After overnight refrigeration, filtration gave 16.5 g. of a greenish solid. Two recrystallizations from 10% sulfuric acid (Norit) yielded yellow crystals, which melted slowly with decomposition above 185°. Refrigeration of the filtrate gave a small amount of additional solid, total yield 14.8 g. (*ca.* 50%). The product appeared to be a sulfate salt on the basis of microanalysis.

Anal. Calcd. for $C_4H_5N_3OS \cdot 0.5H_2SO_4$: C, 25.00; H, 3.14; N, 21.88, S, 25.00. Found: C, 24.51; H, 3.31; N, 21.91; S, 24.81.

[1,2,3]Thiadiazolo[5,4-*d*]pyrimidin-5(4*H*)-one (21).—To 5.0 g. (*ca.* 0.026 mole) of the sulfuric acid salt of 5-amino-4-thiouracil (**20**) dissolved in 170 ml. of 2.5 *N* hydrochloric acid and cooled to 0° was added, with stirring, 2.3 g. (excess) of sodium nitrite in 15 ml. of water during 15 min. After an additional 1.5 hr. at 0–5°, the solid was filtered, washed with a little cold water, and oven-dried to yield 3.1 g. (77%) of yellow solid, m.p. 239° (effervescence). Two recrystallizations from a large volume of ethanol gave a pale cream-colored solid, m.p. 239° dec.; λ_{max} 236, 287 mμ ($\epsilon \times 10^3$ 3.7, 8.2).

Anal. Calcd. for $C_4H_2N_4OS$: C, 31.16; H, 1.31; N, 36.35; S, 20.81. Found: C, 31.20; H, 1.65; N, 36.30; S, 20.80.

4-Carboxymethylthio-6-methoxy-5-nitropyrimidine (25).—To a suspension of 9.0 g. (0.047 mole) of 4-chloro-6-methoxy-5-nitropyrimidine in 125 ml. of water immersed in ice, there was added 4.3 g. (0.047 mole) of mercaptoacetic acid (Fisher). At 0° and with vigorous stirring a solution of 3.8 g. (0.095 mole) of sodium hydroxide in 30 ml. of water was added over 20 min. During this addition, color changes of yellow to green to brown were observed. After stirring for an additional 4.5 hr. at 0–5°, the now blue solution was filtered to remove 0.75 g. of starting material, and the ice-cooled filtrate was acidified with concentrated hydrochloric acid. After standing for 5 min. at room temperature the precipitated blue-purple solid was filtered and dissolved in a large volume of ethanol. Three treatments with Norit gave a yellow-green solution which was concentrated to a small volume, treated with a little water and refrigerated. Filtration and vacuum drying (80°) yielded 6.4 g. (55%) of yellow-green crystals, m.p. 136–138°, with preliminary shrinking about 120°. One additional recrystallization from ethanol brought the melting point to 138–139°.

Anal. Calcd. for $C_7H_7N_3O_5S$: C, 34.29; H, 2.88; N, 17.14; S, 13.06. Found: C, 34.49; H, 2.77; N, 16.92; S, 12.77.

4-Methoxy-7*H*-pyrimido[4,5-*b*][1,4]thiazine-6(5*H*)-one (26).—A solution of 2.5 g. (0.01 mole) of 4-carboxymethylthio-6-methoxy-5-nitropyrimidine (**25**) in 70 ml. of methanol was treated with 0.5 g. of platinum oxide and hydrogenated in a Parr apparatus (*ca.* 2 atm.). After 2 hr., the catalyst was filtered off and the filtrate was concentrated to dryness to give a red oily solid. Two treatments with 25-ml. portions of ethyl acetate followed by evaporation of solvent gave 1.8 g. of brown solid. Two recrystallizations from ethanol–petroleum ether (b.p. 60–70°) yielded white crystals, 1.4 g. (70%), m.p. 190–191°; λ_{max} 236, 246 (sh), 283 (sh), 295 mμ ($\epsilon \times 10^3$ 15.0, 13.5, 5.0, 5.5).

Anal. Calcd. for $C_7H_7N_3O_2S$: C, 42.64; H, 3.58; N, 21.32; S, 16.14. Found: C, 42.68; H, 3.48; N, 21.39; S, 16.11.

4-Methoxy-6-phenyl-7*H*-pyrimido[4,5-*b*][1,4]thiazine (30).—A solution of 4.9 g. (0.031 mole) of 5-amino-6-mercapto-4-methoxypyrimidine (**2**) in 40 ml. of 10% sodium hydroxide was treated with 4.9 g. (0.031 mole) of phenacyl chloride and stirred for 24 hr. at room temperature. After filtering and washing with a little ether, the resultant tan solid, m.p. 175–180°, weighed 5.8 g. Two recrystallizations from ethanol–benzene gave 5.0 g. (62%) of pale yellow needles, m.p. 177–179° (does not form a clear melt); λ_{max} 233, 268, 295, 344 mμ ($\epsilon \times 10^3$ 13.6, 20.0, 6.4, 8.4).

Anal. Calcd. for $C_{13}H_{11}N_3OS$: C, 60.69; H, 4.31; N, 16.34. Found: C, 60.60; H, 4.63; N, 16.29.

4-Hydrazino-6-phenyl-7*H*-pyrimido[4,5-*b*][1,4]thiazine (31).—A solution of 0.5 g. (0.002 mole) of 4-methoxy-6-phenyl-7*H*-pyrimido[4,5-*b*][1,4]thiazine (**30**) in 10 ml. of ethanol was treated with 2 ml. of 85% hydrazine and refluxed for 5 hr. The solution was filtered hot. Cooling of the filtrate then gave 0.35 g. (70%) of long, yellow needles, m.p. 198–202°. The analytical sample was recrystallized from ethanol to give deep orange needles, m.p. 198–200°; λ_{max} 276, 378 (broad) mμ ($\epsilon \times 10^3$ 21.0, 7.5).

Anal. Calcd. for $C_{12}H_{11}N_5S$: C, 56.02; H, 4.31; N, 27.23; S, 12.44. Found: C, 56.01; H, 4.33; N, 27.01; S, 12.35.

Heterocyclic Studies. XII. The Base-Catalyzed Deuterium Exchange and Rearrangement of 2,3-Dihydro-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one to α-Aminopyridines[1,2]

JAMES A. MOORE AND ESTELLE C. ZOLL

Department of Chemistry, University of Delaware, Newark, Delaware

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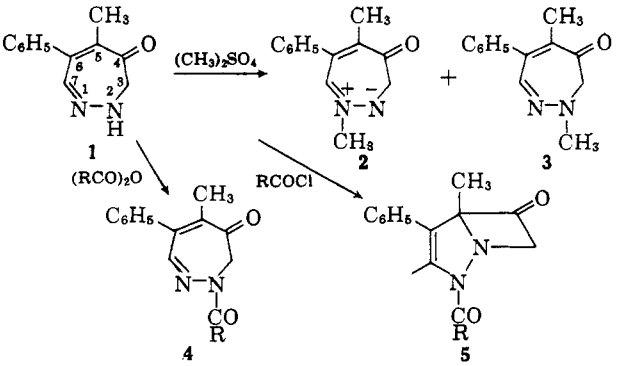
Deuterium exchange of the diazepinone **1** in basic solution was determined by n.m.r. spectra and found to occur at C-3 and more slowly at C-7 to give the 3,3,7-d_3 compound by deuteration of the anions **6** and **7**. Rearrangement of **1** in basic solution gives 2- and 6-amino-3-hydroxy-4-methyl-5-phenylpyridines in approximately equal amounts. The 2-methyldiazepinone **3** gives the 2-methylaminopyridine **11**. A suggested mechanism for the rearrangement is cleavage to the acyclic intermediate **14** and recyclization.

In previous papers we have described the formation of and structural evidence for the diazepinone **1**.[3,4] Electrophilic reagents attack **1** at both nitrogen atoms; with methyl sulfate in alkaline solution, equal amounts of the 1- and 2-methyl derivatives **2** and **3** are produced. Acylation with acid chlorides in pyridine solution occurs at N-1; in this case the substitution is accompanied by bridging to give the bicyclic ketone **5**.[5] With acid anhydrides the 2-acyl derivatives **4** are obtained.

The factors governing the position of attack of **1** with various reagents are not yet fully understood;



1 2 3 4 5

some of these products have been assumed to arise by participation of the anion **6** and others from the neutral molecule.[4] The ketone **1** is soluble in dilute aqueous alkali, and this acidic character has been attributed to

(1) Supported in part by Grant No. DA-CML-18-108-61-6-24 from the Army Chemical Corps.

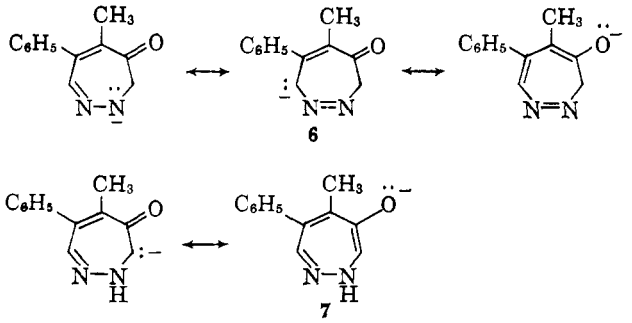
(2) Paper XI: J. A. Moore and C. L. Habraken, *J. Am. Chem. Soc.*, **86**, 1456 (1964).

(3) J. A. Moore and R. W. Medeiros, *ibid.*, **81**, 6026 (1959).

(4) J. A. Moore and J. Binkert, *ibid.*, **81**, 6029 (1959).

(5) J. A. Moore, F. J. Marascia, R. W. Medeiros, and E. Wyss, *ibid.*, **84**, 3022 (1962).

the delocalization of negative charge in **6**. The NH group is clearly the most acidic center in the mo ecule, and, since no alkylation or acylation products involving attack at the potentially enolizable C-3–C-4 system have been encountered, the possible role of the enolate anion **7** in reactions of **1** has not been considered. In connection with studies on the aldol condensation of **1**,



described in the following paper,[6] it was of interest to examine this possibility by means of deuterium exchange studies. This work has established that enolization at C-3 is in fact rapid, and has also revealed a new rearrangement pathway of this highly reactive molecule.

The deuterium exchange of **1** was carried out in 2.5 *N* sodium deuterioxide–deuterium oxide solution at room temperature. The extent and position of exchange was determined by observing the changes in the n.m.r. spectrum at 60 Mc., both in the D_2O solution directly and also of the diazepinone **1** recovered from the exchange in $CDCl_3$ (tetramethylsilane) solution. In $CDCl_3$, and also dimethyl sulfoxide, the singlet (δ = 7.03 p.p.m.) from the C-7 proton of **1** was clearly separated (upfield) from the phenyl–NH multiplet at 7.08–7.50 p.p.m. (Fig. 1A), although not far enough for independent integration. The multiplet from 7.03–7.50 p.p.m. corresponded to seven protons, C_6H_5, C–7 *H*, and N*H*. In aqueous sodium hydroxide or sodium deuterioxide (Fig. 1C) the C-7 proton signal was again separated from the phenyl peak, but was now downfield. The phenyl signal in this case was a single peak without fine structure. (Peak positions in the D_2O spectra cannot be given since no internal standard was present.) That the separate peak was due to the C-7 proton in both cases follows from the exchange results described below. The signals from the C*H*$_3$ and C*H*$_2$ groups (1.88 and 3.86 p.p.m., respectively, in $CDCl_3$) corresponded exactly to three and two protons both in $CDCl_3$ and H_2O–NaOH solutions. The CH_2 peak in the $CDCl_3$ spectrum was a doublet (J = 3 c.p.s.) due to spin coupling with the N*H*; this splitting was absent in the spectrum of the 2-methyldiazepinone **3**.

Twenty-two spectra of a solution of **1** in D_2O–NaOD were recorded and integrated at intervals over an extended period; values for the areas of the CH_3, CH_2, combined phenyl–C-7, and water peaks during the first 4 days are given in Table I. The area of the methyl peak was used as a reference in calculating the loss in protons from the C-3 and C-7 positions. In the first spectrum, integrated 15 min. after the solution was prepared, the CH_2 peak area corresponded to 1.4 protons; after 3 days this peak was no longer detectable, indicating complete exchange at this position. The peak due

(6) R. K. Bly, E. C. Zoll, and J. A. Moore, *J. Org. Chem.*, **29**, 2128 (1964).

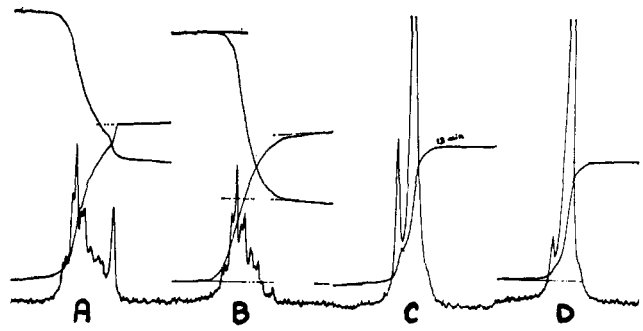


Fig. 1.—Phenyl–C-7 peaks of n.m.r. spectra of compound **1**: A, $CDCl_3$ solution before exchange; B, $CDCl_3$ solution after 96-hr. exchange; C, D_2O–NaOD solution after 13 min.; D, D_2O–NaOD solution after 72 hr.

to the C-7 proton diminished more slowly and had not disappeared completely until the tenth day; the change during 72 hr. is indicated in Fig. 1C and 1D. The area of the combined phenyl–C-7 peak dropped from an initial value of 6.3 protons (theoretical value 6.0, since NH exchange is very rapid) to a minimum corresponding to about 5.1 protons after 4 days. The area of the water peak increased during this period, but the integration was too erratic to permit correlation with the number of protons lost as water by exchange at C-3 and C-7. No loss of protons from the methyl and phenyl groups was apparent. The ratio of the phenyl–C-7 peak to the total integral fluctuated after the fourth day, but there was no consistent drift.

TABLE I

INTEGRATION OF N.M.R. SPECTRUM OF **1** IN D_2O–NaOD

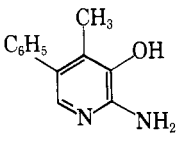
Time, hr.	Peak area[a] CH_3	CH_2	H_2O	Phenyl-C-7	Number of protons[b] CH_2	Phenyl-C-7
0.25	6.9	3.2	9.1	14.6	1.4	6.3
0.5	6.9	3.1			1.35	
1.6	7.0	1.8	10.3	14.8	0.8	6.3
3.6	7.2	1.0	10.3	14.5	0.4	6.1
7.2	7.3	0.8	10.9	14.5	0.3	5.9
25	7.3	0.4	11.8	13.8	0.15	5.6
72	6.9	0	11.4	12.7	0	5.5
96	7.2		11.9	12.4		5.1

[a] In units of 0.5 cm. on integration curve. [b] Three times peak area/methyl area.

Another solution of **1** in sodium deuterioxide was acidified after 4 days and the precipitated diazepinone was purified by recrystallization. The n.m.r. spectrum (Fig. 1B) contained no discernible peaks for the C-3 or C-7 protons; the ratio of phenyl–NH to methyl peaks was 6.0:3.0, although this agreement is probably fortuitous. These data demonstrate that the deuterated product is the 3,3,7-d_3 compound, exchange at C-3 arising by deuteration of anion **7** and at C-7 by deuteration of **6**. The fact that exchange at C-7 is slower than at C-3, even though **6** is presumably present in much larger concentration, may be due to a low negative charge density at C-7 or possibly shielding by the adjacent phenyl group.

In the course of these exchange experiments it became evident from the n.m.r. data and isolation of the deuterated compound that solutions of **1** in alkali were not, as earlier believed,[4] stable on prolonged standing. The material recovered from the exchange solution after 4 days contained an appreciable impurity and, on

refluxing an alkaline solution of **1** for a few hours, a colorless amphoteric product was isolated which was identified as 2-amino-3-hydroxy-4-methyl-5-phenylpyridine (**8**) by comparison with an authentic sample.[7] This structure, coupled with n.m.r. evidence discussed below, prompted a search for the isomeric 6-amino-hydroxymethylphenylpyridine (**9**), and this was isolated in smaller amount after chromatography on cellulose. Neither of the pyridines was obtained in pure form, but both compounds were characterized by conversion to derivatives and comparison with previously prepared specimens.[7]



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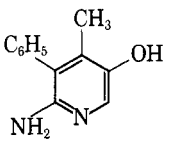

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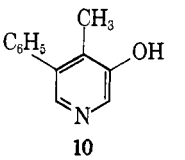


10

Concurrent with the isolation of these pyridines, independent evidence of the rearrangement was obtained from the n.m.r. spectra of the D_2O solution discussed above. Two peaks, displaced downfield from the methyl resonance of **1**, became visible after 3 days and steadily increased in intensity until, after 46 days, the three methyl peaks were of comparable area, with the two new peaks separated by 9 and 22 c.p.s. from the methyl peak of **1**. It was apparent that these new peaks arose from the methyl groups of **8** and **9**, and the assignment of the higher field signal to **9** and the lower to **8** was made by comparison with the shifts of the methyl peaks of authentic samples of the pyridines in alkaline D_2O solution. The n.m.r. data for **8** and **9** and two related pyridines are given in Table II. To permit the assignment of the peaks in the exchange spectrum,

TABLE II

N.M.R. PEAKS[a] OF AMINO-3-HYDROXY-4-METHYL-5-PHENYLPYRIDINES IN D_2O–NaOD[a]

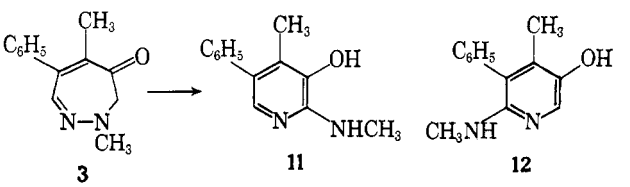
Compound	Methyl	Phenyl	2- or 6-H	Other
8	122	444	426	
9	109	448	*b*	
11	123	443	431	N-CH_3, 177
10	122	438	448, 472	

[a] Peak positions in c.p.s. relative to methyl peak of **1** taken as 100. [b] Peak could not be identified.

the diazepinone **1** was used as an internal reference; the methyl peak of **1** was assigned an arbitrary shift value of 100 c.p.s. The δ-values of 22 and 9 c.p.s. for **8** and **9**, respectively, coincide precisely with those observed in the spectrum of **1**. It is of interest that the position of the methyl peak of **8** corresponds exactly to that of the methyl peak of the desamino pyridine **10**, showing no effect of the 2-amino group, while the presence of the 6-amino group in **9** causes a diamagnetic shift of the methyl signal of 13 c.p.s.

In the isolation of the pyridines **8** and **9** on a preparative scale, the 2-amino isomer **8** appeared to be present in larger amount, but the yields on isolation are a poor measure since the compounds are extremely sensitive to oxidation and can be purified only with substantial losses. The yield of the crude pyridine mixture was 39%, but only a few per cent of the purified separate isomers was obtained. A better indication of the yields was provided by the relative areas of the methyl peaks in the n.m.r. spectrum. Within the limits of error of the integration (about 10%), the ratio of the area of the methyl peaks to the total integral (all protons in the solution) remained constant (20.5 to 23%) throughout the entire series of spectra, indicating no significant deuterium exchange of methyl protons, either in **1** or in the pyridines. In the later spectra, a small peak or peaks, evidently due to methyl groups in unidentified decomposition products, became apparent upfield from the methyl peaks of **1**, **8**, and **9**. In the spectrum after 46 days, the pyridines comprised about 45% of the total methyl integral, about 35% appeared to be due to unreacted **1**, and the remainder to other species. Moreover, the relative areas of the two pyridine peaks differed by no more than 10%; if either was in excess, it appeared to be **9** rather than **8**. From these data it can be concluded that the yields of **8** and **9** are in the range of 25%.

The isolation of the pyridines **8** and **9** from the reaction of **1** with base suggested the identity of an amphoteric product that had been obtained previously in the attempted alkoxide-catalyzed aldol condensation of the 2-methyldiazepinone **3**.[6] By analogy with the reaction of **1**, it was clear that this compound was either 2- or 6-methylamino-3-hydroxy-4-methyl-5-phenylpyridine (**11** or **12**). Accordingly, the reaction of **3** with base was repeated in aqueous methanolic alkali and a product was isolated (94% of crude crystalline material) which had the composition $C_{13}H_{14}N_2O$ and whose properties corresponded in all respects with those expected for **11**. Treatment with acetic anhydride–pyridine furnished a diacetyl derivative. The pK_A values and ultraviolet spectra in neutral, acid, and basic solutions of the rearrangement product were very similar to those of **8**, but these properties do not distinguish between **8** and **9**,[7] and did not rule out the 6-methylamino structure **12**. A distinction between **11** and **12** was possible, however, from the n.m.r. spectrum in alkaline D_2O (Table II). Two three-proton peaks were present 23 and 77 c.p.s. downfield from the methyl peak of **1**, corresponding to the C-methyl and N-methyl peaks, respectively; the shift of 23 c.p.s. may be compared to those of 22 and 9 c.p.s. for the 2- and 6-amino derivatives, and provides conclusive proof of the 2-methylamino structure **11** for the rearrangement product. The other peaks in the spectrum are consistent with this structure but do not distinguish between the 2- and 6-isomers.

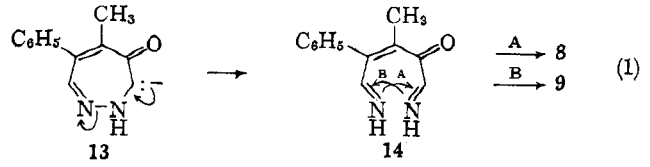


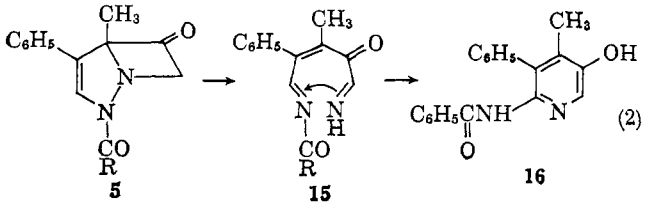
3 **11** **12**

The over-all path of the rearrangements of **1** and **3** to the amino pyridines is quite obvious; barring an implausible series of changes, N-2 of the diazepinone ring is extruded in the formation of the 2-amino compounds **8** and **11**, and N-1 is extruded in the formation of the 6-aminopyridine **9**. The formation of two isomers in the case of **1** and of a single isomer from **3** is inevitable from these structural changes, and shows only that alkyl migration does not occur. The ring contraction is al-

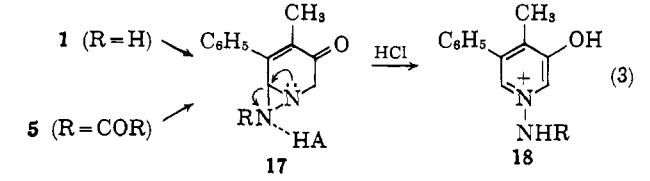
(7) J. A. Moore and F. J. Marascia, *J. Org. Chem.*, **81**, 6049 (1959).

most certainly a consequence of enolate formation at C-3, and a mechanism which suggests itself is the cleavage of this anion (**13**) by β-elimination to give an acyclic precursor **14** which can cyclize in two ways to give **8** and **9**. In the case of **3**, only path A would lead to product. A very similar intermediate (**15**) has been suggested previously as the precursor of the 6-benzamidopyridine (**16**) formed by solvolysis of the bicyclic ketone **5**[5]; in this case only path B is operative.

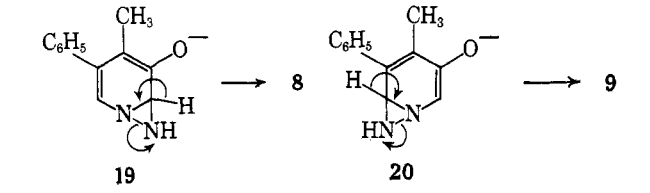




The ring contraction of **1** to **8** and **9** completes a set of four rearrangements that have been observed with **1** and the tautomeric benzoyldiazabicyclo[3.2.0]heptenone **5**. The α-aminopyridines **8**, **9**, **11**, and **16** are obtained from the diazepine and bicyclic systems in basic and neutral conditions, respectively (eq. 1 and 2), and in both systems mineral acid leads to 1-aminopyridinium salts **18** (eq. 3).[4,5] These acid-catalyzed rearrangements in both series have been suggested to occur by way of a 1,7-diazabicyclo[4.1.0]heptenone (**17**). A similar mechanism has been proposed for the ring contraction which accompanies acylation of an anilinoazepine to give *o*-phenylenediamine derivatives.[8]



A similar pathway, involving the bicyclic anions **19** and **20**, might be considered also for the formation of **8** and **9**. This appears very unlikely, however, since it requires that the diazabicyclo[4.1.0]heptane systems in



17 and **20** collapse to give exclusively **18** in acid and **9** in base. A careful search for the presence of **18** (R = H) in the base reaction was not made, but the yield of **18** isolated in the acid reaction was as high as 95%, with no indication of the presence of **9**. Furthermore, it is attractive to view the formation of the 6-aminopyridines from both **1** and **5** as proceeding by a common mechanism (acyclic intermediates **14** and **15**, eq. 1 and 2). Although **15** is not definitely established as the precursor of **16**, it is extremely improbable that **16** arises from the intermediate **18** (R = C_6H_5CO).[5] If parallel behavior of the two systems is assumed, an acyclic route to the α-aminopyridine products and a bicyclic route to the 1-aminopyridinium products presents the most consistent pattern available at present for all four rearrangements.

(8) R. Huisgen, D. Vossius, and R. Appl, *Chem. Ber.*, **91**, 1 (1958).

Experimental

Deuterium Exchange of 1.—Freshly cut sodium (115 mg.) was added to 2 ml. of deuterium oxide (<99%) while a slow stream of dry nitrogen was passed over the surface. To 1 ml. of this solution was added 200 mg. of **1** and the solution was sealed in a Varian n.m.r. sample tube.

The n.m.r. spectra were recorded on a Varian A-60 instrument with these settings throughout the series: filter band width, 1; radiofrequency field, 0 16; sweep time, 250 sec.; spectrum amplitude, 4.0; integral amplitude, 8.0. The total integral curve recorded on 22 spectra over a 46-day period varied from 15.6 to 17.7 cm. in height.

A solution of 200 mg. of **1** in 1 ml. of the above sodium deuterioxide solution was allowed to stand for 4 days and was then acidified by the addition of a solution of 310 mg. of phosphorus pentoxide in 1 ml. of deuterium oxide. The yellow precipitate, 193 mg. after drying in *vacuo*, was recrystallized from methylene chloride–ether to give orange needles, m.p. 150°.

Rearrangement of 2,3-Dihydro-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one (1).—A solution of 500 mg. of **1** in 5 ml. of 5% aqueous sodium hydroxide was refluxed for 3 hr. under a stream of nitrogen. The dark solution was cooled and acidified with hydrochloric acid; a small amount of tar was removed by filtration. The resulting yellow solution was treated with charcoal, which removed some of the color, and then brought to pH 7 with base. A total of 195 mg. of greenish white solid, m.p. 170–190° dec., was collected in several crops.

A 34-mg. portion of the first crop was sublimed twice at 0.1 mm. to give white crystals, m.p. 200–204° dec., pK_A 6.0 and 10.1, λ_{max}^{EtOH} 312 mμ (ϵ 5900), $\lambda_{max}^{EtOH,HCl}$ 322 mμ (7300), $\lambda_{max}^{EtOH,NaOH}$ 324 mμ (6400). The infrared spectrum was identical with that of authentic 2-amino-3-hydroxy-4-methyl-5-phenylpyridine (**8**).[7]

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.31; H, 6.29; N, 13.83.

A solution of 120 mg. of the crude solid material from above in 2 ml. of methanol was then placed on a column of Ecteola cellulose powder (10 g.) and eluted with pH 7.8 phosphate buffer. Fractions (5 ml.) were collected and aliquots were spotted on coated paper. The paper strips were developed with phosphate buffer and the pyridine components were visualized with ultraviolet light. The earlier fractions contained mainly the 2-amino-5-hydroxypyridine **9**. These were combined and extracted with several portions of methylene chloride. The dried extracts were evaporated to give 25 mg. of pale yellow residue which crystallized from ethyl acetate–ether to give a white powder, m.p. 193–195°; infrared spectrum was nearly identical with that of authentic **9**.

Later fractions eluted with buffer and with methanol contained the 2-amino-3-hydroxypyridine **8**. Extraction with methylene chloride and crystallization gave a very small amount of white solid, m.p. 200–205° dec. The infrared spectrum was the same as that from sublimed material.

For further characterization, 25 mg. of the crude 2-amino-3-hydroxy isomer from the original solid before chromatography was dissolved in methanol containing 15 mg. of sodium and treated with 50 mg. of picryl. After heating for 10 min. and dilution with water, a red precipitate was obtained which was recrystallized to give 15 mg. of 7,9-dinitro-4-methyl-3-phenyl-10*H*-pyrido[3,2-*b*][1,4]benzoxazine, m.p. 196°, undepressed on mixture with authentic sample.[7]

A sample of the other aminohydroxypyridine isomer obtained from the earlier fractions of the cellulose chromatography was treated with benzoyl chloride and pyridine at 70°. After isolation in the usual manner colorless crystals of 2-benzamido-5-benzoyloxy-4-methyl-3-phenylpyridine, m.p. 198–200°, were obtained. The infrared spectrum, λ^{KBr} 3.10, 5.74, and 6.08 μ, was identical with that of a sample previously prepared[7] from authentic **9**.

Rearrangement of 2,3-Dihydro-2,5-dimethyl-6-phenyl-4*H*-1,2-diazepin-4-one (3).—A solution of 604 mg. of **3** in 3 ml. of methanol and 2.5 ml. of aqueous 5% sodium hydroxide was refluxed (70°) for 3 hr. under a stream of nitrogen. The solution was cooled then and neutralized with dilute hydrochloric acid. A white precipitate, total of 570 mg. in several crops, was collected, washed with water, and dried. The material could not be sublimed without extensive decomposition. Recrystallization was finally accomplished with extensive loss from a very small volume of methanol to give colorless crystals of 3-hydroxy-4-methyl-2-methylamino-5-phenylpyridine (**11**), m.p. 200° dec., pK_A 5.7 and 9.7 (50% MeOH), λ_{max}^{MeOH} 276 (infl.) and 310 mμ (ε 10,000), $\lambda_{max}^{MeOH,\ HCl}$ 258 and 313 mμ (11,000), λ_{max}^{MeOH} 319 mμ (12,800).

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 73.11; H, 6.67; N, 12.99.

A solution of 37 mg. of the base in 1 ml. of methanol was treated with 0.5 ml. of concentrated hydrochloric acid. Evaporation of the methanol gave a crystalline mass which was collected and washed with a very small volume of iced water. Recrystallization from methanol–ether gave colorless needles of the **hydrochloride**, m.p. 235–240° dec.

Anal. Calcd. for $C_{13}H_{14}N_2O \cdot HCl$: C, 62.27; H, 6.03. Found: C, 62.45; H, 6.08.

3-Acetoxy-4-methyl-2-methylacetamido-5-phenylpyridine.—A solution of 300 mg. of the above base in 1.8 ml. of acetic anhydride and 3 ml. of pyridine was allowed to stand overnight at 25° and then was concentrated at reduced pressure to about one-third volume. Methanol was added, the solution was again evaporated, the residue was then dissolved in ether, and the solution was washed with dilute aqueous acid, base, and water and then evaporated to give 228 mg. of colorless solid. Recrystallization from acetone–ether gave colorless prisms, m.p. 135–136°, λ^{KBr} 3.32, 5.69, and 6.04 μ.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.39; H, 6.24; N, 9.21.

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Heterocyclic Studies. XIII. The Aldol Condensation of 2,3-Dihydro-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one and Rearrangement to a Pyridazine[1]

RUTA K. BLY, ESTELLE C. ZOLL, AND JAMES A. MOORE

Department of Chemistry, University of Delaware, Newark, Delaware

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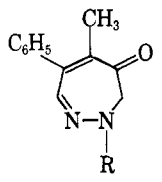
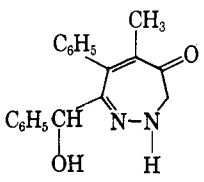
The aldol condensation of the diazepinone **1a** with benzaldehyde gives the 3α-hydroxybenzyl compound **3**, which is dehydrated to the 2-acetyl-3-benzylidene derivative **7** with acetic anhydride. Rearrangement of **7** to benzyl 3-(4-methyl-5-phenylpyridazinyl) ketone **8** occurs on hydrolysis. The structure **8** was based on degradation to the pyridazine carboxylic acid **12**, the pyridazine **13**, and the dicarboxylic acid **15a**. By carrying out the sequence of reactions with **1a** labeled at C-3 with C^{14} it was shown that C-3 is extruded in the ring contraction to **8**. The mechanisms of the aldol condensation and rearrangement and the instability of diazatropone and diazatropilidene derivatives are discussed.

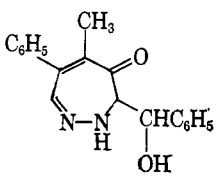
One of the reactions of the diazepinone **1a** mentioned in the first report[2] of the compound was the base-catalyzed condensation with benzaldehyde to give an aldol product considered to be **2**.[3] Physical data and evidence from a degradative sequence now require revision to structure **3**.



1a, R = H
b, R = CH_3



2



3

The infrared and ultraviolet spectra of the aldol, which were very similar to those of **1a**, did not clearly distinguish between **2** and **3**, but the n.m.r. spectrum, obtained after chemical evidence for **3** was in hand, was consistent only with this structure. In $CDCl_3$ solution (TMS) containing D_2O the C-3 and benzyl protons formed a pair of doublets (C-3, δ = 3.35 and 3.47 p.p.m.; benzyl, δ = 5.18 and 5.30 p.p.m.; J_{AB} = 7.5 c.p.s.) in addition to the single peaks at 1.92 and 6.99 p.p.m. due to methyl and C-7 protons, respectively, and phenyl multiplet at 7.2–7.7 p.p.m. Without D_2O, peaks due to N–H at 6.87 p.p.m. and OH at 4.0–4.2 p.p.m. (doublet, position concentration dependent) were also present, and the peak due to the benzyl proton was further split into a complex multiplet at 5.2–5.5 p.p.m.

The aldol product was remarkably resistant to acid-catalyzed dehydration and was recovered unchanged from acid treatment sufficient to cause the rearrangement of **1a** to the 1-aminopyridine.[4] Treatment with thionyl chloride in pyridine gave a dark tar. With polyphosphoric acid a small amount of the parent ketone **1a** was isolated. In contrast to **1a**, neither an oxime nor semicarbazone could be prepared from the aldol. Mixtures of unstable products which could not be characterized were obtained with dimethyl sulfate.

The formation of **3** can be viewed as a simple aldol condensation of the C-3 enolate of **1a** with benzaldehyde. It has been shown by n.m.r. studies[5] that the protons at both C-3 and C-7 in **1a** exchange with deuterium in NaOD. This work also revealed that ring contraction of **1a** and **1b** to α-aminopyridines occurs in alkaline solution, presumably by cleavage of the C-3 enolate anion. A point that must be accounted for in formulating the conversion of **1a** to **3** is the fact that the 2-methyldiazepinone **1b** does not undergo an analogous condensation; under a variety of conditions only the 2-methylaminopyridine was obtained. The product was isolated as a complex of unknown nature, and the pyridine structure was not established until the completion of the work described in the preceding paper.[5]

(1) Supported in part by a grant from the Geschickter Fund for Medical Research.

(2) J. A. Moore, *J. Am. Chem. Soc.*, **77**, 3417 (1955).

(3) The structure originally proposed[2] was based on an enolic formula for **1a**.

(4) J. A. Moore and J. Binkert, *J. Am. Chem. Soc.*, **81**, 6029 (1959).

(5) J. A. Moore and E. C. Zoll, *J. Org. Chem.*, **29**, 2124 (1964).