Anal. Calcd. for $C_9H_9N_5O$: C, 53.2; H, 4.5; N, 34.5. Found: C, 53.2; H, 4.6; N, 34.5.

5-(4'-Aminophenyl)tetrazole (II). (a) In a similar manner 17.2 g. of 5-(4'-nitrophenyl)tetrazole and 35 g. of granular tin were treated with 75 ml. of concentrated hydrochloric acid. II was isolated as in the preceeding preparation, yield 12.7 g. (88%), m.p. 267° with decomposition, after crystallization from aqueous ethanol.

(b) A suspension of 7.3 g. of 5-(4'-nitrophenyl)tetrazole in 150 ml. of glacial acetic acid was shaken with 150 mg. of platinum oxide catalyst at an initial hydrogen pressure of 49 p.s.i. After the theoretical amount of hydrogen had been absorbed, the chilled suspension of catalyst and product was filtered. The product was extracted from the mixture with hot ethanol and the solvent removed from the extract under reduced pressure. The residue was recrystallized from aqueous ethanol using Norit, yield 5.0 g. (82%), m.p. 267° with decomposition. Finnegan, Henry, and Lofquist[10] report m.p. 268–270° with decomposition.

Anal. Calcd. for $C_7H_7N_5$: C, 52.2; H, 4.4; N, 43.5. Found: C, 51.9; H, 4.3; N, 43.3.

5-(4'-Acetamidophenyl)tetrazole obtained from II with acetic anhydride in glacial acetic acid was recrystallized from glacial acetic acid with some difficulty. It separated as a colorless crystal powder, m.p. 278° with decomposition.

Anal. Calcd. for $C_9H_9N_5O$: C, 53.2; H, 4.5; N, 34.5. Found: C, 53.1; H, 4.7; N, 34.3.

5-(2'-Hydroxy-4'-aminophenyl)tetrazole (III). A suspension of 22.9 g. of the dry sodium salt of 5-(2'-hydroxy-4'-nitrophenyl)tetrazole in 150 ml. of water was shaken with 250 mg. of platinum oxide catalyst at an initial hydrogen pressure of 50 p.s.i. When hydrogen absorption was complete, the catalyst was filtered off and the filtrate warmed with a little sodium hydrosulfite to destroy a faint orange coloration. After treatment with Norit concentrated hydrochloric acid was added slowly to the cooled filtrate until no further precipitation occurred. The colorless, crystalline product was filtered off and dried, yield 13 g. (74%), m.p. 261–262° with decomposition.[15]

Anal. Calcd. for $C_7H_7N_5O$: C, 47.5; H, 4.0; N, 39.6. Found: C, 47.3; H, 4.2; N, 39.7.

5-(2'-Hydroxy-4'-acetamidophenyl)tetrazole was prepared from III by treatment with acetic anhydride in refluxing glacial acetic acid. It crystallized from water, in which it is difficultly soluble, as colorless needles, m.p. 281–282° with decomposition.

Anal. Calcd. for $C_9H_9N_5O_2$: C, 49.3; H, 4.1; N, 32 0. Found: C, 49.2; H, 4.3; N, 32.1.

EAST LANSING, MICH.

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

Alkylation Studies with Aminotetrazoles[1]

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A group of 1,4-disubstituted 5-iminotetrazolines has been prepared by alkylation of 1-cyclohexyl-, 1-cyclohexylmethyl- and 1-β-cyclohexylethyl-5-aminotetrazole with benzyl chloride, substituted benzyl halides and β-phenylethyl and γ-phenylpropyl bromide. The products were characterized as hydrochlorides and as substituted thioureas formed by interaction with phenyl isothiocyanate. A brief summary of their activity in microbiological systems is included.

Recently it was shown that 1,4-dialkyl-5-iminotetrazolines with a benzyl or substituted benzyl group in one position and a moderately large alkyl group, *n*-octyl for instance, at the other position exert a marked inhibitory action on growth of bacteria, protozoa, and fungi.[4,5] The purpose of the present investigation was to prepare a variety of 1,4-dialkyl-5-iminotetrazolines in which cyclohexyl or cyclohexylalkyl groups replaced the *n*-alkyl group. The resulting compounds were submitted for screening of their activity in microbiological systems; a brief summary of these results is included.

The iminotetrazolines were prepared by heating a mixture of the appropriate 1-cyclohexyl- or 1-cyclohexylalkyl-5-aminotetrazole with a small excess of benzyl, substituted benzyl, β-phenylethyl or γ-phenylpropyl halide. The iminotetrazoline hydrohalide so formed was subjected to steam distillation to remove excess aralkyl halide. Liberation of the base and extraction of the base with ether or benzene served to separate the product from unused 5-aminotetrazole derivative. The bases were converted into hydrochlorides as which they were isolated and characterized (Table I). The hydrochlorides are only very slightly soluble in water, moderately soluble in the common alcohols, but show the unique characteristic of rather marked solubility in hot benzene, toluene, or chloroform. The bases can be liberated from the hydrochlorides by shaking a suspension of the latter in dilute aqueous alkali and extraction with ether or benzene. Continuous removal of the coating of insoluble base from the sparingly soluble hydrochloride is essential for the success of the process. Many of the bases are viscous liquids; a few are solids and can be crystallized from cyclohexane (Table II). The

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bases react readily with phenyl isothiocyanate to form substituted thioureas which served to further characterize all the iminotetrazolines (Table III).

Structure assignment of the products is based on analogy of the method of preparation and upon characteristics of their infrared spectra. It has been shown[6,7] that alkylation of 1-substituted 5-aminotetrazoles under the conditions here employed results primarily in the formation of 1,4-dialkyl-5-iminotetrazolines. In one instance structure assignment has been verified experimentally. 1-β-Cyclohexylethyl-4-benzyl-5-iminotetrazoline was prepared both by benzylation of 1-β-cyclohexylethyl-5-aminotetrazole and by alkylation of 1-benzyl-5-aminotetrazole with β-cyclohexylethyl bromide. Hydrogenolytic removal of the benzyl group[8] from the latter product resulted in the formation of 1-β-cyclohexylethyl-5-aminotetrazole. The formation of the same product regardless of the order of introduction of the substituents and the result of the hydrogenolysis can be explained only if the two substituents are symmetrically placed in the 1 and 4 positions.[6,7]

Percival[9] has shown that infrared spectra of 1,4-dialkyl-5-iminotetrazoline hydrochlorides are characterized by strong absorption at about 5.95 μ and a notable absence of absorption at 2.9–3.2 μ and 3.7–4.4 μ, regions usually associated with N—H vibrations and amine hydrochlorides. 1-Alkyl-5-alkylaminotetrazole hydrochlorides can be distinguished from the isomeric 1,4-dialkyl-5-iminotetrazoline hydrochlorides by virtue of a strong and broad absorption band at 4.0–4.4 μ in the spectra of the former.[9] The iminotetrazoline hydrochlorides described in the present work uniformly show strong bands at about 3.4 μ and 6.0 μ, but no absorption at 2.9–3.2 μ or 3.7–4.4 μ. Percival also noted that 1,4-iminotetrazoline bases have a strong absorption band at 6.03 μ which is replaced by a band at 6.28 μ in spectra of the 1-alkyl-5-alkylaminotetrazoles. The free iminotetrazolines described here show strong bands at about 3.4 μ and 6.0 μ, but no absorption in the 6.3 μ region.

In addition the iminotetrazoline hydrochlorides have two peaks, one usually in the range 9.1–9.3 μ, the other around 9.5–9.6 μ, while the corresponding bases exhibit three peaks in the range 9.0–9.6 μ. These peaks may correspond to the absorption at about 9.4 μ shown by tetrazole itself and a number of 5-substituted tetrazoles which has been associated with the ring modes.[10] The possibility that absorption peaks in the 9.1–9.2 μ range shown by a number of 1,5-disubstituted tetrazoles is also associated with the ring modes has been suggested recently.[11]

The 1-cyclohexyl-, 1-cyclohexylmethyl- and 1-β-cyclohexylethyl-5-aminotetrazoles required were prepared from the appropriate primary amines by interaction in aqueous ethanol successively with cyanogen bromide and hydrazoic acid by adaptation of a procedure previously described for the preparation of 1-alkyl-5-aminotetrazoles.[4] The hydrazoic acid was liberated *in situ* from sodium azide. Cyclohexylmethylamine and β-cyclohexylethylamine were made from cyclohexylacetic acid and β-cyclohexylpropionic acid in 77% and 81% yields, respectively, by the Schmidt reaction.[12]

Microbiological screening was done in the Parke, Davis Laboratories; their cooperation is gratefully acknowledged.[13] Significant bacteriostatic activity measured by *in vitro* action on *Streptococcus pyogenes* appears uniformly in the cyclohexylethyl series (Compounds 19–27) all of which inhibit growth at concentrations of 20 γ per ml. or less. In the cyclohexylmethyl series only the mono- and dichlorobenzyl and the phenylpropyl derivatives (Compounds 11–14 and 18) are effective at this concentration, while in the cyclohexyl series only the *p*-chlorobenzyl derivative (Compound 3) is active at comparable concentrations. *In vitro* activity against *M. tuberculosis* (H 37 Rv) at levels of 10 γ per ml. or less was noted with Compounds 4, 5, 11–15, 18, 19, 26, and 27. None of the compounds was active against the same agents *in vivo*. Antitrichomonal action as measured *in vitro* against *Trichomonas vaginalis* is shown by almost all of the compounds at concentrations of 25 γ per ml. or less but is most marked in the cyclohexylethyl series where the *p*-chlorobenzyl derivative (Compound 21) is effective at concentrations as low as 1.6 γ per ml. All compounds were inactive *in vivo* against *Trichomonas fetus* in mice at levels up to 40 mg. per kg. per day. *In vitro* amebicidal activity was also apparent with most compounds and again most pronounced in the cyclohexylethyl series where Compounds 20, 26, and 27 were effective at concentrations of 20 γ per ml. *In vivo* amebicidal action was not realized. Pharmacodynamic effects such as hypotensive, analeptic, depressant, or diuretic action were absent when representative compounds were tested. Neither antiviral nor anticancer activity was observed with a few representative compounds selected for testing.

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EXPERIMENTAL[14]

Cyclohexylmethylamine. A 5-l. flask fitted with a reflux condenser, alcohol thermometer, stirrer, and 500-ml. dropping funnel, and set over a cold water bath that could be elevated or lowered easily, was charged with 213 g. (1.5 moles) of cyclohexylacetic acid, 2500 ml. of benzene, and 715 ml. of concentrated sulfuric acid. From the dropping funnel 475 ml. of a benzene solution of hydrazoic acid[15] (17.0 g. hydrazoic acid per 100 ml.) was added with vigorous stirring at a rate of about 3 ml. per min. The exothermic reaction which took place was controlled by keeping the reaction mixture at 42–48° by adjustment of the degree of immersion in the water bath. If the temperature falls too low, the reaction slows markedly and may stop. Should this occur, addition of hydrazoic acid solution should be interrupted immediately until the temperature can be raised and interaction again induced. After complete addition of the hydrazoic acid solution the mixture was maintained at 42–48° for 1 hr. by gentle warming on a steam bath with continued stirring. After cooling the reaction mixture in an ice bath, the layers were separated. The sulfuric acid layer was poured slowly, with stirring, into a 4-l. beaker filled with crushed ice. The dense precipitate of amine salt that formed was filtered rapidly with suction, pressed as dry as possible on the filter, and transferred immediately to a large flask. The salt was resuspended in a liter of water, treated with 600 g. of potassium hydroxide as 50% solution, and the liberated amine separated by steam distillation. The amine was separated from the distillate by extraction with ether. After drying the ether solutions over potassium carbonate, fractionation at atmospheric pressure gave 131 g. (77%) of cyclohexylmethylamine, b.p. 162–163°, n_D^{25} 1.4632.[17]

β-Cyclohexylethylamine was prepared in essentially the same manner. From 203 g. of β-cyclohexylpropionic acid, 134 g. (81%) of β-cyclohexylethylamine, b.p. 184–185°, n_D^{25} 1.4637[18] was obtained.

1-Cyclohexyl-5-aminotetrazole was prepared from cyclohexylamine by treatment successively with cyanogen bromide and hydrazoic acid in aqueous ethanolic solution, overall yield 62%, m.p. 217–218°. The procedure has been described previously in detail for other 1-alkyl-5-aminotetrazoles[4] and was adapted without significant change. The product was identical with a sample[19] prepared from cyclohexyl cyanide by the technique of von Braun and Keller.[20]

1-Cyclohexylmethyl-5-aminotetrazole. From 113 g. (1 mole) of cyclohexylmethylamine, 106 g. (1 mole) of cyanogen bromide, and 81 g. (1.25 moles) of sodium azide, following the technique used in the foregoing example, 145 g. (80%) of 1-cyclohexylmethyl-5-aminotetrazole was obtained, m.p. 250–251°.

Anal. Calcd. for $C_8H_{15}N_5$: C, 53.0; H, 8.3; N, 38.6. Found: C, 52.9; H, 8.3; N, 38.8.

The *acetyl* derivative, prepared by heating with acetic anhydride, was recrystallized from 50% ethanol, m.p. 129–130°.

Anal. Calcd. for $C_{10}H_{17}N_5O$: C, 53.8; H, 7.7; N, 31.4. Found: C, 53.7; H, 7.6; N, 31.4.

1-β-Cyclohexylethyl-5-aminotetrazole. From 127 g. (1 mole) of β-cyclohexylethylamine, 106 g. (1 mole) of cyanogen bromide, and 78 g. (1.2 moles) of sodium azide, following the procedure of the foregoing examples, 89 g. (47%) of 1-β-cyclohexylethyl-5-aminotetrazole was obtained. The product was recrystallized from 99% isopropyl alcohol, m.p. 212.5–213.5°.

Anal. Calcd. for $C_9H_{17}N_5$: C, 55.4; H, 8.8; N, 35.9. Found: C, 55.4; H, 8.5; N, 35.8.

The *acetyl* derivative, prepared by warming with acetic anhydride, was recrystallized from cyclohexane, m.p. 95.5–96.5°.

Anal. Calcd. for $C_{11}H_{19}N_5O$: C, 55.7; H, 8.1; N, 29.5. Found: C, 55.6; H, 8.0; N, 29.7.

5-Iminotetrazolines were prepared by interaction of 1-cyclohexyl-, 1-cyclohexylmethyl-, and 1-β-cyclohexylethyl-5-aminotetrazole with benzyl, substituted benzyl, β-phenylethyl and γ-phenylpropyl halides as previously described for similar compounds.[4] The preparation of 1-cyclohexyl-4 *p*-chlorobenzyl-5-iminotetrazoline hydrochloride will serve as a typical example. A mixture of 8.4 g. (0.05 mole) of 1-cyclohexyl-5-aminotetrazole and 12.1 g. (0.075 mole) of *p*-chlorobenzyl chloride was heated in an oil bath at 140°. A homogeneous melt formed during the first 0.5 hr. and resolidified slowly during the ensuing 0.5 hr. Heating was continued for 2 hr. after the melt had solidified completely. The crude hydrochloride was taken up in 200 ml. of hot 50% ethanol, the solution diluted with water, and steam distilled to remove ethanol and excess *p*-benzyl chloride. The residual aqueous suspension was treated with 4 g. of sodum hydroxide and shaken vigorously for 0.5 hr. Extraction with 3 portions of ether removed the free base. The combined ether solutions were dried over potassium carbonate. Evaporation of the solvent left the iminotetrazoline as a pale yellow oil which was taken up in 50 ml. of ethanol and treated with concentrated hydrochloric acid to precipitate the hydrochloride. The hot suspension was diluted with about 50 ml. of ethanol and 100 ml. of water to bring the hydrochloride into solution, treated with Norit and chilled. Recrystallization of the hydrochloride from 50% isopropyl alcohol gave 11.6 g. (70%) of pure product. Melting points, yields, and analytical data for all the iminotetrazoline hydrochlorides are given in Table I.

In a number of instances the free bases could be obtained as solids from the pure hydrochlorides by suspending the latter in 2*N* sodium hydroxide solution, shaking vigorously, and extracting the base with ether. Evaporation of the solvent after drying the ether solution over sodium sulfate left a solid in some instances, but more frequently a pale yellow oil that in a few cases could be induced to solidify on thorough chilling. Either cyclohexane or petroleum ether was used to recrystallize the solid bases. Melting points and analytical data for the bases are given in Table II.

Thiourea derivatives. All of the iminotetrazolines were characterized by formation of thiourea derivatives. The base liberated from 1 g. of hydrochloride suspended in aqueous sodium hydroxide was extracted with ether. The residual oil remaining after evaporation of the ether was warmed on a steam bath, without further purification, with phenyl isothiocyanate. After washing the crude thiourea derivatives with petroleum ether and 50% isopropyl alcohol, they were recrystallized from 75–80% isopropyl alcohol. In a few instances thorough chilling was necessary to induce crystallization of the crude thioureas. Melting points and analytical data for all the thioureas are recorded in Table III.

1-β-Cyclohexylethyl-4-benzyl-5-iminotetrazoline hydrochloride was prepared both by interaction of 1-β-cyclohexylethyl-5-aminotetrazole and benzyl chloride and by alkylation of 1-benzyl-5-aminotetrazole with β-cyclohexylethyl bromide. In the latter case the base was liberated from the crude hydrobromide and converted into the hydrochloride as described in the foregoing general procedure. The products prepared in both ways were identical. The iminotetrazoline hydrochloride (3.2 g.) obtained by alkylation of 1-benzyl-5-aminotetrazole was dissolved in 50 ml. of ethanol and shaken with 1 g. of 5% palladium-on-charcoal at an initial

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

(15) Solutions of hydrazoic acid in benzene were prepared as previously described.[16] All work with hydrazoic acid must be done in a well ventilated hood.

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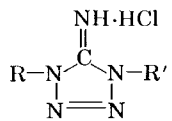
TABLE I

1,4-DISUBSTITUTED 5-IMINOTETRAZOLINE HYDROCHLORIDES

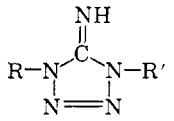


Compd. No.	R	R′	M.P., °C.[a]	Yield, %	Formula	Analyses							
						Calculated, %				Found, %			
						C	H	Cl	N	C	H	Cl	N
1	Cyclohexyl	Benzyl	230	72	$C_{14}H_{20}ClN_5$	57.2	6.8	12.1	23.8	56.9	6.8	12.2	23.6
2		*o*-Chlorobenzyl	222–223	54	$C_{14}H_{19}Cl_2N_5$	51.2	5.8	21.6	21.3	51.2	5.7	21.4	21.2
3		*p*-Chlorobenzyl	229–230	70	$C_{14}H_{19}Cl_2H_5$	51.2	5.8	21.6	21.3	51.2	6.0	21.6	21.4
4		2,4-Dichlorobenzyl	235–236	49	$C_{14}H_{18}Cl_3N_5$	46.4	5.0	29.3	19.3	46.4	5.1	29.4	19.3
5		3,4-Dichlorobenzyl	219–220	58	$C_{14}H_{18}Cl_3N_5$	46.4	5.0	29.3	19.3	46.3	5.0	29.3	19.3
6		*m*-Nitrobenzyl	217–218	64	$C_{14}H_{19}ClN_6O_2$	49.6	5.6	10.5	24.8	49.5	5.9	10.7	24.8
7		*p*-Nitrobenzyl	241–242	54	$C_{14}H_{19}ClN_6O_2$	49.6	5.6	10.5	24.8	49.8	5.7	10.3	24.8
8		β-Phenylethyl	220–221	53	$C_{15}H_{22}ClN_5$	58.5	7.2	11.5	22.8	58.6	7.2	11.5	23.0
9		γ-Phenylpropyl	222–223	54	$C_{16}H_{24}ClN_5$	59.5	7.5	11.0	21.7	59.6	7.6	11.3	21.3
10	Cyclohexylmethyl	Benzyl	217–218	61	$C_{15}H_{22}ClN_5$	58.5	7.2	11.5	22.8	58.7	7.2	11.5	22.6
11		*o*-Chlorobenzyl	234–235	58	$C_{15}H_{21}Cl_2N_5$	52.6	6.2	20.7	20.5	52.6	6.3	21.0	20.6
12		*p*-Chlorobenzyl	210–211	70	$C_{15}H_{21}Cl_2N_5$	52.6	6.2	20.7	20.5	52.8	6.2	20.7	20.6
13		2,4-Dichlorobenzyl	220	66	$C_{15}H_{20}Cl_3N_5$	47.8	5.4	28.2	18.6	48.1	5.6	28.3	18.9
14		3,4-Dichlorobenzyl	216	73	$C_{15}H_{20}Cl_3N_5$	47.8	5.4	28.2	18.6	48.1	5.4	28.2	18.7
15		*m*-Nitrobenzyl	218–219	65	$C_{15}H_{21}ClN_6O_2$	51.1	6.0	10.0	23.8	51.2	6.1	10.0	23.8
16		*p*-Nitrobenzyl	232	71	$C_{15}H_{21}ClN_6O_2$	51.1	6.0	10.0	23.8	51.2	5.9	10.1	23.9
17		β-Phenylethyl	234–235	67	$C_{16}H_{24}ClN_5$	59.7	7.5	11.0	21.8	59.5	7.3	11.2	22.0
18		γ-Phenylpropyl	240–241	69	$C_{17}H_{26}ClN_5$	60.8	7.8	10.6	20.8	60.6	7.9	10.7	21.1
19	Cyclohexylethyl	Benzyl	209–210	81	$C_{16}H_{24}ClN_5$	59.7	7.5	11.0	21.8	59.8	7.5	11.0	21.8
20		*o*-Chlorobenzyl	224–225	75	$C_{16}H_{23}Cl_2N_5$	53.9	6.5	19.9	19.7	54.0	6.4	19.7	19.7
21		*p*-Chlorobenzyl	208–209	81	$C_{16}H_{23}Cl_2N_5$	53.9	6.5	19.9	19.7	54.1	6.5	19.8	19.8
22		2,4-Dichlorobenzyl	210–211	74	$C_{16}H_{22}Cl_3N_5$	49.2	5.7	27.2	17.9	49.3	5.8	27.0	18.0
23		3,4-Dichlorobenzyl	208–209	71	$C_{16}H_{22}Cl_3N_5$	49.2	5.7	27.2	17.9	49.0	5.5	27.2	17.9
24		*m*-Nitrobenzyl	205–206	73	$C_{16}H_{23}ClN_6O_2$	52.4	6.3	9.7	22.9	52.5	6.4	9.8	22.9
25		*p*-Nitrobenzyl	210–211	58	$C_{16}H_{23}ClN_6O_2$	52.4	6.3	9.7	22.9	52.7	6.5	9.4	23.1
26		β-Phenylethyl	250–251	52	$C_{17}H_{26}ClN_5$	60.8	7.8	10.6	20.9	60.8	7.8	10.7	20.9
27		γ-Phenylpropyl	214–215	55	$C_{18}H_{28}ClN_5$	61.8	8.1	10.1	20.0	62.0	8.1	10.2	20.3

[a] All compounds melt with decomposition.

TABLE II

1,4-DISUBSTITUTED 5-IMINOTETRAZOLINES

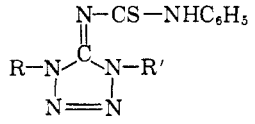


Compd.[a] No.	M.P., °C.	Formula	Analyses							
			Calculated, %				Found, %			
			C	H	Cl	N	C	H	Cl	N
10	93–94	$C_{15}H_{21}N_5$	66.4	7.8		25.8	66.4	7.8		25.7
12	82–83	$C_{15}H_{20}ClN_5$	58.9	6.6		22.9	58.3	6.7		23.1
13	103–104	$C_{15}H_{19}Cl_2N_5$	53.0	5.6	20.8	20.6	52.9	5.9	21.0	20.7
14	75–76	$C_{15}H_{19}Cl_2N_5$	53.0	5.6	20.8	20.6	53.0	5.7	20.7	20.7
15	90–91	$C_{15}H_{20}N_6O_2$	56.9	6.4		26.6	57.0	6.6		26.7
19	120–121	$C_{16}H_{23}N_5$	67.3	8.1		24.5				
20	58–59	$C_{16}H_{22}ClN_5$	60.1	6.9	11.1	21.9	60.2	7.1	11.3	21.7
21	53–54	$C_{16}H_{22}ClN_5$	60.1	6.9	11.1	21.9	59.9	6.8	11.3	21.7
22	70–71	$C_{16}H_{21}Cl_2N_5$	54.2	6.0	20.0	19.8	54.2	5.9	20.1	19.9
23	94–95	$C_{16}H_{21}Cl_2N_5$	54.2	6.0	20.0	19.8	54.3	6.1	20.0	19.8
24	84–85	$C_{16}H_{22}N_6O_2$	58.2	6.7		25.4	58.4	6.7		25.3
25	108–109	$C_{16}H_{22}N_6O_2$	58.2	6.7		25.4	58.1	6.9		25.6
26	50–51	$C_{17}H_{25}N_5$	68.2	8.4		23.4	68.2	8.2		23.2

[a] Numbers correspond with compounds described in Table I.

TABLE III

PHENYLTHIOUREAS DERIVED FROM 1,4-DISUBSTITUTED 5-IMINOTETRAZOLINES



Compd.[a] No.	M.P., °C.	Formula	Analyses					
			Calculated, %			Found, %		
			Cl	N	S	Cl	N	S
1	147–148	$C_{21}H_{24}N_6S$		21.4	8.2		21.2	8.0
2	135–136	$C_{21}H_{23}ClN_6S$	8.3	19.7	7.5	8.0	19.7	7.6
3	154–155	$C_{21}H_{23}ClN_6S$	8.3	19.7	7.5	8.1	19.5	7.4
4	121–122	$C_{21}H_{22}Cl_2N_6S$	15.4	18.2	7.0	15.2	18.5	7.0
5	188–189	$C_{21}H_{22}Cl_2N_6S$	15.4	18.2	7.0	15.4	18.5	6.9
6	174–175	$C_{21}H_{23}N_7O_2S$		22.4	7.3		22.7	7.2
7	161–162	$C_{21}H_{23}N_7O_2S$		22.4	7.3		22.7	7.3
8	106–107	$C_{22}H_{26}N_6S$		20.7	7.9		20.7	7.7
9	99–100	$C_{23}H_{28}N_6S$		20.0	7.6		20.0	7.8
10	174–175	$C_{22}H_{26}N_6S$		20.7	7.9		21.0	7.9
11	131–132	$C_{22}H_{25}ClN_6S$	8.0	19.1	7.3	8.0	19.3	7.0
12	156–157	$C_{22}H_{25}ClN_6S$	8.0	19.1	7.3	7.8	19.0	7.2
13	129–130	$C_{22}H_{24}Cl_2N_6S$	14.9	17.7	6.7	14.8	17.8	6.5
14	179–180	$C_{22}H_{24}Cl_2N_6S$	14.9	17.7	6.7	15.0	17.8	6.5
15	160–161	$C_{22}H_{25}N_7O_2S$		21.7	7.1		21.6	7.0
16	158–159	$C_{22}H_{25}N_7O_2S$		21.7	7.1		21.8	7.0
17	88–89	$C_{23}H_{28}N_6S$		20.0	7.6		20.2	7.5
18	117–118	$C_{24}H_{30}N_6S$		19.3	7.4		19.5	7.3
19	139–140	$C_{23}H_{28}N_6S$		20.0	7.6		20.0	7.3
20	118–119	$C_{23}H_{27}ClN_6S$	7.8	18.5	7.1	7.5	18.7	7.0
21	128–129	$C_{23}H_{27}ClN_6S$	7.8	18.5	7.1	7.7	18.6	7.1
22	115–116	$C_{23}H_{26}Cl_2N_6S$	14.5	17.2	6.6	14.3	17.3	6.6
23	144–145	$C_{23}H_{26}Cl_2N_6S$	14.5	17.2	6.6	14.3	17.3	6.6
24	129–130	$C_{23}H_{27}N_7O_2S$		21.1	6.9		21.2	7.0
25	134–135	$C_{23}H_{27}N_7O_2S$		21.1	6.9		21.0	6.9
26	86–87	$C_{24}H_{30}N_6S$		19.3	7.4		19.5	7.2
27	113–114	$C_{25}H_{32}N_6S$		18.7	7.2		18.7	7.1

[a] Numbers correspond to compounds described in Table I.

pressure of 50 p.s.i. Hydrogenolysis was complete in 0.5 hr. The catalyst was removed by filtration and washed with hot ethanol. The combined filtrate and washings were treated with 0.5 g. of sodium carbonate. Concentration of the solution gave 1.4 g. (71%) of 1-β-cyclohexylethyl-5-aminotetrazole, m.p. and mixture m.p. 212.5–213.5°.

Infrared spectra of the iminotetrazoline hydrochlorides and the corresponding bases were determined using a Perkin-Elmer double beam recording spectrophotometer, Model 21, and have been recorded.[21,22] All spectra were determined with oil mulls of the compounds at concentrations of the solid great enough to give strong absorption in the 6-μ region.

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The Manganese Dioxide Oxidation of Allylic Alcohols

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It has been found that the rate and specificity of the manganese dioxide oxidation of allylic alcohols to allylic aldehydes is dependent on the quantity of oxidizing agent, the temperature, the solvent, and the method of preparation of the oxidizing agent. Allyl, benzyl, propyl, and isopropyl alcohols and *N*,*N*-dimethylaniline were oxidized with varying yields under different conditions and with a wide variety of manganese dioxides.

Manganese dioxide has been considered to be a specific reagent for the oxidation of allylic alcohols to allylic aldehydes and ketones. It has been used for the oxidation of vitamin A_1 and other polyene alcohols[2]; for unsaturated steroidal alcohols[3]; for α-santonins[4]; for alcohols in which an aromatic ring replaced the vinyl group[5]; for the determination of the stereochemistry of 10-hydroxycodeine derivatives[6]; for acetylenic alcohols[7]; and for ferrocene alcohols.[8]

The nonspecificity of manganese dioxide as an oxidizing agent for allylic alcohols has recently been reported. It was found to: oxidize primary and secondary amines to imine dimers in low yields,[9] 2 - hydroxytetrahydropyran to δ - valerolactone,[9] aniline to azobenzene,[10] *N*-methyl amines to *N*-formyl amines,[10] *N*-alkyl amines to the amine and the corresponding aldehyde from the alkyl group[10]; dehydrogenate an *N*-alkyl amine followed by oxidative cleavage of the enamine[10]; cleave tetrasubstituted ethylenediamines[10]; oxidize aliphatic primary and secondary alcohols to the corresponding aldehydes or ketones,[11] aldehydes to the acids,[11] and 1,2-glycols in steroids to give ketones and products resulting from bond cleavage[12]; and convert an allylic methylene group into an alcoholic or ketonic grouping.[13]

Several different types of manganese dioxide have been used for the above mentioned oxidations. The first was that of Ball, Goodwin, and Morton;[2b] followed by Attenburrow's "active" manganese dioxide;[2a] one by Rosenkranz, Sondheimer, and Mancera;[14] and two by Harfenist, Bavley, and Lazier,[5a] who reported one of their dioxides to be specific for benzyl type alcohols but unaffective on allyl alcohol.

The purpose of this research was to investigate the oxidation of allylic alcohols with the manganese dioxides mentioned above, others which had been reported in the literature, two commercial dioxides,

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