[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

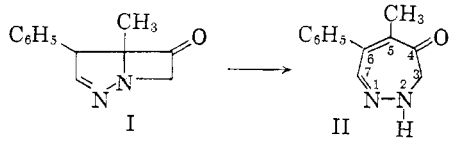
Heterocyclic Studies. IV. Evidence for the Structure of 2,3-Dihydro-5-methyl-6-phenyl-4H-1,2-diazepin-4-one[1]

BY JAMES A. MOORE AND JACOB BINKERT[2]

RECEIVED FEBRUARY 19, 1959

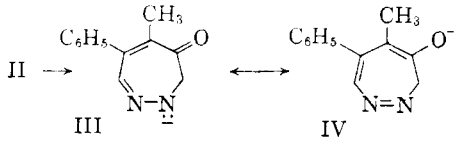
A number of reactions of the diazepinone II are discussed from the standpoint of structure proof. The presence of -NH and carbonyl groups is demonstrated by the formation of N-acyl derivatives and the derived semicarbazones. Methylation of II gives rise to two N-methyldiazepines with the alkyl substituents on different nitrogen atoms. The rearrangement of II and one of the N-methyl derivatives, but not the other, to N-aminopyridines establishes the carbon–nitrogen skeleton and indicates that tautomeric shifts of II to other double bond structures do not participate in reactions of II. The reaction of the diazepinone II and the N-2 methyl derivative VIII with hydroxylamine leads to cleavage to a hydroxamic acid identified as XXI; it is suggested that this reaction proceeds by attack at the C=N bond while attack of semicarbazide takes place at the carbonyl group. The 2-acyldiazepines react with both reagents to give derivatives which are either bicyclic or tricyclic iminohemiketals.

In the preceding paper,[2] the formation of an orange-colored, weakly acidic product by isomerization of a compound assigned the diazabicyclo-[3.2.0] structure I was reported. The diazepine structure II was suggested for the product on the basis of the spectral properties and probable mode of formation from I. In the present article is described a portion of the investigations which have been undertaken with the object of establishing this diazepine structure.



I II

A. Functional Groups.—The infrared spectrum of the colored product indicated the presence of a conjugated carbonyl system and an N–H (or O–H) group, the latter presumably being responsible for the weakly acidic nature of the diazepine. The compound was readily soluble in 10% aqueous alkali, furnishing a dark red solution (λ_{max} 418 mμ) from which it was reprecipitated unchanged on acidification (with an acid as weak as hydrogen peroxide, pK_A 12). The color is ascribed to the contribution of forms such as III and IV to the anion.



III IV

Treatment of the diazepine with acetic or benzoic anhydride in pyridine solution led to monoacetyl and -benzoyl derivatives, respectively. The ultraviolet and visible spectra of these products were very similar to those of the parent compound. The infrared spectrum of the acetate contained a doublet carbonyl band at 5.85 and 5.90 μ, while that of the benzoyl derivative showed a single carbonyl band at 5.95 μ even in a high resolution instrument; both spectra were devoid of absorption in the 3.0 μ region. These derivatives were very readily hydrolyzed to the starting diazepine; hydrolysis of the acetate with 0.01 N base was complete within a few seconds. These observations, and the fact the 6.05 μ band associated with the carbonyl group of II was shifted to lower wave length and was not resolved in the spectra of the acylation products, led to the earlier erroneous conclusion that the compounds were O-acyl derivatives, as suggested in the first communication of this series.[3]

That the acylation products were in fact N-acetyl and -benzoyl derivatives became apparent when the presence of a carbonyl group in the parent diazepine and in the acyl derivatives was established by chemical evidence. As discussed in Sect. C, the reaction of these compounds with carbonyl reagents was not uncomplicated, but a yellow semicarbazone (V) was obtained in good yield from II, and the ketone could be regenerated by hydrolysis of V in the presence of pyruvic acid. Acetylation of V furnished the acetylsemicarbazone VII which was also obtained, albeit in low yield, by treatment of the acetylated diazepine with semicarbazide acetate. These transformations, summarized in Chart 1, demonstrate conclusively the presence of both N–H and carbonyl groups in II. The reversibility of the reactions, together with the close ultraviolet and visible spectral similarities of II and VI and of V and VII, confirms the assignment of the 2-acyldiazepine structures VIa and VIb to the acetate and benzoate, respectively.

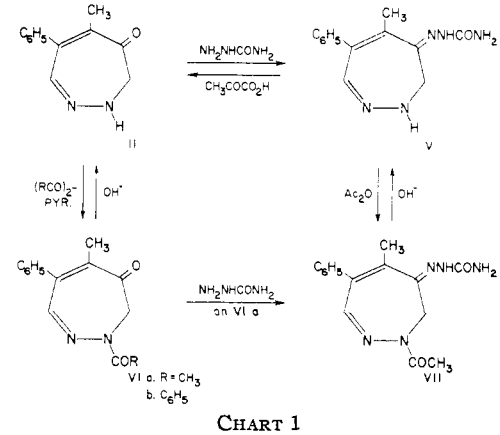


CHART 1

Methylation of II provided additional evidence of the presence of an N–H function in the molecule.

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

(2) Paper III, J. A. Moore and R. W. Medeiros, THIS JOURNAL, **81**, 6026 (1959).

(3) J. A. Moore, *ibid.*, **77**, 3417 (1955).

Two products were formed, each in 30–40% yield, on treatment of II with methyl sulfate in alkaline solution at 0°. Separation of the two products was effected readily since one of them proved to be neutral and the other basic. Both compounds had the composition of monomethylation products, and both were found to contain an N-methyl group and no methoxyl under the conditions of the Zeisel determination.

The neutral product was a low-melting yellow substance, very soluble in ether, but insoluble in aqueous alkali, whose ultraviolet and visible spectrum was nearly identical with that of II in neutral solution. The infrared spectra of the two compounds showed many similarities, but the 3.05 band characteristic of the N–H group in II was absent in the spectrum of the methyl derivative. This methylation product furnished a semicarbazone which was again very similar in spectra to V, obtained from the parent diazepine; attempts to obtain the methylated semicarbazone by treatment of V with methyl sulfate were unsuccessful. The close correspondence to II in physical and chemical properties, and the absence of acidic character, provide strong presumptive evidence that the neutral product is the 2-methyldiazepine VIII, differing from II only in replacement of N–H by N–CH_3. Support for this structural relationship is afforded by a reaction, discussed in Sect. C, in which II and VIII give, under very mild conditions, an identical fragment comprising C_4–C_7 together with hydrazine and methylhydrazine, respectively.

The second methylation product was isolated by treatment of the mixed products with acid, removal of the 2-methyldiazepine and reprecipitation with base. The compound separated from alkaline solution as crimson plates which were very sparingly soluble in non-polar solvents but extremely soluble in methanol or methanol–water mixtures. The infrared spectrum showed no absorption bands below 6.0 μ, but a strong band was present at 6.25 μ. Treatment of the base with hydrogen chloride in chloroform solution gave a bright yellow hydrochloride, pK_A 4.9, which had ultraviolet and infrared spectra very similar to those of the diazepine II; a strong carbonyl band was present at 6.0 μ. The free base was a highly labile substance and, on standing, the red crystals became light yellow and a new isomeric product, still containing an N-methyl group, was isolated in high yield. The nature of this product is not yet known; it is very soluble in ether, and contains no carbonyl group.

The color, solubility properties and basicity of this methylation product suggested a quaternary betaine structure in which the diazepine nucleus is retained. Diazepinium structures with the methyl group at either N-1 (IX) or N-2 (X) can be considered; in both structures the negative charge can reside on either nitrogen or oxygen. Since the two methylation products are not interconvertible, VIII being unaffected by fairly vigorous alkaline treatment, it appeared highly improbable that the two products were tautomers, as would be the case if the basic isomer had the N-2 methyl structure X. The basic methylation product is therefore assigned the N-1 methyldiazepinium structure IX, and the hydrochloride, which by infrared evidence must contain a carbonyl group, is considered to be XI. Further data substantiating structure IX are presented in the following section.

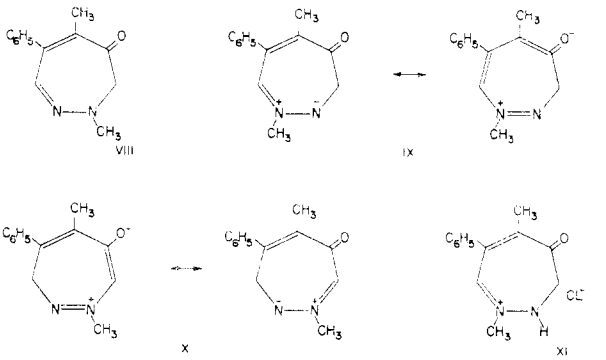
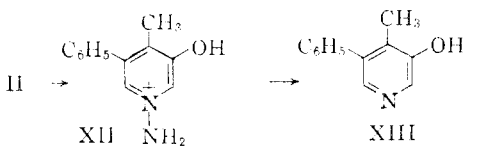


CHART 2

The formation of almost exactly equal amounts of VIII and IX by methylation of the secondary and tertiary nitrogen atoms of II at equal rates is quite unlikely. It is suggested rather that the betaine IX arises by quaternization of the diazepinone, whereas VIII is formed by reaction of methyl sulfate with the conjugate base III.

B. Skeletal Structure.—Although the formation of II from the bicycloketone I can be represented by a very straightforward mechanism,[2] it was necessary to establish that rearrangement leading to a different carbon–nitrogen skeleton had not intervened in the transformation I → II, and that II did, in fact, contain a seven-membered heterocyclic ring. Important information bearing on these points was provided by the reaction of II with 6 *N* hydrochloric acid, which afforded a colorless crystalline product in 90% yield. This compound proved to be the hydrochloride, $C_{12}H_{12}ON_2 \cdot HCl$, of a base isomeric with II. The isomerization product contained a primary amino group as indicated by formation of a Schiff base with cyclopentanone, and on treatment with nitrous acid furnished in 95–98% yield an amphoteric *deamination* product, $C_{12}H_{11}ON$, having the characteristics of a 3-hydroxypyridine. These findings, taken together with the assumption that rearrangement of skeletal substituents had not occurred, led to the formulation of the hydrochloride and the deamination product as 1-amino-3-hydroxy-4-methyl-5-phenylpyridinium chloride (XII) and the corresponding 3-hydroxypyridine XIII, respectively. The corroboration of structure XIII for the deamination product, and synthesis by an independent route, are described in the following paper.[4]

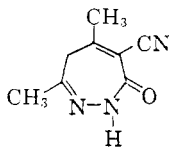


The quaternary pyridinium structure XII for the hydrochloride derived from II is uniquely defined by the deamination to XIII, since neither the 2-

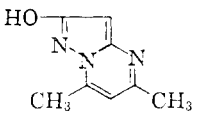
(4) J. A. Moore and H. H. Püschner, THIS JOURNAL, **81**, 6041 (1959), paper V.

nor 6-amino-3-hydroxy-4-methyl-5-phenylpyridine could conceivably lead to a deamination product. These two compounds have in fact been prepared from XIII, and their diazotization products have been studied in connection with a related problem.[5] On the other hand, nitrous acid has been reported to bring about deamination in the case of the only other analogous compound[6] which has been described, namely, the simple 1-aminopyridinium chloride.[8] The conversion of XII to XIII was also accomplished by catalytic hydrogenation, although in lower yield. Further data on the characterization of XII and some other reactions of this quaternary hydrazine are presented in paper VI.[9]

The formation of the pyridine XII, in which the carbon–nitrogen skeleton of the diazepine precursor I is preserved, establishes quite definitely that the atomic skeleton of the diazepine is as represented in II. While it cannot be said that the conversion of II to XII constitutes rigorous proof of the presence in II of a seven-membered heterocyclic ring, the contraction to the resonance-stabilized pyridine is completely consistent with this formulation. Since monocyclic 1,2-diazepine derivatives at the level of oxidation of II have not, to our knowledge, been previously described,[10] a precise analogy for



i

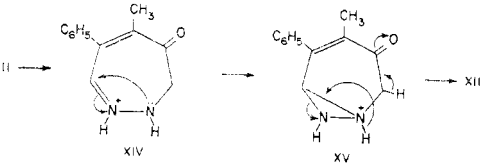


ii

the rearrangement of II to XII is not available. It is pertinent, however, that this paucity of information on 1,2-diazepines stems from the fact that reactions which might be expected to lead to members of this class from acyclic hydrazine precursors often furnish 1-aminopyridine or 1-aminopiperidine derivatives.

The preferential closure of a six-membered ring was first encountered by Fischer,[11] who obtained N-aminocarbostyril from the acid treatment of *o*-hydrazinocinnamic acid; the analogous formation of a 1-aminopyridone has been reported recently by Ried and Meyer.[12] Another pertinent reaction is the formation of 1-aminopyridinium salts by condensation of trisubstituted pyrylium salts with arylhydrazines[13]; a related ring closure has been observed in the formation of N-amino-3,4-dihydroisoquinolinium derivatives from *o*-(β-haloethyl)-benzaldehyde hydrazones.[14]

In the light of these diverse reactions leading to 1-aminopyridine derivatives, it seems clear that the transformation of II to XII would be a highly favorable process provided that a suitable reaction path is available. The rearrangement is presumably initiated by protonation of the C=N bond as in the hydrolysis of a hydrazone. The reaction could then proceed through the carbinol-amine and aldehyde with ring closure to N_2. Alternatively, formation of the C_7–N_2 bond can be formulated as in XIV, with a further shift of electrons (XV) leading directly to XII. The analogous conversion of a cycloheptadienone system to a valence-tautomeric bicyclo(4.1.0)heptene has been observed in certain reactions of eucarvone.[15]



The two methylated diazepines VIII and IX exhibited a striking difference in their behavior under acid conditions. The 2-methyl derivative VIII, like II, was unaffected by mild acid treatment; under anhydrous conditions a substance, very readily hydrolyzed to VIII and assumed to be a hydrochloride, was formed. On heating with 6 *N* hydrochloric acid, VIII furnished only a dark amorphous resin, and neither a pyridine nor hydrolysis product could be isolated.

The 1-methyldiazepinium chloride XI, on the other hand, was converted simply by *brief warming in aqueous solution* to a colorless isomeric hydrochloride in 84% yield. This product was very similar in physical properties to XII, and on treatment with nitrous acid gave the deaminated pyridine XIII in 95% yield. Catalytic hydrogenation of the rearrangement product led to XIII and a volatile base which was identified as methylamine by paper chromatography. These findings establish quite firmly the 1-methylaminopyridinium structure XVIII (Chart 3). The further characterization of XVIII is discussed in paper VI.[9]

The conversion of XI to XVIII establishes beyond reasonable doubt that the skeleton postulated as a diazepine is preserved intact in XI and in the unstable conjugate base IX. The isomerization of XI can occur by the same path as that of the parent diazepine II, the methylated nitrogen atom being extruded with bond formation between C_7 and N_2. The reaction would be expected to take place more readily with XI by virtue of the quaternary ammonium function at N_1. The isomerization of the 2-methyldiazepine VIII to the 1-methylaminopyridine XVIII, on the other hand, could not occur by this path, since ring contraction of the corresponding intermediate XVII or its equivalent would be blocked, and XVIII could be formed from VIII only if a tautomeric shift involving C_3 and C_7 occurred, with formation of the conjugate acid XIX of the 2-methyldiazepinium derivative X.

(5) Paper VII, J. A. Moore and F. J. Marascia, THIS JOURNAL, **81**, 6049 (1959).

(6) A series of N-amino-2-pyridones has been reported recently by K. Hoegerle, *Helv. Chim. Acta*, **41**, 539 (1958)[7] and these compounds likewise undergo deamination with nitrous acid, but these cyclic hydrazides are, of course, quite different from the 2-unsubstituted N-aminopyridines which are quaternary hydrazine derivatives.

(7) *Cf.* also ref. 12.

(8) J. N. Ashley, G. L. Buchanan and A. P. T. Easson, *J. Chem. Soc.*, 60 (1947).

(9) J. A. Moore and J. Binkert, THIS JOURNAL, **81**, 6045 (1959).

(10) A compound assigned the 1,2-diazepine structure (i) by W. Ried and E.-U. Köcher, *Angew. Chem.*, **70**, 164 (1958), has been suggested by P. Schmidt, K. Meier and J. Druey, *ibid.*, **70**, 344 (1958), to be instead the pyrazolopyrimidine (ii).

(11) E. Fischer, *Ber.*, **14**, 478 (1881); C. Ainsworth, THIS JOURNAL, **80**, 967 (1958).

(12) W. Ried and A. Meyer, *Chem. Ber.*, **90**, 2841 (1957).

(13) W. Schneider, *Ann.*, **438**, 115 (1924); W. Schneider and W. Riedel, *Ber.*, **74**, 1252 (1941).

(14) E. Schmitz, *Chem. Ber.*, **91**, 1495 (1958).

(15) E. J. Corey and H. J. Burke, THIS JOURNAL, **78**, 174 (1956).

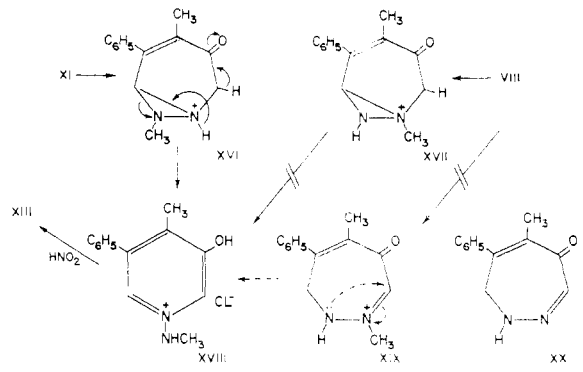


Chart 3

The failure of VIII to give a detectable amount of XVIII must mean either that tautomerization between Δ^7-forms such as II or IX and Δ^2-forms such as XIX is completely suppressed or else that reaction of the latter in acid medium takes an entirely different course. It seems reasonable to anticipate that the pyridine XVIII would be produced from XIX by a parallel rearrangement comprising bond formation between C_3 and N_1 with extrusion of N_2 as indicated by the dotted arrows in Chart IV. We are, therefore, presently inclined to the view that tautomeric equilibria between the Δ^7- and Δ^2-dienone systems do not play a significant role in the reactions of these diazepines. This premise is supported by other reactions of II and its derivatives which will be discussed in subsequent papers.

Regardless of the question of the mobility of the tautomeric forms of the diazepine II and its derivatives, it is necessary to consider alternative isomeric and tautomeric structures for the compounds which have been described. Although some twenty double bond structures for a 4-oxygenated 5-methyl-6-phenyl-1,2-diazepine at this oxidation level can be written, all of these except II and the Δ^2-tautomer XX can be ruled out on the basis of the spectra of the compounds and the reactions which have been described. It is noteworthy in this connection that no products derived from a Δ^5-eno ic tautomer have been encountered. If the possibility of the conversion of either XI or XIX to the methylaminopyridinium derivative XVIII is admitted, however, it is possible to interpret all of the reactions which have been discussed so far on the basis of XX rather than II. The path by which the diazepine is formed from I, if correctly understood, leads uniquely to II and the corresponding structures which have been written for the derivatives of II. As stated in the preceding article, however, the structure of the bicyclic ketone I rests at present largely on its conversion to II. Since a satisfactory alternative structure for I, or a path by which I could give rise to XX, are equally difficult to formulate, structures I and II appear to be most satisfactory. Further evidence for II as opposed to XX can be adduced from certain reactions described in the following section.

C. Transannular Reactions.—It was mentioned in Sect. A that complexities were encountered in certain reactions of II and the 2-acyl derivatives VIa and VIb, with carbonyl reagents. In sharp contrast to the smooth conversion of the diazepine II and the 2-methyl derivative VIII to the respective semicarbazones, the reaction of either compound with hydroxylamine in the usual buffered media gave in 50–60% yield the *same* colorless acidic product, having the composition $C_{11}H_{11}O_2N$. The product exhibited a single absorption maximum at 250 mμ in the ultraviolet; the infrared spectrum contained a broad absorption band at 3.2–3.6 μ, indicative of a strongly bonded hydroxyl group, and a sharp band at 6.0 μ. The compound gave an intense greenish-blue color with ferric chloride. Acetylation yielded a neutral monoacetate which was readily hydrolyzed; the infrared spectrum showed no hydroxyl absorption and two bands in the carbonyl region, at 5.58 and 5.9 μ. The color reaction and short wave length carbonyl absorption of the acetate[16] strongly indicated a cyclic hydroxamic acid structure for the acidic product, and support for this formulation was obtained by reduction with zinc and acetic acid, which furnished a neutral product, $C_{11}H_{11}ON$, whose properties corresponded to those expected for an unsaturated lactam.

On the premise that the $C_6H_5C{=}CCH_3$ fragment of the diazepines was retained in the hydroxamic acid, the structural possibilities consistent with the properties of the latter were narrowed to the N-hydroxy-3-methyl-4-phenyl-Δ^3-pyrrolin-2-one (XXI) and the corresponding pyrrolin-5-one structure (XXVI) or tautomeric modifications of these pyrrole derivatives. That the former was correct was shown by hydrogenation of the reduced hydroxamic acid (XXII) to the 3-methyl-4-phenyl-2-pyrrolidone (XXV), which was identical with an authentic sample.

The synthesis of XXV followed the straight-forward procedure of Koelsch.[17] The pyrrolidone XXIII obtained by hydrogenation of ethyl α-carbethoxy-β-cyano-β-phenylpropionate was alkylated with methyl iodide, furnishing an oily ester (XXIVb) together with a small amount of unalkylated material isolated as the sodium salt. Saponification of the ester gave the acid XXIVa which was decarboxylated by heating at the m.p. to give what appeared to be a mixture of stereoisomeric pyrrolidones. By chromatography a compound was separated which was identical to the hydrogenation product of the unsaturated lactam with the exception of a weak band in the infrared spectrum and a slightly lower m.p.; these differences are attributed to a trace of the other stereoisomer in the decarboxylation product. The pyrrolidone obtained by catalytic hydrogenation of XXII is probably the *cis* racemate XXV, but this configurational assignment is tentative.

The question of the double bond structure of the hydroxamic acid and the unsaturated lactam is the same one which has arisen in several other cases of 2-oxygenated pyrroles. It has recently been established[18] by chemical and physical methods that 3,4-dialkyl derivatives such as hydroxyopsopyrrole[19] possess the Δ^3-pyrroline-2-one structure. On

(16) D. E. Ames and T. F. Gray, *J. Chem. Soc.*, 631 (1955).

(17) C. F. Koelsch and C. H. Stratton, THIS JOURNAL, **66**, 1883 (1944).

(18) H. Plieninger and M. Decker, *Ann.*, **598**, 198 (1956).

(19) W. Siedel, *ibid.*, **554**, 144 (1943).

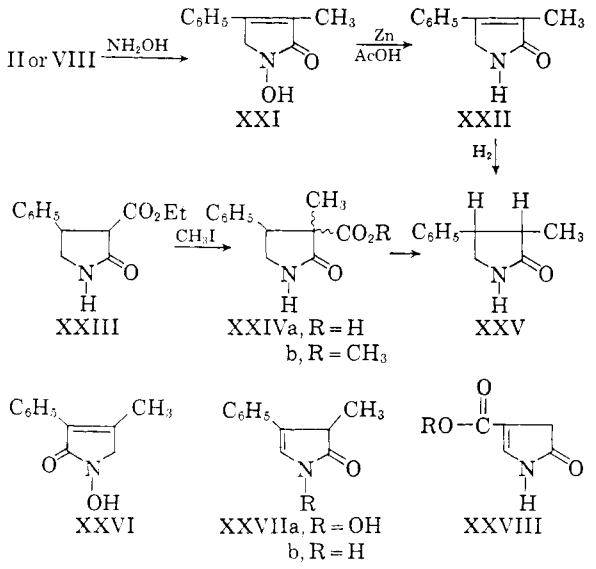


CHART 4

the other hand, the 4-carbalkoxy-2-hydroxypyrroles obtained by the Emery reaction are best represented as the Δ^4-pyrrolin-2-ones[20] (XXVIII) and it is evident that the tautomeric structure of these compounds is largely dependent on the nature of the 3- and 4-substituents. Conclusive evidence that the 3-methyl-4-phenyl derivatives in the present series have the Δ^3-pyrrolin-2-one structure rather than the Δ^4-structures XXVII was obtained by consideration of the ultraviolet spectra of the compounds in question with those of a number of related substances; the relevant data are presented in Table I.

It is apparent that the absorption maxima of the hydroxamic acid (B) and of the derived lactam A are in better accord with the chromophore present in the cinnamoyl amides C and D than that in the β-phenylvinylamines E and F.[21] A calculated λ_{max} value of 261–266 mμ for the 4-phenyl-Δ^3-pyrrolin-2-one system can be derived from the value of 216 mμ for the 4-methyl unsaturated lactam G by adding a contribution of 45–50 mμ for the substitution of a phenyl group at the terminus of the chromophore. This increment is obtained from the corresponding γ-lactones H and I and the cyclopentenones J and K. Alternatively, the effect of ring formation on the cinnamyl chromophore of the amides C and D can be estimated as a hypsochromic shift of 5–10 mμ from the values for the open chain ester L and lactone H and those for the corresponding ketones (*cf.* footnote *i*, Table I); this leads to a value of 248–253 mμ for the lactam XXII (A) and hydroxamic acid XXI (B). Although these two calculated values differ considerably, it will be noted that the observed λ_{max} for XII and XXI lies mid-way between them.

Further support for the conclusion that the unsaturated lactam is XXII rather than XXVIIb was

(20) C. A. Grob and P. Ankli, *Helv. Chim. Acta*, **32**, 2010 (1949).

(21) The λ_{max} value of 259 mμ for N-methyl-α-methylcinnamamide represents a hypsochromic shift of 8 mμ from that of the methyl ester, in marked contrast to the bathochromic shift of 19 mμ reported by L. Crombie, *J. Chem. Soc.*, 2997 (1952), for an N-alkyl *trans*-crotonamide with respect to the parent acid.

TABLE I

	Compound	λ_{max}^{EtOH}, mμ	ϵ
A	3-Methyl-4-phenyl-Δ^3-pyrrolin-2-one (XXII)	258[a]	15,000
B	N-Hydroxy-3-methyl-4-phenyl-Δ^3-pyrrolin-2-one (XXI)	250[a]	13,000
C	N-Methyl-α-methylcinnamamide[b]	258[a]	17,000
D	α-Methylcinnamhydroxamic acid[c]	258[a]	14,000
E	4-Carbethoxy-Δ^4-pyrrolin-2-one (XXVIII)	279[d]	13,000[d]
F	α-Acetamidocinnamic acid	278[a]	13,500
G	3,4-Dimethyl-Δ^3-pyrrolin-2-one	215–216[e]	14,000[e]
H	3-Phenyl-Δ^2-butenolide[f]	269[a]	19,000
I	3-Alkyl-Δ^2-butenolide	217[g]	15,000[g]
J	3-Phenyl-Δ^2-cyclopentenone	281[h]	23,000[h]
K	2,3-Dialkyl-Δ^2-cyclopentenone	237[i]	
L	Methyl cinnamate	274[a]	19,000

[a] Values determined in present work. [b] Prepared from methyl ester and methylamine; prisms, m.p. 80–81° from ether–pentane. *Anal.* Calcd. for $C_{11}H_{13}ON$: C, 75.40; H, 7.48. Found: C, 75.80; H, 7.84. [c] Prepared from methyl ester and hydroxylamine; plates, m.p. 149–151° from methanol–ether; violet color with $FeCl_3$. *Anal.* Calcd. for $C_{10}H_{11}O_2N$: C, 67.78; H, 6.26. Found: C, 68.71; H, 6.36. [d] Values estimated from curve, ref. 20. [e] Values estimated from curve, ref. 18. [f] We thank Dr. T. H. Bembry, City College of New York, for supplying this sample. [g] Average values; *cf.* L. Dorfman, *Chem. Revs.*, **53**, 47 (1953). [h] A. L. Wilds, L. W. Beck, W. J. Close, C. Djerassi, J. A. Johnson, T. L. Johnson and C. H. Shunk, THIS JOURNAL, 69, 1985 (1947). [i] A. Gillam and E. S. Stern, "Introduction to Electronic Absorption Spectroscopy," E. Arnold Ltd., London, 1954, p. 96.

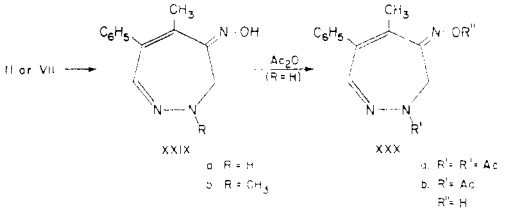
obtained from proton magnetic resonance measurements.[22] The spectrum of the compound in chloroform solution showed two peaks on the low frequency side of the chloroform band; the latter masked both aromatic C–H and N–H resonance. The two peaks, at 13 and 97 c.p.s. below the water reference, had heights in the ratio of 2:3, corresponding to the methylene and methyl protons in XXII.

With the establishment of structure XXI for the cleavage product of the diazepines II and VIII it was of considerable interest to determine the nature of the fragments derived from the nitrogen atoms and from C-3. Since no gas was evolved during the reaction it was clear that oxidation of the =N—N—R grouping had not occurred and accordingly, a search was made for basic products. When the reaction mixture from VIII, after removal of XXI, was made strongly alkaline and extracted with ether, methylhydrazine was isolated as 2-methyl-4-phenylsemicarbazide. From the reaction of II, hydrazine was detected by paper chromatography, and in addition, formaldehyde, evidently derived from C-3, was isolated by distillation of the acidified solution.

The reaction of II and VIII with hydroxylamine in alkaline solution took an entirely different course, the respective yellow oximes XXIX being formed in excellent yield. The structures of these derivatives were inferred from the visible and ultraviolet spectra, which resembled those of the semicarbazones, and behavior on acetylation. A diacetate

(22) We are indebted to Dr. E. G. Brame, Polychemicals Department, E. I. du Pont de Nemours, Inc., for these measurements and the interpretation of the spectra.

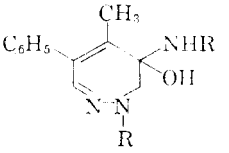
XXXa of the diazepine oxime XXIXa was obtained on mild treatment with acetic anhydride; the infrared spectrum contained two sharp bands at 5.70 and 5.95 μ. Brief hydrolysis of this derivative furnished a monoacetate which was assigned the 2-acetyldiazepine oxime structure XXXb on the basis of the single carbonyl band in the infrared at 6.0 μ. The 5.70 μ band in the spectrum of the diacetate which disappears on hydrolysis corresponds almost exactly with that reported[23] for the carbonyl absorption in simple oxime acetates, and the bands at 5.95 and 6.0 μ in the spectra of XXXa and XXXb, respectively, must arise from the 2-acetyl group. The shift of these bands from the position (5.85 μ) of the acetyl band in the spectrum of the acetyl ketone VIa is noteworthy; an even larger displacement was observed in the spectrum of the acetyl semicarbazone VII (Chart 1), in which a strong band provisionally assigned to the 2-acetyl group appears at 6.12 μ. This effect of the functional group at C-4 on the 2-acetyl group is also reflected in the much greater ease of hydrolysis of the acetyl group in the ketone VIa as compared to the oxime XXXb.



Before considering possible explanations for the contrasting reactions of II and VIII with hydroxylamine and semicarbazide, or a mechanism for the formation of XXI, it will be instructive to discuss the reactions of the 2-acetyl- (VIa) and 2-benzoyldiazepinones (VIb) with these reagents. As noted previously, treatment of VIa with semicarbazide acetate furnished the semicarbazone VII (Chart 1) in low yield, but the major product (65% yield) was a colorless substance having the composition of a hydrated semicarbazone. The compound was readily converted with base to II, and with acetic anhydride to the starting 2-acetyldiazepine VIa. It was impossible, however, to effect the transformation of the product to the 2-acetyldiazepine semicarbazone (VII) or the diazepine semicarbazone V by dehydration; acid treatment led to intractable amorphous material. In an analogous fashion, the 2-benzoyldiazepine VIb with buffered semicarbazide acetate furnished the 2-benzoylated semicarbazone and a colorless "hydrate."[24] The latter product was obtained in 39% yield when excess sodium acetate was present, but only a low yield of the semicarbazone and no "hydrate" was isolated when semicarbazide acetate alone was employed. The "hydrate" gave the 2-benzoyldiazepine VIb with acetic anhydride.

The reactions of the acyl ketones VIa and VIb with hydroxylamine acetate furnished colorless "hydrated" oximes as the sole product in each case; no trace of the normal oximes (XXXb and the benzoyl counterpart) was found in the reaction mixtures. With this reagent the reaction of the benzoyldiazepine was much more satisfactory, giving a 94% yield of the adduct. These products were quite similar in their behavior to the "hydrated" derivatives obtained with semicarbazide. Treatment of the acetyl derivative with base furnished II, and the benzoyl product was readily cleaved to VIb with acetic anhydride or by mild permanganate oxidation; attempted conversion of this derivative to II with base was unsuccessful. No trace of the hydroxamic acid XXI was observed during the formation or reactions of these hydroxylamine adducts.

The composition of these "hydrates" and their facile conversion with base to the parent diazepine II are compatible with the addition products XXXI of the reagent and ketone; such intermediates have been isolated in certain carbonyl addition reactions. This type of product would scarcely be anticipated with a highly conjugated carbonyl group, however, and should certainly furnish the corresponding semicarbazone or oxime with great ease. The infrared spectra of the semicarbazide products were complex and not particularly informative. The "hydrated oximes" each exhibited several more-or-less resolved peaks at about 3 μ and a very strong band at 6.22–6.25 μ, which is a longer wave length than that encountered in any other 2-acyldiazepine derivatives.



XXXI

The ultraviolet spectra were highly significant; with three of the four compounds the single absorption maximum occurred between 245 and 250 mμ. In the case of the product from VIb and semicarbazide, which was obtained in lowest yield of all four reactions, the maximum was at 272 mμ, but the compound was not otherwise distinctive. If the chromophoric system in these derivatives were that in XXXI, involving conjugation of two double bonds and an unshared electron pair on N-2, the maximum would be expected at *ca.* 300–320 mμ. This has been observed in the carbinols obtained from II and VIII by sodium borohydride reduction; these compounds, which will be described in a later paper, have λ_{max} 310–320 mμ. The maxima (ϵ 16,000–20,000) at *ca.* 250 mμ are compatible with a simple styryl chromophore, and it thus appears that in the "hydrated" carbonyl derivatives of VIa and VIb, addition to the Δ^7-C=N bond has occurred.

Two structural possibilities for these adducts, both consistent with the chemical properties and ultraviolet spectra, have been considered. One of these comprises the triazabicyclo(3.2.1) systems XXXVII and XXXVIII (Chart 5), which would arise by nucleophilic attack at the C=N bond by the —NH— grouping in XXXIII, bridging of the

(23) H. Bredereck, A. Wagner, D. Hummel and H. Kreiselmeier, *Chem. Ber.*, **89**, 1532 (1956).

(24) This and several related compounds tenaciously retained 0.5 mole of methanol of crystallization.

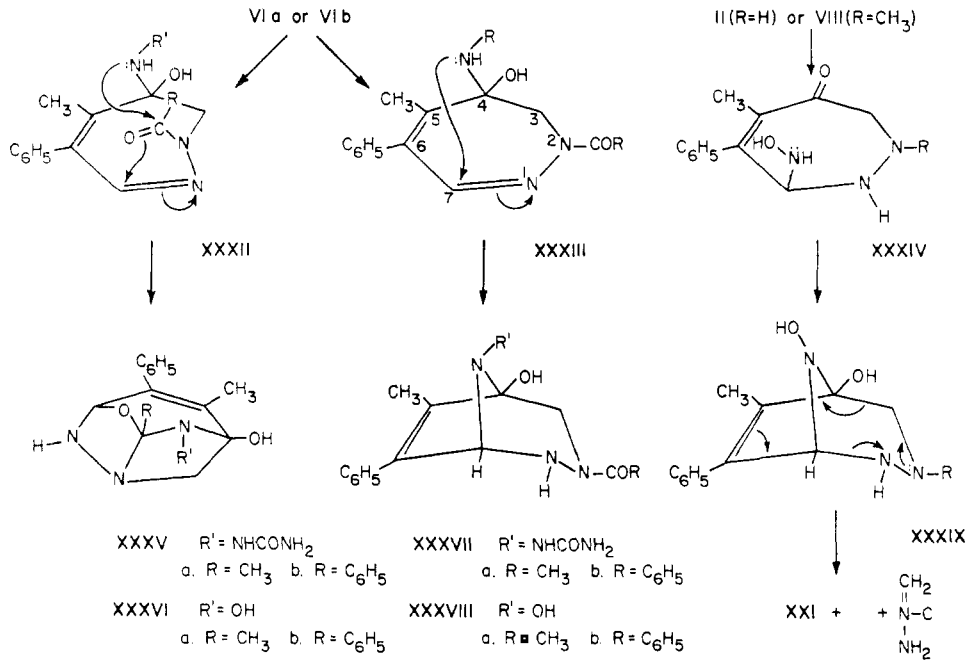
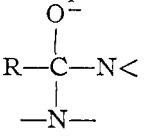


Chart 5

seven-membered ring competing with dehydration. A similar transannular addition has been encountered by Corey and Burke[18] in the condensation of eucarvone with benzaldehyde. Alternative structures for the carbonyl reagent adducts are the tricyclic orthoamides XXXV and XXXVI, which would be formed as indicated in XXXII by participation of the 2-acyl group in the bridging step. These structures, which are completely strainless, bear a certain resemblance to the polycyclic orthoacetates obtained in the cevine alkaloid series,[25] but precedent for the incorporation of the



grouping in a fused ring system appears to be lacking. Further considerations on the formation of these adducts from VIa and b are discussed below.

The base-catalyzed hydrolysis of these bicyclic or tricyclic iminohemiketals can be represented simply as reversal of the addition steps, initiated by removal of a proton from the hydroxyl group; the resulting 2-acyldiazepines would immediately undergo further hydrolysis to II. Since this reaction, or the cleavage with acetic anhydride, can be formulated equally well with either the bicyclic or tricyclic iminoketal structures, a choice between these alternatives on the basis of chemical properties is scarcely possible. Unfortunately, the spectral data were also ambiguous. As opposed to the orthoamides XXXVIa and b, the bicyclic structures should display carbonyl absorption in the infrared, but is uncertain whether the 6.23 μ band in the spectra of the hydroxylamine adducts arises from the acyl group of XXXVIII or from some other function. Until further information is available, a decision on the structure of these products is unwarranted. It must also be noted that there is no basis for the assumption, implied in the foregoing discussion, that the adducts formed with hydroxylamine and with semicarbazide have the same skeletal structure. Regardless of the precise formulation of these adducts, however, the fact that the products must arise from a transannular addition lends additional support to the conclusion discussed in Sect. B that the diazepines are correctly represented as the Δ^7- rather than the Δ^2-tautomers.

The cleavage of the diazepines II and VIII with hydroxylamine to the acid XXI and the formation of the acyldiazepine adducts, both occurring under the same conditions and both involving C_4 and C_7 of the diazepine ring, are obviously closely related processes, and several features common to the course of the two reactions suggest themselves. With semicarbazide acetate, carbonyl addition at C_4 must occur with all four compounds, with formation of the respective semicarbazones. In the 2-acyl ketones VIa and VIb, however, participation of the acyl group, either directly, leading to the orthoamides XXXV, or indirectly by mobilization of the Δ^7-double bond, leading to the bicyclic adducts XXXVII, is a competing reaction.

The contrasting behavior of hydroxylamine acetate, which gives rise to cleavage of II and VIII, and to the exclusive formation of the adducts with the acyldiazepines, can be accounted for by attack at the C=N bond in all cases. Formation of the adducts with VIa and VIb could proceed by further transannular addition entirely analogous to that encountered with the C_4-addition product of semicarbazide, but *oxime* formation would be impossible. With the ketones II and VIII, an alternative path, as indicated in XXXIX or some equivalent, would lead to the observed products. Such a fragmentation would be effectively suppressed by an acyl substituent at N_2. Precedent for the attack of hy-

(25) S. M. Kupchan, THIS JOURNAL, 77, 686 (1955).

droxylamine at the C=N bond is found in the facile cleavage of pyrrole with this reagent to furnish succindialdoxime,[26] a reaction which has no counterpart with semicarbazide. The postulation of attack at different positions by the two reagents appears to furnish the only tenable explanation for the completely different reactions observed.

Experimental[27]

2-Acetyl-2,3-dihydro-5-methyl-6-phenyl-4H-1,2-diazepin-4-one (VIa).—A solution of 300 mg. of II in 1.7 ml. of pyridine and 0.9 ml. of acetic anhydride was warmed to 70° for 30 min., cooled and treated with ice. The resulting solution was concentrated *in vacuo* until oil began to separate and then seeded; a total of 252 mg. (69%) of orange prisms was obtained in two crops. (The first crystals of this compound were obtained only after prolonged standing of an oil obtained by ether extraction.) Recrystallization of the derivative from ether furnished dark yellow needles, m.p. 89–90°; λ_{max}^{EtOH} 221 (ε 19,000), 315 (6400), 390 mμ (2600); $\lambda_{max}^{EtOH+NaOH}$ (*cf.* spectrum of II in alkaline soln.[2]) 242 mμ (23,000), 344 mμ (2400), 417 mμ (5600); λ^{KBr} (P. E. 13U) 5.876(s), (sh5.9), 5.984(s), 6.306(w), 6.362(w) μ.

Anal. Calcd. for $C_{14}H_{14}O_2N_2$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.40; H, 6.05; N, 11.95.

A sample of this acetate (20 mg.) was dissolved in 1 ml. of methanol and the solution was treated with 4 drops of 1% potassium hydroxide solution. The color changed immediately from pale yellow to dark orange; after 30 sec. the solution was diluted with water and acidified, giving the diazepine II, m.p. 147–149°.

2-Benzoyl-2,3-dihydro-5-methyl-6-phenyl-4H-1,2-diazepin-4-one (VIb).—A solution of 200 mg. of II and 256 mg. (1.1 equiv.) of freshly recrystallized benzoic anhydride in 1 ml. of pyridine was set aside for 16 hr. at 25°. The solution was then warmed briefly and treated with water, giving an oil which rapidly crystallized on scratching. The flat yellow prisms were collected and washed with water; 187 mg., m.p. 143–145°. The aqueous pyridine mother liquor subsequently deposited 56 mg. of unchanged II, m.p. 146–149°. Recrystallization of the benzoyl derivative from ether and then methanol–water gave golden laths, m.p. 147–148°; λ_{max}^{EtOH} 225(sh), 300 (ε 7800), 394 mμ (3500); λ^{KBr} (P.E. 13U) 5.937(vs), 6.254(w), 6.300(w) μ.

Anal. Calcd. for $C_{19}H_{16}O_2N_2$ (304.3): C, 74.98; H, 5.30; N, 9.21. Found: C, 74.95; H, 5.26; N, 9.43.

A sample of this compound in methanol solution was treated with a few drops of 10% potassium hydroxide solution; after standing for 30 sec. the solution was acidified and II crystallized, m.p. and m.m.p. 147–149°.

2,3-Dihydro-5-methyl-6-phenyl-4H-1,2-diazepin-4-one Semicarbazone (V).—To a solution of 203 mg. of the ketone II in 2 ml. of methanol was added a solution of semicarbazide acetate prepared by grinding together 300 mg. of semicarbazide hydrochloride and 450 mg. of sodium acetate trihydrate, extracting with 1.5 ml. of methanol and filtering to remove salt. After standing for 12 hr. the crystals which had separated were filtered and washed with methanol and ether; 190 mg. (75%) of pale yellow needles, m.p. 191–195°, was obtained. Several recrystallizations from relatively large volumes of methanol gave analytically pure material, m.p. 194–196°; λ_{max}^{EtOH} 242 (17,300), 305 (7,300), 350 mμ (6700); $\lambda_{max}^{EtOH+NaOH}$ 242 mμ (17,000), > 370 mμ; λ^{KBr} 2.9(m), 3.1–3.3(s,br), 5.9(s), 6.3(s) μ.

Anal. Calcd. for $C_{13}H_{15}ON_5 \cdot {}^1/_2CH_3OH$: C, 59.32; H, 6.27; N, 25.63. Found (dried 2 hr., 60°): C, 59.40; H, 6.34; N, 25.62. Calcd. for $C_{13}H_{15}ON_5$(257.29): C, 60.68; H, 5.88; N, 27.22. Found (dried 6 hr., 120°): C, 61.14; H, 6.15; N, 27.14; wt. loss, 6.6%.

Cleavage of Semicarbazone V.—A solution of 38 mg. of the semicarbazone V in 1 ml. of glacial acetic acid was treated with 0.2 ml. of water and 0.18 ml. of a 1.5 *N* aqueous pyruvic acid and stored at room temperature for 18 hr. The orange solution was then extracted with three portions of chloroform; the chloroform solution was washed with water, bicarbonate solution and again water, dried and evaporated to give 12 mg. of an orange oil. Crystallization from a small volume of methanol gave orange prisms, m.p. 148–149°, no melting point depression with the diazepine II; the infrared spectrum was identical to that of II.

2-Acetyl Semicarbazone (VII).—A solution of 200 mg. of the semicarbazone V (dried 2 hr., 60°) in 2 ml. of acetic anhydride and 3 ml. of pyridine was stored at room temperature for 12 hr. and then poured onto ice. The precipitated solid was filtered and dried, giving 115 mg. of yellow powder. The aqueous filtrate was then extracted with ether; the ether solution was washed with dilute acid, chilled carbonate solution and water, dried and evaporated to give 37 mg. of oil which on crystallization gave 10 mg. of crystals. The combined solid product (53% yield) was recrystallized from methanol and methanol-ether, furnishing tiny yellow prisms, m.p. 216–218°; λ_{max}^{EtOH} 241 (>20,000), 298 (7100), 360 mμ (8300); λ^{KBr} 2.89, 2.99(s), 5.85(sh), 5.92(s), 6.08–6.12(s), 6.26–6.32(s) μ.

Anal. Calcd. for $C_{15}H_{17}O_2N_5$ (299.33): C, 60.19; H, 5.72; N, 23.40. Found: C, 60.13; H, 5.69; N, 23.64.

A small sample of this compound was warmed (60°) for 10 min. in 1% methanolic potassium hydroxide solution; the color changed from pale yellow to orange. On seeding with the semicarbazone V, crystals were obtained immediately. After filtration, washing with methanol and drying, the material had m.p. 189–191°, no melting point depression with V.

Methylation of II.—A solution of 1.76 g. of II in 10 ml. of 10% aqueous potassium hydroxide was cooled to 0° and treated dropwise with stirring with a solution of 1.4 ml. of methyl sulfate in 2 ml. of methanol. After a few seconds a deep red precipitate began to separate; after a few minutes the mixture was diluted with 10 ml. of water and filtered, and the solid washed with methanol–water (1:9). The solid was then suspended in 10 ml. of methanol and 15 ml. of 2 *N* hydrochloric acid was added slowly. The solid dissolved, and the color simultaneously became light orange-yellow. As the last of the acid was added, orange crystals of the 2-methyldiazepine (VIII) began to separate from the clear solution. An additional 10 ml. of water was then added to complete the crystallization of VIII and the slurry was chilled and filtered. The light yellow filtrate was then made alkaline by the dropwise addition of chilled 40% potassium hydroxide. The color immediately became wine-red, and beautiful red plates of the 1-methyldiazepinium betaine (IX) separated which were filtered and washed with chilled dilute aqueous methanol and dried *in vacuo*.

Yields of 40% of each of the two products were obtained reproducibly by this procedure, but unless these conditions are closely followed the results may be very erratic. It is particularly important that the ratio of water and methanol are adjusted so that a second phase of methyl sulfate does not separate, and the products precipitate almost immediately as a filterable solid; if too much methanol is used, the precipitation is incomplete and the yields are low. In order to obtain a good yield of the betaine IX it is necessary to remove it rapidly from the reaction solution and purify it at once; the entire operation should be carried out in less than 15 minutes.

2,3-Dihydro-2,5-dimethyl-6-phenyl-4H-1,2-diazepin-4-one (VIII).—The orange crystals obtained from aqueous methanol in the above experiments were dried *in vacuo*, furnishing 740 mg. (39%), m.p. 71–72°. The compound crystallized in needles from methanol–water or ether–pentane mixtures; samples for analysis and physical properties were purified by sublimation, m.p. 73–74°; λ_{max}^{EtOH} 260 (6800), 316 (4770), 408 mμ (4230); λ^{KBr} 6.15 μ.

Anal. Calcd. for $C_{13}H_{14}ON_2$ (214.26): C, 72.87; H, 6.59; N, 13.08; (N)-CH_3, 7.02. Found: C, 73.03; H, 6.67; N, 13.04; (N)-CH_3, 6.85; no OCH_3.

In an attempt to convert VIII to a pyridine derivative, 40 mg. of the compound was dissolved in 2 ml. of 18% hydrochloric acid at 45°; after several min. a brown oil separated which was extracted with ethyl acetate. This material was partially soluble in concd. acid, giving a dark brown solu-

(26) R. Willstätter and W. Heubner, *Ber.*, **40**, 3869 (1907).

(27) Infrared spectra of all compounds were obtained in KBr disks. Only the most significant bands of the more important compounds are recorded, the following abbreviations have been used: (s), strong; (w) weak; (br) broad. Most infrared spectra were recorded with a Baird Associates model B spectrophotometer; in a few cases the carbonyl region was examined in a Perkin–Elmer model 13U high resolution grating spectrophotometer, these are designated (P.E. 13U). We are indebted to Mr. G. W. Tarbet for these measurements.

tion from which a black tar separated on standing. With anhydrous methanolic hydrogen chloride, VIII dissolved to give an orange solution; addition of ether gave orange prisms, m.p. 106–120°, which was evidently the **hydrochloride**. Treatment of these crystals with water or recrystallization from methanol–ether gave the original compound, m.p. and m.m.p. 74°.

Semicarbazone of VIII.—Solutions of 80 mg. of VIII in 1 ml. of methanol and semicarbazide acetate prepared from 150 mg. of semicarbazide hydrochloride and 225 mg. of sodium acetate in 1 ml. of methanol and semicarbazide acetate prepared from 150 g. of semicarbazide hydrochloride and 225 mg. of sodium acetate in 1 ml. of methanol were mixed at room temperature. After standing for 5 hr. several volumes of water were added and the turbid solution was extracted with ether. After washing and drying, the ether was evaporated to give 62 mg. of orange oil which crystallized from methanol–ether. After three recrystallizations from methanol, 33 mg. of yellow needles was obtained, m.p. 201–204° dec.; λ_{max}^{EtOH} 248 (15,000), 307 (7400), >370 mμ; λ^{KBr} 2.9, 3.1(br), 5.9–6.0(br) μ.

Anal. Calcd. for $C_{14}H_{17}ON_5$ (271.32): C, 61.97; H, 6.32; N, 25.81. Found: C, 62.04; H, 6.74; N, 25.28.

For the **cleavage** of the semicarbazone, a solution of 45 mg. of the derivative in 1 ml. of acetic acid was treated with 2 ml. of 1.5 *N* pyruvic acid and 0.2 ml. of water. After standing overnight at room temperature the solution was diluted with water, extracted with ether and the ether solution washed with carbonate, dried and evaporated. The orange residue (18 mg.) was sublimed at 110° bath temp., giving orange crystals, m.p. 68–70°, mixed m.p. with VIII no depression, infrared curves identical.

2,3-Dihydro-1,5-dimethyl-6-phenyl-4H-1,2-diazepinium-4-one Betaine (IX).—The red plates obtained by reprecipitation with alkali in the above described methylation of II were dried *in vacuo*, furnishing 760 mg. (41%), m.p. 90–91° with color change. The compound was very soluble in methanol and could not be recovered on dilution with water; it was moderately soluble in chloroform but very sparingly soluble in ether. The compound dissolved readily in dilute hydrochloric acid, giving a light yellow solution. Material for analysis and properties was purified by recrystallization from a large volume of ether, m.p. 91–95° (to yellow melt). These crystals could be preserved by storage in the dark at −20°, but changed to a yellow solid on standing at room temperature for a number of hours. This change occurred very rapidly in dilute solutions exposed to light and reproducible visible spectra could not be obtained; in several spectra, maxima or inflections of decreasing intensity were present at 250–260, 350–360 and 420–440 mμ; λ^{KBr} 6.23(s) μ. The extent to which isomerization to the yellow substance occurred in the sample prior to analysis is unknown.

Anal. Calcd. for $C_{13}H_{14}ON_2$ (214.26): C, 72.87; H, 6.59; N, 13.08; (N)–CH_3, 7.02. Found (corrected for 2.3% ash): C, 72.93; H, 6.19; N, 13.33; (N)–CH_3, 6.45; no –OCH_3.

For preparative conversion to the *isomerization product*, a solution of 280 mg. of the base IX in 2 ml. of methanol was warmed on the water-bath until the red color faded to light yellow (10–15 min.); the solution was then cooled and diluted with a few drops of water, giving 220 mg. of yellow prisms, m.p. 73–75°, m.m.p. with VIII (m.p. 72–73°) was 62–69°. The product was conveniently purified by recrystallization from ether–pentane or by sublimation; m.p. 74–75°; λ_{max}^{EtOH} 225 (12000), 302 (6400), 351 mμ (7500), no change on addition of acid or base; λ^{KBr} 6.38–6.40(s) μ.

Anal. Calcd. for $C_{13}H_{14}ON_2$ (214.26): C, 72.87; H, 6.59; N, 13.08; (N)–CH_3, 7.02. Found: C, 73.01; H, 6.62; N, 12.92; (N)–CH_3, 6.33; no OCH_3.

2,3-Dihydro-1,5-dimethyl-6-phenyl-4H-1,2-diazepinium-4-one Chloride (XI).—A solution of 570 mg. of the base IX in 15 ml. of chloroform (1% ethanol) was treated for ten seconds with a stream of dry hydrogen chloride. Ether was then added and the red color immediately changed to bright yellow. The addition of more ether precipitated a voluminous yellow powder. (In several experiments the color change occurred within a few seconds, before the addition of ether, and the hydrogen chloride addition was then immediately discontinued; the introduction of a large excess of hydrogen chloride leads to a brown solution from which no solid can be obtained.) The precipitate was filtered, washed with ether containing a little chloroform and dried *in vacuo*, giving 510 mg. (76%) of a microcrystalline powder, m.p. 134°. Recrystallization from methanol–ether gave dark gold microprisms, m.p. 133–135°; λ_{max}^{EtOH} 232 (12,000), 305 (5000), 420 mμ (1600); λ^{KBr} 3.3–3.6(br), 6.0 μ; pK_A 4.9.

Anal. Calcd. for $C_{13}H_{15}ON_2Cl$ (250.74): C, 62.27; H, 6.03; N, 11.17; (N)–CH_3, 5.98. Found: C, 63.23; H, 6.17; N, 11.13; (N)–CH_3, 4.16; no OCH_3.

1-Amino-3-hydroxy-4-methyl-5-phenylpyridinium Chloride (XII).—To a suspension of 1.53 g. of II in 50 ml. of 10% hydrochloric acid was added 12 ml. of concentrated hydrochloric acid. The mixture was warmed to 50° with shaking and the orange solid rapidly dissolved to give a dark yellow solution with a small amount of brown amorphous solid. The warm solution was filtered rapidly and on cooling a mass of heavy tan prisms separated. The crystals were filtered, washed with a small volume of iced water and dried; 1.69 g. This material was recrystallized from a small volume of water (treatment with charcoal is sometimes necessary) to give a total of 1.58 g. of cream-colored prisms in two crops, m.p. 192–195° with change in crystal form at 90–100°. Recrystallization from ethanol–petroleum ether gave slender white prisms, m.p. 192–194°, λ_{max}^{EtOH} 229 (20,000), 265–270 (infl.), 296 mμ (7000).

Anal. Calcd. for $C_{12}H_{13}ON_2Cl$ (236.70): C, 60.88; H, 5.53; N, 11.84; Cl^-, 14.98. Found: C, 61.64, 61.52; H, 5.31, 5.74; N, 11.93, 12.11; Cl^-, 14.94.

The compound was almost completely insoluble in hydrochloric acid and was only sparingly soluble in cold water, from which it crystallized as a hydrate. In a limited volume of ethanol, the hydrate readily dissolved and the apparently unsolvated material then crystallized.

Cyclopentanone Hydrazone of XII.—A solution of 100 mg. of the hydrochloride XII in 1 ml. of ethanol was treated with 0.5 ml. of cyclopentanone and the solution was heated 5 min. on the steam-bath, cooled and diluted with hexane. The material which crystallized on scratching, m.p. 192–196° dec., was recrystallized from ethanol–ether to give tiny white prisms; 55 mg., m.p. 205–206° dec.; λ_{max}^{EtOH} 228 (22,000), 297 (7000), 334 mμ (1200).

Anal. Calcd. for $C_{17}H_{19}ON_2Cl$ (302.8): C, 67.43; H, 6.32; N, 9.25; Cl^-, 11.71. Found: C, 67.21; H, 6.48; N, 9.27; Cl^-, 11.93.

This derivative was extremely soluble in water. A 20-mg. sample was converted to the free base by treatment with 0.2 *N* potassium hydroxide. The clear aqueous solution was extracted with a large volume of ether and the ether solution was evaporated to give an oil which could not be crystallized; treatment with alcoholic picric acid gave the **picrate** as rosettes of yellow needles, m.p. 188–190°.

3-Hydroxy-4-methyl-5-phenylpyridine (XIII).—A solution of 1.09 g. of XII in 23 ml. of ethanol was treated with 5 ml. of 10% hydrochloric acid and a solution of 700 mg. of sodium nitrite in 2 ml. of water. The clear solution was warmed to 50° until gas evolution had ceased and the ethanol was then evaporated in a stream of air. White prisms of the hydrochloride of XIII separated at small volume; a sample of this compound was removed and recrystallized from a small volume of water, m.p. 215–218° (subl.). The hydrochloride was then redissolved by the addition of 10 ml. of water and the solution was neutralized with saturated sodium bicarbonate solution. The base XIII crystallized in white prisms which were washed with water and dried; 775 mg. (93%), m.p. 197–198° (subl.). Spectra and further characterization are described in ref. 4.

Anal. Calcd. for $C_{12}H_{11}ON$ (185.22): C, 77.81; H, 5.99; N, 7.56. Found: C, 77.62; H, 6.09; N, 7.34.

Catalytic Hydrogenation of XII.—A solution of 19.6 mg. of XII in 6 ml. of acetic acid and 1 ml. of concd. hydrochloric acid was stirred with pre-reduced platinum oxide in a hydrogen atmosphere. After four hours, 2.4 ml. of hydrogen had been absorbed, corresponding to 1.2 moles. The semicrystalline residue obtained after removal of catalyst and evaporation was dissolved in a small volume of aqueous ethanol and neutralized with base. The crystalline precipitate of XIII was filtered, washed with water and dried; 8.8 mg., (58%) of prisms, m.p. 186–187°, was obtained. Recrystallization from aqueous methanol raised the m.p. to 189–191°; m.m.p. with product from deamination (m.p. 198°) was 190–193°.

1-Methylamino-3-hydroxy-4-methyl-5-phenylpyridinium Hydrochloride (XVIII).—A suspension of 290 mg. of the diazepinium hydrochloride XI in 1 ml. of water was warmed to 70°, giving a clear amber solution. After 90 seconds the solution was cooled and scratched; 138 mg. of small colorless plates crystallized. The filtrate from these crystals was evaporated to dryness and the residue crystallized from methanol–ether giving a second crop of 105 mg. of plates. The combined crops, 243 mg. (84%), had m.p. 203–206°. Analysis, spectra and further characterization are described in ref. 9.

Deamination of XVIII. a. Nitrous Acid.—A solution of 104 mg. of the hydrochloride XVIII in 3.5 ml. of ethanol was treated with 188 mg. of sodium nitrite in 0.5 ml. of water and 1 ml. of 10% hydrochloric acid. After standing for 40 min. the pale yellow solution was evaporated *in vacuo* and the residue crystallized from a very small volume of water; a total of 93 mg. (95%) of the hydrochloride of XIII was obtained as colorless plates, m.p. 215–225° (subl.). For comparison with the pyridine obtained from XII a sample was converted to the free base, m.p. and mixed m.p. 194–195°; superimposable infrared spectra.

b. Catalytic Reduction.—A solution of 62 mg. of the hydrochloride XVIII in 10 ml. of ethanol containing 0.1 ml. of concd. hydrochloric acid was shaken in a hydrogen atmosphere at 40 p.s.i. with 20 mg. of platinum oxide for two hours. The filtered solution was evaporated and the residue treated with 5% sodium bicarbonate solution. The tan precipitate was extracted with ethyl acetate; the ethyl acetate solution furnished 42 mg. of solid which on recrystallization from ether gave 20 mg. of XIII, m.p. 194–195°. The aqueous solution after extraction was acidified and concentrated, then made strongly alkaline and distilled into hydrochloric acid. The distillate was then evaporated to dryness, giving 3 mg. of solid residue. A portion of this salt was applied to a paper strip and chromatographed in butanol–acetic acid–water (4:1:5).[28] A single ninhydrin-violet spot appeared, R_f 0.35, identical with that from authentic methylamine hydrochloride which was run concurrently.

1-Hydroxy-3-methyl-4-phenyl-Δ^3-pyrrolin-2-one (XXI). a. From VIII.—A solution of hydroxylamine acetate was prepared by grinding together 166 mg. (2.24 mmoles) of hydroxylamine hydrochloride and 304 mg. (2.24 mmoles) of sodium acetate trihydrate and extracting the resulting slurry with 5 ml. of methanol. This solution was added in four portions during one hour to a methanol solution of 240 mg. (1.12 mmoles) of freshly sublimed 2-methyldiazepine (VIII). The solution was maintained at room temperature during the addition and then was evaporated *in vacuo* and the oily residue was dissolved in ether and water. The pale yellow ether solution was extracted several times with small portions of 1 *N* hydrochloric acid; the first several portions of aqueous acid became brilliant yellow. The ether solution was then washed well with water, dried and evaporated. A total of 131 mg. (62%) of the **hydroxamic acid XXI** was obtained as cream-colored prisms, in three crops, m.p. 144–148°. The compound was recrystallized from methanol–ether, colorless prisms, m.p. 146–148°, λ_{max}^{EtOH} 250 mμ (12,800); λ^{KBr} 3.4–3.6, 6.0(s) μ.

Anal. Calcd. for $C_{11}H_{11}O_2N$ (189.21): C, 69.82; H, 5.86; N, 7.40. Found: C, 69.87; H, 6.16; N, 7.37; no OCH_3, no (N)-CH_3.

The compound gave an immediate greenish-blue color with ferric chloride. It was freely soluble in 1 *N* alkali; the compound dissolved in 10% sodium carbonate solution on warming and then deposited long needles of the sodium salt which were soluble in water and on acidification furnished the original acid.

The original aqueous phase and the acid extracts from the above preparation were combined and evaporated in an air stream to an orange-colored sirup. This residue was then made basic with 50% potassium hydroxide and extracted with four 20-ml. portions of ether. The nearly colorless ether solution was dried with potassium hydroxide pellets and treated with 0.15 ml. of phenyl isothiocyanate. The solution was then concentrated on the steam-bath until crystallization commenced. The mixture was chilled and the crystals collected and recrystallized from methanol–ether after charcoal treatment. A total of 32 mg. of colorless prisms was obtained, m.p. 144–145°. A mixed m.p. with authentic 2-**methyl-4-phenylthiosemicarbazide,** m.p. 144–145°,[29] prepared in the same way from methylhydrazine and phenyl isothiocyanate, was 144–145°; the infrared spectra of the two samples were superimposable.

b. From II.—A solution of 100 mg. of II in 1 ml. of methanol was treated with a methanolic solution of 2 equiv. of hydroxylamine acetate prepared as described above. After standing at room temperature for 3 hours, the solution was diluted with water and extracted with ether. After washing and drying, the ether solution was evaporated to give 56 mg. of pale yellow amorphous solid. Recrystallization from methanol–ether furnished colorless shiny prisms of XXI, m.p. 146–148°, identical by mixed m.p. with material obtained from VIII.

In another experiment starting with 400 mg. of II and 2 molar equiv. of hydroxylamine, the aqueous solution after ether extraction of the hydroxamic acid was acidified to congo paper and approximately three-quarters of the solution was distilled. The distillate was treated with dimedon and then concentrated to give colorless needles of the dimedon–formaldehyde derivative, 10 mg., m.p. and mixed m.p. with authentic material 188–189°; identical infrared spectra.

In a third run using 100 mg. of II, the aqueous solution after ether extraction was evaporated *in vacuo* to a brown amorphous residue which was dissolved in methanol and applied as a spot on a 25-cm. strip of Whatman No. 1 filter paper. Approximately equivalent quantities of hydrazine sulfate and methylhydrazine sulfate were applied separately and the chromatogram was developed ascendingly with the 1-butanol–6 *N* hydrochloric system of Bremner.[30] The paper was dried and sprayed with Ehrlich reagent (dimethylaminobenzaldehyde), giving yellow spots corresponding to the hydrazines. The R_f values of the spot from the reaction residue and that from hydrazine sulfate were identical (0.3); the spot from methylhydrazine sulfate had R_f about 0.4. A bright yellow spot also appeared near the solvent front in the lane from the reaction mixture.

Acetate of Hydroxamic Acid XXI.—A solution of 120 mg. of XXI in 1 ml. of acetic anhydride was heated for 5 min. at 60° and then cooled and treated with water. The solution was then evaporated to dryness and the residue was crystallized from methanol–ether giving 100 mg. of tan plates, m.p. 130–133°. The material was recrystallized from methanol–ether for analysis as colorless plates, m.p. 132–133°; λ^{KBr} 5.58, 5.90 μ.

Anal. Calcd. for $C_{13}H_{13}O_3N$: (231.24): C, 67.52; H, 5.67; N, 6.06. Found: C, 67.61; H, 5.79; N, 6.17.

The compound was insoluble in 10% aqueous potassium hydroxide; on warming, the material dissolved to give a yellow solution which on neutralization furnished shiny prisms of the acid, m.p. 144–146°.

3-Methyl-4-phenyl-Δ^3-pyrrolin-2-one (XXII).—A solution of 52 mg. of XXI in 2 ml. of acetic acid was heated with 100 mg. of zinc dust for 2 hr. under gentle reflux at 120°. The reaction mixture was then diluted with water to dissolve zinc acetate and the excess zinc was filtered off. The clear yellow filtrate was neutralized to *p*H 6 with alkali and then extracted with ether. The ether solution was dried and evaporated to give 50 mg. of a light yellow semi-crystalline residue which on trituration with ether gave 35 mg. of stout needles, m.p. 152°. The mixed m.p. with XXI was 110°. Recrystallization from methanol–ether gave colorless needles, m.p. 154°, λ_{max}^{EtOH} 258 mμ (15.000); λ^{KBr} 3.2–3.3 (double), 6.0(s) μ. This material was identical (m.m.p. and infrared) with a sample of the compound obtained from II by another route; the latter sample was analyzed.

Anal. Calcd. for $C_{11}H_{11}ON$ (173.21): C, 76.27; H, 6.40; N, 8.09. Found: C, 76.38, 76.21; H, 6.41, 6.60; N, 7.97.

For further characterization the compound was converted to the previously obtained **N-benzoyl derivative.** A solution of 10 mg. of XXII was treated with sodium ethoxide and the sodium salt was then allowed to stand for four hours, with occasional shaking, with a solution of benzoyl chloride in ether. The reaction mixture was hydrolyzed with water, made alkaline and extracted with ether. The dark ether solution was treated with Norite and then evaporated. Crystallization from methanol–ether–pentane gave short nee-

(28) J. M. Bremner and E. Keuten, *Biochem. J.*, **48**, 651 (1951).

(29) G. V. Bruning, *Ann.*, **253**, 5 (1889), reports m.p. 143°.

(30) J. M. Bremner, *Analyst*, **79**, 198 (1954).

dles, m.p. 145–146°. This derivative was also identical with a sample obtained in another series which gave satisfactory analytical data.

cis-3-Methyl-4-phenyl-2-pyrrolidone (XXV) by Hydrogenation of XXII.—To a solution of 140 mg. of XXII in 6 ml. of methanol was added 0.5 g. of freshly prepared Raney nickel and the mixture was shaken in a hydrogen atmosphere for 4 hr. at room temperature. Filtration of the catalyst through carbon gave a water-white solution which was evaporated to give 116 mg. of white amorphous solid. This material was crystallized from a methanol–ether–hexane mixture to give 70 mg. of colorless prisms, m.p. 96–97°, unchanged by further crystallization from the same solvents; λ^{KBr} 3.12(s), 3.22(s), 3.35(s), 3.46(s), 5.95(s,br), 6.73(s), 6.89(s), 7.25(m,br), 7.60(m), 7.90(s,br), 8.27(w), 8.50(w), 9.20(s), 9.30(m) μ.

Anal. Calcd. for $C_{11}H_{13}ON$ (175.22): C, 75.40; H 7.48; N, 7.99. Found: C, 75.04; H, 7.58; N, 7.99.

Ethyl 4-phenyl-2-pyrrolidone-3-carboxylate (XXIII) was prepared as described by Koelsch and Stratton[17] by reduction of ethyl α-carbethoxy-β-cyano-β-phenylcarboxylate,[31] but the hydrogenation was more conveniently carried out under milder conditions. The cyanodiester, 10 g., in 90 ml. of methanol was shaken under 45 lb. hydrogen pressure at room temperature for 9 hr. with 5 g. of Raney nickel, giving 6.9 g. (82%) of XXIII, m.p. 113–115°[32] from benzene–pentane, which was used directly in the next step.

3-Methyl-4-phenyl-2-pyrrolidone-3-carboxylic Acid (XXIVa).—A solution of 6.7 g. (0.03 mole) of XXIII from the above-described hydrogenation in 30 ml. of anhydrous methanol was treated with a solution of 1.2 g. of sodium in methanol; the solution became dark brown and a mass of white crystals separated. Methyl iodide (2.1 ml., 0.33 mole) was then added and the mixture was refluxed for 1 hr. and allowed to stand an additional hour at room temperature. A small amount of white crystalline material was collected by filtration and the dark brown filtrate was then diluted with water, concentrated to remove most of the methanol and then extracted with chloroform. Evaporation of the chloroform gave an oil which was hydrolyzed by refluxing 40 min. in 50 ml. of methanol containing 5 g. of potassium hydroxide. The solution was then diluted with water and concentrated *in vacuo* until crystals began to separate; 450 mg., m.p. 111–112° after recrystallization from methanol–ether–pentane. This material was identical with the *methyl* ester described below and evidently arose by ester exchange of the ethyl ester and incomplete hydrolysis; further saponification gave the acid XXIVa, m.p. 185–187°.

The main portion of the acid XXIVa was obtained by acidification of the aqueous alkaline filtrate; the precipitate was collected, dried and recrystallized from methanol to give 2.5 g. of colorless prisms, m.p. 186–190°. Repeated recrystallizations from methanol and methanol–ether mixtures gave stout pointed prisms of XXIVa, m.p. 183–184°.

Anal. Calcd. for $C_{12}H_{13}O_3N$ (219.23): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.69; H, 5.95; N, 6.46.

A 200-mg. sample of this acid was converted to the methyl ester with diazomethane. Recrystallization from methanol–ether–pentane gave colorless needles of XXIVb, m.p. 112°, no depression with the ester isolated from the hydrolysis.

Anal. Calcd. for $C_{13}H_{15}O_3N$ (233.26): C, 66.93; H, 6.48; N, 6.01. Found: C, 67.07; H, 6.50; N, 6.28.

Isolation and Characterization of 4-Phenyl-2-pyrrolidone-3-carboxylic Acid.—The crystalline solid (700 mg.) which was filtered directly from the methylation reaction mixture was a water-soluble sodium salt. Acidification and recrystallization from methanol gave white prisms, m.p. 163–164°.[33] A small sample of the acid was converted to the methyl ester with ethereal diazomethane; recrystallization from methanol–ether gave colorless prisms, m.p. 130–131°.

Anal. Calcd. for $C_{12}H_{13}O_3N$ (219.23): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.57; H, 5.85; N, 6.49.

A sample of the acid, m.p. 163–164°, was heated at atmospheric pressure in a sublimation apparatus at 175° until gas evolution was complete. The amber oil was then distilled at 0.1 mm. (130° bath). The crystalline distillate on the finger was recrystallized several times from methanol–ether, m.p. 70–71°, m.m.p. with authentic 4-phenyl-2-pyrrolidone[34] (m.p. 74–75°) gave no depression; infrared spectra identical.

Anal. Calcd. for $C_{10}H_{11}ON$(161.2): C, 74.51; H, 6.88. Found: C, 74.85; H, 6.92.

cis-3-Methyl-4-phenyl-2-pyrrolidone (XXV) by Decarboxylation of XXIVa.—The acid, 360 mg., was heated at 190° at atmospheric pressure until gas evolution ceased. The yellow oil was dissolved in benzene and the solution chromatographed on 8 g. of alumina. Earlier fractions eluted with benzene (70 mg.) gave crystals, m.p. 70–90°; elution with chloroform gave 61 mg. of material, m.p. 84–94°, which on further recrystallization from ether–hexane gave colorless prisms, m.p. 94–95°, no depression on mixed m.p. with sample prepared by hydrogenation of XXII; the infrared spectra were identical except for the presence in the spectrum of the decarboxylation product of a weak band at 13.2 μ.

Anal. Calcd. for $C_{11}H_{13}ON$ (175.22): C, 75.40; H, 7.48; N, 7.99. Found: C, 75.31; H, 7.61; N, 7.94.

In a preliminary experiment, a sample of the acid was decarboxylated as described above and the oil was then distilled *in vacuo* as in the case of the low-melting acid. The oily distillate gave crystals from methanol–ether–pentane, m.p. 57–61°; further recrystallization resulted in material having m.p. 88–91° which gave a m.p. depression of 20° with the pure *cis*-pyrrolidone. Similar low-melting mixtures were also obtained on sublimation of the pure *cis* isomer, which is apparently susceptible to isomerization at relatively low temperatures.

2,3-Dihydro-5-methyl-6-phenyl-4H-1,2-diazepin-4-one Oxime (XXIXa).—A solution of hydroxylamine was prepared by dissolving 300 mg. of hydroxylamine hydrochloride and 170 mg. of solid sodium hydroxide in 1.5 ml. of water; 10% sodium hydroxide solution was then added until the solution was basic to litmus but not to phenolphthalein. To this solution was added a solution of 100 mg. of the diazepine II in 4 ml. of ethanol. The light yellow reaction mixture was kept at 75° for one hr.; yellow crystals began to separate after about 10 min. After cooling, the mixture was treated with ice and the solid filtered from the still alkaline solution, giving 100 mg. of bright yellow needles, m.p. 214–222°. The derivative was recrystallized several times from methanol for analysis, m.p. 228–229° dec.; λ_{max}^{EtOH} 227 (23,000), 284 (7400) (sh), 342 mμ (5700); $\lambda_{max}^{EtOH + HCl}$ 236 (23,000), 336 mμ (7490); $\lambda_{max}^{EtOH + KOH}$ 246 (19,000), 348 mμ (11,400); λ^{KBr} 3.0–3.6(s,br), 6.24(w) μ.

Anal. Calcd. for $C_{12}H_{13}ON_3$ (215.25): C, 66.95; H, 6.09; N, 19.52. Found: C, 66.70; H, 6.18; N, 19.56.

2-Acetyldiazepine Oxime (XXXb).—A mixture of 50 mg. of the oxime XXIXa and 1 ml. of acetic anhydride was warmed to 60° for 3 min. and the clear solution was then allowed to stand at room temperature for 2 hr. After adding water, the unreacted acetic anhydride was hydrolyzed by gentle warming and the solution was then evaporated in a stream of air and dried *in vacuo* to remove traces of acetic acid. Attempts to crystallize this material from ether–hexane or aqueous methanol were fruitless. The oil was then hydrolyzed by treatment with 10 drops of 10% methanolic potassium hydroxide for 4 hr. at room temperature. After acidification the solution was extracted with ether; after washing and drying the ether solution, 18 mg. of oil was obtained on evaporation. Crystallization of this oil from methanol gave 10 mg. of cream colored plates, m.p. 190–192°; λ_{max}^{EtOH} 227 (>20,000), 299 (9300), 340 mμ (8700); $\lambda_{max}^{EtOH + KOH}$ 248 (24,700), >370 mμ (no change in spectrum in acid solution); λ^{KBr} 3.0, 6.0(s), 6.3(w) μ.

Anal. Calcd. for $C_{14}H_{15}O_2N_3$ (257.28): C, 65.35; H, 5.88; N, 16.33. Found: C, 65.32; H, 6.15; N, 16.74.

2-Acetyldiazepine Oxime Acetate (XXXa).—Crystals of this compound were originally obtained by acetylation of the

(31) A. Bredt and B. Kallen, *Ann.*, **293**, 342 (1896).

(32) Reported[17] m.p. 119–120°.

(33) From the results of methylation and decarboxylation, this material must be the 4-phenylpyrrolidone-3-carboxylic acid, although the m.p. of this compound, recrystallized from ethanol–water, is reported[17] as 127–131°, and correct analytical data were obtained. Unfortunately, our preparation of the acid was not analyzed. Because of the difference in m.p.'s, which may be due to polymorphism, we originally thought that this acid (m.p. 164°) was a stereoisomer of XXIVa and, therefore, proceeded with decarboxylation experiments.

(34) We thank Prof. C. F. Koelsch for his kindness in furnishing this sample.

acetyldiazepine oxime (XXXb); the oil obtained crystallized after one month. In a subsequent preparation, the diazepine oxime (XXIXa) (115 mg.) was acetylated as described above. The oil obtained after removal of the acetic acid crystallized from aqueous methanol on seeding, giving 40 mg. of cream-colored needles. After recrystallization from ether–hexane and then methanol–water, the compound had m.p. 108°; λ_{max}^{EtOH} 225 (33,000), 300 (10,000), 346 mμ (10,400); $\lambda_{max}^{EtOH + KOH}$ 247 (20,000), ~370 (spectrum in acid same as neutral except for lower values); λ^{KBr} 5.70(s), 5.95(s), 6.26(w) μ.

Anal. Calcd. for $C_{16}H_{17}O_3N_3$ (299.32): C, 64.20; H, 5.72; N, 14.04. Found: C, 64.43; H, 5.87; N, 14.85 (1.12-mg. sample).

The mother liquor (58 mg.) from the above crystals was hydrolyzed with methanolic potassium hydroxide at room temperature for two hours; the reaction mixture was extracted with ether in the usual way to give 46 mg. of oil which crystallized from methanol. The flat cream colored prisms had m.p. 191–192°, m.m.p. with the 2-acetyl oxime XXXb, 190–192°. This partially hydrolyzed material was then treated with 10% aqueous alkali at 60° for one minute. After extraction with ether and washing, the product was crystallized from methanol, m.p. and m.m.p. with the diazepine oxime 226–228°.

2,3-Dihydro-2,5-dimethyl-6-phenyl-4H-1,2-diazepine-4-one Oxime (XXIXb).—One-hundred mg. of VIII was treated in alkaline ethanol solution with hydroxylamine as described for the diazepine II. After cooling the reaction mixture, 75 mg. of yellow plates was obtained, m.p. 225–227°. The analytical sample was recrystallized from methanol, m.p. 232–235°; λ_{max}^{EtOH} 233 (20,000), 362 mμ (5200); $\lambda_{max}^{EtOH + KOH}$ 254 (14,300), 363 mμ (6200); λ^{KBr} 3.1–3.6(s,br) μ.

Anal. Calcd. for $C_{13}H_{15}ON_3$ (229.27): C, 68.10; H, 6.59; N, 18.33. Found: C, 68.29; H, 6.55; N, 18.27.

Acetylation of this oxime gave an oil which could not be crystallized; hydrolysis furnished the original oxime. The oxime was unaffected by treatment with pyruvic acid–acetic acid under the conditions used for the cleavage of the semicarbazone.

Treatment of 2-Acetyldiazepine (VIa) with Semicarbazide.—A 60-mg. sample of VIa was liquefied with 0.1 ml. of methanol and then treated with 1 ml. of methanolic semicarbazide acetate prepared from 50 mg. of semicarbazide hydrochloride (0.45 mmole) and 75 mg. of sodium acetate trihydrate (0.55 mmole). After standing for 1 hr. at 0° the solution was scratched, and 51 mg. of the iminohemiketal separated as a pale yellow precipitate. Recrystallization of this material from methanol gave colorless needles, m.p. 169–171° dec.; λ_{max}^{EtOH} 250 mμ (19,000); $\lambda_{max}^{EtOH + NaOH}$ 254 mμ; $\lambda_{max}^{EtOH + HCl}$ 226 mμ (sh 280 mμ); λ^{KBr} 2.85–3.1(s,br), 5.9–6.2(s,br) μ.

Anal. Calcd. for $C_{15}H_{19}O_3N_5$ (317.34): C, 56.77; H, 6.04; N, 22.07. Found: (Dried 12 hr., 60°, yellow color formed): C, 56.75; H, 6.16; N, 22.17.

The methanolic mother liquor from the above product was diluted with water and extracted with ether. After washing with acid, carbonate solution and water, the solution was dried and evaporated to give 10 mg. of yellow foam. Crystallization from methanol–ether furnished 6 mg. of yellow needles, m.p. 215–219°; no melting point depression with the acetyl semicarbazone VII obtained by acetylation of VIa. The infrared spectra of the product from the two routes were identical.

Regeneration of Diazepine II and 2-Acetyldiazepine (VIa).—Ten mg. of the above product was dissolved in 1 ml. of 10% methanolic potassium hydroxide solution. The solution became yellow immediately; after warming for 45 min. at 70°, it was cooled and diluted with water. Ether was added and dilute sulfuric acid was added dropwise until all color had gone into the ether layer. After drying and evaporation, the residue (8 mg.) was crystallized from ether, m.p. and mixed m.p. with the diazepine II, 149–150°; identical infrared and ultraviolet spectra.

For conversion to the 2-acetyldiazepine, a solution of 24 mg. of the iminohemiketal in 0.8 ml. of acetic anhydride was warmed for 5 min. at 60° and then allowed to stand for 15 min. at room temp. After adding water, the solution was extracted with ether, the ether washed with bicarbonate, dried and evaporated to give 12 mg. of yellow oil which crystallized on seeding with VIa. Recrystallization from ether gave yellow prisms, m.p. and m.m.p. with VIa 89–90°; infrared curves identical.

Treatment of 2-Acetyldiazepine (VIa) with Hydroxylamine.—Solutions of hydroxylamine acetate in 1.5 ml. of methanol (prepared from 70 mg. (1.0 mmole) and 150 mg. (1.1 mmoles) of sodium acetate trihydrate) and 100 mg. (0.39 mmole) of VIa in 2.5 ml. of methanol were mixed and allowed to stand at room temperature for 30 min.; the color became perceptibly lighter. The solution was then diluted with 4 ml. of water and then concentrated in an air stream until pale yellow needles separated. These crystals of the iminohemiketal, 55 mg. (48%), were recrystallized from methanol–ether, giving colorless prisms, m.p. 135–138°; λ_{max}^{EtOH} 249 mμ (18,300); $\lambda_{max}^{EtOH + HCl}$ 249 (9000), 294 mμ (sh) (no change in alkaline soln.); λ^{KBr} 3.05, 6.228 μ (P.E. 13U).

Anal. Calcd. for $C_{14}H_{17}O_3N_3$ (275.30): C, 61.08; H, 6.22; N, 15.26. Found: C, 60.94; H, 6.40; N, 15.32.

A solution of 35 mg. of the above material in 1 ml. of 2% aqueous methanolic potassium hydroxide solution was heated for 1 min. at 70°. The yellow solution was layered with ether and acidified, and the ether solution separated, dried and evaporated to give 20 mg. of yellow prisms, m.p. 145–146°; mixed m.p. with II, 146–147°.

Treatment of 2-Benzoyldiazepine with Semicarbazide.—To a solution of 150 mg. (0.49 mmole) of VIb in 10 ml. of methanol was added 2 ml. of methanolic semicarbazide acetate prepared as described previously from 100 mg. (0.9 mmole) of the hydrochloride and 170 mg. (1.25 mmoles) of sodium acetate. After standing for 3 hr. at room temperature the solution was concentrated to one-third volume, cooled and scratched, giving 70 mg. (39%) of nearly colorless needles of the iminohemiketal. The compound was recrystallized from methanol for analysis, m.p. 163–165°; λ_{max}^{EtOH} 220 (23,000), 272 mμ (16,500); $\lambda_{max}^{EtOH + HCl}$ 226 (23,600), 280 mμ (17,000); $\lambda_{max}^{EtOH + KOH}$ 225 (19,000), 282 mμ (15,600); λ^{KBr} 2.9–3.1(br), 5.9–6.4(br) μ.

Anal. Calcd. for $C_{20}H_{21}O_3N_5 \cdot {}^1/_2CH_3OH$ (395.43): C, 62.26; H, 5.86; N, 17.71. Found: C, 62.70; H, 5.94; N, 17.75; wt. loss on drying 4.0%, equiv. to 0.5 CH_3OH.

The mother liquors from the above crystallization were further concentrated and chilled to 0°, and a small quantity of bright yellow prisms separated; 12 mg. (7%), m.p. 217°. This was combined with similar material from other experiments and recrystallized three times from methanol, giving the **2-benzoyldiazepine semicarbazone**, m.p. 222–224°; λ_{max}^{EtOH} 241 (28,000), 365 mμ (9800); λ^{KBr} 2.85, 3.1–3.2(br), 5.88–6.08 μ(double).

Anal. Calcd. for $C_{20}H_{19}O_2N_5$(361.39): C, 66.47; H, 5.30; N, 19.38. Found: C, 66.95; H, 5.72; N, 19.02.

For comparison, the semicarbazone was also prepared by benzoylation of the diazepine semicarbazone V. A solution of 110 mg. of V and 240 mg. of benzoic anhydride in 1.5 ml. of pyridine was allowed to stand for 22 hr. After adding water the solution was allowed to stand again overnight and the crystalline precipitate was filtered; this material was unreacted V, 70 mg., m.p. and mixed m.p. 192–193° after recrystallization from methanol. The aqueous pyridine solution was then concentrated, giving 15 mg. of yellow powder which after three recrystallizations from methanol had m.p. 219–223°, no depression on mixing with the benzoyl semicarbazone described above. A sample of this material was warmed in aqueous methanolic potassium hydroxide; after cooling and dilution with water, pale yellow needles separated, which after crystallization from methanol had m.p. 192–194°, no depression with V.

2-Benzoyldiazepine (VIb) from Benzoyldiazepine–Semicarbazide Adduct.—A solution of 23 mg. of the iminohemiketal in 0.5 ml. of acetic anhydride was warmed to 70° for 5 min.; the colorless solid dissolved to give a clear yellow solution. Water was then added and the mixture was allowed to stand for 10 min., during which yellow prisms separated. This material, 18 mg., m.p. 140–143°, was recrystallized from methanol to give the 2-benzoyldiazepine, m.p. 148°; identical by m.m.p. and infrared with VIb prepared from II.

Treatment of 2-Benzoyldiazepine (VIb) with Hydroxylamine.—Methanolic hydroxylamine acetate prepared from 70 mg. of the hydrochloride and 150 mg. of sodium acetate trihydrate was mixed with a solution of 155 mg. of VIb in 12 ml. of methanol; the solution rapidly became lighter in color.

After 10 min. water was added and the solution was then concentrated until crystals began to separate. A total of 163 mg. of colorless needles, m.p. 109–117°, was obtained in several crops. Recrystallization from methanol gave short white needles of the iminohemiketal, m.p. 114–117°; λ_{max}^{EtOH} 245 mμ (20,000); $\lambda_{max}^{EtOH + HCl}$ 230 mμ (17,000); $\lambda_{max}^{EtOH + KOH}$ 247 mμ (19,000); λ^{KBr} 2.80, 2.90, 3.1, 6.224, 6.254(double, s), 6.352(m) μ (P.E. 13U).

Anal. Calcd. for $C_{19}H_{19}O_3N_3 \cdot CH_3OH$: C, 65.02; H, 6.28; N, 11.38. Calcd. for $C_{19}H_{19}O_3N_3 \cdot {}^1/_2CH_3OH$: C, 66.27; H, 5.99; N, 11.89. Found (Dried to constant wt. 50°): C, 65.80, 65.64; H, 6.47, 6.21; N, 11.31.

Eighteen mg. of the above-described material was dissolved in 0.3 ml. of acetic anhydride and the yellow solution was warmed to 80° for 5 min. After hydrolysis of the excess anhydride the solution was seeded with VIb and deposited 8 mg. of yellow prisms, m.p. 138–139°. Recrystallization from methanol gave VIb, m.p. and m.m.p. 147–148°; identical infrared spectra.

A small sample of the compound in methanol solution was treated with a 5% solution of potassium permanganate in acetone. As soon as a permanent purple color was present the mixture was diluted with water and extracted with ether. After washing with water the ether was dried and evaporated to give a yellow oil which crystallized on addition of a few drops of methanol; recrystallization from methanol gave yellow prisms of VIb, m.p. and mixed m.p. 145–147°.

Acknowledgment.—Part of the work described in this paper and in paper VI was carried out in the research laboratories of Parke, Davis and Co., and the senior author expresses his appreciation to Dr. L. M. Long and Dr. L. A. Sweet for their permission to continue the work at the University of Delaware. We thank numerous colleagues for their patient interest in the work, and the Geschickter Fund for Medical Research for their generous support.

NEWARK, DEL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

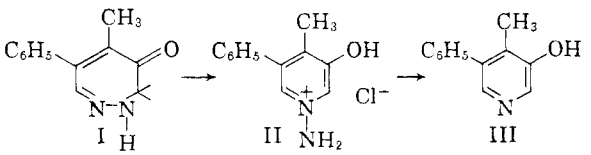
Heterocyclic Studies. V. Proof of Structure and Synthesis of 3-Hydroxy-4-methyl-5-phenylpyridine, A Degradation Product of 2,3-Dihydro-5-methyl-6-phenyl-4H-1,2-diazepin-4-one[1]

BY JAMES A. MOORE AND HEINZ H. PÜSCHNER

RECEIVED FEBRUARY 19, 1959

Evidence establishing the 3-hydroxypyridine structure III for a degradation product of the diazepine I is presented and a synthesis of III is described. The synthesis begins with 2-hydroxy-3-cyano-4-methyl-5-phenyl-6-aminopyridine and proceeds, with stepwise removal of the α-substituents, to 4-methyl-5-phenylnicotinic acid, which is then transformed by Hofmann degradation and diazotization to the hydroxypyridine.

As discussed in the foregoing article,[2] isomerization of the diazepinone I led to a product which was formulated as 1-amino-3-hydroxy-4-methyl-5-phenylpyridinium chloride (II) on the basis of its facile deamination to a compound which was in turn assigned the 3-hydroxy-4-methyl-5-phenylpyridine structure (III). Evidence supporting this latter structure, and definitive proof by synthesis, are presented in this paper.



The deamination product was characterized as a 3-hydroxypyridine by the red ferric chloride reaction, pK_A values (4.6, 9.5), characteristic ultraviolet spectra including changes in alcohol and aqueous solution with pH,[3] formation of an N-oxide (pK_A 6.9[4]) and formation of an acetate, and with diazomethane a methyl ether. A positive Gibbs reaction confirmed the presence of an unsubstituted 6-position[5] and in later work[6] the absence of substituents from both 2- and 6-positions was established by coupling with *p*-nitrobenzenediazonium chloride.

These results narrowed the structural possibilities to III and the 3-hydroxy-5-methyl-4-phenyl isomer. An attempt was made to demonstrate the presence of a 4-methyl substituent by condensation with benzaldehyde on both the base and the N-oxide, a reaction diagnostic of α- and γ-picoline derivatives, but a benzylidene derivative was not obtained, perhaps because of steric interference of the phenyl substituent and/or electron release by the hydroxyl group.[7] At this point, the necessity of a synthetic approach became apparent, but before embarking on the synthesis of III, it was hoped to simplify the task by elimination of the hydroxyl group, since synthesis of the resulting 4-methyl-3-phenylpyridine by the very satisfactory procedure[8] available for 3-phenylpyridine should be a relatively easy matter.

The conversion of 3-hydroxypyridine to pyridine by zinc dust distillation was reported in the earliest description of the compound,[9] and this reaction has subsequently been cited by many authors, apparently without further confirmation. We have been unable to carry out this transformation with III or with 3-hydroxypyridine under a variety of conditions with zinc, although the reduction of 2-pyri-

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

(2) J. A. Moore and J. Binkert, THIS JOURNAL, **81**, 6029 (1959), paper IV.

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(7) D. Jerchel and H. E. Heck, *Ann.*, **613**, 171 (1958), have reported that formation of the benzylidene derivative of 3-hydroxy-2-methylpyridine is slower than in the case of α-picoline.

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