zole was recrystallized from ether-petroleum ether, m.p. 73–74°. Admixture of the same product prepared by method A-1 or A-2 caused no depression of the melting point; yield 48% based on crude aminoguanidine hydriodide.

The hydrochloride was prepared in ether solution with dry hydrogen chloride and recrystallized from ether–isopropyl alcohol, m.p. and mixture m.p. 156–157°.

All the 1-alkyl-5-alkylaminotetrazoles and their hydrochlorides prepared by this procedure are listed in Tables II and VI, respectively. In all cases the products were identical with the materials prepared by Method A-1 or A-2.

EAST LANSING, MICH.

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[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY]

# Synthesis of 1-Substituted Tetrazoles[1]

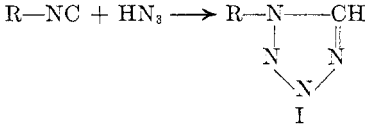
FRANCES G. FALLON[2] AND ROBERT M. HERBST

*Received March 8, 1957*

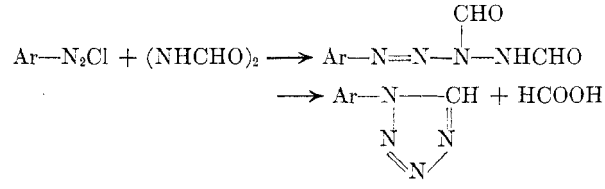
A group of seven 1-alkyltetrazoles was prepared by interaction of alkyl isocyanides and hydrazoic acid in benzene solution. The same method was applied to the synthesis of 1-phenyltetrazole but the yield was very poor. The Dimroth procedure for preparation of 1-aryltetrazoles by coupling diformyl hydrazide and diazonium salts also gave very poor yields of 1-phenyltetrazole. A new procedure involving an adaptation of the von Braun synthesis of 1,5-disubstituted tetrazoles was developed. Interaction of formanilides successively with phosphorus pentachloride and hydrazoic acid in toluene gave fair yields of the desired 1-aryltetrazoles. A group of eight 1-aryltetrazoles was prepared in this way. Their ultraviolet absorption spectra were determined and compared with those of comparable 5-aryltetrazoles.

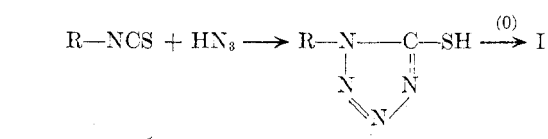
Although many 5-substituted tetrazoles are known, only very few 1-substituted tetrazoles have been described. Benson,[3] in his review of tetrazole chemistry, listed only seven examples including the questionable 1-hydroxytetrazole. It was the purpose of this study to investigate the preparation and properties of a larger group of 1-substituted tetrazoles.

Of the known methods for synthesis of 1-substituted tetrazoles three appeared to offer possibilities of rather general application. Oliveri-Mandalà and Alagna[4] obtained 1-methyl-, 1-ethyl-, and 1-phenyltetrazole by addition of hydrazoic acid to the appropriate isocyanide in ether solution. 1-Aryltetrazoles were prepared by Dimroth and de



Montmollin[5] by coupling aryl diazonium salts with diformyl hydrazide in aqueous alkaline medium and cyclizing the resulting diazohydrazide with warm aqueous alkali. Freund and Paradies[6] and later Stollé and Henke-Stark[7] oxidized 1-substituted-5-mercaptotetrazoles which had been prepared by interaction of isothiocyanates and hydrazoic acid or sodium azide. Although only 1-methyl- and 1-phenyltetrazole have been prepared this way, a variety of 1-substituted 5-mercaptotetrazoles have been described.[3]





For the preparation of 1-alkyltetrazoles the addition of hydrazoic acid to alkyl isocyanides[4] appeared to be the most generally applicable procedure. A series of seven 1-alkyltetrazoles was prepared in this way (Table I) but the method leaves much to be desired because of the disagreeable character of the requisite alkyl isocyanides. The latter were best prepared by the technique of Guillemard[8] by interaction of alkyl iodides and silver cyanide at steam bath temperature under reflux. Crude yields of the isocyanides were generally satisfactory, although the products were probably contaminated with dimerized or polymerized material in increasing quantity on standing which necessitated immediate use of the crude products in the next step of the synthesis. An attempt to estimate the isocyanide content of the crude products by a bromide-bromate titration in-

(1) Based on a thesis submitted by Frances G. Fallon to the School for Advanced Graduate Studies at Michigan State University in 1956, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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(3) F. R. Benson, *Chem. Revs.*, **41**, 1 (1947).

(4) E. Oliveri-Mandalà and B. Alagna, *Gazz. chim. ital.*, **40**, II, 441 (1910).

(5) O. Dimroth and G. de Montmollin, *Ber.*, **43**, 2904 (1910).

(6) M. Freund and T. Paradies, *Ber.*, **34**, 3110 (1901).

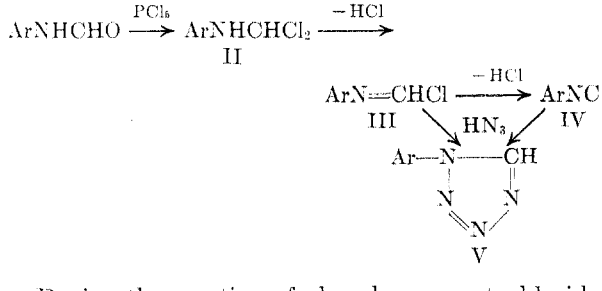
(7) R. Stollé and F. Henke-Stark, *J. prakt. Chem.*, **124**, 261 (1930).

(8) H. Guillemard, *Ann. chim. et phys.*, (8) **14**, 311 (1908).

dicated a marked decrease of titratable material during 24 hr., but it was not possible to standardize the procedure for lack of a standard of known purity. The crude alkyl isocyanides were added immediately to a benzene solution of hydrazoic acid and heated under reflux on a steam bath for periods of 1–5 hr. The 1-alkyltetrazoles were subsequently isolated by fractionation under reduced pressure. 1-Phenyltetrazole was also prepared from phenyl isocyanide and hydrazoic acid, but the unsatisfactory yield of tetrazole coupled with poor yields of the isocyanide in the carbylamine reaction prompted investigation of other methods of synthesis for 1-aryltetrazoles.

Application of the Dimroth procedure for the synthesis of 1-phenyltetrazole[5] gave only a very small yield of the desired product in our hands although the technique had been applied with considerable success to other diacyl hydrazides in the preparation of 1-aryl-5-alkyltetrazoles.[5,9]

In view of these difficulties an attempt was made to extend the von Braun technique[10] for the preparation of 1,5-disubstituted tetrazoles to *N*-substituted formamides. Wallach[11] had reported the formation of *N*,*N*′-diphenylformamidine by interaction of formanilide and phosphorus pentachloride. Since Wallach worked without solvent and without temperature control of the exothermic reaction and isolated the product by distilling the reaction mixture at atmospheric pressure, the formation of formimidyl chlorides under more moderate conditions was not precluded. Experiments in which formanilide was treated in toluene solution with phosphorus pentachloride at or below room temperature led to the formation of an intermediate that reacted with hydrazoic acid in the same solvent to give moderate quantities of 1-phenyltetrazole. The procedure was extended successfully to substituted formanilides and *N*-isobutylformamide; however, the yield of 1-isobutyltetrazole from the latter was poor and the process does not appear promising for the synthesis of 1-alkyltetrazoles under the conditions studied.




During the reaction of phosphorus pentachloride with the formanilides at ice bath temperature a heavy oil ranging from yellow to bright red in color separated without evolution of hydrogen chloride. When the reaction mixture was allowed to come to room temperature, hydrogen chloride was evolved. These observations could be interpreted as initial formation of an unstable amide chloride (II) which subsequently lost hydrogen chloride with formation of the formimidyl chloride (III) or possibly the aryl isocyanide (IV), either of which could react with hydrazoic acid to form the tetrazole (V). Since hydrogen chloride is also evolved during the reaction with hydrazoic acid, II would appear to be the more likely intermediate. The 1-aryltetrazoles prepared in this way are listed in Table I. They are all solids of considerably lower melting point than the corresponding 5-aryltetrazoles.[12] The product from the reaction with *o*-formotoluidide could not be made to crystallize nor could it be purified by distillation.

Ultraviolet absorption spectra of a number of 1-alkyl- and 1-aryltetrazoles were examined in the region of 210–300 mμ. Neither tetrazole nor the 1-alkyl- or 5-alkyltetrazoles exhibited appreciable absorption in this range, a pattern also shown by 5-cyclohexyltetrazole.[13] All the 1-aryltetrazoles showed strong absorption bands with maxima and extinction coefficients as noted in Table II. It is interesting that substitution on the benzene ring of the 1-phenyl- and the 5-phenyltetrazole systems has similar effects. In both instances *meta* and *para* substituents cause a progressively greater shift of the maximum toward longer wave lengths, while *ortho* substituents cause a shift of the maximum toward shorter wave lengths. Just as in the 5-aryltetrazole series[12] the strong absorption band of the 1-aryltetrazoles may be attributed to the resonance interaction of the phenyl and tetrazole rings (Figure 1). The shift of the maximum to much shorter wave lengths in the *ortho* substituted compounds may similarly be attributed to interference with the attainment of a coplanar configuration by the two rings due to a bulky group in the *ortho* position.

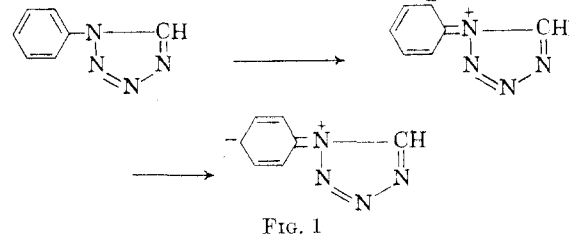


FIG. 1

Infrared spectra for the 1-substituted tetrazoles here described as well as comparable 5-substituted and 1,5-disubstituted tetrazoles have been recorded.[14]

(9) D.-Y. Wu and R. M. Herbst, *J. Org. Chem.*, **17**, 1216 (1952).

(10) J. von Braun and W. Rudolph, *Ber.*, **74**, 264 (1941).

(11) O. Wallach, *Ann.*, **214**, 193 (1882).

(12) R. M. Herbst and K. R. Wilson, unpublished results.

(13) B. Elpern and F. C. Nachod, *J. Am. Chem. Soc.*, **72**, 3379 (1950).

(14) F. G. Fallon, *The Synthesis of 1-Substituted Tetrazoles and Spectrographic Studies with Tetrazoles*. Ph.D. Thesis, Michigan State University, 1956.

## EXPERIMENTAL[15]

*Alkyl isocyanides* were prepared from alkyl iodides and silver cyanide under the conditions recommended by Guillemard.[8] The normal alkyl isocyanides from ethyl to heptyl as well as isobutyl and isoamyl isocyanide were prepared in this way. Phenyl isocyanide was prepared by the carbylamine reaction under the conditions recommended by Malatesta.[16] An attempt was made to estimate the amount of isocyanide in the crude products by treatment of their benzene solutions with excess standard bromide-bromate solution, addition of potassium iodide, and back-titration with standard thiosulfate. Bromide-bromate solution was used up in decreasing amounts as the isocyanides were kept for a day or two. Lack of a pure standard prevented further exploration of this procedure.

*Diformyl hydrazide* was prepared from sodium formate and hydrazine sulfate according to Pellizzari.[17]

*Formanilides and N-alkylformamides* were prepared by heating the appropriate amines with excess formic acid. Most of the formanilides were purified by crystallization; the *N*-alkylformamides, formanilide, and *m*-formotoluidide were distilled.

*1-Alkyltetrazoles* were prepared from the alkyl isocyanides and hydrazoic acid in benzene solution. The preparation of *n*-hexyltetrazole serves as a typical example. A mixture of 8.0 g. of crude *n*-hexyl isocyanide and 100 ml. of a 16% solution of hydrazoic acid in benzene was heated under reflux in a well-ventilated hood for 3 hr. The solvent was removed under reduced pressure and the residue was boiled under reflux for an hour with 20% hydrochloric acid. After making the cooled solution alkaline with sodium hydroxide, the crude tetrazole layer was separated and the aqueous layer was shaken with ether. The combined tetrazole layer and ether solution were dried over sodium sulfate before the ether was removed by distillation and the residue fractionated under reduced pressure. Physical constants and analytical data are given in Table I. The 1-alkyltetrazoles are sparingly soluble in water, soluble in concentrated aqueous acids, and most of the common organic solvents except petroleum ether. Their aqueous suspensions are neutral or weakly basic to litmus.

*1-Aryltetrazoles* were prepared from the formanilides by reaction successively with phosphorus pentachloride and hydrazoic acid in toluene. The preparation of 1-*m*-tolyltetrazole serves as a typical example. A solution of 33.8 g. (0.25 mole) of *m*-formotoluidide in 100 ml. of toluene was stirred and cooled in an ice bath during the portion-wise addition of 52 g. (0.25 mole) of phosphorus pentachloride. Upon complete reaction with the phosphorus pentachloride the resulting bright yellow solution was treated with 100 ml. of a 16% solution of hydrazoic acid in toluene, stirred at room temperature for 24 hr., poured over ice, made alkaline with sodium hydroxide, and filtered. The filter cake was washed by resuspension first in 4% sodium hydroxide and then in water. A further quantity of the crude product was obtained by separating the toluene layer from the filtrate and evaporating the toluene. The two crops were combined and recrystallized from aqueous isopropyl alcohol. Final purification was accomplished by repeated extraction with warm cyclohexane from which the tetrazole separated as colorless crystals. Physical constants and analytical data are given in Table I. 1-Phenyltetrazole and 1-*o*-methoxyphenyltetrazole were also crystallized from cyclohexane. All the other 1-aryltetrazoles were crystallized from isopropyl alcohol. In some instances the formanilide was insoluble and was used as a suspension in toluene. The product of reaction with phosphorus pentachloride varied

TABLE I

1-SUBSTITUTED TETRAZOLES (I)

| R | B.P. (M.P.),[a] °C. at mm. | $n_D^{20}$ | Yield, % | Formula | Analyses | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Calculated | | | Found | | |
| | | | | | C | H | N | C | H | N |
| $C_2H_5$ | 147–148/14 | 1.4601 | 30 | $C_3H_6N_4$ | 36.7 | 6.2 | 57.1 | 36.8 | 6.3 | 56.9 |
| *n*-$C_4H_9$ | 143–145/2 | 1.4604 | 63 | $C_5H_{10}N_4$ | 47.6 | 7.9 | 44.4 | 47.9 | 7.7 | 44.3 |
| *iso*-$C_4H_9$ | 121–123/1 | 1.4590 | 18 | $C_5H_{10}N_4$ | 47.6 | 7.9 | 44.4 | 47.9 | 8.2 | 44.6 |
| *n*-$C_5H_{11}$ | 138–139/1 | 1.4608 | 57 | $C_6H_{12}N_4$ | 51.4 | 8.6 | 40.0 | 51.4 | 8.7 | 40.0 |
| *iso*-$C_5H_{11}$ | 143–145/1 | 1.4607 | 37 | $C_6H_{12}N_4$ | 51.4 | 8.6 | 40.0 | 51.8 | 8.8 | 39.4 |
| *n*-$C_6H_{13}$ | 144–146/1 | 1.4610 | 57 | $C_7H_{14}N_4$ | 54.6 | 9.1 | 36.4 | 54.7 | 9.2 | 36.2 |
| *n*-$C_7H_{15}$ | 150–152/1 | 1.4613 | 9 | $C_8H_{16}N_4$ | 57.1 | 9.5 | 33.3 | 57.5 | 9.3 | 32.6 |
| $C_6H_5$ | (65–66) | *b* | 16 | $C_7H_6N_4$ | 57.5 | 4.1 | 38.3 | 57.5 | 3.9 | 38.6 |
| *m*-$CH_3C_6H_4$ | (53–54) | *b* | 34 | $C_8H_8N_4$ | 60.0 | 5.0 | 35.0 | 60.1 | 5.0 | 34.9 |
| *p*-$CH_3C_6H_4$ | (93–94) | *c* | 28 | $C_8H_8N_4$ | 60.0 | 5.0 | 35.0 | 59.8 | 4.9 | 34.9 |
| *o*-$ClC_6H_4$[d] | (86–87) | *c* | 41 | $C_7H_5N_4Cl$ | 46.6 | 2.8 | 31.0 | 46.6 | 2.9 | 31.1 |
| *m*-$ClC_6H_4$[e] | (101–102) | *c* | 43 | $C_7H_5N_4Cl$ | 46.6 | 2.8 | 31.0 | 46.5 | 2.9 | 31.2 |
| *p*-$ClC_6H_4$[f] | (155–156) | *c* | 32 | $C_7H_5N_4Cl$ | 46.6 | 2.8 | 31.0 | 46.6 | 2.9 | 31.0 |
| *o*-$CH_3OC_6H_4$ | (48–49) | *b* | 32 | $C_8H_8N_4O$ | 54.5 | 4.6 | 31.8 | 54.8 | 4.6 | 32.0 |
| *p*-$CH_3OC_6H_4$ | (116–117) | *c* | 35 | $C_8H_8N_4O$ | 54.5 | 4.6 | 31.8 | 54.7 | 4.6 | 32.1 |

[a] Parentheses indicate m.p. [b] Crystallized from cyclohexane. [c] Crystallized from isopropyl alcohol. [d] Calcd.: Cl, 19.6. Found: Cl, 19.7. [e] Calcd.: Cl, 19.6. Found: Cl, 19.7. [f] Calcd.: Cl, 19.6. Found: Cl, 19.7.

(15) Microanalyses were done by Micro-Tech Laboratories, Skokie, Ill.

(16) L. Malatesta, *Gazz. chim. ital.*, **77**, 238 (1947); *Chem. Abstr.*, **42**, 869 (1948).

(17) G. Pellizzari, *Gazz. chim. ital.*, **39**, I, 520 (1909).

in color from bright yellow to bright red and in some instances separated as a pasty mass or an oil without interference in the subsequent reaction with hydrazoic acid.

1-Phenyltetrazole was also prepared from phenyl isocyanide and hydrazoic acid[4] in benzene solution and by Dimroth's method from benzene diazonium chloride and diformyl hydrazide. In both instances the yields were poor but the products were identical with the material prepared from formanilide.

*1-Isobutyltetrazole* was prepared by interaction of 17.9 g. (0.18 mole) of *N*-isobutylformamide in 100 ml. of toluene with 37 g. (0.18 mole) of phosphorus pentachloride followed by treatment with 100 ml. of a 16% solution of hydrazoic acid in toluene. After addition of the hydrazoic acid solution the reaction mixture was stirred for 1 hr. at room temperature and then for 3 hr. under reflux on a steam bath. The mixture was poured onto ice and made alkaline with sodium hydroxide. After separation of the toluene layer the aqueous layer was shaken once with toluene and then discarded. The combined toluene solutions were dried and the residue left after removal of the solvent was fractionated. 1-Isobutyltetrazole was collected at 121–123° at 1 mm., $n_D^{20}$ 1.4590, yield 4.0 g. (18%). This product and the material prepared from isobutyl isocyanide gave identical infrared spectra.

*Ultraviolet absorption spectra* were determined with $1 \times 10^{-4}M$ solutions in 95% ethanol using a Beckman Model DU spectrophotometer. Readings were made with 1-cm. cells with 95% ethanol as the blank. The region 210–300 mμ was scanned at 5-mμ intervals and near the maxima readings were taken at 1-mμ intervals. Tetrazole and the 1-alkyltetrazoles showed only little absorption and no maxima in the region examined although in these cases concentrations as high as $1 \times 10^{-2}M$ were used. All the 1-aryltetrazoles exhibited a broad absorption band; maxima and extinction coefficients are recorded in Table II.

TABLE II

ULTRAVIOLET ABSORPTION MAXIMA OF SOME 1- AND 5-ARYLTETRAZOLES

| Aryl | 1-Aryltetrazoles Max. (mμ) | ε | 5-Aryltetrazoles Max. (mμ) | ε |
|---|---|---|---|---|
| Phenyl | 236 | 9,300 | 241[a] | 15,900 |
| *m*-Tolyl | 239 | 8,700 | 243 | 13,600 |
| *p*-Tolyl | 243 | 10,100 | 246 | 16,700 |
| *o*-Chlorophenyl | (215)[b] | (10,400) | 234[a] | 9,600 |
| *m*-Chlorophenyl | 239 | 8,800 | 242[a] | 14,000 |
| *p*-Chlorophenyl | 242 | 14,000 | 247[a] | 20,400 |
| *o*-Methoxyphenyl | 235 | 5,800 | 246[a] | 11,600 |
| | 282 | 3,800 | 294 | 4,900 |
| *p*-Methoxyphenyl | 255 | 10,900 | 259[a] | 16,900 |

[a] Ref. 12. [b] Shoulder.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POMONA COLLEGE]

# Catalytic Synthesis of Heterocycles. IX.[1] Dehydrocyclization of 2-Methyl-5-ethyl-4-pyridinethiol to 6-Methyl-5-azathianaphthene

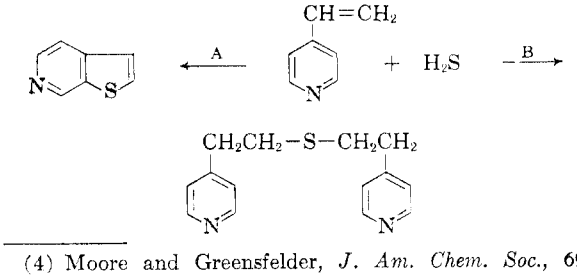
CORWIN HANSCH AND WAYNE CARPENTER

*Received February 25, 1957*

A procedure for the synthesis of 2-methyl-5-ethyl-4-pyridinethiol from 2-methyl-5-ethylpyridine has been developed. The dehydrogenation of this *o*-ethylthiol to 6-methyl-5-azathianaphthene is discussed.

After considering suitable systems in which to extend the use of the dehydrocyclization reaction it was decided that the pyridine ring offered a highly stable and interesting structure for such a study. In particular this ring system offers an approach to the synthesis of heterocycles containing two hetero atoms. The fact that ethylpyridines are available commercially and that improved methods have been worked out for the introduction of substituents into the pyridine ring[2,3] indicated that the necessary starting materials should be relatively easy to prepare. Formation of the thiophene ring was chosen for the first of these experiments because previous work[1] had shown that the dehydrocyclization reaction is particularly useful in its formation.

It was first expected that azathianaphthenes could be obtained by the reaction of hydrogen sulfide with vinyl pyridines. It is known[4] that styrene and hydrogen sulfide react at 600° to give thianaphthene. A number of runs were made using the catalyst of Moore and Greensfelder,[4] as well as with the catalyst used in the dehydrocyclization of *o*-ethylthiophenol.[1] The products from the reaction of 4-vinylpyridine and hydrogen sulfide at 600° were separated into two fractions: one was a red, tarry material soluble in water, but insoluble in ether, and the other was a yellow oil which was soluble in ether and insoluble in water. Of two possible paths which the reaction might take, A or B, a work-up of the ether soluble fraction indicated that this material was formed *via* path B as follows:




(1) For the previous paper in this series see *J. Org. Chem.*, 21, 265 (1956).

(2) Den Hertog and Combe, *Rec. trav. chim.*, 70, 581 (1951).

(3) Ochiai, *J. Org. Chem.*, 18, 534 (1953).

(4) Moore and Greensfelder, *J. Am. Chem. Soc.*, 69, 2008 (1947).