saturating with carbon dioxide, the solution was filtered and made acid to congo. Continuous ether extraction for twenty-four hours and removal of the solvent *in vacuo*, yielded an oil which crystallized after seeding with riddellic acid. Recrystallization from ether–petroleum ether (b. p. 30–60°) gave 0.35 g. of a white crystalline solid melting at 61–62° (cor.). A mixed melting point with riddellic acid monohydrate (m. p. 62°) gave no depression.

B. Retronecanol.—The aqueous solution remaining after ether extraction of the acid just described was made alkaline with 10% aqueous sodium hydroxide and extracted with ether. After drying the ether extracts over anhydrous magnesium sulfate and distilling the ether, a solid remained. This product, recrystallized from petroleum ether (b. p. 30–60°), melted at 95–96° (cor.) which is identical with the melting point of retronecanol.

A picrate was prepared from water which melted at 211° with decomposition. A mixed melting point with retronecanol picrate (m. p. 211°) showed no depression.

Hydrogenation of Riddelliine (PtO_2 Catalyst).—A solution of 5 g. of riddelliine in 150 cc. of ethanol and 25 cc. of water was hydrogenated at 2–3 atmospheres pressure using 0.1 g. of platinum oxide catalyst. A total of four mole equivalents of hydrogen was absorbed within one hour. The catalyst was filtered off and the solvent removed *in vacuo*. A white amorphous solid material remained which was very hygroscopic and soluble in ethanol. Attempts to obtain a crystalline product failed.

One gram of this material was taken up in 5 cc. of water and 10 cc. of 50% aqueous sodium hydroxide added. After refluxing one hour and cooling, the mixture was extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and the ether distilled. A solid product remained which after one recrystallization from petroleum ether melted at 95–96°. Retronecanol melts at 95–96°. A picrate of the above base was prepared in ethanol and melted at 213°. A mixed melting point with authentic retronecanol picrate showed no depression.

Acidification and continuous ether extraction of the aqueous solution remaining after removal of the retronecanol yielded an acid fraction as a brown viscous oil. This has not been obtained in a pure state.

Summary

1. Riddelliine, the alkaloid of *Senecio Riddellii*, has been isolated and shown to have the molecular formula reported by Manske, $C_{18}H_{23}O_6N$.

2. Upon saponification, riddelliine gives a molecule of retronecine and one molecule of a crystalline acid, $C_{10}H_{14}O_6$, designated as riddellic acid. It is dibasic and with diazomethane gives a dimethyl ester.

3. Riddellic acid, upon reduction with hydrogen and platinum oxide, absorbs two moles of hydrogen but no pure product was isolated. Dimethyl riddellate under similar conditions absorbs only one mole of hydrogen to give dimethyl dihydroriddellate.

4. Riddelliine, upon reduction with hydrogen and Raney nickel, absorbs two moles of hydrogen to form tetrahydroriddelliine which has the properties of an amino acid and can be hydrolyzed to retronecanol and riddellic acid. With platinum oxide as a catalyst, four moles of hydrogen are absorbed but the product has not been obtained in a pure state. On saponification the crude octahydroriddelliine yields retronecanol.

5. Riddelliine is thus shown to be an ester from one mole of the dibasic acid, riddellic acid, and one mole of retronecine, each of the two hydroxyls in the molecule being utilized.

URBANA, ILLINOIS RECEIVED SEPTEMBER 18, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE CALCO CHEMICAL DIVISION OF THE AMERICAN CYANAMID COMPANY]

Sulfanilamide Derivatives. VIII. Sulfanilylamidines[1]

BY E. H. NORTHEY, ALAN E. PIERCE AND D. J. KERTESZ

In view of the fact that most of the recently developed chemotherapeutic agents of high potency, including sulfapyridine, sulfathiazole and sulfadiazine, have the structure of sulfanilyl cyclic amidines, 4-$(NH_2)C_6H_4SO_2NHC(=N-)$ it was thought desirable to prepare an analogous series of amidine derivatives of the type 4-(NH_2)-$C_6H_4SO_2NHC(R)=NR'$. A number of such compounds have been made, however, the structure appears to be better represented by the formula 4-$(NH_2)C_6H_4SO_2N=C(R)NHR'$, because the monosulfanilylamidines did not form alkali salts corresponding to the well known sodium salts of the above sulfanilamido heterocycles. This would indicate lack of ionizable hydrogen associated with the amide nitrogen. Also, while sulfapyridine is stable to alkaline hydrolysis and is cleaved by mineral acids to sulfanilic acid and 2-aminopyridine,[2] the sulfanilylamidines are cleaved to sulfanilamide by either

(1) Presented in part before the Division of Medicinal Chemistry, A. C. S., Buffalo, N. Y., September, 1942.

(2) Crossley, Northey and Hultquist, THIS JOURNAL, **62**, 372 (1940).

TABLE I

Compound (S=$H_2NC_6H_4SO_2$—)	Formula	Melting range, °C. Int. nitro cpd.[a]	Melting range, °C. Finished product	% Assay by nitrite	Analyses, % Calculated C	H	N	S	Found C	H	N	S
S-Acetamidine[b]	$C_8H_{11}N_3O_2S$	190.7–191.3	151.4–152.0[b]	100.6	45.0	5.2	19.7	15.0	45.0	5.3	19.7	14.9
Di-S-acetamidine	$C_{14}H_{18}N_4O_4S_2$	189.0–190.7	191.6–191.8	100.5	45.6	4.4	15.2	17.4	45.5	4.7	15.3	17.2
S-Isocaproamidine	$C_{12}H_{19}N_3O_2S$	247.0–250.0 dec.	126.0–127.2	99.3	53.4	7.1	15.6	11.9	52.7	7.0	15.9	11.9
S-α-Phenylacetamidine[c]	$C_{14}H_{15}N_3O_2S$	194.3–195.8	177 –179		52.6	3.8	13.2	10.0	51.8	4.0	12.9	10.0
S-Benzamidine[b]	$C_{13}H_{13}N_3O_2S$	180.3–181.0	210.2–210.7[d]	100.3	56.8	4.8	15.3	11.6	56.4	5.0	15.4	11.5
Di-S-benzamidine	$C_{19}H_{16}N_4O_4S_2$	241.8–242.6	206.4–207.6 dec.	100.3	53.0	4.2	13.0	14.9	53.0	4.2	13.3	15.2
S-p-Toluamidine	$C_{14}H_{15}N_3O_2S$	149.5–160	234.9–235.4	100.3	58.0	5.2	14.6	11.1	57.4	5.1	14.7	11.2
Di-S-p-toluamidine	$C_{29}H_{20}N_4O_4S_2$	213.7–214.9	166.9–167.5	100.3	54.0	4.5	12.6	14.4	52.4	4.7	12.9	14.2
S-Nicotinamidine	$C_{12}H_{11}N_4O_2S$	232.5–233.5	208.1–208.2	100.0	51.4	4.0	20.4	11.6	52.1	4.5	20.4	11.5
N-S-N'-Methylbenzamidine	$C_{14}H_{16}N_3O_2S$	181.2 dec.	228.1–229.2	100.0	58.1	5.2	14.5	11.1	57.9	5.0	14.6	11.1
N-S-N'-Diethylbenzamidine	$C_{17}H_{21}N_3O_2S$		193.7–194.0	100.0	61.5	6.4	12.7	9.7	61.1	6.4	12.6	10.0
N-S-N'-α-Pyridylbenzamidine	$C_{18}H_{16}N_4O_2S$	180.7 dec.	206.8–207.5	99.8	61.3	4.6	15.9	9.1	61.7	4.5	16.3	8.7

[a] Melting point taken on samples crystallized from alcohol or from water. [b] Melting point, lit. 149°. [c] Analysis given for the nitro compound. [d] Melting point, lit. 203°.

acid or alkaline hydrolysis, indicating a different type of linkage between amide nitrogen and carbon.

Further information on structure was given by synthesis from the corresponding imido chloride, —SO_2N=C(R)Cl, by reaction with secondary amines giving compounds of the type, —SO_2N=C(R)N(R')R'', where the possibility of tautomerism was eliminated.

As by-products in the reaction of unsubstituted amidines with sulfonyl chlorides, we isolated disulfonyl derivatives of the probable structure —SO_2N=C(R)NHSO_2—, which formed neutral alkali salts with one equivalent of base.

Preliminary pharmacological tests[3] showed low chemotherapeutic activities for all of the compounds with the possible exception of sulfanilylacetamidine which was approximately equal to sulfanilamide.

After the work here reported was completed, two patents[4,5] came to our attention. However, the preparation of disulfanilylamidines was not described in these references.

In preliminary work, acetylsulfanilylacetamidine was prepared from acetylsulfanilyl chloride and acetamidine, but it was not found possible to hydrolyze this product to sulfanilylacetamidine. Hence, this method of preparation was abandoned in favor of the preparation of nitrobenzene sulfonylamidines as intermediates. These were prepared in two ways. Amidine hydrochlorides, where readily available, were treated in acetone with *p*-nitrobenzenesulfonyl chloride, in the presence of excess sodium hydroxide. Both mono- and *bis*-nitrobenzenesulfonylamidines were formed in this reaction, the proportion varying with the amount of *p*-nitrobenzenesulfonyl chloride used in excess. The two types of products were easily separated, since only the latter were soluble in alkali. The first eight compounds in Table I were prepared through the use of this procedure. The second method involved the preparation of aromatic or heterocyclic N-acyl-*p*-nitrobenzenesulfonamides from the acid chloride and *p*-nitrobenzenesulfonamide in dry pyridine. The acyl sulfonamides were treated with phosphorus pentachloride to yield the corresponding imido chlorides which with ammonia or amines were converted to amidines. This method, as applied to N-benzoylbenzenesulfonamide, has been previously described[6,7,8] and was used for the preparation of the last four compounds listed in Table I.

All nitro compounds were reduced with iron to give the corresponding sulfanilylamidines, which were obtained as white microcrystalline substances upon purification by crystallization from alcohol or precipitation from acid or alkaline solution.

Experimental

N^4-Acetylsulfanilylacetamidine.—To 9.5 g. of acetamidine hydrochloride and 19.5 g. of 50% sodium hydroxide solution in 75 cc. of acetone, was added 25.2 g. of 95% acetylsulfanilyl chloride in portions, with vigorous stirring, over twenty minutes, at 10–20°. Cooling was necessary. After further stirring for twenty minutes, the slurry was diluted with 2 volumes of cold water, filtered, and the solid washed and dried. The yield of acetylsulfanilylacetamidine was 16.0 g., or 62.5%. A small sample recrystallized from hot water melted at 244.2 to 244.7° (all m. p.'s corrected).

Anal. Calcd. for $C_{10}H_{13}N_3O_3S$: C, 47.0; H, 5.1; N, 16.5; S, 12.6. Found: C, 47.0; H, 4.5; N, 16.8; S, 12.5.

Hydrolysis of acetylsulfanilylacetamidine was carried out in six moles of 7.5 *M* hydrochloric acid at 60°. Solu-

(3) Pharmacological tests were carried out under the direction of W. H. Feinstone at the Stamford, Conn., Laboratories of the American Cyanamid Co.

(4) Hungarian Patent 127,837, 1941; *C. A.*, **36**, 2271 (1942).

(5) British Patent 538,822, 1941; *Brit. Chem. Abs.*, **BIII**, 344 (1941).

(6) Gerhardt, *Ann.*, **108**, 214 (1858).

(7) Wolkoff, *Ber.*, **5**, 137 (1872).

(8) Wallach and Gossman, *ibid.*, **11**, 753 (1878).

tion was complete in two and three-fourths hours, but hydrolysis of the acetyl group was not complete, as determined by titration with sodium nitrite, until the end of three and one-half hours, when heating was stopped. Sulfanilamide was isolated in 90% yield. No sulfanilylacetamidine was identified.

p-Nitrobenzenesulfonylamidines from Amidines.—The procedure given above for acetylsulfanilylacetamidine was followed using a 5–10% excess of *p*-nitrobenzenesulfonyl chloride instead of acetylsulfanilyl chloride. In the alkaline filtrate from the mono-nitrobenzenesulfonylamidines, the *bis*-nitrobenzenesulfonylamidines were precipitated by acidification with hydrochloric acid. The yields ranged from 40–80% for the monosubstituted amidines and 20 to 35% for the disubstituted derivatives.

p-Nitrobenzenesulfonylamidines from Imido Chloride.—This method is illustrated by the preparation of *p*-nitrobenzenesulfonylnicotinamidine. 76.8 g. of N^1-nicotinyl-*p*-nitrobenzenesulfonamide[9] was mixed with 57 g. of phosphorus pentachloride and 100 cc. of phosphorus oxychloride, then heated at 80–85° for five hours. The excess phosphorus oxychloride was removed by distillation at reduced pressure and by washing the residue with petroleum ether. The imido chloride was added with stirring to 300 cc. of 15% aqueous ammonia. The *p*-nitrobenzenesulfonylnicotinamidine was filtered off, in 44% yield, and the corresponding amide was recovered, in 50% yield, by acidification of the filtrate.

The preparation of N^1-substituted *p*-nitrobenzenesulfonylbenzamidines was analogous. Aqueous methylamine and an acetone solution of diethylamine or 2-aminopyridine was used instead of ammonia for reaction with the imido chloride.

Reduction of Nitro Compounds.—All the nitro compounds were reduced with iron. The procedure for preparation of sulfanilylbenzamidine is illustrative. A mixture of 84 g. of finely divided iron and 19 cc. of 5 *N* hydrochloric acid in 500 cc. of water was stirred at 95–100°. The mixture was alkaline to congo red. To the slurry was added 91.5 g. of *p*-nitrobenzenesulfonylbenzamidine. There was slight heat evolution, and the color of the insoluble substance changed from yellow to gray. After two hours of stirring at a temperature near the boiling point the mixture was made just alkaline with sodium carbonate solution, cooled and filtered. The dried iron sludge was extracted with 3A alcohol, which on evaporation yielded 73 g. of crude product. This was purified by crystallization from glacial acetic acid and from 3A alcohol, using decolorizing carbon; 35 g. of pure sulfanilylbenzamidine was obtained.

The disulfanilyl compounds were dissolved by the sodium carbonate addition, and were obtained by making the filtrate slightly acid. The other sulfanilylamidines were practically insoluble in hot water, except sulfanilylacetamidine.

The products were purified by reprecipitation from acid or alkaline solution, by crystallization from 60–95% ethyl alcohol or acetic acid, or by both methods.

Hydrolysis of Sulfanilylacetamidine.—Sulfanilylacetamidine (1.066 g., 0.005 mole) was distilled in a Kjeldahl distillation apparatus with 100 cc. of 0.25 *N* sodium hydroxide, catching the ammoniacal distillate in standard acid. During forty-five minutes, the still solution was evaporated to 15–25 cc., and 0.00496 mole of ammonia was distilled. The contents of the still were filtered and neutralized to *p*H 9; the white precipitate obtained was filtered off, washed, and dried. The product weighed 0.66 g. and was identified as sulfanilamide by m. p. and mixed m. p. with an authentic sample.

Sulfanilylacetamidine (1.066 g., 0.005 mole) was gently boiled for half an hour with 60 cc. of 2 *N* hydrochloric acid. The solution was made strongly alkaline and distilled as described in the preceding paragraph. The titer of the distillate corresponded to an evolution of 0.00498 mole of ammonia. No sulfanilic acid was detected in the still contents. The acid hydrolysis was repeated on another 1.066-g. sample of sulfanilylacetamidine. The resulting solution was concentrated and neutralized. The solid which precipitated was recrystallized from hot water and dried. The white crystalline product weighed 0.63 g. and was identified as sulfanilamide, as previously described.

Summary

1. A series of sulfanilylamidines of the structure 4-$(NH_2)C_6H_4SO_2N{=}C(R)N(R')R''$ were prepared, where R was alkyl, aryl, aralkyl or heterocyclic, and R′ and R″ were hydrogen, alkyl or heterocyclic. None of these compounds formed sodium salts.

2. As by-products in some preparations disulfanilylamidines were isolated having the probable structure, 4-$(NH_2)C_6H_4SO_2N{=}C(R)NHSO_2C_6H_4$-$(NH_2)$-(4)′. These formed neutral sodium salts.

3. None of the compounds was more active than sulfanilamide in preliminary chemotherapeutic studies.

BOUND BROOK, N. J. RECEIVED JULY 25, 1942

(9) Prepared in the manner described for N^1-nicotinyl-N^4-acetylsulfanilamide but starting with *p*-nitrobenzenesulfonamide, see Crossley, Northey and Hultquist, THIS JOURNAL, **61**, 2950 (1939).