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Tetrazole Derivatives. III. Tetrazole Acid Derivatives

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A series of fifty-five derivatives of tetrazole acids including simple and substituted amides, hydrazides, and basic esters and amides has been prepared. Routine pharmacological screening of these compounds has shown that some of them possess signs of physiologic action.

Recently Jacobson and Amstutz[1,2] have reported two methods for the synthesis of tetrazolylacetic acids. The first method involved transmetalation of 1,5-disubstituted tetrazoles containing a hydrogen atom on the *alpha*-carbon atom of the substituent in the 5-position followed by carbonation and hydrolysis to produce 1-substituted-5-tetrazolylacetic acids. The second method adapted a well known synthesis of 1,5-disubstituted tetrazoles[3,4] to starting materials already containing an ester group. Both 1-substituted-5-tetrazolylacetic acids and the isomeric 5-substituted-1-tetrazolylacetic acids were prepared by this procedure, the latter isomers not being available through the first method.

The first two papers in this series[5,6] describe a number of new tetrazole derivatives that have been prepared and screened for potentially useful physiologic action such as that possessed by many simple 1,5-disubstituted tetrazoles. The inclusion of the carboxyl group as a new functional component of tetrazole compounds has now made possible the preparation of a series of tetrazole acid derivatives including simple and substituted amides, basic esters and amides, and hydrazides for screening as possible therapeutic agents. During the course of this investigation a series of fifty-five of these derivatives has been prepared from sixteen tetrazole acids or the corresponding simple esters. They are listed in Table I together with the pertinent physical data.

The tetrazolylacetic acids were found to be resistant to thionyl chloride although phosphorus pentachloride generally produced the acid chloride. With the 1-substituted-5-tetrazolylacetic acids gentle warming with phosphorus pentachloride in benzene solution was usually sufficient to promote reaction, excessive heating frequently causing decarboxylation of the acid and the production of tarry by-products. However, no acid chloride could be isolated from 1-*n*-butyl-5-tetrazolylacetic acid, no appreciable reaction taking place at room temperature and decarboxylation of the acid occurring upon heating the reaction mixture. The 5-substituted-1-tetrazolylacetic acids, which are less prone to decarboxylate in hot solution,[2] generally required several hours of refluxing with phosphorus pentachloride in benzene in order to produce good yields of the acid chlorides. The acid chlorides were either viscous oils or solids, generally unstable on standing in the air, although several of the solid acid chlorides could be purified by recrystallization from dry solvents. As recrystallization of some of the solid acid chlorides resulted in considerable loss and a questionable increase in purity, the acid derivatives were usually prepared by interaction of the crude acid chloride with the appropriate reagent immediately after its isolation.

Pentamethylenetetrazole-6-carboxamide (51) was prepared from both the methyl and ethyl ester, the methyl ester giving a much better yield. It is interesting to note that in the first preparation of this amide two different crystalline modifications were obtained from the two esters (see Table I.) The lower-melting form was converted into the higher-melting one by seeding during recrystallization. Thereafter, several attempts to repeat the preparation of the lower-melting modification failed, only the higher-melting form being isolated.

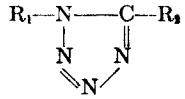
Pharmacology. All of the compounds in Table I with the exception of two (23 and 25) were subjected to routine pharmacological screening. Of the fifty-three compounds screened forty-one were devoid of any significant physiologic action other than toxic manifestations at the higher dose levels when administered to rats intraperitoneally in graded doses of 100–800 mg./kg. The remaining twelve compounds (2,3,18,19,22,24,27,30,32,35,37 and 55) produced signs of central nervous system depression below the lethal dose. The most active depressants were No. 2 which produced depression at 100 mg./-kg. and drowsiness at 400 mg./kg. and No. 37 which produced depression at 200 mg./kg. and unconsciousness at 600 mg./kg.

None of the compounds produced more than transient pressor or depressor effects on the blood pressure of nembutalized dogs when administered intravenously in aqueous or propylene glycol solutions at 5 or 10 mg./kg. Neither did they influence the

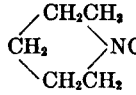
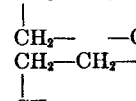
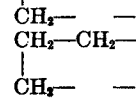
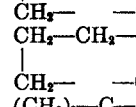
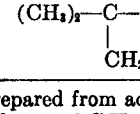
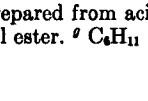
(1) Jacobson and Amstutz, *J. Org. Chem.*, **18**, 1183 (1953).
(2) Jacobson and Amstutz, *J. Org. Chem.*, **21**, 311 (1956).
(3) von Braun and Rudolph, *Ber.*, **74**, 264 (1941).
(4) Harvill, Herbst, Schreiner, and Roberts, *J. Org. Chem.*, **15**, 662 (1950).
(5) Cosgrove and LaForge, *J. Org. Chem.*, **21**, 197 (1956).
(6) D'Adamo and LaForge, *J. Org. Chem.*, **21**, 340 (1956).

TABLE I

TETRAZOLE ACID DERIVATIVES



No.	R_1[g]	R_2[g]	Yield, %	M.p., °C.	Recryst. Solvent	Analyses Calc'd C	Calc'd H	Calc'd N	Found C	Found H	Found N
1	CH_3	$CH(C_6H_5)CONH_2$	52[a]	179.5–181	Propanol-2	55.3	5.1	32.3	55.1	5.2	32.1
2	CH_3	$CH(C_6H_5)CONHC_6H_{11}$	24[a]	152–153.5	Methanol	64.2	7.1	23.4	64.2	7.2	23.2
3	CH_3	$CH(C_6H_5)CONHNH_2$	64[b]	126–127.5	Propanol-2-heptane	51.7	5.2	36.2	51.8	5.4	36.2
4	n-C_4H_9	CH_2CONH_2	77[b]	93.5–95	Chloroform	45.9	7.2	38.2	46.0	7.3	38.1
5	n-C_4H_9	$CH_2CONHC_2H_5$	52[b]	61.5–63	Benzene-heptane	51.2	8.1	33.2	51.2	8.2	33.1
6	C_6H_{11}	$CH(CH_3)CONH_2$	49[a]	154–155.5	Water	53.8	7.6	31.4	53.8	7.7	31.5
7	C_6H_{11}	$CH(CH_3)CO_2C_2H_4N(C_2H_5)_2 \cdot HCl$	10[a]	132.5–134.5	Methanol-ether	53.4	8.4	19.5	53.4	8.5	19.4
8	C_6H_{11}	$C(CH_3)_2CONH_2$	73[a]	241–243	Methanol	55.7	8.1	29.5	55.7	8.0	29.7
9	C_6H_{11}	$C(CH_3)_2CONHCH_2C_6H_5$	75[a]	171–173	Methanol	66.0	7.7	21.4	65.9	7.6	21.5
10	C_6H_{11}	$C(CH_3)_2CON(C_2H_5)_2$	53[a]	68.5–70	Petr. ether	61.4	9.3	23.9	61.4	9.2	23.8
11	C_6H_{11}		88[a]	141.5–143	Heptane	58.6	8.2	22.8	58.7	8.3	22.7
12	C_6H_{11}	$C(CH_3)_2CONHCH(OH)CCl_3$	47	239.5–241	Ethanol	40.6	5.3	18.2	40.6	5.2	18.4
		$\cdot HCl$	69[a]	185–187	Methanol-ether	54.8	8.9	22.5	54.7	9.3	22.4
13	C_6H_{11}	$C(CH_3)_2CONHC_2H_4N(C_2H_5)_2$									
		$\cdot CH_3I$	75[c]	191.5–193	Propanol-2	45.2	7.4	17.6	45.2	7.3	17.3
		$\cdot HCl$	40[a]	188–189	Propanol-2-benzene	52.1	8.2	20.3	52.0	8.1	20.2
14	C_6H_{11}	$C(CH_3)_2CO_2C_2H_4N(CH_3)_2$									
		$\cdot CH_3I$	77[c]	203–204	Propanol-2	42.6	6.7	15.5	42.4	6.8	15.3
15	C_6H_{11}	$C(CH_3)_2CO_2C_2H_4N(C_2H_5)_2 \cdot HCl$	45[a]	169–170.5	Propanol-2	54.6	8.6	18.7	54.5	8.7	18.7
16[d]	C_6H_5	CH_2CONH_2	90[b]	176–177	Water	—	—	—	—	—	—
17	C_6H_5	$CH_2CONHCH_3$	19[b]	126.5–128	Benzene	55.3	5.1	32.3	55.2	5.2	32.1
18	C_6H_5	$CH_2CONHCH_2C_6H_5$	19[a]	158–160	Benzene	65.5	5.2	23.9	65.7	5.3	24.2
19	C_6H_5	$CH_2CONHNH_2$	82[b]	168.5–170	Propanol-2	49.5	4.6	38.5	49.5	4.6	38.6
20	C_6H_5	$CH_2NHCONHC_6H_5$	21	159.5–161	Propylene dichloride	61.2	4.8	28.6	61.0	4.8	28.8
21[e]	C_6H_5		27[b]	229 (d.)	From sodium salt	—	—	—	—	—	—
22	α-$C_{10}H_7$	CH_2CONH_2	54[a]	159.5–161	Water	61.7	4.4	27.7	61.7	4.4	27.6
23	α-$C_{10}H_7$	$CH_2CONHC_6H_{11}$	43[a]	164–166	Propanol-2	68.0	6.3	20.9	68.2	6.3	20.8
24	C_6H_{11}	$CH_2CH_2CONH_2$	45[a]	161.5–162	Methanol	53.8	7.7	31.4	53.7	7.7	31.2
25	$H_2NNHCOCH_2$	CH_3	92[b]	137.5–138.5	Ethanol	30.8	5.2	53.8	30.5	5.0	53.7
26	$C_6H_5CH_2NHCOCH_2$	CH_3	50[a]	153.5–154	50% Propanol-2	57.1	5.7	30.3	57.2	5.9	30.2
27	H_2NCOCH_2	C_6H_{11}	52[a]	205.5–207	Water	51.7	7.2	33.5	51.6	7.2	33.6
28	$C_6H_{11}NHCOCH_2$	C_6H_{11}	64[a]	131–132	50% Propanol-2	61.8	8.7	24.0	62.1	8.7	24.1
29	$C_6H_5CH_2NHCOCH_2$	C_6H_{11}	69[a]	124.0–124.5	50% Propanol-2	64.2	7.1	23.4	64.1	7.3	23.3

30	H_2NCOCH_2	$CH_2C_6H_5$	70[a]	158.5–159.5	Water	55.3	5.1	32.2	55.4	5.4	32.2
31	$H_2NCONHCOCH_2$	$CH_2C_6H_5$	69[a]	215–220 (d.)	50% Acetic acid	50.8	4.7	32.3	50.8	4.8	32.2
32	$C_6H_{11}NHCOCH_2$	$CH_2C_6H_5$	77[a]	164–165	Propanol-2	64.2	7.1	23.4	64.5	7.2	23.3
33	$C_6H_5CH_2NHCOCH_2$	$CH_2C_6H_5$	74[a]	159–160	Propanol-2	66.4	5.6	22.8	66.4	5.5	22.8
34[d]	H_2NCOCH_2	C_6H_5	50[b]	166.5–167.5	Water	—	—	—	—	—	—
			74[a]								
35	$H_2NNHCOCH_2$	C_6H_5	29[b]	149.5–150.5	Propanol-2	49.5	4.6	38.5	49.6	4.6	38.5
36	$HCl\cdot(C_2H_5)_2NC_2H_4O_2CCH_2$	C_6H_5	43[a]	135–137	Propanol-2	53.0	6.5	20.6	53.2	6.6	20.6
37	$H_2NCOC(CH_3)_2$	C_6H_5	74[a]	148.5–149.5	Water	57.1	5.7	30.3	57.2	5.8	30.2
38	$CH_3NHCOC(CH_3)_2$	C_6H_5	72[a]	206–208	Methanol	58.8	6.2	28.6	58.9	6.2	28.6
39	$C_6H_{11}NHCOC(CH_3)_2$	C_6H_5	71[a]	212–213.5	Methanol-propanol-2	65.2	7.4	22.4	65.4	7.5	22.2
40	$C_6H_5CH_2NHCOC(CH_3)_2$	C_6H_5	63[a]	149–150.5	Propanol-2	67.3	6.0	21.8	67.5	6.1	21.7
41	$(C_2H_5)_2NCOC(CH_3)_2$	C_6H_5	47[a]	107–109	Propanol-2-water	62.7	7.4	24.4	62.8	7.4	24.4
42		C_6H_5	70[a]	117.5–119	Propanol-2	64.2	7.1	23.4	63.9	6.8	23.0
43	$[SO_4\cdot(C_2H_5)_2NC_2H_4NHCOC(CH_3)_2$	C_6H_5	30[a]	149.5–151	Methanol-propanol-2	47.6	6.6	19.6	47.7	6.6	19.6
44	$HCl\cdot(C_2H_5)_2NC_2H_4O_2CC(CH_3)_2$	C_6H_5	52[a]	144–145.5	Propanol-2	55.5	7.1	19.0	55.4	7.1	19.0
45	$[HCl\cdot(CH_3)_2NCH_2]_2CHO_2CC(CH_3)_2$	C_6H_5	24[a]	206.5–208	Methanol-propanol-2	49.9	7.0	19.4	50.0	6.7	19.2
46	$(p)H_2NCOC_6H_4$	CH_3	57[a]	198–199.5	Ethanol	53.2	4.5	34.5	53.2	4.4	34.4
47	$(p)(C_2H_5)_2NC_2H_4NHCOC_6H_4\cdot HCl$	CH_3	45[a]	163–164.5	Methanol-ether	53.2	6.8	24.8	52.9	6.5	24.8
48	$(p)(C_2H_5)_2NC_2H_4O_2CC_6H_4\cdot HCl$	CH_3	44[a]	169.5–170.5	Methanol-ether	53.0	6.5	20.6	53.0	6.5	20.8
49	$(p)(CH_3)_2NCH_2CH(CH_3)O_2CC_6H_4\cdot HCl$	CH_3	51[a]	194–195	Methanol-ether	51.6	6.2	21.5	51.6	6.2	21.4
50	$(p)(C_2H_5)_2NC_3H_7O_2CC_6H_4\cdot HCl$	CH_3	21[a]	160–161	Methanol-ether	54.3	6.8	19.8	54.3	6.9	19.8
			30[b]	137.5–139							
51			64[f]	178–179.5	Methanol	46.4	6.1	38.7	46.4	6.1	38.7
52			82[f]	158–159	Propanol-2	42.9	6.2	42.8	42.7	6.1	42.8
53			89	83.5–84.5	Ether	48.0	6.7	31.1	48.2	6.7	31.2
54			58	254–255 (d.)	Ethanol	38.0	6.4	36.9	38.1	6.4	37.0
55			38[f]	207–209	Methanol	50.4	7.6	35.3	50.2	7.6	35.2

[a] Prepared from acid through intermediate acid chloride. Yield based on acid. [b] Yield from ethyl ester. [c] Yield from hydrochloride salt. [d] Reference 2. [e] Reference 7. [f] From the methyl ester. [g] C_6H_{11} = cyclohexyl; $C_{10}H_7$ = naphthyl.

typical responses to test doses of epinephrine, acetylcholine, or histamine under the same experimental conditions.

All water-soluble derivatives were tested in the isolated rabbit heart and the isolated guinea pig gut, no desirable action being observed in the former case at dilutions of 1:2000 and no antispasmodic activity being detected in the latter case at dilutions at 1:25,000.

Four of the hydrazides were tested for *in vitro* antituberculosis activity against the human H37Rv strain of tubercule bacilli in liquid media of three types (Tween-Albumin, Proskauer and Beck, and P & B with 10% horse serum). None of the compounds produced more than a partial inhibition in concentrations of 0.1 mg./ml. in any of these media. In most instances, no inhibition whatsoever was seen in this concentration.

It is interesting to note that the three derivatives of pentamethylenetetrazole (Metrazol®) (52, 53, 54) resulting from this work are remarkably inactive, showing neither pronounced stimulant nor depressant properties. In general, there appears to be no obvious relationship between the chemical structures of the compounds in this series and the physiologic properties that they possess.

Acknowledgment. The authors are indebted to Dr. Erwin G. Gross and Dr. Hugh H. Keasling of the State University of Iowa for carrying out the pharmacological screening of these compounds. The tests for *in vitro* antituberculosis activity were done by the Trudeau Laboratories, Trudeau, New York.

EXPERIMENTAL

Tetrazole acids and esters. The tetrazole acids and esters from which the derivatives were prepared were synthesized by the procedures of Jacobson and Amstutz[1,2,7] (except where otherwise noted). Preparation of the following compounds by these methods has not been previously reported.

α-(1-Cyclohexyl-5-tetrazolyl)propionic acid was prepared in 59% yield by metalation and carbonation[1] of 1-cyclohexyl-5-ethyltetrazole. Recrystallization from water gave pure product of m.p. 137.5–138.5° (dec.).

Anal. Calc'd for $C_{10}H_{16}N_4O_2$: C, 53.6; H, 7.2; N, 25.0. Found: C, 53.6; H, 7.2; N, 25.2.

1-p-Carboxyphenyl-5-methyltetrazole. Application of the tetrazole ring closure synthesis[2] to ethyl *p*-acetamidobenzoate gave *1-p-carbethoxyphenyl-5-methyltetrazole* in 60% yield after recrystallization from propanol-2; m.p. 89–91°.

Anal. Calc'd for $C_{11}H_{12}N_4O_2$: C, 56.9; H, 5.2; N, 24.1. Found: C, 56.8; H, 5.2; N, 24.0.

Hydrolysis of the ester in hydrochloric acid-acetic acid solution gave an 85% yield of the acid after recrystallization from methanol, m.p. 255–257° (dec.).

Anal. Calc'd for $C_9H_8N_4O_2$: C, 52.9; H, 4.0; N, 27.4. Found: C, 53.0; H, 4.0; N, 27.4.

β-(1-Cyclohexyl-5-tetrazolyl)propionic acid was prepared in 29% yield by condensation of 1-cyclohexyl-5-chloromethyltetrazole with diethyl sodiomalonate followed by alkaline saponification. The product was obtained as a colorless solid after recrystallization from dilute propanol-2; m.p. 176–178°.

Anal. Calc'd for $C_{10}H_{16}N_4O_2$: C, 53.6; H, 7.2; N, 25.0. Found: C, 53.7; H, 7.3; N, 24.9.

Ethyl α-(1-methyl-5-tetrazolyl)phenylacetate was obtained in 76% yield by Fischer esterification of α-(1-methyl-5-tetrazolyl)phenylacetic acid,[1] b.p. 178–180°/1.5 mm. n_D^{25} 1.5330.

Anal. Calc'd for $C_{12}H_{14}N_4O_2$: C, 58.5; H, 5.7; N, 22.8. Found: C, 58.6; H, 5.8; N, 23.3.

Ethyl 1-n-butyl-5-tetrazolylacetate. Jacobson and Amstutz[2] report isolation of this ester in the tetrazole ring closure synthesis but give no physical constants as the crude product decomposed on attempted distillation. The corresponding acid was prepared in 74% yield by the metalation and carbonation procedure and underwent Fischer esterification in 77% yield to give the pure ester of b.p. 136–137°/0.1 mm. n_D^{25} 1.4643.

Anal. Calc'd for $C_9H_{16}N_4O_2$: C, 50.9; H, 7.6; N, 26.4. Found: C, 51.1; H, 7.7; N, 26.5.

Methyl pentamethylenetetrazole-6-carboxylate was prepared by Fischer esterification of the corresponding acid.[1] Yield, 73%; b.p. 174–177°/1.0 mm.; m.p. 56–59° (from ether-petr. ether).

Anal. Calc'd for $C_8H_{12}N_4O_2$: C, 49.0; H, 6.2; N, 28.6. Found: C, 49.1; H, 6.2; N, 28.7.

The corresponding *ethyl ester* was prepared in 70% yield, b.p. 169–172°/0.8 mm. n_D^{25} 1.4931.

Anal. Calc'd for $C_{10}H_{14}N_4O_2$: C, 51.4; H, 6.7; N, 26.7. Found: C, 51.3; H, 7.0; N, 26.7.

Methyl 7,9,9-trimethylpentamethylenetetrazole-7-carboxylate was prepared by the method of Roberts, Herbst, and Harvill.[8]

Tetrazole acid derivatives. As most of the tetrazole acid derivatives were prepared by the same procedures either from the acid through the intermediate acid chloride or from the ester, only a few illustrative examples of typical reactions are given below.

N-Benzyl-5-cyclohexyl-1-tetrazolylacetamide (29) (from the acid). A mixture of 5-cyclohexyl-1-tetrazolylacetic acid (15.8 g., 0.075 mole) and phosphorus pentachloride (15.6 g., 0.075 mole) in 150 ml. of dry benzene was stirred and refluxed for two hours until hydrogen chloride evolution had ceased. The resulting colorless solution was concentrated to dryness under reduced pressure at a bath temperature of 60–70°. Then 50 ml. of dry benzene was added to the residue and the system was again concentrated to dryness to insure complete removal of the phosphorous oxychloride. The crude solid acid chloride was dissolved in 200 ml. of warm dry benzene and the filtered solution was added during 30 minutes to a stirred solution of benzylamine (16.1 g., 0.15 mole) in 100 ml. of dry benzene cooled in an ice-bath. The resulting mixture was warmed to 60–70° for one hour, chilled, and the colorless solid was filtered off and dried. After the crude solid was washed with 200 ml. of cold water to remove the benzylamine hydrochloride, it was twice recrystallized from 50% propanol-2 giving fine colorless needles of the amide. Yield, 15.5 g. (69%), m.p. 124–124.5°.

β-Dimethylaminoethyl α-(1-cyclohexyl-5-tetrazolyl)isobutyrate hydrochloride, (14) (from the acid). Phosphorus pentachloride (69.8 g., 0.334 mole) was added portionwise during one hour to a stirred suspension of α-(1-cyclohexyl-5-tetrazolyl)isobutyric acid monohydrate (39.0 g., 0.152 mole) in 390 ml. of dry benzene at 25–30°. The resulting clear solution was warmed to 45° for 30 minutes and then it was concentrated to dryness under reduced pressure. The colorless solid residue was kept under 5 mm. pressure in a water-bath at 50° for one hour to insure complete removal of the

(7) Jacobson, Kerr, and Amstutz, *J. Org. Chem.*, **19**, 1909 (1954).

(8) Roberts, Herbst, and Harvill, *J. Org. Chem.*, **15**, 671 (1950).

solvent and phosphorus oxychloride. Recrystallization of the crude acid chloride from 220 ml. of heptane gave 37.5 g. (96%) of colorless product of m.p. 109–111°.

A solution of the acid chloride (19.0 g., 0.074 mole) in 150 ml. of dry benzene was added during one hour to a cooled (5–10°) stirred solution of β-dimethylaminoethanol (6.6 g., 0.074 mole) in 200 ml. of dry benzene. While the resulting solution was stirred for three hours without further cooling a colorless solid separated and the mixture was allowed to stand overnight. The crude product was filtered from the reaction mixture, washed with dry benzene, dried and twice recrystallized from 1:1 propanol-2—benzene mixture to give 10.3 g. (40%) of the basic ester hydrochloride, m.p. 188–189°. An additional quantity (8–9 g.) of less pure product was recovered by concentration of the recrystallization filtrates.

Unsubstituted amides from acid chlorides were prepared by addition of a benzene solution of the acid chloride to ice-cold concentrated ammonium hydroxide solution. The crude solid amide was filtered off and recrystallized from the appropriate solvent.

Amides from esters were prepared by allowing a mixture of the ester and concentrated ammonium hydroxide or an aqueous amine solution to stand for one to three days. The amide was isolated either by filtration or concentration of the reaction mixture followed by recrystallization from the appropriate solvent.

The *hydrazides* were prepared by refluxing the esters with hydrazine hydrate in alcoholic solution for two to five hours. The hydrazides usually separated readily upon cooling of the reaction mixture and after filtration were recrystallized from the appropriate solvent.

Miscellaneous derivatives: N-(α-hydroxy-β,β,β-trichloroethyl)-α-(1-cyclohexyl-5-tetrazolyl)isobutyramide (12) was prepared from α-(1-cyclohexyl-5-tetrazolyl)isobutyramide and freshly distilled anhydrous chloral by adaption of the method of Willard and Hamilton.[9]

5-Benzyl-1-tetrazolylacetic acid ureide (31) was prepared by heating a paste of the acid chloride (16.4 g., 0.075 mole) and urea (9.6 g., 0.16 mole) in 30 ml. of toluene to 90° for one hour. The cooled mixture was filtered, washed with water, and twice recrystallized from 50% acetic acid solution to give 13.6 g. (69%) of the ureide of m.p. 215–220° (slow dec.).

Ethyl N-(6-pentamethylenetetrazolyl)urethan (53). Pentamethylenetetrazole-6-carboxhydrazide (52) (24.5 g., 0.115 mole) was dissolved in a solution of 19.5 ml. of 6 *N* hydrochloric acid in 200 ml. of water and the resulting solution was covered with 100 ml. of ether. With vigorous stirring and cooling below 10° in an ice-bath, a solution of sodium nitrite (8.5 g., 0.123 mole) in 40 ml. of water was slowly dropped into the reaction mixture. After the addition was complete the mixture was stirred below 10° for 30 minutes and then the colorless azide was filtered off and dried *in vacuo* over phosphorus pentoxide. Yield, 19.2 g. (80%), m.p. 78° (dec.). A small additional quantity of the azide could be isolated by evaporation of the ether layer in which it was only slightly soluble. The dry azide decomposed explosively when heated rapidly.

A stirred suspension of the azide (19.2 g., 0.093 mole) in 300 ml. of absolute ethanol was heated at 60–70° until the smooth evolution of nitrogen ceased and then the milky suspension was refluxed for one hour. A small quantity of insoluble matter was filtered from the cooled solution which then was concentrated to dryness under reduced pressure. The solid residue was extracted with 1000 ml. of boiling ether which upon cooling and final chilling in a salt-ice bath deposited colorless needles of the urethan. Concentration of the ether filtrate to 200 ml. followed by chilling gave an additional quantity of product. Yield, 18.6 g. (89%), m.p. 83.5–84.5°.

6-Aminopentamethylenetetrazole hydrochloride (54). A solution of ethyl N-(6-pentamethylenetetrazolyl)urethan (53) (19.5 g., 0.087 mole) in 100 ml. of concentrated hydrochloric acid was refluxed for 8.5 hours. Concentration of the solution to dryness under reduced pressure left a colorless viscous oil as a residue which slowly solidified upon standing. Recrystallization of the solid from 99% ethanol gave colorless needles of the amine hydrochloride. Yield, 9.5 g. (58%), m.p. 254–255° (dec.).

Anal. Calc'd for $C_6H_{12}ClN_5$: Neut. equiv., 190. Found: Neut. equiv., 192.

N-Phenyl-N'-(1-phenyl-5-tetrazolylmethyl)urea (20). The preparation of *1-phenyl-5-tetrazolylacetazide* from the corresponding hydrazide (19) (17.5 g., 0.08 mole) followed the foregoing procedure except that additional ether (125 ml.) was used to take up the ether-soluble azide. The resulting yellow-green ether solution was separated, washed with saturated sodium bicarbonate solution and water, and dried over sodium sulfate.

To the dry ether solution of the azide was added 100 ml. of dry toluene and the ether was distilled off through a short column. Upon heating the toluene solution, evolution of a gas began at 100° accompanied by the separation of some solid material. Refluxing was continued for one hour and after cooling the mixture a solution of aniline (7.5 g., 0.083 mole) in 100 ml. of dry toluene was slowly added. An exothermic reaction took place with simultaneous separation of a tan solid. The mixture was again refluxed for 1.5 hours most of the solid dissolving and being reprecipitated upon cooling. The crude product was filtered off and recrystallized with considerable loss first from toluene and then from propylene dichloride. The yield of colorless product was 5 g. (21%), m.p. 159.5–161°.

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(9) Willard and Hamilton, *J. Am. Chem. Soc.*, **75**, 2370 (1953).