The Acetylation of 3-Amino-1,2,4-triazole (I)

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Previous studies (2,3) of the acetylation of 3-amino-1,2,4-triazole (I) have shown that I reacts with one equivalent of acetyl chloride in the presence of *s*-collidine to produce an *N*-acetyl-3-amino-1,2,4-triazole, which rearranges to the isomeric 3-acetylamino-1,2,4-triazole when heated above its melting point (150°). Both monoacetyl derivatives were converted to an *N*-acetyl-3-acetylamino-1,2,4-triazole upon treatment with acetyl chloride. Hydrolysis of the diacetyl derivative gave 3-acetylamino-1,2,4-triazole.

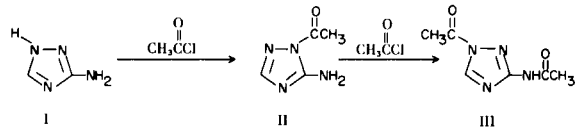
In connection with another problem (4), we established the structures of the *N*-acetyl derivatives of I by comparing the nmr chemical shifts of their triazole protons with those of appropriate model compounds (Table I) and applying the interpretations used by Potts (5) in determining the structures of other *N*-acyl-1,2,4-triazoles. Thus, the monoacetylation of I gives an *N*-acetyl derivative in which the triazole proton is not deshielded; therefore, the acetyl group is not adjacent to this proton and the product is 1-acetyl-5-amino-1,2,4-triazole (II). In contrast, the triazole proton of the diacetyl derivative is significantly deshielded; therefore, the *N*-acetyl group is at one of the adjacent positions. Since 1,2,4-triazoles normally acetylate in the 1 or 2 positions (5), the diacetyl derivative of I is probably 1-acetyl-3-acetylamino-1,2,4-triazole (III), which means that the acetylation of II is accompanied by migration of the *N*-acetyl group.

TABLE I

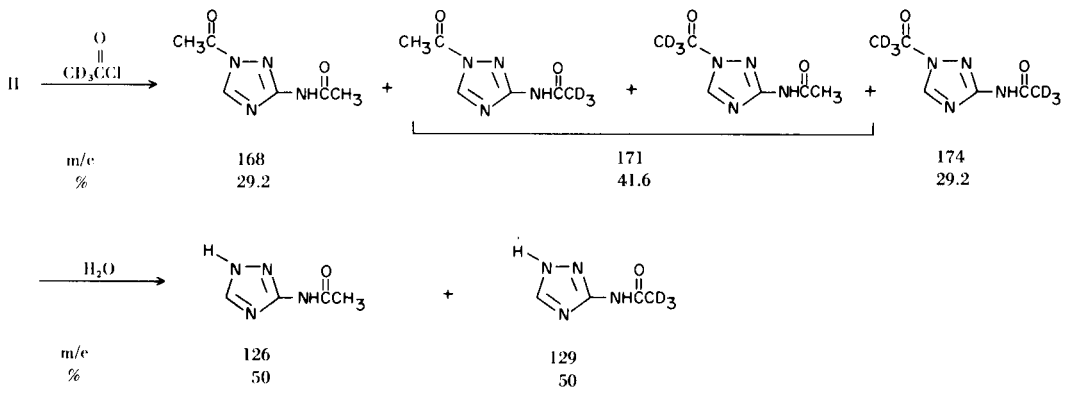
Chemical Shifts of the C-5 Protons (a)

Compound	δ_{C-H} (ppm)
1,2,4-Triazole	8.52
1-Acetyl-1,2,4-triazole	(8.28) 9.29
3-Amino-1,2,4-triazole	7.71
1-Acetyl-5-amino-1,2,4-triazole	(7.57)
3-Acetylamino-1,2,4-triazole	7.84
1-Acetyl-3-acetylamino-1,2,4-triazole	9.12
3-Trifluoroacetylamino-1,2,4-triazole	8.44
1-Acetyl-3-trifluoroacetylamino-1,2,4-triazole	9.28

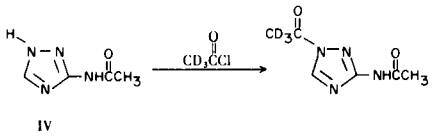
(a) Determined with a Varian A-60A spectrometer as dimethylsulfoxide solutions using tetramethylsilane as an internal standard.



In order to learn something about the course of this reaction, the acetylation of II was performed with an equimolar quantity of acetyl chloride-d_3. The product distribution was determined by mass spectrometry, with the results shown below. When the product mixture was hydrolyzed, a 1:1 mixture of 3-acetylamino-1,2,4-triazole and 3-acetyl-d_3-amino-1,2,4-triazole was obtained.



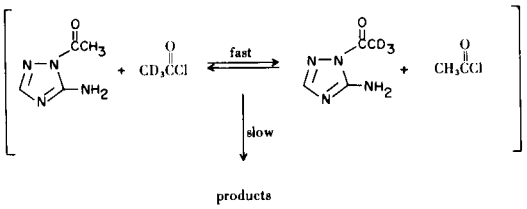
In another experiment, 3-acetylamino-1,2,4-triazole (IV) was treated with acetyl chloride-d_3 under identical conditions. In this case, 1-acetyl-d_3-3-acetylamino-1,2,4-triazole (m/e 171) was formed exclusively as shown by its hydrolysis back to IV (m/e 126). Thus the acetyl group of IV does not exchange with acetyl chloride-d_3.



IV

IV

A mechanism involving a rapid exchange of the acetyl group of II with acetyl chloride-d_3, followed by the slow acetylation of the amino group, is consistent with the experimental data thus far obtained. The possibility of an internal rearrangement of II to IV followed by acetylation is excluded.

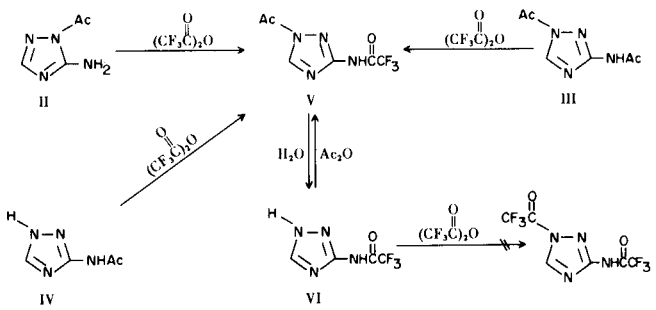


products

Our hypothesis is that I acetylates preferentially at the 2-position where the electron density initially is probably highest because of the adjacent 3-amino group. However, after the 3-amino group is acetylated, the electron density becomes greater at the 1-position because of the electron-withdrawing character of the acetyl group. As a result, the labile *N*-acetyl group migrates to form the thermodynamically more stable product (III).

Compounds II, III, and IV were converted into the same product, 1-acetyl-3-trifluoroacetylamino-1,2,4-triazole (V), when refluxed with an excess of trifluoroacetic anhydride. The structure of V was confirmed by its elemental analysis, nmr spectrum, and hydrolysis to 3-trifluoroacetylamino-1,2,4-triazole (VI). Treatment of VI with an excess of acetic anhydride also gave V; however, VI was recovered unchanged after treatment with an excess of trifluoroacetic anhydride.

From these results it is clear that irreversible transacylation occurs between trifluoroacetic anhydride and the 3-acetylamino groups of III and IV to give the mixed anhydride along with V and VI, respectively. In the latter



II V III

IV VI

case the mixed anhydride then acetylates VI to produce V since 1-trifluoroacetyl-3-trifluoroacetylamino-1,2,4-triazole is not stable. Compound II is probably converted to V by direct trifluoroacetylation of the amino group followed or accompanied by migration of the *N*-acetyl group to form the thermodynamically more stable product.

EXPERIMENTAL (6)

The acetylation of 3-amino-1,2,4-triazole and its monoacetyl derivatives was accomplished according to the procedures described by van den Bos (3). Our yields and the melting points of the products were in good agreement with those reported by this author. The hydrolysis of the diacetyl derivatives was performed as described by Staab and Seel (2).

All mass spectra were obtained with a Consolidated Electrodynamics Corporation Model 21-110B mass spectrometer equipped with a direct introduction probe and a combination electron multiplier-photoplate detector system. The ion source was maintained at 150° while the probe temperature was varied from 90° to 140°. An ionizing voltage of 150 volts was used with an ion accelerating voltage of 8 kilovolts. Relative abundances of parent ions were obtained by scanning the photoplate using a Jarrell-Ash Model 24-300 scanning microphotometer.

1-Acetyl-3-trifluoroacetylamino-1,2,4-triazole (V).

3-Acetylamino-1,2,4-triazole (2.52 g., 0.02 mole) was refluxed with 50 ml. of trifluoroacetic anhydride for 2 hours. The excess trifluoroacetic anhydride was removed under reduced pressure and 100 ml. of anhydrous ether was added to the residue. The solid was collected by filtration, washed with anhydrous ether, and dried to give 2.32 g. (52%) of 1-acetyl-3-trifluoroacetylamino-1,2,4-triazole, m.p. 175-176°.

Anal. Calcd. for $C_6H_5F_3N_4O_2$: C, 32.44; H, 2.27; N, 25.22. Found: C, 32.42; H, 2.34; N, 25.36.

1-Acetyl-5-amino-1,2,4-triazole and 1-acetyl-3-acetylamino-1,2,4-triazole were treated with trifluoroacetic anhydride under the conditions described above. The product obtained in each case was identical with that obtained from 3-acetylamino-1,2,4-triazole.

3-Trifluoroacetylamino-1,2,4-triazole (VI).

1-Acetyl-3-trifluoroacetylamino-1,2,4-triazole (2.24 g., 0.01 mole) was stirred with 50 ml. of water at 25° for 16 hours. The solid was collected by filtration, washed with water, and dried to give 1.37 g. (76%) of 3-trifluoroacetylamino-1,2,4-triazole, m.p. 249-251° (sealed capillary), which contained no 3-acetylamino-1,2,4-triazole according to nmr analysis. Recrystallization from

acetone provided an analytically pure sample, m.p. 258-259° (sealed capillary).

Anal. Calcd. for $C_4H_3F_3N_4O$: C, 26.68; H, 1.68; N, 31.11. Found: C, 26.55; H, 1.93; N, 31.21.

REFERENCES

(1) This work was performed under the auspices of the U. S. Atomic Energy Commission and was presented at the 159th National Meeting of the American Chemical Society, Houston, Texas, February 1970, Abstract 128.

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(6) Microanalyses by M. J. Naranjo. All melting points are corrected.

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