, 1940
Journal of the American Pharmaceutical Association	March, 1940
The Journal of Biological Chemistry	April, 1940
Journal of the Chemical Society (London)	January, 1940
The Journal of Pharmacology and Experimental Therapeutics	April, 1940
The Lancet	April 13, 1940
Physiological Abstracts	March, 1940
Proceedings of the Society of Experimental Biology and Medicine	April 1, 1940
Recueil des travaux chimiques des Pays-bas	January, 1940
Science	April 19, 1940

This search has excluded references which were primarily reports of clinical results on, or further pharmacological testing of, the well-known sulfanilamide derivatives

(3) AKTIEN-GES. VORM. B. SIEGFRIED: Swiss patent 198,137 (September 1, 1938); Chem. Abstracts **33,** 3530.
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