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

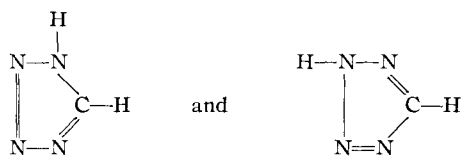
Preparation of Some 1-Substituted 1,2,3,4-Tetrazole-5-thiones

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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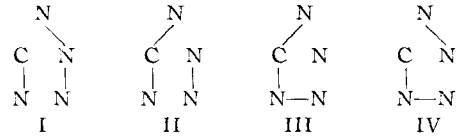
† Present address: University of Kentucky College of Pharmacy, Lexington.

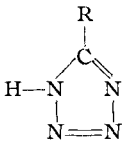
Theoretically, there are four general methods for the preparation of a tetrazole. The following examples show the nuclei needed for all possible combinations



I II III IV

Specifically, tetrazole and its derivatives have been prepared by method I by condensation of an azoimide with prussic acid and its derivatives and by the reaction of the imidochlorides and similar compounds with sodium azide. The reaction of nitrous acid with hydrazadines or amidines, followed by reduction, follows the method III scheme. The condensation of phenylazoimide with aldehyde phenylhydrazones, using sodium alcoholate in ethanol, and the reaction of diazohydrazides and mono- and diacylhydrazines with diazonium salts in the presence of alkali are method IV syntheses. Method II, as yet, has not been used for the preparation of the tetrazole nucleus. The oxidation of suitable tetrazolium compounds is another approach.

Some of the tetrazole derivatives which have been synthesized are illustrated by the general formula



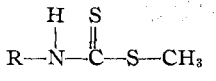
5-R-1,2,3,4, 1-H-tetrazoles where R may be phenyl, tolyl, furyl, anisyl, bromo, amino, or mercapto

With the knowledge that pentylenetetrazole U.S.P. is used in medicine for its central nervous system stimulation in certain mental disorders, particularly in schizophrenia and depressive psychoses (2), it is felt that the tetrazole nucleus is one which should be investigated more extensively in conjunction with pharmaceuticals. Pentylenetetrazole has also been used as an antidote in poisoning by depressant drugs, however it appears to be inferior to picrotoxin (3).

A number of methyl-(N-alkyl- and N-aryldithiocarbamates) have previously been prepared (4). This paper deals in part with the preparation of several new esters, the attempt to purify and characterize these, and a few prepared in earlier investigations.

The esters of N-alkyl- and N-aryldithiocarbamate prepared were used to synthesize some 1-aryl-and 1-alkyl-1,2,3,4-tetrazole-5-thiones not previously reported.

TABLE I.—METHYL ESTERS OF N-ALKYL- AND N-ARYLDITHIOCARBAMIC ACID PREPARED



	Nitrogen, % Calcd.	Found	Yield, %[a]	B.P., °C./mm.
H[b]	13.3	12.9	60	...
Methyl[b]	11.6	12.0	40	153–156/20
Ethyl	10.4	10.1	35	115/8
n-Propyl	9.39	9.22	81	124/8
Isopropyl	9.39	9.13	49	76/5
n-Butyl	8.59	8.40	63	...
Cyclohexyl[b]	7.41	7.78	68	89/5
Benzyl[b]	7.10	6.89	45	...
Phenyl[b]	7.65	7.48	34	97[c]

[a] Based on 0.5 mole of amine. [b] Previously prepared. [c] Melting point.

EXPERIMENTAL

Methyl Esters of N-Aryl- and N-Alkyldithiocarbamic Acid.—In a 1-L. round-bottom, three-necked flask, surrounded by an ice bath and fitted with a mechanical stirrer, a reflux condenser, thermometer, and a 250-ml. dropping funnel, were placed a cold solution of 72 Gm. (1.8 mole) of sodium hydroxide in 160 ml. of water and 1.8 moles of primary amine. To this mixture, cooled to 0–10°, 137 Gm. (1.8 mole) of carbon disulfide was added dropwise with continuous stirring. The reaction was exothermic and the mixture turned red in color. When the reaction subsided, 1.8 moles of methyl iodide was added dropwise over a period of 1 hour and, as the reaction proceeded, the color disappeared. The procedure used to separate the esters from the reaction mixtures varied slightly with each ester as follows:

Methyl-N-ethyldithiocarbamate was obtained by repeatedly extracting the reaction mixture with small portions of carbon disulfide or carbon tetrachloride, evaporating the solvent, and washing with water. The thick, yellow oil was fractionally distilled under reduced pressure.

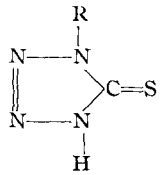
Methyl-N-n-propyldithiocarbamate was obtained by extracting the reaction mixture with many small portions of diethylether, drying over calcium chloride, filtering, and evaporating the solvent. A good yield of thick, yellow oil was fractionally distilled under reduced pressure.

Methyl-N-isopropyldithiocarbamate was prepared by refluxing the mixture for 24 hours after the addition of the methyl iodide. Separation and purification was carried out in the same manner as described for methyl N-*n*-propyldithiocarbamate.

Methyl-N-n-butyldithiocarbamate also required refluxing for 24 hours after the addition of methyl iodide. The ester was isolated from the reaction mixture and distilled, as described under methyl-N-*n*-propyldithiocarbamate. The analyses and boiling points of the methyl esters of N-alkyl- and N-aryldithiocarbamic acid are given in Table I.

1-Ethyl-1,2,3,4-tetrazole-5-thione was prepared by dissolving 24.3 Gm. (0.18 mole) of methyl-N-ethyldithiocarbamate and 8.1 Gm. (0.18 mole) of sodium azide in 100 ml. of 95% ethanol, then diluting to 130 ml. with water to solubilize the inorganic azide. Warming aided in effecting solution at this point. The solution was refluxed over a water bath at 60°

TABLE II.—1-ALKYL- AND 1-ARYL-1,2,3,4-TETRAZOLE-5-THIONES PREPARED



R	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found	Yield, %	M.P., °C.
Methyl	...	...	...	...	48.3	49.1	7.00	124–126
Ethyl	27.6	27.4	4.61	4.57	43.0	42.5	24.00	240–245
n-Propyl	33.2	33.0	5.54	5.62	38.4	37.7	22.00	74– 76
Cyclohexyl	...	...	...	...	30.5	30.5	...	102–103
Benzyl	...	...	...	...	29.2	28.4	43.00	145–146
Phenyl	...	...	...	...	31.5	31.9	48.00	152

for several hours, then cooled in an ice bath and acidified. The cold mixture was filtered and the clear filtrate was reduced in volume by evaporation on a steam bath. At the first sign of crystallization, the concentrated filtrate was slowly cooled allowing fine, white, needle-like crystals to precipitate. The crystals were washed with a small portion of water and, upon drying, were taken up in absolute alcohol and precipitated by the addition of absolute ether. The pure crystals melted at 240–245°.

1-n-Propyl-1,2,3,4-tetrazole-5-thione was prepared by dissolving 7.5 Gm. (0.05 mole) of methyl-N-*n*-propyldithiocarbamate and 3.3 Gm. (0.05 mole) of sodium azide in 30 ml. of 95% ethanol. Enough water was added to bring the azide into solution. The reaction mixture was refluxed for 2 hours then cooled in ice, acidified, and filtered. The filtrate was concentrated to small volume. Upon cooling the tetrazole was separated as long, white needles. After purifying in the same manner as used for the ethyl analog, crystals melted at 76°.

The analyses and melting points of 1-alkyl- and 1-aryl-1,2,3,4-tetrazole-5-thiones are given in Table II.

DISCUSSION

A search of the literature revealed that many of the methyl esters of N-alkyl- and N-aryldithiocarbamic acid had previously been prepared as intermediates, but few physical constants were tabulated. It was also found in the preparation of the esters that as the alkyl chain of the primary amine was lengthened, the reactivity with carbon disulfide in aqueous sodium hydroxide decreased slightly and the reactivity with the methylating agent decreased markedly. The methylating agents used, in the order of their reactivity, were methyl iodide, methyl sulfate, and methyl *p*-toluenesulfonate. It was found that primary aliphatic amines with alkyl chains longer than four carbons did not yield appreciable amounts of methyl esters.

In an attempt to find a more general method for the preparation of 1-alkyl- and 1-aryl-1,2,3,4-tetrazole-5-thiones, phenylisothiocyanate was reacted with sodium azide giving near quantitative yields of the phenyl derivative of the tetrazole-5-thiones (5). 1-Allyl-1,2,3,4-tetrazole-5-thione was prepared from allyl isothiocyanate and sodium azide in low yields (6).

It was found that the methyl esters of N-isopropyl-, N-*n*-butyl-, and N-isobutyldithiocarbamic acid did not react under the given conditions to form the corresponding tetrazoles. It became apparent that an increase in chain length and branching decreased the reactivity of the isothiocyanate with sodium azide.

SUMMARY

1. Eight N-substituted methyl esters of dithiocarbamic acid were prepared. Of these, the ethyl, *n*-propyl, isopropyl, *n*-butyl-, and cyclohexyl- had not been reported.

2. Six 1-alkyl- and 1-aryl-1,2,3,4-tetrazole-5-thiones were prepared from the corresponding dithiocarbamate esters. Of these, the ethyl and *n*-propyl had not been reported.

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