Heterocyclic Studies. XXI. 1,2,3,7-Tetrahydro-1-acyl-7-methoxy-5-methyl-6-phenyl-4H-1,2-diazepin-4-ones[1,2]

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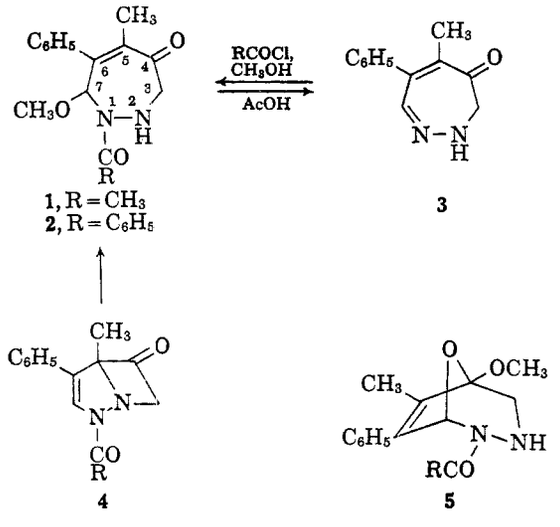
Received June 22, 1965

The title compounds (1 and 2) undergo base-catalyzed rearrangement to 5-methoxy-3-methyl-4-phenyl-2-pyrrolealdehyde (6). This pyrrole was characterized by acid hydrolysis and deformylation to 4-methyl-3-phenyl-3-pyrrolin-2-one (9). The pyrrolinone 9 was synthesized by cyclization of phenylacetamidoacetone and the pyrrolealdehyde 6 was resynthesized from 9 *via* the methoxypyrrole 7. A concerted mechanism is proposed to account for several unusual aspects of the rearrangement of 2. The tetrahydrodiazepinone 2 is dehydrogenated with N-bromosuccinimide to the 1-acyl-7-methoxy-1,7-dihydro compound 17; the latter on alkaline hydrolysis gives the 7-methoxy-2,3-dihydrodiazepinone 18. The n.m.r. spectra of 2 and the 2-acetyl derivative 21 show unusual temperature dependence, indicating considerable steric crowding in these tetrahydrodiazepinones.

The preparation of the 7-methoxy-1-acetyl- and 1-benzoyltetrahydrodiazepinones **1** and **2** from the diazepinone **3** or bicyclic ketone **4** was described in the accompanying article.[3] Structures **1** and **2** were based primarily on the formation from **3** and **4** and the reversion to **3** in acetic acid,[3] but the alternative bridged hemiketal structure **5**, which is suggested by the transannular oxides derived from the diazepinol,[4] could not be excluded, and structural information must be assessed with both possibilities in view.



The ultraviolet maximum of the methoxyacyl compounds occurred at 260 mμ (ε 13,000), an abnormally low wave length for the styryl ketone chromophore. The infrared spectrum in a KBr pellet contained bands at 5.95 and 6.06 μ, suggesting two carbonyl groups, but in solution only one carbonyl band was present, at 6.04 μ. The n.m.r. spectrum, discussed later, could be interpreted on the basis of either structure. The compounds, in contrast to the diazepinone **3**, were unreactive toward semicarbazide or sodium borohydride. These preliminary data appeared to strongly favor the hemiketal structure **5**.

The reaction of **1** or **2** with aqueous potassium hydroxide gave in 85% yield a product, $C_{13}H_{13}NO_2$, corresponding to retention of the methoxyl group and loss of the acyl group and one nitrogen atom. Benzamide was isolated in the reaction of the methoxybenzoyl compound. The C_{13} product was identified as 5-methoxy-3-methyl-4-phenyl-2-pyrrolealdehyde (**6**). Evidence for a pyrrole ring arose in an unexpected way when the C_{13} compound was heated with hydrochloric acid in an attempt to adduce evidence for a tentative pyridone structure. The methoxyl group and the elements of carbon monoxide were lost, and the pyrrolinone **9** was obtained. The latter structure was apparent from the similarity of the infrared spectrum to that of the isomeric pyrrolone **8**,[5] reduction to a dihydro compound, and oxidation to methylphenylmaleimide (**11**). This oxidation product was also obtained from **8** and directly from **6**.

To provide a more direct source of the pyrrolinone **9** for further work, a very simple synthesis was effected by cyclization of phenylacetamidoacetone (**12**). This ring closure is similar to the pyrrolone synthesis developed by Almström[6] from the original Knorr synthesis, which involved condensation of an α-amino ketone and β-keto ester without solvent. The success of this ring closure with **12** probably depends to a large extent on the additional activation of the methylene group by the phenyl substituent; an attempted parallel cyclization of α-propionamidoacetophenone to the pyrrolinone **8** failed.[7]

The methoxypyrrolealdehyde structure **6** was developed from the hydrolysis to **9** and the striking similarity in properties to those of 5-ethoxy-3,4-dimethyl-2-pyrrolealdehyde recently reported by Plieninger, *et al.*[8] The n.m.r. spectrum contained an aldehyde proton peak at δ 9.42; the compound showed pronounced enolic properties. Since the location of the methoxy and formyl groups was of crucial importance in the original structural problem, resynthesis of **6** from the pyrroline **9** was undertaken. Condensation of **7** with ethyl formate gave the 5-formylpyrrolone **10**, but methylation of this product with diazomethane was unsuccessful. A structurally unequivocal route to **6** required the reverse sequence, namely, conversion of the pyrrolinone to the methoxypyrrole followed by formylation. Alkylation of the dimethylpyrrolinone[8]

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

(2) Part XX: W. J. Theuer and J. A. Moore, *Chem. Commun.*, 468 (1965).

(3) J. A. Moore, F. J. Marascia, R. W. Medeiros, and R. L. Wineholt, *J. Org. Chem.*, **31**, 34 (1966).

(4) J. A. Moore, R. W. Medeiros, and R. L. Williams, *ibid.*, **31**, 52 (1966).

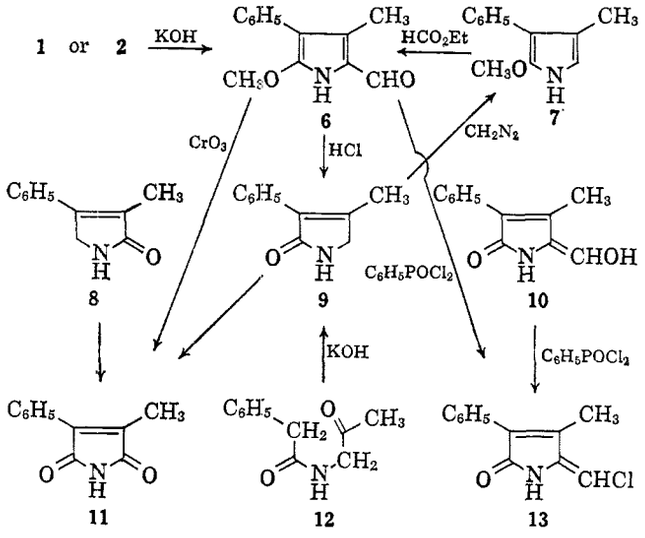
(5) J. A. Moore and J. Binkert, *J. Am. Chem. Soc.*, **81**, 6029 (1959).

(6) G. K. Almström, *Ann.*, **411**, 350 (1916).

(7) We thank Dr. John Eby for this result.

(8) H. Plieninger, H. Bauer, A. R. Katritzky, and U. Lerch, *Ann.*, **654**, 165 (1962).

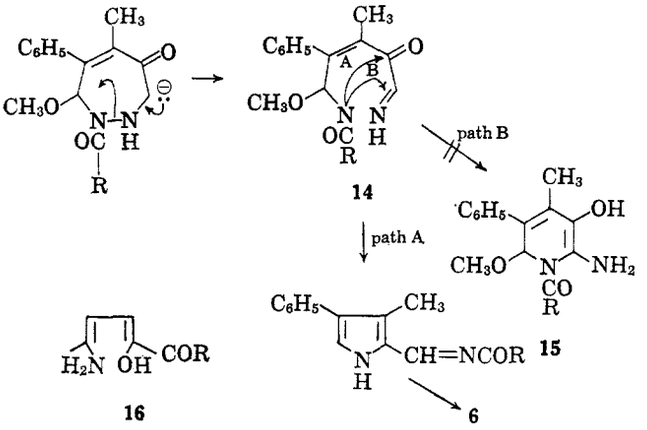
was carried out in several ways, including heating in neat dimethyl or diethyl sulfate or fusion with triethyloxonium fluoroborate. The first of these procedures reduced the pyrrolone **9** to a black mass; no reaction was observed on gentle warming with the trimethyloxonium reagent. Treatment of **9** with diazomethane and boron trifluoride caused a vigorous reaction, however, and a boron-containing complex of the methoxypyrrole **7** was obtained. Alkaline hydrolysis gave the easily oxidized pyrrole which could not be distilled, but was characterized as an unstable picrate. Formylation of the crude pyrrole furnished the aldehyde **6**, identical with the alkaline rearrangement product of **1** and **2**.



On an early incorrect structural premise, the pyrrolealdehyde **6** was treated with dichlorophenylphosphine oxide. A product containing a chlorine atom but no methoxy group was obtained in good yield. The same compound was produced by similar treatment of the formylpyrrolone **10** and is clearly the 5-chloromethylenepyrrolone **13**. The facile cleavage of the methoxy group in **7** with dilute acid or phosphoryl chloride in pyridine parallels the behavior of alkoxypyrroles reported by Siedel.[9]

Establishment of the methoxypyrrole structure **6** permitted a final decision in favor of the 7-methoxydiazepinone structures **1** and **2**. Conversion of the hemiketal **5** to **6** in aqueous base would require transannular transfer of the methoxy group, a reaction for which no tenable mechanism has been envisioned. A problem remaining with either structure is the apparent extrusion of benzamide in the reaction. On the assumption, however, that the nitrogen eliminated as benzamide is not the one originally bearing the benzoyl group, a plausible pathway to **6** from the 7-methoxy-1-acyltetrahydrodiazepinones **1** and **2** could be reconstructed.

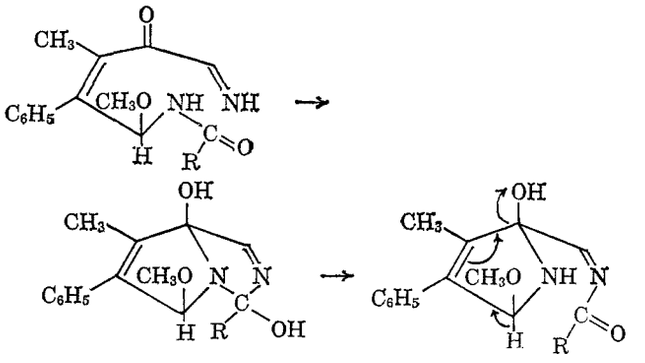
A characteristic reaction of the diazepinone **3** and 2-substituted derivatives is a base-catalyzed ring contraction to 2-amino-3-hydroxypyridines which has been formulated as a β elimination to an acyclic diimine and recyclization.[10] In the context of the diazepinones **1** and **2**, this cleavage would lead to the intermediate **14**. Cyclization of **14** to a pyridine would involve attack (path B) of the benzamido group at the C=NH terminus, giving a 1-benzoyl-6-methoxydihydropyridine **15**. Although this pathway has invariably been observed heretofore,[10] an alternative cyclization (path A) to the carbonyl group of **14**, with benzoyl migration, can be conceived. Two cyclization paths are in fact observed in some cases with the closely related intermediates **16**, which are involved in the ammonolysis of 2-acylfurans and give rise to mixtures of 3-hydroxypyridines and 2-acylpyrroles.[11] The diversion of **14** to a pyrrole instead of a pyridine



product must be due to the altered nucleophilic character of the —NHCOR group compared with =NH in earlier cases.[10] A mechanism can be suggested, as shown in Scheme I, that accounts for several important features of the cyclization. Adequate basicity for the amide nitrogen, selective attack at the carbonyl group and the observed benzoyl migration would be provided by a bicyclic intermediate resembling the cyclols which are involved in amide–amine interactions of peptides.[12] The geometry and juxtaposition of functional groups in the acyclic precursor **14** appear quite suitable for the formation of such a "biscyclol".

With a firm basis for structures **1** and **2**, some further reactions are understandable. Treatment of **2**

SCHEME I



with N-bromosuccinimide and pyridine gave in excellent yield the dehydro compound **17**. Under these conditions the dihydrodiazepinone **3** leads to completely intractable products. A similar smooth de-

(9) W. Siedel, *Ann.*, **544**, 144 (1943).

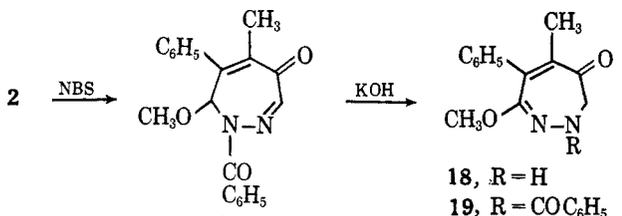
(10) (a) J. A. Moore and E. C. Zoll, *J. Org. Chem.*, **29**, 2124 (1964); (b) J. A. Moore and W. J. Theuer, *ibid.*, **30**, 1887 (1965).

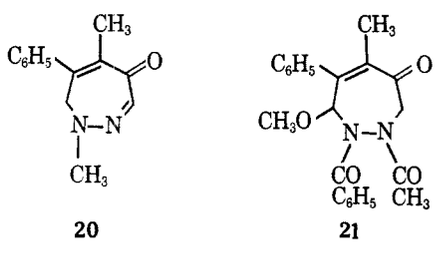
(11) A. P. Dunlop and F. M. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, pp. 667–673. The precise structure and tautomeric form of the intermediates in these reactions cannot be specified, but **16** is an adequate representation.

(12) A recent summary of the literature was given by G. I. Glover, R. B. Smith, and H. Rapoport, *J. Am. Chem. Soc.*, **87**, 2003 (1965).

hydrogenation has been observed, however, with two other compounds in this series containing the RCON–$NHCH_2$– system.[4] The 1-benzoyl-7-methoxy-1,7-dihydrodiazepinone structure **17** rests largely on the formation from **2** and the n.m.r. spectrum, which contained singlet peaks due to H-3 and H-7 at δ = 6.88 and 7.14 p.p.m., respectively. The ultraviolet maximum [λ 300 mμ (ϵ 12,000)] of **17** may be compared with that of **20**[10b] [λ_{max} 302 mμ (ϵ 6400) and 350 mμ (ϵ 7500)], which is the most closely related compound in the series. The difference in the position of the major absorption maximum is in the direction anticipated for the contrasting influences of methyl and benzoyl groups on the RN—N=C—C=O system, although somewhat larger than expected for a purely electronic effect.

The reaction of **17** with acid did not lead to clearly defined products, but mild alkaline hydrolysis gave the methoxydihydrodiazepinone **18**, arising from two successive 1,3-prototropic rearrangements. The spectra of **18** [λ_{max} 217 mμ (ϵ 14,000) and 390 mμ (ϵ 720); ν 3280 (NH), 1650 (C=O) cm.$^{-1}$; δ = 1.85 (CH_3), 3.61 (OCH_3), 3.88 (s) (CH_2), 5.07 (NH), 7.0–7.5 (C_6H_5) p.p.m.] closely resemble those of the 7-unsubstituted diazepinone **3**. Treatment of **18** with benzoyl chloride and dimethylaniline gave the 2-benzoyl-7-methoxydiazepinone (**19**), in contrast to the N-1 acylation with bridging observed with **3** under these conditions. This rather circuitous route provides the first simple C-7 substitution product of **3** having the same tautomeric structure.





A final point that requires comment is some apparently anomalous properties of **2** and the acetylation product **21** obtained from **2** under forcing conditions with acetic anhydride. In contrast to **1** and **2**, the 2-acetyl compound **21** on treatment with alkali did not furnish the pyrrole **6** but rather the parent diazepinone **3**. This result, which for some time beclouded the structural question of **2**, is explained by the preferential hydrolysis of the benzoyl group in **21** and loss of methanol. The resulting 2-acetyldiazepinone is rapidly hydrolyzed to **3**.[5] The unusual hydrolysis of **21**, the abnormal ultraviolet spectra of these tetrahydrodiazepinones, and the depressed carbonyl reactivity must be associated with steric crowding in these highly substituted compounds, but a detailed analysis cannot be made.

A further indication of abnormal steric effects in **2** and **21** was observed in the n.m.r. spectra. In the spectrum of **2** at room temperature after D_2O addition the methoxyl peak (δ 3.27) was slightly broadened, the H-7 peak (δ 6.26) was very broad, and the C-3 methylene protons formed a distorted AB pattern. All of these signals were sharper and better resolved at 50°: for the CH_2 peak, $\delta_A - \delta_B$ = 17 c.p.s., J_{AB} = 18 c.p.s. In all of the dihydrodiazepines in this series with tautomeric structure **3**, the C-3 methylene protons are magnetically equivalent. In the spectrum of the acetyl derivative **21** at room temperature, the H-7 peak was scarcely discernible and the methoxyl group was a broad hump (*ca.* 3.2–3.5 p.p.m.). As the temperature was raised, the methoxyl peak sharpened first into an unsymmetrical doublet and then at 80° to a single peak slightly broadened at the base. At −20°, two sets of very sharp peaks appeared for H-7 (δ 5.55 and 6.60), the methoxyl protons (δ 3.02 and 3.54), and the methylene protons [two superimposed AB patterns, almost exactly same midpoints (δ 4.62), $\delta_A - \delta_B$ = 65 c.p.s., J = 19 c.p.s., and $\delta_A - \delta_B$ = 51 c.p.s., J = 18 c.p.s.]. The two sets of peaks were in the ratio of 2:1, with those of the minor component at higher field for the H-7 and CH_3O peaks. This behavior demonstrates the existence of two isomers of **21**, with quite dissimilar magnetic environments at C-7 but a comparatively small energy difference, at a relatively high temperature. The extreme broadening of the methoxyl peak at room temperature and the complex changes through a temperature range of 100° are unique and evidently reflect unusually large energy barriers among conformations.

Experimental Section[13]

5-Methoxy-3-methyl-4-phenyl-2-pyrrolealdehyde (6).—A suspension of 685 mg. of the benzoylmethoxydiazepinne **2**[3] in 30 ml. of 10% aqueous KOH was warmed at 60° for 40 min. After 20 min. all of the solid had dissolved to give a clear bright yellow solution. The solution was cooled, neutralized to pH 4 with 2.0 *N* H_2SO_4, and extracted with methylene chloride (the product **6** can also be extracted from the alkaline solution without prior neutralization). The methylene chloride solution was evaporated and diluted with ether to give 370 mg. (85%) of colorless crystals of the pyrrole **6**: m.p. 196–198°; λ^{EtOH} 220 mμ (ϵ 11,500), 255 (10,700), 330 (25,000); $\lambda^{EtOH-OH^-}$ 345 mμ (ϵ 28,000); λ^{KBr} 6.10 μ; δ^{CDCl_3} = 2.37 (s, 3, CH_3), 4.03 (s, 3, OCH_3), 7.36 (s, 5, C_6H_5), 9.40 p.p.m. (s, 1, CHO).

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51; OCH_3, 14.40. Found: C, 72.42; H, 6.04; 6.64; OCH_3, 14.42.

The mother liquor from crystallization of **6** was evaporated and the residue, 250 mg., was chromatographed on alumina in benzene–chloroform. The fractions eluted with 20% chloroform were crystallized from chloroform to give colorless plates of benzamide, m.p. 126–127°, identical (mixture melting point and infrared spectrum) with an authentic sample.

A much inferior yield of **6** was obtained when the reaction was carried out in homogeneous methanol solution instead of heterogeneous aqueous medium.

In the same general procedure, 100 mg. of the acetylmethoxydiazepinone **1** gave 25 mg. of **6**, identical with the material described above from **2**.

4-Methyl-3-phenyl-3-pyrrolin-2-one (9).—A suspension of 88 mg. of the methoxypyrrole **6** in 20 ml. of 10% HCl was refluxed for 90 min. After 20 min. the solid had dissolved to give a dark yellow solution; the color disappeared after longer heating. Extraction of the cooled solution gave 51 mg. (72%) of white powder, m.p. 187–194°. Recrystallization from methylene chloride–ether gave 32 mg. of **9**: m.p. 200–202°; λ^{MeOH} 230 mμ

(13) General experimental procedures are given in the preceding article.[2]

(ϵ 10,400); λ^{KBr} 5.93, 3.05 μ; δ^{CDCl_3} = 2.15 (s, 3, CH_3), 3.95 (s, 2, CH_2), 7.41 p.p.m. (s, 5, C_6H_5) (slight broadening of 2.15 and 3.95 peaks due to weak coupling).

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.52; H, 6.32; N, 7.99.

4-Methyl-3-phenyl-2-pyrrolidone.—A solution of 57 mg. of the pyrrolone **9** was shaken with 20 mg. of palladium on charcoal for 2 hr. under 40 p.s.i. of hydrogen. After removal of catalyst, the solution was evaporated and the residue was crystallized from ether to give 40 mg. of colorless plates: m.p. 137–139°; λ^{KBr} 3.19, 6.01 μ; δ^{CDCl_3} = 0.72 (d, J = 6 c.p.s., CH_3), 2.9–3.7 (m, 3), 7.27 p.p.m. (m, 5).

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48. Found: C, 75.05; H, 7.26.

3-Methyl-4-phenylmaleimide (11).—To a solution of 400 mg. of the pyrrolone **9** in 10 ml. of 50% aqueous acetic acid was added 400 mg. of CrO_3. After heating for 90 min. at 95°, the solution was allowed to stand overnight and was then evaporated to dryness. The green semisolid residue was extracted with ethyl acetate and the solution was washed with sodium sulfite, dried, and evaporated to give 250 mg. of white powder. Crystallization from ether gave 128 mg. (30%) of the imide **11** as colorless plates, m.p. 168–173°. The analytical sample was recrystallized from methanol: m.p. 178°; λ_{max}^{MeOH} 223 mμ (ϵ 11,00), 252 (infl.), 324 (2000); λ^{KBr} 2.95, 3.05, 5.60, 5.80 μ; δ^{CDCl_3} = 2.21 (s, 3, CH_3), 7.50 p.p.m. (s, 5, C_6H_5).

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.13; H, 4.84; N, 7.58.

Similar oxidation of the pyrrole **6** and the pyrrolone **8** furnished the imide in 29 and 54% yield, respectively. A sample with the same infrared spectrum was also prepared in low yield by treatment of methylphenylmaleic anhydride with ammonia in a sealed tube at 150°.

Phenylacetamidoacetone (12).—A solution of 10 g. of isonitrosoacetone in 120 ml. of ethanol containing 10 ml. of concentrated HCl was shaken in a hydrogen atmosphere with 6 g. of 10% palladium on charcoal. After 84% of the theoretical amount of hydrogen was consumed (45 min.), the catalyst was removed and the solution was brought to a viscous oil which was then dissolved in 30 ml. of water. A solution of 14 g. of sodium acetate was added and then 15 ml. of phenylacetyl chloride was added dropwise.[14] After 30 min. the reaction mixture, which contained an oily layer, was treated with K_2CO and extracted with methylene chloride. The extract was evaporated to give 4.8 g. of colorless prisms of **12**: m.p. 126–128° (lit.[15] m.p. 128–129°); λ^{KBr} 5.80, 6.10 μ.

4-Methyl-3-phenyl-3-pyrrolin-2-one (9) from Phenylacetamidoacetone (12).—A suspension of 4.8 g. of **12** in 300 ml. of 3.0 *N* KOH was heated on a steam bath with stirring for 2 hr. The dark red reaction mixture was cooled and extracted with methylene chloride. The extract was evaporated to dryness, dissolved in methanol, and treated with charcoal; the product was then isolated by crystallization from ether as pale yellow needles, m.p. 198–200°, 2.5 g. (58%). The infrared spectrum was identical with that of material from the hydrolysis of **6**.

The reaction conditions are probably not optimal, but an aqueous medium was found to be much superior to alcohol.

5-Hydroxy-3-methyl-4-phenyl-2-pyrrolealdehyde (10).[16]—To a stirred solution prepared from 300 mg. of sodium and 6 ml. of ethanol was added a solution of 533 mg. of the pyrrolone **9** and 4 ml. of ethyl formate in 15 ml. of ethanol. After heating for 1 hr.; the sodio salt of **10** separated on cooling. A solution of the salt in water was then treated with a few drops of acetic acid and the pyrrole crystallized. A total of 440 mg. (71%) of crude **10**, m.p. 160–170°, was obtained. Recrystallization from methanol–water gave a sample with m.p. 193–194°; λ_{max}^{MeOH} 323, 365 mμ; λ^{KBr} 3.1–3.2, 5.90, 6.05 μ.

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.70; H, 5.73; N, 6.75.

Acid hydrolysis of 16 mg. of **10** as described for **6** gave 8 mg. of the pyrrolone **9**.

2-Methoxy-4-methyl-3-phenylpyrrole (7).—To a solution of 190 mg. (1.1 mmoles) of the pyrrolone **9** in methylene chloride was added 0.14 ml. of boron trifluoride etherate and then, at 0°, about 10 mmoles of ethereal diazomethane. Gas evolution was rapid and a white solid separated from solution. This material, 210 mg., which gave a green flame test indicating a boron-containg complex, was shaken with ether and 5% KOH solution and the ether layer was then washed, dried, and evaporated to an oil containing **7** and some unreacted starting material. The oil rapidly became red on exposure to air. An attempt to distil the oil at 0.1 mm. resulted in extensive decomposition and a very small amount of distillate with the same infrared spectrum as the crude oil, still showing contamination with **9**.

In another, similar, experiment a portion of the ether solution containing **7** was treated with picric acid. The resulting yellow solid was recrystallized from ethanol to give the picrate of **7**, m.p. 140–145° dec., apparently containing 1 mole of ethanol. Vigorous drying at 100° caused decomposition.

Anal. Calcd. for $C_{18}H_{16}N_4O_8 \cdot C_2H_6O$: C, 51.95; H, 4.80; N, 12.12. Found: C, 52.39; H, 4.36; N, 12.23.

Methoxypyrrolealdehyde 6 from 7.—A solution of 110 mg. of crude methoxypyrrole in 4 ml. of ethanol containing 0.5 ml. of ethyl formate was added at 0° to a sodium ethoxide solution prepared from 185 mg. of sodium. The solution was then refluxed for 40 min., cooled, neutralized, and extracted to give 38 mg. (30%) of pale yellow crystals, m.p. 192–195°. Recrystallization from methylene chloride–ether gave **6**, m.p. 195–196°, infrared spectrum identical with that of a sample obtained from **2**.

5-(Chloromethylene)-4-methyl-3-phenyl-3-pyrrolin-2-one (13).—A solution of 492 mg. of the methoxypyrrolealdehyde **6** in 20 ml. of dichlorophenylphosphine oxide ($C_6H_5POCl_2$) was allowed to stand at 25° for 20 min. The red solution was then hydrolyzed by addition of 250 ml. of water and the resulting red solid was extracted with methylene chloride. After treatment with charcoal, the solution was concentrated and diluted with ether to give 340 mg. of orange solid. Recrystallization from methylene chloride with further charcoal treatment gave 191 mg. (39%) of colorless needles of **13**: m.p. 223–324°; λ_{max}^{MeOH} 297 mμ (ϵ 23,000); λ^{KBr} 3.1, 5.92 μ; δ^{CDCl_3} = 2.20 (s, 3, CH_3), 5.95 p.p.m. (s, 1, =CHCl).

Anal. Calcd. for $C_{12}H_{10}ClNO$: C, 65.60; H, 4.59; Cl, 16.14; N, 6.38. Found: C, 65.43; H, 4.73; Cl, 16.63; N, 6.54.

Similar treatment of the hydroxypyrrolealdehyde **10** gave **13** in 43% yield.

1-Benzoyl-1,7-dihydro-7-methoxy-5-methyl-6-phenyl-4H-1,2-diazepin-4-one (17).—To a solution of 1.00 g. of the 1-benzoyl-7-methoxytetrahydrodiazepinone **2** in 130 ml. of methylene chloride was added a solution of 535 mg. of N-bromosuccinimide in 32 ml. of pyridine. After 6 hr. (25°), 66 ml. of iced concentrated HCl was added. The methylene chloride solution was washed, dried, and evaporated to a thick syrup which crystallized on chilling. Recrystallization from methanol–water gave 840 mg. (84%) of **17** as light tan prisms. Further recrystallization from methanol gave pale yellow prisms: m.p. 118°; λ_{max}^{MeOH} 300 mμ (ϵ 11,900); λ^{KBr} 3.40, 5.94, 6.07, 6.35 μ; δ^{CDCl_3} = 1.97 (s, 3, CH_3), 3.30 (s, 3, OCH_3), 6.88 (s, 1, H.7), 7.14 (s, 1, H.3), 7.3–7.9 p.p.m. (m, 10, C_6H_5).

Anal. Calcd. for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.83; H, 5.24; N, 8.30.

The same product was obtained in 4% yield by oxidation of **2** with chromic anhydride–pyridine.

2,3-Dihydro-7-methoxy-5-methyl-6-phenyl-4H-1,2-diazepin-4-one (18).—A solution of 1.00 g. of the 1-benzoyl-7-methoxy-1,7-dihydro ketone **17** in 130 ml. of methanol was warmed to 35° and then treated with 3.3 ml. of 10% aqueous KOH. The solution immediately became bright yellow. After standing for 15 min., the solution was diluted with 1 l. of water and extracted with methylene chloride. The methylene chloride solution was washed, dried, and evaporated to an orange oil; the odor of methyl benzoate was present. Crystallization of the oil from ether–hexane gave 603 mg. of dark yellow prisms of **18**, m.p. 99–101°, in two crops. (A double melting point, 85 and 100°, was sometimes observed.) Recrystallization from ether–hexane gave yellow prisms, m.p. 101°; for spectral data, see discussion.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.48; H, 6.15, N, 11.68.

2-Benzoyl-2,3-dihydro-7-methoxy-5-methyl-6-phenyl-4H-1,2-diazepin-4-one (19).—A solution of 270 mg. of the methoxydiazepinone **18** in methylene chloride containing 1 ml. of dimethylaniline was treated with 0.14 ml. of benzoyl chloride. After 90

(14) This superior procedure was suggested by J. B. Hendrickson, R. Rees, and J. F. Templeton, *J. Am. Chem. Soc.*, **86**, 107 (1964).

(15) "The Chemistry of Penicillin," H. T. Clark, J. R. Johnston, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949, p. 170.

(16) The data available do not permit assignment of the tautomeric structure of **10**; the hydroxypyrrolealdehyde structure was suggested for the 3,4-dimethyl compound.[8]

min. the solution was treated with water and the methylene chloride was then washed, and evaporated to an oil which was crystallized from ether. Recrystallization from ether–hexane gave 280 mg. of **19** as yellow crystals: m.p. 115°; λ_{max}^{MeOH} 215 mμ (ε 22,000), 367 (890), λ^{KBr} 5.96, 6.24 μ; δ^{CDCl_3} = 1.88 (s, 3, CH_3), 3.60 (s, 3, OCH_3), 4.83 (s, 2, CH_2), 7.0–7.8 p.p.m. (m, 10, C_6H_5).

Anal. Calcd. for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 72.22; H, 5.62; N, 8.28.

2-Acetyl-1-benzoyl-7-methoxy-5-methyl-6-phenyl-1,2,3,7-tetrahydro-4H-1,2-diazepin-4-one (21).—A solution of 500 mg. of the benzoyl-7-methoxydiazepinone **2** in 16 ml. of acetic anhydride was heated 4 hr. on a steam bath. The solution was evaporated and methanol was added twice and evaporated. The oil was crystallized from methanol to give 388 mg. of **21** as colorless prisms: m.p. 153–54°; λ_{max}^{EtOH} 266 mμ; λ^{KBr} 5.89, 6.00 μ; λ^{CHCl_3} 5.87, 5.95 μ; for the n.m.r. spectrum, see discussion.

Anal. Calcd. for $C_{22}H_{22}N_2O_4$: C, 69.82; H, 5.86; N, 7.40; O, 16.91. Found: C, 70.14, 69.71; H, 6.04, 5.82; N, 7.40; O, 17.25.

A solution of 50 mg. of **21** in 5 ml. of 5% methanolic KOH was allowed to stand 12 hr. at 25° and was then diluted with water and extracted with methylene chloride. Evaporation of the methylene chloride gave 26 mg. of yellow solid which was crystallized from ether to give 12 mg. (45%) of **14**, m.p. 151°, infrared spectrum identical with that of authentic sample.

Heterocyclic Studies. XXII. The Rearrangement of 2,3-Dihydro-1,2-diazepin-4-ols to Furfurylhydrazine[1]

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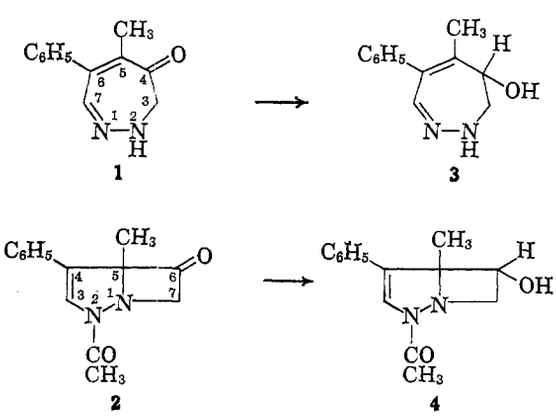
Received June 8, 1965

Reduction of the dihydrodiazepinone **1** and the 2-acetyl derivative with $NaBH_4$ gives the carbinols **3** and **5**, respectively. The diazepinol **3** is converted on acetylation in the presence of pyridine to the diazabicyclo[3.2.0]-heptenone system **4**, which is also obtained by reduction of the bicyclic ketone **2**. In the absence of base, acetylation of **3** leads to the transannular oxide **8**, which can also be obtained from **4**. The diazepinols **3** and **5** and the mono- and diacetyl oxides **8** and **9** undergo rearrangement in acid to 3-methyl-4-phenylfurfurylhydrazine (**10**) and the mono- and diacetyl derivatives **11–13**. A number of characterization reactions and interconversions of these hydrazines are described. Vigorous acid hydrolysis of **10** leads to hydrazine and the butenolide **20**. The oxide **8** and the furan **12** are dehydrogenated with N-bromoacetamide to the unsaturated compound **21** and the hydrazone **22**, respectively, and these compounds have been interrelated. An elimination mechanism is suggested for the formation of the furans.

Previous studies on the chemistry of the diazepinone **1** and the related bicyclic ketone **2** have revealed a variety of rearrangements and transannular reactions.[2] In a continuation of work in this diazepine series, reactions of the carbinols **3** and **4** have been explored and form the subject of this paper.



The alcohols **3** and **4** and several N-substituted derivatives of **3** were readily obtained by reduction of the corresponding ketones with sodium borohydride. The yields were quite good, and no products arising by reduction of other unsaturated centers were isolated. The carbinols could be oxidized back to the respective ketones with N-bromoacetamide or by Oppenauer conditions. The spectral properties of **3** and the 2-acetyl derivative **5**, with λ_{max} 303 and 308 mμ, respectively, were consistent with the diazepinol structures.[3]

The *endo* configuration of the hydroxyl group in the bicyclic alcohol **4** is assigned on the assumption of *exo* attack on a bicyclo[3.2.0]heptane system.

Acetylation of **3** in the presence of pyridine gave an oil whose infrared spectrum showed bands at 1750 and 1670 $cm.^{-1}$ corresponding to O- and N-acetyl groups. This product was characterized as the diazabicyclo[3.2.0] acetate **7** by mild alkaline hydrolysis to the crystalline alcohol **4**. This substitution of **3** at N-1 parallels the formation of the bicyclic ketone **2** from **1**. Acetylation of the 2-acetyldiazepinol **5**, however, occurred at the hydroxyl group; apparently the nucleophilic character of N-1 is sufficiently depressed by the adjacent acetyl group to prevent reaction at this center in **5**. The diazepinol acetate **6** could be hydrolyzed to **5** with base.

The reaction of **3** with acetic anhydride, either neat or preferably in ethanol solution, gave a third N-monoacetyl compound, different from **4** and **5**. This product was also obtained by treatment of **4** with acetic acid, indicating attachment of the acetyl group at the diazepine N-1 position and suggesting the transannular oxide structure **8**. This construction is in harmony with the ultraviolet maximum of 253 mμ and the infrared spectrum (ν^{CCl_4} 3400, 1690 $cm.^{-1}$), corresponding to NH and N-acetyl groups but no OH frequency, and thus requires an oxide function for the oxygen atom. Further reaction of **8** with acetyl chloride in pyridine or boiling acetic anhydride gave the diacetyl derivative **9**.

The 8-oxa-1,2-diazabicyclo[3.2.1]octene structures **8** and **9** are in good accord with the n.m.r. data. After exchange with D_2O, the spectrum of **8** contained an AB pattern for the C-4 methylene group, δ_A = 3.45 p.p.m., δ_B = 2.50 p.p.m., J_{AB} = 14 c.p.s. The lines

(1) This work was supported by a grant from the Geschickter Fund for Medical Research.

(2) Part XIX: J. A. Moore, *Trans. N. Y. Acad. Sci.*, **27**, 591 (1965).

(3) L. A. Paquette [*J. Am. Chem. Soc.*, **86**, 4092 (1964)] reported λ_{max} 301 mμ for a comparable 2,3-dihydroazepine.