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Synthesis of Some New Derivatives of N^4-*p*-Cyanobenzoyl Sulfanilamide

By LAWRENCE J. FISCHER and BERNARD ECANOW

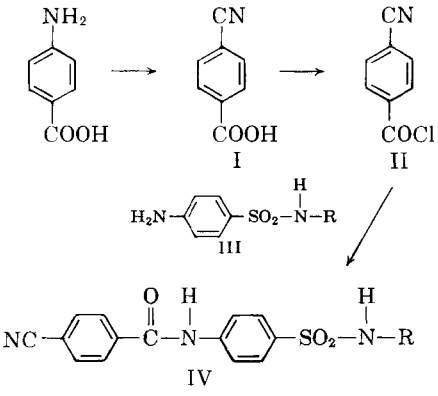
Six new derivatives of N^4-*p*-cyanobenzoyl sulfanilamide were prepared: N^4-*p*-cyanobenzoyl sulfanilamide, N^4-*p*-cyanobenzoyl-N^1-2-pyrimidinylsulfanilamide, N^4-*p*-cyanobenzoyl-N^1-(4-methyl-2-pyrimidinyl)sulfanilamide, N^4-*p*-cyanobenzoyl-N^1-2-thiazolylsulfanilamide, N^4-*p*-cyanobenzoyl-N^1-2-pyridylsulfanilamide, N^4-*p*-cyanobenzoyl-N^1-2-pyrazylsulfanilamide. Infrared spectra of the new compounds were determined. Common absorption bands of the compounds occurred at 2240–2210 cm.$^{-1}$, 1160–1130 cm.$^{-1}$, 1325–1310 cm.$^{-1}$, and 1580–1560 cm.$^{-1}$.

N^4-SUBSTITUTED sulfanilamides have shown important pharmacological actions. N-Sulfanilylbenzamide, which is similar to the derivatives prepared here, has been shown to be effective against the bacillary dysentery organism (1) and against pneumococcus in mice (2).

Some N - alkyl - *p* - cyanobenzamides have been prepared and shown to possess local anesthetic and antimicrobial properties (3). The amidines and imidazolines prepared from these compounds have also shown significant activity (4).

The synthesis of some new sulfonamides containing the *p*-cyanobenzoyl and sulfanilyl moieties was successfully completed.

The synthesis of the N^4-*p*-cyanobenzoyl sulfanilamide derivatives was initiated with the preparation of *p*-cyanobenzoic acid I, which was prepared according to the procedure of Miller and Gisvold (5). *p*-Cyanobenzoyl chloride II was prepared by refluxing the acid with thionyl chloride and recrystallizing from petroleum ether.



Equimolar quantities of *p*-cyanobenzoyl chloride and the finely powdered sulfanilamide derivative III were refluxed in *p*-dioxane for 2 hours. Mechanical stirring was required if the reactants were not completely soluble in dioxane. The solvent was removed and the N^4-*p*-cyanobenzoyl sulfanilamide derivative IV was treated with dilute-hydrochloric acid to remove any unreacted material. Recrystallization was from a mixture of solvents.

The solubility characteristics of the new derivatives (see Table I) were generally predictable.

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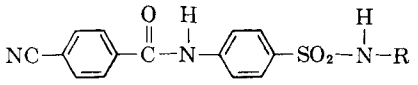
TABLE I.—N^4-*p*-CYANOBENZOYLSULFANILAMIDE DERIVATIVES



R	Formula	Yield, %	M.p., ° C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
—H	$C_{14}H_{11}N_3O_3S$	62.2	277–280	55.81	55.79	3.68	3.70	...	...
	$C_{18}H_{13}N_5O_3S$	70.1	317–318 (decompn.)	57.00	56.96	3.45	3.61	18.44	18.51
	$C_{19}H_{15}N_5O_3S$	78.4	295–297 (decompn.)	58.01	57.89	3.84	4.09	...	...
	$C_{17}H_{12}N_4O_3S_2$	75.2	286–288 (decompn.)	53.10	53.22	3.15	3.29	...	...
	$C_{19}H_{14}N_4O_3S$	83.5	286–288 (decompn.)	60.35	60.48	3.73	3.75	14.81	14.93
	$C_{18}H_{13}N_5O_3S$	82.6	290–291	56.99	57.07	3.45	3.42	18.46	18.36

They were found to be insoluble in the common laboratory solvents such as water, alcohol, ether, and chloroform. The products were soluble to sparingly soluble in *p*-dioxane, and very soluble in dimethylacetamide. Salt formation occurred readily in sodium hydroxide solution, the sodium salts being soluble in water.

EXPERIMENTAL

Infrared spectra were obtained using a Beckman IR-4 infrared recording spectrophotometer. All of the compounds prepared exhibited the characteristic cyano band in the range 2240–2210 cm.$^{-1}$. The spectra of the *p*-cyanobenzoyl sulfanilamide derivatives contained absorption bands common to each member of the series. Such bands occurred at 1160–1130 cm.$^{-1}$, 1325–1310 cm.$^{-1}$, and 1580–1560 cm.$^{-1}$

Preparation of *p*-Cyanobenzoic Acid and *p*-Cyanobenzoyl Chloride.—This was done according to the procedure of Miller and Gisvold (*5*).

Preparation of N^4-*p*-Cyanobenzoyl sulfanilamide.—Four grams of powdered sulfanilamide U.S.P. (0.0242 mole) and 4.1 Gm. (0.0242 mole) of *p*-cyanobenzoyl chloride were placed in a 500-ml., round-bottomed flask fitted with a reflux condenser and mechanical stirrer. The solvent, 270 ml. of *p*-dioxane, was added and the suspension refluxed, while stirring slowly, for 1.5 hours.

The reaction mixture was allowed to cool to room temperature. The solid product formed during the reaction was filtered with suction. The crude product was treated with two 75-ml. portions of 10% hydrochloric acid by mixing in a mortar, filtered with suction, and washed with distilled water after each treatment. The product was dried under vacuum and weighed 4.5 Gm.

Recrystallization was from a dimethylacetamide-distilled water mixture (1:1). The recrystallized product was placed in an oven at 200° for 1.5 hours to remove any adhering solvent.

N^4-*p*-Cyanobenzoyl-N^1-2-pyrimidinyl sulfanilamide.—Sulfadiazine U.S.P., 10.0 Gm. (0.08 mole), and 13.2 Gm. (0.08 mole) of *p*-cyanobenzoyl chloride were placed in a 500-ml., round-bottomed flask, fitted with a reflux condenser and a mechanical stirrer. A 200-ml. quantity of *p*-dioxane was added and the mixture refluxed, while stirring slowly, for 1.5 hours. The reaction mixture was allowed to stand overnight and the product filtered with suction. The product, a white powder, was allowed to dry at room temperature. It was then treated with 150 ml. of 10% hydrochloric acid by mixing in a mortar, filtered with suction, and washed with generous amounts of distilled water. The product was recrystallized from dimethylacetamide.

N^4-*p*-Cyanobenzoyl-N^1-(4-methyl-2-pyrimidinyl)-sulfanilamide.—To a 500-ml., round-bottomed flask equipped with a reflux condenser, 3.44 Gm. (0.013 mole) of sulfamerazine U.S.P. powder and 2.16 Gm. (0.013 mole) of *p*-cyanobenzoyl chloride were added. A 125-ml. quantity of *p*-dioxane was added and a clear, brown, solution resulted. The solution was refluxed for 2 hours and cooled to room temperature. The solvent was removed on a flash evaporator and the residue recrystallized from a dioxane-water mixture.

N^4-*p*-Cyanobenzoyl-N^1-2-thiazolylsulfanilamide.—Sulfathiazole U.S.P. powder, 1.4 Gm. (0.0055 mole), and 0.9 Gm. (0.0055 mole) of *p*-cyanobenzoyl chloride were added to a 250-ml., round-bottomed flask equipped with a reflux condenser. The solvent, 70 ml. of *p*-dioxane, was added and a clear solution was obtained. The solution was refluxed for 1.75 hours and allowed to cool to room temperature.

The solvent was removed on a flash evaporator and the residue treated with 75 ml. of 4% hydrochloric acid by mixing in a mortar. The product was recrystallized by dissolving it in approximately 3 ml. of dimethylacetamide, adding 25 ml. of 95% ethanol, and adding distilled water to the hot solution until the cloudiness just disappeared upon heating. The

light tan crystals were placed in an oven at 165° for 1 hour to remove any adhering solvent.

N^4-*p*-Cyanobenzoyl-N^1-2-pyridylsulfanilamide.—To a 250-ml., round-bottomed flask, equipped with a reflux condenser and a mechanical stirrer, was added 1.52 Gm. (0.00606 mole) of sulfapyridine U.S.P. powder and 1.0 Gm. (0.00606 mole) of *p*-cyanobenzoyl chloride. Seventy milliliters of *p*-dioxane was added and the mixture refluxed, while slowly stirring, for 2 hours.

The reaction mixture was allowed to cool to room temperature and the solvent removed on a flash evaporator. The residue was treated successively with two 100-ml. portions of 4% hydrochloric acid by mixing in a mortar, filtering, and washing with distilled water.

The product was recrystallized by dissolving in 5 ml. of hot dimethylacetamide, then adding 20 ml. of dioxane, and finally adding distilled water until the cloudiness produced just disappeared upon heating. The pale yellow crystals were dried in an oven at 130° to remove any adhering solvent.

N^4-*p*-Cyanobenzoyl-N^1-2-pyrazylsulfanilamide.—Three grams (0.0121 mole) of sulfapyrazine powder and 2.0 Gm. (0.0121 mole) of *p*-cyanobenzoyl chloride were added to a 500-ml., round-bottomed flask, equipped with a mechanical stirrer and a reflux condenser. The solvent, 140 ml. of *p*-dioxane, was added and the mixture refluxed, while stirring, for 2 hours.

The dioxane was removed on a flash evaporator and the residue mixed with 100 ml. of 10% hydrochloric acid in a mortar. The product was filtered with suction, washed with distilled water, and the acid treatment repeated.

The product was recrystallized from a solution consisting of one part dimethylacetamide, four parts dioxane, and four parts of distilled water. The pale yellow crystals were placed in an oven at 140–150° for one-half hour to remove any adhering solvent.

SUMMARY

1. Six new derivatives of N^4-*p*-cyanobenzoyl sulfanilamide were prepared: N^4-*p*-cyanobenzoylsulfanilamide, N^4-*p*-cyanobenzoyl-N^1-2-pyrimidinylsulfanilamide, N^4-*p*-cyanobenzoyl-N^1-(4-methyl-2-pyrimidinyl)sulfanilamide, N^4-*p*-cyanobenzoyl-N^1-2-pyridylsulfanilamide, N^4-*p*-cyanobenzoyl-N^1-2-pyrazylsulfanilamide, N^4-*p*-cyanobenzoyl-N^1-2-thiazolyl-sulfanilamide.

2. The infrared spectra of the new compounds were determined. Common absorption bands of the compounds occurred at 2240–2210 cm.$^{-1}$, 1160–1130 cm.$^{-1}$, 1325–1310 cm.$^{-1}$, and 1580–1560 cm.$^{-1}$.

3. The results of the pharmacologic investigation of the new compounds will be reported in a forthcoming paper.

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Cyclized Substituted Thioureas II

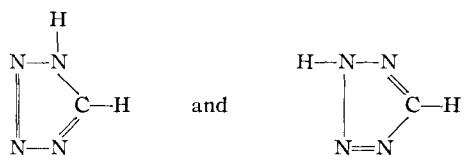
Preparation of Some 1-Substituted 1,2,3,4-Tetrazole-5-thiones

By RONALD E. ORTH† and JAMES W. JONES

Some 1-alkyl- and 1-aryl-1,2,3,4-tetrazole-5-thiones are synthesized by preparing methyl-(N-alkyl- and N-aryl)-dithiocarbamates by dropwise addition of carbon disulfide to a cold solution of the amine in aqueous sodium hydroxide, followed by slowly esterifying, separating, and purifying the ester. Sodium azide is refluxed with the various esters forming, in several cases, the substituted tetrazole-5-thione on purification.

PREVIOUSLY it has been demonstrated that thiourea has great antithyroidal activity. It appears that the introduction of this moiety into a ring system causes a general decrease in toxicity. However, conjugation of a second ring decreases the physiological activity with respect to the single ring systems. In addition, it has been found that at least one of the thiourea nitrogen must contain hydrogen. This leads investigators to hypothesize that tautomerism within the H—N—C=S portion of the molecule is paramount to good suppression of iodine-uptake.

The synthesis of tetrazole (1) led to much investigation regarding the various substitution products which could be obtained. The parent compound melts at 155° and exists in two isomeric forms



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