

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, TULANE UNIVERSITY]

The Tetrazole-Azidoazomethine Equilibrium<sup>1</sup>

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Five molecules (I, II, IV, V, VI) structurally capable of existing both as tetrazoles and as azides have been examined using spectrophotometric and chromatographic techniques. In the solid state compounds I, II, IV and V are tetrazoles. In solution I and II retain their identity as tetrazoles but IV and V now appear as azides probably together with corresponding tetrazoles. Compound VI appears to be an azide in both the solid state as well as in solution. The results indicate that tetrazole ring destabilization through fusion to another five- or six-membered ring is insufficient for isomerization of tetrazoles into azides, their less stable tautomers. On the other hand, electron-withdrawing substituents not only destabilize a tetrazole ring but stabilize the electron-donating azido group. This effect may be sufficient for the isomerization of tetrazoles into azides.

An equilibrium between tetrazoles and their tautomeric azidoazomethine derivatives has been assumed but not established heretofore.<sup>2</sup> At one extreme monocyclic tetrazole structures rather than linear azides are present,<sup>3</sup> whereas at another extreme certain aromatic heterocyclic azides but not isomeric bicyclic tetrazoles are found.<sup>4</sup> Tetrazole destabilization in bicyclic systems may occur for at least two probable reasons, the strain of ring-fusion and/or electron withdrawal. Electron-withdrawing substituents may be doubly effective by not only destabilizing the electron-attracting tetrazole ring,<sup>5</sup> but, at the same time, stabilizing the electron donating azido group. Four molecules (I, II, IV and V) reported as tetrazoles and one (VI) reported as an azide are now re-examined in search for a

molecular system which possesses a tautomeric mixture of an azide and a tetrazole, each of which may be detected, and reveals information useful in evaluating certain probable reasons for tetrazole ring destabilization.

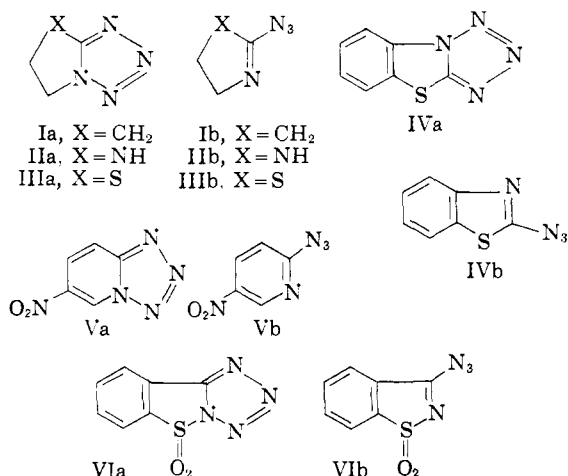
Tetrazole fusion to non-aromatic, but presumably planar, five-membered rings has been reported for trimethylenetetrazole<sup>6</sup> (Ia) and its nitrogen analog, 5,6-dihydro-7-imidazo[1,2]tetrazole<sup>2</sup> (IIa), in each case without structure confirmation.

Trimethylenetetrazole (Ia), previously produced by an intramolecular cyclization of  $\gamma$ -azido-butyronitrile,<sup>6</sup> is now obtained from 2-methylmercaptopyrroline and hydrazoic acid. In attempts to prepare tetrazolo- or azidothiazoline (III), replacement of the thioether group in 2-methylmercaptothiazoline using either hydrazoic acid or hydrazine was unsuccessful.

Infrared bands for either Ib or IIb are not found in the 2160–2120 and 1340–1180  $\text{cm}^{-1}$  regions in which azido groups give, respectively, strong and weak absorption.<sup>7</sup> Bands at 1080, 995 and 735  $\text{cm}^{-1}$  are characteristic of the tetrazole ring (Ia).<sup>8</sup> Absorption bands indicative of the presence of IIa are found at 1101, 1086, 1018, 757 and 732  $\text{cm}^{-1}$ . In ethanol solution II absorbs in the ultraviolet at 232  $\text{m}\mu$ ,  $\log \epsilon$  3.25, a band characteristic of a 2-imidazoline ring.<sup>9</sup> Assignment of this band to IIa is in agreement with the absence of absorption at 290  $\text{m}\mu$  (azido group) and tetrazole transparency<sup>10</sup> in the ultraviolet region.

Apparently ring fusion strain in IIa is small or non-existent since the absence of steric distortion of the chromophoric system is indicated by neither a shift in absorption nor reduction in its intensity.<sup>9,11</sup>

The unique example of fusion of a tetrazole ring to an aromatic five-membered ring is reported for 1,5-tetrazolobenzothiazole-1,3 (IVa), together with



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(2) In the pyrolytic interconversion of 5-substituted tetrazoles and 1-substituted 5-aminotetrazoles at 180–190°, W. G. Finnegan, R. A. Henry and E. Lieber, *J. Org. Chem.*, **18**, 779 (1953), and R. A. Henry, W. G. Finnegan and E. Lieber, *THIS JOURNAL*, **76**, 88 (1954), suggest an intermediate equilibrium mixture of activated tautomeric guanyl azides and tetrazoles. W. S. McEwan and M. W. Rigg, *THIS JOURNAL*, **73**, 4725 (1951), found that certain simple monocyclic tetrazoles are more stable by 10–12 kcal./mole than the isomeric non-cyclic azides.

(3) Certain guanyl azides ( $\text{RNHC}(\text{N}_3)=\text{NR}'$ ) are exceptional; see J. Thiele, *Ann.*, **270**, 1 (1892); A. Hantzsch and A. Vagt, *ibid.*, **314**, 339 (1901); W. S. McEwan and M. W. Rigg, ref. 2.

(4) J. H. Boyer and F. C. Canter, *Chem. Revs.*, **54**, 22, 23 (1954).

(5) For a discussion of the electronegativity of the tetrazole ring see E. Lieber, C. N. R. Rao, T. S. Chao and J. Ramchandran, *J. Org. Chem.*, **23**, 1916 (1958), and R. A. Henry, W. G. Finnegan and E. Lieber, *THIS JOURNAL*, **77**, 2264 (1955).

(6) V. Kereszty and E. Wolf, German Patent 611,692; *C. A.*, **29**, 5995 (1935).

(7) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 1st ed., John Wiley and Sons, Inc., New York, N. Y., 1954, p. 223.

(8) E. Lieber, D. Levering and L. Patterson, *Anal. Chem.*, **23**, 1594 (1951), report that tetrazoles give characteristic absorption between 1110 and 1000  $\text{cm}^{-1}$  where up to three bands may occur and in the 763 to 758  $\text{cm}^{-1}$  and 741 to 735  $\text{cm}^{-1}$  regions.

(9) R. J. Ferm, J. L. Riebsomer, E. L. Martin and G. H. Daub, *J. Org. Chem.*, **18**, 643 (1953), report absorption at 230  $\text{m}\mu$   $\epsilon_{\text{max}}$  2250 for 1-isopropyl-4,4-dimethyl-2-imidazoline and 231  $\text{m}\mu$   $\epsilon_{\text{max}}$  7480 for the acetate salt in acid solution.

(10) W. L. Garbrecht and R. M. Herbst, *J. Org. Chem.*, **18**, 1003 (1953); F. W. Schueler, S. C. Wang, R. M. Featherstone and E. G. Gross, *J. Pharm. and Exp. Therapeutics*, **97**, 266 (1949); B. Elpern and F. C. Nachod, *THIS JOURNAL*, **72**, 3379 (1950).

(11) W. Wilson and R. Woodger, *J. Chem. Soc.*, 2943 (1955).

ring-substituted derivatives, but without structure analysis.<sup>12</sup> This compound has now been re-examined using spectrophotometric and paper chromatographic data. Marked differences between solid state and solution absorption in the infrared are found. Azido absorption bands are absent for IV in both a potassium bromide disk and a Nujol mull. Tetrazole bands between 1110 and 1000  $\text{cm}^{-1}$  cannot be clearly differentiated from thiazole absorption<sup>13</sup> in this region; however, the band at 761  $\text{cm}^{-1}$  is also characteristic of the tetrazole ring.<sup>8</sup> In chloroform solution IV shows a strong azido band at 2141  $\text{cm}^{-1}$  with weaker bands at 1318 and 1290  $\text{cm}^{-1}$ .<sup>7</sup>

Presence of the azido group in IV in ethanol solution is indicated by absorption in the ultraviolet at 291  $\mu$ ,  $a$  47.04, and in chloroform solution by absorption at 292  $\mu$ ,  $a$  46.25. Preliminary work with a potassium bromide disk of IV shows the absence of the azido band near 290  $\mu$ .

The spectral data for IV requires the presence of the tetrazole IVa and the absence of the azide IVb in the solid state. Both species (IVa,b) are probably present in solution; however, the absorption data from chloroform solution provides strong evidence only for an azide (IVb). Presence of IVa is not conclusively established because of thiazole absorption interference in the infrared, and tetrazole transparency in the ultraviolet. Two species, assumed to be IVa  $\rightleftharpoons$  IVb, are detected in ethanol solution using paper chromatography (see Experimental). Presence of the azide IVb in solution is consistent with the reported<sup>12</sup> transformation of IV into a linear triazene by a Grignard reagent.

Apparently one, but not two, tetrazole rings may be fused to the same six-membered aromatic ring.<sup>4</sup> Certain chemical properties of 8-nitropyridotetrazole,<sup>14</sup> not shared with pyridotetrazole, have suggested the presence of isomeric 2-azido-3-nitropyridine at higher temperatures and in acid solutions. From its infrared absorption, isomeric 6-nitropyridotetrazole (Va) is now found similar to IV insofar as data from a potassium bromide disk require the absence of azide Vb whereas data from a chloroform solution require the presence of an azido group (bands at 2155 and 1302  $\text{cm}^{-1}$ ) and suggest the presence of a tetrazole ring (bands at 1094, 1040 and 1015 and 987  $\text{cm}^{-1}$ ). Paper chromatography again was useful in demonstrating the presence of two species, assumed to be Va  $\rightleftharpoons$  Vb, in solution.

Similar infrared spectra for 3-azidobenzisothiazole-1,1-dioxide (Vib) from either potassium bromide disks or from chloroform solution reveal strong azido bands at 2174-2169 and 1311-1302  $\text{cm}^{-1}$ .<sup>7</sup> With this indication of probable tetrazole VIa absence in solution, bands in the 1110 to 1000  $\text{cm}^{-1}$  region and at 748  $\text{cm}^{-1}$  may be ascribed to the benzthiazole nucleus. Displacement of the azido group in Vib with aniline, ethanol or acids has been reported.<sup>15</sup>

(12) M. Colonna, *Pubbli. ist. chim. ind. univ. Bologna*, 3 (1943); *C. A.*, 41, 754 (1947); V. Ya. Pochinok, S. D. Zaitseva and R. G. El' Gort, *Ukrain. Khim. Zhur.*, 17, 509 (1951); *C. A.*, 48, 11392 (1954).

(13) J. Metzger and C. Cherrier, *Compt. rend.*, 228, 239 (1949).

(14) J. H. Boyer, D. I. McCane, W. J. McCarville and A. T. Tweedie, *THIS JOURNAL*, 75, 5298 (1953); J. H. Boyer and W. Schoen, *ibid.*, 78, 423 (1956).

(15) E. Schrader, *J. prakt. Chem.*, 95, 312 (1917).

TABLE I  
INFRARED ABSORPTION ( $\text{CM}^{-1}$ ) KBr DISKS

Trimethylenetetrazole (Ia)	5,5-Dihydro-7-midazo[1,2]tetrazole (IIa)	1,5-Tetrazolobenzothiazole-1,3 (IVa)	6-nitropyridotetrazole (Va)	3-Azido-1,1-dioxobenzothiazole-1,2 (VIb)
3425m	3205m	1481s	3436m	3472m
2976m	1613m	1466s	3096m	3096m
1531s	1520m	1433m	1653m	2364m
1499s	1471m	1422m	1567m	2232s
1471m	1387m	1404m	1531m	2174s
1439m	1318m	1385s	1502m	1613m
1323m	1256m	1266m	1429m	1527s
1266m	1225m	1217s	1357s	1475m
1244m	1205m	1136m	1333s	1366s
1186m	1170m	1101m	1276m	1330s
1145m	1101m	1087m	1242m	1302s
1080s	1086m	1074m	1167m	1163s
996w	1018w	1060s	1133m	1126s
964m	950m	1018m	1094m	1064m
907m	875m	1012m	1048m	1029m
842w	810m	993m	993m	1015m
708w	756m	964m	935m	926s
675w	732m	945m	873m	833m
	677m	760s	823m	776s
		723m	800m	748s
		719m	757m	707m
			727m	675m
			706m	652s

INFRARED ABSORPTION ( $\text{CM}^{-1}$ ) NUJOL MULLS AND CHLOROFORM SOLUTIONS

Mull	Ia		IIa		IVa,b		Va,b Soln.	VIb Soln.
	Soln.	Mull	Mull	Soln.	Soln.	Soln.		
3344m	3460w	3205s	2941s	3012w	3115w	3030w		
2924s	3003m	2924s	2865s	2353w	2410w	2232w		
2865s	2469w	1613s	1466s	2315w	2283w	2169s		
1529m	1531w	1522m	1435m	2227m	2155s	1623m		
1497m	1502m	1468s	1425m	2183s	1653m	1567s		
1466s	1464m	1383s	1404m	2141s	1608s	1541m		
1383s	1443w	1318s	1383s	1504s	1585s	1473w		
1321m	1328m	1256m	1266m	1488s	1527m	1414w		
1264m	1263w	1225m	1256m	1475s	1464s	1361s		
1242m	1245w	1205m	1217s	1443s	1393m	1311s		
1186m	1179w	1170m	1134m	1397m	1351s	1277w		
1144m	1143w	1101m	1101m	1318m	1333m	1170s		
1080m	1082m	1086m	1087m	1290m	1302s	1131w		
994w	962w	1018m	1073m	1258s	1276s	1065w		
964m	905w	950m	1060m	1166w	1133w	1010w		
906m	840w	875m	1017m	1138w	1116w	917m		
844w		810m	1010m	1114m	1094w	863w		
735m		737m	993m	1086w	1040w			
673m		732m	964m	1062m	1015w			
		677m	944m	1020m	987w			
			759s	962w	945w			
			723m	939w	883w			
			718m	907m	869w			
			684m		840w			

In agreement with assignments previously reported, compounds I,<sup>6</sup> II,<sup>2</sup> VI<sup>12</sup> and V<sup>14</sup> are tetrazoles in the solid state. In solution it is now seen that I and II retain their identity as tetrazoles, but IV and V now appear as azides probably together with corresponding tetrazoles. Absence of the azido group in the solid state for IV and V possibly reflects a greater insolubility for the tetrazole tautomer. Finally, the assignment of VI as an azide<sup>15</sup> is now supported by spectrophotometric analysis which gives no indication of the presence of an isomeric tetrazole in either the solid state or in solution.

Tetrazole destabilization through fusion to a five- or six-membered ring appears to be negligible. Of much greater significance is the effect of electron withdrawal upon destabilizing a tetrazole ring and stabilizing an azido group. All known examples of heterocyclic azides for which the isomeric fused-ring

tetrazole is unknown<sup>4</sup> may be explained by these effects of electron withdrawal. From the present work it appears that the nitro group in the 6-position of pyridotetrazole and the thiazole group in tetrazolobenzthiazole-1,3 have comparable effect in destabilizing the tetrazole ring, whereas the thiazole dioxide group, e.g., VIb, is demonstrably more effective. These conclusions allow the prediction that electron donating substituents will stabilize the pyridotetrazole ring system relative to an isomeric azide. Investigations are now being carried out to test this hypothesis.

#### Experimental<sup>16</sup>

**Trimethylenetetrazole.**—A solution of 4.15 g. (0.04 mole) of thiopyrrolidone,<sup>17</sup> 11.36 g. (0.08 mole) of methyl iodide and 40 ml. of benzene was stored at room temperature for 4 hours. A pale yellow solid reprecipitated from an ethanol and ether mixture as a colorless solid, 9.79 g., which was dissolved in 20 ml. of water and neutralized with 15 ml. of 5 *N* sodium hydroxide. The aqueous solution was saturated with salt and extracted with ether. From the dried ether extracts, 1.39 g. of crude 2-methylmercaptopyrrolone was obtained as residue after evaporation. To this residue was added 14 ml. of a chloroform solution of hydrogen azide (from 0.02 mole of sodium azide<sup>18</sup>). The solution, after standing for 44 hours, was refluxed 2.5 hours. Trimethylenetetrazole, a solid residue after removal of solvent by distillation, recrystallized from xylene as small colorless needles, m.p. 109–110° (lit.<sup>6</sup> m.p. 110°), 0.89 g. (20%).

Literature methods were followed for the preparation of compounds II,<sup>9</sup> IV,<sup>12</sup> V<sup>14</sup> and VI.<sup>15</sup>

(16) We are indebted to Mr. R. T. O'Connor, Southern Regional Research Laboratory, for infrared and ultraviolet absorption data.

(17) J. Tafel and P. Lawaczek, *Ber.*, **40**, 2842 (1907).

(18) H. Wolff, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 327.

Infrared absorption data for compounds I, II, IV, V and VI are found in Table I.

**Chromatography.**<sup>19</sup>—Ascending chromatograms of analytically pure samples of IV and V were developed on strips of Whatman No. 2 filter paper using benzene or chloroform as eluents in the presence of ultraviolet light. Chromatograms near 0° were obtained by immersing the entire chamber in ice-water and those above room temperature were obtained by heating a paper containing an initial spot for 5 to 10 minutes at the desired temperature and then developing at room temperature. In all cases the solvent front was allowed to ascend 3 to 4 inches from the origin. Concentration of material at a spot was judged by intensity of fluorescence in ultraviolet light. It was assumed that the moving spot corresponds to a less polar species (presumably tetrazole) whereas the stationary spot corresponds to a polar species<sup>19</sup> (presumably azide).

An ethanolic solution of 6-nitropyridotetrazole (V) was chromatographed at 0°, 25° and near 25° immediately after heating at 70°. Eluent was benzene except at 0° where chloroform was used. At each temperature two spots were obtained, one at the origin and one just behind the solvent front. At 0° the residual spot at the origin was weak and the spot which traveled with the solvent was very strong. Both spots were of nearly equal intensity at 25°, and at higher temperatures the residual spot at the origin became very strong as the traveling spot nearly disappeared.

Similar results were obtained with an ethanolic solution of 1,5-tetrazolobenzthiazole-1,3 (IV). The intensity of the traveling spot varied from very strong at 0°, to strong at 25°, to disappearance at 100° while the intensity of the residual spot at the origin varied from very weak at 0°, to medium at 25°, to very strong at 100°.

Satisfactory eluents have not been found for similar chromatographic study of pyridotetrazole and trimethylenetetrazole (I).

(19) E. Lederer and M. Lederer, "Chromatography," Elsevier Publishing Co., New York, N. Y., 1953, p. 75.

NEW ORLEANS 18, LA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

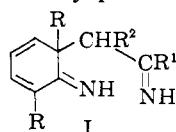
## The Fischer Indole Synthesis. VI. A Non-aromatic Intermediate and a New Class of Hydroindoles<sup>1</sup>

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2,6-Dimethylphenylhydrazine has been prepared from 2,6-xylydine by a much improved procedure and converted to acetophenone 2,6-dimethylphenylhydrazone (II). Treatment of the latter with zinc chloride in nitrobenzene at 120° led to a mixture from which five products were isolated: a crystalline solid C<sub>24</sub>H<sub>25</sub>NO<sub>2</sub> of unknown structure (trace); 2,6-xylydine (8%); acetophenone (trace); 2-phenyl-4,7-dimethylindole (III, 4%); and the chief product, 2-phenyl-3a,5-dimethyl-3a,4,7,7a-tetrahydro[3H]pseudoindolone-4 (IV, 33%). The structure of III was established by independent synthesis and that of IV substantially by degradation to 2,6-dimethyl-2-(β-phenylethyl)-cyclohexanone, which was also synthesized independently. In the course of the degradation of IV, evidence was obtained suggesting that IV has a *cis* ring junction. A mechanism previously proposed to account for the formation of 2-carbethoxy-4,7-dimethylindole from ethyl pyruvate 2,6-dimethylphenylhydrazone readily accounts also for the formation of IV, a new kind of indole derivative; in fact, a single non-aromatic intermediate of type I would be expected to give rise to both III and IV.

The behavior of 2,6-disubstituted arylhydrazones thus far investigated in the Fischer indole synthesis has been rationalized by postulating non-aromatic



(1) Submitted by D. Peter Carlson in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Carnegie Institute of Technology. The work reported here has been the subject of a Communication to the Editor (*THIS JOURNAL*, **79**, 3605 (1957)).

(2) Allied Chemical and Dye Co. Fellow, 1956–1957.

intermediates of structure I. When R is halogen, it may undergo allylic rearrangement with or without exchange of halogen with the promoting agent (a zinc or a stannous halide), and the product is then a 5,7-dihalogenoindole.<sup>3</sup> Also when R is halogen, it may be substituted by hydrogen, particularly when a stannous halide is the promoter; a 7-mono-halogenoindole is the product of this reaction.<sup>4</sup> In one case in which R was methyl, a small amount of

(3) (a) R. B. Carlin and E. E. Fisher, *THIS JOURNAL*, **70**, 3421 (1948); (b) R. B. Carlin and G. W. Larson, *ibid.*, **79**, 934 (1957).

(4) R. B. Carlin, J. G. Wallace and E. E. Fisher, *ibid.*, **74**, 990 (1952); R. B. Carlin and L. M. Amoros-Marin, *ibid.*, **80**, 730 (1958).