Equilibrium Protonation Studies.—A wholly aqueous solution of 1 (0.0618 *M*, 20 μl) was placed in a clean, dry cuvette. To this was added 3.00 ml of an acid solution of the desired strength previously equilibrated at 25.3°. The contents of the cuvette were thoroughly mixed by several rapid inversions and placed in the thermostated cell compartment of the Cary 16 spectrophotometer. The absorbance was monitored as a function of time and the initial absorbance obtained by a back extrapolation to the time of mixing. Acid concentrations were determined by mixing carefully weighed amounts of standardized acid and distilled water.

Registry No.—**1**, 1073-14-9; **2**, 6611-78-5.

Acknowledgment.—The author wishes to acknowledge with gratitude the hospitality shown him by the Department of Chemistry, University of Kansas, during his tenure as a Visiting Instructor for the academic year, 1968–1969. Special thanks are also due Professor R. L. Schowen for many helpful and stimulating discussions throughout the course of this work. Thanks are also due Professor J. Swenton for experimental details for the synthesis of **1**.

Alkylation of 5-Substituted Tetrazoles with α-Chlorocarbonyl Compounds

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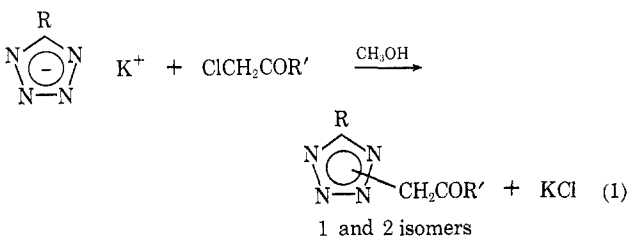
Received February 11, 1969

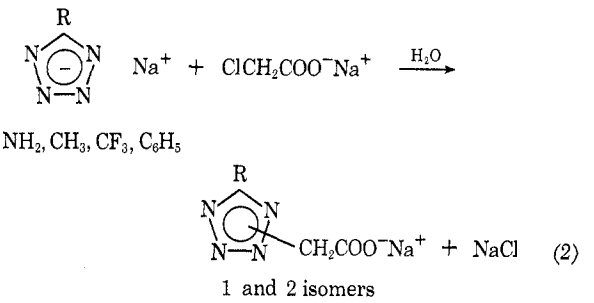
As part of a study on the preparation of polyfunctional tetrazoles, we have alkylated 5-substituted tetrazoles with α-chlorocarbonyl compounds to prepare 1- and 2-carbonyl substituted isomers. Substitutions of 5-substituted tetrazoles with α-haloacetates and triethylamine in acetone have recently been reported.[1] 5-Substituted 1-carboalkoxymethyltetrazoles were previously prepared by an indirect method involving ring closure to form the tetrazole ring.[2] The alkylation of tetrazoles with alkyl halides, dialkyl sulfates, and diazomethane also has been reported.[3] Our work[4] has included several chlorocarbonyl compounds other than chloroacetate, and the reactions were conducted in methanolic potassium hydroxide except that with chloroacetic acid, the reactions also were carried out in aqueous sodium hydroxide. The substitution reactions in methanolic potassium hydroxide (eq 1) and in aqueous sodium hydroxide (eq 2) were as follows.



1 and 2 isomers

(1)

R = NH_2; R′ = OH, OCH_3, OC_2H_5, CH_3, C_6H_5, NH_2 and
R = CH_3, CF_3, C_6H_5, *p*-$NO_2C_6H_5$; R′ = OCH_3



1 and 2 isomers

(2)

The reaction of potassium 5-aminotetrazolate with α-chlorocarbonyl compounds (eq 1) in methyl alcohol gave mostly 1-substituted products and minor products substituted in the 2 position. The yield of 2-substituted isomer varied from 0 to *ca.* 21% (Table I). The chlorocarbonyl compounds evidently exerted some influence in directing substitution on the tetrazole ring in addition to the strong inductive effect of the 5-substituent group. Substitution on the 1- and 2-ring positions of different tetrazoles with chloroacetate in methyl alcohol or chloroacetic acid in water clearly demonstrated the inductive effect of the 5 substituents. Electron-donating groups favored 1 substitution and electron-withdrawing groups favored 2 substitution. This inductive effect also was demonstrated in the work reported by Raap[1] and in prior work[3] on the alkylation of 5-substituted tetrazoles. In the reactions with chlorocarbonyl compounds in methanolic potassium hydroxide or in aqueous sodium hydroxide, neutralization of the strong base by formation of the salts of the tetrazoles and of chloroacetic acid prevented hydrolysis of the chlorocarbonyl compounds. With chloroacetic acid 2 mol of base per mol of tetrazole were required to give an appreciable yield of substitution product. Apparently, substitution on the ring occurred only in reaction with the tetrazolate anion which formed after all or most of the chloroacetic acid was converted to salt. Decreased yields were obtained with excess base owing to hydrolytic reaction with chloroacetic acid or ester.

The 1- and 2-carbomethoxymethyl-5-aminotetrazole isomers were readily acetylated with acetic anhydride to stable diacetyl derivatives (Table I). The acetylated 2-substituted isomer could be distilled at low pressure at 180–190° without decomposition. 1-Acetonyl-5-aminotetrazole also was acetylated to a diacetyl derivative, but it was hydrolyzed rapidly in boiling water to monoacetyl derivative.

The strong acidity (see Table II) of 1- and 2-carboxymethyl-5-aminotetrazole and of 2-carboxymethyl-5-trifluoromethyltetrazole manifests the strong electron-withdrawing effect of the tetrazole ring.[5] Rapid hydrolysis of the tetrazolyl acetate esters in cold aqueous alkali also demonstrated the same electron-withdrawing effect. This is in accord with the known fact that strong electron-withdrawing groups substituted in the α position of acetates greatly accelerate hydrolysis.[5] The 5-substituent group apparently has only a weak

(1) R. Raap and J. Howard, *Can. J. Chem.*, **47**, 813 (1969).
(2) C. R. Jacobson and E. D. Amstutz, *J. Org. Chem.*, **21**, 311 (1956).
(3) Robert C. Elderfield, "Heterocyclic Compounds," Vol. 8, Frederick R. Benson, Ed., Wiley, New York, N. Y., 1961, Chapter 1. Section on alkylation of tetrazoles and references there.
(4) F. Einberg, Abstracts, 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969, p ORGN, 173.
(5) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehard and Winston, New York, N. Y., 1959.

TABLE I
CARBONYL SUBSTITUTED TETRAZOLES

Substituted[a] tetrazole	Registry no.	Yield,[b] %	Mp or bp (mm), °C	Recrystallization solvent	—Nmr, chemical shifts, δ (ppm)— Solvent	NH_2	CH_2
1-CH_2COOH-5-NH_2	21743-62-4[c]	53.1	212–213 dec	Water	$(CD_3)_2S{=}O$	6.78	5.04
2-CH_2COOH-5-NH_2	21743-72-6		211–212 dec	Water	$(CD_3)_2S{=}O$	5.97	5.28
1-CH_2COOCH_3-5-NH_2	21744-59-2	43	185–186 dec	Alcohol	$(CD_3)_2S{=}O$	6.82	5.17
2-CH_2COOCH_3-5-NH_2	25828-03-9	14	133–134	Benzene	$(CH_3)_2S{=}O$[d]	6.01	5.43
1-$CH_2COOC_2H_5$-5-NH_2	21744-57-0	50	147–148	Alcohol			
2-$CH_2COOC_2H_5$-NH_2	21744-50-3	21	106–107	Benzene			
1-CH_2COCH_3-5-NH_2	25828-06-2	53	204.5–205.5 dec	Alcohol	$(CD_3)_2S{=}O$	6.70	5.21
2-CH_2COCH_3-5-NH_2	25876-96-4	14	105.0–105.5	Benzene	$(CH_3)_2S{=}O$[e]	5.96	5.50
1-$CH_2COC_6H_5$-5-NH_2	25828-07-3	49	214.0–214.5 dec	Alcohol			
2-$CH_2COC_6H_5$-5-NH_2	25876-97-5	7	124–125.0	Benzene			
1-CH_2CONH_2-5-NH_2	25828-08-4	84	208.0–208.5 dec	Water			
1-CH_2COOCH_3-5-$N(COCH_3)_2$	25828-09-5		137.5–138.5	Alcohol	$CDCl_3$		5.10
2-CH_2COOCH_3-5-$N(COCH_3)_2$	25828-10-8		71–73, 180 (0.1)	Alcohol			
1-CH_2COCH_3-5-$NHCOCH_3$	25828-11-9		114.0–114.5	Alcohol			
1-CH_2COOCH_3-5-CH_3	25828-12-0	48	67–68	Benzene	$CDCl_3$		5.03
2-CH_2COOCH_3-5-CH_3	25828-28-8	33	70–71 (0.8)		CCl_4		5.30
2-CH_2COOCH_3-5-CF_3	25876-98-6	11.5	55–56 (0.1)		CCl_4		5.52
2-$CH_2COOC_2H_5$-5-CF_3	25876-99-7	25.4	68–69 (0.6)				
2-CH_2COOCH_3-5-C_6H_5	25828-29-9	60[b]	93–94, 130 (0.1)		CCl_4		5.38
2-CH_2COOCH_3-5-*p*-$NO_2C_6H_5$	25828-30-2	92	136.5–137.5	Alcohol	$CHCl_3$		5.54

[a] Satisfactory analytical values (±0.35 for C, H, and N) were reported for all compounds except for 1-$CH_2CO_2C_2H_5$-5-NH_2 tetrazole (Calcd: H, 5.26. Found: 5.79.) and 2-$CH_2CO_2C_2H_5$-5-NH_2 (Calcd: H, 5.26. Found: 6.02.): Ed. [b] From reaction of chlorocarbonyl compounds with potassium tetrazolate in methanol. [c] Pyridine salt, registry no. 25828-00-6. [d] In $(CD_3)_2C{=}O$, overlap of amino and methylene protons at 5.37. In CF_3COOH, NH_2, 5.65, CH_2, 5.53. [e] In $(CD_3)C{=}O$, overlap of amino and methylene protons at 5.47. In CF_3COOH, NH_2, 5.77, CH_2, 5.68.

TABLE II
CARBOXYMETHYL SUBSTITUTED TETRAZOLES

Substituted tetrazole	Yield,[a] %	Mp, °C	Recrystallization solvent	pK_a[c]
1-CH_2COOH-5-NH_2	53.1	212–213 dec (lit.[1] 202–203 dec)	Water	2.7
2-CH_2COOH-5-NH_2	23.8	211–212 dec (lit.[1] 185–186 dec)	Water	2.6
1-CH_2COOH-5-CH_3	32.5	193–194 dec (lit.[1] 184–186 dec)	Water	
2-CH_2COOH-5-CH_3	18.3	153–155 dec (lit.[1] 155–156 dec)	Acetonitrile	
1-CH_2COOH-5-C_6H_5	18.6	146–148 dec (lit.[1] 148–150 dec)	Acetonitrile	
2-CH_2COOH-5-C_6H_5	56.9	186–187 dec[b] (lit.[1] 182–184 dec)	Water	
2-CH_2COOH-5-CF_3	65.3	Oil, did not distil at 150° (0.15 mm), began to decompose		2.5

[a] From reaction with chloroacetic acid and aqueous sodium hydroxide. [b] Melting point sample from hydrolysis of methyl ester. Note reversal of usual lower melting point for 2 isomer. [c] Determined from pH at half-neutralization.

effect on the electron-withdrawing capacity of the tetrazole ring since a strong electron donor and a strong electron-withdrawing group produce only a small difference in the acid strength of the substituted acetic acids (Table II).

1 and 2 ring substitution of 5-aminotetrazole with methyl and ethyl chloroacetate and chloroacetone was established based on their diacetylation, neutrality, and infrared and nmr spectra. However, assignment of the 1- and 2-substituted structures to the isomers was based on the known greater solubility of the 1-substituted isomers in polar solvents and of the 2-substituted isomers in nonpolar solvents and of the higher melting points of the 1-substituted isomers compared with the 2-substituted isomers.

There was a significant difference in nmr chemical shift for the amino and methylene protons of the 1- and 2-acetate and acetonyl-substituted 5-aminotetrazole isomers, Table I ($\Delta\delta$ for amino protons, 0.7–0.8 ppm, and for methylene protons, 0.26–0.31 ppm). This difference in chemical shift has been shown previously for tetrazolyl acetates[1] and acetic acids and also has been shown for alkyl 1- and 2-substituted isomers.[6,7] The chemical shifts for the methylene protons of different 5-substituted tetrazolyl methyl acetates also showed a similar increase in δ vs. for 2 vs. 1 substitution (Table I). The highly electronegative trifluoromethyl and *p*-nitrophenyl groups in the 5 position apparently decrease the electronic shielding of the acetate methylene protons by exerting an electron-withdrawing effect through the tetrazole ring (Table I). This is indicated by the smaller δ values for methylene absorptions with amino, methyl, and phenyl compared with trifluoromethyl and *p*-nitrophenyl groups in the 5 position.

Experimental Section

The chlorocarbonyl compounds were the purest commercially available grade and were used as received. 5-Aminotetrazole monohydrate obtained commercially was dehydrated at 90–100° for about 24 hr in a vacuum oven evacuated with a vacuum pump. Other reagents were the purest commercially available grade. Infrared spectra were obtained in Nujol mulls with a Perkin-Elmer Model 21 instrument. Nmr spectra were obtained at the Temple University Chemistry Department and at the Sadtler Research Laboratories, Inc., with Varian A-60

(6) J. H. Markgraf, W. T. Backmann, and D. P. Hollis, *J. Org. Chem.*, **30**, 3472 (1965).
(7) F. L. Scott, R. N. Butler, and S. Feeney, *J. Chem. Soc.*, **8**, 919 (1967).

instruments using tetramethylsilane as internal reference. Melting points were uncorrected and were obtained with a Hoover–Thomas capillary melting point apparatus. Analyses were done at this laboratory and at the Schwarzkopf Microanalytical Laboratory.

5-Methyltetrazole,[8] 5-trifluoromethyltetrazole,[8] and 5-phenyltetrazole[9] were prepared according to the methods described in the literature.

General Procedure for the Reaction of Chlorocarbonyl Compounds with Potassium Tetrazolate in Methanol (Products Listed in Table I).—The 5-substituted tetrazole (1 mol) was added to a solution of potassium hydroxide (1 mol) in methanol, followed by the addition of chlorocarbonyl compound (1 mol). With chloroacetic acid, 2 mol of potassium hydroxide was used (see procedure below for reaction with 5-aminotetrazole). The mixture was refluxed 18–24 hr, cooled in a refrigerator several hours or overnight, and the crystalline precipitate of crude 1-substituted isomer was collected on a filter, extracted with benzene and recrystallized. The methanolic filtrate was evaporated to dryness and the solid residue was extracted with benzene. The benzene solutions were combined and evaporated to dryness, and the crude 2-substituted isomer was recrystallized.

General Procedure for the Reaction of Chloroacetic Acid with Sodium Tetrazolate in Water (Products Listed in Table II).—The 5-substituted tetrazole (1 mol) dissolved in an aqueous solution of sodium hydroxide (2 mol) and chloroacetic acid (1 mol) was refluxed 18–24 hr. The mixture was cooled and made strongly acidic with concentrated hydrochloric acid (pH less than 2). The precipitate which formed was collected and recrystallized. The filtrate or the acidified reaction mixture was evaporated to dryness and the residue was extracted with solvent used for recrystallization. The residual sodium chloride was discarded and the extracted solid was recrystallized. Typical preparations are described below.

1- and 2-Carboxymethyl-5-aminotetrazole (I and II). Method 1.—Chloroacetic acid (47.3 g, 0.5 mol), 5-aminotetrazole (42.5 g, 0.5 mol), and potassium hydroxide (56.2 g, 1.0 mol) in 1 l of methyl alcohol was refluxed 24 hr, cooled to room temperature, and filtered. The collected solid (74.8 g) was dissolved in water (200 ml) and the pH of the solution (~6) was reduced to less than 2 with concentrated hydrochloric acid (30 ml). The mixture was cooled overnight in a refrigerator and filtered to give 37.9 g of I, 53.0% yield, mp 209–210° dec. The presence of II in the residue from the water filtrate was indicated by its ir spectrum. However, it could not be readily purified. Using a mole ratio of 2:1:3, respectively, and the same procedure, a 52.9% yield of I based on the moles of 5-aminotetrazole, but no disubstituted product was obtained. Using a 1:1:1 mol ratio, no substitution product was obtained. After twice recrystallizing I from water, the melting point was 209–210° dec.

Method 2.—Chloroacetic acid (9.4 g, 0.1 mol), 5-aminotetrazole monohydrate (10.3 g, 0.1 mol), and sodium hydroxide (8.0 g, 0.2 mol) in 100 ml of water was refluxed 20 hr, cooled, and made strongly acidic with concentrated hydrochloric acid. The mixture was cooled overnight and filtered to give 7.6 g of I, 53.1% yield, mp 212–213° dec (high purity without recrystallization). The filtrate was evaporated to a low volume and 3.4 g of solid, 23.8% yield, mp 203–205° dec, was collected on a filter. The ir spectrum of the solid showed it to be mostly II.

Pyridine Salt of I.—I was dissolved in hot pyridine and the pyridine salt came out of the cooled solution. Recrystallization from pyridine gave a crystalline solid: mp 185–186° dec; ir 3460, 3300 (NH), 1640, 1610 (C=O), 1550 (C=N), 1087, 1013 cm^{-1} (ring).

Anal. Calcd for $C_8H_{10}N_6O_2$: C, 43.24; H, 4.50; N, 37.84. Found: C, 42.93; H, 4.37; N, 37.61.

1- and 2-Carbomethoxymethyl-5-aminotetrazole (III and IV).—Methyl chloroacetate (54.2 g, 0.5 mol), 5-aminotetrazole and potassium hydroxide (28.0 g, 0.5 mol) in 500 ml of anhydrous methyl alcohol was refluxed 24 hr with stirring. The methyl alcohol was removed under reduced pressure and the dry solid was extracted in a Soxhlet extractor for 24 hr with benzene. The solid insoluble in benzene was extracted with alcohol and the alcohol filtrate was evaporated to dryness yielding 33.7 g, 42.9% of III, mp 177–178° dec. After further extraction for 24 hr in a Soxhlet extractor with benzene and crystallization from alcohol gave mp 185–186° dec: ir 3300, 3120 (NH), 1740 (C=O), 1668, 1640, 1590, 1495 (C=N), 1010 cm^{-1} (ring).

Evaporation of the benzene solution yielded 10.9 g, 13.9% of IV, mp 128–130°. After recrystallization from benzene the melting point was 132–133°: ir 3450, 3320, 3230, 3170 (NH), 1740 (C=O), 1650, 1627 (C=N), 1087, 1015 cm^{-1} (ring).

Hydrolysis of III and IV.—Compounds III and IV were refluxed 2 and 1.5 hr, respectively, in excess 5% sodium hydroxide and the solutions made strongly acidic with hydrochloric acid. After recrystallization of I (hydrolyzed III) from water the melting point was 212–213° dec. After recrystallization of hydrolyzed IV from water, the melting point was 211–212° dec: neut equiv (I) (calcd 143.0); neut equiv 142.5, 142.2, (II) 143.5; ir (I) 3380, 3330, 3260, 3200 (NH), 1700 (C=O), 1645, 1598 (C=N), 1090, 1053 cm^{-1} (ring); ir (II) 3460, 3340 (NH), 1730 (C=O), 1645 (C=N), 1023 cm^{-1} (ring).

1- and 2-Carbomethoxymethyl-5-*N*,*N*-diacetylaminotetrazole (V and VI).—Compound III (3.14 g, 0.02 mol) and 50 ml of acetic anhydride was refluxed 1.5 hr. The acetic anhydride then was removed on a rotating film evaporator and a light tan solid slurried and washed with ether was collected on a filter. The solid was treated with decolorizing carbon and crystallized from alcohol to give 2.3 g of shiny, white crystals, V: mp 137.5–138.5°; ir (V) 1770, 1755, 1735 (C=O), 1540 (C=N), 1042, 1031, 1005 cm^{-1} (ring).

Compound IV was acetylated as above, the acetic anhydride removed, and the residue dissolved in a minimum of hot benzene. The solution was cooled and unreacted IV was collected on a filter. The benzene was evaporated and the liquid residue was distilled in a short-path distillation apparatus at approximately 180° and 0.1 mm pressure. The distillate was a crystalline solid: mp 71–73°; ir (VI) 1760, 1740, 1725 (C=O), 1510 (C=N), 1040, 1020 cm^{-1} (ring).

1- and 2-Acetonyl-5-aminotetrazole (VII and VIII).—Chloropropanone (18.5 g, 0.2 mol), anhydrous 5-aminotetrazole (17.0 g, 0.2 mol), and potassium hydroxide (11.2 g, 0.2 mol) in 200 ml of methyl alcohol was refluxed 24 hr with stirring. The mixture then was allowed to stand overnight at room temperature and filtered. The solid, 15.0 g, 53.2% yield of VII, mp 204.5–205.5° dec, was collected. Recrystallization from alcohol or water gave shiny, white platelets: mp 204.5–205.5° dec; ir (VII) 3300, 3150 (NH), 1725 (C=O), 1645, 1485 (C=N), 1045 cm^{-1} (ring).

The methyl alcohol filtrate from the reaction mixture was evaporated to dryness and the solid was extracted with boiling benzene. Evaporation of the benzene solution gave 4.0 g, 14.2% yield of VIII as a yellowish solid, mp 103–105°. Treatment with decolorizing carbon in boiling benzene and crystallization from benzene gave fluffy white needles: mp 105.0–105.5°; ir (VIII) 3430, 3320 (NH), 1725 (C=O), 1630, 1550 (C=N), 1085, 1040, 1010 cm^{-1} (ring).

1-Acetonyl-5-*N*-acetylaminotetrazole (IX).—1-acetonyl-5-aminotetrazole (2.8 g, 0.02 mol) and 50 ml of acetic anhydride was refluxed 1 hr. The mixture turned a dark reddish-amber color. The acetic anhydride was evaporated under reduced pressure and a crystalline solid was collected on a filter and washed with hot alcohol. The solid (1.5 g) had mp 208–209° dec. A small portion rapidly recrystallized from hot water melted at 210.0–210.5° dec. The remaining solid was dissolved in boiling water from which it did not crystallize even on evaporation to a low volume. The water then was completely evaporated and the solid was crystallized from alcohol. The solid, 0.6 g, mp 114.0–114.5°, was analyzed for monoacetylated 1-acetonyl-5-aminotetrazole (X): ir (X) 3340, 3230 (NH), 1725 (C=O), 1603, 1550 (C=N), 1045, 1015 cm^{-1} (ring).

Apparently, the initial product isolated was diacetylated and hydrolyzed rapidly in boiling water to monoacetylated product.

Acknowledgment.—The author wishes to express his appreciation for initial samples of 5-methyltetrazole, sodium-5-trifluoromethyltetrazole, and *p*-nitrophenyltetrazole kindly furnished by Dr. R. A. Henry. He also wishes to thank Dr. Charles W. Jefford, formerly of the Temple University Chemistry Department, and Mr. William Peterson of this laboratory for assistance in obtaining nmr spectra.

(8) W. P. Norris, *J. Org. Chem.*, **27**, 3248 (1962).

(9) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Amer. Chem. Soc.*, **80**, 3908 (1958).