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Tetrazole Derivatives I. Tetrazole Alkamine Ethers

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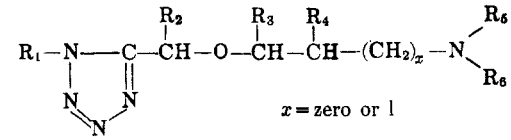
Thirty-seven new tetrazole alkamine ethers, three related derivatives, and ten new 1-substituted-5-chloromethyltetrazoles have been prepared. The relationship between the chemical structure and the hypotensive activity of certain of these derivatives has been indicated. It appears that 1-aryl-5-dimethylaminoethoxymethyltetrazoles are active hypotensive agents.

Of all the tetrazole derivatives known, only pentamethylenetetrazole, Metrazole, has attained widespread usage as a useful therapeutic agent. This potent respiratory and circulatory stimulant has been studied intensively and the literature references pertaining to it are numbered in the thousands. It is therefore somewhat surprising that relatively little is known about the physiological properties of other tetrazole compounds. Subsequent to the original report by Hildebrandt[1] describing the useful analeptic properties of pentamethylenetetrazole, Issekutz and co-workers,[2,3] Ruzicka,[4] and more recently, Gross and Featherstone[5] have found stimulant properties in varying degrees among the related unsubstituted and alkyl-substituted tri-, tetra-, penta-, hexa-, and hepta-methylenetetrazoles. Similarly, Barwanietz[6] and Gross and Featherstone[7] have discovered that 1,3-dioxotetramethylenetetrazole-2-carboxamide and certain 1,5-dialkyltetrazoles respectively are also potent stimulants of the central nervous system. Later, in a systematic study of a variety of amino derivatives of 1,5-disubstituted tetrazoles for their effects on the central nervous system, Gross and Featherstone[8–10] demonstrated that not all tetrazole derivatives are stimulatory in their action but range from potent convulsant and analeptic agents to depressants which may produce sedation or even anesthesia. In more recent investigations, Miller *et al.*[11] have found 1-phenyl-5-tetrazolylsulfonamide to possess appreciable activity as a carbonic anhydrase inhibitor and Ettel and Nosek[12] have reported that amides derived from 5-aminotetrazole produce positive inotropic and chronotropic effects on the isolated heart.

During the course of a routine examination of tetrazole derivatives it was observed that 1-phenyl-5-dimethylaminoethoxymethyltetrazole (TT-209) produced a pronounced and prolonged lowering of blood pressure when administered intravenously to an anesthetized dog in a dose of 10 mg./kg. In view of the limited knowledge of the physiological properties of tetrazole derivatives, the great interest in hypotensive agents, and the novelty of the chemical structure of TT-209 with respect to those agents already known and employed to advantage in the treatment of hypertension, it seemed important to determine the optimum structure-activity relationship for this type of compound. The results of this investigation are reported here.

An extensive series of compounds encompassing the most obvious structural variations which would be of interest on the basis of the observed activity of 1-phenyl-5-dimethylaminoethoxymethyltetrazole has been prepared and these compounds have been examined for their effects on the blood pressure of the anesthetized dog. The variants studied are indicated in general formula (I).



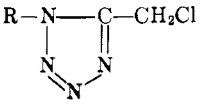
I

In addition, the thio ether (TT-290) corresponding to 1-phenyl-5-dimethylaminoethoxymethyltetrazole was also prepared.

In a further effort to evaluate the importance of the tetrazole ring system in these basic ethers, two open chain analogs, *alpha*-dimethylaminoethoxyacetanilide (RL-30) and *beta*-dimethylamino-*beta'*-anilinodiethyl ether (RL-30), were included for comparison as well as one analog, dimethylaminoethyl *o*-phenylbenzyl ether (RL-34), in which the 1-phenyltetrazolyl radical is replaced by an *o*-diphenyl radical.

(1) Hildebrandt, *Klin. Wochschr.*, **4**, 1678 (1925).
(2) Issekutz, Leinzinger, and Novak, *Arch. Exptl. Path. Pharmakol.*, **177**, 397 (1935).
(3) Issekutz, *Arch. Exptl. Path. Pharmakol.*, **177**, 415 (1935).
(4) Ruzicka, Goldberg, and Hurbin, *Helv. Chim. Acta*, **16**, 1335 (1933).
(5) Gross and Featherstone, *J. Pharmacol. Exptl. Therap.*, **87**, 291 (1946).
(6) Barwanietz, *Arch. Wiss. Prakt. Tierheilk.*, **71**, 297 (1937).
(7) Gross and Featherstone, *J. Pharmacol. Exptl. Therap.*, **87**, 299 (1946).
(8) Gross and Featherstone, *J. Pharmacol. Exptl. Therap.*, **88**, 353 (1946).
(9) Gross and Featherstone, *J. Pharmacol. Exptl. Therap.*, **92**, 323 (1948).
(10) Gross and Featherstone, *J. Pharmacol. Exptl. Therap.*, **92**, 330 (1948).
(11) Miller, Dessert, and Roblin, *J. Am. Chem. Soc.*, **72**, 4893 (1950).
(12) Ettel and Nosek, *Collection Czechoslov. Chem. Commun.*, **15**, 335 (1950).

TABLE I
1-SUBSTITUTED-5-CHLOROMETHYLTETRAZOLES



No.	R	Yield	M.P., °C.	Analysis Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found	Nitrogen Calc'd	Nitrogen Found
TT-211	C_2H_5—	43	125–127[a]	32.77	32.84 32.70	4.81	4.94 4.83	38.23	38.10 38.35
TT-298	*o*-CH_3O—C_6H_4—	71	67–69	48.12	48.05 48.10	4.04	4.05 4.09	24.94	25.28 25.25
TT-352	*o*-C_2H_5O—C_6H_4—	51	60–62	50.31	50.50 50.35	4.65	4.67 4.65	23.48	23.40 23.30
TT-339	*m*-C_2H_5O—C_6H_4—	43	68–69	50.31	50.30 50.25	4.65	4.79 4.67	23.48	23.25 23.30
TT-340	*p*-C_2H_5O—C_6H_4—	63	68–70	50.31	50.10 50.25	4.65	4.69 4.60	23.48	23.30 23.40
TT-323	*o*-Cl—C_6H_4—	62	56.5–58.5	41.94	42.00 41.90	2.64	2.82 2.83	24.46	24.42 24.30
TT-332	*p*-Cl—C_6H_4—	23	71–73	41.94	42.10 41.95	2.64	2.85 2.68	24.46	24.45 24.55
TT-341	*p*-Br—C_6H_4—	53	73–75	35.13	35.40 35.30	2.21	2.29 2.38	20.48	20.28 20.30
TT-348	*2,5*-$(CH_3O)_2$—C_6H_3—	63	87–89	47.16	47.05 47.25	4.35	4.17 4.22	22.00	21.70 21.75
TT-349	*2*-CH_3O—*5*-Cl—C_6H_3—	44	125–127	41.72	41.80 41.70	3.11	3.28 3.16	21.62	21.50 21.60

[a] Boiling point at 1.3 mm.

EXPERIMENTAL

N-Monosubstituted-chloroacetamides. All of the amides employed as intermediates for the preparation of 1-substituted-5-chloromethyltetrazoles are described in the literature with the exception of N-(5-chloro-2-methoxyphenyl)-chloroacetamide, m.p. 103–104°, and N-(2,5-dimethoxyphenyl)chloroacetamide, m.p. 78–80°. These were prepared in 85% yields by addition of one mole of chloroacetyl chloride to a benzene solution containing one mole each of the substituted aniline and of pyridine at 5–10°. Attempts to prepare N-ethylchloroacetamide by a similar process using aqueous ethylamine or by modified Schotten-Baumann procedures were generally unsatisfactory. Yields were variable (10–40%) and it was difficult to isolate the water-soluble product from the reaction mixture. The following procedure was found to give an excellent yield of N-ethylchloroacetamide:

Gaseous ethylamine was passed into one liter of benzene until 111.5 g. (2.48 mole) had been absorbed. The resulting solution was cooled to 5–10° and 140.1 g. (1.24 mole) of chloroacetyl chloride was added dropwise. After stirring for one hour the precipitated ethylamine hydrochloride was removed by filtration. The filtrate was distilled to yield 126.8 g. (84%) of N-ethylchloroacetamide, b.p. 108–110°/22 mm., $n^{25}D$ 1.4702.

1-Substituted-5-chloromethyltetrazoles. The 1-substituted-5-chloromethyltetrazoles required as intermediates were conveniently prepared by treatment of the appropriate N-monosubstituted-chloroacetamide in benzene solution with phosphorus pentachloride and hydrazoic acid in the manner described by Harvill, *et al.*[13] Ten of the chloromethyltetrazoles employed in this study are apparently new compounds and are listed in Table I with their physical constants and other pertinent data.

1-SUBSTITUTED-5-DIALKYLAMINOALKOXYMETHYLTETRAZOLES

(*A*) *Amino alcohols.* The following amino alcohols were obtained commercially from Eastman Kodak Co. and were dried over sodium sulfate and distilled before use: dimethylaminoethanol, diethylaminoethanol, dibutylaminoethanol, 2-diethylamino-1-propanol, 1-dimethylamino-2-propanol, and 3-diethylamino-1-propanol. The 1,3-bis(dimethylamino)-2-propanol was prepared as described by Campbell, *et al.*[14] and N-benzyl-N-methyl-2-aminoethanol, b.p. 100–105°/2 mm., $n^{25}D$ 1.5260, was prepared in 79% yield by the reaction of benzylmethylamine with ethylene chlorohydrin under the reaction conditions described by Clinton, *et al.*[15] The following process was found most convenient for the laboratory scale preparation of 3-dimethylamino-1-propanol:

A solution of 69.5 g. (0.5 mole) of 3-bromo-1-propanol, 300 ml. of 25% aqueous dimethylamine, and 600 ml. of 95% ethyl alcohol was heated to reflux. Two additional 300-ml. portions of dimethylamine were added at two-hour intervals. After a total reaction time of seven hours the alcohol was removed by atmospheric distillation. The residual aqueous phase was chilled, saturated with sodium hydroxide, and extracted with 500 ml. of chloroform followed by three 200-ml. portions of ether. After drying and removal of solvent from the combined extracts, distillation yielded 26.0 g. (50%) of 3-dimethylamino-1-propanol, b.p. 68–69°/18 mm., n^{25}_D 1.4349.

(*B*) *Preparation of dialkylaminoalkyl ethers from 5-chloromethyltetrazoles.* In general, the preparation of dialkylaminoalkyl ethers from 5-chloromethyltetrazoles involved treatment of a benzene solution of the appropriate sodium alkoxide with a solution of the 1-substituted-5-chloromethyltetrazole in benzene; in some cases the latter benzene solution was warmed to effect complete solution of the tetrazole. Reaction was completed by refluxing for 8–16 hours. The following examples serve to typify the details of the procedures employed:

1-Phenyl-5-dimethylaminoethoxymethyltetrazole (TT-209).

(13) Harvill, Herbst, and Schreiner, *J. Org. Chem.*, **17**, 1597 (1952).

(14) Campbell, La Forge, and Campbell, *J. Org. Chem.*, **14**, 346 (1949).

(15) Clinton, Salvador, and Laskowski, *J. Am. Chem. Soc.*, **71**, 3366 (1948).

To a solution of 25.0 g. (0.281 mole) of dimethylaminoethanol in 400 ml. dry benzene was added 5.9 g. (0.257 g.-atom) of metallic sodium and the mixture was refluxed until the sodium had completely reacted forming a clear, pale yellow solution of the sodium alkoxide. A solution of 50.0 g. (0.257 mole) of 1-phenyl-5-chloromethyltetrazole in 500 ml. of benzene was added at room temperature, the reaction mixture immediately turning dark red in color. After refluxing for eight hours the mixture was cooled and filtered from the gelatinous precipitate of sodium chloride. The benzene was removed from the filtrate *in vacuo*. The oily residue was treated with 150 ml. of water, made strongly acidic, and extracted with benzene to remove any unreacted chloromethyl tetrazole. The aqueous phase was made strongly alkaline and the oily product was extracted into ether, dried, and distilled.

1-(2-Methoxy-5-chlorophenyl)-5-dimethylaminoethoxymethyltetrazole hydrochloride (TT-350). A solution of 12.2 g. (0.137 mole) of dimethylaminoethanol in 250 ml. of dry benzene was refluxed with 2.6 g. (0.115 g.-atom) of metallic sodium until all had dissolved forming a clear yellow solution of the sodium alkoxide. A suspension of 30.0 g. (0.115 mole) of 1-(2-methoxy-5-chlorophenyl)-5-chloromethyltetrazole in 300 ml. of dry benzene was warmed sufficiently to effect complete solution and was added to the sodium alkoxide solution at room temperature. After refluxing overnight, the mixture was cooled, filtered from precipitated sodium chloride, and stripped of solvent *in vacuo*. The viscous oily residue was treated with 100 ml. of water and made strongly acidic. A small amount of unreacted 1-(2-methoxy-5-chlorophenyl)-5-chloromethyltetrazole crystallized and was removed by filtration. Any additional traces of starting material were removed by extraction with benzene. The aqueous phase was made strongly alkaline and the oily product was extracted into ether and dried. After distillation of the ether, the residue was heated in a bath at 150° and 0.3 mm. to remove any unreacted dimethylaminoethanol. The crude base (30.7 g.) was converted to the hydrochloride salt with isopropanolic hydrogen chloride. Recrystallization of the crude salt from isopropyl alcohol gave 34.0 g. (85%) of the desired hydrochloride.

The pertinent data for the 1-substituted-5-dialkylaminoalkoxymethyltetrazoles prepared in a similar manner are recorded in Table II. Those derivatives containing branch methyl groups on the substituent attached to the 5-position of the tetrazole ring are included in Table III, *viz.* TT-221, 203, 284, and 269.

(C) Preparation of 1-substituted-5-alkylaminoalkoxymethyltetrazoles. A solution of 45.0 g. (0.125 mole) of 1-phenyl-5-(N-benzyl-N-methyl-*beta*-aminoethoxymethyl)tetrazole hydrochloride (TT-263) in 200 ml. of absolute ethanol containing 1.2 g. of 10% palladium on activated charcoal catalyst was shaken under a pressure of three atmospheres of hydrogen until hydrogen absorption ceased. The catalyst was removed by filtration and the alcohol removed *in vacuo* leaving a viscous oily residue which readily crystallized on scratching. Two recrystallizations of this crude product from chloroform gave 28.0 g. or 83% of 1-phenyl-5-methylaminoethoxymethyltetrazole hydrochloride (TT-266).

A similar process using 33.2 g. of 1-ethyl-5-(N-benzyl-N-methyl-*beta*-aminoethoxymethyl)tetrazole (TT-293) neutralized with ethanolic hydrogen chloride yielded, after removal of the catalyst and the ethanol, an oily crude hydrochloride which could not be induced to crystallize. It was dissolved in water and the solution was made strongly alkaline. After extraction into ether, drying and removal of the ether, the residue was distilled to yield 6.7 g. (30%) of 1-ethyl-5-methylaminoethoxymethyltetrazole (TT-294), n_D^{25} 1.4770.

(D) Quaternary derivatives. A solution of 4.7 g. (0.018 mole) of 1-cyclohexyl-5-dimethylaminoethoxymethyltetrazole (TT-215) in 150 ml. of acetone was saturated at 0° with gaseous methyl chloride. After standing overnight in a stoppered flask, 5.1 g. (93%) of pure 1-cyclohexyl-5-dimethylaminoethoxymethyltetrazole methochloride had precipitated from the reaction mixture. Recrystallization from acetonitrile left the melting point unchanged at 183–184° (dec.).

A similar procedure with TT-209 and an excess of methyl iodide gave a 90% yield of 1-phenyl-5-dimethylaminoethoxymethyltetrazole methiodide.

1-Phenyl-5-dimethylaminoethylthiomethyltetrazole. A mixture of 39.0 g. (0.2 mole) of 1-phenyl-5-chloromethyltetrazole and 15.2 g. (0.2 mole) of thiourea in 100 ml. of 95% ethyl alcohol was refluxed for 16 hours and cooled. A solution of 12.0 g. (0.3 mole) of sodium hydroxide in 120 ml. of water was added to the clear yellow solution and refluxing was continued an additional eight hours. After removal of the solvent *in vacuo*, the residual white solid was dissolved in water and filtered from a small amount of insoluble material. The filtrate was acidified and chilled and the crude *1-phenyl-5-mercaptomethyltetrazole* was removed by filtration. The yield was 29.0 g. or 76%, m.p. 45–47°. This material was suitable for use as an intermediate. An analytical sample, m.p. 45.5–47.5°, was obtained by recrystallization from aqueous methanol; chilling and constant scratching are required to prevent the product from separating as an oil.

Anal. Calc'd for $C_8H_8N_4S$: C, 49.98; H, 4.19; N, 29.15. Found: C, 50.20, 50.25; H, 4.19, 4.17; N, 29.05, 29.10.

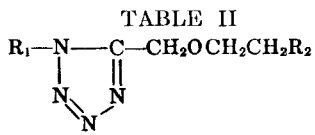
A solution of 19.2 g. (0.1 mole) of 1-phenyl-5-mercaptomethyltetrazole in 75 ml. of water containing 8.8 g. (0.22 mole) of sodium hydroxide was treated by the dropwise addition of a solution of 14.4 g. (0.1 mole) of dimethylaminoethyl chloride hydrochloride in 75 ml. of water. The resulting turbid mixture was warmed on a steam-bath for 1.5 hours. The orange oily layer which separated from the cooled reaction mixture was extracted into chloroform and dried. The viscous oily residue from the chloroform extract readily formed a hydrochloride salt. After one recrystallization from a 5:1 mixture of isopropyl alcohol and methanol there was obtained a yield of 22.8 g. or 80% of 1-phenyl-5-dimethylaminoethylthiomethyltetrazole hydrochloride (TT-290).

alpha-Dimethylaminoethoxyacetanilide (RL-30). A solution of 10.5 g. (0.118 mole) of dimethylaminoethanol in 200 ml. of dry benzene was refluxed with 2.7 g. (0.118 g.-atom) of metallic sodium until all the sodium had reacted. To the clear solution of the sodium alkoxide a solution of 20.0 g. (0.118 mole) of chloroacetanilide in 300 ml. of dry dioxane was added dropwise and the resulting mixture was stirred at room temperature overnight. The precipitated white solid was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was treated with 100 ml. of water, acidified, and extracted with chloroform to remove non-basic materials. The acidic aqueous layer was made strongly alkaline and the oily product was extracted into chloroform and dried. Distillation of the residue from the chloroform extract gave a yield of 3.9 g. or 15% of *alpha*-dimethylaminoethoxyacetanilide (RL-30), n_D^{25} 1.5330. From the solid material filtered from the original reaction mixture there was obtained 5.6 g. of a water-insoluble, non-basic product which was free of halogen. Recrystallization from chloroform followed by recrystallization from dioxane gave a white flocculent solid, m.p. 273–275° (dec.). This material is apparently 1,4-diphenyl-2,5-diketopiperazine, formed by interaction of two molecules of chloroacetanilide, and helps account for the unexpectedly low yield of the desired product.

Anal. Calc'd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.10, 71.95; H, 5.51, 5.67; N, 10.72, 10.62.

beta-Dimethylamino-beta'-anilinodiethyl ether (RL-31). Chloroacetyl chloride (56.5 g., 0.5 mole) was added dropwise to a solution of 183 g. (1.0 mole) of benzylaniline in 1500 ml. of benzene chilled to 0–5°. When addition was completed the mixture was allowed to stir two hours at room temperature. The precipitated benzylaniline hydrochloride was removed by filtration and washed with several portions of

TABLE II



TETRAZOLE ALKAMINE ETHERS

TT No.	R_1	R_2	Yield, %	B.P., °C.	Mm.	HCl M.P., °C.	Analysis Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found	Nitrogen Calc'd	Nitrogen Found
294	C_2H_5—	—$NHCH_3$	30	151–155	0.3	—	45.39	45.50 45.45	8.16	8.24 8.17	37.81	37.65 37.75
293	C_2H_5—	—$N(CH_3)CH_2C_6H_5$	81	197–203	0.3	101–102 (dec.)[a]	52.59	52.65 52.80	6.35	6.37 6.37	19.16	18.88 18.95
206	C_2H_5—	—$N(CH_3)_2$	60	144–146	1.0	98–99	40.76	41.10 41.00	7.70	7.54 7.32	29.71	29.55 29.65
205	C_2H_5—	—$N(C_2H_5)_2$	78	151–153	0.9	104–105 (dec.)	45.53	45.70 45.75	8.41	7.93 7.89	26.55	26.55 26.65
227	Cyclohexyl	—CH_2—$N(C_2H_5)_2$	33	189–191	0.6	140–141[b]	53.97	53.80 53.95	8.56	8.70 8.66	17.49	17.38 17.45
216	Cyclohexyl	—$\overset{+}{N}(CH_3)_3Cl^-$	93	—	—	183–184 (dec.)	51.38	51.35 51.50	8.63	8.72 8.67	23.05	22.85 23.00
215	Cyclohexyl	—$N(CH_3)_2$	85	161–163	0.3	111.5–112.5 (dec.)[a]	48.97	49.05 49.15	7.34	7.50 7.42	20.40	20.50 20.40
201	Cyclohexyl	—$N(C_2H_5)_2$	76	194–197	1.3	149–151	52.90	53.05 52.90	8.88	8.91 8.80	22.03	22.15 22.00
303	C_6H_5—CH_2—	—$N(CH_3)_2$	68	192.5–194	0.3	—	59.75	59.90 59.80	7.33	7.20 7.34	26.80	26.75 26.80
204	C_6H_5—CH_2—	—$N(C_2H_5)_2$	59	210–214	1.4	—	55.29	55.40 55.20	7.42	7.44 7.46	21.50	21.50 21.40
266	C_6H_5—	—$NHCH_3$	83	—	—	135–136	48.97	48.90 49.00	5.98	5.91 6.00	25.97	26.20 26.00
209	C_6H_5—	—$N(CH_3)_2$	83	175–176	0.6	146–147	50.79	51.10 50.90	6.39	6.51 6.35	24.68	24.80 24.70
262	C_6H_5—	—$\overset{+}{N}(CH_3)_3I^-$	90	—	—	141–143	40.11	40.00 39.95	5.18	5.08 5.11	18.00	18.10 18.25
263	C_6H_5—	—$N(CH_3)CH_2C_6H_5$	56	—	—	134–136	60.08	60.20 60.15	6.16	6.14 6.04	19.46	19.40 19.35
259	C_6H_5—	—$N(C_2H_5)_2$	77	199–200	2.0	138–139	53.93	53.80 54.00	7.11	7.07 7.12	22.46	22.52 22.40
264	C_6H_5—	—$N(C_4H_9)_2$	54	210–212	1.0	—	65.22	65.45 65.30	8.82	8.86 8.71	21.13	20.95 21.02
271	C_6H_5—	—$CH_2N(CH_3)_2$	41	171–172	0.27	—	59.75	59.70 59.60	7.33	7.25 7.30	26.80	27.10 27.03
299	*o*-CH_3O—C_6H_4—	—$N(CH_3)_2$	44	—	—	147–148 (dec.)	49.76	49.80 49.92	6.42	6.54 6.50	22.32	22.16 22.23
297	*p*-CH_3O—C_6H_4—	—$N(CH_3)_2$	12	—	—	136–138	49.76	49.95 50.10	6.42	6.54 6.51	22.32	22.10 22.18
353	*2,5*-$(CH_3O)_2$—C_6H_3—	—$N(CH_3)_2$	88	—	—	135–137	48.91	49.05 49.10	6.45	6.40 6.45	20.37	20.15 20.20
350	*2*-CH_3O—*5*-Cl—C_6H_3—	—$N(CH_3)_2$	85	—	—	157–159	44.84	44.85 44.80	5.50	5.56 5.51	20.11	20.15 20.00

355	*o*-C_2H_5O—C_6H_4—	—$N(CH_3)_2$	74	—	—	129–131	51.29	51.30	6.76	6.70	21.37	21.25
								51.45		6.66		21.35
344	*m*-C_2H_5O—C_6H_4—	—$N(CH_3)_2$	72	186–188	0.2	97–99 (dec.)	51.29	51.42	6.76	6.75	21.37	21.05
								51.50		6.78		21.10
342	*p*-C_2H_5O—C_6H_4—	—$N(CH_3)_2$	73	—	—	123–125 (dec.)	51.29	51.40	6.76	6.62	21.37	21.40
								51.50		6.80		21.35
325	*o*-Cl—C_6H_4—	—$N(CH_3)_2$	67	—	—	136–138	45.29	45.50	5.38	5.48	22.01	22.20
								45.60		5.50		22.30
331	*m*-Cl—C_6H_4—	—$N(CH_3)_2$	5	—	—	136–138	45.29	45.35	5.39	5.27	22.01	21.85
								45.45		5.32		21.85
330	*p*-Cl—C_6H_4—	—$N(CH_3)_2$	81	—	—	141–143	45.29	45.24	5.39	5.36	22.01	22.10
								45.18		5.24		22.20
343	*p*-Br—C_6H_4—	—$N(CH_3)_2$	87	—	—	148–150 (dec.)	39.74	39.90	4.73	4.88	19.31	19.45
								39.80		4.91		19.35
295	*o*-C_6H_5—C_6H_4—	—$N(CH_3)_2$	83	—	—	170–172	60.08	60.30	6.16	6.34	19.46	19.33
								60.35		6.35		19.22
255	*p*-C_6H_5—C_6H_4—	—$N(CH_3)_2$	58	—	—	203–204	60.08	60.00	6.16	6.30	19.46	19.30
								60.05		6.34		19.42
256	α-$C_{10}H_7$—	—$N(CH_3)_2$	67	—	—	177–179	57.57	57.75	6.04	6.20	20.98	20.82
								57.60		6.23		20.58
257	β-$C_{10}H_7$—	—$N(CH_3)_2$	69	—	—	147–148	57.57	57.45	6.04	6.09	20.98	20.83
								57.35		6.02		20.90

[a] Oxalate salt. [b] Bimucate salt.

ether. After removal of ether and benzene from the filtrate, the residue was an orange oil which readily solidified on chilling. After recrystallization from isopropyl alcohol there was obtained 109.0 g. (84%) of N-benzylchloroacetanilide, m.p. 81–82°.

To a solution of sodium dimethylaminoethoxide prepared from 4.4 g. (0.19 g.-atom) of sodium and 21.0 g. (0.22 mole) of dimethylaminoethanol in 350 ml. of dry benzene, a solution of 50.0 g. (0.19 mole) of N-benzylchloroacetanilide in 200 ml. of dry benzene was added dropwise at room temperature. The mixture was refluxed for 16 hours, cooled, and filtered from the gelatinous precipitate of sodium chloride. After removal of benzene from the filtrate under reduced pressure, the residue was treated with 100 ml. of water, acidified, and extracted with ether. The aqueous phase was made strongly alkaline and the oily product was extracted into ether and dried. The residue from the ether extract was distilled to give a yield of 40.0 g. or 68% of N-benzyl-α-dimethylaminoethoxyacetanilide, b.p. 186–187°/0.3 mm., n_D^{25} 1.5510.

Anal. Calc'd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.50, 73.55; H, 7.95, 8.00; N, 8.67, 8.60.

A solution of 27.2 g. (0.087 mole) of N-benzyl-α-dimethylaminoethoxyacetanilide in 100 ml. of anhydrous ether was added dropwise at room temperature to a suspension of 6.8 g. (0.18 mole) of lithium aluminum hydride in 400 ml. of anhydrous ether. After addition was completed, the mixture was refluxed for seven hours and allowed to stand overnight. After the cautious addition of 50 ml. of water to destroy excess hydride, the precipitated hydroxides were separated by filtration and the ether filtrate was dried. Distillation of the residue from the ether extract gave a yield of 22.0 g. or 85% of β-dimethylamino-β′-benzylanilinodiethyl ether, b.p. 160–163°/0.25 mm., n_D^{25} 1.5622. A small sample of this material was converted to the *tartrate salt*, m.p. 117–118° (*from* isopropyl alcohol).

Anal. Calc'd for $C_{23}H_{24}N_2O_7$: C, 61.59; H, 7.19; N, 6.25. Found: C, 61.30, 61.20; H, 7.05, 7.07; N, 6.14, 6.08.

A solution of 10 g. (0.034 mole) of β-dimethylamino-β′-benzylanilinodiethyl ether in 150 ml. of absolute ethanol containing 2.8 ml. of 12 *N* hydrochloric acid and 0.35 g. of 10% palladium on activated charcoal catalyst was shaken under a pressure of three atmospheres of hydrogen until hydrogen absorption ceased. Removal of the catalyst by filtration and evaporation of the alcohol under reduced pressure yielded a viscous, oily residue which solidified upon trituration under isopropyl alcohol to yield a crude, hygroscopic *hydrochloride salt*. After three recrystallizations from isopropyl alcohol there was obtained 3.2 g. (39%) of β-dimethylamino-β′-anilinodiethyl ether hydrochloride (RL-31). When pure this material was stable in air.

Dimethylamino o-phenylbenzyl ether (RL-34). A solution of 20.0 g. (0.108 mole) of *o*-phenylbenzyl alcohol[16] in 400 ml. of dry benzene containing 100 ml. of *tert*-butyl alcohol was refluxed with 2.5 g. (0.108 g.-atom) of metallic sodium until all the sodium had reacted to form a clear solution of the sodium alkoxide. To this solution 17.4 g. (0.16 mole) of freshly distilled dimethylaminoethyl chloride was added dropwise at room temperature. The mixture was refluxed for eight hours, cooled, and filtered to remove precipitated sodium chloride. Removal of the solvents from the filtrate under reduced pressure yielded an oily solid residue which was treated with 200 ml. of water, acidified, and extracted with benzene. The aqueous acidic layer was made strongly alkaline and the product was extracted into ether and dried. The product was purified by distillation.

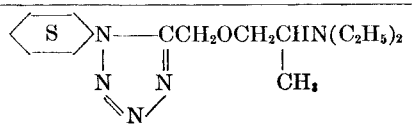
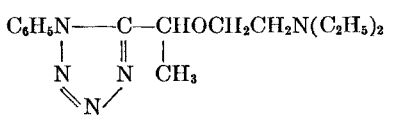
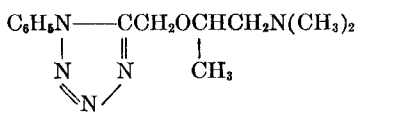
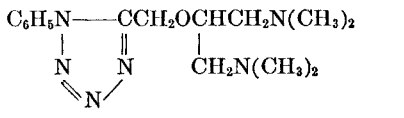
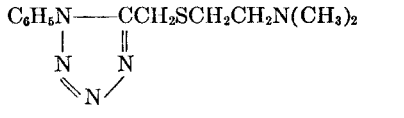
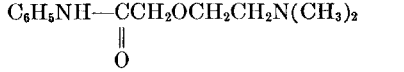
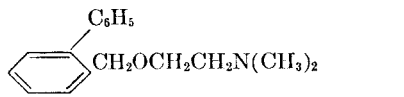
DISCUSSION

The hypotensive action of the compounds in Tables II and III, with the exception of TT-271, 293, and 294, was determined by recording the caro-

(16) Cookson and Mann, *J. Chem. Soc.*, 2888 (1949).

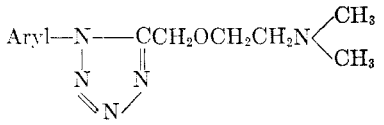
TABLE III

MISCELLANEOUS TETRAZOLE ALKAMINE ETHERS AND RELATED COMPOUNDS

No.	Compound	Yield, %	B.P., °C.	Mm.	HCl M.P., °C.	Analysis Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found	Nitrogen Calc'd	Nitrogen Found
TT-221		63	192–194	1.3	149.5–150.5[a]	53.97	53.90 53.70	8.56	8.70 8.72	17.49	17.45 17.32
TT-203		31	—	—	59 (dec.)[b]	52.38	52.05 51.90	6.49	6.53 6.56	14.55	14.85 14.80
TT-284		63	172–174	1.0	175.5–176.5	52.43	52.50 52.55	6.77	6.70 6.78	23.52	23.45 23.32
TT-269		44	174–176	0.35	—	59.18	58.90 59.02	7.95	7.98 7.92	27.61	27.25 27.30
TT-290		80	—	—	154–156	48.07	48.05 48.10	6.05	6.12 5.94	23.36	23.15 23.30
RL-30		15	159–159.5	1.8	119–121	55.69	55.70 55.55	7.40	7.57 7.66	10.83	10.70 10.74
RL-31		91	120–122	0.4	156–158[c]	51.25	51.40 51.55	7.88	7.90 7.92	9.96	10.05 9.98
RL-34		41	140–141	0.3	157.5–158.5	69.97	70.30 70.10	7.60	7.46 7.40	4.80	4.78 4.84

[a] Bimucate salt. [b] Citrate salt. [c] Dihydrochloride salt.

tid blood pressure following intravenous injection of 10 mg./kg. of the compounds as 10% aqueous solutions into the dog anesthetized with sodium pentobarbital (36 mg./kg., intravenously). Of the 34 tetrazoles tested only TT-209, 299, 297, 353, 350, 355, 344, 342, 325, 331, 330, 343, 295, 255, 256, and 257 produced a considerable blood pressure drop for at least five minutes. It therefore appears that formula II expresses the structural requirements necessary for optimum hypotensive activity among this series of tetrazole alkamine ethers.



II

The tetrazole ring itself is apparently not essential since RL-30 and 31 are also active. However the replacement of the tetrazole ring by an aryl radical attached directly to the methylene carbon, as in RL-34, yields an inactive compound.

Detailed reports on the mechanism by which TT-209 and its congeners produce their hypotensive effect are in preparation and will be published separately by Drs. E. G. Gross and H. H. Keasling of the State University of Iowa and Professor F. Hildebrandt and Dr. Straub of Heidelberg, Western Germany.

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