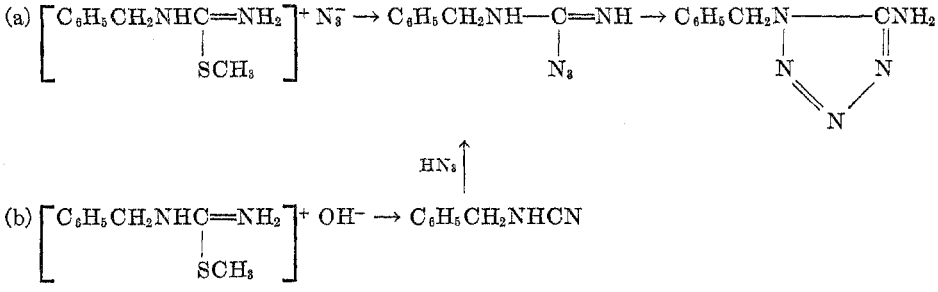
[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

THE SYNTHESIS OF CERTAIN 5-AMINOTETRAZOLE DERIVATIVES. III. THE SYNTHESIS OF 5-MONOALKYLAMINOTETRAZOLES[1]

WILLIAM L. GARBRECHT[2,3] AND ROBERT M. HERBST

Received February 27, 1953

When the action of hydrazoic acid on monoalkylcyanamides failed to give 5-alkylaminotetrazoles (1), it became necessary to consider other, less direct, methods for the preparation of these compounds. Since thiouronium salts are known to react with a variety of nitrogen compounds with replacement of the thioalkyl group by an amino or a substituted amino group, it was thought that they might react with sodium azide in a similar manner. The interaction of S-methyl-N-benzyl-, and S-methyl-N-methyl-thiouronium iodide with sodium azide in alcoholic solution gave low yields of 1-benzyl-, and 1-methyl-5-aminotetrazole, respectively. The reaction could follow several courses including (a) interaction of the thiouronium ion and the azide ion to form an alkylguanyl azide and methyl mercaptan followed by cyclization to the tetrazole and (b) the initial hydrolysis of the thiouronium salt to form an alkylcyanamide which could then undergo addition of hydrazoic acid to form an alkylguanyl azide and cyclization of the latter to the tetrazole.



Scheme (b) bears a close resemblance to the reactions suggested by Stollé (2) for the formation of 5-aminotetrazoles upon treatment of N-substituted thioureas with sodium azide in the presence of lead oxide or carbonate in a carbon dioxide atmosphere. Stollé had postulated a carbodiimide as the intermediate in this reaction, but when applied to monosubstituted thioureas the intermediate could equally well be written as the tautomeric monoalkylcyanamide.

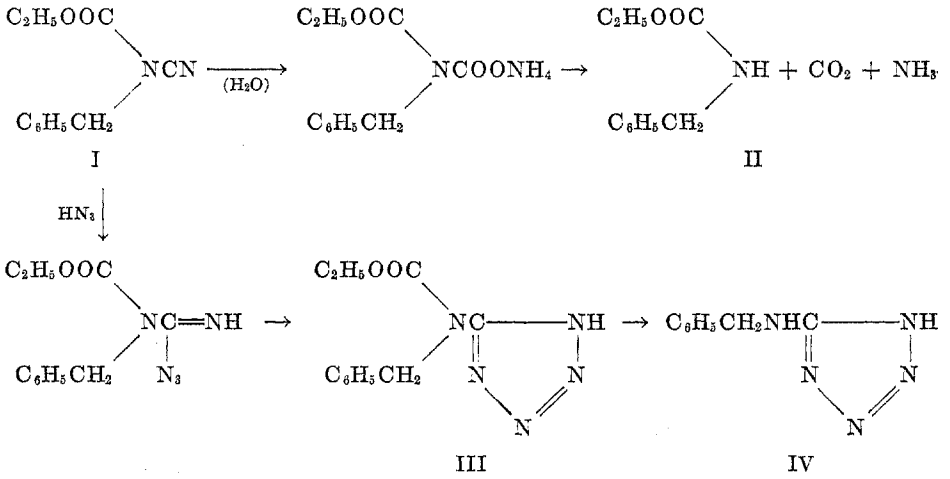
Since this procedure was not as advantageous for the preparation of 1-alkyl-5-aminotetrazoles as the direct action of hydrazoic acid on monoalkylcyanamides (1), its study was not pursued.

[1] Based on a thesis submitted to the School of Graduate Studies at Michigan State College in 1952 by William L. Garbrecht in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Parke-Davis Fellow in Organic Chemistry, 1951–1952.

[3] Present address: Eli Lilly and Company, Indianapolis, Indiana.

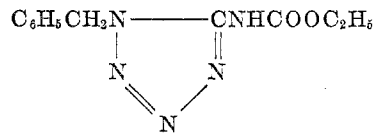
The successful formation of 5-alkylaminotetrazoles from cyanamides apparently requires a completely substituted cyanamide so that the cyclization of the intermediate guanyl azide is directed to the imino group. The immediately obvious possibility of substituting the monoalkylcyanamides with an easily removable blocking group through acylation suggested itself. However, acylation of the cyanamides proved to be largely fruitless. Generally, only acylated urea derivatives could be isolated from the reaction mixture in poor yield. The possibility of acetylating the monoalkylcyanamides with ketene in non-hydrolyzing medium could be of promise but this technique was not investigated. Only in the case of benzylcyanamide was partial success attained. Carbethoxylation gave a mixture containing the acylated cyanamide (I) and benzylurethan (II) which could not be completely separated. Since the carbethoxylation was done in an aqueous alcoholic solution in the presence of sodium carbonate, it is likely that the benzylurethan was formed by the hydrolysis of the benzylcarbethoxycyanamide. This mixture, when treated with hydrazoic acid in benzene at 100° under pressure, formed an acidic product that gave the correct elementary analysis for 5-benzylcarbethoxyaminotetrazole (III). The acidic nature of the product and the ease with which it could be hydrolyzed to 5-benzylaminotetrazole (IV) were in conformity with the structure indicated by the elementary analysis.



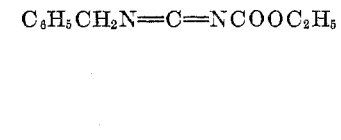
The 5-benzylaminotetrazole formed by hydrolysis of the carbethoxy derivative is soluble in dilute aqueous acid or alkali and forms an insoluble silver salt. It was characterized by analysis and by comparison with the amphoteric product obtained by benzylation of 5-aminotetrazole (3) with which it was identical in all respects.

The possibility was considered that an N-benzyl-N′-carbethoxycarbodiimide (V) might be formed during the carbethoxylation if benzyl cyanamide reacted in the tautomeric carbodiimide form. The reaction of such an intermediate with hydrazoic acid could result in the formation of either 1-benzyl-5-carbethoxy-

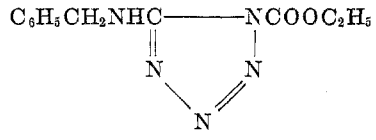
aminotetrazole (VI) or 1-carbethoxy-5-benzylaminotetrazole (VII). Compounds of the former type are acidic in character while compounds of the latter type are neutral (4). This course of the reaction was rather unlikely since the formation of VII could be excluded by the acidic nature of the product isolated. On the other hand, if the acidic 1-benzyl-5-carbethoxyaminotetrazole (VI) had been formed, hydrolysis would be expected to lead to 1-benzyl-5-aminotetrazole, a well-known compound (1) of only weakly basic character and no acidic properties. However, the hydrolysis product of the benzylcarbethoxyaminotetrazole was amphoteric and showed a marked depression of the melting point on admixture of 1-benzyl-5-aminotetrazole which excluded identity. These observations supported the conclusion that 5-benzylcarbethoxyaminotetrazole (III) was formed in the reaction with hydrazoic acid.



VI

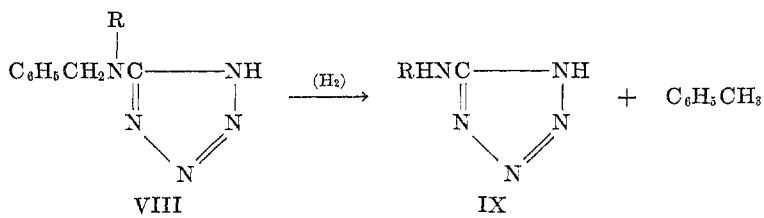


V



VII

Another possible method of obtaining the 5-monoalkylaminotetrazoles was an adaptation of the von Braun degradation of tertiary amines with cyanogen bromide (5). In this way it might be possible to eliminate an alkyl group from a 5-dialkylaminotetrazole. The method was not attempted for at this time 5-benzylmethylamino-, 5-benzylethylamino-, and 5-dibenzylamino-tetrazole (VIII) had become available (6) and their selective catalytic debenzylation (7) seemed more readily achievable. Hydrogenolysis of the benzyl group was accomplished by shaking the 5-benzylalkylaminotetrazoles in ethanol solution with 5% palladium-charcoal at about 65° under three atmospheres of hydrogen pressure. In the case of 5-dibenzylaminotetrazole stepwise debenzylation was feasible with the formation first of 5-benzylaminotetrazole and then 5-aminotetrazole. The 5-benzylaminotetrazole obtained in this way was identical with the product formed upon hydrolysis of 5-benzylcarbethoxyaminotetrazole.



VIII IX

R = CH_3, C_2H_5, $C_6H_5CH_2$

The 5-alkylaminotetrazoles (IX) were characterized through elementary analysis, formation and analysis of their silver salts, and determination of their equivalent weights and apparent dissociation constants by potentiometric titration. In most of their properties they are very similar to the 5-dialkylaminotetrazoles. Their titration curves have the form typical of weak acids (Figure 1). Discussion of the factors influencing their strength as acids and the significance of their behavior on melting will be reserved for later communications.

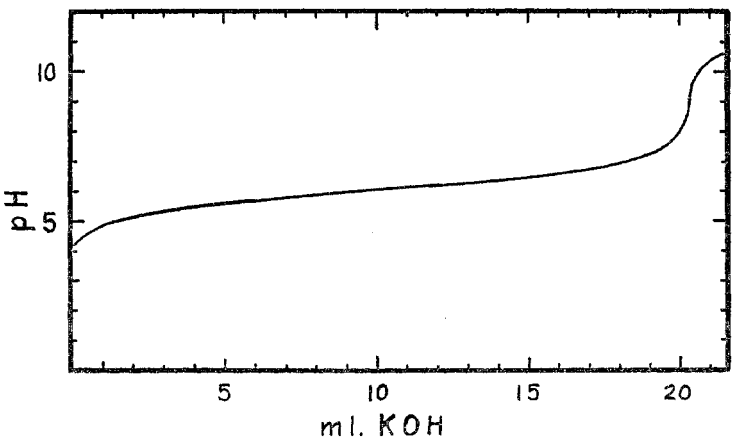


FIG. 1. POTENTIOMETRIC TITRATION CURVE FOR 5-METHYLAMINOTETRAZOLE (0.2113 g.) in 200 ml. of water with 0.1043 *N* potassium hydroxide

EXPERIMENTAL[4, 5]

REACTION OF SODIUM AZIDE WITH THIOURONIUM SALTS

1-Benzyl-5-aminotetrazole. A solution of 6.5 g. of sodium azide and 31 g. of S-methyl-N-benzylthiouronium iodide (10) in 240 ml. of ethanol and 15 ml. of water was heated under reflux for about 50 hours. Methyl mercaptan was evolved throughout the reaction period. Removal of the solvent left a gummy residue which left a crystalline solid when leached with ethyl acetate. The solid was recrystallized from 50% isopropyl alcohol, yield 4 g., m.p. 191–192° not depressed by admixture of 1-benzyl-5-aminotetrazole (1). Evaporation of the ethyl acetate extract left a gummy residue part of which crystallized from a mixture of ethanol and ether, yield 4.5 g., m.p. 100–101°, and was identified as starting material. The remaining gummy material was not identified.

1-Methyl-5-aminotetrazole. A solution of 23 g. of S-methyl-N-methylthiouronium iodide (11) and 6.5 g. of sodium azide in 240 ml. of ethanol and 15 ml. of water was boiled under reflux for seven days. Evolution of methyl mercaptan had ceased at this point. Removal of the solvent by evaporation left a solid residue that was taken up in the minimum amount of boiling water. On cooling large, flat needles crystallized, yield 2.1 g., m.p. 228–229° not depressed by admixture of 1-methyl-5-aminotetrazole (1).

ACYLATION OF MONOALKYLCYANAMIDES

Ethylcyanamide. Several attempts to acylate different monoalkylcyanamides resulted in a preponderance of side reactions yielding urea derivatives and unidentified gummy ma-

[4] Micro-analyses were done by the Micro-Tech Laboratories, Skokie, Illinois.

[5] Melting points were taken in open capillary tubes; temperatures are corrected.

terials. A typical example is the preparation and acetylation of ethylcyanamide. Ethylamine (22.5 g., 0.5 mole) was dissolved in 200 ml. of ether. After the addition of 84 g. (1 mole) of sodium bicarbonate the vigorously stirred and cooled suspension was treated with a solution of 53 g. (0.5 mole) of cyanogen bromide in 100 ml. of ether added dropwise during 1½ hours. The thick, white sludge was treated dropwise with 39 g. (0.5 mole) of acetyl chloride. Stirring was continued at room temperature for two hours. The solids were separated by filtration, extracted with ethyl acetate, and the extract was added to the filtrate and evaporated to a small volume. On cooling the yellow residue crystallized partially as colorless blades which were collected, washed with ether, and dried, crude yield 7.8 g., recrystallized from ethyl acetate, m.p. 126–127°. This product was identical with material made by acetylation of ethylurea and is probably N-acetyl-N′-ethylurea (12).

Benzylcarbethoxycyanamide. A mixture of 48 g. (0.45 mole) of benzylamine, 126 g. (1.5 moles) of sodium bicarbonate, and 200 ml. of water was chilled in an ice-bath and stirred vigorously while a solution of 53 g. (0.5 mole) of cyanogen bromide in 100 ml. of ethanol was added dropwise, followed by 54 g. (0.5 mole) of ethyl chloroformate also added dropwise. Stirring was continued at room temperature until gas evolution ceased. The heavy organic layer was taken up in ether and dried over magensium sulfate. After removal of the solvent, the residue was distilled through a Vigreaux column under reduced pressure. The product was a colorless liquid, b.p. 131–135° at 2.0 mm., and, although not a pure substance, was used without further purification in the next preparation. The main contaminant, which precipitated partially on chilling and seeding, was benzyl urethan, m.p. 48–49° showing no depression on admixture of an authentic sample (8).

5-Benzylcarbethoxyaminotetrazole. A solution of 13.8 g. of impure benzylcarbethoxycyanamide in 32 ml. of benzene containing about 0.1 mole of hydrazoic acid was heated at 95° for 54 hours in a sealed tube. After cooling, the tube contents were removed and the solvent was evaporated. The brown, oily residue was taken up in ether and extracted with dilute aqueous sodium hydroxide. On neutralizing the alkaline extract a solid separated as fine, nearly colorless needles, yield 6.8 g. Crystallization from cyclohexane gave fine needles, m.p. 81–81.5°. The product was soluble in dilute aqueous alkali and insoluble in dilute aqueous acid. The structure of 5-benzylcarbethoxyaminotetrazole was assigned on the basis of elementary analysis, the acidic character, and the hydrolysis products of the substance.

Anal. Calc'd for $C_{11}H_{13}N_5O_2$: C, 53.4; H, 5.3; N, 28.3.

Found: C, 53.5, 53.6; H, 5.4, 5.4; N, 28.2, 28.2.

Hydrolysis of 5-benzylcarbethoxyaminotetrazole. A solution of 1 g. of 5-benzylcarbethoxyaminotetrazole in 25 ml. of 0.1 *N* aqueous potassium hydroxide was boiled for 20 minutes. Neutralization of the cooled solution precipitated a colorless solid, yield 0.8 g., m.p. 181–181.5° when heated very slowly in a capillary tube. When heated more rapidly melting points as high as 193° were observed. The product is sparingly soluble in cold water, but readily soluble in either aqueous acid or aqueous alkali. It was identical with 5-benzylaminotetrazole prepared according to Thiele and Ingle (3).

Anal. Calc'd for $C_8H_9N_5$: N, 40.0. Found: N, 40.3.

HYDROGENOLYSIS OF 5-BENZYLALKYLAMINOTETRAZOLES

5-Methylaminotetrazole.[6] A mixture of 18.9 g. (0.1 mole) of 5-benzylmethylaminotetrazole (6), 150 ml. of absolute ethanol, and 3 g. of 5% palladium-charcoal was shaken under three atmospheres of hydrogen pressure at about 65° for 24 hours in a Burgess-Parr low-pressure hydrogenation apparatus equipped with a heated reaction vessel. Removal of the catalyst by filtration and evaporation of the solvent left 9.5 g. of colorless solid, recrystallized first from absolute ethanol then from water, yield 7 g., m.p. 184–184.5° followed by resolidification and remelting at 225–226°. The behavior of the compound on melting will be discussed in a subsequent paper. The product was identified as 5-methylaminotetrazole on the basis of

[6] Dr. R. A. Henry in a private communication has informed us of the preparation of these compounds by an essentially similar method.

TABLE I

5-MONOALKYLAMINOTETRAZOLES AND THEIR SILVER SALTS

5-SUBSTITUTED TETRAZOLE	FORMULA	ANALYSIS		APPARENT[a] pK_a	APPARENT[a] $K_a \times 10^8$	EQUIVALENT WT.[a]		SILVER SALTS		
		Calc'd	Found			Calc'd	Found	Formula	Silv	
									Calc'd	Found
Methylamino	$C_2H_5N_5$	C, 24.2 H, 5.09 N, 70.7	24.3 5.10 70.4	6.67 (6.06)	21 (87)	99	99 (100)	$C_2H_4AgN_5$	52.3	52.5
Ethylamino	$C_3H_7N_5$	C, 31.9 H, 6.24 N, 61.9	31.9 6.42 62.0	6.66 (6.12)	22 (76)	113	113 (114)	$C_3H_6AgN_5$	48.9	49.2
Benzylamino	$C_8H_9N_5$	N, 40.0	40.2	6.52	30	175	176	$C_8H_8AgN_5$	38.2	38.4

[a] Determined in 50% methanol by volume. The values in parentheses were determined in aqueous solution.

elementary analysis, formation and analysis of the silver salt, and its equivalent weight and apparent acidic dissociation constant as determined by potentiometric titration (Table I).

5-Ethylaminotetrazole.[6] Hydrogenolysis of 13.7 g. of 5-benzylethylaminotetrazole (6) in 150 ml. of absolute ethanol in the presence of 2 g. of 5% palladium-charcoal was carried out essentially as just described for the methyl analog. The product was recrystallized from absolute ethanol, yield 7.6 g., m.p. 175–175.5°. Identification of the product as 5-ethylaminotetrazole was based on elementary analysis, formation and analysis of the silver salt, and its equivalent weight and apparent acidic dissociation constant (Table I).

5-Benzylaminotetrazole. A mixture of 12.5 g. of 5-dibenzylaminotetrazole (6), 100 ml. of absolute ethanol, and 2 g. of 5% palladium-charcoal was subjected to hydrogenolysis as just described for 11 hours at 65°. Removal of the catalyst and evaporation of the solvent left a residue that was crystallized from absolute ethanol as colorless plates, yield 6.4 g., m.p. 181–181.5° on slow heating. The product was identical with the 5-benzylaminotetrazole prepared by hydrolysis of 5-benzylcarbethoxyaminotetrazole and by benzylation of 5-aminotetrazole (3). Elementary analysis, formation and analysis of the silver salt, equivalent weight, and acidic dissociation constant were in conformity with the structure assigned (Table I).

5-Aminotetrazole. Hydrogenolysis of 8.8 g. of 5-benzylaminotetrazole in 100 ml. of absolute ethanol in the presence of 2 g. of 5% palladium-charcoal was completed in 20 hours at 65° as described above. Evaporation of the solvent and crystallization of the residue from water gave a colorless, translucent solid that became opaque on drying, yield 3.9 g. after drying at 100°, m.p. 201.5–202°. The product was identical with an authentic sample of 5-aminotetrazole (9).

SILVER SALTS OF THE 5-MONOALKYLAMINOTETRAZOLES

Silver salts were prepared by dissolving small amounts (0.2–0.5 g.) of the 5-alkylaminotetrazole in 10 ml. of water and adding a slight excess of aqueous silver nitrate solution. The white precipitate of silver salt was digested on the steam-bath for 15 minutes, filtered hot, washed with hot ethanol, and dried at 70° for several hours. Silver determinations were carried out as previously described (6). Results are recorded in Table I. None of the salts appears to be sensitive to shock or to light; however, on heating on a spatula they soon decompose with a flash.

POTENTIOMETRIC TITRATIONS

Apparent acidic dissociation constants and equivalent weights were determined by titration of weighed samples of the 5-alkylaminotetrazoles in water or 50% by volume aqueous methanol solution with standard potassium hydroxide solution. Weighed samples of the compounds were made up to volume in a 250-ml. volumetric flask with water or methanol. Aliquots (100 ml.) were diluted with an equal volume of water so that the final concentrations were about 0.01 *molar*. The titration with 0.1043 *N* potassium hydroxide was done in a thermostat at 25° and the *p*H was determined after each addition of alkali with a Beckman *p*H Meter, Model G. From these data the region of half neutralization was plotted on a large scale, the best straight line was drawn, and the *p*H at half neutralization was determined from the plot. A typical titration curve is reproduced in Figure 1. Equivalent weights were calculated from the volume of alkali required for neutralization. The results are given in Table I.

SUMMARY

The interaction of S-methyl-N-alkylthiouronium salts and sodium azide has been shown to give 1-alkyl-5-aminotetrazoles in modest yield. The interaction of benzylcarbethoxycyanamide and hydrazoic acid resulted in the formation of 5-benzylcarbethoxyaminotetrazole. On alkaline hydrolysis the latter was converted into 5-benzylaminotetrazole. Due to difficulties encountered in the prep-

aration of alkylacylcyanamides this method of preparation of 5-alkylaminotetrazoles has not been explored extensively. Catalytic hydrogenolysis of 5-benzylalkylaminotetrazoles gives the corresponding 5-alkylaminotetrazoles three of which have been prepared and characterized.

EAST LANSING, MICHIGAN

REFERENCES

(1) GARBRECHT, AND HERBST, *J. Org. Chem.*, **18,** Paper II, this issue (1953).
(2) STOLLÉ, *J. prakt. Chem.*, **134,** 282 (1932).
(3) THIELE AND INGLE, *Ann.*, **287,** 233 (1895).
(4) Unpublished data.
(5) VON BRAUN, *Ber.*, **33,** 1438 (1900).
(6) GARBRECHT AND HERBST, *J. Org. Chem.*, **18,** Paper I, this issue (1953).
(7) BIRKOFER, *Ber.*, **75,** 429 (1942).
(8) BASTERFIELD, WOODS, AND WRIGHT, *J. Am. Chem. Soc.*, **48,** 2371 (1926).
(9) MIHINA AND HERBST, *J. Org. Chem.*, **15,** 1082 (1950).
(10) BRAUN AND RANDALL, *J. Am. Chem. Soc.*, **56,** 2134 (1934).
(11) SCHENCK, *Z. physiol. Chem.*, **77,** 328 (1912).
(12) LEUCKART, *J. prakt. Chem.*, [2] **21,** 1 (1880); MAUGUIN, *Ann. chim.*, [8] **22,** 333 (1911).