[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Absorption Spectra and Structure of Some Tetrazoles

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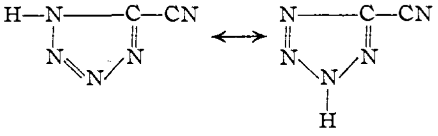
An examination of the literature revealed that direct alkylation of 5-monosubstituted-tetrazoles may lead to either 1,5- or 2,5-disubstituted-tetrazoles, or both. Thus Lossen[1] treated 5-phenyltetrazole with ethyl iodide and potassium ethoxide and pointed out that he was not able to determine the structure of the resulting phenylethyltetrazole. Pinner[2] treated 5-(2-naphthyl)-tetrazole with sodium ethoxide and methyl iodide and gave the structure of the product as 1-methyl-5-(2-naphthyl)-tetrazole without any proof. He also reported the ethyl analog but did not assign the position of the ethyl group.

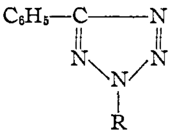
Oliveri-Mandalà and Passalacqua[3] converted 5-cyanotetrazole to the silver salt and treated this with methyl and ethyl iodides. They stated that only 2-alkyl-5-cyanotetrazoles were formed. Proof of the structure was obtained by hydrolyzing, and decarboxylating and comparing the resulting alkyltetrazoles with the known 1-alkyltetrazoles. They suggested that only one isomer was obtained in the alkylation because the strongly electronegative character of the cyano group enhanced the acidity of tautomer II and favored its equilibrium concentration. Fries and Saftien[4] prepared 2-ethyl-5-tetrazolecarboxylic acid by heating silver 5-tetrazolecarboxylate and ethyl iodide at 100° in a bomb followed by saponification with potassium hydroxide.



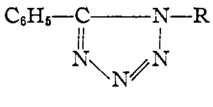
I II

In view of the fact that the K_a values of several 5-substituted tetrazoles have been reported[5] as being 10^{-5} or greater and further since Lossen[1] titrated 5-phenyltetrazole with strong bases using phenolphthalein as an indicator it seemed unlikely that such strong alkylating conditions as reported in the literature were necessary. Therefore, 5-phenyltetrazole was alkylated with methyl iodide in the presence of aqueous sodium hydroxide. A single product was isolated, which differed in melting point from the 1-methyl-5-phenyltetrazole reported by von Braun and Rudolph[6] which had been prepared by treating N-methylbenzimidyl chloride with hydrazoic acid.

Benson[7] noted that no spectrophotometric data on tetrazoles had been reported at the time his review was published. Since that time only one incidental spectral observation on a tetrazole derivative has been described in the literature.[8,8a] It thus seemed to us that it would be of interest to obtain ultraviolet spectral data on several tetrazole derivatives and structurally related compounds and in so doing derive a method for distinguishing between the two series of 5-aryltetrazoles, III and IV.



III



IV

A linear-conjugated structure might be expected to absorb in the longer wave length range, say between 270–290 mμ, whereas a cross-conjugated compound should have a shorter wave length absorption band. In structure III we have an example of cross-conjugation and in structure IV an example of linear conjugation. Although when R is H we might expect a tautomeric equilibrium between III and IV, actually we find a peak at 239 mμ which would indicate that we have only one tautomer, probably the cross-conjugated one, the phenyl group thus acting like the cyano group in stabilizing the structure III.

To obtain a better understanding of the spectral characteristics of linear and cross-conjugated systems, we turned our attention to a number of model compounds. The simplest aryl linear-conjugated compound with two double bonds is 1-phenylbutadiene, which exhibits a maximum at 280 mμ.[9]

Next we examined the spectra of arylheterocycles having linear conjugation. The curves for 2-phenylpyrrole and 2-phenylfuran-5-propionic acid[10] are shown in Fig. 1. Both compounds show a close similarity and exhibit broad maxima at 287 mμ.

No attempt is made to distinguish between the ease of transition of π electrons in double bonds formed between carbon–carbon, carbon–nitrogen,

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[1] Lossen and Lossen, *Ann.*, **263**, 106 (1891).

[2] Pinner, *ibid.*, **298**, 39 (1897); *Ber.*, **30**, 1882 (1897).

[3] Oliveri-Mandalà and Passalacqua, *Gazz. chim. ital.*, **41**, II, 431 (1911); **43**, II, 465 (1913).

[4] Fries and Saftien, *Ber.*, **59**, 1251 (1926).

[5] Oliveri-Mandalà, *Gazz. chim. ital.*, **44**, II, 175 (1914); **45**, I, 303 (1915).

[6] von Braun and Rudolph, *Ber.*, **74**, 267 (1941).

[7] Benson, *Chem. Rev.*, **41**, 1 (1947).

[8] Havinga and Veldstra, *Rec. trav. chim.*, **66**, 262 (1947).

[8a] Since this paper was completed, an article by Schueler, Wang, Featherstone and Gross appeared (*J. Pharm. Expt. Ther.*, **97**, 266 (1949)) in which pharmacological action and absorption spectra of various tetrazoles were correlated. The only compound common to their series and ours is 5-phenyl-1-methyltetrazole (compound no. 15 in their series). The values of these workers are in close agreement with the data reported here (*cf.* figure 4).

[9] Smakula, *Angew. Chem.*, **47**, 657 (1934).

[10] Turner, THIS JOURNAL, **71**, 612 (1949).

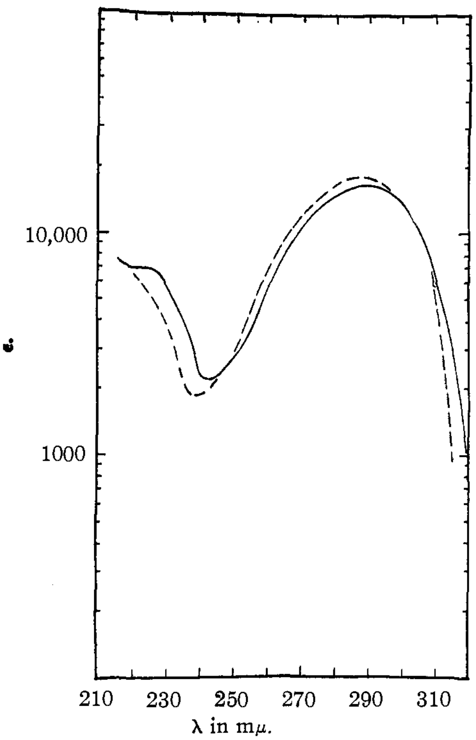


Fig. 1.—Absorption spectra of — 2-phenylpyrrole, - - - - 2-phenylfuran-5-propionic acid, in ethanol.

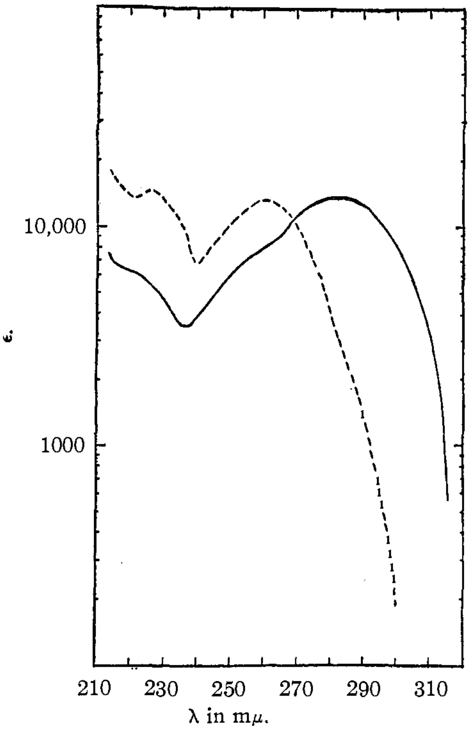
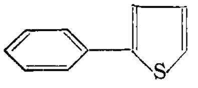


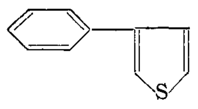
Fig. 2.—Absorption spectra of — 2-phenylthiophene, - - - 3-phenylthiophene, in ethanol.

and nitrogen–nitrogen, an approximation which apparently is permissible.[11]

To establish critical differences between linear and cross-conjugated structures, it appeared advisable to select isomeric pairs of compounds and investigate their spectra.

The first pair studied was 2-phenylthiophene (V) and 3-phenylthiophene (VI). The maxima

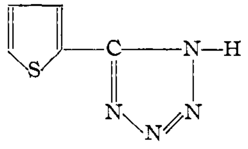

V (linear)

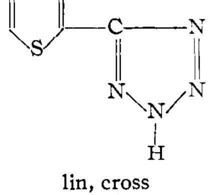

VI (cross)

observed were 282 mμ for the linearly-conjugated isomer and 259 mμ for the cross-conjugated one (Fig. 2). The bathochromic shift in the case of the 3-substituted compound is easily understood, as thiophene itself absorbs in the 230–240 mμ range[12] and vinyl substitution alone produces a bathochromic shift of about 32 mμ.[13,14]

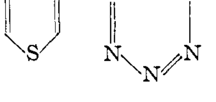
The characteristic difference between the linear- and cross-conjugated structures is, however, apparent; the smaller Δλ of 23 mμ against an expected 30–40 mμ is probably due to the thiophene contribution.

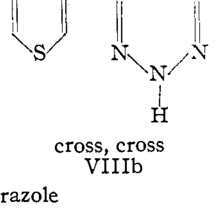
Another group of compounds, containing the tetrazole nucleus, was next investigated. These were 5-(2-thienyl)-tetrazole (VII) and 5-(3-thienyl)-tetrazole (VIII). In Fig. 3 the curve of the 3-thienyl isomer shows a maximum at 249–250 mμ, whereas that of the 2-thienyl isomer has maxima at 255 mμ and 270 mμ. The Δλ of 21 mμ again may be explained by the contribution of the thiophene ring, and by the fact that contributions from linear- and cross-conjugated structures are conceivable for both compounds, as the tetrazole double bonds are not fixed. The principal tautomeric structures and their respective contributions are shown in VII and VIII.


lin, lin
VIIa


lin, cross
VIIb

5-(2-Thienyl)-tetrazole


cross, lin
VIIIa


cross, cross
VIIIb

5-(3-Thienyl)-tetrazole

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[11] Hertel and Siegel, *Z. physik. Chem.*, **B52**, 167 (1942).

[12] Smakula, *Z. physiol. Chem.*, **230**, 238 (1934).

[13] Kuhn and Dann, *Ann.*, **547**, 293 (1941).

[14] Jackman, Bolen, Nachod, Tullar and Archer, THIS JOURNAL, **71**, 2301 (1949).

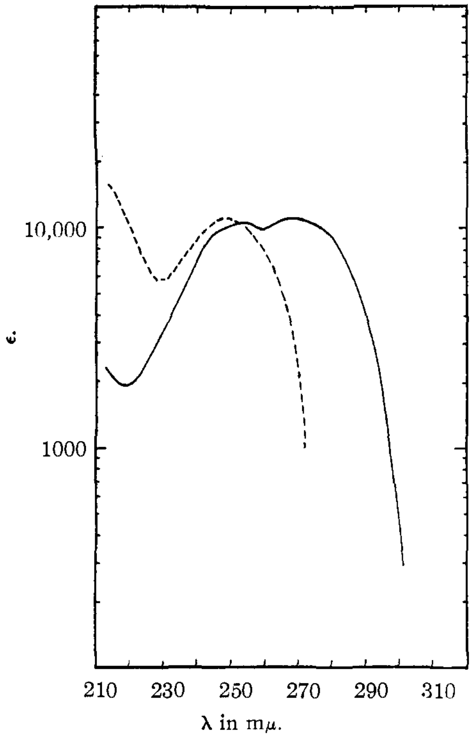

Fig. 3.—Absorption spectra of — 5-(2-thienyl)-tetrazole, - - - 5-(3-thienyl)-tetrazole, in ethanol.

Although in the case of 5-(3-thienyl)-tetrazole we have two possible tautomers, the spectrum has only one peak at 249 mμ indicating cross–cross type, *i. e.*, VIIIb, whereas the spectrum of 5-(2-thienyl)-tetrazole shows two nearly equal peaks, at 255 and 270 mμ, indicating that both possible tautomers are present.

In Fig. 4, the spectra of 5-phenyltetrazole, 5-cyclohexyltetrazole, 5-phenyl-1-methyltetrazole and 5-phenyl-2-methyltetrazole are compared. It is readily seen (compare phenyl and cyclohexyltetrazoles) that the tetrazole ring does not have any appreciable absorption *per se;* in this respect it is similar to benzene. However, due to its lesser resonance energy, it does not have the characteristic envelope but only end absorption.

This difference in resonance energies between benzene and tetrazole can also be demonstrated by comparing Figs. 2 and 3. The thiophene nucleus is common to all four compounds, and the bathochromic shift of 12 mμ of both phenyl structures is a direct measure of the larger resonance energy of benzene.

5-Phenyltetrazole and 2-methyl-5-phenyltetrazole show essentially the same position of maxima, the former at 239 mμ and the latter at 240 mμ. From the spectrochemical evidence we are led to believe that the structure of the compound prepared by the direct alkylation of 5-phenyltetrazole should have the cross-conjugated configuration indicated by III where R is alkyl.

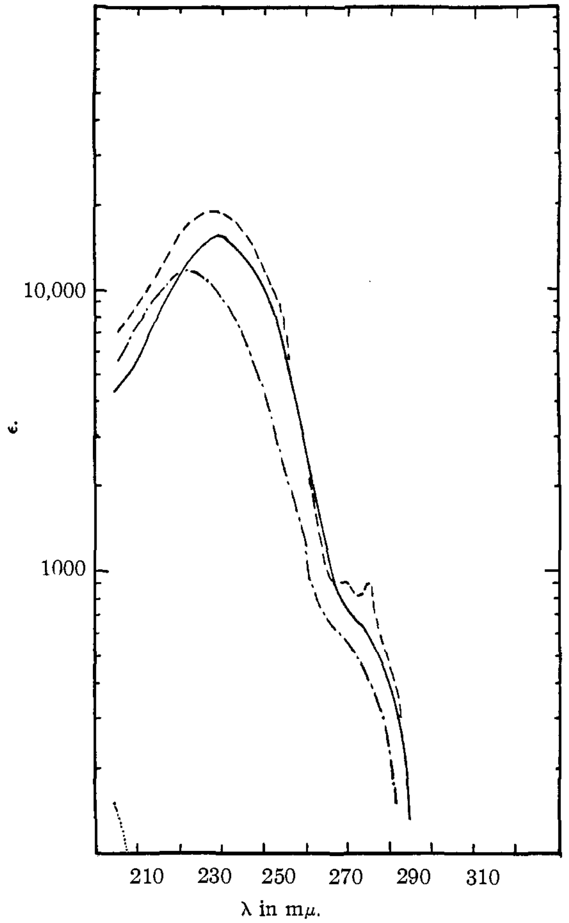

Fig. 4.—Absorption spectra of — 5-phenyltetrazole, —·—· 5-phenyl-1-methyltetrazole, — — — 5-phenyl-2-methyltetrazole, ... 5-cyclohexyltetrazole, in ethanol.

A number of alkylated tetrazoles which will be reported later also exhibit maxima at 240 mμ as their hydrochlorides and at a somewhat shorter wave length in the case of their methiodides. They, therefore, are also believed to have the cross-conjugated configuration.

5-Phenyl-1-methyltetrazole prepared in the manner described by von Braun and Rudolph,[6] however, proved to be an exception. This compound exhibits a maximum at 232 mμ, whereas we expected it to absorb at 270–290 mμ, in view of its presumed linear conjugation.

Since both 5-phenyltetrazole and 5-(3-thienyl)-tetrazole each have only one peak, corresponding to the cross-conjugated tautomer; and further, since it has been demonstrated by means of dipole measurements[15] that tetrazoles exhibit substantial charge separation in solution, the hypsochromic shift of 1-methyl-5-phenyltetrazole may be readily explained by the equilibrium shown below.

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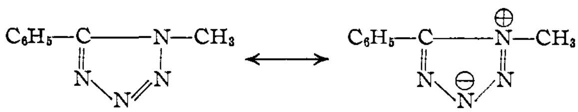
[15] Jensen and Friediger, *Kgl. Danske Videnskab. Selskab. Math.-fys. Medd.*, **20**, 1 (1943); *cf. C. A.*, **39**, 2068[5] (1945).



Experimental[16,17]

Ultraviolet Absorption Measurements.—The ultraviolet absorption spectra were determined with a Beckman quartz spectrophotometer, Model DU Serial No. D-337, using a minimum slit width, 10 mm. quartz cells and 95% ethanol as solvent.

3-Phenylthiophene,[18] **5-phenyltetrazole,**[19] and **1-methyl-5-phenyltetrazole**[6] were prepared using the appropriate procedures reported in the literature.

5-Cyclohexyltetrazole.—Twenty-two grams (0.15 mole) of 5-phenyltetrazole and 0.7 g. of Adams catalyst were suspended in 120 ml. of glacial acetic acid and subjected to hydrogen at 50 lb. pressure at a temperature of 65° in a Parr hydrogenation apparatus. The hydrogen uptake stopped after fifteen hours. The catalyst was removed by filtration and the filtrate concentrated to dryness on a steam-bath and using reduced pressure. The white residual solid was dissolved in 10% sodium hydroxide solution, filtered, and precipitated with dilute hydrochloric acid. The white crystalline product weighed 13 g. (57%); m. p. 127–128°. Recrystallization from water gave glistening platelets, m. p. 130.4–132.4°.

Anal. Calcd. for $C_7H_{12}N_4$: C, 55.24; H, 7.95; N, 36.83. Found: C, 55.41; H, 8.09; N, 37.05.

Ethyl 2-Thenimidate Hydrochloride.—2-Thienyl nitrile[20] (23 g., 0.21 mole) and 9.7 g. (0.21 mole) of absolute ethanol were dissolved in 100 ml. of dry ether and the resulting solution cooled to 0° and saturated with gaseous hydrochloric acid. After standing forty-eight hours at room temperature the dark crystals were collected and washed free of color with dry ether. The product weighed 32 g. (80%); m. p. 124–126° (dec.).

5-(2-Thienyl)-tetrazole VII.—Ethyl 2-thenimidate hydrochloride (32 g., 0.17 mole) was added to a solution of 29 g. (0.51 mole) of potassium hydroxide and 22 g. (0.17 mole) of hydrazine sulfate in 65 ml. of water, while maintaining the temperature below 20°. Ethyl alcohol (35 ml.) was added and the mixture was left to stand for eighteen hours at room temperature. The precipitated salts were removed by filtration and to the filtrate was added 11.7 g. (0.17 mole) of sodium nitrite. After cooling to 0°, 100 ml. of 6 *N* hydrochloric acid was added dropwise with stirring. A white flocculent precipitate gradually formed which was finally collected on a funnel, dissolved in potassium carbonate solution, filtered free of a very small amount of insoluble red material and reprecipitated with 6 *N* hydrochloric acid. The white product weighed 13.5 g. (52.3%); m. p. 204.7–205°.

Anal. Calcd. for $C_5H_4N_4S$: C, 39.46; H, 2.65; S, 21.07. Found: C, 39.32; H, 2.97; S, 21.20.

3-Thienylnitrile.—3-Thenaldehyde[21] was converted to the oxime[22] and dehydrated following the general procedure exemplified in "Organic Syntheses"[23] to give the nitrile, b. p. 203–205°, $n^{25}\text{D}$ 1.5534.

5-(3-Thienyl)-tetrazole VIII.—3-Thienylnitrile was converted to ethyl 3-thenimidate hydrochloride (92%), m. p. 110–111° (dec.), treated with hydrazine and then nitrous acid to give 5-(3-thienyl)-tetrazole in 43% yield; m. p. 244.8–245.3°.

Anal. Calcd. for $C_5H_4N_4S$: C, 39.50; H, 2.63; S, 21.02. Found: C, 39.66; H, 2.48; S, 20.91.

2-Methyl-5-phenyltetrazole.—5-Phenyltetrazole (7.3 g., 0.05 mole) was dissolved in a solution of 4 g. (0.1 mole) of sodium hydroxide in 20 ml. of water. Acetone (80 ml.) containing 7.1 g. (0.05 mole) of methyl iodide was added slowly and the resulting mixture was refluxed two hours. After cooling to room temperature, extracting with benzene and concentrating the benzene extract, there was left behind a straw-colored oil. It was distilled and 4.5 g. (56%) of oil, b. p. 127–128° (2–5 mm.), was collected. The oil solidified in the receiver and melted at 41.9–46.9°.

Anal. Calcd. for $C_8H_8N_4$: C, 59.93; H, 5.04; N, 34.98. Found: C, 59.93; H, 5.16; N, 35.06.

Acknowledgment.—The authors are indebted to Dr. F. F. Blicke, University of Michigan, for supplying a sample of 2-phenylpyrrole; to Dr. E. Campaigne, University of Indiana, for supplying a sample of 2-phenylthiophene; and to Dr. W. S. Johnson, University of Wisconsin, for suggestions in interpreting the spectrum of 1-methyl-5-phenyltetrazole.

Summary

4-Aryltetrazoles were directly alkylated and a cross-conjugated configuration was assigned to the products on the basis of spectrochemical evidence.

A theory for absorption bands of linear and cross-conjugated systems has been developed, assuming equal transition in π-electron bonds for C=C, N=N and C=N bonds, based on pairs of model compounds.

Several new tetrazole derivatives have been described.

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(16) The authors are indebted to Mrs. M. Becker for technical assistance.

(17) All melting points are corrected. Microanalyses were performed by Messrs. M. E. Auerbach, K. D. Fleischer and staff.

(18) Brown and Voronkov, *J. Gen. Chem.* (*U. S. S. R.*), **17**, 1162 (1947).

(19) Pinner, *Ber.*, **27**, 984 (1894).

(20) Douglas, *ibid.*, **25**, 1311 (1892).

(21) Campaigne and LeSeur, THIS JOURNAL, **70**, 1557 (1948).

(22) Steinkopf and Schmitt, *Ann.*, **533**, 266 (1938).

(23) Buck and Ide, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 622.