Heterocyclic Studies. XIV. Some Further Rearrangements in the Dihydro-1,2-diazepinone Series*[1,2]

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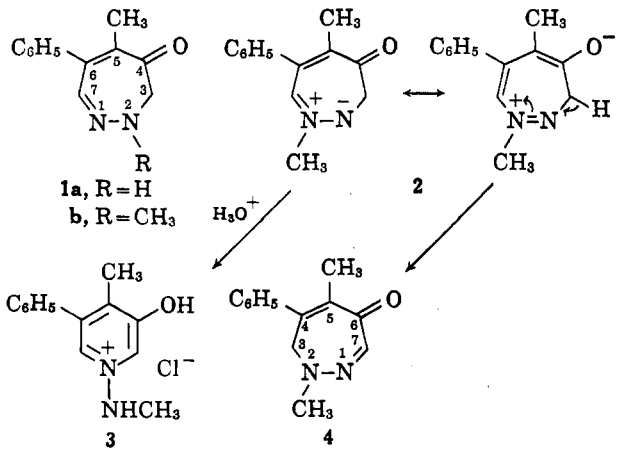
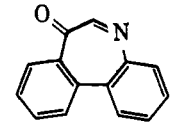
Tautomerization of 1,5-dimethyl-6-phenyl-2,3-dihydro-4H-1,2-diazepinium-4-one betaine (**2**) occurs on standing to give 2,5-dimethyl-4-phenyl-2,3-dihydro-6H-diazepin-6-one (**4**). On warming in acid, **4** undergoes ring contraction to 1,4-dimethyl-5-phenyl-1,6-dihydropyridazine-3-carboxaldehyde (**8**). On warming in base, **4** undergoes ring contraction to 3-hydroxy-4-methyl-6-methylamino-5-phenylpyridine (**22**).

Methylation of the dihydrodiazepinone **1a** with dimethyl sulfate in base gives equal amounts of the 1- and 2-methyl derivatives **1b** and **2**.[3] The principal structural evidence for the betaine **2** is the rearrangement of the hydrochloride to the 1-methylaminopyridinium salt **3**.[3] Another transformation product of **2** is a pale yellow isomeric substance which forms when the red base is allowed to stand at room temperature for a day or is warmed in solution. We now present evidence that this isomer is 2,5-dimethyl-2,3-dihydro-4-phenyl-6H-diazepin-6-one (**4**), arising by a simple proton shift from the zwitterion to an uncharged tautomer.



The ultraviolet spectrum of the isomerization product was quite distinct from that of **1a**, **1b**, or **2**; the most intense band was at the longest wave length, 357 mμ (ε 7300). The n.m.r. spectrum[4] contained peaks at δ = 1.87 (s, 3), 3.43 (s, 3), 4.20 (s, 2), 6.75 (s, 1), and 7.35 p.p.m (m, 5). This spectrum was very similar to that of **1b**, which contained the same peaks at 1.87 (s, 3), 3.45 (s, 3), 3.75 (s, 2), 6.92 (s, 1), and 7.36 p.p.m. (m, 5). These n.m.r. values require a structure for the isomer having =C—C*H*$_3$, N—C*H*$_3$, —C*H*$_2$—, C*H*=N, and C$_6$*H*$_5$ groups with only slightly different environments from those in **1b**. On this evidence **4** was clearly indicated, and is confirmed by two characteristic rearrangements described below.

The infrared spectrum of **4** contained a strong band at 1590 cm.$^{-1}$ in $CHCl_3$ solution or KBr disk, with a very weak band at 1640 cm.$^{-1}$ in KBr; the latter is a shoulder in $CHCl_3$. This low value of 1590 cm.$^{-1}$ for the presumed carbonyl stretching frequency of **4** is in the range characteristic for β-aminocyclenones ($\nu_{C=O}$ 1610–1630 cm.$^{-1}$)[5] and γ-pyridones (1575–1580 cm.$^{-1}$),[6] but the N—C=O interaction should not be larger in **4** than in the extended conjugated system of **1b**, which has $\nu_{C=O}$ 1635 cm.$^{-1}$. Moreover, the lower value of $\nu_{C=O}$ in **4** is in sharp contrast to the much *higher* frequency reported for $\nu_{C=O}$ in the cross-conjugated 2,6-cycloheptadienone (1723 cm.$^{-1}$)[7] compared to a 2,4-cycloheptadienone (1665 cm.$^{-1}$).[8] The infrared spectrum of **4** is comparable, however, to that of the dibenzazatropone **5**, which contains bands at 1590 and 1620 cm.$^{-1}$.[9,10] The abnormally low value of $\nu_{C=O}$ in **5** has been attributed to extensive π-electron delocalization, but this possibility seems remote in the case of **4**, and we can only regard the 1590-cm.$^{-1}$ band as characteristic for the —N=CH—C=O system in a seven-membered ring.



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The first of the two rearrangements that have been observed with **4** occurs on warming the compound briefly in 6 *N* hydrochloric acid; dilution of the resulting solution gives the dihydropyridazine **8** in 90–95% yield. This product showed well-defined carbonyl properties, with a strong infrared band at 1670 cm.$^{-1}$; an oxime and semicarbazone were obtained. The n.m.r. spectrum contained peaks at δ = 2.05 (t, *J* = 1 c.p.s., 3), 3.25 (s, 3), 4.10 (q, *J* = 1 c.p.s., 2), 7.30 (m, 5), and 9.28 p.p.m. (s, 1), showing an aldehyde function. The ultraviolet spectrum of the product, λ_{max} 266 and 368 mμ, may be compared with that of 1,6-dihydronicotinamide, λ_{max} 270 and 360 mμ.[11]

A characteristic property of the compound was its sensitivity to oxidation, which was manifested by rapid decomposition in warm solutions exposed to air. A

* To Professor Louis F. Fieser.

(1) Supported by Grant DA-CML-18-108-61-G-24 from the Army Chemical Corps.

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

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

(4) N.m.r. spectra were measured at 60 Mc. in $CDCl_3$ solution with $(CH_3)_4Si$ (δ = 0.00 p.p.m.) as internal standard. The symbol s means singlet; d, doublet; m, multiplet; the numeral is the number of protons from integration.

(5) (a) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, *J. Am. Chem. Soc.*, **71**, 3337 (1949); (b) N. J. Leonard and J. A. Adamcik, *ibid.*, **81**, 595 (1959).

(6) A. R. Katritzky and R. A. Jones, *J. Chem. Soc.*, 2947 (1960).

(7) W. Treibs and P. Grossman, *Chem. Ber.*, **92**, 267 (1959).

(8) G. P. Scott and D. S. Tarbell, *J. Am. Chem. Soc.*, **72**, 240 (1950).

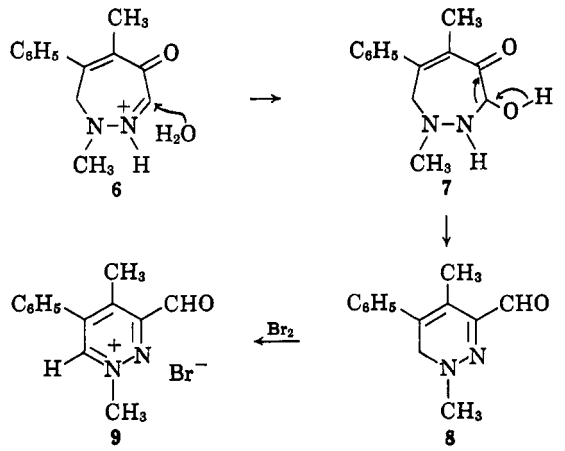
(9) G. R. Proctor, *Chem. Ind.* (London), 408 (1960); W. Paterson and G. R. Proctor, *J. Chem. Soc.*, 3468 (1962).

(10) There is some uncertainty as to whether the 1590-cm.$^{-1}$ band in the spectrum of this and other benzotropones is due to C=O or C=C stretching: E. Kloster-Jensen, N. Tarkoy, A. Eschenmoser, and E. Heilbronner, *Helv. Chim. Acta*, **39**, 786 (1956).

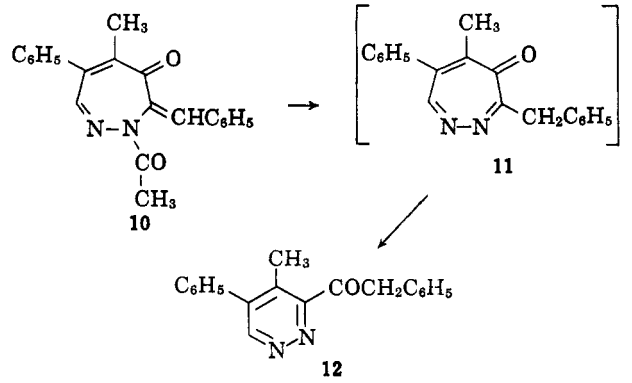
(11) W. Traber and P. Karrer, *ibid.*, **41**, 2066 (1958).

solution of the compound in methylene chloride immediately decolorized 1 equiv. of bromine with formation of the water-soluble quaternary bromide **9**. A similar oxidation could also be carried out with the semicarbazone, and the quaternary base was characterized as the crystalline perchlorate. The facile dehydrogenation of **8** with bromine is amply precedented in the pyridine series, although 1,6-dihydropyridazines and pyridazinium compounds have been very little studied. Attempts to convert the quaternary bromide **9** to a pyridazone by alkaline ferricyanide oxidation were not successful.

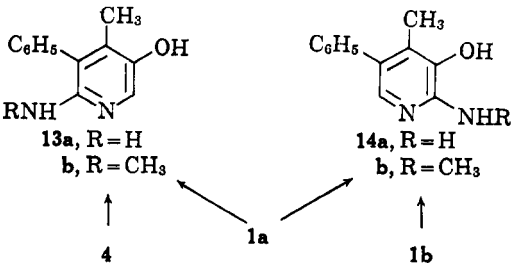
The quaternary bromide showed a normal aldehyde carbonyl band in the infrared (λ^{KBr} 5.75 μ) but no formyl proton was seen in the n.m.r. spectrum in D_2O solution, which contained the expected peaks for C–CH_3, N–CH_3, and C_6H_5 and one-proton singlets at 6.63 and 9.75 p.p.m. The low-field peak was also present at 9.70 p.p.m. in the spectrum of the quaternary semicarbazone and was assigned to the pyridazine C-6 proton. The absence of an aldehydic proton signal in the D_2O spectrum of **9** and the presence of a peak at 6.63 p.p.m. indicate that the quaternary aldehyde exists in aqueous solution entirely as the hydrate. This behavior parallels that of quaternary pyridinium aldehydes, which form stable hemiacetals in alcohol solution.[12]



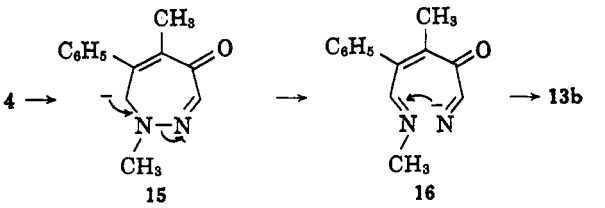
The conversion of the diazepine **4** to **8** can be formulated as a solvolytic displacement at C-7 (**6** → **7**) in exactly the same manner discussed previously[2] for the ring contraction of the completely unsaturated compound **10** to **12**. In the latter case it was suggested that deacetylation of **10** led to the diazatropone **11** and thence to **12**.



The other rearrangement of **4** occurs on warming with methanolic alkali. The unsubstituted diazepinone **1a** undergoes rearrangement in base to give essentially equal amounts of the α-aminopyridines **13a** and **14a**; **1b** gives the 2-methylaminopyridine **14b**.[13] It was anticipated that the corresponding reaction of **4** should furnish the 6-methylaminopyridine **13b**, and this was found to be the case. The amphoteric product obtained from **4** had the characteristic ultraviolet spectra and dissociation constants for aminohydroxypyridines,[14] and the n.m.r. spectrum in D_2O confirmed the 6 position of the methylamino substituent. It was previously found[13] that the C-methyl peaks in the n.m.r. spectra of the primary amines **13a** and **14a** in D_2O–NaOD solution were displaced downfield 9 and 22 c.p.s., respectively, from that of **1a**. The location of the 2-methylamino group in **14b** was diagnosed by the 23-c.p.s. difference in the C-methyl peak relative to **1a**. The C-methyl peak in the spectrum of the pyridine obtained from **4** was 9 c.p.s. downfield from that of **1a**; these data seem adequate to define structure **13b**.



The conversion of **4** to **13b** ties in very nicely with the previously observed rearrangements of **1a** and **b**. The reaction is presumed to occur *via* the extended enolate anion **15** which undergoes β-elimination to the acyclic intermediate **16** followed by cyclization to the aromatic system.



Experimental[15]

1,4-Dimethyl-5-phenyl-1,6-dihydropyridazine-3-carboxaldehyde (8).—A suspension of 535 mg. of the diazepinone **4**[3] in 8.0 ml. of 6 *N* hydrochloric acid was warmed to 65–70°. After 90 sec. the resulting clear, deep yellow solution was chilled and a total of 509 mg. of yellow solid was obtained in several crops; the melting point of the first crop was 93–96°. Recrystallization from methanol–water gave yellow needles of **8**, m.p. 99–100°. The compound was very soluble in ether and other organic solvents, but solutions frequently decomposed on concentration. The analytical sample was sublimed, m.p. 98–100°; spectral data are given in the discussion section.

(12) G. M. Steinberg, E. J. Poziomek, and B. E. Hackley, Jr., *J. Org. Chem.*, **26**, 369 (1961).

(13) J. A. Moore and E. C. Zoll, *ibid.*, **29**, 2124 (1964).

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

(15) Melting points were observed on a Fisher-Johns block with a calibrated thermometer. Infrared spectra were obtained either in KBr pellets with a Perkin-Elmer Infracord or in chloroform solution with a Model 337 grating infrared spectrophotometer.

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08; N-(CH_3), 7.02. Found: C, 72.65; H, 6.71; N, 13.45; N-(CH_3), 6.84.

The **oxime** of **8** was prepared with methanolic hydroxylamine acetate and crystallized from aqueous methanol as pale yellow prisms: m.p. 160–162° dec.; n.m.r. 2.00 (s, 3), 3.07 (s, 3), 3.70 (s, 2), 7.35 (m, 5), 7.87 (s, 1), and 8.03 (s, 1—exchanged by D_2O) p.p.m.

Anal. Calcd. for $C_{13}H_{15}N_3O$: N, 18.33. Found: N, 18.47.

The **semicarbazone** was prepared from 88 mg. of **8** with methanolic semicarbazide acetate. After standing for 30 min. the solution was diluted with water, giving 131 mg. of colorless prisms, m.p. 184° dec. Recrystallization from methanol–water and ethanol–ether gave prisms: m.p. 184–185° dec.; n.m.r. 2.05 (s, 3), 3.05 (s, 3), 3.70 (s, 2), 7.30 (m, 5), 7.43 (s, 1), and 8.00 (s, 3—exchanged by D_2O) p.p.m.

Anal. Calcd. for $C_{14}H_{17}N_5O$: C, 61.97; H, 6.32; N, 25.81. Found: C, 61.82; H, 6.40; N, 26.45.

1,4-Dimethyl-3-formyl-5-phenylpyridazinium Bromide (10).—To a solution of 144 mg. (0.67 mmole) of the dihydropyridazine aldehyde **8** in 3 ml. of methylene chloride was added a solution of 104 mg. (0.65 mmole) of bromine in 2 ml. of methylene chloride. A yellow oil immediately separated from the pale yellow solution; evaporation gave a glass: softening point 74–75°; n.m.r. (in D_2O) 1.67 (s, 3), 4.78 (s, 3), 6.63 (s, 1), 7.80 (m, 5), and 9.75 (s, 1) p.p.m.[16]

Semicarbazone of 1,4-Dimethyl-3-formyl-5-phenylpyridazinium Perchlorate.—A solution of 124 mg. (0.46 mmole) of the semicarbazone of **4** in methylene chloride was treated with 0.46 mmole of bromine and the resulting suspension was evaporated to an orange glass containing the quaternary bromide: n.m.r. (in D_2O) 2.82 (s, 3), 4.73 (s, 3), 7.69 (m, 5), 8.50 (s, 1), and 9.68 (s, 1) p.p.m.[16]

To a solution of 88 mg. of the bromide in 2 ml. of water at 0° was added 0.03 ml. of 70% aqueous perchloric acid. The resulting yellow precipitate, m.p. 212–213°, was recrystallized from ethanol to give colorless needles, m.p. 215–216°.

(16) The n.m.r. spectrum was measured at 60 Mc. with internal standard of 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt.

Anal. Calcd. for $C_{14}H_{16}ClN_5O_5$: C, 45.47; H, 4.36; N, 18.94. Found: C, 45.37; H, 4.54; N, 19.03.

3-Hydroxy-4-methyl-6-methylamino-5-phenylpyridine (13b).—To a solution of 250 mg. of the diazepinone **4** in 2 ml. of methanol was added 1 ml. of 5% aqueous NaOH. After refluxing 3 hr. under a nitrogen atmosphere, the solution was chilled and neutralized to pH 8 with hydrochloric acid. The resulting brown precipitate was collected and washed with water, giving 248 mg. of tan solid, softening at 80°, complete melting at 150°. The material was sublimed at 0.1 mm. to give 157 mg. of long, pale yellow crystals of **13b**, m.p. 155–156°, λ_{max}^{MeOH} 327 mμ (ε 5180), $\lambda_{max}^{MeOH + HCl}$ 219 mμ (ε 20,000) and 332 mμ (ε 7300), $\lambda_{max}^{MeOH + KOH}$ 228 mμ (ε 14,600) and 339 mμ (ε 4900), pK_A' 5.9 and 10.1. Satisfactory analytical values for carbon could not be obtained.

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.24; H, 6.63; N, 13.05.

3-Hydroxy-4-methyl-6-(N-methyl)benzamido-5-phenylpyridine.—To a solution of 118 mg. of the pyridine **13b** in 5 ml. of 5% aqueous KOH solution was added 0.3 ml. of benzoyl chloride. After shaking until all of the benzoyl chloride had reacted, water was added and the mixture was extracted with methylene chloride. Evaporation of the washed and dried methylene chloride solution gave 205 mg. of the **O,N-dibenzoyl derivative**, $\lambda_{C=O}^{KBr}$ 5.72 and 6.03 μ, as a colorless glass which could not be crystallized.

The amorphous dibenzoyl compound was hydrolyzed for 30 min. in methanolic KOH solution, the methanol was then removed, water was added, and the solution was neutralized by addition of acid and then $NaHCO_3$. Extraction with methylene chloride gave 79 mg. of a crystalline powder, m.p. 110°. Recrystallization from ether–hexane gave colorless prisms of the N-benzoyl-3-hydroxypyridine, m.p. 150–151°, λ^{KBr} 3.20 and 6.10 μ, λ_{max}^{MeOH} 290 mμ (ε 5200).

Anal. Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.10; H, 5.86; N, 8.72.

Acknowledgment.—We thank Dr. J. M. Vandenbelt and Mrs. Carola H. Spurlock, Parke, Davis and Company, for the ultraviolet data.

Heterocyclic Studies. XV. 5-Methyl-4-phenylpyrazole-1-acetic Acid. An Oxidation Product of 2,3-Dihydro-5-methyl-6-phenyl-4H-1,2-diazepin-4-one*,[1]

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Oxidation of the diazepinone (**1**) with hydrogen peroxide gives 5-methyl-4-phenylpyrazole-1-acetic acid (**2**). Condensation of 1-ethoxymethylene-1-phenylacetone (**7**) with ethyl hydrazinoacetate and alkylation of 5-methyl-4-phenylpyrazole (**5**) with ethyl bromoacetate gives both **2** and the 3-methyl isomer **9**. The structures of these pyrazoles are assigned on the basis of the formation of **2** from **1**.

During studies on the chemistry of the diazepinone **1**, it was found that treatment of this orange ketone with alkaline hydrogen peroxide gave a colorless acid containing one additional oxygen atom. This product was of interest originally as a source of structural information for the parent ketone and later in revealing another pathway for rearrangement of **1**. The acid has been shown to be 5-methyl-4-phenylpyrazole-1-acetic acid (**2**); the evidence for this structure, independent synthesis, and the formation of **2** from **1** are discussed in this paper.

Initial consideration of the formula and standard transformations to the ester **3** and carbinol **6** suggested a pyrazoleacetic acid structure for the oxidation product, and the rather low pK_A value (3.6) indicated an N-acetic acid. A neutral by-product was later obtained in another oxidation of **1** under more vigorous conditions and was identified as 5-methyl-4-phenylpyrazole (**5**).[3] This compound was shown to arise from **2** under the conditions of the oxidation, supporting the methylphenylpyrazole-N-acetic acid formula. Earlier attempts to remove the suspected N-acetic acid group by a Barbier–Wieland degradation of **3** or direct oxidation of **2** with permanganate were unsuccessful. Treatment of

* To Professor Louis F. Fieser.

(1) (a) Supported in part by Grant DA-CML-18-108-61-G-24 from the Army Chemical Corps. (b) Part XIV: J. A. Moore and W. J. Theuer, *J. Org. Chem.*, **30**, 1887 (1965).

(2) Visiting Land Grant Assistant Professor, 1961–1962, on leave of absence from the University of Leiden.

(3) G. N. Walker and B. N. Weaver, *J. Org. Chem.*, **26**, 4441 (1961); the tautomeric structure **5** for this pyrazole has been defined by n.m.r. studies presented in the following paper.[4]

(4) C. L. Habraken and J. A. Moore, *ibid.*, **30**, 1892 (1965).