[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

N^1,N^4-Nicotinyl Derivatives of Sulfanilamide

BY T. C. DANIELS AND HARRY IWAMOTO

A comparatively large number of N^1 and N^4 acyl derivatives[1] of sulfanilamide have been described and several have been reported to be of pharmacologic interest in the treatment of bacterial infections.[2,3,4] The pharmacologic properties of nicotinic acid and of sulfanilamide suggested the desirability of preparing the nicotinyl derivatives. One of us in 1937 prepared the N^4-nicotinylsulfanilamide. Crossley, Northey and Hultquist[3] have described the N^1-nicotinylsulfanilamide and reported a melting point of 256–257.5°. Our N^4 product had the same melting point and we therefore became interested in ascertaining whether rearrangement had occurred or the melting point of the two derivatives was a coincidence. Partial rearrangement of certain of the N^1-acylsulfanilamides had been observed by Crossley, Northey and Hultquist.[3]

We have prepared the N^4-nicotinyl derivative by two general methods: (1) by the action of nicotinyl chloride[5] on sulfanilamide in anhydrous pyridine, and (2) by treating the anilide of nicotinic acid with chlorosulfonic acid followed by ammonia. The products obtained by the above methods give the same melting point and mixed melting point (257–258°). They do not titrate to a phenolphthalein end-point.

We prepared the N^1-nicotinylsulfanilamide from N^4-acetylsulfanilamide by the method of Crossley, Northey and Hultquist.[3] This product melts at the same temperature as the N^4-nicotinyl derivative (257–258°) but because of its greater acidity titrates quantitatively to a phenolphthalein end-point. A 50% mixture with the N^4-nicotinyl derivative melts at 233–235°. The N^1-derivative after melting can still be titrated quantitatively with sodium hydroxide to a phenolphthalein end-point, which shows that rearrangement does not occur during the melting.

All of the N^4-acyl derivatives of sulfanilamide thus far described, with the exception of the nicotinyl, have a considerably higher melting point than the corresponding N^1 compounds.[2,3]

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

(2) Miller, Rock and Moore, *ibid.*, **61**, 1198 (1939).

(3) Crossley, Northey and Hultquist, *ibid.*, **61**, 2950 (1939).

(4) Stuart, U. S. Patent 2,117,260; *C. A.*, **32**, 5160 (1938).

(5) Ingersoll and Robbins, THIS JOURNAL, **48**, 2451 (1926).

The compounds studied crystallized in general as fine needles. Table I gives the analyses and melting points.

TABLE I

N^1 acyl group	N^4 acyl group	Theoretical mol. wt.	Assay, % NaOH	Assay, % Nitrite	Melting points, °C.
Acetyl	Nicotinyl	319.3	99.8	..	255–256
Nicotinyl	Acetyl[a]	319.3	99.8	..	293–294
Nicotinyl	Nicotinyl[b]	383.4	98.4	..	222–248
Nicotinyl[a]	.....	277.3	100.5	..	257–258
.....	Nicotinyl	277.3	...	99.9	257–258

[a] Prepared by the method of Crossley, Northey and Hultquist.[3] [b] Product exists in two forms, one of which melts sharply at 222, the other at 248°.

Pharmacology.—Although the work of Fourneau, *et al.*,[6] indicated that the introduction of acyl groups on the N^4 nitrogen of sulfanilamide greatly reduces the antistreptoccic activity, compounds of this class have since been described which have equal or greater effectiveness.[2,4] The N^4-nicotinylsulfanilamide has been studied by Leake, Karr, Finnegan and Murayama.[7] The preliminary work has indicated an effectiveness greater than that of sulfanilamide in the treatment of experimental hemolytic streptococcal infections and equal to sulfapyridine in experimental pneumococcal infections. The toxicity is much less than that of sulfanilamide or of sulfapyridine. Studies are now in progress on the N^1,N^4-dinicotinylsulfanilamide and on the N^1-acetyl-N^4-nicotinylsulfanilamide. The details of the pharmacologic investigation will be published elsewhere.

Experimental Part

N^4-Nicotinylsulfanilamide.—(1) To 14.2 g. (0.1 mole) of nicotinyl chloride and 17.2 g. (0.1 mole) of sulfanilamide was added 18.0 g. of anhydrous pyridine. The mixture was refluxed on a water-bath for one hour, cooled and several volumes of cold water added. The precipitate was collected on a filter and washed thoroughly with water followed by recrystallization from 50% alcohol; yield 50 to 75%.

(2) To 58.3 g. (0.5 mole) of chlorosulfonic acid in a three-necked flask, equipped with a mechanical stirrer and reflux condenser cooled to 0°, was added 9.9 g. (0.05 mole) of nicotinylanilide in divided portions with continuous agitation. The temperature during the addition was kept below 15°, then gradually raised to 60° on a water-bath

(6) Fourneau, *et al.*, *Compt. rend. soc. biol.*, **122**, 258 (1936).

(7) Leake, Karr and Murayama, unpublished report.

and maintained at this temperature for two hours. The reaction mixture was cooled and treated directly with an excess of cold 28% ammonia solution, adding the ammonia in divided portions with continuous stirring. The stirring was continued for approximately one hour and the precipitate collected and washed several times with water followed by recrystallization from 50% alcohol; yield 40 to 50%. The melting point was identical with that of the product from (1) and gave the same mixed melting point.

N^1-Acetyl-N^4-nicotinylsulfanilamide.—To 25 cc. of acetic anhydride was added gradually 2.8 g. (0.01 mole) of N^4-nicotinylsulfanilamide. The mixture was refluxed for one hour and cooled in an ice-bath. The precipitate was collected and washed with water, then dissolved in sodium hydroxide (*p*H 8), decolorized with activated charcoal and precipitated by the addition of dilute hydrochloric acid to *p*H of 5. The precipitate was filtered, washed and dried; yield approximately 50%.

N^1,N^4-Dinicotinylsulfanilamide.—To 5.5 g. (0.02 mole) of N^4-nicotinylsulfanilamide and 5.7 g. (0.04 mole) of nicotinyl chloride was added 20 cc. of anhydrous pyridine and the product refluxed for one hour. Several volumes of water were added to the cooled reaction product and the solution acidified with dilute hydrochloric acid to a *p*H of 5. The precipitate was collected and washed with several portions of water, redissolved with sodium hydroxide to a *p*H of 8, filtered and reprecipitated by the addition of dilute hydrochloric acid to a *p*H of 5. The product was again washed and dried; yield approximately 40%. The product melts sharply at 222°, resolidifies on heating and melts again at 248°. Titration with sodium hydroxide of the form melting at 248° gives the same equivalent weight as before melting.

Summary

1. The N^4-nicotinylsulfanilamide and N^1,N^4-dinicotinylsulfanilamide are described.

2. The melting points of N^1 and N^4-nicotinylsulfanilamide are the same.

3. The preliminary pharmacologic investigation indicates that the N^4-nicotinylsulfanilamide is effective in the treatment of experimental hemolytic streptococcus infections and also certain types of pneumococcus infections. The toxicity of the N^4-nicotinylsulfanilamide is lower than either sulfanilamide or sulfapyridine.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

α-Furfurylpropylamine and Di-α-furfuryl Tertiary Amines

BY J. E. ZANETTI AND J. T. BASHOUR

α-Furfurylpropylamine has now been synthesized by the same general method as previously used with other secondary α-furfuryl amines.[1] It is a colorless oil with a faint fishy odor boiling at 80–81° under 20 mm. pressure, d^{25}_{25} 0.947, $n^{20}D$ 1.4679. Its hydrochloride melts at 138–140°.

Anal. Calcd. for $C_8H_{13}ON$: N, 10.1. Found: N, 10.2.

Very little has been done in the field of tertiary α-furfuryl amines and only one tertiary amine containing two furfuryl groups has been reported, namely, the tri-α-furfurylamine synthesized by Zanetti and Beckmann.[2] Von Braun and Kohler[3] synthesized several tertiary furfurylamines which, however, contained only one α-furfuryl group and Von Braun and Braunsdorf[4] made an analog of novocaine containing one α-furfuryl group on the tertiary nitrogen.

In our synthesis of secondary α-furfurylamines,[5] tertiary amines were suspected in the small amount of high boiling residue accompanying each preparation. However, in the synthesis of these amines, unfavorable yields are obtained unless the purified secondary amines be made to react with furfuryl bromide.

These tertiary amines are either high boiling liquids or solids and are miscible with most organic solvents. Their properties and the analyses are given in Table I. They are colorless when pure but turn yellow on standing. They have only faint ammoniacal odors. With hydrochloric acid in ether solution they form stable hydrochlorides. As in the case of the secondary furfurylamines, excess of hydrochloric acid must not be used as dark decomposition products will readily form.

Experimental Part

In a flask provided with an air condenser the furfuryl bromide in ether solution is allowed to stand for one to three hours over crushed potassium hydroxide and then the secondary amine is added with agitation. With intermittent shak-

(1) Zanetti and Bashour, THIS JOURNAL, **61**, 3133 (1939).
(2) Zanetti and Beckmann, *ibid.*, **50**, 2081 (1928).
(3) Von Braun and Kohler, *Ber.*, **51**, 86 (1918).
(4) Von Braun and Braunsdorf, *Ber.*, **54**, 2081 (1921).
(5) Zanetti and Bashour, THIS JOURNAL, **61**, 3133 (1939).