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

# Synthesis of Iminotetrazoline Derivatives as Trichomonacidal and Fungicidal Agents[1, 2]

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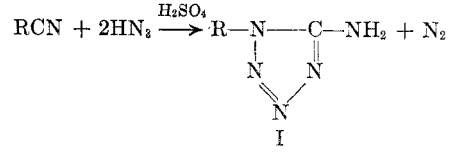
An extensive series of 1,4-disubstituted 5-iminotetrazolines was prepared by interaction of 1-alkyl-5-aminotetrazoles with benzyl, substituted benzyl, 2-phenylethyl and 3-phenylpropyl halides. The products were usually isolated as the easily crystallizable hydrochlorides. The structure of the compounds was supported by the formation of the same product in several instances regardless of the order of introduction of the alkyl and benzyl substituents. The structure was also substantiated by the removal of the benzyl group by hydrogenolysis from a product prepared by the alkylation of 1-benzyl-5-aminotetrazole and isolation of the 1-alkyl-5-aminotetrazole.

Several years ago it was observed that the salts of dialkylated 5-aminotetrazoles in which one of the alkyl groups was of moderate size were surface active agents. With the thought that these compounds might possess bacteriostatic or bactericidal activity the synthesis of a number of dialkylated aminotetrazoles was undertaken. The methylation and ethylation of 1-*n*-octyl-5-aminotetrazole gave products which exhibited a modest degree of bacteriostatic action on cultures of *Staphylococcus aureus* and *Eberthella typhosa*. The activity was markedly increased by alkylation of 1-*n*-octyl-5-aminotetrazole with benzyl chloride. For the resulting octyl benzyl aminotetrazole a phenol coefficient of about 100 was estimated. On the basis of these observations the synthesis of an extensive group of 1-alkyl-5-aminotetrazoles (I) and the products of their alkylation with benzyl and substituted benzyl halides was undertaken to determine the structural requirements for optimum bacteriostatic activity. Extensive microbiological screening[3] showed that these compounds possessed an even higher degree of cidal action against both protozoan and fungal cultures.[4]

Several methods for the synthesis of the requisite 1-alkyl-5-aminotetrazoles were used. Initially the method of von Braun and Keller[5] involving interaction of alkyl cyanides with excess hydrazoic acid in the presence of concentrated sulfuric acid was employed.

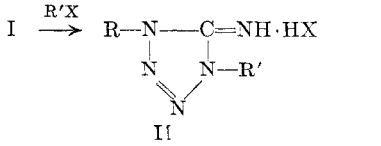


I

Subsequently, the more convenient method involving interaction of primary amines and cyanogen bromide to form monoalkylcyanamides and addition of hydrazoic acid to the latter[6] was employed. 1-Benzyl-5-aminotetrazole was prepared both from benzyl cyanide and benzylamine as well as by benzylation of 5-aminotetrazole.[7]

The 1-alkyl-5-aminotetrazoles prepared by these reactions are described in Table I.

The dialkylated products were prepared by heating without solvent to temperatures of 120–150°, the 1-alkyl-5-aminotetrazoles (I) with slightly more than an equimolar amount of the alkylating agent. Purification of the crude product was effected by several recrystallizations or by way of the free base. The latter procedure was often advantageous for the elimination of small quantities of unreacted starting materials. Most of the bases were liquids, but in several instances they could be isolated as low melting solids. The solubility of the 1-alkyl-4-aralkyl-5-iminotetrazoline hydrochlorides in both aromatic hydrocarbons and in aqueous alcohols is striking. The iminotetrazoline hydrochlorides (II) prepared in this way are described in Table II.



II

R = $CH_3(CH_2)_n$, n = 4 to 16

R′ = $CH_3$, $CH_3CH_2$, and

(1) Presented before the Division of Medicinal Chemistry at the Spring Meeting of the AMERICAN CHEMICAL SOCIETY, Dallas, Tex., April 1956.

(2) Based in part on a thesis presented by Charles F. Froberger in partial fulfillment of the requirements for the degree of Master of Science at Michigan State University.

(3) The alkyl benzyl iminotetrazolines were screened in the Parke, Davis Laboratories. The results have been published elsewhere.[4] The cooperation of Drs. T. F. Reutner, P. E. Thompson, and A. B. Hillegas in the extensive microbiological screening is gratefully acknowledged.

(4) E. F. Elslager, T. F. Reutner, and J. C. Peters, Abstracts of papers presented before the Division of Medicinal Chemistry at the Spring Meeting of the AMERICAN CHEMICAL SOCIETY, Dallas, Tex., April 1956. p. 7M.

(5) J. von Braun and W. Keller, *Ber.*, **65**, 1677 (1932).

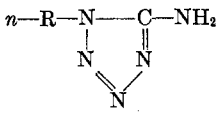
(6) W. L. Garbrecht and R. M. Herbst, *J. Org. Chem.*, **18**, 1014 (1953).

(7) R. M. Herbst and W. L. Garbrecht, *J. Org. Chem.*, **18**, 1283 (1953).

(8) R. M. Herbst, C. W. Roberts, and E. K. Harvill, *J. Org. Chem.*, **16**, 139 (1951).

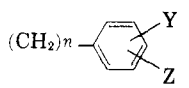
TABLE I

1-ALKYL-5-AMINOTETRAZOLES



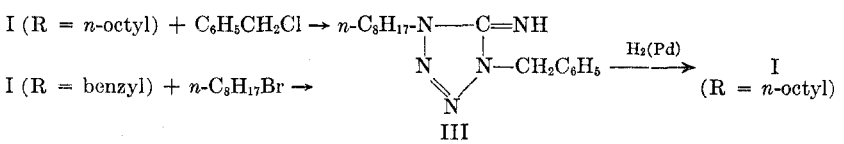
| *n*-R | Method | Yield[a] % | M.P.°C. | Formula | Analyses % N Calcd. | Found | Reference |
|---|---|---|---|---|---|---|---|
| $C_5H_{11}$ | B | 52 | 165–166 | $C_6H_{13}N_5$ | 45.1 | 45.6 | 6, 8 |
| $C_6H_{13}$ | B | 49 | 166–167 | $C_7H_{15}N_5$ | 41.4 | 41.7 | 5, 6 |
| $C_7H_{15}$ | B | 56 | 164–165 | $C_8H_{17}N_5$ | 38.2 | 38.5 | 6 |
| $C_8H_{17}$ | A | 48 | 161–162 | $C_9H_{19}N_5$ | 35.5 | 35.5 | 8 |
| | B | 64 | 161–162 | | | | 6 |
| $C_9H_{19}$ | A | 36 | 160–161 | $C_{10}H_{21}N_5$ | — | — | 8 |
| $C_{10}H_{21}$ | A | 45 | 161–162 | $C_{11}H_{23}N_5$ | 31.1 | 31.3 | |
| | B | 51 | 162–163 | | | | |
| $C_{11}H_{23}$ | A | 43 | 158–159 | $C_{12}H_{25}N_5$ | — | — | 8 |
| $C_{13}H_{27}$ | A | 38 | 157–158 | $C_{14}H_{29}N_5$ | 26.2 | 27.0 | |
| $C_{14}H_{29}$ | A | 31 | 156–157 | $C_{15}H_{31}N_5$ | 24.9 | 24.7 | |
| $C_{15}H_{31}$ | A | 35 | 155–156 | $C_{16}H_{33}N_5$ | 23.7 | 23.6 | |
| $C_{17}H_{35}$ | A | 40 | 154–155 | $C_{18}H_{37}N_5$ | 21.7 | 21.8 | |
| $C_6H_5CH_2$ | A | 29 | 187–188 | $C_8H_9N_5$ | 40.0 | 40.1 | 5 |
| | B | 72 | 187–188 | | — | — | 6 |
| | C | 19[b] | 189–190 | | — | — | 7 |
| $C_6H_5CH_2CH_2$ | B | 81 | 176 | $C_9H_{11}N_5$ | 37.0 | 37.2 | 11 |

[a] Based on alkyl cyanide (Method A); Alkylamine (Method B). [b] Based on 5-aminotetrazole, other benzylated products also formed.



n = 1 to 3
Y and/or Z = H, Cl, $CH_3$, $OCH_3$, $NO_2$, OH.

Although the alkylation of 1-alkyl-5-aminotetrazoles (I) has been shown to lead predominantly to 1,4-dialkyl-5-iminotetrazolines (II),[9–11] the validity of these conclusions in the present instances was demonstrated by the formation of 1-*n*-octyl-4-benzyl-5-iminotetrazoline (III) by either the octylation of 1-benzyl-5-aminotetrazole (I, R = benzyl) or by the benzylation of 1-*n*-octyl-5-aminotetrazole (I, R = *n*-octyl). Similarly the methylation or ethylation of I (R = *n*-octyl) gave products identical with those obtained on octylation of I (R = $CH_3$ or $C_2H_5$).



Hydrogenolytic removal of the benzyl group from III formed by octylation of 1-benzyl-5-aminotetrazole gave only 1-*n*-octyl-5-aminotetrazole, a result which requires that the substituents be in equivalent positions.

## EXPERIMENTAL[12]

*1-Alkyl-5-aminotetrazoles* were prepared from alkyl cyanides by interaction with excess hydrazoic acid in benzene solution in the presence of concentrated sulfuric acid,[5] Method A; by the successive addition of cyanogen bromide and hydrazoic acid to primary amines in aqueous alcoholic solution,[6] Method B; and in one case by the benzylation of 5-aminotetrazole,[7] Method C.

*Method A.* The preparation of 1-*n*-octyl-5-aminotetrazole by a modification of previously described techniques[8] serves as an example. A solution of 83 g. (0.6 mole) of *n*-octyl cyanide in 550 ml. of a 14% solution of hydrazoic acid[13] in benzene (75 g., 1.8 moles of hydrazoic acid) was treated with 175 ml. of concentrated sulfuric acid added dropwise below the surface of the liquids. The mixture was stirred vigorously throughout and the temperature was maintained at 33–38° with only intermittent cooling. After complete addition of the sulfuric acid the mixture was allowed to cool to room temperature while stirring was continued for a total of 23 hr. The layers were separated and the sulfuric acid layer was poured onto about 1.5 kg. of crushed ice, neutralized to litmus with 50% potassium hydroxide, and chilled in ice. The mixture of potassium sulfate and tetrazole was filtered by suction, washed with cold water and while still moist extracted first with 1 l. of boiling 99% isopropyl alcohol and then with 750 ml. of 90% isopropyl alcohol. The tetra-

(9) R. M. Herbst and D. F. Percival, *J. Org. Chem.*, **19**, 439 (1954).

(10) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Am. Chem. Soc.*, **76**, 2894 (1954).

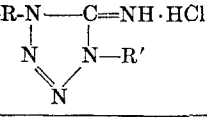
(11) D. F. Percival and R. M. Herbst, *J. Org. Chem.*, **22**, 925 (1957).

(12) All analyses were done by Micro-Tech Laboratories, Skokie, Ill.

(13) Reactions involving cyanogen bromide, hydrazoic acid, or sodium azide must be done in a well ventilated hood. Care must be exercised in disposing of filtrates and distillates that may contain hydrazoic acid to avoid exposure to its highly toxic vapors.

TABLE II

1-ALKYL-4-ARALKYL-5-IMINOTETRAZOLINE HYDROCHLORIDES



| | | | | | Analyses | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Calcd. | | Found | |
| *n*-R | R′ | Yield, % | M.P.°C. | Formula | Cl | N | Cl | N |
| $C_5H_{11}$ | *p*-$ClC_6H_4CH_2$ | 60 | 151–152 | $C_{13}H_{19}Cl_2N_5$ | 22.4 | 22.2 | 22.5 | 22.0 |
| $C_5H_{11}$ | $C_6H_5CH_2CH_2CH_2$ | 51 | 177–178 | $C_{15}H_{24}ClN_5$ | 11.4 | 22.6 | 11.2 | 22.9 |
| $C_6H_{13}$ | *p*-$ClC_6H_4CH_2$ | 82 | 166–167 | $C_{14}H_{21}Cl_2N_5$ | 21.5 | 21.2 | 21.3 | 21.1 |
| $C_6H_{13}$ | $C_6H_5CH_2CH_2$ | 43 | 229–230d. | $C_{15}H_{24}ClN_5$ | 11.4 | 22.6 | 11.6 | 22.4 |
| $C_6H_{13}$ | $C_6H_5CH_2CH_2CH_2$ | 55 | 171–172 | $C_{16}H_{26}ClN_5$ | 11.0 | 21.6 | 11.0 | 21.4 |
| $C_7H_{15}$ | *p*-$ClC_6H_4CH_2$ | 90 | 151–152 | $C_{15}H_{23}Cl_2N_5$ | 20.6 | 20.3 | 20.5 | 20.4 |
| $C_8H_{17}$ | $C_6H_5CH_2$ | 95 | 163–165 | $C_{16}H_{26}ClN_5$ | 11.0 | 21.6 | 11.0 | 21.4 |
| $C_8H_{17}$ | *o*-$CH_3C_6H_4CH_2$ | 54 | 161–162 | $C_{17}H_{28}ClN_5$ | 10.5 | 20.7 | 10.8 | 20.7 |
| $C_8H_{17}$ | *m*-$CH_3C_6H_4CH_2$ | 66 | 163–164 | $C_{17}H_{28}ClN_5$ | 10.5 | 20.7 | 10.7 | 20.5 |
| $C_8H_{17}$ | *p*-$CH_3C_6H_4CH_2$ | 21 | 159–160 | $C_{17}H_{28}ClN_5$ | 10.5 | 20.7 | 10.8 | 20.5 |
| $C_8H_{17}$ | *o*-$ClC_6H_4CH_2$ | 73 | 167–168 | $C_{16}H_{25}Cl_2N_5$ | 19.8 | 19.5 | 20.0 | 19.7 |
| $C_8H_{17}$ | *p*-$ClC_6H_4CH_2$ | 89 | 165–166 | $C_{16}H_{25}Cl_2N_5$ | 19.8 | 19.5 | 19.8 | 19.4 |
| $C_8H_{17}$ | *p*-$CH_3OC_6H_4CH_2$ | 42 | 155–156 | $C_{17}H_{28}ClN_5O$ | 10.0 | 19.8 | 9.9 | 19.8 |
| $C_8H_{17}$ | *p*-$NO_2C_6H_4CH_2$ | 70 | 168–169 | $C_{16}H_{25}ClN_6O_2$ | 9.6 | 22.8 | 9.5 | 22.8 |
| $C_8H_{17}$ | 2,4-$Cl_2C_6H_3CH_2$ | 68 | 167–168 | $C_{16}H_{24}Cl_3N_5$ | 27.1 | 17.8 | 27.0 | 17.9 |
| $C_8H_{17}$ | 3,4-$Cl_2C_6H_3CH_2$ | 74 | 159–160 | $C_{16}H_{24}Cl_3N_5$ | 27.1 | 17.8 | 26.9 | 17.7 |
| $C_8H_{17}$ | 2-HO-5-$NO_2C_6H_3CH_2$ | 47 | 184–186 | $C_{16}H_{25}ClN_6O_2$ | 9.2 | 21.8 | 9.1 | 21.9 |
| $C_8H_{17}$ | $C_6H_5CH_2CH_2$ | 64 | 207–208 | $C_{17}H_{28}ClN_5$ | 10.5 | 20.7 | 10.3 | 20.8 |
| $C_8H_{17}$ | $C_6H_5CH_2CH_2CH_2$ | 62 | 153–154 | $C_{18}H_{30}ClN_5$ | 10.1 | 19.9 | 9.9 | 19.7 |
| $C_9H_{19}$ | $C_6H_5CH_2$ | 86 | 161–162 | $C_{17}H_{28}ClN_5$ | 10.5 | 20.7 | 10.5 | 20.8 |
| $C_9H_{19}$ | *p*-$ClC_6H_4CH_2$ | 79 | 152–153 | $C_{17}H_{27}Cl_2N_5$ | 19.1 | 18.8 | 18.9 | 18.8 |
| $C_9H_{19}$ | 2,4-$Cl_2C_6H_3CH_2$ | 65 | 143–144 | $C_{17}H_{26}Cl_3N_5$ | 26.1 | 17.2 | 25.9 | 17.4 |
| $C_{10}H_{21}$ | $C_6H_5CH_2$ | 75 | 156–157 | $C_{18}H_{30}ClN_5$ | 10.1 | 19.9 | 10.2 | 20.0 |
| $C_{10}H_{21}$ | *p*-$ClC_6H_4CH_2$ | 83 | 152–154 | $C_{18}H_{29}Cl_2N_5$ | 18.4 | 18.1 | 18.3 | 18.1 |
| $C_{11}H_{23}$ | $C_6H_5CH_2$ | 90 | 154–155 | $C_{19}H_{32}ClN_5$ | 9.7 | 19.1 | 9.9 | 19.1 |
| $C_{11}H_{23}$ | *p*-$ClC_6H_4CH_2$ | 90 | 145–146 | $C_{19}H_{31}Cl_2N_5$ | 17.7 | 17.5 | 17.9 | 17.4 |
| $C_{13}H_{27}$ | $C_6H_5CH_2$ | 67 | 155–156 | $C_{21}H_{36}ClN_5$ | 9.0 | 17.8 | 9.1 | 17.9 |
| $C_{14}H_{29}$ | $C_6H_5CH_2$ | 83 | 153–154 | $C_{22}H_{38}ClN_5$ | 8.7 | 17.2 | 8.7 | 17.0 |
| $C_{14}H_{29}$ | 3,4-$Cl_2C_6H_3CH_2$ | 78 | 139–141 | $C_{22}H_{36}Cl_3N_5$ | 22.3 | 14.7 | 22.4 | 14.6 |
| $C_{15}H_{31}$ | $C_6H_5CH_2$ | 87 | 152–153 | $C_{23}H_{40}ClN_5$ | 8.4 | 16.6 | 8.6 | 16.4 |
| $C_{15}H_{31}$ | *m*-$CH_3C_6H_4CH_2$ | 60 | 141–142 | $C_{24}H_{42}ClN_5$ | 8.1 | 16.1 | 8.3 | 15.8 |
| $C_{17}H_{35}$ | $C_6H_5CH_2$ | 89 | 145–146 | $C_{25}H_{44}ClN_5$ | 7.9 | 15.6 | 7.7 | 15.4 |
| $C_{17}H_{35}$ | *p*-$CH_3C_6H_4CH_2$ | 50 | 133–135 | $C_{26}H_{46}ClN_5$ | 7.6 | 15.1 | 7.8 | 14.9 |
| $C_{17}H_{35}$ | *o*-$ClC_6H_4CH_2$ | 74 | 143–145 | $C_{25}H_{43}Cl_2N_5$ | 14.6 | 14.5 | 14.5 | 14.7 |

zole crystallized from the alcoholic solutions on cooling and was recovered by systematic concentration of the mother liquors and recrystallization from 90% isopropyl alcohol. Appreciable amounts of low melting material, probably amide, accumulated in the last fractions obtained from the original mother liquors. Yields, physical constants and analytical data for the tetrazoles prepared in this way are given in Table I.

*Method B.* The preparation of 1-*n*-octyl-5-aminotetrazole by a modification of the technique of Garbrecht and Herbst[6] serves as an example. *n*-Octylamine (45 g., 0.33 mole) was dissolved in 350 ml. of 95% ethanol. Keeping the temperature of the reaction below 10° in all subsequent steps, a solution of 36 g. (0.33 mole) of cyanogen bromide in 60 ml. of water and 60 ml. of 95% ethanol was added dropwise with stirring, followed immediately by 13 g. of sodium hydroxide in 40 ml. of water. The solution was stirred for an hour at ice bath temperature after which 44 g. (0.66 mole) of sodium azide dissolved in 125 ml. of water[13] was added rapidly, followed more slowly by 57 ml. of concentrated hydrochloric acid diluted with an equal volume of water. The reaction mixture was stirred for 2 hr. at ice bath temperature when it was transferred to a steam bath and boiled under reflux for 3 hr. On chilling the solution 1-*n*-octyl-5-aminotetrazole crystallized in almost pure form. Further smaller fractions were obtained by concentrating the reaction mixture. The product was recrystallized from 90% isopropyl alcohol. Physical constants, yields, and analytical data for the tetrazoles prepared in this way are given in Table I.

*Method C.* The benzylation of 5-aminotetrazole followed a previously described procedure.[7] 1-Benzyl-5-aminotetrazole is formed together with other benzylation products and is described in Table I.

*1,4-Dialkyl-5-iminotetrazolines. 1-n-Octyl-4-methyl-5-iminotetrazoline hydrochloride.* A mixture of 19.7 g. (0.1 mole) of 1-*n*-octyl-5-aminotetrazole and 12.6 g. (0.1 mole) of methyl sulfate was heated in an oil bath at 120–125° for 3 hr. The crude methosulfate was dissolved in 75 ml. of water, the solution made alkaline with 25 ml. of 40% sodium hydroxide, saturated with potassium carbonate, and the base extracted with benzene. After drying the benzene solution over potassium carbonate, the solvent was removed on a water bath under reduced pressure and the residue taken up in 50 ml. of 99% isopropyl alcohol. The hydrochloride was precipitated by addition of 15 ml. of concentrated hydrochloric acid and 50 ml. of ether. Recrystallization was effected from 75 ml. of 99% isopropyl alcohol by addition of an equal volume of ether; yield 16.1 g., (65%), m.p. 200–201°.

*Anal.* Calcd. for $C_{10}H_{22}ClN_5$: N, 28.2. Found: N, 28.2.

The free base is a liquid, b.p. 147–151° at 4 mm.

A phenylthiourea was formed by interaction of the base with phenyl isothiocyanate and crystallized from 95% ethanol, m.p. 83.5–84°.

*Anal.* Calcd. for $C_{17}H_{26}N_6S$: N, 24.3. Found: N, 24.4.

The 3,5-dinitrobenzoyl derivative obtained from the base on treatment with 3,5-dinitrobenzoyl chloride crystallized from aqueous ethanol, m.p. 70.5–71°.

*Anal.* Calcd. for $C_{17}H_{28}N_7O_5$: N, 24.2. Found: N, 24.1.

The same base, hydrochloride, and derivatives were isolated after interaction of 1-methyl-5-aminotetrazole and *n*-octyl bromide in ethanol solution at 180° for 48 hr. in a sealed tube.

*1-Ethyl-5-n-octyl-5-iminotetrazoline hydrochloride* was prepared both by interaction of 1-*n*-octyl-5-aminotetrazole and ethyl sulfate or 1-ethyl-5-aminotetrazole[10] and *n*-octyl chloride in a similar manner. The hydrochloride crystallized from 99% isopropyl alcohol, m.p. 165–166°.

*Anal.* Calcd. for $C_{11}H_{24}ClN_5$: N, 26.8. Found: N, 27.1.

The free base is a liquid, b.p. 160–164° at 8 mm.

The *p*-nitrobenzoyl derivative was crystallized from aqueous ethanol, m.p. 56–57°.

*Anal.* Calcd. for $C_{18}H_{26}N_6O_3$: N, 22.5. Found: N, 22.7.

The 3,5-dinitrobenzoyl derivative was crystallized from aqueous ethanol, m.p. 57–58°.

*Anal.* Calcd. for $C_{18}H_{25}N_7O_5$: N, 23.4. Found: N, 23.5.

*1-Alkyl-4-aralkyl-5-iminotetrazolines.* The 1,4-disubstituted 5-iminotetrazolines were prepared by interaction of 1-alkyl-5-aminotetrazoles and benzyl, substituted benzyl, 2-phenylethyl, and 3-phenylpropyl halides as illustrated by the following examples.

*1-n-Octyl-4-benzyl-5-iminotetrazoline hydrochloride.* A mixture of 15 g. of 1-*n*-octyl-5-aminotetrazole and 11.4 g. of benzyl chloride was heated in an oil bath at 120–125° for 8 hr. A homogeneous melt formed which resolidified after a mildly exothermic reaction. The solid product was dissolved in 100 ml. of hot 95% ethanol, the solution diluted with 300 ml. of warm water, decolorized with charcoal and chilled. The crude hydrochloride which crystallized was filtered by suction, washed with cold aqueous ethanol, air dried, and washed again with benzene to remove unreacted benzyl chloride. Recrystallization from a mixture of 170 ml. of water, 85 ml. of 95% ethanol and 2.5 ml. of concentrated hydrochloric acid gave pure hydrochloride as colorless needles. Physical constants, yield, and analytical data are given in Table II.

The hydrobromide was prepared in a similar manner from benzyl bromide and 1-*n*-octyl-5-aminotetrazole. It was crystallized from 50% aqueous ethanol; yield 81%, m.p. 165–166°.

*Anal.* Calcd. for $C_{16}H_{26}BrN_5$: Br, 21.7; N, 19.0. Found: Br, 21.8; N, 19.0.

*1-n-Octyl-4-p-chlorobenzyl-5-iminotetrazoline hydrochloride.* A mixture of 15 g. of 1-*n*-octyl-5-aminotetrazole and 15 g. of *p*-chlorobenzyl chloride was heated in an oil bath at 120–125° for 4 hr. during which a homogeneous melt formed and resolidified after a mildly exothermic reaction. The crude hydrochloride was taken up in the minimum amount of hot 95% ethanol, the solution diluted with 500 ml. of water and distilled to remove unreacted *p*-chlorobenzyl chloride. The residual aqueous solution was made strongly alkaline to litmus with 25% sodium hydroxide solution and the organic base was extracted with several portions of benzene. The benzene solutions were combined and dried over potassium carbonate, and the solvent was removed under reduced pressure on a water bath. The residual base was taken up in 75 ml. of 95% ethanol and converted into hydrochloride by addition of 15 ml. of concentrated hydrochloric acid. The mixture was heated to boiling, diluted with 75 ml. of hot water and allowed to crystallize. The hydrochloride was recrystallized from aqueous ethanol from which it separates as colorless needles. Physical constants, yield, and analytical data are given in Table II.

In another preparation the free base left on evaporation of the benzene solutions crystallized on chilling and could be recrystallized from *n*-hexane, m.p. 52–53°.

*Anal.* Calcd. for $C_{16}H_{24}ClN_5$: Cl, 11.0; N, 21.6. Found: Cl, 11.0; N, 21.8.

In a number of instances, particularly when the crude hydrochlorides were pigmented, it was advantageous to recrystallize the salts from toluene or benzene before the final recrystallization from aqueous ethanol. The hydrochlorides are quite soluble in the hot aromatic hydrocarbon solvents but almost insoluble in the cold. Pigments generally remain in the solvents. In addition to their solubility in hot aqueous alcohol and hot benzene or toluene, most of the hydrochlorides are also soluble in chloroform, ethyl acetate and hot ethylene chloride, but almost insouble in cold water and aliphatic hydrocarbons. Physical constants, yields, and analytical data for all the iminotetrazoline hydrochlorides prepared as just described are given in Table II.

*1-n-Octyl-4-benzyl-5-iminotetrazoline hydrochloride* was also prepared by heating a mixture of 8.7 g. of 1-benzyl-5-aminotetrazole and 10.5 g. of *n*-octyl bromide at 135° for 8 hr. The crude hydrobromide was converted into base and hydrochloride as described in the preceding preparations. The hydrochloride was identical with the material made by benzylation of 1-*n*-octyl-5-aminotetrazole.

The position of the octyl group was further established by hydrogenolysis of a solution of 1.6 g. of 1-*n*-octyl-4-benzyl-5-iminotetrazoline hydrochloride (prepared by octylation of 1-benzyl-5-aminotetrazole) in 75 ml. of 95% ethanol in presence of 0.05 g. of palladium oxide catalyst at 50 p.s.i. hydrogen at room temperature. Hydrogenolysis was complete in 1 hr. The catalyst was filtered off, washed with 95% ethanol, then water. The combined filtrates were evaporated to incipient crystallization, neutralized with potassium carbonate, and the solid product recrystallized twice from 50% ethanol; yield 0.9 g., m.p. 161–162°, no depression on admixture of 1-*n*-octyl-5-aminotetrazole.

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