The solution was then filtered to remove a small amount of insoluble material and concentrated to half its original volume. Fifty ml. of petroleum ether (b.p. 30–60°) was then added and the solid which deposited was collected giving 1.63 g. of material, m.p. 184–186°. Additional petroleum ether (200 ml.) was added to the filtrate and an additional 0.80 g. of material was deposited, m.p. 183–186°. The total yield of tris(phenylcarbamoyl)phosphine (IIa) was 13%. The analytical sample was prepared by recrystallization from acetic acid giving white crystalline material of m.p. 212–213° (resolidifies to an orange solid).

Anal. Calcd. for $C_{21}H_{18}N_3O_3P$: C, 64.45; H, 4.64; N, 10.74; P, 7.92. Found: C, 64.68; H, 4.86; N, 10.73; P, 8.10.

ν_{max}^{Nujol}: 3200 (w), 1665, 1605 (s), 1505, 1470, 1455 (s), 1320, 1255, 1180, 1105 (w), 1080 (w), 910 (w), 895 (w), 880 (w), 750 (s), and 685 cm.$^{-1}$

The petroleum ether–benzene filtrate was evaporated and the residual liquid was examined by infrared spectroscopy. The spectrum was virtually identical with that of phenyl isocyanate.

Reaction with p-chlorophenyl isocyanate (Ib). A solution of 15.4 g. (0.1 mole) of Ib and 0.5 ml. of triethylamine in 100 ml. of dry benzene was reacted with phosphine for 6 hr. The crystalline solid which deposited was collected to give 9.1 g. (55%) of tris(*p*-chlorophenylcarbamoyl)phosphine (IIb) which turned yellow at 235° and melted with immediate resolidification at 245°. An analytical sample was prepared by recrystallization from acetic acid. There was no change in melting point behavior.

Anal. Calcd. for $C_{21}H_{15}Cl_3N_3O_3P$: C, 50.98; H, 3.06; Cl, 21.50; N, 8.49; P, 6.26. Found: C, 50.94; H, 3.22; Cl, 21.23; N, 8.36; P, 6.55.

ν_{max}^{Nujol}: 3200 (w), 1655, 1595 (s), 1535 (s), 1495 (s), 1405, 1305, 1285 (w), 1240, 1170 (w), 1115, 1090, 1015, 875 (w), 825 (s), and 745 cm.$^{-1}$

Reaction with p-nitrophenyl isocyanate (Ic). A solution of 16.4 g. (0.1 mole) of Ic and 1.0 ml. of triethylamine in 100 ml. of dry benzene was reacted with phosphine for 4 hr. The yellow solid was collected and dried giving 17.5 g. (100%) of tris-(*p*-nitrophenylcarbamoyl)phosphine (IIc), m.p. 267–270°. It was insoluble in all common organic solvents. An analytical sample was prepared by extracting the solid with boiling acetone. Two such treatments gave 15.9 g. (91%) of IIc with a single band in the infrared carbonyl region at 1675 cm.$^{-1}$ Five melting point determinations were carried out with this material in a heated bath. In three cases the samples decomposed suddenly in the range of 245–250°. In the other two cases the samples melted at 277–278° (dec.).

Anal. Calcd. for $C_{21}H_{15}N_6O_9P$: C, 47.92; H, 2.87; P, 5.89. Found: C, 47.96; H, 2.96; P, 5.82.

ν_{max}^{Nujol}: 3200 (w), 1675, 1620, 1605, 1555 (s), 1515 (s), 1420, 1345 (s), 1310, 1260, 1190 (w), 1170, 1125, 1115, 885 (w), 860 (s), 810, 755, and 680 (w) cm.$^{-1}$

Thermal decomposition of tris(p-nitrophenylcarbamoyl)-phosphine (IIc). Five g. of IIc was suspended in 25 ml. of dimethylformamide and the mixture was heated until it boiled gently. Smooth decomposition took place, gas was evolved, and the bulk of the solid dissolved. The solution was filtered hot and the amorphous red phosphorus which formed was collected. The filtrate was allowed to cool and 3.1 g. (72%) of 4,4′-dinitrocarbanilide was obtained as shiny pale yellow plates decomposing at 323°. This material gave bright yellow needles having a similar decomposition point when recrystallized from either pyridine or nitrobenzene. Plates were again obtained when the latter was recrystallized from dimethylformamide. The two crystalline forms showed major differences in the infrared (Nujol mull). An authentic specimen was prepared by reacting *p*-nitrophenyl isocyanate and *p*-nitroaniline in refluxing benzene containing a trace of triethylamine. It showed the same behavior in recrystallization as the thermal decomposition product of IIc, and samples from both sources showed decomposition points varying from 320–330°, depending on the rate of heating. The infrared spectra were identical provided the samples were recrystallized from the same solvent. The melting points recorded for this substance vary considerably. One of the more recent reports gives a value of 310.5° (from pyridine).[14] The analysis was carried out with a sample recrystallized from dimethylformamide.

Anal. Calcd. for $C_{13}H_{10}N_4O_5$: C, 51.66; H, 3.34; N, 18.54. Found: C, 51.48; H, 3.55; N, 18.83.

IIc (1.388 g.) was placed in a small bulb connected to a gas buret filled with mercury and equipped with a leveling bulb. The system was swept with helium and the bulb was heated to 275°. The gas which formed was evolved suddenly and a total of 57.8 ml. (STP) was collected. Mass spectrographic analysis indicated that the gas consisted of 61% carbon monoxide and 39% carbon dioxide.

STAMFORD, CONN.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MICHIGAN STATE UNIVERSITY]

Tetrazole Analogs of Pyridinecarboxylic Acids[1]

J. M. McMANUS[2,3] and ROBERT M. HERBST

Received March 30, 1959

The isomeric 5-tetrazolylpyridines were prepared as anlogs of the pyridine carboxylic acids by interaction of the cyanopyridines with hydrazoic acid. Interaction of 2,6-dicyanopyridine and hydrazoic acid gave the tetrazole analog of dipicolinic acid. Hydrogenation of the tetrazolylpyridines gave the corresponding 5-tetrazolylpiperidines, the analogs of the several isomeric piperidine carboxylic acids.

One of the first instances of vitamin antagonism observed was the interference by pyridine-3-sulfonic acid (I) and its amide (II) with the utilization of niacin (III) and niacinamide (IV) as evidenced by inhibition of staphylococcus growth.[4] Subsequently, 3-acetylpyridine[5] and thiazole-5-

(1) Based on the doctoral thesis submitted to Michigan State University in 1958 by James M. McManus.

(2) White Laboratories Fellow, 1956–1958.

(3) Present address: Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

(4) H. McIlwain, *Brit. J. Expt. Pathol.*, **21**, 136 (1940).

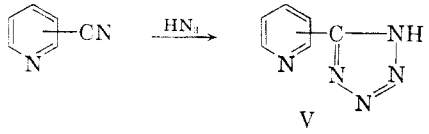
(5) E. Auhagen, *Z. physiol. Chem.*, **274**, 48 (1942).

carboxamide[6] were also reported to exhibit nicotinic acid antagonism.

I, R = SO_3H
II, R = SO_2NH_2
III, R = COOH
IV, R = $CONH_2$

In view of the acidic character of the 5-tetrazolyl group, it has been suggested that analogs of biologically active carboxylic acids in which the carboxyl group is replaced by the 5-tetrazolyl group might be antagonistic to the utilization of the corresponding carboxylic acids in biological systems.[7] For this reason the synthesis of the isomeric 5-tetrazolylpyridines (V) was undertaken.

The general procedure developed for the synthesis of 5-aryltetrazoles from nitriles[8] was adapted to the preparation of the tetrazolylpyridines. The isomeric cyanopyridines were heated in *n*-butyl alcohol solution with sodium azide and acetic acid. Although the method requires continuous heating at reflux temperature for 3–4 days, the yields were excellent in each case. After completion of the reaction, replacement of the butyl alcohol by dilution with water and distillation resulted in a clear solution of the sodium salt of the tetrazole. Careful acidification of the solution precipitated the tetrazoles in sufficiently pure form so that a single recrystallization from water provided analytically pure products. After completion of this work, a procedure which permitted a shorter reaction period for the synthesis of 5-substituted tetrazoles involving interaction of nitriles and lithium azide or ammonium azides in dimethylformamide was described.[9]

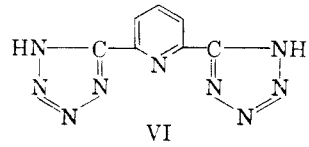


V

All the pyridyltetrazoles are solids that decompose at the melting point. They display typical amphoteric character and precipitate from aqueous acid or alkaline solution upon adjustment of the acidity to about *p*H 5. Their solubility in water, although appreciably lower than that of the pyridine carboxylic acids, decreases in the same order: *i. e.*, 2 isomer > 3 isomer > 4 isomer.

The pyridyltetrazoles are reduced easily in glacial acetic acid solution with hydrogen and platinum oxide catalyst to the respective piperidyltetrazoles. As reduction of the pyridine ring to the piperidyl structure is accompanied by an increase in the strength of the basic function, the physical characteristics of the piperidyltetrazoles differ markedly from those of the pyridyltetrazoles. In addition to amphoteric character the piperidyltetrazoles have higher melting points and greater water-solubility than the corresponding pyridyltetrazoles. Purification is best accomplished by precipitation from a saturated aqueous solution with acetone. The piperidyltetrazoles are easily acetylated with acetic anhydride in acetic acid solution to the expected acetyl derivatives; the latter also serve to characterize the products.

Recently it was reported that pyridine-2,6-dicarboxylic acid is involved in the formation and germination of the spores of a number of bacilli.[10,11] Thus it seemed of interest to prepare the tetrazole analog. 2,6-Di(5-tetrazolyl)pyridine (VI) was prepared easily and in excellent yield by interaction of 2,6-dicyanopyridine with sodium azide and acetic acid in *n*-butyl alcohol. As the tetrazole is only slightly soluble in hot water and rather insoluble in most common organic solvents, purification was best accomplished by precipitation from hot, aqueous alkaline solution by careful addition of hydrochloric acid.



VI

Biological evaluation of the tetrazolylpyridines is still incomplete. On the basis of preliminary tests, the nicotinic acid analog appears to inhibit growth of a number of types of bacteria.[12]

EXPERIMENTAL[13]

5-(2'-Pyridyl)tetrazole. 2-Cyanopyridine (26 g., 0.25 mole), 20 g. (0.33 mole) of glacial acetic acid and 22 g. (0.33 mole) of sodium azide were added to 100 ml. of *n*-butyl alcohol and heated under reflux for 4 days.[14] At this point 5 g. of sodium azide and 10 g. of glacial acetic acid were added and heating continued for 2 days. (In other experiments 3 and 4 day heating periods gave approximately the same yields of product.) The reaction mixture was diluted with about 300 ml. of water and distilled until the *n*-butyl alcohol was removed. The clear aqueous solution was carefully acidified with concentrated hydrochloric acid until precipitation of the tetrazole was complete. The product

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(11) J. F. Powell and R. E. Strange, *Biochem. J.*, **63**, 661 (1956).

(12) We are indebted to Dr. J. L. Nemes, Department of Bacteriology, Georgetown University School of Medicine, for preliminary evaluation of some of these compounds.

(13) Microanalyses were done on all compounds by Micro-Tech Laboratories, Skokie, Illinois. Melting points were done in open capillaries and are not corrected.

(14) The entire preparation except the final recrystallization must be done in a well ventilated hood because of the presence of hydrazoic acid.

was obtained as a colorless, crystalline solid from water, yield 33.4 g. (91%), m.p. 211–211.5° with decomposition.[15]

Anal. Calcd. for $C_6H_5N_5$: C, 49.0; H, 3.4; N, 47.6. Found: C, 49.2; H, 3.7; N, 47.8.

5-(3'-Pyridyl)tetrazole was prepared from 3-cyanopyridine. Using the same quantities of reagents as in the foregoing example, the product was obtained as a colorless, crystalline solid from water, yield 33.3 g. (91%), m.p. 234–235° with decomposition.[15]

Anal. Calcd. for $C_6H_5N_5$: C, 49.0; H, 3.4; N, 47.6. Found: C, 49.2; H, 3.4; N, 47.7.

5-(4'-Pyridyl)tetrazole was prepared from 4-cyanopyridine in the same way with the same quantities of reagents. It crystallized from water as a colorless solid, yield 34.3 g. (93%), m.p. 253–254° with decomposition.[15]

Anal. Calcd. for $C_6H_5N_5$: C, 49.0; H, 3.4; N, 47.6. Found: C, 49.2; H, 3.6; N, 47.3.

2,6-Di(5'-tetrazolyl)pyridine. A solution of 27.5 g. (0.21 mole) of 2,6-dicyanopyridine in 100 ml. of *n*-butyl alcohol was refluxed for 2 days with 38.2 g. (0.59 mole) of sodium azide and 38 ml. of glacial acetic acid.[14] At this point another 10 g. of sodium azide and 20 ml. of glacial acetic acid were added. Refluxing continued for 2 days. The crude product, 45.6 g. (99%), was obtained by diluting the reaction mixture with water, distilling and acidifying as in the foregoing examples. The product was purified by dissolving it in aqueous sodium hydroxide and reprecipitating from the hot, colorless solution with acid. The analytical sample was recrystallized from hot water in which the product was only sparingly soluble, m.p. 290° with decomposition.

Anal. Calcd. for $C_7H_5N_9$: C, 39.1; H, 2.3; N, 58.6. Found: C, 39.2; H, 2.6; N, 58.6.

5-(2'-Piperidyl)tetrazole. A suspension of 11 g. of 5-(2'-pyridyl)tetrazole in 150 ml. of glacial acetic acid was shaken with 250 mg. of platinum oxide and hydrogen at an initial pressure of 50 p.s.i. Hydrogenation was complete in 24 hr. After removal of the catalyst by filtration the solution was evaporated to a small volume and diluted with ether to precipitate the product. Purification was effected by dissolving the colorless solid in the minimum amount of warm water, treating with Norit and reprecipitating with acetone, yield 10.5 g. (92%), m.p. 287° with decomposition.

Anal. Calcd. for $C_6H_{11}N_5$: C, 47.1; H, 7.2; N, 45.7. Found: C, 47.0; H, 7.1; N, 46.0.

The *acetyl* derivative was prepared by refluxing for 2 hrs. in glacial acetic acid with an equimolar amount of acetic anhydride. After removal of the solvent under reduced pressure, the residue of acetyl derivative was obtained as a colorless, crystalline solid from water, m.p. 135.5–136.5°.

Anal. Calcd. for $C_8H_{13}N_5O$: C, 49.2; H, 6.7; N, 35.9. Found: C, 49.1; H, 6.6; N, 35.6.

For preparative purposes it was advantageous to form the acetyl derivative directly by hydrogenation of the pyridyltetrazole as just described; after removal of the catalyst, acetic anhydride was added to the glacial acetic acid solution and acetylation was completed as just described. The over-all yield from the pyridyltetrazole was 84%.

5-(3'-Piperidyl)tetrazole was obtained in almost quantitative yield as a colorless, crystalline solid by hydrogenation of the pyridyltetrazole in a completely analogous manner, m.p. 296–297° with decomposition. The analytical sample was recrystallized from the minimum amount of water; the remainder of the product was precipitated from water with acetone.

Anal. Calcd. for $C_6H_{11}N_5$: C, 47.1; H, 7.2; N, 45.7. Found: C, 47.1; H, 7.3; N, 45.7.

The *acetyl* derivative, prepared as described for the isomer, separated from isopropyl alcohol as a colorless, crystalline solid, m.p. 170–171°.

Anal. Calcd. for $C_8H_{13}N_5O$: C, 49.2; H, 6.7; N, 35.9. Found: C, 49.5; H, 6.7; N, 36.1.

5-(4'-Piperidyl)tetrazole was obtained in 86% yield by hydrogenation of the pyridyltetrazole in a completely analogous manner. The product crystallized from water as dense colorless prisms; it did not decompose below 370° but showed some shrinking and browning at 237°.

Anal. Calcd. for $C_6H_{11}N_5$: C, 47.1; H, 7.2; N, 45.7. Found: C, 47.0; H, 7.2; N, 46.0.

The *acetyl* derivative, obtained as described for the isomers, separated from isopropyl alcohol as a colorless, crystalline solid, m.p. 156.5–157.5°.

Anal. Calcd. for $C_8H_{13}N_5O$: C, 49.2; H, 6.7; N, 35.9. Found: C, 49.3; H, 6.8; N, 35.8.

East Lansing, Michigan

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[Contribution from the Department of Chemistry, Michigan State University]

Tetrazole Analogs of Plant Auxins[1]

J. M. McMANUS[2,3] AND ROBERT M. HERBST

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A group of chlorinated 5-phenoxymethyltetrazoles has been prepared as analogs of the corresponding substituted phenoxyacetic acids. Two methods of synthesis were used to corroborate the structure of the products. The tetrazole analog of the natural plant auxin, 3-indolylacetic acid, in which the carboxyl group is replaced by the acidic tetrazole moiety, has been prepared from the corresponding nitrile. An improved method for the synthesis of phenoxyacetonitriles is described.

The isolation and identification of 3-indolylacetic acid as a natural growth hormone in plants[4] initiated a search for other substances which could elicit this type of activity. Among those synthetic materials shown to stimulate growth was a group of chlorinated compounds derived from phenoxyacetic acid. Varying degrees of activity were demonstrated depending on the number and position of the chlorine atoms in the benzenoid portion of the structure; the most active are 2,4-dichloro-

(1) Based on a doctoral thesis submitted to Michigan State University in 1958 by James M. McManus.

(2) White Laboratories Fellow, 1956–1958.

(3) Present address: Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

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