# Heterocyclic Studies. 47. Rearrangements of 1-Acyl-4-(acyloxy)-1,2-diazepines. Formation and Properties of a 1-Acyl-5-(acyloxy)-1,3-diazepine

James A. Moore,* Howard B. Yokelson, Walter J. Freeman, and John F. Blount[1]

*Department of Chemistry, University of Delaware, Newark, Delaware 19711, and Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110*

*Received February 6, 1979*

1-Acyl-1,5-dihydrodiazepinones **9** undergo enolization and ring contraction to 3-hydroxy-6-benzamidopyridines **14**. The enol **13** was characterized by NMR. The enol esters **11** rearrange thermally to a mixture of (acyloxy)pyridines **15** and 1-acyl-1,3-diazepines **16**. The isomeric enol acetate **12** in the 2,3-dihydrodiazepinone series rearranges to the 2,3-disubstituted pyridine **17**, indicating parallel and separate pathways for the formation of 2- and 6-aminopyridines from 1,2-diazepines. The relative rates of rearrangements of ketones and enol esters suggest that the oxygen substituent is a dominant factor in these reactions. The 1,3-diazepine **16** undergoes facile hydrolytic ring opening to the 1,4-bis(acylamido)butadiene **22**, whose structure was established by crystallography. Alkaline hydrolysis of **16** causes ring contraction via the enol to the 6-benzamidopyridine **14**.

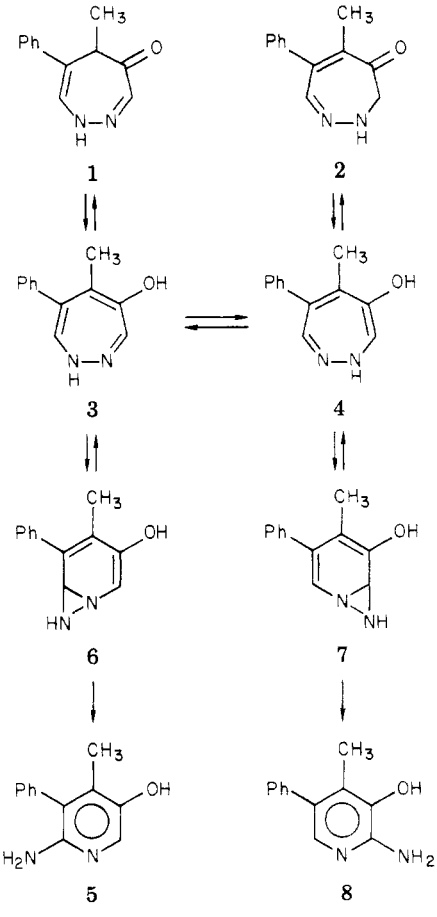
The dihydrodiazepinones **1** and **2** undergo equilibration in base and, more slowly, are converted to mixtures of the 6- and 2-amino-3-hydroxypyridines **5** and **8**.[2] These reactions have been interpreted in terms of the interconversion and valence isomerization of the enols **3** and **4** (Scheme I), but there is no direct evidence for this pathway, and the formation of **5** and **8** can also be formulated with ring scission and recyclization steps.[3]

More recently the ketones **1** and **2** have been converted to *N*-acyl derivatives **9** and **10**, respectively, and thence to enol esters **11** and **12** (Scheme II).[4] Enol ester formation from the 1-acyl-1,5-dihydro ketone **9** is about 15-fold faster than with the 2-acyl-2,3-dihydro isomer **10**. The availability of these derivatives, in which interconversion between the two isomeric series is blocked by substitution, has permitted us to examine more closely the conversion of these diazepines to $\alpha$-aminopyridines.

***N*-Acyl-1,2-diazepinone Reactions.** The acyldiazepinones **9** and **10** are deacylated to the parent NH ketones **1** and **2** by hydroxide, but the 1-acyl ketones **9** are converted in a thermal process to the 6-(acylamido)-pyridines **14** on heating at 120 °C in chlorobenzene. No other products were observed by NMR or TLC. The rates of the thermal reaction for the benzoyl, *p*-nitrobenzoyl and *p*-methoxybenzoyl ketones **9b–d** were very similar ($k_1$ = (1.6–3.2) × $10^{-3}$ $s^{-1}$ at 120 °C). The rate of the 1-acetyl ketone **9a** was much slower ($k^1 \approx 1.0 \times 10^{-4}$ $s^{-1}$); the product was less clean and was isolated in low yield.

Direct evidence for an intermediate in this rearrangement was obtained from NMR studies with the benzoyl ketone **9b**. A chloroform solution of **9b**, with or without addition of 0.2 equiv of pyridine, showed no detectable change after 1 week at 35 °C. However in $CDCl_3$–$CD_3OD$ solution (1:1) at 35 °C the spectrum of **9b** after 60 h developed peaks due to the benzamidopyridine **14b** at $\delta$ 2.07 ($CH_3$) and 8.03 (H.2). In addition, transient peaks were present at $\delta$ 1.85 and 6.5 in a ratio of ~3:1. The latter signals are assigned to $CH_3$ and H-3 in the enol **13**; the chemical shifts may be compared to $\delta$ 1.78 and 6.67 for the corresponding protons in the enol acetate **11b**. The enol is evidently stabilized in the hydroxylic solvent, and enolization is further promoted by addition of 0.1–0.2 equiv of pyridine in $CDCl_3$–$CD_3OD$. Under these conditions,

Scheme I



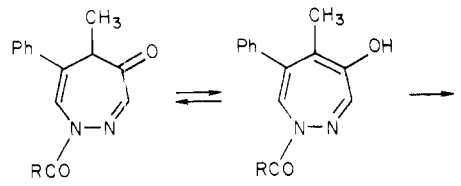

NMR peaks due to the enol were detectable after 2 h and reached a maximum intensity of about 20% of the total mixture of ketone **9b**, enol, and **14b**. The enol signals then decreased, along with those for the ketone, as those of **14b** increased. In the presence of 0.2 equiv of pyridine, the half-life of **9b** was about 12 h.

To confirm that this transient peak is due to the enol, we neutralized a solution with acid in $D_2O$; the intensity of the 1.85 ppm peak was shifted to that of the singlet peak due to the $CH_3$–CD signal of the ketone **9b**.

In the 2,3-dihydro series the thermal reactions of the ketones **10** (R = $CH_3$ or $C_6H_5$) were very slow and led to extensive decomposition; NMR examination suggested the formation of some pyridine, but pure products were not

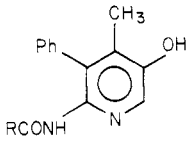
(1) Hoffmann-La Roche Inc.
(2) Pleiss, M. G.; Moore, J. A. *J. Am. Chem. Soc.* **1968**, *90*, 1369.
(3) Moore, J. A.; Zoll, E. C. *J. Org. Chem.* **1964**, *29*, 2124.
(4) Moore, J. A.; Freeman, W. J.; Kurita, K.; Pleiss, M. G. *J. Org. Chem.* **1973**, *38*, 2939.

0022-3263/79/1944-2683$01.00/0 



9a, R = $CH_3$
b, R = $C_6H_5$
c, R = $p$-$NO_2C_6H_4$
d, R = $p$-$MeOC_6H_4$

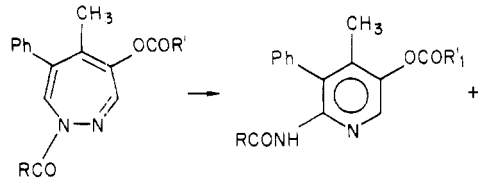
13



14

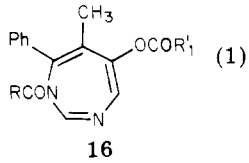
isolated. The contrasting behavior of the ketones **9** and **10** reflects the much slower rate of enolization in the 2,3-dihydro series **10**. The 2-tosyl ketone (**10**, RCO = $SO_2C_7H_7$) (but not the 2-acetyl compound) has been found to undergo rearrangement to the 2-(tosylamido)pyridine on heating in the presence of $Et_3N$.[5]

**1,2-Diazepine Enol Ester Reactions.** The enol esters **11a–c** (1-acyl-4-(acyloxy)diazepines) derived from the 1,5-dihydro ketones **9** rearrange in toluene or chlorobenzene at 120 °C to a mixture of two products which are readily observed by NMR (eq 1). The major product



11a, R = R′ = $CH_3$
b, R = $C_6H_5$, R′ = $CH_3$
c, R = R′ = $C_6H_5$

15



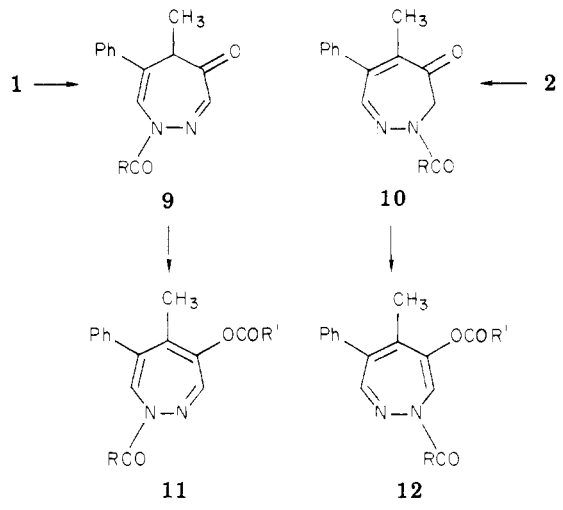
16

(1)

(60–70% by NMR) in each case was the 6-(acylamido)-3-(acyloxy)pyridine **15a–c**. The identities of these compounds were established by prior syntheses or interconversions with the hydroxypyridines **14**. The minor product from the *N*-benzoyl enol acetate **11b** was isolated (26% yield) by fractional crystallization of the mixture as pale yellow blocks. Its structure was established as 5-acetoxy-1-benzoyl-6-methyl-7-phenyl-1*H*-1,3-diazepine (**16b**) by X-ray crystallography as previously described.[6] The minor products from **11a,c** have not been isolated, but from the similarity of the NMR spectra of the product mixtures with that from **11b**, these products are assumed to be the corresponding 1,3-diazepines **16a,c**.

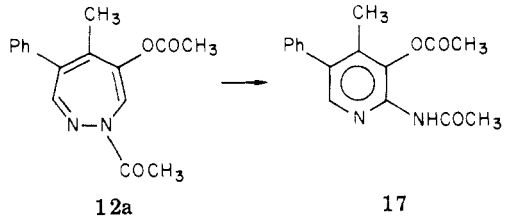
The rates of the thermal reactions of the 1-benzoyl enol esters **11b,c** at 120 °C in chlorobenzene were nearly the same ($k_1 = 9 \times 10^{-3}$ s$^{-1}$) and were about 3 times faster than that of the 1-benzoyl ketone **9b**. The rate of the *N*-acetyl enol acetate **11a** was again much slower ($k_1 = 1.8 \times 10^{-4}$ s$^{-1}$) than that of the benzoyl compounds and was about twice as fast as the corresponding 1-acetyl ketone **9a**.

Scheme II



In 1:1 $CDCl_3$–$CD_3OD$ solution containing 0.2 equiv of pyridine at 35 °C, the rearrangement of diazepine **11b** to a mixture of **15b** and **16b** was *slower* ($t_{1/2} \approx 45$ h) than that of the ketone **9b** ($t_{1/2} \approx 12$ h) under the same conditions. The rate of **11b** was the same in the absence of added pyridine; the rate in $CDCl_3$ alone was slower ($t_{1/2} \approx 75$ h) than that in $CDCl_3$–$CD_3OD$.

The only enol ester available in the 2,3-dihydro series is the *N*-acetyl enol acetate (1-acetyl-6-acetoxydiazepine, **12a**). Thermal rearrangement of this compound gave the



12a

17

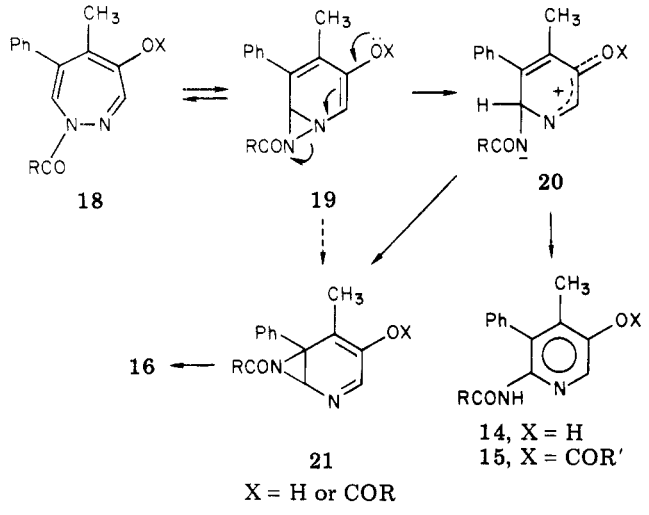
2-acetamido-3-acetoxypyridine **17** plus a minor second product. The latter may again be an isomeric 1,3-diazepine, but the data are insufficient to assign a structure. The rearrangement of **12a** ($k_1 = 6 \times 10^{-4}$ s$^{-1}$) was much more rapid than that of the 2,3-dihydro ketone **10a** (and in fact was faster than that of the isomeric 4-acetoxy enol acetate **11a**). Thus when the enolization step has been surmounted by formation of the ester, thermal reorganization in the two series occurs with approximately the same activation requirement.

It should be noted that the NMR spectra of the reaction mixture from the isomeric enol acetates **11a** and **12a** showed no crossover between the two series. Each spectrum contained two distinctive sets of three $CH_3$ signals corresponding to the pyridine and minor product, and the presence of the signals in the mixture from the 4-acetate **11a** was not detectable in the spectrum of that from the 6-acetate **12a** or vice versa. This finding is consistent with a picture of parallel pathways from the diazepines to the aminopyridines suggested earlier (Scheme I) but separated in the case of **11** and **12** because equilibrium between the two series is blocked by substitution at nitrogen.

The rearrangement of the benzoyl enol ester **11b** to 3-hydroxy-6-benzamidopyridine **15b** also occurs in 50% yield to glacial acetic acid at 65 °C. As discussed below, any 1,3-diazepine formed would not be expected to survive these conditions. Thus the rearrangement of this 4-acetoxy-1-benzoyldiazepine appears to take the same

(5) Moore, J. A.; Völker, E. J.; Kopay, C. M. *J. Org. Chem.* **1971**, *36*, 2676.
(6) Preliminary communication: Moore, J. A.; Freeman, W. J.; Gearhart, R. C.; Yokelson, H. B. *J. Org. Chem.* **1978**, *43*, 787.

Scheme III




course in hydrocarbon solvent and in acidic media.

The pathway suggested for the reactions in the 1,5-dihydro series is indicated in Scheme III, with initial formation of a [4.1.0] bicyclic isomer, as suggested for many related rearrangements of seven-membered heterocyclic to six-membered aromatic systems.[7] In the 1-acyl-1,2-diazepine series opening of the three-membered ring can lead to either 2-(acylamido)pyridines or to 1-imidopyridinium ylides. Both types of products have been observed,[8] but the simple 1-benzoyl-1*H*-1,2-diazepine rearranges in 72% yield at 110 °C to 1-benzimidopyridinium ylide;[9] 1,3-diazepines have not been reported.

The contrasting formation of 6-benzamidopyridines in the present work and the appearance of the 1,3-diazepine in the enol ester reaction must be attributed to some structural difference between this series and the unsubstituted 1-acyl-1,2-diazepines. The C-4 oxygen substituent in **18** is the obvious point to consider. Electron release by the hydroxy group in the enol, or the acyloxy group in the ester, provides assistance for breaking the N–N bond in the 1,7-diaza [4.1.0] valence isomer **19** to give the dipolar intermediate **20**. Proton transfer then leads to the 6-benzamidopyridine, while cyclization to the 2,7-diaza bicyclic isomer and isomerization give **16**.

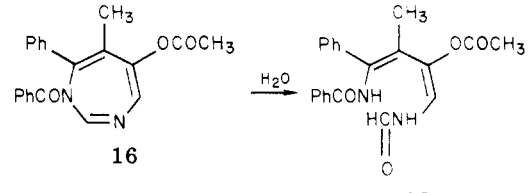
The rearrangement of heteroatoms that occurs in going from the 1,2- to the 1,3-diazepine recalls the conversion of quinoline *N*-oxides[10] and heavily aryl-substituted pyridine *N*-oxides[11] by irradiation to 1,3-oxazepines. These reactions are suggested to occur by photochemical generation of a 1-aza-7-oxabicyclo[4.1.0] intermediate followed by migration of the oxide ring and valence isomerization. A thermal 1,5-sigmatropic rearrangement mechanism is favored for the oxide rearrangement step, although a zwitterionic intermediate related to **20** was not excluded.[10] In the present series the direct rearrangement **19** → **21** is not ruled out, but in view of the additional stabilization available to **20**, we favor a stepwise process.

The greater basicity of the OH group in the bicyclic enol **19** (X = H) compared to that of the ester (X = $COCH_3$) should provide a more powerful driving force for the formation of **20**, as reflected in the faster rate of the ketone reactions under conditions ($CHCl_3$–MeOH) in which enolization is rapid. In the reactions in chlorobenzene, enolization is assumed to be rate determining, and rearrangement of the enol esters is more rapid.

The results with the enols and enol esters in this series nicely complement the recent observations of Streith et al. in the irradiations of 1-benzimido-3-(acyloxy)- and 3-hydroxypyridinium ylides, which presumably lead to isomeric 1,7-diazabicyclo[4.1.0] intermediates.[12] The acyloxy compound undergoes ring expansion to a mixture of 4- and 6-(acyloxy)diazepines analogous to **11** and **12** in this paper, whereas the 3-hydroxypyridinium ylide is converted to a mixture of 6-benzamido- and 2-benzamido-3-hydroxypyridines. A "push–pull" ring opening of the bicyclic intermediate, analogous to **19**, is proposed for the 3-hydroxy compounds. The two sets of results are fully consistent with the formation of the same 1,7-diazabicyclo[4.1.0]heptadiene intermediates from either photochemically activated 1-(acylimido)pyridines or thermally activated 1-acyl-1,2-diazepines.

**Chemistry of 1,3-Diazepine 16.** 1,3-Diazepines are much less well-known than either 1,2- or 1,4-diazepines. A number of 2-substituted tetrahydro-1,3-diazepines have been prepared from 1,4-diamines, but only one fully unsaturated monocyclic compound, a 2-amino derivative, has been described and the structural evidence was very limited.[13] Several benzo-1,3-diazepines with various functional groups in the ring have been prepared.[14]

The acetoxy-1,3-diazepine **16** is quite stable thermally, in contrast to the 1,2-diazepines **11** and **12**. A solution of **16** in chlorobenzene was kept at 120 °C for 6 days; although some darkening occurred, the NMR spectrum remained essentially unchanged. However, the 1,3-diazepine reacted slowly in air or in nominally dry solvents to give a high-melting, sparingly soluble compound. This substance was first obtained as a minor product in the thermal rearrangement of **11b**, and the structure was determined by crystallography to be the 1,4-bis(acylamido)butadiene **22**. The unit cell contained two mol-




ecules of **22**; examination of the torsion angles (Table V[15]) show that the conformations of the two independent molecules (primed and unprimed in Table I[15]) are essentially the same. The butadiene system is skewed, with a C=C–C=C torsion angle of 69°. In the crystal, the NH of the benzoyl group is within hydrogen-bonding distance (2.01 Å) of the C=O oxygen of the acetoxy group. A stereoprojection of the molecules is shown in Figure 1.

The formation of **22** involves the attack of water and hydrolysis of the highly susceptible acylformamidine system; **22** was prepared in good yield by warming a solution of **16** in aqueous THF. The facile hydrolytic ring opening of **16** suggested that addition products with the ring intact might be isolated with other nucleophiles. The

(7) Paquette, L. A. In "Non-Benzenoid Aromatics"; J. P. Snyder, Ed.; Academic Press: New York, 1969. van der Plas, H. C. "Ring Transformations of Heterocycles"; Academic Press; New York, 1973; Vol. 2.
(8) Streith, J.; Luttringer, J. P.; Nastasi, M. *J. Org. Chem.* **1971**, *36*, 2962.
(9) Streith, J.; Cassal, J. M. *Bull. Soc. Chim. Fr.* **1969**, 2175.
(10) Spence, G. G.; Taylor, E. C.; Buchardt, O. *Chem. Rev.* **1970**, *70*, 257.
(11) Buchardt, O.; Pedersen, C. L.; Harrit, N. *J. Org. Chem.* **1972**, *37*, 3592.
(12) Fritz, H.; Gleiter, R.; Nastasi, M.; Schuppiser, J.-L.; Streith, J. *Helv. Chim. Acta* **1978**, *61*, 2887.
(13) Troxler, F.; Weber, H. P.; Jaunin, A.; Loosli, H.-R. *Helv. Chim. Acta* **1974**, *57*, 750.
(14) Golik, U. *J. Heterocycl. Chem.* **1975**, *12*, 903.
(15) Supplementary material.

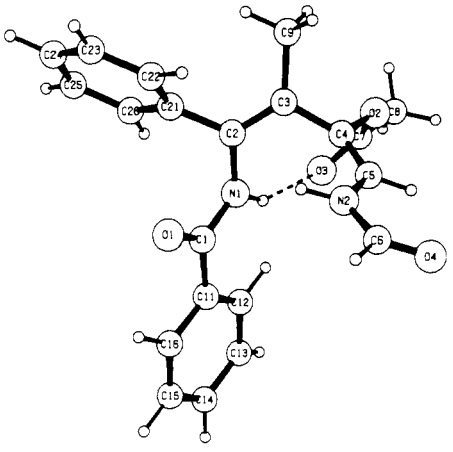
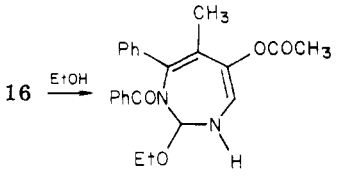


**Figure 1.** ORTEP projection of **22**.

diazepine reacted on warming in methanol or ethanol, but the butadiene **22** was isolated in each case, apparently because of the reaction of **16** or the initial addition product with traces of water. After several weeks standing at 25 °C in absolute ethanol the NMR spectrum of the reaction mixture showed signals (see Experimental Section) consistent for the 2-ethoxy-2,3-dihydro compound **23**, but a pure sample was not obtained.



**23**

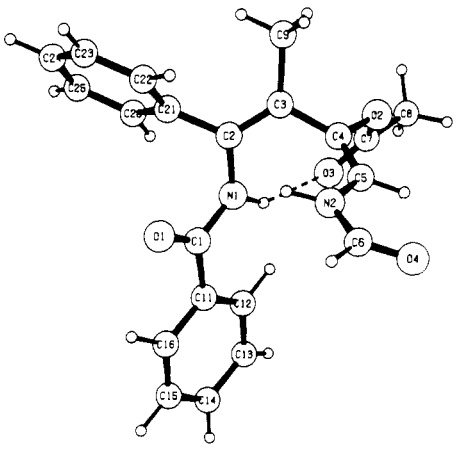
The structure of the 1,3-diazepine **16** is that of an enol ester of the dihydro-1,3-diazepinone **25**, and it was of considerable interest to explore the possible conversion of **16** to **25** by deacetylation, paralleling the conversion of enol acetate **11b** to the 1,2-diazepinone **9b**, which is accomplished with ethanolic KOH. Although the ring opening of **16** at the 2,3 bond was a potential problem, deacetylation of **16** in fact occurred rapidly with aqueous ethanolic KOH, with no significant hydrolysis to **22**. However, the product, isolated in high yield, was not the diazepinone **25** but rather the 3-hydroxy-6-benzamidopyridine **14**.

This rearrangement, which is analogous to the ring contraction of a 1,3-oxazepine to 3-hydroxypyridine observed by Buchardt,[11] is formulated (Scheme IV) via the 1,3-diazepine enol **24** and the 2,7-diaza bicyclic enol **26**. At the latter point, this pathway then converges with those of Scheme III, accounting for the fact that the 6-benzamidopyridine is the exclusive product in the reaction of the 1,2-diazepine ketone. It should be noted that under the same hydrolytic conditions which cause ring contraction of the 1,3-diazepine, the 1,2-diazepine **11** is converted in 50% yield to the 1,2-diazepinone, indicating a lower activation barrier for valence isomerization of the free enol in the 1-acyl-1,3-diazepine system.

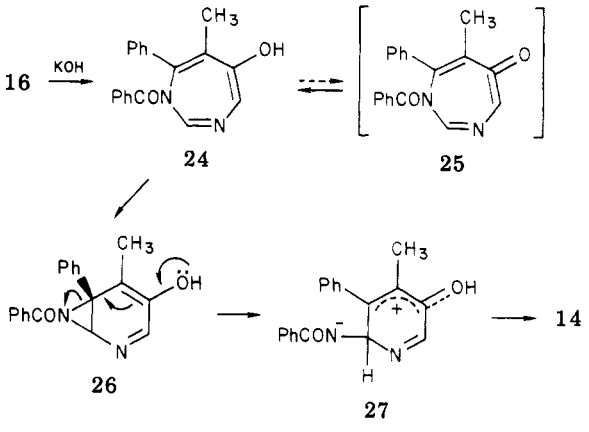
## Experimental Section

NMR spectra were obtained at 60 MHz on a Varian Model A-60-A or Perkin-Elmer R-12 instrument. Infrared spectra were obtained on a Perkin-Elmer Model 137 or Unicam SP-1100. Melting points were determined on a Fisher-Johns block.

**Thermal Rearrangements.** In the general procedure a solution of the diazepinone or enol ester in chlorobenzene was sealed in an NMR tube under $N_2$. The tube was placed in an oil bath at 120 °C and the reaction was followed by changes in the NMR spectrum.



**Scheme IV**



For rate measurements, the $CH_3$ region of the NMR spectrum was integrated 6–10 times during the course of the reaction and the areas of the peaks were measured vs. hexamethyldisiloxane as an internal standard. The data were fitted by linear regression analysis to a first-order rate expression; correlation coefficients were in the order of 0.997 ± 0.002.

For product isolation the diazepine was sealed in a heavy-wall tube in benzene or chlorobenzene and heated at 120 °C or other temperatures as given. When the reaction was complete (by NMR), the tube was cooled and opened. In most cases the pyridine product crystallized directly or after addition or ether.

**Thermal Rearrangement of Diazepinones.** The **benzoyl** ketone **9b**[4] (225 mg) was heated 60 min; cooling gave 168 mg of 6-benzamido-3-hydroxy-4-methyl-5-phenylpyridine **14b**; mp 209–212 °C. Spectra were identical with those of an authentic sample.[16]

The ***p*-nitrobenzoyl** ketone[4] **9c** (200 mg) after 30 min gave 110 mg of **14c** in several crops: mp 132–135 °C (same melting point after recrystallization); $\nu$ (KBr) 3600–2800 (br), 1660, 1520, 1340 $cm^{-1}$; $pK_a$ (50% MeOH) 2.1 (below), 8.9 (above);[17] $\delta$ ($Me_2SO$-$d_6$) 1.97 (s, 3), 2.8–3.8 (br, 2), 7.25 (s, 5), 7.79 (d, 2, $J$ = 8.5 Hz), 8.04 (s, 1, H-2), 8.20 (d, 2, $J$ = 8.5 Hz).

Anal. Calcd for $C_{19}H_{15}N_3O_4$: C, 65.32; H, 4.33; N, 12.03. Found: C, 64.89; H, 4.30; N, 11.89.

The ***p*-methoxybenzoyl** ketone **9d** (78 mg) after 7.5 min at 140 °C gave a yellow oil which did not crystallize: $\delta$ ($CDCl_3$) 1.88 (s, 3), 3.71 (s, 3), 7.20 (d, 2, $J$ = 9 Hz), 7.27 (s, 5), 7.50 (d, 2), 7.90 (s, 1), 8.37 (br, 2).

The **acetyl** ketone **9a** (215 mg) after 9.5 h gave a dark oil which was decolorized twice in $CHCl_3$ with charcoal. Crystallization from $CHCl_3$–ether gave 64 mg (30%) of the 3-hydroxy-6-acetamido-

(16) Moore, J. A.; Staskun, B. *J. Org. Chem.* **1978**, *43*, 4021.

(17) These $pK_a$ values are characteristic for proton gained and proton lost in 3-hydroxy-6-(acylamido)pyridines; see footnote 10 in: Moore, J. A.; Volper, E. J.; Kopay, C. N. *J. Org. Chem.* **1971**, *36*, 2676.

pyridine **14a**; mp 105–110 °C. Recrystallization from $CHCl_3$–ether gave crystals: mp 110–111 °C (lit.[18] mp 110–112 °C); $\nu$ (KBr) 3200, 1665 $cm^{-1}$; $\delta$ ($CDCl_3$) 1.89 (s, 3), 1.92 (s, 3), 7.0–7.6 (m, 5), 7.86 (s, 1). The analysis was not satisfactory (a previous analysis of this compound indicated that $H_2O$ was present).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83. Found: C, 68.86; H, 5.97.

**Rearrangement of 1-Benzoyldiazepinone 9b in Chloroform–Methanol.** (a) A solution of 100 mg of **9b** in 0.6 mL of $CDCl_3$ and 0.3 mL of $CD_3OD$ was placed in an NMR tube and kept at 35 °C. After 60 h the spectrum contained new singlet peaks at $\delta$ 1.85 (due to enol **13**) and $\delta$ 2.07 and 8.03 (due to benzamidopyridine **14b**), with a small singlet growing in between the doublet $CH_3$ peaks of **9b** due to deuterium exchange of H-5. After 85 h the spectrum showed a mixture of D-exchanged **9b** (30%), enol **13** (10%), and **14b** (60%). After 160 h the spectrum was essentially that of **14b**. After the solution cooled, fine white crystals which separated were collected; 59 mg; mp 206–207 °C. The IR spectrum matched that of authentic **14b**.

(b) A solution of 100 mg of **9b** in 0.9 mL of $CDCl_3$ plus 0.9 mL of $CD_3OD$ was divided among three NMR tubes. To one tube was added 0.001 mL (~0.1 mequiv/mmol of diazepinone) and to another was added 0.002 mL of pyridine. The three tubes were kept at 35 °C and spectra were recorded and integrated at intervals. In the solution containing 0.001 mL of pyridine the following data were obtained: at 7 h the enol content was 10% and **14b** was 4%; at 20 h the enol was 20% of the total and **14b** was 40%. With 0.002 mL of added pyridine at 7 h the enol was 17% and **14b** was 12%; at 13 h the enol reached a maximum value of 22% and **14b** was 30%.

**Reaction of 9b in Chloroform–Pyridine.** In $CDCl_3$ containing 0.2 equiv (0.002 mL/30 mg of **9b**) of pyridine and no $CD_3OD$, a trace of **14b** (<4%) was detected after 90 h at 35 °C.

In a solution of **9b** in $CDCl_3$ + pyridine-$d_5$ (1:1), a peak at $\delta$ 1.85 due to enol **10** amounting to 22% of the total $CH_3$ integral was present after 15 min and remained unchanged for 2 h; the peak due to **14b** represented 7% of the total. Addition of $D_2O$ caused an increase in the enol peak to about 40% of the diazepine $CH_3$ signal and the $CH_3$ doublet of **9b** became a singlet due to D exchange. A solution of 6 N $H_2SO_4$ in $D_2O$ was then added to the tube and the spectrum of the $CDCl_3$ layer showed $CH_3$ peaks for **9b** (singlet at $\delta$ 1.3) and **14b** ($\delta$ 2.0).

**4-Acetoxy-1-benzoyl-5-methyl-6-phenyl-1*H*-1,2-diazepine (11b).** A mixture of 2.5 g of 1-benzoyldiazepinone **9b** (mp 116–117 °C (not recrystallized); lit.[4] mp 127–129 °C), 4 mL of pyridine, and 3 mL of $Ac_2O$ was warmed with stirring to 40 °C. After 24 h the resulting pale green solution was treated with 6 mL of $H_2O$ in portions. Droplets of oil which separated were crystallized by rubbing, and crystallization then occurred to give a mass of yellow crystals which were collected, washed with water, and dried: 2.50 g; mp 125–126 °C. Recrystallization from $CH_2Cl_2$–pentane raised the melting point to 128–129 °C; $\nu$ ($CHCl_3$) 1760, 1665 $cm^{-1}$; $\delta$ ($CDCl_3$) 1.78 (s, 3), 2.30 (s, 3), 6.67 (s, 1), 7.2–7.6 (m, 9), 7.7–7.9 (m, 2).

Anal. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.25. Found: C, 72.71; H, 5.02.

**Thermal Rearrangement of 11b.**[19] A solution of 3.0 g of the enol acetate **11b** in 35 mL of toluene was heated at 90 °C for 90 min; TLC showed two products and no **11b** remaining. After the solution cooled, a mass of white crystals separated; these were collected and washed with ether to give 1.2 g of the 3-acetoxy-6-benzamidopyridine **15b**: mp 168–169 °C; $\nu$ (KBr) 3300 (NH), 1755, 1650 $cm^{-1}$; $\delta$ ($CDCl_3$) 1.97 (s, 3), 2.38 (s, 3), 7.2–7.7 (m, 10), 7.82 (br, 1), 8.33 (s, 1).

Anal. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24. Found: C, 72.61; H, 4.98.

The toluene–ether filtrate from **15b** was evaporated to an oil; further crystallization from $CH_2Cl_2$–ether gave 0.59 g of large prisms of the 1,3-diazepine **16b**: mp 146–148 °C; $\lambda_{max}$ (MeOH) 270 nm ($\epsilon$ 11 000); $\nu$ (KBr) 1760, 1670, 1635; $\delta$ ($CDCl_3$) 1.74 (s, 3), 2.28 (s, 3), 6.7–7.7 (m, 12); *m/e*(calcd) 346.131, *m/e*(found) 346.131.

Anal. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24. Found: C, 72.93; H, 5.11.

Further crystallization from $CHCl_3$–ether gave in succession further crops of **15b** (total 1.68 g, 56%) and **16b** (total 0.77 g, 26%) [later (mixed) crops were separately recrystallized]. From crops 10–12 were obtained also 60 mg (2%) of the butadiene **22**, mp 206–208 °C, and 51 mg of unreacted **11b**, mp 126–127 °C.

**Thermal Rearrangement of 11c.** A solution of 220 mg of the 1-benzoyl enol benzoate **11c** in chlorobenzene was heated 90 min in a sealed tube at 120 °C. After the solution had cooled and was diluted with ether, 110 mg of white solid crystallized. Recrystallization from ethyl acetate gave 40 mg of the 3-(benzoyloxy)-6-benzamidopyridine **15c**: mp 194–198 °C (lit.[20] mp 199–200 °C); $\delta$ ($CDCl_3$) 2.04 (s, 3), 7.0–7.7 (m, 13), 7.92 (s, 1), 8.1–8.4 (m, 3). The IR spectrum matched that of an earlier sample.[20]

**Thermal Rearrangement of 11a. (a) NMR Study.** A solution of 1-acetyl-4-acetoxy-5-methyl-6-phenyldiazepine (**11a**), in chlorobenzene plus dimethylsiloxane, was kept at 120 °C and the NMR spectrum was scanned and integrated 10 times during 6 h (A-60-A, 250-Hz sweep). The initial spectrum due to **11a**, with $CH_3$ peaks at 83, 114, and 128 Hz, changed progressively to a final spectrum with six peaks for the $CH_3$ groups in **15a** and the second product (presumed 1,3-diazepine). The peaks due to **15a** appeared at 102, 119, and 125 Hz and those from the second product at 92, 98, and 113 Hz; the area ratio was 7:3.

**(b) Product Isolation.** A solution of 225 mg of **11a** in chlorobenzene was kept 9.5 h at 120 °C and then evaporated. Addition of ether caused the dark residue to crystallize, and 120 mg of tan crystals, mp 141–142 °C, was obtained. Decolorization and recrystallization from ether gave 107 mg of **15a**: mp 143–144 °C; $\nu$ (KBr) 3400, 1750, 1690 $cm^{-1}$; $\delta$ ($CDCl_3$) 1.90 (s, 3), 2.21 (s, 3), 2.33 (s, 3), 2.33 (s, 3), 7.1–7.6 (m, 6), 8.1 (br s, 1).

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.95; H, 5.23; N, 9.78.

A 24-mg sample of this compound was hydrolyzed with NaOH in aqueous MeOH. The clear solution was then neutralized with 0.1 N HCl. After evaporation of most of the methanol, white crystals were obtained on chilling: 6.8 mg; mp 108–112 °C. The IR spectrum matched that of **14a** prepared from **9a**.

**Rearrangement of 11b in Acetic Acid.** A solution of 100 mg of **11b** in 1 mL of glacial acetic acid was kept 5.5 h at 65 °C. The dark red solution was evaporated several times with toluene to remove AcOH and the resulting oil was chromatographed on 3 g of silica gel. The yellow oil eluted with $CHCl_3$ was crystallized from $CHCl_3$–ether to give 50 mg of white crystals of 3-acetoxy-6-benzamidopyridine **15b**; mp 167–169 °C.

**Thermal Rearrangement of 12a. (a) NMR Study.** The NMR spectrum of 1-acetyl-6-acetoxy-5-methyl-4-phenyldiazepine (**12a**) at 120 °C was followed as described for **11a**. The initial spectrum due to **12a** with three $CH_3$ peaks at 88, 110, and 127 Hz downfield changed progressively to a final spectrum which contained five peaks for the two sets of $CH_3$ peaks in **17** and the second product, with the high-field peak of **17** and the low-field peak of the second product coinciding within 1 Hz. The peaks due to **17**, confirmed from a separate spectrum in chlorobenzene of the compound after isolation, were at 113, 126, and 134 Hz; those due to the second product were at 82, 110, and 113 Hz.

**(b) Product Isolation.** A solution of 135 mg of the diazepine **12a** in 3 mL of benzene was heated under $N_2$ in a sealed tube at 120 °C for 5 h. The resulting amber solution was evaporated to a crystalline residue which was recrystallized from $CH_2Cl_2$–pentane to give 60 mg of 2-acetamido-3-acetoxy-4-methyl-5-phenylpyridine (**17**): mp 163–166 °C; IR 3200, 1760, 1680 $cm^{-1}$.

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.81; H, 5.74; N, 9.62.

Acetylation of this product ($Ac_2O$, $Et_3N$, 25 °C) gave a triacetyl derivative, recrystallized from $CHCl_3$–pentane; mp 148–150°. The IR spectrum of this material (1760, 1700, 1680 (sh)) matched that of a sample prepared by acetylation of 2-amino-3-hydroxy-4-methyl-5-phenylpyridine (**8**).

**2-Acetoxy-4-benzamido-1-formamido-3-methyl-4-phenyl-1,3-butadiene (22).** A solution of 60 mg of the 1,3-diazepine **16** in 2 mL of tetrahydrofuran and 1 mL of water was

(18) Moore, J. A.; Wineholt, R. L.; Marascia, F. J.; Medeiros, R. W.; Creegan, F. J. *J. Org. Chem.* **1967**, *32*, 1353.

(19) This procedure, at 90 °C, is a significant improvement over that previously given.[6]

(20) Moore, J. A.; Marascia, F. J. *J. Am. Chem. Soc.* **1959**, *81*, 6049.

kept at 45 °C for 22 h. Fine white crystals separated on cooling. The mixture was extracted with $CH_2Cl_2$. After the extracts were washed with water, dried, and evaporated, crystallization from $CH_2Cl_2$–ether gave 43 mg (68%) of **22**: mp 212–215 °C; $\lambda_{max}$ (MeOH) 234 ($\epsilon$ 31 000), 280 (14 000), (sh)) nm; $\nu$ (KBr) 3315, 1730, 1700, 1680, 1660, 1630 $cm^{-1}$; $\delta$ ($CDCl_3$) 1.84 (s, 3), 2.22 (s, 3), 7.0–8.3 (m, 13), 9.2–9.5 (br s, 1); $m/e$(calcd) for $C_{21}H_{20}N_2O_4$ 364.121, $m/e$(found) 364–121.

Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.21; H, 5.53. Found: C, 69.29; H, 5.45.

**Reaction of 16 in Ethanol.** A solution of 25 mg of 1,3-diazepine **16** in 2 mL of absolute ethanol was allowed to stand for 2 weeks at 22 °C; the color changed from yellow to pale orange. The solution was evaporated and after traces of ethanol were codistilled with $CCl_4$, the $^1H$ NMR spectrum ($CDCl_3$) showed $CH_3$ signals for unreacted **16** at $\delta$ 1.77 and 2.32 and the following peaks due to **23**: $\delta$ 1.97 (t, $J$ = 7 Hz, $CH_3CH_2$), 1.74 (s, ring $CH_3$), 2.22 ($COCH_3$), 2.70 (q, $J$ = 7 Hz, $CH_3CH_2O$), 5.78 (m, NH), 6.44 (d, $J$ = 3.2 Hz, C2-H). Deuterium exchange caused loss of the 5.78 peak and the peak at 6.44 became a singlet. The areas of the two sets of peaks were in ratio of ~1:1. After the analyte was redissolved in ethanol and the resulting solution allowed to stand for 6 weeks, the peaks due to **23** and **16** were in a ratio of about 8–9:1, and the $CCH_3$ peak of **22** was visible at $\delta$ 1.86.

**Reaction of 16 with Base.** To a solution of 100 mg of **16** in 2.5 mL of methanol was added 0.7 mL of aqueous 1.0 N NaOH. After 3 h at 25 °C the pale yellow solution was acidified with 2 N HCl and then neutralized with $NaHCO_3$. At neutral pH the amphoteric product crystallized as a white solid: 80 mg; mp 115–126 °C. This was identified by IR and $^1H$ NMR comparison as the methanol solvate of the 6-benzamido-3-hydroxypyridine **14b**. Recrystallization from $CHCl_3$–ether gave crystals: mp 214–217 °C; the mixture melting point with **14b** of mp 212 °C showed no depression.

**Crystallographic Analysis of 22.** The crystals of **22** were monoclinic, space group $P2_1/n$, with $a$ = 18.838 (4) Å, $b$ = 19.853 (5) Å, $c$ = 10.580 (4) Å, $\beta$ = 95.68 (3)°, and $d_{calcd}$ = 1.229 g $cm^{-3}$ for $Z$ = 8 ($M_r$ = 364.40 for $C_{21}H_{20}N_2O_4$). The intensity data were collected on a Hilger-Watts diffractometer (Ni-filtered Cu K$\alpha$ radiation, $\theta$–$2\theta$ scans, pulse-height discrimination). A crystal measuring approximately 0.10 × 0.12 × 0.4 mm was used for data collection; the data were not corrected for absorption ($\mu$ = 7.1 $cm^{-1}$). A total of 3735 reflections were measured for $\theta$ < 48°, of which 2769 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple-solution procedure[21] and was refined by full-matrix least squares. In the final refinement anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are $R$ = 0.048 and $R_w$ = 0.051 for the 2769 observed reflections. The final difference map has no peaks greater than ±0.2 e $A^{-3}$.

**Registry No. 9a**, 40711-78-2; **9b**, 40711-79-3; **9c**, 40711-81-7; **9d**, 40711-80-6; **10b**, 17827-20-2; **11a**, 40711-83-9; **11b**, 65594-62-9; **11c**, 40711-84-0; **12a**, 40711-76-0; **13b**, 70321-02-7; **14a**, 10137-08-3; **14b**, 10137-10-7; **14c**, 70321-03-8; **14d**, 70321-04-9; **15a**, 70321-05-0; **15b**, 65594-63-0; **15c**, 70321-06-1; **16b**, 65594-64-1; **17**, 70321-07-2; **22**, 70321-09-4; **23**, 70321-10-7; **8**, 70321-01-6; **17** acetyl derivative, 70321-08-3.

**Supplementary Material Available:** Tables I–V containing final atomic parameters, anisotropic thermal parameters, bond lengths, bond angles, and torsion angles for **22** (6 pages). Ordering information is given on any masthead page.

(21) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr. Sect. A*, **1971**, *27*, 368.

# Synthesis and Chemistry of *N*-Methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepinium Derivatives

Jackson B. Hester, Jr.,* Constance G. Chidester, and Jacob Szmuszkovicz

*Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001*

*Received March 5, 1979*

8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine was alkylated at N-2 of the triazole ring with trimethyloxonium fluoroborate. Mild alkaline hydrolysis of this derivative cleaved the triazole system to give acetic acid 2-(7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)-1-methylhydrazide, the structure of which was confirmed by an independent synthesis. The synthesis of several 8-chloro-3-methyl-6-phenyl-4*H*-*s*-triazolo-[4,3-*a*][1,4]benzodiazepinium derivatives is also presented.

The discovery that the 6-phenyl-4*H*-*s*-triazolo[4,3-*a*]-[1,4]benzodiazepines[1,2] (viz., alprazolam, **4**; see Chart I) have useful anxiolytic activity[3] has generated an intense interest in the chemistry of this class of compounds. Early in the development of this series we became interested in the structural requirements for biological activity. In particular we wondered if the seven-membered ring was required or if the biological activity might be retained if the ring were opened between N-5 and C-6 to give an amino benzophenone. From independent synthetic studies we had found that the primary amino ketone was unstable relative to the cyclic structure.[4] We therefore decided to alkylate this nitrogen (N-5 of **1**) and thus stabilize the ring-opened form. Since we had previously found that alkylation of **2** with trimethyloxonium fluoroborate occurred exclusively at N-5 to give, after aqueous workup, the ring-opened product,[5] we chose these conditions for the present study. In the event, however, alkylation of **1** with the Meerwein reagent occurred on the triazole ring rather than on the azepine nitrogen (N-5).[6] This paper describes these results.

Alkylation of **1** with trimethyloxonium fluoroborate followed by hydrolysis of the product with aqueous potassium carbonate at ambient temperature gave a ring-

(1) J. B. Hester, Jr., A. D. Rudzik, and B. V. Kamdar, *J. Med. Chem.*, **14**, 1078 (1971).
(2) K. Meguro, H. Tawada, H. Miyano, Y. Sato, and Y. K. Uwada, *Chem. Pharm. Bull.*, **21** 2382 (1973).
(3) T. M. Itil, N. Polvan, S. Egilmez, B. Saletu, and J. Marasa, *Curr. Ther. Res. Clin. Exp.*, **15**, 603 (1973).
(4) J. B. Hester, Jr., U.S. Patent 3 709 898 (1973).
(5) J. B. Hester, Jr., and P. F. VonVoigtlander, *J. Med. Chem.*, in press.
(6) The successful preparation of the ring-opened compounds is described in M. Gall, J. B. Hester, Jr., A. D. Rudzik, and R. A. Lahti, *J. Med. Chem.*, **19**, 1057 (1976).

0022-3263/79/1944-2688$01.00/0 