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

N^1,N^4-Pyrazinoyl[1] Derivatives of Sulfanilamide

BY T. C. DANIELS AND HARRY IWAMOTO

Nicotinyl derivatives of sulfanilamide have been described.[1a,2] At least one of these derivatives, the N^4-nicotinylsulfanilamide has been employed successfully in the treatment of various types of bacterial infections.[3] Because of the low toxicity of this type of compound it appears desirable to determine the effect on bactericidal activity and toxicity that is produced by the introduction of a second nitrogen in the acyl ring. For this purpose pyrazinoyl derivatives of sulfanilamide have been prepared. In at least one instance derivatives of pyrazinoic and nicotinic acids have been shown to have common pharmacologic properties. Dalmer and Walter[4] have described a number of disubstituted amides of pyrazinoic acid and reported the compounds as useful analeptics similar to the disubstituted amides of nicotinic acid.

The pyrazinoyl derivatives of sulfanilamide were obtained by treating pyrazinoyl chloride with the appropriate sulfanilamide derivative. A number of methods were employed for the preparation of the acid chloride, but best results were obtained by agitating the acid with a mixture of phosphorus penta- and tri-chlorides at room temperature for several days. The yields for the most part were unsatisfactory due to incomplete conversion of the acid to the acid chloride and to excessive loss in the purification of the highly colored crude products.

The N^4-pyrazinoylsulfanilamide[5] has been prepared in sufficient quantity for pharmacologic evaluation. This phase of the study is now being carried out by Leake and Murayama and will be reported elsewhere.

All of the compounds described are white crystalline substances, sparingly soluble in water and organic solvents. Melting points and analyses are given in Table I. The N^1 and N^4-pyrazinoylsulfanilamides have the same melting point. This is also true of the N^1 and N^4-nicotinylsulfanilamides.[1] The N^1-acylsulfanilamides, as distinguished from the N^4-acylsulfanilamides are relatively strong acids and may be titrated quantitatively using phenolphthalein as an indicator.

TABLE I

N^1 acyl group	N^4 acyl group	Mol. wt.	Assay % NaOH	Assay % Nitrite	M. p. °C. (cor.)
....	Pyrazinoyl	278.3	...	101.0	247–248
Pyrazinoyl	....	278.3	101.3	...	246–248
Acetyl	Pyrazinoyl	320.3	99.9	...	249–250
Pyrazinoyl	Pyrazinoyl	384.3	100.7	...	286–290
Pyrazinoyl	Acetyl	320.3	101.3	...	262–264

Experimental Part

1. Impure Pyrazinoyl Chloride.—To 4.96 g. (0.4 mole) of pyrazinoic acid suspended in 50 cc. of phosphorus trichloride was added 8.32 g. (0.4 mole) of phosphorus pentachloride The mixture was stoppered and shaken intermittently with a mechanical shaker for ninety-three hours. The product was collected on a Buchner funnel, washed 5 times with 15 cc. of dry benzene and dried in a vacuum desiccator over calcium chloride and paraffin wax. The product is impure and quite unstable. Attempts to purify further were unsuccessful. The mixture probably consists of pyrazinoyl chloride, pyrazinoyl chloride hydrochloride, small amounts of unchanged acid and possibly traces of the phosphorus halides. The product melts at 110–117° with vigorous decomposition.

2. Alternate Method.—To 1.24 g. (0.01 mole) of pyrazinoic acid contained in a Pyrex test-tube, was added 2.08 g. (0.01 mole) of phosphorus pentachloride previously dissolved in 10–15 cc. of dry benzene. The tube was sealed and heated (80–85°) with intermittent shaking for a period of twenty minutes. After cooling the tube was opened, the product collected on a filter, washed 5–6 times with 5-cc. portions of dry benzene and dried as before.

N^4-Pyrazinoylsulfanilamide.—To 5 g. (0.035 mole) of the crude pyrazinoyl chloride and 6 g. (0.035 mole) of sulfanilamide was added 40 cc. of dry pyridine. The mixture was refluxed gently for one hour, cooled, and diluted with 300 cc. of water. No immediate precipitation occurred but upon storing in an ice chest overnight a dark colored precipitate was formed. The precipitate was filtered, washed several times with ice water, and decolorized (activated charcoal) and recrystallized from 50% alcohol; yield 3 g. (30%).

N^1-Acetyl-N^4-pyrazinoylsulfanilamide.—To 30 cc. of acetic anhydride was added 0.5 g. (0.002 mole) of N^4-pyrazinoylsulfanilamide. The mixture was refluxed for three hours and allowed to cool. On cooling the acetyl derivative separated as long white needles. The product was filtered, washed several times with ice water, and recrystallized from 75% alcohol; yield 0.46 g. (approximately 80%).

(1) Since there is only one monocarboxylic acid derivative of pyrazine the name pyrazinoic acid is proposed for pyrazine monocarboxylic acid and pyrazinoyl for the radical. We have communicated with Professor Austin M. Patterson of Antioch College relative to the nomenclature of this acid.

(1a) Daniels and Iwamoto, THIS JOURNAL, **62**, 741 (1940).

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

(3) Leake, *et al.*, unpublished report.

(4) Dalmer and Walter, German Patent 632,257; *C. A.*, **30**, 6894 (1936).

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

N^1,N^4-Dipyrazinoylsulfanilamide.—To 1.1 g. (0.004 mole) N^4-pyrazinoylsulfanilamide and 1.0 g. (0.007 mole) of pyrazinoyl chloride was added 12 cc. of dry pyridine. The mixture was refluxed gently for one hour, cooled, and diluted with 100 cc. of ice water. The product was precipitated by strongly acidifying with concentrated hydrochloric acid and the precipitate filtered and washed several times with water. The product was then dissolved in 400 cc. of 95% alcohol and decolorized with activated charcoal. The volume of alcohol was reduced until precipitation occurred. The yield was 0.5 g. (33%).

An alternate procedure for purification consists of dissolving the impure product in sodium hydroxide (*p*H 8), decolorizing with activated charcoal and precipitating with hydrochloric acid.

N^4-Acetyl-N^1-pyrazinoylsulfanilamide.—To 1.5 g. (0.007 mole) of N^4-acetylsulfanilamide and 1.0 g. (0.007 mole) of pyrazinoyl chloride was added 12 cc. of dry pyridine. The mixture was refluxed gently for one hour, cooled, and diluted with 100 cc. of ice water. Precipitation was induced by strongly acidifying with concentrated hydrochloric acid. The precipitate was collected on a filter and washed several times with water. The crude product was decolorized (activated charcoal) and recrystallized from 50% alcohol and dried, yield 0.4 g. (20%).

N^1-Pyrazinoylsulfanilamide.—Two cc. of 10% sodium hydroxide was added to 0.3 g. of N^4-acetyl-N^1-pyrazinoylsulfanilamide. The mixture was heated gently for ten minutes, cooled, and strongly acidified with hydrochloric acid to precipitate the crude product. The precipitate was collected, washed with ice water, recrystallized from 50% alcohol, and dried; yield approximately 30%.

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Summary

1. The name pyrazinoic acid is proposed for pyrazine monocarboxylic acid.

2. Five new pyrazinoyl derivatives of sulfanilamide have been prepared and described. The compounds were obtained by treating (impure) pyrazinoyl chloride with the appropriate sulfanilamide derivative.

3. There is reason to expect that some of the compounds may be of pharmacologic interest.

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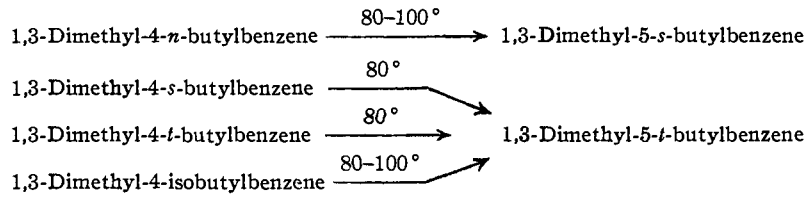
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, UNIVERSITY OF MISSOURI]

The Action of Anhydrous Ferric Chloride on Alkylbenzenes[1]

BY DOROTHY NIGHTINGALE, RICHARD G. TAYLOR AND H. WAYNE SMELSER

The principal changes which take place when the 1,3-dimethyl-4-butylbenzenes are warmed with ferric chloride parallel for the most part those reactions which take place when these hydrocarbons react with aluminum chloride.[1a] A higher temperature is required, however, especially in the case of the 4-*n*-butyl and 4-isobutyl hydrocarbons. While pure 1,3-dimethyl-5-*t*-butylbenzene was not isolated from the reaction products of this latter hydrocarbon, the trialkyl fraction contains the 5-*t*-butyl hydrocarbon. The rearrangement reactions may be summarized as follows



The 1,3-dimethyl-4-propyl- and 4-ethylbenzenes do not form appreciable amounts of 1,3,5-hydrocarbon even on heating with ferric chloride at 150° for six hours. With aluminum chloride, the yields of 1,3,5-hydrocarbon under comparable conditions were approximately 45%.[2]

These results illustrate not only the effect of temperature but also of the structure of the radical in the 4 position on the ease with which the radical migrates. The secondary and tertiary butyl radicals migrate more readily than the primary radicals.

The trialkyl fraction from the 4-*t*-butyl hydrocarbon after heating with ferric chloride for three hours at 65–70° was mainly unchanged hydrocarbon. At 80° for one and one-half hours, the yield of 1,3,5-hydrocarbon was 68%. Similar results were obtained with the 4-*s*-butyl hydrocarbon.

Some 1,3,5-hydrocarbon was formed from the 4-*n*-butyl hydrocarbon when the time and temperature of the reaction were increased. The trinitro derivative of 1,3-dimethyl-5-*s*-butylbenzene was not isolated from the nitra-

(1) Original manuscript received October 16, 1939.

(1a) Nightingale and Smith, THIS JOURNAL, **61**, 101 (1939).

(2) Nightingale and Carton, *ibid.*, **62**, 280 (1940).