[CONTRIBUTION FROM THE RESEARCH LABORATORY OF E. BILHUBER, INC.]

Tetrazole Derivatives. II. Tetrazole Aminoalkanes, Aminoalkenes, and Aminoalkanols

ANTHONY D'ADAMO AND RAYMOND A. LAFORGE

Received December 7, 1955

A series of 14 tetrazole aminoalkanes, aminoalkenes, and aminoalkanols has been prepared by the reaction of 1-phenyl-5-lithiomethyltetrazole and 1-methyl-5-*alpha*-lithiobenzyltetrazole with acetonitrile, dialkylaminoalkyl halides, and Mannich aldehydes and ketones, and suitable modification of the resulting products. None of these compounds possess physiological properties of significant interest.

As noted in the first paper in this series,[1] many 1,5-disubstituted-tetrazoles possess interesting and potentially useful physiologic properties. However, further syntheses in this direction have been handicapped by the fact that although numerous 1,5-disubstituted-tetrazoles are reported in the literature, the functional groups available for further chemical modifications are largely limited to the halogen, amino, hydroxyl, and mercapto groups. As a further handicap, we are unaware of any report wherein the successful preparation of a Grignard reagent from a 5-halo- or 5-haloalkyl-tetrazole is described. Recently, however, Jacobson and Amstutz[2] found that those 1,5-disubstituted-tetrazoles containing a hydrogen atom on the *alpha* carbon atom of the substituent in the 5-position could be transmetallated with phenyllithium to yield the corresponding 5-*alpha*-lithiotetrazoles which, in turn, could be carbonated to yield the corresponding carboxylic acids. With the availability of these reactive lithiotetrazoles as intermediates it became possible to undertake the synthesis of 1,5-disubstituted-tetrazoles of possible therapeutic interest which were previously difficult or impossible to attain. The results of such an investigation are reported herein.

During the course of this work 1-phenyl-5-lithiomethyltetrazole and 1-methyl-5-*alpha*-lithiobenzyltetrazole have been found to react in a normal manner with acetonitrile, Mannich aldehydes and ketones, and dialkylaminoalkyl halides to yield the expected ketone, secondary and tertiary dialkylaminoalkanols, and dialkylaminoalkyl tetrazoles respectively. As a further extension of the work the ketone, 1-phenyl-5-acetonyltetrazole, has been converted into 1-phenyl-5-*beta*-methylaminopropyltetrazole and several of the dialkylaminoalkanols have been dehydrated to the corresponding dialkylaminoalkenes. The compounds prepared during this study are listed in Table I together with the pertinent physical data. Most of them have been examined for their effects on the cardiovascular system.

(1) Cosgrove and LaForge, *J. Org. Chem.*, **21**, 197 (1956).

(2) Jacobson and Amstutz, *J. Org. Chem.*, **18**, 1183 (1953).

EXPERIMENTAL[3]

REACTION OF LITHIOTETRAZOLES WITH MANNICH BASES

A. Aldehydes. 1-Phenyl-1-(1'-methyl-5'-tetrazolyl)-3,3-dimethyl-4-(1'-piperidyl)-2-butanol (VII). Phenyllithium was prepared in the usual manner from 57.0 g. (0.36 mole) of bromobenzene and 5.1 g. (0.72 g.-atom) of lithium wire in 525 ml. of anhydrous ether and was treated, over a period of 1.25 hours, by the dropwise addition of a solution of 52.5 g. (0.3 mole) of 1-methyl-5-benzyltetrazole[2] in one liter of a 1:1 mixture of anhydrous ether and benzene under an atmosphere of nitrogen. To the resulting dark red suspension a solution of 26.0 g. (0.15 mole) of α,α-dimethyl-β-(1-piperidyl)propionaldehyde[4] in 75 ml. of anhydrous ether was added dropwise over a period of 15 minutes. The reaction mixture was refluxed for one hour, then cooled to 20° in a cold water-bath, and hydrolyzed with 50 ml. of water. Upon the dropwise addition of 150 ml. of 6 *N* hydrochloric acid below 20°, all solid materials dissolved. The aqueous phase was separated, chilled in ice-bath, and made strongly alkaline with 50% sodium hydroxide. The crude product separated as a tan solid which was removed by filtration, dried, and recrystallized to purity.

A similar procedure using α,α-dimethyl-β-diethylaminopropionaldehyde[4] gave 1-phenyl-1-(1'-methyl-5'-tetrazolyl)-3,3-dimethyl-4-diethylamino-2-butanol (VI). Likewise, 1-phenyl-5-methyltetrazole[5] reacted with α,α-dimethyl-β-(1-piperidyl)propionaldehyde under similar experimental conditions to yield 1-(1'-phenyl-5'-tetrazolyl)-3,3-dimethyl-4-(1'-piperidyl)-2-butanol (XII).

B. Ketones. 1,2-Diphenyl-1-(1'-methyl-5'-tetrazolyl)-4-dimethylamino-2-butanol (IX). The lithio derivative of 1-methyl-5-benzyltetrazole, prepared from 41.4 g. (0.27 mole) of bromobenzene, 3.8 g. (0.54 g.-atom) of lithium wire, and 38.4 g. (0.22 mole) of the tetrazole in 900 ml. of anhydrous ether containing 400 ml. of dry benzene in the manner indicated above, was treated by the dropwise addition of a solution of 30.0 g. (0.17 mole) of β-dimethylaminopropiophenone[6] in 100 ml. of anhydrous ether at such a rate as to maintain moderate reflux. Stirring and refluxing were continued for 1.5 hours after addition was completed. The resulting orange suspension was cooled, hydrolyzed with 75 ml. of water, and strongly acidified with 200 ml. of 6 *N* hydrochloric acid. The aqueous phase was separated, chilled, and made strongly alkaline with 50% sodium hydroxide. The crude product was removed by filtration, dried, and converted to the hydrochloride salt by the addition of 2-propanolic hydrogen chloride to its benzene solution.

Reaction of 1-phenyl-5-methyltetrazole with 1-(1'-

(3) All melting points are uncorrected.

(4) Mannich and Lesser, *Ber.*, **65**, 378 (1932).

(5) Harvill, Herbst, Schreiner, and Roberts, *J. Org. Chem.*, **15**, 662 (1950).

(6) Mannich and Heilner, *Ber.*, **55**, 356 (1922).

piperidyl)-3-butanone[7] under similar conditions gave 1-(1'-phenyl-5'-tetrazolyl)-2-methyl-4-(1'-piperidyl)-2-butanol (XI) in comparable yield. In this case, however, the hydrochloride salt was hygroscopic and the product was therefore purified as the free base by recrystallization from petroleum ether.

In a similar experiment 1-phenyl-5-methyltetrazole reacted with β-dimethylaminopropiophenone to yield a viscous, oily base which could not be induced to crystallize or form crystalline salts with the usual mineral or organic acids. However on standing overnight with an excess of methyl iodide in ether solution, 1-(1'-phenyl-5'-tetrazolyl)-2-phenyl-4-dimethylamino-2-butanol methiodide (X) was isolated.

PREPARATION OF TETRAZOLE-SUBSTITUTED ALKENYLAMINES

1-Phenyl-1-(1'-methyl-5'-tetrazolyl)-3,3-dimethyl-4-(1'-piperidyl)-1-butene (VIII). To a suspension of 12.0 g. (0.035 mole) of 1-phenyl-1-(1'-methyl-5'-tetrazolyl)-3,3-dimethyl-4-(1'-piperidyl)-2-butanol (VII) in 100 ml. of pyridine a solution of 50 ml. of phosphorus oxychloride in 50 ml. of dry pyridine was added dropwise with cooling as required to maintain the reaction temperature below 25°. The resulting clear solution was warmed on a steam-bath for one hour, cooled, and then was decomposed by its gradual addition to 1 liter of ice water. The aqueous solution was made strongly alkaline and the crude product was removed by filtration, washed well with water, and recrystallized.

An identical experiment with 1-(1'-phenyl-5'-tetrazolyl)-3,3-dimethyl-4-(1'-piperidyl)-2-butanol (XII) gave 1-(1'-phenyl-5'-tetrazolyl)-3,3-dimethyl-4-(1'-piperidyl)-1-butene (XIII). The crude base was an oil which was most easily isolated and purified as the hydrochloride salt.

Similarly, 1-phenyl-1-(1'-methyl-5'-tetrazolyl)-3,3-dimethyl-4-diethylamino-2-butanol (V) gave 1-phenyl-1-(1'-methyl-5'-tetrazolyl)-3,3-dimethyl-4-diethylamino-1-butene (VI) under the same reaction conditions. In this case the crude oily base could not be induced to form crystalline salts with the usual mineral or organic acids and was purified by distillation.

ALKYLATION OF LITHIOTETRAZOLES WITH DIALKYLAMINOALKYL CHLORIDES

1-Phenyl-1-(1'-methyl-5'-tetrazolyl)-3-diethylaminopropane (II). The lithio derivative of 1-methyl-5-benzyltetrazole, prepared from 28.2 g. (0.18 mole) of bromobenzene, 2.5 g. (0.36 g.-atom) of lithium wire, and 26.2 g. (0.15 mole) of the tetrazole in 675 ml. of dry ether in the manner previously described was treated by the dropwise addition of a solution of 17.5 g. (0.13 mole) of freshly distilled diethylaminoethyl chloride in 50 ml. of anhydrous ether. The reaction mixture was refluxed for three hours, cooled, and treated with 75 ml. of water to destroy any unreacted lithiotetrazole. After addition of 200 ml. of 6 *N* hydrochloric acid, the aqueous phase was separated and made strongly alkaline. The crude oily base was extracted into ether, dried, and converted to the hydrochloride salt with 2-propanolic hydrogen chloride.

On standing overnight in ether solution with an excess of methyl iodide, the crude base also yielded the quaternary salt, 1-phenyl-1-(1'-methyl-5'-tetrazolyl)-3-diethylaminopropane methiodide (III).

Similar reactions of 1-methyl-5-α-lithiobenzyltetrazole with dimethylaminoethyl chloride and β-(1-piperidyl)ethyl chloride gave 1-phenyl-1-(1'-methyl-5'-tetrazolyl)-3-dimethylaminopropane (I) and 1-phenyl-1-(1'-methyl-5'-tetrazolyl)-3-(1'-piperidyl)propane (IV) respectively. Both of the compounds were isolated as their hydrochloride salts.

REACTION OF 1-PHENYL-5-LITHIOMETHYLTETRAZOLE WITH ACETONITRILE

1-Phenyl-5-acetonyltetrazole (XIV). To the lithio derivative of 1-phenyl-5-methyltetrazole, prepared in the usual manner from 69.0 g. (0.44 mole) of bromobenzene, 6.2 g. (0.88 g.-atom) of lithium wire, and 64.0 g. (0.40 mole) of the tetrazole in 1800 ml. of a 2:1 solution of anhydrous ether and benzene, 16.4 g. (0.4 mole) of acetonitrile in 25 ml. of anhydrous ether was added dropwise at room temperature and the resulting mixture was refluxed for two hours. The chilled reaction mixture was hydrolyzed by the addition of 200 ml. of water, made strongly acidic with 200 ml. of 6 *M* sulfuric acid, and warmed to reflux for two hours to insure complete hydrolysis of the ketimine. After cooling, the organic layer was separated, washed with a saturated solution of sodium chloride until the washings became neutral, and dried over sodium sulfate. The solid residue remaining after removal of the ether and benzene was heated to 90° for 30 minutes with a solution of 100 g. of sodium bisulfite in 500 ml. of water. After chilling, 25 g. of unreacted 1-phenyl-5-methyltetrazole was removed by filtration. The filtrate was acidified with 175 ml. of concentrated hydrochloric acid, refluxed for 1.5 hours, and chilled. The crude product (29.5 g.) was removed by filtration, air-dried, and recrystallized from a mixture of chloroform and petroleum ether. Yield, 23.5 g. or 29%, m.p. 103–104.5°.

The *semicarbazone* of 1-phenyl-5-acetonyltetrazole crystallized from methanol as fine needles, m.p. 175–176.5°.

Anal. Calc'd for $C_{11}H_{13}N_7O$: C, 50.95; H, 5.05; N, 37.82. Found: C, 51.04, 51.17; H, 4.98, 5.16; N, 37.80, 37.80.

1-(1'-Phenyl-5'-tetrazolyl)-2-methylaminopropane hydrochloride (XV). To a solution containing 20.2 g. (0.1 mole) of 1-phenyl-5-acetonyltetrazole (XIV), 40 ml. of 40% aqueous methylamine, and 200 ml. of 87% 2-propanol, was added 8.5 g. (0.3 g.-atom) of aluminum shot (activated with 40 ml. of a hot, saturated solution of mercuric chloride in 87% 2-propanol just prior to reaction) followed by 70 ml. of warm 33% aqueous 2-propanol. Sufficient external heat was supplied to maintain an internal temperature of 60–70° for 18 hours. The cooled reaction mixture was filtered, the filtrate was acidified with hydrochloric acid, and the 2-propanol was removed from the filtrate by atmospheric distillation. Unreacted ketone (8.5 g.) was removed from the cooled residue by filtration. The aqueous filtrate was made strongly alkaline and crude oily base was extracted into chloroform and dried. The residue from the chloroform extracts was dissolved in ether and converted to the hydrochloride salt by the addition of a 2-propanolic solution of hydrogen chloride. After two recrystallizations from 2-butanone there was obtained 9.0 g. (36%) of pure hydrochloride, m.p. 130–132.5°.

Pharmacology. All compounds in Table I were subjected to routine pharmacological screening with the exception of nos. IV, VIII, and XII. None produced significant effects on the blood pressure of the anesthetized dog when administered intravenously at a dose level of 10 mg./kg., other than a transient drop in pressure at the time of injection. Neither did they exert any influence on the typical responses to test doses of epinephrine, acetylcholine, or histamine under the same experimental conditions. In the isolated rabbit heart, concentrations of 1:1000 produced no significant effects. In general the amplitude of the contraction was decreased with little or no change in heart rate and no change to a slight decrease in coronary flow. Most of the compounds had no effect on the motility of the isolated guinea pig gut at a dilution of 1:50,000, except for nos. I, II, and X which were slightly stimulatory at this concentration. In the rat XIV produced sedation at 800 mg./kg. intraperitoneally. Under the same conditions VII was sedative at 100 mg./kg. but lethal at 200 mg./kg. In contrast, VI produced violent convulsions at 100 mg./kg. and was lethal at 200 mg./kg. A dose of 100 mg./kg. did not arouse nembutalized rats.

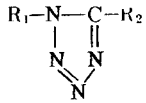
It should be pointed out that VII and VIII are related to 1,1-diphenyl-3,3-dimethyl-4-(1-piperidyl)butanol-1 and 1,1-diphenyl-3, 3-dimethyl-4-(1-piperidyl)butene-1 respectively, differing only in that a 1-methyl-5-tetrazolyl radical has replaced a phenyl group. Katz, *et al.*[8] have reported that

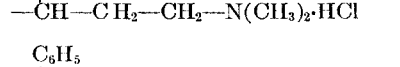
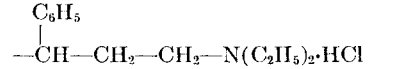
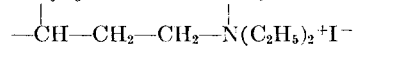
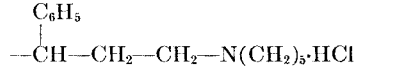
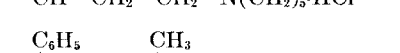
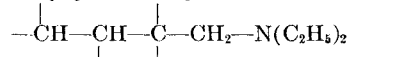
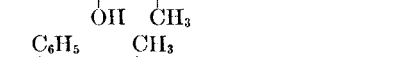
(7) Mannich and Hof, *Arch. Pharm.*, **265**, 589 (1927).

(8) Katz, Karger, and Cohen, *J. Org. Chem.*, **19**, 1225 (1954).

TABLE I

TETRAZOLE AMINOALKANES, AMINOALKENES, AND AMINOALKANOLS



No.	R_1	R_2	Yield, %	M.P., °C.	Recrystallization Solvent	Analyses Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found	Nitrogen Calc'd	Nitrogen Found
I	CH_3		34	209–211	Methanol-2-propanol	55.40	55.45 55.30	7.15	7.04 7.00	24.86	24.78 24.90
II	CH_3		48	151–153	2-Butanone	58.14	58.20 58.35	7.81	7.83 7.78	22.61	22.40 22.35
III	CH_3		28	144–146	2-Butanone	46.26	46.30 46.25	6.31	6.29 6.18	16.87	16.80 16.65
IV	CH_3		29	183–185	2-Propanol-ether	59.70	59.55 59.45	7.52	7.70 7.69	21.76	21.55 21.65
V	CH_3		41	95–97	Ligroin	65.22	65.20 65.25	8.82	8.55 8.54	21.13	20.75 20.85
VI	CH_3		67	182–185[a] 0.75 mm.	—	68.97	68.70 68.90	8.68	8.47 8.50	22.35	22.35 22.45
VII	CH_3		53	150–152	2-Propanol	66.44	66.50 66.40	8.51	8.56 8.68	20.39	20.35 20.50
VIII	CH_3		59	81–82	Aqueous methanol	70.11	70.40 70.25	8.36	8.35 8.40	21.52	21.60 21.70
IX	CH_3		23	204–205.5	Methanol-2-propanol	61.92	62.20 62.30	6.76	6.85 6.90	18.06	18.08 18.10

X	C_6H_5	$-CH_2-\underset{\underset{OH}{|}}{\overset{\overset{C_6H_5}{|}}{C}}-CH_2-CH_2-N(CH_3)_3^+I^-$	17	181–182.5	Methanol-2-propanol	50.11	50.40 50.30	5.47	5.41 5.48	14.61	14.65 14.65
XI	C_6H_5	$-CH_2-\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_2-CH_2-N(CH_2)_5$	27	88–90	Ligroin	64.73	64.70 64.85	7.98	8.14 8.05	22.21	22.00 22.15
XII	C_6H_5	$-CH_2-\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{\overset{\overset{OH}{|}}{C}}}}-CH_2-N(CH_2)_5$	26	83–85	Ligroin	65.62	65.70 65.80	8.26	8.25 8.25	21.26	21.25 21.20
XIII	C_6H_5	$-CH=CH-\underset{\underset{CH_3}{|}}{\overset{\overset{H}{|}}{\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}}}-CH_2-N(CH_2)_5\cdot HCl$	54	191–194	Methanol-ether	62.14	62.20 62.30	7.53	7.50 7.58	20.14	20.03 20.10
XIV	C_6H_5	$-CH_2-\underset{\underset{CH_3}{	}}{\overset{\overset{O}{|}}{C}}-CH_3$	29	103–104.5	Chloroform-Petr. ether	59.39	59.40 59.50	4.98	4.85 4.84	27.71	27.55 27.60
XV	C_6H_5	$-CH_2-\underset{\underset{NHCH_2\cdot HCl}{|}}{\overset{\overset{CH_3}{|}}{CH}}-CH_3$	36	130–132.5	2-Butanone	52.06	52.05 52.15	6.36	6.38 6.40	27.61	27.65 27.50

[a] Boiling Point.

these latter compounds are active antispasmodics, comparable to Trasentine and to Artane. Similarly, I differs from the γ-phenyl-γ-(2-pyridyl)-N,N-dimethylpropylamine (Trimeton), a known histamine antagonist,[9] in that the 2-pyridyl has been replaced by the 1-methyl-5-tetrazolyl radical. The absence of activity in these tetrazole relatives of compounds with known physiological properties points up the difficulty in predicting the physiological effects of tetrazole compounds on the basis of analogy to other structures of known activity.

Acknowledgment. The authors are indebted to Drs. Erwin G. Gross and Hugh H. Keasling of the State University of Iowa for the pharmacologic data included here.

ORANGE, NEW JERSEY

(9) Sperber, Papa, Schwenk, Sherlock, and Fricano, *J. Am. Chem. Soc.*, **73**, 5752 (1951).