(1:1) 1.5 *N* sodium hydroxide was allowed to stand for 3 hr in an ice bath. A pale yellow color slowly developed. The mixture was then treated with 0.04 ml (0.36 mmole) of benzoyl chloride, allowed to stand for an additional 25 min, and acidified with 6 *N* HCl. Benzoic acid precipitated from the solution, and then on prolonged standing, white needles slowly formed. These were collected to give 41 mg of 3-methyl-4-phenylsuccinimide, (**18**), mp 107–108°; the infrared spectrum was identical with that of a sample prepared from **19**.

B.—A suspension of 100 mg (0.54 mmole) of the amide (**17**) in 2 ml of chloroform was chilled in an ice–salt bath and saturated with dry hydrogen chloride gas; the solid rapidly went into solution. After standing for several days at 0°, the mixture solidified. Trituration with ether furnished a white solid which was collected; this material became an oil on contact with air. This product was immediately dissolved in 4 ml of pyridine and treated with 0.08 ml (0.72 mmole) of benzoyl chloride. The reaction mixture became warm, and a precipitate slowly settled. Filtration gave **18** mg of white solid which was insoluble in water and in methylene chloride, and which did not melt when heated to 300°. Dilution of the pyridine solution with 50 ml of water caused precipitation of 2 mg of brownish solid; thin layer chromatography showed two components. Acidification of the solution with 1 *N* hydrochloric acid and extraction with methylene chloride furnished 106 mg of sticky, red-brown solid; tlc showed that this was mainly benzoic acid.

Registry No.—**2**, 10137-20-9; **14**, 10137-21-0; **3**, 10137-22-1; **7c**, 10137-23-2; **7d**, 10137-24-3; **7a**, 10137-25-4; **7b**, 10137-26-5; **8**, 10137-27-6; **5**, 5109-46-6; **7e**, 10137-28-7; **6**, 10137-29-8; 1-hydroxymethyl-3-methyl-4-phenylmaleimide, 10137-30-1; **4**, 10137-31-2; **9**, 10137-32-3; **11** (R = CH_3), 10137-33-4; **11** (R = H), 10137-34-5; **10**, 10137-07-2; **12**, 10137-36-7; 1-nitroso-3-methyl-4-phenyl-3-pyrrolin-2-one, 10137-37-8; **16**, 10137-38-9; **19**, 10137-39-0; **18**, 10137-40-3; **17**, 10147-14-5.

Heterocyclic Studies. XXV. Rearrangements of 2-Acyl-1,2-diazabicyclo[3.2.0]-3-hepten-6-ones in Methanol and in Base[1]

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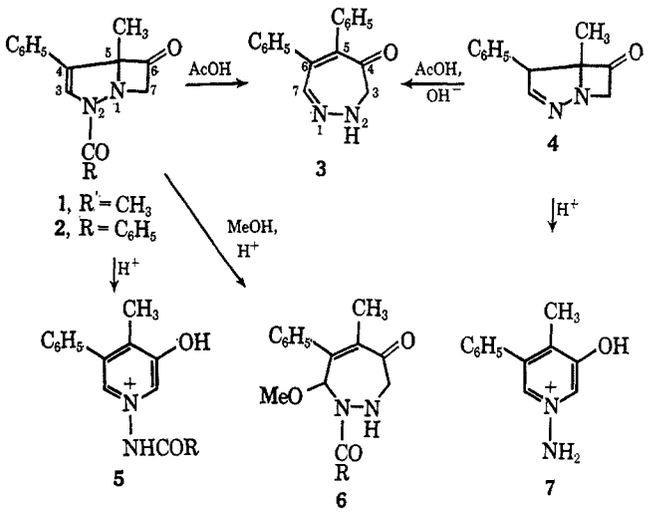
The unsaturated acyldiazabicyclic ketones (**1** and **2**) are converted by heating in methanol to the acylpyrrolinones (**8**) and 6-acylamidopyridines (**9**). In aqueous base the acetyl ketone (**1**) and the methoxy ketone (**10**) give the 4-aminopiperidines (**11** and **12**), respectively, which are readily converted to the pyridone (**13**). The benzoyl ketone (**2**) in aqueous base gives predominately the enamino ketone (**15**), with a small amount of **13**. Mechanisms for these reactions and for the thermal conversion of **2** to the uretidine (**17**) are proposed. Initial fragmentation of **1** and **2** is suggested to give the azetinone (**18**) which is then attacked by water or methanol to give intermediates that undergo cyclizations or fragmentations leading to **8**, **9**, **11**, and **15**. Recyclization of **18** leads to **17**.

The 2-acyl-Δ^3-bicyclic ketones (**1** and **2**) are converted under acidic conditions to the diazepinones (**3** or **6**) or the 1-acylamidopyridine (**5**).[2] In these reactions, the chemistry of **1** and **2** closely resembles that of the Δ^2-ketone (**4**). The latter compound gives the diazepine (**3**) or the pyridine (**7**) in acid solution; treatment of **4** with base also causes rapid isomerization to **3**[2] (see Scheme I). Under neutral or basic conditions, however, a different spectrum of products is obtained from the 2-acyl ketones (**1** and **2**); these transformations are described in this paper.[3]

On brief warming in methanol solution, the 2-acyl ketones (**1** and **2**) give rise to mixtures containing two principal products in each case. From the acetyl ketone (**1**) the 1-acetylpyrrolinone (**8a**) and 6-acetamidopyridine (**9a**) were obtained as the major and minor products, respectively. Traces of **3** and probably **6** (R = CH_3) were also detected. Under comparable conditions, (somewhat longer heating), the correspondbenzoyl compounds (**8b** and **9b**) were isolated from the methanolysis of **2**, but the pyridine (**9b**) predominated. The structures of these products were deduced from spectral and chemical properties and confirmed by conversion to known compounds. Mild alkaline hydrolysis of the pyrrolinones (**8**) gave the parent compound (**8c**) which has been described previously.[4] Likewise, hydrolysis of the 6-acylamidopyridines (**9**) under vigorous acid conditions led to the free 6-aminopyridine, the synthesis of which has been reported.[5]

SCHEME I



Qualitatively similar results were observed in solutions of **1** and **2** in methanolic sodium methoxide; under these conditions, however, the yield of the pyrrolines (**8**) was somewhat higher than in neutral solution. An increase in the yield of **8b** at the expense

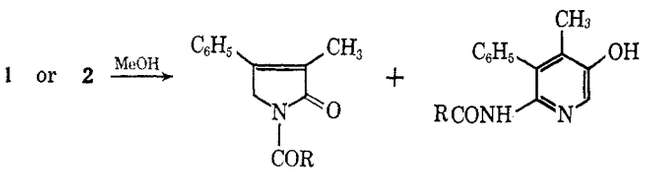
(1) Supported in part by Grant DA-CML-18-108-61-G-24 from the Army Chemical Corps, and Grant GP-5219 from the National Science Foundation.

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

(3) A preliminary account of part of this work has been presented: J. A. Moore, F. J. Marascia, R. W. Medeiros, and E. Wyss, *J. Am. Chem. Soc.*, **84**, 3022 (1962).

(4) J. A. Moore and J. Binkert, *ibid.*, **31**, 6029 (1959).

(5) J. A. Moore and F. J. Marascia, *ibid.*, **31**, 6049 (1959).



8a, R = CH_3
b, R = C_6H_5
c, COR = H

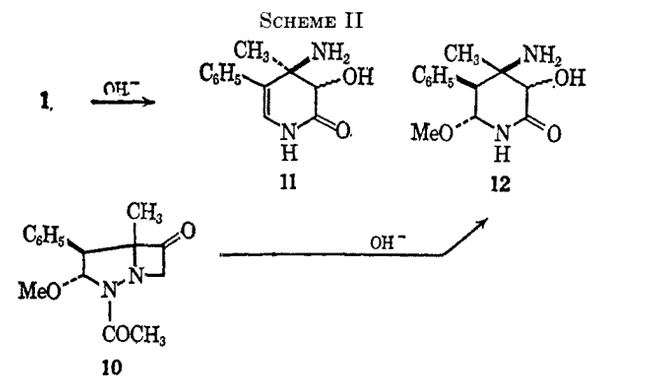
9a, R = CH_3
b, R = C_6H_5
c, COR = H

of the aminopyridine (**9b**) was also effected by addition of sodium benzoate or sodium bicarbonate in the reaction of the benzoyl ketone (**2**). The same products (**8b** and **9b**) were obtained in low yields from the reaction of the bicyclic ketone in ethanol, but more noncrystalline residue was present.

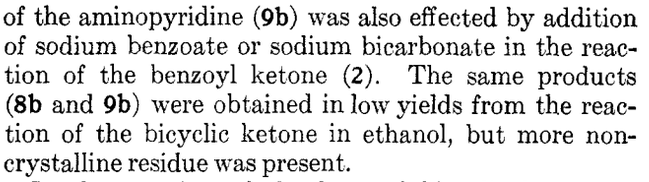
In the reaction of the benzoyl bicyclic ketone in neutral methanol, ammonia was identified as a volatile product, accounting for the nitrogen atom lost in the formation of the pyrrolinone; the yields of ammonia and of **8b** corresponded well. In the formation of **8b** and ammonia, the carbon atom which is lost would be at the oxidation level of formic acid provided that methanol is not oxidized or reduced. In consonance with this stoichiometry, the presence of methyl orthoformate in the reaction mixture from **2** was established by vpc. No ammonia was detected in reactions of **1** or **2** in methanolic sodium methoxide. However, a positive test for cyanide ion was obtained in the reaction mixture from **1**.

Entirely different products were formed when the acylbicyclic ketones were subjected to aqueous base and in this case, the reactions of the acetyl and benzoyl compounds take distinctly different paths. Under these conditions the 2-acetyl-3-methoxy ketone (**10**),[2] undergoes the same reaction as the unsaturated acetyl compound (**1**). The bicyclic ketones (**1** and **10**) dissolved in aqueous potassium hydroxide to give nearly clear solutions. Extraction with methylene chloride gave in each case a crystalline base corresponding in composition to loss of the acetyl group and addition of 1 mole of water. These products were characterized by the data given below as the 4-amino-3-hydroxy-2-piperidones (**11** and **12**; see Scheme II).

SCHEME II



A second product was isolated in each of these reactions by acidification of the aqueous, alkaline solution. This compound, which was a very high-melting phenolic substance ($C_{12}H_{11}O_2N$) giving a characteristic greenish blue color with ferric chloride, was identified as 3-hydroxy-4-methyl-5-phenyl-2-pyridone (**13**). An indication of this structure was originally gained by persulfate oxidation of 3-hydroxy-4-methyl-5-phenylpyridine, which gave in low yield a mixture in which the pyridone (**13**) and the 5-hydroxy-3-phenyl isomer[5] were tentatively identified. Conclusive evidence for the hydroxypyridone structure (**13**) was obtained by conversion of the $C_{12}H_{11}O_2N$ compound in 44% yield to the same azaquinone (**14**) previously obtained from the 5-hydroxypyridone.[5] The sequence **1** → **13** → **14** represents a considerably more practical route to **14**.



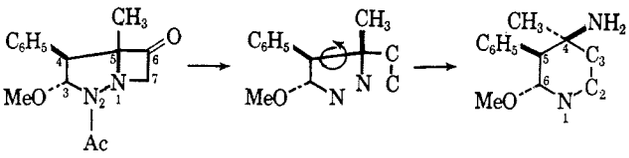
The primary basis for the aminopiperidone structures **11** and **12** was the conversion of these bases to the pyridone (**13**) on further treatment with base or on heating. Because of this facile elimination of ammonia, the relative yields of piperidone and pyridone in the reactions of the bicyclic ketones depended to a considerable degree on the conditions used; on heating **1** or **10** in aqueous base, **13** was isolated in 70–80% yield. There is no reason to suppose that the pyridone obtained as a by-product of **11** or **12** did not arise from the initially formed 4-aminopiperidone.

The amines (**11** and **12**) gave diacetyl derivatives with acetic anhydride; in one case the elimination of methanol was observed from the diacetyl methoxy derivative, leading to the diacetate of **11**. The methoxyamine (**12**) showed only phenyl absorption in the ultraviolet; the aminopiperdeinone (**11**) had a maximum at 271 mμ (ε 10,000) corresponding to conjugation of the phenyl group. The infrared spectra of both bases showed broad carbonyl bands at 1690 cm^{-1}. The nmr spectrum of the methoxyamine (**12**) contained peaks at δ^{CDCl_3},[6] 1.03 (s, 3-4-Me), 2.93 (d, 1, J = 7.5 cps, *H*-5), 3.21 (s, 3, OMe), 4.02 (s, 1, *H*-3), 5.13 (dd, 1, J = 2.5 and 7.5 cps, *H*-6), and 7.3 ppm (s, 5, Ph). In addition to these sharp signals, absorption in very broad bands at *ca.* 1.3, 3.9, and 7.5 ppm corresponded to a total of four additional protons in the spectrum integral. These latter signals disappeared on addition of D_2O and the double doublet at δ 5.13 owing to splitting of *H*-6 and N*H*, collapsed to a doublet, (J = 7.5 cps). In the spectrum of the diacetyl derivative of **12**, the *H*-3 peak was shifted to 5.53 ppm. The spectrum of the unsaturated base **11** (in DMSO) contained peaks for *H*-3 at 3.70 and *H*-6 at 5.80 ppm; acetylation shifted the *H*-3 peak to 4.99 ppm. These data are consistent for amines **11** and **12**; the absence of splitting of the proton on the OH-bearing carbon rules out the 2-hydroxy-3-oxopiperidone structure which might conceivably also give rise to **13**.

The configurations at C-4, C-5, and C-6 indicated in **12** follow from the stereo structure of the bicyclic ketones.[2] Regardless of the details of the transformation of **1** and **10** to **11** and **12**, which are discussed below, the gross changes comprising cleavage of the C-7–N-1 and N–N bonds in the bicyclic ketone, accompanied by rotation about the C-4–C-5 bond to

(6) Nmr spectra obtained on Varian A-60 instrument: s = singlet, d = doublet, dd = doubled doublet, m = multiplet, *etc.* Numerals indicate number of protons by integration.

permit recyclization, lead to the configuration shown. It seems quite inconceivable that the bonds to the substituents at C-4, C-5 and C-6, if broken, could be re-

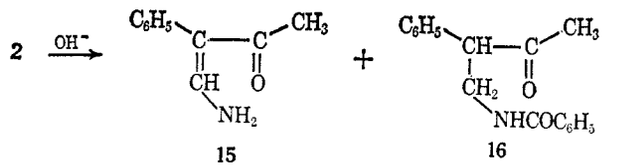


formed. The configuration of the newly formed hydroxyl group cannot be specified with certainty. The fact that acetylation leads to a diacetyl derivative rather than an oxazoline suggests that the hydroxyl and amino groups are *trans*.

The 2-benzoylbicyclic ketone (**2**) in aqueous methanolic base gave a mixture of three nitrogen-containing compounds in addition to ammonia, benzoic acid, and other unidentified substances. The main product (35%) was a crystalline base ($C_{10}H_{11}ON$) which was rapidly hydrolyzed with loss of ammonia and was converted with hydrazine to 3-methyl-4-phenylpyrazole. This behavior indicated that the compound was 1-amino-2-phenyl-1-buten-3-one (**15**); this structure was verified by comparison with an authentic sample prepared from phenylacetone.[7]

The second product (5%) was a neutral compound corresponding in composition to a benzoyldihydro derivative of **15**. This substance gave a semicarbazone; the nmr spectrum contained a nine-line, three-proton multiplet at 3.72–4.42 ppm as well as peaks for phenyl, benzoyl, and CH_3CO groups. These facts suggested that the compound was in fact the benzoyl derivative (**16**) of the saturated amino ketone, and an identical specimen was synthesized by hydrogenation of the benzoylated enamine.

The final product (2–5%) identified from the reaction of **2** was the pyridone (**13**) characterized in the reaction of **1**.



15 **16**

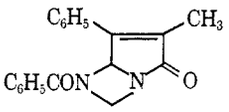
One other point concerns the completion of the two reaction pathways of the bicyclic ketones observed in methanol or methanolic base on one hand, and in aqueous base on the other. When the acetyl ketone **1** was treated with aqueous methanolic potassium hydroxide containing 25% by volume of methanol, a small amount of the hydrolyzed pyrrolinone (**8c**) was obtained, and a trace of pyrrolinone was observed on one occasion from the reaction of **2** in largely aqueous medium. There was no significant amount of the pyridone (**13**), however, in the reaction of **1** in methanol containing aqueous potassium hydroxide. Although these data are fragmentary, it appears that the formation of the pyrrolinones (**8**) and the acylamidopyridines (**9**), which occurs in methanol regardless of the presence of added base, is overriding in the reactions of the unsaturated ketones (**1** and **2**) in media containing both methanol and water. The 2-acetyl-3-methoxy ketone (**10**) is important in this connection since it is completely stable in pure methanol (or acidic methanol).[2] The reaction of this compound in methanolic base, in contrast to the unsaturated ketones, does give the pyridone (**13**), revealing that the double bond in **1** and **2** is indispensable in the formation of the pyrrolinones. It is noteworthy that the reaction of the methoxy ketone **10** in base does not lead to the methoxy diazepinone (**6**), parallel to the rapid formation of the diazepinone (**3**) from the Δ^2-bicyclic ketone (**4**). Apparently, the cyclic C=N bond in **4** is crucial for the stabilization of the anion formed on loss of the benzylic proton at C-4.

(7) J. A. Moore and C. L. Habraken, *J. Org. Chem.*, **30**, 1889 (1965).

Discussion

We shall now consider some pathways which we feel provide a basis for understanding the remarkably diverse assortment of products that arise from the bicyclic ketones. The suggested mechanisms are necessarily of a completely "operational" nature, and no attempt can be made to define the charge state of intermediates, nor the exact sequence of steps in all cases.

As a preliminary classification, the transformations of **1** and **2** can be divided into two groups. First are the acid-catalyzed reactions similar to those observed with the Δ^2-ketone (**4**), leading to **3**, **5**, and **6**. The general nature of these processes, which depend upon protonation at N-1, has been discussed previously.[2] The remaining reactions are those leading to **8** and **9** in methanol, to **11** and **12** or **15** and **16** in aqueous base, and finally, to the bicyclic uretidine **17**[8] in aprotic solvents.



17

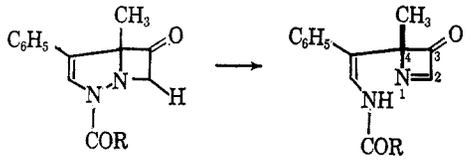
This second group of products has in common several obvious but distinctive features. In first place, the N–N bond of the bicyclic ketone is broken in every case. Second, with the exception of **9**, a carbon atom at the carboxylate oxidation level is found adjacent to the annular nitrogen atom on the methyl side. On the other hand, the fragment of the original ketone corresponding to the N-2–C-5 portion of the five-membered ring is generally intact. These elementary structural considerations lead to the conclusion that in this group of reactions, cleavage of the N–N bond and disruption of the four-membered ring are primary events, with sequelae that depend on the reaction medium and the nature of the acyl group.

We suggest that the initial step in this second group of reactions is a β elimination in the α-hydrazinocarbonyl system which forms the backbone of the bicyclic ketones, leading to the azetinone (**18**). This mode of cleavage has been demonstrated with α-hydrazino ketones, as discussed in the preceding paper,[9] and provides a unifying basis for several base-catalyzed rearrangements of the diazepinones (**3** and **6**). In the reaction of **3**, enolization is much more rapid than cleavage, but with the 1-benzoyldiazepinone (**6**), enolization is the rate-controlling step owing to stabilization of negative charge by the amide carbonyl.

(8) J. M. Eby and J. A. Moore, *ibid.*, **32**, 1346 (1967).

(9) J. A. Moore, H. Kwart, G. Wheeler, and H. Bruner, *ibid.*, **32**, 1342 (1967).

The same factors should obtain in the cleavage of the bicyclic ketones (1 and 2), the acylated enamine providing a particularly good leaving group in the elimination. As discussed below, no deuterium exchange at C-7 occurs in the reaction of 1 in D_2O–NaOD, and the formation of 18 evidently involves rapid β elimination in the enolate.

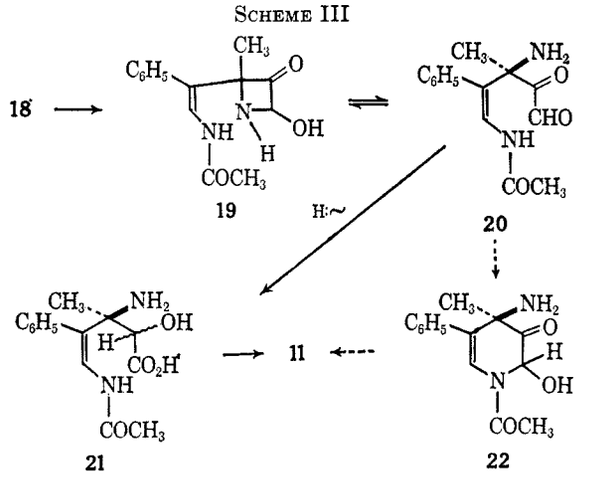


18

The azetinone ring in 18 contains in effect a strained α-dicarbonyl system in which a very high degree of electrophilic character would be anticipated at C-2. Formation of the observed products in alkali, methanol, and benzene can be interpreted in terms of solvation of this species in three different ways.

The rearrangement of the acetyl ketones (1 and 10) to the hydroxypiperidones is best considered first since no fragments are lost and the structures reveal clearly the bonds broken and formed in their formation. In these reactions, attack of water on the unsaturated azetinone would furnish the carbinolamine (19) and β-amino-α-ketoaldehyde (20). The subsequent stages to the product (11) are hydrolysis of the acetyl group and disproportionation of the two-carbon chain. The latter reaction might occur either by a hydride shift in 20, leading to the acid 21, or by an enolization mechanism involving the carbinolamine 22 (or the deacetylated carbinolamine; see Scheme III).

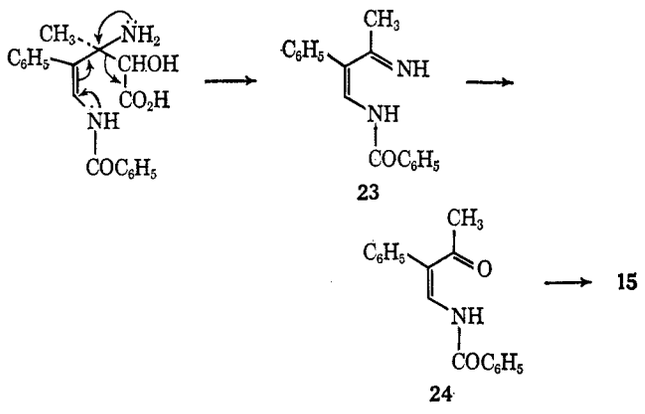
SCHEME III



Direct hydride shift in the aldehyde (20) is favored for two reasons. The base-catalyzed rearrangement of α-ketoaldehydes is known to be a strictly intramolecular process;[10] in keeping with this view, no deuterium was incorporated at C-3 in 11 or 12 when the acetylbicyclic ketones were treated with D_2O–OD. Extensive deuterium substitution would be expected if 11 were formed from 22 *via* an enediol. Another indication for the route 20 → 21 → 11 was the solubility behavior of the unsaturated acetyl ketone (1). The ketone dissolved fairly rapidly in 5% aqueous potassium hydroxide to give a yellow solution, but the maximum yield (40%) of the piperidone (11) was obtained only on prolonged extraction. When the solution was extracted immediately with methylene chloride, only a small amount of the base was removed and a further quantity separated on standing. (Unless the base was removed from the aqueous phase by frequent extraction, the yield was reduced because of conversion to the pyridone 13.) This behavior indicates that the neutral ketone dissolves initially to give an acidic substance which is then more slowly transformed to base 11. It seems probable that the intermediate acid is 21; efforts to isolate the compound or detect it by nmr were unsuccessful. The final slow step in the sequence would then be hydrolysis of the acetyl group.

The same over-all sequence outlined above must also obtain in the formation of the pyridone (13) from the benzoyl ketone (2), but the major path in this case is loss of the two-carbon chain. The contrasting behavior of the acetyl and benzoyl ketones is attributed to the somewhat slower hydrolysis of a benzamide compared to an acetamide, permitting an alternative reaction to compete with deacylation and cyclization of the acid (21) in the benzoyl compound.

Both the aldehyde (20) and the acid (21) are very favorably disposed for a fragmentation reaction which would lead to the imine (23), or some equivalent tautomer, and the anion of glycolic acid. The formation of the aminomethylene ketone (15) then requires two simple hydrolytic steps. The intermediate benzoyl enamine (24) is a vinylogous diacylimide, hydrolysis of which would be much faster than that of the saturated benzamido ketone (16). The latter compound thus arises by hydride transfer at some stage prior to hydrolysis of the benzoyl group; the aldehyde



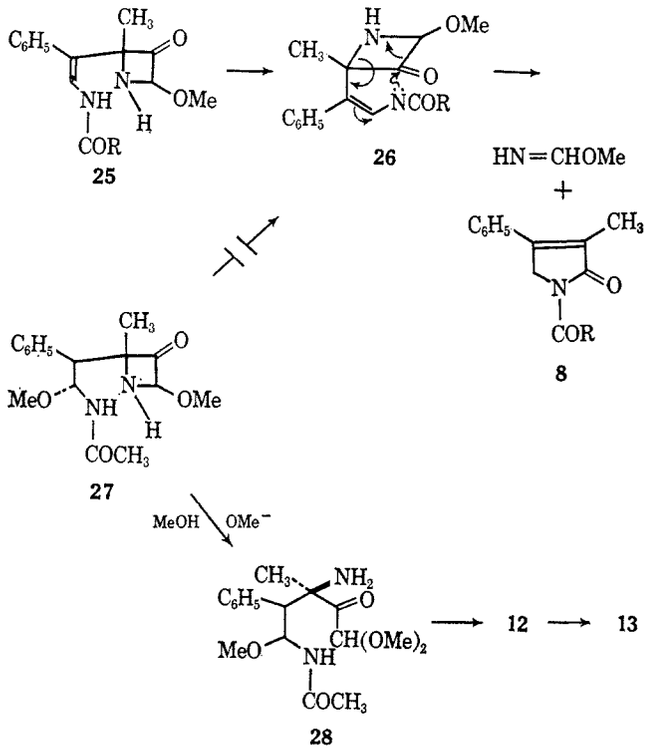
group must again be the hydride donor. It is interesting that hydride transfer can occur in two different modes in the same system; whether the transfer to the double bond, leading to 16, occurs intramolecularly before fragmentation or in a bimolecular reaction is problematic.

In the methanolysis reactions of 1 and 2, formation of the pyrrolinones (8) requires nucleophilic attack by the amide nitrogen on the carbonyl carbon of the bicyclic ketone, while the pyridines (9) which are produced concurrently require the opposite situation, with attack of the central nitrogen atom of C-3 of the bicyclic ketone. Both of these reactions are provided for in the intermediate methoxyazetidinone (25) which

(10) W. von E. Doering, T. I. Taylor, and E. F. Schoenwaldt, *J. Am. Chem. Soc.*, **70**, 455 (1948).

would be formed by solvation of the azetinone (**18**) in methanol. Cyclization as in **26** could lead directly to two stable products, the pyrrolinone (**8**) and methyl formimidate. The corresponding dimethoxy compound (**27**) could not lead to **8** by this mechanism; the formation of the piperidinone system (isolated as the pyridone) from **27** in basic methanol may involve further displacement by methanol at C-2 to give the acetal **28** (see Scheme IV).

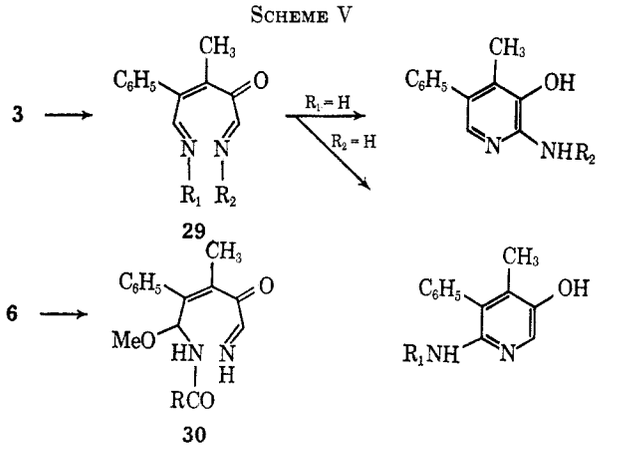
SCHEME IV



The decomposition of methyl formimidate in methanol solution to the ortho ester and ammonia is entirely consistent with the well-known behavior of imidates.[11] In the presence of base, however, ethyl formimidate has been shown to undergo elimination of alcohol with formation of cyanide ion. This reaction was observed by Nef[12] who actually considered it to be evidence against Pinner's structure for ethyl formimidate.[13] Disregarding this controversy, the reaction, although neglected in later reviews of imidate chemistry, was clearly documented and provides a basis for understanding the formation of cyanide in the reactions of **1** and **2** in the presence of methoxide ion.

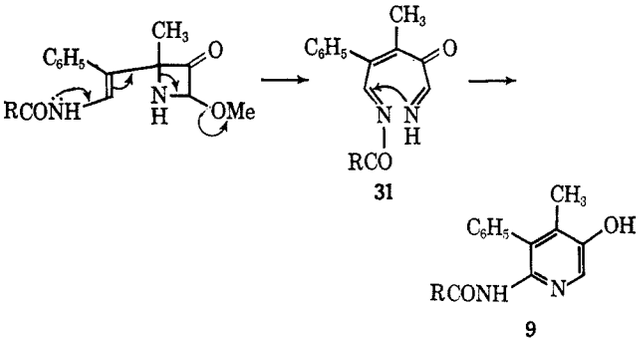
The 6-acylamidopyridines (**9**) are the only products among those under discussion that are familiar from the reactions of the related diazepinone (**3**). The unsubstituted compound (**9c**) is produced, together with the 2-amino isomer, on treatment of **3** with base; substitution at either nitrogen atom blocks one of the two paths. These rearrangements are thought to occur by cleavage to an acyclic intermediate (**29**) and recyclization, as discussed in an accompanying paper.[9] The related benzoyl imine (**30**) arises in the rearrangement of **6**, but in this case a pyridine cannot be formed

SCHEME V



by addition as with **29**, and a more complex cyclization to a pyrrole is observed[14] (see Scheme V).

The acylated diimine (**31**) would be an appropriate precursor of the pyridines (**9a** and **b**), however, and this versatile mechanism provides the simplest pathway to these products. A source of this acylated imine can be found in fragmentation of the methoxyazetidinone (**25**), the dichotomy here being exactly parallel to that previously seen in acid **21**. It is noteworthy that in this case also there is a preference, although less pronounced, for fragmentation in the benzoyl member and for cyclization in the acetyl, suggesting that steric effects may play a role in the partitioning of these intermediates between the two possible reactions.



Coming finally to the rearrangement of **2** in benzene, the same initial elimination is assumed; here a cyclic transition state (**32**) for the fragmentation can be envisioned. In the absence of an external nucleophile, the azetinone (**18**) can now be solvated only by attack of the amide nitrogen at C-2, giving rise to the bicyclo[3.1.1] system (**33**). Several possibilities, such as those shown in **34** and **35**, could be envisioned for the reorganization of **33** to the product (**17**)[8] (see Scheme VI). The nature of the acyl group in this reaction is also of considerable importance; only a trace of a compound which appeared to be the acetyl counterpart of **17** was obtained by heating acetyl ketone **1** in benzene. No other products have been identified as yet.

In conclusion, it may be observed that in examining possible mechanisms for the reactions of **1** and **2**, it is necessary to take cognizance of all of the products observed. Various alternatives can be advanced, and have been considered, for one or more of the individual reactions, but the proposals outlined above provide

(11) R. Roger and D. Neilson, *Chem. Rev.*, **61**, 179 (1961).
(12) J. U. Nef, *Ann.*, **287**, 328 (1895).
(13) A. Pinner, *Ber.*, **16**, 355 (1883); **28**, 2457 (1895).
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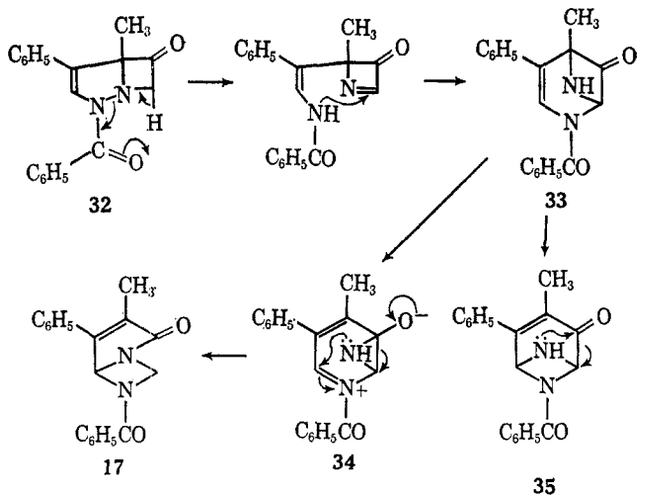
SCHEME VI



the only basis that we have been able to devise to account for all of the observations in a consistent way.

Experimental Section[15]

1-Acetyl-3-methyl-4-phenyl-3-pyrrolin-2-one (8a).—One hundred milligrams of the acetyl bicyclic ketone (1) was dissolved in 5 ml of methanol containing 29 mg of freshly dissolved sodium. The yellow solution stood for 80 min at room temperature and was then neutralized with 1 *N* HCl and diluted with water. The acetylpyrrolone (8a) separated as a mass of white needles (58 mg, 60%): mp 141–142°; ν^{KBr} 1725, 1695, 1650 cm^{-1}; δ^{CDCl_3} 2.08 (t, 3, J = 1.6 cps), 2.60 (s, 3, CH_3CON[16]), 4.58 (q, 2, J = 1.6 cps), 7.48 ppm (s, 5).

Anal. Calcd for $C_{13}H_{13}NO_2$: N, 6.51. Found: N, 6.64.

Hydrolysis of a sample of **8a** by warming for 30 sec with 1 *N* aqueous methanolic KOH gave the deacetylated pyrrolinone (**8c**) as long needles, mp 159–161°.

Reaction of Acetylbicyclic Ketone 1 in Methanol.—A solution of 100 mg of 1 in 2 ml of methanol was refluxed for 1 hr and evaporated to dryness *in vacuo*. The solid residue was partitioned between aqueous K_2CO_3 and ether. Evaporation and crystallization of the ether solution gave 29 mg (35%) of the N-acetylpyrrolinone (**8a**) as a white powder, mp 120–121°. Recrystallization gave needles, mp 123°; the infrared spectrum was essentially the same (positions and relative intensities of 23 peaks) as the higher melting sample described above.

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.80; H, 6.20; N, 6.44.

The aqueous carbonate solution was neutralized with HCl; a precipitate of 17 mg (17%) of 6-acetamido-3-hydroxy-4-methyl-5-phenylpyridine (**9a**) was obtained. Recrystallization from ethyl acetate gave poorly formed crystals, mp 110–112°.

Anal. Calcd for $C_{14}H_{14}N_2O_2 \cdot H_2O$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.84; H, 6.50; N, 11.12.

Hydrolysis of a sample of **9a** with concentrated H_2SO_4 gave the 6-aminopyridine (**9c**), mp 195–196°; mixture melting point with a sample prepared by hydrolysis of the 6-benzamidopyridine was 195–196°.

Similar yields of **8a** and **9a** were obtained when a solution of the bicyclic ketone (1) in methanol was allowed to stand in methanol for 20 hr. The methanol solution after refluxing for 30 min showed a total of five products by tlc ($CHCl_3$–MeOH, 23:2). In addition to **8a** and **9a**, the presence of the diazepinone (**3**) and the deacetylated pyrrolinone (**8c**) was indicated by nonseparation of spots on addition of authentic samples.

Reaction of Benzoylbicyclic Ketone 2 in Methanol.—A solution of 500 mg of 2 in 20 ml of methanol was refluxed for 2 hr and was then concentrated to small volume. During the reflux the vapor turned indicator paper blue. The residue was diluted with 20 ml of water and the solid was dissolved in 10 ml of 10% Na_2CO_3 solution and 50 ml of ether. The aqueous phase was extracted with ether and was then neutralized. The resulting flocculent precipitate was collected and recrystallized from methanol to give 315 mg (63%) of heavy prisms of **6-benzamido-3-hydroxy-4-methyl-5-phenylpyridine (9b)**, mp 129–135°. Analysis showed that this material contained about one molecule of methanol; solvent-free samples of **9b** were obtained by crystallization from chloroform–ether as needles: mp 216–217°, pK_A = 2.7, 9.4, λ_{max}^{EtOH} 281 mμ (ε 7350), $\lambda_{max}^{EtOH\text{-}HCl}$ 303 mμ (ε 7600), $\lambda_{max}^{EtOH\text{-}NaOH}$ 307 mμ (ε 8000). For analysis, see ref 5.

The combined ether solutions from the above separation were washed, dried, and evaporated to give 74 mg (16%) of colorless cubes, mp 145–146°, of **1-benzoyl-3-methyl-4-phenyl-3-pyrrolin-2-one (8b)**.[4] Recrystallization from methanol gave filaments: mp 146°; λ_{max}^{EtOH} 280 mμ (ε 21,000); ν^{KBr} 1720, 1668 cm^{-1}.

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.39; H, 5.70; N, 5.31.

A solution of 100 mg of **2** in 8 ml of methanol containing 0.5 ml of 0.2 *N* sodium methoxide was heated at 60° for 3 hr. The products were isolated as described above, giving 30 mg (30%) of pyridine **9b** and 40 mg (46%) of pyrrolinone **8b**.

A solution of 250 mg (0.82 mmole) of **2** in 20 ml of methanol was refluxed for 2 hr while a slow stream of nitrogen was passed through the solution into 25 ml of 0.102 *N* hydrochloride acid. Titration of the excess acid to a methyl red end point required 120.2 ml of 0.020 *N* sodium hydroxide, corresponding to 0.21 mequiv of volatile base from the reaction (26% yield of ammonia). The methanol solution furnished 62 mg (27%) of pyrrolinone **8b**.

A solution of 2.00 g (6.56 mmoles) of **2**, 200 mg of benzoic acid, and 100 mg of sodium benzoate in 40 ml of methanol was refluxed for 2 hr. The solvent was distilled to a nearly dry residue and the distillate was redistilled through a 10-in. packed column. The residue from this distillation displayed a peak (retention time 7.6 min) in a vpc on a Ucon polar column at 85°. The height of this peak was enhanced by addition of authentic trimethyl orthoformate.

Reaction of Acetylbicyclic Ketone 1 with Aqueous KOH.—The crystalline ketone (1, 1.18 g) was stirred with 25 ml of 5% aqueous KOH for 30 min; a slightly turbid, yellow solution was obtained. The solution was periodically shaken with 150 ml of methylene chloride during 1 hr and was further extracted with several 80-ml portions of fresh solvent during a 2-hr period. The methylene chloride solution was washed with water, dried, and evaporated at 20° to give 401 mg (38%) of **4-amino-3-hydroxy-4-methyl-5-phenyl-5-piperdein-2-one (11)** as shiny, white plates: mp 280° dec; λ_{max}^{MeOH} 271 mμ (ε 10,400); pK_A (50% MeOH) = 6.7; ν^{KBr} 3550, 3300, 1690, 1655 cm^{-1}; $\delta^{DMSO\text{-}d_6}$[17] 0.88 (s, 3), 3.70 (s, 1), 5.80 (s, 1), 7.0–7.3 ppm (m, 5).

Some, but not all, preparations of **11** obtained by this procedure gave a green color with $FeCl_3$–MeOH, indicating the presence of pyridone **13**. This color test was much more sensitive than tlc for the detection of **13**; melting points were completely uninformative. A sample for analysis was purified by dissolving 58 mg of slightly contaminated material in 1 ml of 0.1 *N* HCl and removing the insoluble pyridone by filtration. Adjustment of the pH to 8 gave 37 mg of white crystals of **11** which gave no $FeCl_3$ color. An additional 12 mg was obtained by extraction with methylene chloride. An analytical sample recrystallized from methanol–ether gave low nitrogen values.

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.12; H, 6.35; N (Dumas), 11.74, 12.23.

A sample precipitated from aqueous acid solution was dried at 110° without recrystallization and nitrogen analyses were carried out by Dumas (total N) and by Kjeldahl distillation from 30% KOH, without prior digestion, to estimate ammonia liberated by base treatment.

Anal. Calcd: total N, 12.84. Found: N (Dumas), 12.59. Calcd for $C_{12}H_{14}O_2N_2 \rightarrow C_{12}H_{11}O_2N + NH_3$: N, 6.42. Found (Kjeldahl distillation): N, 7.08.

The alkaline, aqueous solution from the methylene chloride extraction of **11** was made strongly acid and **3-hydroxy-4-methyl-5-phenyl-2-pyridone (13)** separated as a very finely divided, cream-colored precipitate; 264 mg (27%) was obtained after thorough drying. The compound was most conveniently recrystallized by dissolving the moist filter cake in a large volume

(15) General procedures are given in paper XXII of this series: J. A. Moore, R. W. Medeiros, and R. L. Williams, *J. Org. Chem.*, **31**, 52 (1966).

(16) This value of δ_{CH_3CON} may be compared with the value δ = 2.50 ppn for CH_3CON in 1-acetylpyrrolidinone: Varian Catalog, Vol. II, Varian Associates, Palo Alto, Calif., 1963, Spectrum No. 465.

(17) For spectra in DMSO-d_6, δ values (TMS = 0) were obtained by use of the DMSO-d_5 peak as an internal standard with δ = 2.52 ppm (ref 16, Spectrum No. 376).

of hot methanol and concentrating until crystals appear in the hot solution. The melting point on a hot stage is about 295–300° with extensive sublimation; one or more phase changes are usually seen. A sample purified by sublimation had mp (sealed capillary) 310–315° dec; λ_{max}^{MeOH} 302 mμ (ε 9700), $\lambda_{max}^{MeOH + KOH}$ 312 mμ (ε 1100), $\lambda_{max}^{MeOH + FeCl_3}$ 670 mμ; ν^{KBr} 3360, 1670 cm^{-1}.

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.73; H, 5.58; N, 7.06.

Conversion of aminopiperdeinone **11** to pyridone **13** was observed in several ways. There was no visible change on heating **11** on the melting point block, but the melting point (<280 dec) appeared to be that of **13**. In the nmr in DMSO solution containing NaOD, the spectrum changed from that of **11** to that of **13** in about 10 min; a strong smell of ammonia was present. In 6.6 × 10^{-4} *M* solution in methanol containing KOH, the absorbance at 277 mμ disappeared and a peak at 315 mμ (ε 7700) appeared in 1 hr.

3-Acetoxy-4-acetamido-4-methyl-5-phenyl-5-piperdein-2-one.—A solution of 350 mg of amine **11** in 2 ml of pyridine and 2 ml of acetic anhydride was allowed to stand for 22 hr at room temperature and then about 10 ml of ice was added. The diacetyl derivative crystallized as shiny, white plates: 338 mg; mp 232–233°; ν^{KBr} 1750, 1690, 1660 (C=O), 1230 (C—O) cm^{-1}; δ^{DMSO-d_6} 0.96 (s, 3, sl broad, $w_{1/2}$ = 3 cps), 1.72 (s, 3), 1.98 (s, 3), 4.99 (s, 1), 5.93 (s, 1), 7.12 ppm (s, 5).

Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.72; H, 6.21; N, 9.36.

3-Acetoxy-4-methyl-5-phenyl-2-pyridone.—A solution of 64 mg of pyridone **13** in 0.5 ml of pyridine and 0.4 ml of acetic anhydride was warmed for 3 min and then diluted with water; 70 mg of colorless needles separated: mp 193–195°; ν^{CHCl_3} 1770, 1660 cm^{-1}; δ^{CDCl_3} 2.05 (s, 3), 2.36 (s, 3), 7.3–7.5 ppm (m, 5).

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39. Found: C, 68.71; H, 5.26.

2-Hydroxy-4-methyl-5-phenyl-1-azaquinone (14).—To a suspension of 100 mg of pyridone **13** in 12 ml of 20% H_2SO_4 was added 145 mg of sodium nitrite. After standing for 2 days a light yellow precipitate was collected; additional material was obtained by extraction with methylene chloride. Recrystallization from water gave 47 mg (44%) of the azaquinone as yellow-orange crystals, mp and mmp with a previously prepared sample[5] 157–158°. The two samples had the same infrared spectra (comparison of 20 peaks).

4-Amino-3-hydroxy-6-methoxy-4-methyl-5-phenyl-2-piperidone (12).—A suspension of 215 mg of the methoxybicyclic ketone **10** in 50 ml of water containing 0.6 g of KOH was stirred at 30° for 1.5 hr. The solution was then filtered and 5 mg of undissolved starting material was recovered. The filtrate was extracted with four 30-ml portions of methylene chloride and the methylene chloride solution was washed, dried, and evaporated to give 70 mg (38%) of white crystals of **12**, mp 175–178° dec. Recrystallization from methylene chloride–ether gave colorless rods: mp 177–178°; δ^{CCl_4} 3470, 3410, 3220, 1690 cm^{-1}; ν^{KBr} 1690 cm^{-1}; for nmr, see the Discussion.

Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.76; H, 7.21; N, 11.33.

The aqueous, alkaline solution was acidified and the solution was evaporated to a solid residue which was continuously extracted (Soxhlet) with methylene chloride. The extract on evaporation gave 56 mg (34%) of the pyridone **13**, mp 280–290°.

4-Acetamido-3-acetoxy-6-methoxy-4-methyl-5-phenyl-2-piperidone.—A solution of 180 mg of amine **12** in 4 ml of acetic anhydride and 0.8 ml of pyridine was allowed to stand at 25° for 3 days and then was evaporated *in vacuo* to an oil. After addition of methanol and evaporation 76 mg of solid was obtained which was recrystallized from ethyl acetate to give white rods: mp 198–200°; λ_{max}^{MeOH} 251, 257, 263 mμ (ϵ_{257} 300); ν^{KBr} 3280, 1745, 1670 (br) cm^{-1}; δ^{CDCl_3} 1.25 (s, 3), 1.96 (s, 3), 2.19 (s, 3), ~3.17 (presumably doublet with one leg beneath OMe peak), 3.25 (s, integral 3.1–3.3 = 4), (5.12, dd, 1), 5.53 (s), 5.58 (s, NH) (integral 5.5–5.65 = 2), 7.1 (s, br, 1), 7.36 ppm (s, 5).

Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.06; H, 6.63; N, 8.38. Found: C, 61.10; H, 6.50; N, 8.07.

Some difficulty was encountered in the characterization of the methoxydiacetyl derivative. Preparations with anomalous properties were obtained on some occasions, and solvent was retained rather tenaciously. In one case (but not another) drying at 100° *in vacuo* caused an increase in melting point to 220° and the appearance of the methyl signals in the nmr as doublets. The preparation showed 271 mμ (ϵ_{max} 8000), indicating extensive conversion to the diacetylpiperdeinone derivative. Recrystallization gave material with an infrared spectrum nearly sumperimposable on that of the pure, unsaturated diacetyl derivative.

Reaction of 2-Benzoylbicyclic Ketone 2 with Aqueous KOH.—A mixture of 2 g of **2**, 20 ml of methanol, and 10 ml of water was treated with a solution of 1 g of KOH in 10 ml of water. The ketone rapidly dissolved to give a turbid, yellow solution and a strong odor of ammonia was evolved. After standing for 2 hr at 30° the solution was evaporated at 30° to 30-ml volume, diluted with water, and extracted with ether (five 20-ml portions). The ether solution was washed with water, dried, and evaporated to a pale yellow oil. Crystallization from ether gave a total of 470 mg of colorless solid, mp 88–102°, in four crops and 300 mg of oily residue. On fractional crystallization from methylene chloride–ether, enamine **15** was obtained in the first crops, and then mixed fractions containing the benzamidomethyl ketone were collected and combined according to melting point. Repeated fractionation gave a total of 274 mg of enamine **15**, mp 95–98°, and 90 mg of benzamidomethyl ketone **16**, mp 124–126°. Crystalline mixed fractions (145 mg) were estimated to contain an additional 100 mg of **15** (total 374 mg or 35%) and 10 mg of **16** (total 100 mg or 6%).

In another experiment, enamine **15** and benzamide **16** were partially separated by fractional sublimation; **15** was obtained from initial fractions (bath temperature 70–90°) and **16** in later fractions (bath temperature 90–130°). Since **15** is basic and **16** is neutral, isolation of **16** could be facilitated by extraction of **15** with acid, but this treatment woud destroy **15** (see below).

The aqueous, alkaline solution from the reaction was acidified to pH3. Part of hydroxypyridine **13** slowly separated as a fine powder which was collected. The turbid solution was then extracted with ether and a small additional amount of **13** was obtained after evaporation of the ether, giving a total of 14 mg of **13** mp 280–290°.

1-Amino-2-phenyl-1-buten-3-one (15).—After recrystallization from methanol–ether, this enamine crystallized in colorless rods, mp 96–98°. The infrared spectrum matched that of an authentic sample[7] in the position of 19 bands.

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.50; H, 6.88; N, 8.69. Found: C, 74.42; H, 7.13; N, 8.60.

The compound was soluble in 1 *N* HCl. After 1 hr at 30° an oil separated from the initially clear solution. This oil was extracted with ether; this solution gave a burgundy color with $FeCl_3$. Ammonia was identified in the aqueous solution by precipitation of tetraphenylboronate,[18] mp 225–230°. Ammonia was also evolved on warming the enamine in 2 *N* alkali. Treatment of the enamine (85 mg) with hydrazine gave 56 mg of 3-methyl-4-phenylpyrazole,[19] mp and mmp 143–144°.

1-Benzamido-2-phenyl-3-butanone (16).—Recrystallization from ether gave colorless crystals: mp 125–126°; λ_{max}^{EtOH} 220 mμ (ε 15,000); λ_{max}^{KBr} 2.91, 5.84, 6.11 μ; δ^{CDCl_3} 2.07 (s, 3), 3.72–4.42 (m, 3), 6.9 (broad, 1), 7.2–8.0 ppm (m, 10).

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.25. Found: C, 76.48; H, 6.46; N, 5.30.

The semicarbazone of **16** was crystallized from ethanol–water, mp 172–174°.

Anal. Calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.85; H, 5.88; N, 17.21.

A solution of 0.26 g of 1-benzamido-2-phenyl-1-buten-3-one[7] in 75 ml of ethanol was shaken with 0.1 g of 10% palladium on carbon at 30 psi of hydrogen for 14 hr. After removal of catalyst and excess solvent, the solution deposited crystals of **16**. Recrystallization from ether gave white needles, mp 124–125°, on mixture with material obtained from **2**, mp 124–125°. The semicarbazone was prepared, mp 170–172°.

Registry No.—Methanol, 67-56-1; **8a**, 10147-13-4; **8c**, 10137-07-2; **9a**, 10137-08-3; **9c**, 10137-09-4; **9b**, 10137-10-7; **8b**, 10137-11-8; **11**, 10137-12-9; **13**, 10137-13-0; 3-acetoxy-4-acetamido-4-methyl-5-phenyl-5-piperdein-2-one, 10137-14-1; 3-acetoxy-4-methyl-5-phenyl-2-pyridone, 10137-15-2; **14**, 10137-16-3; **12**, 10168-

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78-2; **15**, 1706-31-6; **16**, 10137-17-4; semicarbazone of **16**, 10137-18-5; 4-acetamido-3-acetoxy-6-methoxy-4-methyl-5-phenyl-2-piperidone, 10137-19-6.

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P–N Heterocycles. Their Synthesis and Use in the Catalytic Conversion of Isocyanates into Carbodiimides

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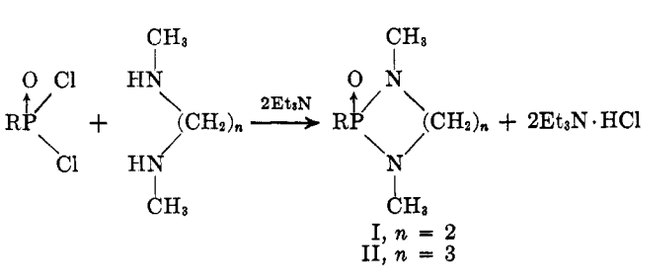
Several novel 1,3-dimethyl-1,3,2-diazaphospholidine 2-oxides and 1,3-dimethylhexahydro-1,3,2-diazaphosphorine 2-oxides were synthesized, and their catalytic activity in the conversion of isocyanates into carbodiimides has been demonstrated.

Although the oxides and sulfides of many organic compounds which contain elements from groups V and VIb of the periodic table are effective catalysts in the conversion of isocyanates to carbodiimides,[1] for the element phosphorus only the cyclic, five-membered phosphine oxides, compounds available form a laborious synthesis,[2] are known to be successful.[3]

The two-step mechanism proposed for these phospholene oxide catalyzed reactions involves the initial formation of a phosphinimide intermediate which reacts with a second molecule of the isocyanate to both afford the carbodiimide and regenerate the catalyst.[3] Since phosphinimides are known to react rapidly with isocyanates,[4] the first step is probably rate determining and would, therefore, be facilitated by a reduction in the polarity of the phosphorous–oxygen bond. In diazaphospholidines, where two nitrogen atoms are juxtaposed to the phosphorous, such a reduction would be anticipated.

Several 1,3-dimethyl-1,3,2-diazaphospholidine 2-oxides (I) and 1,3-dimethylhexahydro-1,3,2-diazaphosphorine 2-oxides (II) were prepared from the reaction of the corresponding N,N′-dimethylalkylenediamines with phosphonic dichlorides in the presence of triethylamine (see Tables I and II).



I, n = 2
II, n = 3

Confirmation of structure was made from elementary analyses and from H^1 nmr spectroscopy. The protons in both the NCH_3 and NCH_2 groupings were coupled with the phosphorus and generally gave rise to well-defined doublets. A correlation of the coupling constants and the chemical shifts is presented in Table III. The protons in the NCH_2 groupings were equivalent, except in the R = CH_2CH_3 (Table III, no. 3) and R = C_6H_5 (Table III, no. 6) derivatives. In the former case two protons, of both NCH_2 groups were equivalent with the remaining two protons giving rise to singulets of equal intensity; in the latter the diamagnetic anisotropy of the benzene ring influenced the chemical shift of both neighboring protons. A similar affect was observed in the diazaphosphorine derivative (Table III, no. 9).

The carbodiimides were prepared by refluxing the isocyanate with 0.5% by weight of the catalyst for 20–30 min, followed by distillation *in vacuo*.

The catalytic activity of several P–N heterocycles in the conversion of *o*-tolyl isocyanate to di-*o*-tolylcarbodiimide is shown in Table IV. Complete conversion was indicated by both the disappearance of the NCO absorption in the infrared at 4.4 μ and by an increase in refluxing temperature.

All of the P–N heterocycles listed in Tables I and II showed some catalytic activity, the diazaphospholidines being much more effective than the hexahydrodiazaphosphorines.[5] The substituents in the α position markedly influenced catalytic activity: ethyl > phenyl > chloromethyl > ethoxy > dimethylamino, the ethyl being the most effective.

The steric sensitivity of the reaction was made apparent by the range of time necessary for complete conversion of non-, 2-, and 2,6-substituted aryl isocyanates (see Table V). Aliphatic isocyanates were less reactive than the aromatic. Octadecyl isocyanate was converted in 2 hr at 200–252°, and phenyl isocyanate in 8 min at 160–230°. *t*-Octyl isocyanate failed to react (see Table V).

The heterocyclic compound (IV) in which the steric hindrance caused by the 1,3-dimethyl groupings in I and II would be absent, was prepared from diethyl minomalonate dihydrochloride (III).

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