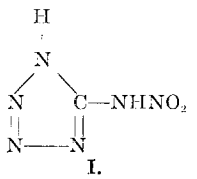
TITRATION OF 5-ACETAMIDOTETRAZOLE IN NON-AQUEOUS MEDIA

EUGENE LIEBER AND EDWIN OFTEDAHL
DePaul University, Chicago

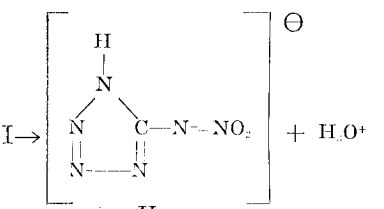
INTRODUCTION

In 1951, Lieber, Patinkin and Tao reported that 5-nitraminotetrazole (I) is a dibasic acid in which k_1 is as strong as the strong inorganic



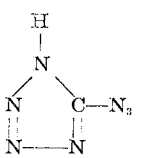
I.

acids and k_2 has the value 9×10^{-7} (pK_a=6.1). This rather surprising value of k_1 for structure I could satisfactorily be accounted for on the basis that the hydrogen of the nitramino-group is the strong acid proton and that its removal results in a very large increase in resonance stabilization (I→II) of the anion (II) with

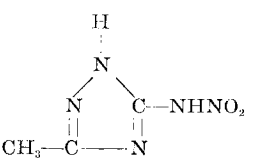


II.

respect to the free acid (I). Confirmation for this hypothesis was obtained by Lieber, Sherman and Patinkin (1951) by a study of the ultraviolet absorption spectra of I and its salts. Further confirmation for the idea that symmetry and resonance considerations were important factors in the dissociation quotients of nitrogen heterocycles was shown by the very strong acidity of 5-azidotetrazole (III) and the greatly reduced value of k_1 exhibited by 3-methyl-5-nitramino-1, 2, 4-triazole (IV) in which the symmetry of the tetrazole ring has been destroyed by the insertion of a carbon atom for a nitrogen atom in position-3 (Lieber, Patinkin and Tao, 1951). The second proton in IV was too weak to be determined potentiometrically. Accordingly, the report by Herbst and Garbrecht (1953) that 5-acetamidotetrazole (V) had an apparent dissociation quotient of 4.5 pK_a units, involving an increase of only 1.5 pK_a units over that of 5-aminotetrazole (VI) (Lieber, Patinkin and Tao, 1951) was of considerable interest. Structure V, by the removal of a proton from the 5-acetamido



III.



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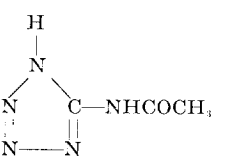
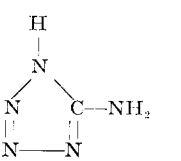


V.

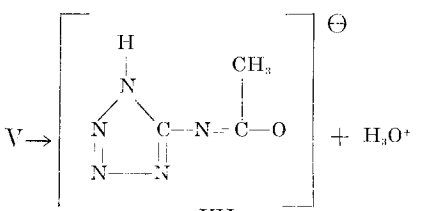
pK_a=4.5



VI.

pK_a 6.0

side chain should exhibit the large increase in resonance stabilization of its anion (VII) with respect to the free acid (V) as that exhibited by structure II. However, Herbst and Garbrecht (1953) could not potentiometrically detect the second proton in aqueous media; they predicted that it might be possible to detect the second proton in non-aqueous media. In view of the conflict of ideas expressed by the above inves-



VII.

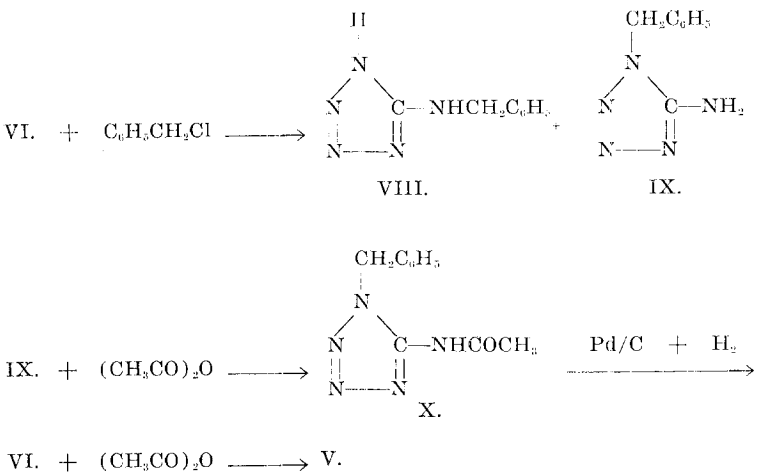
tigations it was decided to investigate the acidic behavior of 5-acetamidotetrazole (V) in both aqueous and nonaqueous media. This communication reports the results of that study. Subsequent to the submission of this communication (January 16, 1958) there has appeared a brief note by Maher and Yohe (1958; submitted February 3, 1958) confirming some of the data in the present paper.

Materials and Methods

The required 5-acetamidotetrazole was prepared by two independent procedures both of which led to identical products. The sequence of reactions is outlined later.

Following the procedure of Herbst and Garbrecht (1953) the benzylation of 5-aminotetrazole (VI) led to the formation of a mixture of 5-benzylaminotetrazole (VIII) and 1-benzyl-5-aminotetrazole (IX). The desired IX was separated from the mixture by extraction with aqueous sodium hydroxide; the insoluble portion after recrystallization from 50% aqueous isopropyl alcohol gave IX melting at 190-192°. Acetylation of IX led to the isolation of 1-benzyl-5-acetamidotetrazole (X) which on catalytic debenzylation by means of hydrogen (50 p.s.i. and room temperature) in the presence of palladium on charcoal gave 5-acetamidotetrazole (V) melting at 268° (Analysis: $C_3H_5N_5O$: Calculated: N,55.1. Found: N, 55.6). The direct acetylation of 5-aminotetrazole (VI) was carried by the procedure of Thiele and Ingle (1895), yielding a product melting at 265-266° (Analysis: $C_3H_5N_5O$: Calculated: N, 55.1. Found: N, 55.1). No depression of the melting point was found on mixing the specimens of 5-acetamidotetrazole prepared by the two different procedures. The 1-benzyl-5-acetamidotetrazole (X) prepared in this investigation had a melting point of 108-110° in agreement with that reported by Herbst and Garbrecht (1953).

The potentiometric aqueous titrations were carried out using calomel and glass electrodes with a photovolt direct reading pH meter and 0.1086 N KOH as titrant. The potentiometric nonaqueous titrations were carried out in both dimethylformamide and 95-100% ethylenediamine, respectively. The apparatus consisted of calomel-antimony electrodes and Beckman model H2 pH meter. Sodium methoxide (0.1170 N) in benzene-methanol mixture was used as titrant. In general, the procedures described by Fritz (1952)



were followed. However, it was found necessary to shield all electrode leads in order to obtain reproducible readings.

Results

Figure 1 summarizes the potentiometric titrations in aqueous medium for 1-benzyl-5-acetamidotetrazole (X) and 5-acetamido-tetrazole (V), respectively. The values of pK_a taken from the pH at the half neutralization point are summarized below:

	pKa	
	This research	Herbst and Garbrecht (1953)
5-Acetamidotetrazole	4.49	4.53
1-Benzyl-5-acetamidotetrazole	8.49	8.61

Figures 2 and 3 summarize the results of the potentiometric titrations conducted with 5-acetamidotetrazole (V) in dimethylformamide and ethylene diamine, respectively. It will be noted (Fig. 2) that a very weak potential break is obtained for the second proton at the expected stoichiometry when the titration is carried out in dimethylformamide, while a much steeper potential break is obtained (Fig. 3) in ethylenediamine as solvent.

Discussion

The present investigation has confirmed the weak monobasic properties of 5-acetamidotetrazole (V) as reported by Herbst and Garbrecht (1953) and the inability to detect potentiometrically the second proton in aqueous medium. In extension of this work it has now been demonstrated that 5-acetamidotetrazole does display dibasic acid properties in nonaqueous media. The important point of discussion involves the question as to what structural factors in 5-acetamidotetrazole are re-

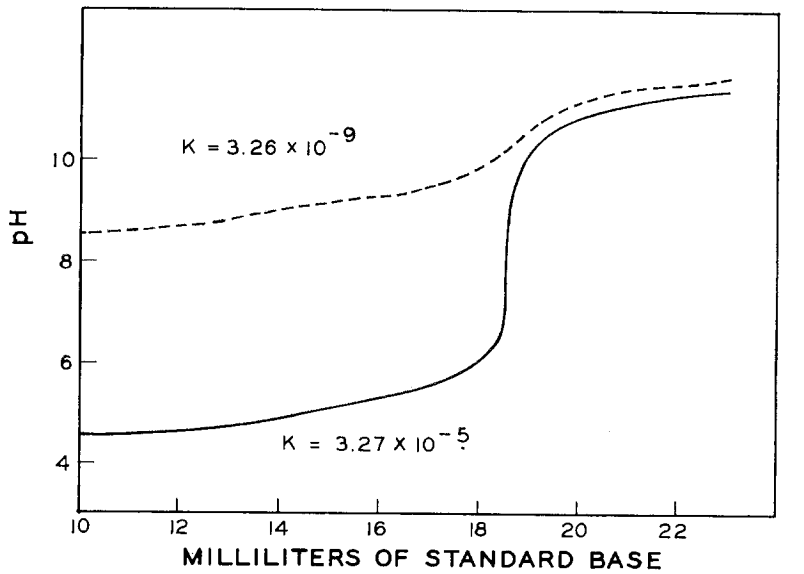


FIG. 1.—Potentiometric titrations in aqueous medium; dashed line, 1-benzyl-5-acetamidotetrazole; solid line, 5-acetamidotetrazole.

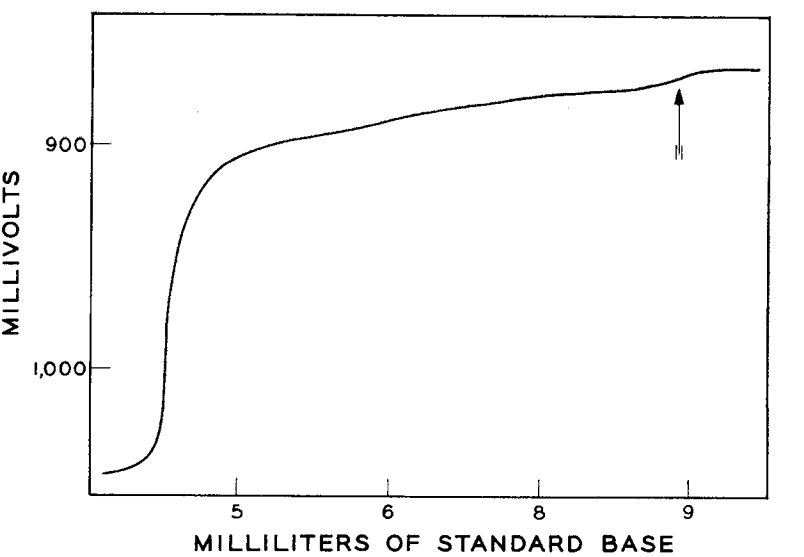
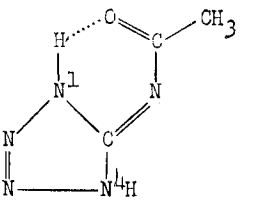
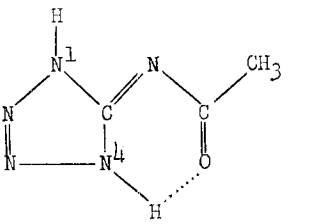


FIG. 2.—Potentiometric titration of 5-acetamidotetrazole in dimethylformamide solvent. Upward pointing arrow indicates potential break at second proton.

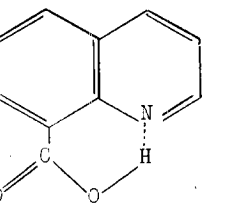
sponsible for its decreased acidity. The various factors which markedly affect acid and base strength have been recently described by Brown, McDaniel and Häfliger (1955). Of these factors hydrogen bonding resulting from internal chelation has been shown to be of considerable importance (Brown, *et al.*, 1955). It is suggested that the chelated structures XI and XII, requiring both of the acidic protons, stabilize the molecule and hence reduce the tendency of the protons, either at the equivalent positions 1 or 4, to dissociate. Badger (1957) has shown that quinoline-8-carboxylic acid is a much weaker acid than any of the isomeric quinoline carboxylic acids and has explained this as due to intramolecular hydrogen bonding stabilizing the undissociated compound as shown by structure XIII.



XI.



XII.



XIII.

The symmetry and equivalency of structures XI and XII, in which the acidic protons are at positions 1 and 4 should be noted. The structure

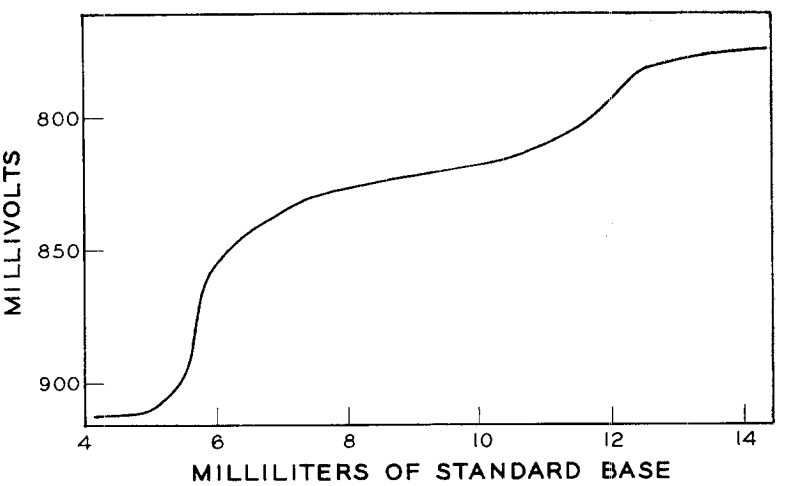
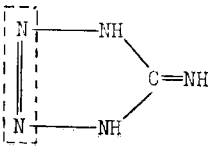


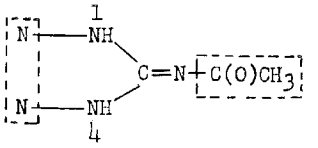
FIG. 3.—Potentiometric titration of 5-acetamidotetrazole in ethylenediamine as solvent.

usually given in the literature for 5-aminotetrazole is VI (for example, see Herbst and Garbrecht, 1953) although considerable evidence exists that the completely symmetrical tetrazoline (dihydrotetrazole) form (XIV)



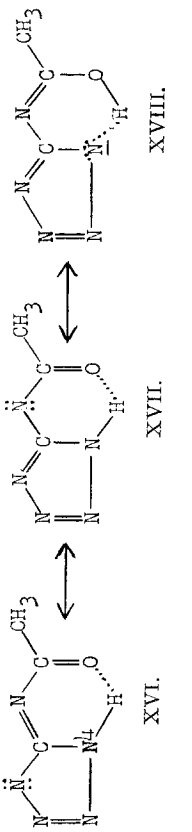
XIV.

more adequately explains the properties of that substance (Henry, Finnegan and Lieber, 1954). Structure XIV may also be described as guanidine which has been tied in the rear by an azo-linkage (indicated by the dotted lines) which exerting a powerful electron-withdrawing effect converts guanidine from a very strong base (equivalent to potassium hydroxide) to an acid. It is for this reason that the extremely weak effect of the acetyl group in the 5-amino side chain (XV)



XV.

requires explanation; the strong inductive effects (pulling in opposite directions) should markedly decrease the electron densities at positions 1 and 4. The stabilization implied by the equivalent structures (XI and XII) must, accordingly, be a very important factor in reducing the inductive effects of the azo-backbone and acetyl-group of structure XV. In addition, the structure XI (or XII) proposed for 5-acetamidotetrazole produces an anion (resulting from the dissociation of the proton at either positions 1 or 4) that is capable of considerable resonance stabilization, as shown by structures XVI to XVIII.



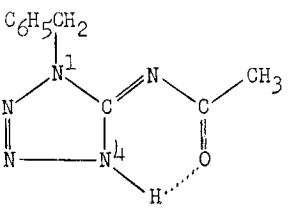
XVIII. XVII. XVI.

(Additional resonance forms are possible but are not shown). This hypothesis accounts for the ability to detect readily the first proton by aqueous or nonaqueous titrations.

While the second proton cannot be detected in aqueous medium, the present investigation has shown that

it can be readily demonstrated in non-aqueous media. A considerable body of evidence exists (Brown, *et al.*, 1955; Fritz, 1954; Deal and Wyld, 1955) that the relative strengths of two acids can vary with the solvent, presumably by modifying the electrical character and apparent inductive effect of groups. This investigation has thus demonstrated this effect for 5-acetamidotetrazole and has shown that under suitable environmental conditions the second proton (for example at position-4 of structure XVI) can dissociate and be detected.

It will be noted from Figure 1 that the introduction of a benzyl substituent in position-1 of 5-acetamidotetrazole (structure IX) markedly reduces the acidic properties of the compound. 1-Benzyl-5-acetamidotetrazole may be represented by structure XIX.



XIX.

The benzyl radical is an electron-donating group and accordingly increases the electron density at the nitrogen atom in position-4 (actually the increased electron density is diffused throughout the entire ring structure but would be expected to have greater electron densities at the electronegative atoms). This factor alone would be insufficient to account for the very large decrease in acid strength. However, a combination of this factor plus the stabilization afforded the remaining proton (at position-4 in structure XIX) offers a satisfying explanation for this decrease in acid strength of 1-benzyl-5-acetamidotetrazole.

Summary

Unequivocal syntheses for 1-benzyl-5-acetamidotetrazole and 5-acetamidotetrazole were carried out and the comparative dissociation quotients determined by potentiometric titration in aqueous medium. The weak monobasic acid properties of these substances were confirmed. Potentiometric titrations in nonaqueous media have demonstrated that 5-acetamidotetrazole is a dibasic acid in these media, the second dissociating proton being readily detected by this means. A theory to account for these observations is presented and discussed.

Literature Cited

Badger, G. M. 1957. Intermolecular hydrogen bonding in organic chemistry. Revs. Pure and Appl. Chem., 7:56.

Brown, H. C., D. H. McDaniel, and O. Häfliger. 1955. Dissociation constants. *In* Braude, E. A., and F. C. Nachod. Determination of organic structures by physical methods. Acad. Press, Inc., New York, pp. 567-655; 629.

Deal, V. Z., and G. E. A. Wyld. 1955. Potentiometric titration of very weak acids. Anal. Chem., 27:47.

Fritz, J. S. 1952. Acid-base titrations in nonaqueous solvents. G. F. Smith Chemical Co., Columbus, Ohio, pp. 24-42.

1954. Selection of the medium for a particular titration. Anal. Chem., 26: 1701.

Henry, R. A., W. G. Finnegan, and E. Lieber. 1954. 1, 3- and 1, 4- Dialkyl-5 iminotetrazoles. Jour. Amer. Chem. Soc., 76:2894.

Herbst, R. M., and W. L. Garbrecht. 1953. The acylation of some 5-amino-

tetrazole derivatives. Jour. Org. Chem., 18:1286.

LIEBER, E., S. H. PATINKIN, and H. H. TAO. 1951. The comparative acidic properties of some 5-substituted tetrazoles. Jour. Amer. Chem. Soc., 73:1792.

LIEBER, E., E. SHERMAN, and H. S. PATINKIN. 1951. The ultraviolet absorption spectra of 5-nitroaminotetrazole and its salts. Jour. Amer. Chem. Soc., 73:2329.

MAHER, T. P., and G. R. YOHE. 1958. Acidic properties of tetrazole derivatives in a nonaqueous medium. Jour. Org. Chem., 23: 1082.

THIELE, J., and H. INGLE. 1895. Ueber einige derivatives des tetrazoles. Liebigs Annalen, 287: 234.