activity showed a tendency to increase when the solutions were permitted to stand for some time. Certain solutions of the freshly prepared tyrosinase also showed this tendency to increase in activity on standing.

9. The ratio of activities of the tyrosinase preparations toward *p*-cresol and catechol could not be altered by various methods of purification, but always remained 10 to 1, respectively. The ratio of the two activities in the case of the solutions of the crystalline material was also 10 to 1.

10. Composition, similarity in absorption spectra, the slight increase in activity when solutions are allowed to stand, all point to a close relationship between the crystals and the highly purified tyrosinase preparations.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE CALCO CHEMICAL COMPANY, INC.]

Sulfanilamide Derivatives. IV. N^1,N^4-Diacylsulfanilamides and N^1-Acylsulfanilamides[1]

BY M. L. CROSSLEY, E. H. NORTHEY AND MARTIN E. HULTQUIST

We have prepared an extended series of N^1-acylsulfanilamide derivatives[2] of the type NH_2—C$_6$H$_4$—SO_2NXCOR, as a continuation of our studies of N^1-substituted sulfanilamides. The scope of the work was extended to include examples where R was alkyl (from one to seventeen carbons in length), alkenyl, aryl, aralkyl, diaralkyl, aralkenyl, cycloalkyl, cycloalkenylalkyl and heterocyclic. Derivatives were also prepared from aliphatic dicarboxylic acids and aryl dicarboxylic acids. A few metanilamide derivatives were prepared, but these appeared to be of little therapeutic interest. X in the above formula was hydrogen, alkyl or a cation.

As intermediates in the preparation of many of the above, N^1,N^4-diacylsulfanilamides of the general formula, R'CONH—C$_6$H$_4$—SO_2NXCOR, were synthesized. In these, R' was usually a methyl group, but several compounds were prepared in which R' was the same as R. This particular series was not extended since the pharmacological results were not encouraging.

Derivatives in which the N^4-nitrogen of the N^1-acylsulfanilamide was substituted by sulfanilyl- or sodium methylenesulfinate groups were also prepared.

Since inception of this work, the first members of both series have been mentioned. A diacetylsulfanilamide, melting at 240–242°, which from the method of preparation was probably impure N^1,N^4-diacetylsulfanilamide, was described by Scudi.[3] N^1-Acetylsulfanilamide has been described by M. Dohrn and P. Diedrich[4] and is being sold abroad under the name "Albucid" for use against gonorrhea.

Several methods of synthesis were employed, but the one most generally useful involved reaction between N^4-acetylsulfanilamide and an acyl halide in the presence of dry pyridine. This reaction proceeded smoothly, giving good yields of the N^1-acyl-N^4-acetylsulfanilamide. The N^4-acetyl group was then removed by boiling with a slight excess of aqueous sodium hydroxide, to give a solution of the sodium salt of the N^1-acylsulfanilamide, from which the free N^1-acylsulfanilamide was obtained by acidification. Other methods successfully used are given in the experimental part.

Attempts to prepare derivatives by reaction of dry N-acetylsulfanilyl chloride with several carbonamides in pyridine failed. The reason for such failure is not understood and is being investigated further.

N^1-Acyl-N^4-sulfanilylsulfanilamides were prepared by condensing an N^1-acylsulfanilamide with N-acetylsulfanilyl chloride in pyridine, followed by hydrolysis of the acetyl group with aqueous sodium hydroxide.

N^4-Sodium formaldehydesulfoxalate derivatives of N^1-acylsulfanilamides were prepared by warming equimolecular amounts of the starting materials in water until solution was complete, then evaporating to dryness *in vacuo*.

(1) Presented in part before the Division of Medicinal Chemistry, Baltimore meeting, American Chemical Society, April, 1939.

(2) For nomenclature, see Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2217 (1938).

(3) Scudi, *Ind. Eng. Chem., Anal. Ed.*, **10**, 346 (1938).

(4) M. Dohrn and P. Diedrich, *Münch. med. Wochschr.*, **85**, 2017 (1938).

The compounds usually were obtained as white crystalline materials, although difficulty was met in crystallizing derivatives of unsaturated long chain acids. In many cases the products were first precipitated in sticky, amorphous form and then slowly crystallized. In the series of derivatives of fatty acids, the lower members were moderately water soluble. On ascending the series, the water solubility decreased and solubility in fat solvents increased. Water solubility of derivatives having chains of twelve carbons or more was less than 0.001 g./100 cc. All of the derivatives in which a hydrogen remained on the amide nitrogen formed very soluble

TABLE I

N^1-ACYLSULFANILAMIDES

N^1-Acyl radical	Calcd. mol. wt.	Assay by NaOH	Assay by nitrite	Melting range, °C.	Solubility	Crystalline form
Acetyl[a]	214.3	99.8	99.7	182.0–184.0	S.h.w.	Bipyramidal prisms
Propionyl	228.3	100.1	99.6	134–135	S.h.w.; mod. s.h. alc.	Prisms
Butyryl	242.3	100.2	100.6	125.4–126.6	Recryst. dil. alc.	Long prisms
Isobutyryl	242.3	100.2	100.5	198.5–200	Recryst. dil. alc.	Glistening prisms
2-Ethylbutyryl	270.4	99.5	98.8	189–193.5	Recryst. 60% alc.	Plates
Hexanoyl[a]	270.4	100.0	99.5	129.2–129.9	Recryst. 60% alc.	Long prisms
Heptanoyl	284.4	99.7	99.7	121.8–123.6	Recryst. 60% alc.	Hex. prisms
2-Ethylhexanoyl	298.4	99.2	100.0	165.5–168	Recryst. 70% alc.	Prisms
Octanoyl	298.4	99.5	100.5	101.0–103.0	V.s.hot toluene; ext. s.al.; i.w.; recryst. 60% alc.	Needles from toluene Fine prisms alc.
Decanoyl	326.5	99.4	99.7	119–121	V.s.hot toluene; ext. s.al.; i.w.; recryst. 60% alc.	Fine prisms
Hendecanoyl	340.5	100.4	99.9	112.5–114.5[b]	V.s.hot toluene; ext. s.al.; i.w.; recryst. 60% alc.	Long flat prisms
Dodecanoyl	354.5	100.0	100.0	127–128.5	V.s.hot toluene; ext. s.al.; i.w.; recryst. 80% alc.	Plates and needles
Tetradecanoyl	382.5	98.3	98.5	113.5–117.7	V.s.hot toluene; ext. s.al.; i.w.; recryst. 80% alc.	Fine, irreg. prisms
Octadecanoyl[c]	438.7	102.9	101.8	98–102	Recryst. 70% alc.	Irreg. plates
9-Octadecenoyl	436.7	100.5	...	...	S.toluene, alc.; i.hexane	Non-cryst.
Hexahydrobenzoyl	281.4	99.8	100.4	198.5–200	Recryst. 80% alc.	Needles
Chaulmoogryl	434.6	99.5	99.7	97.9–99.0	Recryst. 60% alc.	Irregular plates
Benzoyl	276.3	99.8	100.6	181.2–182.3	Recryst. 60% alc.	Hex. prisms
p-Nitrobenzoyl	321.3	100.6	100.3	235–240	Recryst. in acetone–alc.	Prisms
p-Aminobenzoyl	291.3	99.5	99.8	197.8–199	Recryst. in acetone–alc.	Needles
Hydrocinnamoyl	304.4	99.8	100.5	160.3–161.5	Recryst. 60% alc.	Glistening leaves
Cinnamoyl	302.4	99.4	99.7	130–133.[d] 174–175	Recryst. 60% alc.	Glistening leaves
4′-Carboxybenzoyl	340.3	100.5	100.8	>225 dec.	Recryst. 80% alc.	Needles
Mandelyl	305.5	100.2	100.6	192.5–194.5 dec.	Recryst. 80% alc.	Needles and prisms
Diphenylacetyl	366.5	99.7	99.3	210.5–212.0	Recryst. 70% acetone; sl.sol.alc.	Rectangular plates
Furoyl	266.3	99.6	99.9	191.5–192.0	Recryst. 60% alc.	Long prisms
2-Phenylcinchoninyl	403.5	99.4	99.2	305–310	Diss. as Na salt and repptd.	White powder
Nicotinyl	277.3	99.8	99.3	256–257.5	Mod. s.h.w.	Silky needles
3-Hydroxy-2-naphthoyl	342.4	100.1	100.5	245–250	Recryst. 70% alc.	Yellow powder

[a] Geneva names are given for acid radicals of six carbons and more because of confusion of their common names with the corresponding alkyl radicals. [b] Also exists in a form which starts melting at 115° and then changes to the higher melting form. [c] Prepared from stearic acid containing palmitic acid. [d] Softens and changes to high melting form at 130°, but melts immediately at 145°, then solidifies.

TABLE II

N^1-ACYLMETANILAMIDES

N^1-Acyl radical	Calcd. mol. wt.	Assay by NaOH	Assay by nitrite	Melting range, °C.	Solubility	Crystalline form
Acetyl	214.3	99.7	97.0	153.5–155.5	S.h.w.	Prisms
Tetradecanoyl	382.5	99.5	100.1	113.5–114.2	Recryst. 80% alc.	Flat prisms

TABLE III

N^1-ALKYL-N^1-ACYLSULFANILAMIDES

N^1-alkyl radical	N^1-acyl radical	Calcd., mol. wt.	Assay by nitrite	Melting range, °C.	Solubility	Crystalline form
Methyl	Dodecanoyl	368.5	100.6	59.3–60.5	V.s.alc., toluene; sl.s. hexane	Fine needles

sodium salts, which were neutral for the lower members of the series, but became increasingly alkaline for the higher members. All of these compounds could be titrated quantitatively to a phenolphthalein end-point, however, while sulfanilamide itself cannot be so titrated, since its sodium salt is highly hydrolyzed at this *p*H.

In general, the derivatives could be hydrolyzed quantitatively to the organic acid and sulfanilamide (or sulfanilic acid) by boiling with alcoholic hydrochloric acid, or more rapidly by heating to 180–200° with 65% sulfuric acid.

The lower members of the series could be titrated quantitatively by diazotization of the N^4-amino group. The higher members were too insoluble in dilute mineral acids to be diazotized directly, but for purposes of analysis were hydrolyzed, by either of the above methods, to sulfanilamide (or sulfanilic acid) and then diazotized. Hydrolysis of the sample before diazotization also permitted nitrite assays of N^1,N^4-diacylsulfanilamides. Analyses by titration with sodium hydroxide and with sodium nitrite were regarded to be of more significance than fundamental analyses by microchemical methods as criteria of purity since presence of isomeric N^4-acylsulfanilamides could not be distinguished by combustion methods.

Alkylation of the N^1-nitrogen gave derivatives which no longer formed salts with cations. These had increased solubility in organic solvents. These derivatives were sensitive to hydrolytic agents and in this resembled the N^1-alkyldisulfanilamides.[5]

A partial rearrangement of certain of these derivatives has been observed. By heating N^1-dodecanoylsulfanilamide for twenty hours at 130–140°, the material darkened, and became semisolid. On dissolving the mixture in hot alcohol, addition of sodium hydroxide to *p*H 9.5, then diluting with water, N^4-dodecanoylsulfanilamide crystallized as fine needles, identified by melting point and inability to titrate with sodium hydroxide.

On boiling an aqueous solution of N^1-acetylsulfanilamide for two hours, small amounts of N^1,N^4-diacetylsulfanilamide and sulfanilamide were identified. This suggests that two molecules of N^1-acetylsulfanilamide interact with formation of sulfanilamide and N^1,N^4-diacetylsulfanilamide. This interesting reaction will be investigated further.

Pharmacology.—The compounds of the present series have not been investigated in detail pharmacologically. Preliminary results are, however, of considerable interest and center chiefly on derivatives of long-chain fatty acids.

The N^1-acylsulfanilamides were part of our program on disulfanilamides, but the immediate emphasis on long-chain derivatives was due to a suggestion by Dr. D. A. Bryce, our medical director, that some combination of chaulmoogric acid and sulfanilamide might penetrate the tubercle of, and be effective against, tuberculosis. The sodium salt of N^1-chaulmoogrylsulfanilamide seemed to us to be the solution. Lack of chaulmoogric acid led to synthesis from other long-chain fatty acids. It then appeared that the free long-chain derivatives might be of more interest because of their probable fat solubility, and their possible penetration into the bacilli.

While the sodium salts of long-chain N^1-acylsulfanilamides are highly water soluble, they have the characteristics of soaps and are lytic in action. The free long-chain N^1-acylsulfanilamides are almost completely water insoluble, but are soluble in fats and fat solvents. Absorption of these by the oral route appears to be accelerated by administration of fats.

N^1-Dodecanoylsulfanilamide has been investi-

(5) Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2222 (1938).

TABLE IV

N^1,N^4-DIACYLSULFANILAMIDES

N^1-acyl radical	N^4-acyl radical	Calcd. mol. wt.	Assay by NaOH	Melting range, °C.	Solubility	Crystalline form
Acetyl[8]	Acetyl	256.3	99.5	253.5–255.0	Recryst. alc.	Long prisms
Propionyl	Acetyl	270.3	99.9	242.5–244.3	Sl. s.h.alc.	Prisms
Isobutyryl	Acetyl	284.3	99.5	247–248	Recryst. 80% alc.	Needles
Butyryl	Acetyl	284.3	98.4	238.2–240.0	Recryst. 80% alc.	Needles
Isovaleryl	Acetyl	298.3	100.0	215.0–217.5	Recryst. 80% alc.	Rectangular plates
2-Ethylbutyryl	Acetyl	312.4	99.5	270-272	Recryst. 80% alc.	Rectangular plates
Hexanoyl	Acetyl	312.4	98.9	191–193	Recryst. 60% alc.	Prisms
Heptanoyl	Acetyl	326.4	100.0	205.0–207.5	Recryst. 60% alc.	Prisms
2-Ethylhexanoyl	Acetyl	340.4	99.8	214.0–215.6	Recryst. 60% alc.	Prisms
Octanoyl	Acetyl	340.4	99.3	195.0–197.6	Recryst. 50% alc.	Long prisms
Decanoyl	Acetyl	368.5	99.5	143.2–144.8	Recryst. 70% alc.	Irregular plates
Hendecanoyl	Acetyl	382.5	100.5	153.2–155.0	Recryst. 60% alc.	Glistening plates
Dodecanoyl	Acetyl	396.5	99.1	130–136	Recryst. 95% alc.	Irregular plates
Dodecanoyl	Dodecanoyl	536.5	100.4 (nitrite)	144.0–145.0	Recryst. 95% alc.	Flat prisms
Tetradecanoyl	Acetyl	424.6	99.7	144.2–145.0	Recryst. 80% alc.	Leaflets
9-Octadecanoyl	Acetyl	478.7	99.7	131–135	Recryst.-dil. alc.	Glistening plates
Chaulmoogryl	Acetyl	476.7	99.4			
Benzoyl	Acetyl	318.3	99.3	280–285	V.sl.s.alc., acetone, water; recryst. 80% cellosolve	Needles
Hexahydrobenzoyl	Acetyl	323.4	99.4	210–220–222	Recryst. 80% alc.	Needles
p-Nitrobenzoyl	Acetyl	363.3	99.5	270–272	Dissolved as Na salt in alc. and repptd. with acetic acid	White powder
p-Aminobenzoyl	Acetyl	333.3	99.3	260–263	Recryst. acetone	Needles
Hydrocinnamoyl	Acetyl	346.4	100.0 Nitrite	160–202.8–205.4	Recryst. 60% alc.	Leaflets
Cinnamoyl	Acetyl	344.4	99.8	228–229.5	Recryst. 60% alc.	Needles
Diphenylacetyl	Acetyl	408.5	99.1	248.5–251	Recryst. 60% dioxane	Prisms
Furoyl	Acetyl	308.3	97.3	240.5–241.5	Recryst. 60% alc.	Glistening hexagonal plates
2-Phenylcinchoninyl	Acetyl	445.5	98.9	166–170	Dissolved as Na salt and repptd.	Irregular plates
Nicotinyl	Acetyl	319.3	99.4	295–300	Dissolved as Na salt and repptd.	Fine needles
Dodecanoyl	N-Acetylsulfanilyl	551.71	99.3 (nitrite)	120–150–152	Recryst. AcOEt	Prisms
Dodecanoyl	Sulfanilyl	509.67	98.8 (nitrite)	102–104	Recryst. dil. alc.	Needles

gated more fully than other members of the series. It appears to be equal or slightly superior to sulfanilamide, on an equal weight dosage, in experimental mice infections with various beta hemolytic streptococci. Cavies infected with a human strain of mycobacterium tuberculosis showed only localized lesions when treated with the drug. Animals treated with sulfanilamide showed moderate spread of the infection, while untreated controls developed generalized tuberculosis and died.

The pharmacological study has been made under the direction of D. R. Climenko. Further details are being published elsewhere.[6,7]

Experimental Part

General Methods of Synthesis. 1. Use of Acyl Halide in Pyridine.—This method was the most generally applicable and gave the best yields. It is illustrated by the following synthesis of N^1-dodecanoylsulfanilamide. A 1-

(6) D. R. Climenko, "N^1-Dodecanoylsulfanilamide. I. Absorption, Distribution and Toxicity." *Proc. Soc. Expil. Biol. Med.*, in press.

(7) D. R. Climenko and Ruth L. Schmidt, "N^1-Dodecanoylsulfanilamide. II. Experimental Infections with Beta Haemolytic Streptococci and Human Tubercle Bacilli." *ibid.*

TABLE V

Abbreviations: AcSA, N^1-acylsulfanilamide; Alc., alcohol; Ext., extremely; i., insoluble; s., soluble; sl., slightly; v., very.

N^1-Acyl radical	Salt	How prepared	Mol. wt.	Nitrite assay	Solubility	Crystalline form
Acetyl	$Na \cdot H_2O$	AcSA + NaOH in H_2O + alc.	254	100.5%	V.s. H_2O sl.s.alc.	Prisms
Acetyl	NH_4	AcSA + NH_4OH in alc.	231.3	100.3	Ext.s.H_2O s.alc.	Thick prisms
Acetyl	$(C_2H_5)_2NH_2$	AcSA + $(C_2H_5)_2NH$ in alc.	287.4	100.1	V.s.H_2O s.alc.	Coarse prisms
Dodecanoyl	Ag	AcSA + Ag_2O in alc.	461.4	99.2	Sl.s.alc. i.H_2O	Light sensitive
Dodecanoyl	Hg^{++}	NaAcSA + $HgCl_2$ in alc.	907.6	99.3	S.alc. s. acetone	Needle clusters
Dodecanoyl	Ca	AcSA + $Ca(OH)_2$ in H_2O	746.6	100.2	V.sl.s.H_2O s.alc.i.toluene	Needles

TABLE VI

SALTS OF N^1,N^4-DIACYLSULFANILAMIDES

N^1-Acyl	N^4-Acyl	Salt	How prepared	Mol. wt.	Nitrite Assay	Solubility	Crystalline form
2-Ethylhexanoyl	Acetyl	Na	Ac_2SA + NaOH in alc.	362.4	100.5%	Ext.s.H_2O Ext.s.alc.	Amorphous
2-Ethylhexanoyl	Acetyl	Mg	Ac_2SA + Mg in H_2O + MeOH	703.1	Calcd. 3.46% Mg Found 3.35% Mg	Ext.s.H_2O Ext.s.alc.	Amorphous

liter, 3-necked flask was equipped with a hook-type agitator and thermometer. Half of 257 g. (1.2 moles) of dry, finely pulverized N^4-acetylsulfanilamide was added with 250 cc. of dry pyridine. The agitator was started and the mixture heated to 90°. One-third of 219 g. (1 mole) of dodecanoyl chloride (boiling range 125–127°(7 mm.)) was added over five minutes, in portions, via a long-stemmed funnel (to prevent the acid chloride from coming into contact with the walls of the flask where it would have reacted with pyridine vapor to give highly colored impurities). The flask was cooled externally to prevent the temperature from exceeding 110°. The balance of the N^4-acetylsulfanilamide was then added, followed by the balance of the dodecanoyl chloride. The temperature was held at 100–110° for fifteen minutes to complete the reaction. The resulting pyridine solution was drowned in 1 liter of water and 250 cc. of concentrated hydrochloric acid. The product, which first separated as an oil, soon crystallized into soft pellets which were filtered and washed well with water. A portion of the crude N^1-dodecanoyl-N^4-acetylsulfanilamide was dissolved at *p*H 9 in water by addition of sodium hydroxide. The solution was treated with decolorizing carbon and the product reprecipitated by acidification. After three recrystallizations, N^1-dodecanoyl-N^4-acetylsulfanilamide was obtained, having the properties listed in Table IV.

The main portion of the crude material was dissolved in 600 cc. of water (to give approximately a 1 molar concentration) with addition of sodium hydroxide to a definite red spot test on phenolphthalein paper. A 1-cc. sample was taken, hydrolyzed by boiling with 5 cc. of concentrated sulfuric acid and 4 cc. of water for fifteen minutes, diluted with ice and water and titrated at 20° with 0.1 *N* sodium nitrite. For each equivalent in the alkaline solution indicated by the nitrite analysis, 1.4 moles of sodium hydroxide was added. The mixture was then boiled for one and one-half hours to hydrolyze the N^4-acetyl group. The hydrolyzed solution was diluted with an equal amount of water, neutralized to about *p*H 9 and treated with activated charcoal. The clarified liquor was acidified and the product obtained as a sticky oil which soon crystallized. It was recrystallized five times from toluene, using activated charcoal. 80% alcohol was used very satisfactorily for purification in other runs on this compound, and was the solvent most generally used for purification of other N^1-acylsulfanilamides. Average yield in these preparations based on the acid chloride was 60%.

2. Preparation from Acid Anhydrides.—This is illustrated by the preparation of N^1,N^4-diacetylsulfanilamide: 214 g. (1 mole) of N^4-acetylsulfanilamide was added gradually with agitation to 350 cc. of acetic anhydride heated at 70–80°. The mixture was then boiled for one hour. A thick slurry of crystals resulted which was drowned and washed well with water. The crystals were dissolved in 800 cc. of hot water by addition of sodium hydroxide to *p*H 8, treated with activated charcoal, cooled and a trace of N^4-acetylsulfanilamide removed by filtration. Crude N^1,N^4-diacetylsulfanilamide was precipitated by acidifying strongly with hydrochloric acid; yield after recrystallization was 60%.

Hydrolysis of the N^4-acetyl group was carried out by boiling one mole of the diacetyl derivative with 2.5 moles of sodium hydroxide in 1-liter water for one hour. The hydrolysate was neutralized to about *p*H 8 with hydrochloric acid and treated with activated charcoal while warm. The clarified solution on cooling and standing deposited a little sulfanilamide which was removed. The solution was acidified to about *p*H 4 and N^1-acetylsulfanilamide containing a little N^1,N^4-diacetylsulfanilamide crystallized. The mixture was warmed at 30–40° with 10% hydrochloric acid. The N^1-acetylsulfanilamide dissolved, while the N^1,N^4-diacetylsulfanilamide was insoluble and was removed by filtration. The filtrate was treated with activated charcoal, neutralized to *p*H 4 and N^1-acetylsulfanilamide crystallized on cooling. It was recrystallized from hot water, in which it was extremely

soluble at the boil, but only 0.9% at room temperature; the yield from N^1,N^4-diacetylsulfanilamide was 32%.

3. Preparation from N^1-Sodium-N^4-acetylsulfanilamide.—Anhydrous N^1-sodium-N^4-acetylsulfanilamide was prepared as follows. Crude N^4-acetylsulfanilamide paste was dissolved by addition of solid powdered sodium hydroxide to form a warm solution of N^1-sodium-N^4-acetylsulfanilamide. This was treated with activated charcoal, then cooled and crystallized. Large crystals formed containing much water of crystallization. These were filtered off and washed with a little ice water. The crystals were melted in a small amount of water and recrystallized to free from excess sodium hydroxide. As much of the adhering mother liquor as possible was removed by filtration, then by washing with very little ice water. The crystals were dried in a vacuum oven at not over 50° until practically anhydrous. Temperature was then raised to 60 to 70° until the product was anhydrous as indicated by hydrolysis of a sample to sulfanilamide and titration with sodium nitrite. The anhydrous material was finely ground and used in preparing various N^1-acylsulfanilamides, of which the following illustrates a method for the preparation of N^1-butyrylsulfanilamide: 236 g. (1 mole) of N^1-sodium-N^4-acetylsulfanilamide was suspended in 400 cc. of anhydrous dioxane; then 108 g. (1 mole) of butyryl chloride was added under agitation. When the reaction moderated, heat was applied to maintain a slow boiling for three hours under reflux condenser. The product was practically insoluble in the dioxane, was removed by filtration, and recrystallized twice from 70% alcohol. The N^4-acetyl group was hydrolyzed by the procedure described above for making N^1-acetylsulfanilamide.

Other solvents used for this method of preparation were xylene, pyridine and higher pyridine bases having a boiling range of 120 to 140°. Pyridine gave the most satisfactory results, since it had the ability to hold both the reactants and the final product in solution. Because the use of pyridine made unnecessary the preparation and drying of N^1-sodium-N^4-acetylsulfanilamide, this method was soon abandoned.

4. Reaction of N^4-Acetylsulfanilamide and an Acyl Halide in the Absence of Base.—Dry fusion of the N^4-acetylsulfanilamide with several acyl halides led in general to colored decomposition products along with the desired N^1-acetyl-N^4-acetylsulfanilamide. By use of inert solvents, fair yields were obtained in certain cases, as illustrated by the following method for preparing N^1-benzoyl-N^4-acetylsulfanilamide: 214 g. (1 mole) of dry N^4-acetylsulfanilamide, 141 g. of benzoyl chloride, and 700 cc. of toluene were agitated and heated under a reflux condenser for twenty hours. There was slow evolution of hydrogen chloride during this period. The toluene was evaporated and the residue dissolved in about 1 liter of water with sodium hydroxide to *p*H 9. The solution was treated with activated charcoal and a little unreacted N^4-acetylsulfanilamide removed. The solution was acidified, the crude product filtered off, and washed well with alcohol to remove benzoic acid. The product was recrystallized from 90% cellosolve giving 40% yield of N^1-benzoyl-N^4-acetylsulfanilamide.

5. Preparation of N^1-Alkyl-N^1-acylsulfanilamides.—Attempts to prepare N^1-alkyl-N^1-acylsulfanilamides by hydrolysis of the corresponding N^4-acetyl derivatives resulted in complete hydrolysis of the N^1-acyl group. Such derivatives were prepared successfully by starting with N-alkyl-nitrobenzenesulfonamides[8] which were acylated by the general procedure, then reduced using iron and acetic acid with addition of toluene. Metanilamide derivatives were made similarly.

Preparation of Acid Chlorides.—Chaulmoogryl chloride for N^1-chaulmoogrylsulfanilamide was prepared from ethyl chaulmoograte obtained through the courtesy of Professor Roger Adams of the University of Illinois. Eastman Kodak Co. technical chaulmoogric acid was found to have an iodine number approximately half of the theoretical value and could not be purified to give satisfactory starting material.

Long-chain acid chlorides from C_8 to C_{14} were prepared by converting technical lauric acid to the mixed acid chlorides with either thionyl chloride or phosphorus trichloride. The mixed acid chlorides were separated by fractionation through a 120-cm. packed column at 5–15 mm. pressure. The resulting acid chlorides had constants in close agreement with literature values.

Heterocyclic acids containing a nitrogen in the ring were converted to the acid chloride–hydrochlorides with thionyl chloride and isolated as solid products by evaporation of excess thionyl chloride. The condensation with N^4-acetylsulfanilamide was carried out in the presence of excess pyridine.

Summary

1. A large series of N^1-acylsulfanilamides was prepared from aliphatic, aromatic, heterocyclic and carbocyclic acids. As intermediates, N^1,N^4-diacylsulfanilamides were prepared in which the N^4-acyl group was usually acetyl. Salts of both series of compounds with various cations also were prepared.

2. Preliminary pharmacological results indicated that N^1-dodecanoylsulfanilamide was effective in mice against infections by beta hemolytic streptococci and arrested the spread of tuberculous infections in cavies.

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(8) Demény, *Rec. trav. chim.*, **48**, 1145 (1929).