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# AMINOPYRIDINES AS ACYLATION CATALYSTS FOR TERTIARY ALCOHOLS

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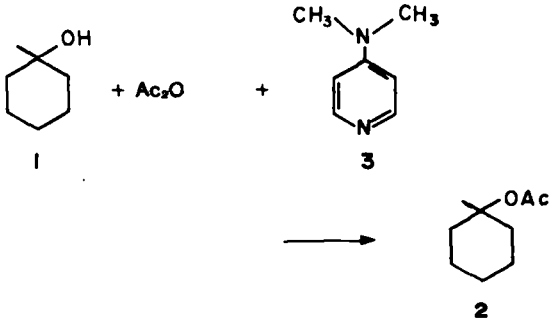
**Abstract**—The acylation of unreactive alcohols with acid anhydrides is greatly facilitated by the addition of a catalytic (0.02–0.1 equivalent) amount of a 4-dialkylaminopyridine. The reaction is faster in nonpolar than in polar solvents and acetyl chloride is not as effective as acetic anhydride. Several pyridine, pyridazine, and quinoline derivatives have been examined as potential acylation catalysts. Of the systems examined, only a few of the 4-substituted pyridines were found to be acylation catalysts, the most effective being 4-pyrrolidinopyridine **4** and 1,1,3,3-tetramethyl-4-(4-pyridyl)guanidine **8**. The reaction of *t*-butanol with an isocyanate is also accelerated by the presence of **4** but not as much as in the case of acylations. The cause of the pronounced effect of these pyridine species in catalyzing acylation reactions seems to be a combination of the increased donor ability of the 4-substituent and the stabilizing effect that this substituent has on an acyl pyridinium intermediate.

## INTRODUCTION

The use of pyridine and an acid anhydride or acid halide for the acylation of alcohols has been known for many years. An *N*-acyl pyridinium species, first suggested by Doering and McEwen, is thought to be the reactive intermediate in these reactions.[2]

Although the acylation of primary and secondary alcohols usually presents few problems, hindered alcohols are often quite resistant to acylation. Several methods have been developed for the acylation of tertiary alcohols. These include acid catalyzed acylations,[3] the use of acetyl chloride in the presence of bases as HCl scavengers,[4] alcohol with acid chlorides,[5] the utilization of mixed anhydrides,[6] and of other reagents.[7]

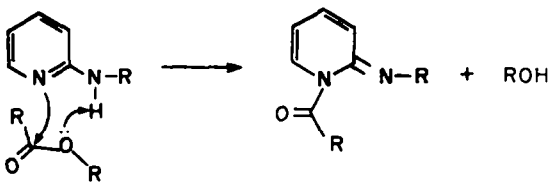
Steglich and Hofle[8] found that the addition of 4-dimethylaminopyridine **3** greatly faciliatated acylation of hindered alcohols with carboxylic acid anhydrides. Aminopyridine **3** has been reported to give a stable *N*-*t*-butoxycarbonyl derivative which was used to protect amino acids.[9] But the most useful aspect of this reagent in acylations is that its action is catalytic.[8] Thus although 1-methyl-cyclohexanol **1** was not acetylated by acetic anhydride and pyridine or triethylamine, the addition of *ca.* 0.05 molar equivalent 4-dimethylaminopyridine **3** to a mixture of 1-methylcyclohexanol **1** and acetic anhydride led to the formation of 1-methylcyclohexyl acetate **2** in 86% isolated yield.




1 3 2

Although this appears to be a generally useful acylation method[10] the reasons for the very pronounced catalytic effect of **3** and the structural requirements for such a catalyst were not investigated.

We had originally conceived the possibility that 2-aminopyridines may act as catalysts in the hydrolysis of ethers according to the following scheme (the reverse of the acylation process):



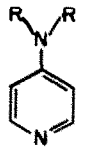

This did not materialize but in the course of these studies[11] we investigated a variety of aminopyridines as acylation catalysts for tertiary alcohols. We are reporting here our results bearing on the structural features of substituted pyridines that are required in their action as acylation catalysts.

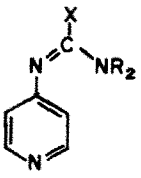
## RESULTS

The first acylation catalysts studied were 4-pyrrolidinopyridine **4**, 4-dimethylaminopyridine **3**, 4-piperidinopyridine **5**, and 4-morpholinopyridine **6**. They were prepared in 50–60% yield by the method of Jerchel and Jakob,[12] that involves heating 4-pyridylpyridinium chloride hydrochloride with phenol, followed by heating with the appropriate secondary amine. An alternative pathway was heating of 4-chloropyridine hydrochloride with an amine.

The 4-substituted pyridines, **8**, and **9**, were prepared from the reaction 4-aminopyridine with tetramethylthiourea or dimethylformamide.

To determine the relative efficiencies of these 4-dialkylaminopyridines in catalyzing the acylation of hindered alcohols, the acetylation of 1,1-diphenylethanol **10** to **11**





3: R: $CH_3$—
4: R, R: —$(CH_2)_4$—
5: R, R: —$(CH_2)_5$—
6: R, R: —$CH_2CH_2OCH_2CH_2$—
7: R, R: —CHCH= CHCH—
$CH_3$ $CH_3$

8: R: $CH_3$; X: $N(CH_3)_2$
9: R: $CH_3$; X: H

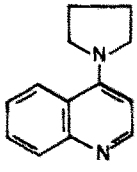
10 11

with 2 molar equivalents of acetic anhydride and triethylamine in the presence of 0.1 molar equivalents of the catalyst was allowed to proceed to partial completion. After quenching and washing, the ratio of acetate **11** to alcohol **10** was determined directly from the NMR spectrum of the mixture. Alternatively, the acetylation of 1-methylcyclo-hexanol **1** under similar conditions was followed by GC analysis. In the absence of the catalyst, neither **10** nor **1** was acylated to an observable (>5%) extent, even after several days reaction time.

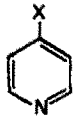
The relative effectiveness of the 4-amino substituent in catalyzing the esterification of alcohols with acetic anhydride is indicated in Table 1. The most effective catalyst was 4-pyrrolidino-pyridine **4**.

The chemical shifts of the $\beta$-protons of the pyridine ring in the 4-aminopyridines studied are also included in Table 1.

Neither 4-pyrrolidinoquinoline **12** nor the imidazole **17** was found to have any catalytic effect in the attempted acetylations of hindered alcohols. Also ineffective were the oxygen **13**, phosphorous **14**, and sulfur **15** substituted pyridines and 4-aminopyridine **16** itself.



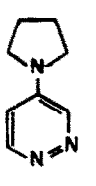
12

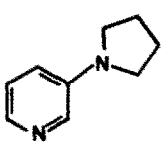


13: X: OPh
14: X: $PPh_2$
15: X: $SCH_2Ph$
16: X: $NH_2$
17: X: —N

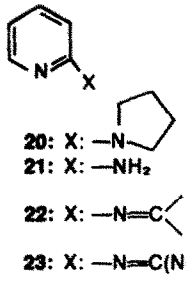
Similarly lacking any catalytic effect in the attempted acetylations of hindered alcohols were 4-pyrrolidinopyridazine **18**, 3-pyrrolidinopyridine **19**, and the 2-substituted pyridines **20**–**23**.

A quantitative comparison of the relative effects of





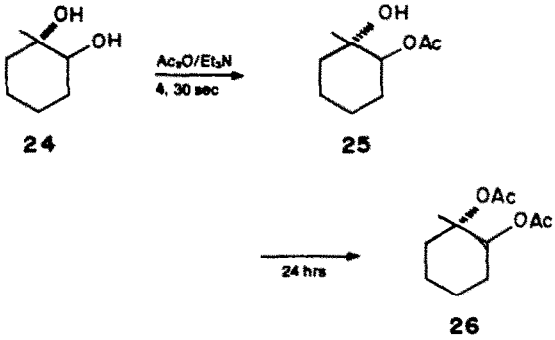
18 19



20: X: —N
21: X: $—NH_2$
22: X: —N=C(H)N$(CH_3)_2$
23: X: —N=C$(N(CH_3)_2)_2$

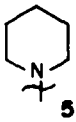
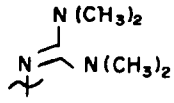
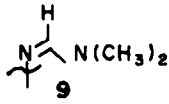
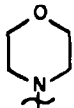
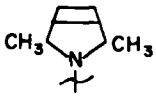
4-pyrrolidinopyridine **4** and pyridine itself in catalyzing the acylation of an alcohol is difficult since the difference is very large and a kinetic study was not undertaken. Russian workers[13] have estimated from kinetic data that 4-dimethylaminopyridine **3** is *ca.* $10^4$ times as effective as pyridine in catalyzing the benzoylation of *m*-chloroaniline.

With pyridine itself, no acetylation of either 1-methylcyclohexanol **1** or 1,1-diphenylethanol **10** was observed. In cases where the use of pyridine does lead to acetylation, as with a secondary alcohol, the use of 4-pyrrolidino-pyridine results in a very rapid reaction, usually complete within a few seconds. Thus the reaction of diol **24** with excess acetic anhydride and pyridine or triethylamine was complete in *ca.* 2 h, as determined by GC analysis. Only the secondary hydroxyl group was acetylated. No further reaction was observed, even after one week. However, when *ca.* 0.1 molar equivalent of 4-pyrrolidinopyridine **4** was added to a solution of diol **24**, excess acetic anhydride and triethylamine, the solution became warm. Immediate injection of an aliquot into the GC showed complete absence of starting diol with consequent formation of monoacetate **25**. After 24 h, monoacetate **25** was completely consumed and a 94% yield of diacetate **26** was isolated.



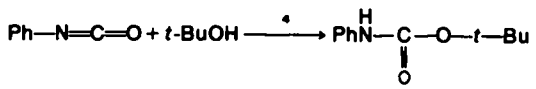

24 25 26

Table 1. Effective acylation catalysts in acetylation of **10**

| 4-substituent on pyridine | Relative effect | Chemical shift of β-hydrogens in **3–9** | 4-substituent on pyridine | Relative effect | Chemical shift of β-hydrogens in **3–9** |
|---|---|---|---|---|---|
|  **4** | 1.0 | δ6.38 |  **5** | 0.40 | 6.55 |
|  **8** | 0.90 | 6.55 |  **9** | 0.30 | 6.92 |
|  **3** | 0.63 | 6.48 |  **6** | 0.12 | 6.67 |
|  **7** | 0.50 | 6.48 | **12** | **6** | **12** |

The acetylation of several other hindered alcohols **27–29** with acetic anhydride and a catalytic amount of 4-pyrrolidinopyridine was found to proceed smoothly at room temperature. These results are shown in Table 2.

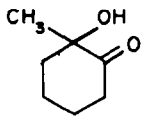
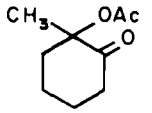
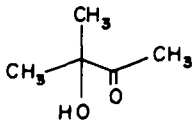
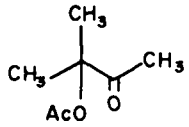
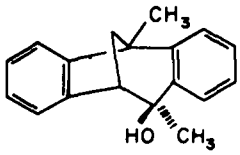
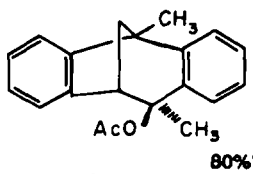
Furthermore, we found the aminopyridine **4** to be effective in speeding up about fourfold the reaction of *t*-butanol with phenylisocyanate.



## DISCUSSION

A 4-aminosubstituent has been shown[14] to augment the basicity of the pyridine system. Thus the $pK_a$ of pyridine

Table 2. Acetylation of tertiary alcohols[a]

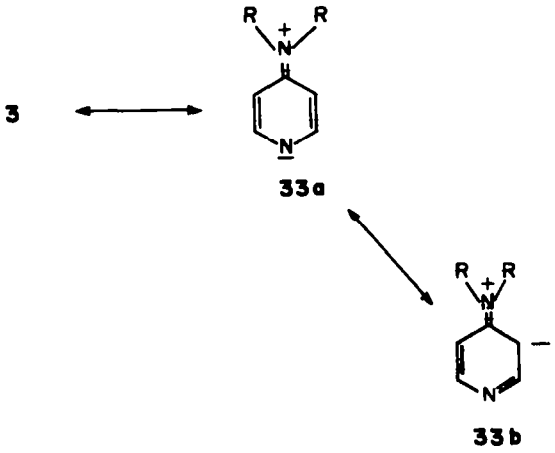
| ROH | Reaction time | Yield of acetate |
|---|---|---|
|  **27** | 45 min |  **30** 87%[b] |
|  **28** | 30 min |  **31** 97%[b] |
|  **29** | 24 h |  **32** 80%[c] |

[a]Conditions: neat reaction, 2 equivalents each of acetic anhydride and triethylamine, 0.01 equivalent of 4-pyrrolidinopyridine and alcohol at room temperature. [b]Yield of purified acetate. [c]Yield estimated from the NMR spectrum–acetate was not stable to attempted purification.

is 5.21,[15] while that of 4-dimethyl-aminopyridine is 9.71. Katritzky[16] has demonstrated from oxidation and alkylation studies that the pyridine ring nitrogen is the basic center of 4-dimethylaminopyridine 3. However, the powerful catalytic acylation effect of the compounds in Table 1 is not simply a reflection of their base strength since the $pK_a$ of triethylamine, which demonstrated no catalytic effect in these acylations, is 10.7.[15] Probably the stability of an acylpyridinium intermediate such as 34 plays an important role.

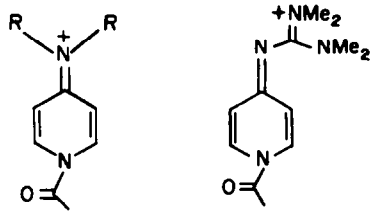
The catalytic activity of the series pyrrolidino 4 > dimethylamino 3 > piperidino 5 > morpholinopyridine 6 follows the same order as the reactivity of enamines of the respective amines toward electrophilic reagents. The enamine reactivity order toward electrophiles has been explained[17] as a combination of steric and electronic effects. The electron density at the $\beta$-carbon of an enamine increases with the $p$-$\pi$ overlap of the nitrogen lone pair electrons with the double bond. Hence, the chemical shift of the olefinic proton of an enamine also reflects the electron density at the $\beta$-carbon, and thus the reactivity of the enamine in a given series.

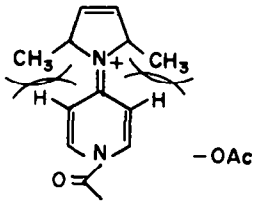
Since similar $p-\pi$ overlap is possible in the 4-dialkylaminopyridines (see resonance form 33), we measured the chemical shifts of the $\beta$-hydrogens (of the pyridine ring) in the 4-dialkylaminopyridines (Table 1) and found that the greatest shielding occurs in the most effective acylation catalyst, 4-pyrrolidinopyridine 4 ($\delta$ 6.38). The order of effectiveness correlates qualitatively with the chemical shift of the $\beta$-protons for the structurally related 4 > 3 ≥ 7 > 5 > 6.




The data in Table 1 suggest that the catalytic effect of the 4-dialkyl-aminopyridines is due to a combination of the donor ability of the amine substituent and the stability of an acyl pyridinium species 34. In acetylation reactions of 1,1-diphenylethanol 10 or 1-methylcyclohexanol 1, the guanidine 8 was found to be *ca.* 90% as effective a catalyst as 4-pyrrolidinopyridine 4 in spite of the fact that tetramethylguanidine is a much stronger base ($pK_a$ 13.9)[15] than pyrrolidine ($pK_b$ 11.27). In this case, however, there is practically no change in the hybridization of the nitrogen at C-4 during the formation of 35 from 8 which may explain the lower effectiveness of this catalyst.

Surprisingly, the 2,5-dimethyl pyrroline compound 7 was found to be *ca.* 50% as effective an acylation catalyst as 4, in spite of the expected unfavorable steric interactions and the increased ring strain in the 5-membered ring of 36. In this case the $\beta$-hydrogens are



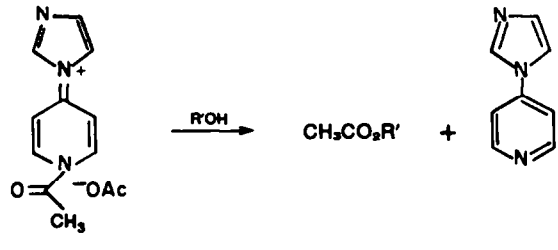




close in the NMR ($\delta$ 6.48) to those of the pyrrolidine compound 4 ($\delta$ 6.38).

The cause for the lack of catalytic activity of the 2-substituted pyridines 20–23 in the acetylation of primary (2-phenylethanol), secondary (diol 24) or tertiary 1 alcohols is a result of steric hindrance.[19]

In spite of the fact that quinolinium intermediates are known[18] to be more stable than corresponding pyridinium intermediates, 4-pyrrolidino-quinoline 12 completely lacked catalytic activity in the attempted acetylation of 10 or 1. Since the $\beta$-hydrogen of 12 resonates at quite high ($\delta$ 6.43, vs $\delta$ 7.28 for quinoline itself), the reason for lack of catalytic activity of 12 is probably also steric in origin.[19b]

The observation that the imidazole substituted pyridine 17 did not act as an acylation catalyst is not too surprising since imidazole is not strongly basic and disruption of aromaticity would occur in the formation of intermediate 37. The lack of activity of the imidazole derivative 17 ($\beta$-protons at $\delta$ 7.40) helps rule out the relative contribution of what is more likely the second step of this procedure, namely attack by alcohol on the acylium species, restoring the aromatic character to the pyridine and in this case also to the imidazole ring. Thus if step 37→17 were rate determining, 17 could have been a very effective catalyst.




The oxygen 13, phosphorous 14, and sulfur 15 substituted pyridines do not provide sufficient overlap to stabilize an acyl pyridinium intermediate. The same must be true for the pyridazine 18 ($pK_a$ pyridazine is only 2.3).

Since 4-pyrrolidinopyridine 4 was determined to be

the most effective acylation catalyst of those prepared in this study, several other aspects of the acetylation reaction with this catalyst were examined. Acetylation was found to be faster in less polar solvents. For instance, the acetylation of 1,1-diphenylethanol **10** with two equivalents each of acetic anhydride and triethylamine in ether or methylene chloride (0.1 M in alcohol) was *ca.* 30% complete after 24 h at room temperature. In carbon tetrachloride or hexane under identical conditions, the reaction proceeded to 75% completion. No acetylation of this unreactive alcohol **10** was observed in acetonitrile, nitromethane, or DMF.[20] The best reaction conditions seemed to be a neat reaction (*ca.* 1.6 M in alcohol). This led to 92% acetylation after 24 h.

Table 3. Reaction of acetic anhydride with *t*-butanol in the presence of 0.2 equivalents of **4** in $CDCl_3$–$CCl_4$

| Time | In presence of 1 equiv. $Et_3N$[a] | Without $Et_3N$[a] |
|---|---|---|
| 40 min | 36% | 28% |
| 15 h | 100% | 62% |
| 10 days | | 90% |

[a]% formation of *t*-butyl acetate as followed by NMR.

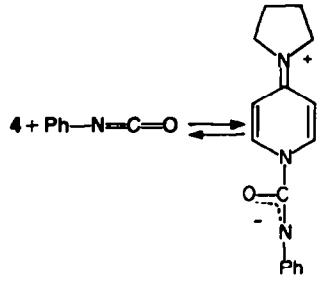
The effect of added base was also examined. With 1,1-diphenylethanol **10**, acetylation proceeded equally rapidly with added excess of triethylamine, diisopropylethylamine, or pyridine. Without any added base, acetylation was slower especially toward the completion of reaction (see Table 3). This is probably due to the catalyst **4** being partially (though not completely) tied up by the acetic acid formed in the reaction.

Acetyl chloride was not as effective as acetic anhydride in the catalyzed acetylation reactions. Only partial acetylation of 1-methyl-cyclohexanol **1** with acetyl chloride alone or in the presence of 4-pyrrolidinopyridine **4** (*ca.* 0.05 molar equivalent) was found. The strongly basic 4-pyrrolidinopyridine **4** probably dehydrohalogenates acetyl chloride to form ketene (which partially dimerizes) and the inactive hydrochloride salt of the catalyst.

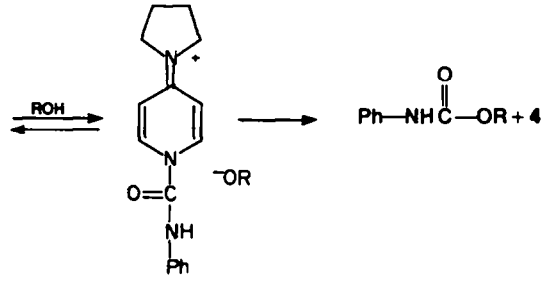
The usefulness of the acylation catalyst is demonstrated by the acetylation of **10**, **25**, **27**–**29**. In particular, 1,1-diphenylethanol **10** easily dehydrates with acylating agents and **29** undergoes rearrangement reactions under various other attempts of acetylation.[21]

The overall results are consistent with the scheme shown below:

The reactivity of the 4-aminopyridine depends on the stabilization of intermediate **34** and is sensitive to steric effects (no reaction occurs in the presence of 2-substituents). The beneficial effect of non-polar solvents is explained by the collapse of the charged intermediate **38** to non-charged products.[20b] While species such as **34** are much more efficient alcohol acylating agents than acid anhydrides, intermediates **39** or **40**, as may be formed in the reaction with isocyanates, are not much more effective toward alcohols than isocyanates.




**39**



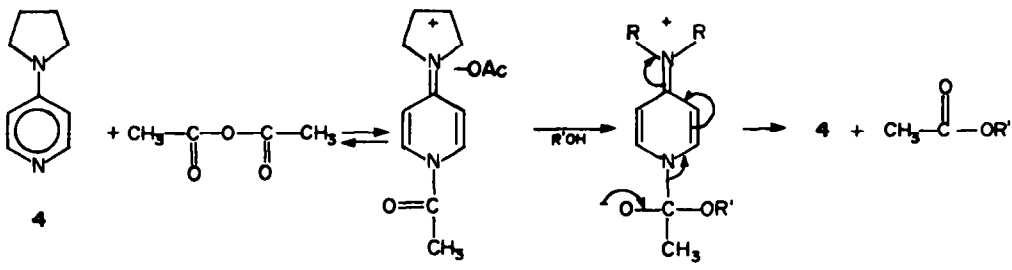

**40**

## EXPERIMENTAL

Mps were determined on a Fisher–Johns block and are uncorrected. IR spectra were obtained of liquid films or carbon tetrachloride solutions as noted on a Perkin–Elmer 457 instrument. NMR spectra were recorded on a Varian A-60A or EM-360 spectrometer with TMS as an internal standard. GC data were recorded on a Varian Aerograph A90-P3 instrument with thermal conductivity detector.

*Preparation of potential catalysts (Methods A and B)*

The 4-dialkylaminopyridines **3**, **4**, **5** and **6** were prepared from 4-pyridylpyridinium chloride hydrochloride[22] by the method of Jerchel and Jakob[12] (Method A) or from 4-chloropyridine hydrochloride[22] (Method B) and have the same physical constants as previously reported.[12,23]




**4** **34** **38**

1,1,3,3 - *Tetramethyl* - 4 - (4 - *pyridyl*)*guanidine* **8**. To a stirred solution of 2.8 g (21.2 mmol) of tetramethylthiourea in 25 ml of anhydrous benzene was added dropwise a solution of 1.94 ml (3.26 g, 21.2 mmol) of $POCl_3$ in 10 ml of anhydrous benzene. The mixture was stirred for 45 min, then 2.0 g (21.2 mmol) of 4-aminopyridine added at once. The orange oil was washed with 20 ml of benzene, then 30 ml of ethanol was added to the orange oil and the mixture was refluxed for 15 min. The ethanol was removed *in vacuo*, and 40 ml of methylene chloride added to the residue. This mixture was stirred and a 20% NaOH solution was added dropwise until all material was in solution. The organic phase was separated and the aqueous phase extracted again with methylene chloride. The organic extracts were dried over $K_2CO_3$ and the solvent removed *in vacuo* to afford 4.1 g of a yellow oil. Distillation afforded 2.73 g (67%) of **8**, b.p. 96–100° (0.07 mm); NMR ($CDCl_3$) $\delta$ 8.32 (m, 2H), 6.55 (m, 2H) and 2.77 (s, 12H); MS *m/e* (%) M+ 192 (40.0), 177 (13.3), 148 (100), 134 (36.6), 132 (36.6). *Anal.* Calcd for $C_{10}H_{16}N_4$: C, 62.50; H, 8.33. Found: C, 62.15; H, 8.52%.

1,1 - *Dimethyl* - 3 - (4 - *pyridyl*)*formamidine* **9**. To a stirred solution of 3.28 ml (3.1 g, 42.4 mmol) of DMF in 25 ml of anhydrous benzene was added dropwise a solution of 1.94 ml (3.25 g, 21.2 mmol) of $POCl_3$ in 10 ml of anhydrous benzene. The mixture was stirred for 45 min, then 2.0 g (21.2 mmol) of 4-aminopyridine added at once. The mixture was refluxed for 2 h, and worked up as described for **8** to produce 2.0 g of a yellow oil. Distillation afforded 1.7 g (54%) of **9**, b.p. 80–85° (0.07 mm) (lit.[24] 84° (0.05 mm)); NMR ($CDCl_3$) $\delta$ 8.42 (m, 2H), 7.62 (s, 1H), 6.87 (m, 2H) and 3.02 (s, 6H); MS *m/e* (%) M+ 149 (100), 148 (60.0).

2,5 - *Dimethyl* - N - (4 - *pyridyl*) - 3 - *pyrroline* **7** was prepared by Method B. Bulb to bulb distillation (oven 150°, 0.1 mm) afforded a 21% yield of **7**, NMR ($CDCl_3$) $\delta$ 8.22 (m, 2H), 6.48 (m, 2H), 5.87 (s, 2H), 4.52 (q, J = 6 Hz, 2H) and 1.37 (d, J = 6 Hz, 6H).

4-*Pyrrolidinoquinoline* **12** was prepared from 4-chloroquinoline hydrochloride[22] and pyrrolidine by a reaction analogous to that of Method B. Bulb to bulb distillation (oven 140°, 0.02 mm) of the crude product from this reaction afforded an 85% yield of **12**,[25] NMR ($CDCl_3$) $\delta$ 8.53 (d, J = 6 Hz, 1H), 8.12 (m, 2H), 7.45 (m, 2H), 6.43 (d, J = 6 Hz, 1H), 3.63 (m, 4H) and 2.0 (m, 4H).

N-(4-*Pyridyl*)*imidazole* **17** was prepared by Method A. Recrystallization from hexane-acetone afforded a 21% yield of **17**, m.p. 113.5–114.5° (lit.[26] 115–116°); NMR ($CDCl_3$) $\delta$ 8.77 (m, 2H), 8.08 (s, 1H) and 7.40 (m, 4H).

4-*Phenoxypyridine* **13**. A mixture of 10.0 g (43.7 mmol) of 4-pyridyl-pyridinium chloride hydrochloride and 4.1 g (43.7 mmol) of phenol was heated for 1 h at 140°. Work-up as in Method A afforded 6.0 g (80%) of **13**, NMR ($CDCl_3$) $\delta$ 8.35 (m, 2H), 7.2 (m, 5H) and 6.70 (2H), m.p. 43–44° (lit.[12] 44–45°).

*Diphenyl*-(4-*pyridyl*)*phosphine* **14**. A mixture of 0.31 g (45 mmol) of clean lithium wire and 3.93 g (15 mmol) of triphenylphosphine was stirred under $N_2$ in 25 ml of anhydrous THF for 4 h.[27] The deep red solution was then added dropwise to a stirred mixture of 2.0 g (13.3 mmol) of 4-chloro-pyridine hydrochloride in 75 ml of refluxing THF under $N_2$. When addition was complete, refluxing was continued for 12 h. The solvent was then removed *in vacuo* and 40 ml of methylene chloride added to the residue. The methylene chloride solution was washed with water and brine, dried over $K_2CO_3$ and the solvent removed *in vacuo*. Bulb to bulb distillation (oven 210°, 0.02 mm) followed by slow recrystallization from aqueous ethanol afforded 0.75 g (21%) of **14**, m.p. 66–66.5°; NMR ($CDCl_3$) $\delta$ 8.48 (m, 2H), 7.45 and 7.38 (2s, 10H) and 7.1 (m, 2H); MS *m/e* (%) M+ 263 (100), 108 (56.6).

4-*Benzylthiopyridine* **15**. A mixture of 2.0 g (13.3 mmol) of 4-chloropyridine hydrochloride and 1.66 g (13.3 mmol) of benzyl mercaptan was heated at 145° for 1 h. After cooling, the residue was recrystallized from ether to afford 2.8 g (90%) of the hydrochloride salt of **15**, m.p. 193–195° (lit.[28] 196–198°). Neutralization with $NaHCO_3$ and recrystallization from hexane afforded 2.01 g (75%) of **15**, m.p. 59–61° (lit.[28] 61–62°); NMR ($CDCl_3$) $\delta$ 8.35 (m, 2H), 7.33 (s, 5H), 7.05 (m, 2H) and 4.08 (s, 2H).

3,6-*Dichloro*-4-*pyrrolidinopyridazine*. To a solution of 0.47 ml (0.40 g, 5.6 mmol) of pyrrolidine in 10 ml of methylene chloride was added dropwise a stirred mixture of 1.0 g (5.5 mmol) of 3,5,6-trichloropyridazine[29] and 0.25 g of $Na_2CO_3$ in 15 ml of methylene chloride. When addition of the solution was complete, the mixture was stirred for 15 h, then filtered and the solvent removed *in vacuo*. Recrystallization of the residue from acetone afforded 0.64 g of 3,6-dichloro-4-pyrrolidinopyridazine m.p. 153–154.5°; NMR ($CDCl_3$) $\delta$ 6.48 (s, 1H), 3.67 (m, 4H) and 2.07 (m, 4H); MS *m/e* (%) M+ 2 219 (62.0), 217 (76.2), 216 (100).

4-*Pyrrolidinopyridazine* **18**. A mixture of 4.0 g (18.4 mmol) of 3,6-dichloro-4-pyrrolidinopyridazine and 2.0 g of 10% Pd/C catalyst in 250 ml of methanol and 5 ml of concentrated $NH_4OH$ solution was hydrogenated at 5 psig for 3 h on a Parr apparatus. The catalyst was then filtered off and the solvent removed *in vacuo*. The residue was taken up in 50 ml of methylene chloride and the solution washed with brine, dried over $K_2CO_3$. The solvent was removed *in vacuo* and the residue recrystallized from carbon tetrachloride-hexane to afford 0.71 g (26%) of **18**, m.p. 93–94°; NMR ($CDCl_3$) $\delta$ 8.70 (m, 2H), 6.43 (m, 1H), 3.38 (m, 4H) and 2.10 (m, 4H); MS *m/e* (%) M+ 149 (100), 148 (53.1), 120 (21.8).

3-*Pyrrolidinopyridine* **19**.[30] To a stirred solution of 4.8 ml (7.9 g, 50 mmol) of 3-bromopyridine[22] and 10.0 ml (17.8 g, 0.25 mol) of pyrrolidine in 275 ml of anhydrous ether under $N_2$ was added dropwise 100 ml of 1.1 M phenyl lithium solution. When addition of the solution was complete, the mixture was refluxed with stirring for 5 h, then stirred at room temp. for 15 h. After the cautious addition of 50 ml of water to the reaction mixture, the layers were separated and the organic phase was washed with water, dried over $K_2CO_3$ and the solvent removed *in vacuo*. Distillation of the residue afforded 3.2 g (43%) of a mixture of **4** and **19**, b.p. 80–100° (0.5 mm). The isomers were separated by column chromatography (silica gel, ether–methanol eluent) to afford 1.2 g (16%) of **19**, NMR ($CCl_4$) $\delta$ 7.80 (m, 2H), 6.80 (m, 2H), 3.27 (m, 4H) and 2.0 (m, 4H).

2-*Pyrrolidinopyridine* **20**. A mixture of 10.0 g (88 mmol) of 2-chloropyridine,[22] 18.4 ml (15.6 g, 0.22 mol) of pyrrolidine and 10 ml of water was heated at reflux for 3 h. The mixture was then cooled and extracted with ether. The ethereal solution was washed with water and a saturated $NaHCO_3$ solution, dried over $K_2CO_3$ and the solvent removed *in vacuo*. Distillation of the residue afforded 6.4 g (50%) of **20**, b.p. 84–86° (1 mm), (lit.[21] 252°); NMR ($CCCl_4$) $\delta$ 8.15 (m, 1H), 7.30 (m, 1H), 6.30 (m, 2H), 3.32 (m, 4H) and 1.80 (m, 4H).

1,1,3,3 - *Tetramethyl* - 4 - (2 - *pyridyl*)*guanidine* **21** was prepared from 2-aminopyridine[22] and tetramethylurea by a reaction analogous to that described for **8**. Distillation afforded a 43% yield of **21**, b.p. 95–100° (0.0 mm) (lit.[24] 67° (0.02 mm); NMR ($CCl_4$) $\delta$ 8.53 (s, 1H), 8.15 (m, 1H), 7.45 (m, 1H), 6.82 (m, 2H) and 3.0 (s, 6H).

*Acylation of alcohols*

*Acetylation of* 1-*methylcyclohexanol* **1**. To a stirred mixture of 1.14 g (10 mmol) and 1-methylcyclohexanol **1**,[32] 2.8 ml (2.0 g, 20 mmol) of triethylamine and 1.9 ml (2.0 g, 20 mmol) of acetic anhydride was added 1.0 mmol of the acylation catalyst. The reaction was monitored by GC (a 10 ft × 3/8 in. 15% DC-550 column at 150° was used). The retention times for the alcohol **1** and the acetate **2** were 3.0 and 5.5 min, respectively. With 4-pyrrolidinopyridine **4** as the catalyst, the reaction was complete in *ca.* 16 h. The reaction mixture was taken up in 50 ml of hexane and the solution washed with a 5% HCl solution, a saturated $NaHCO_3$ solution and brine, and dried over $K_2CO_3$. The solvent was removed *in vacuo* and the residue purified by bulb to bulb distillation (oven 70°, 0.5 mm) to afford 1.45 g (93%) of **2**,[32] IR (neat) 1725 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.0 (s, 3H) and 1.43 (broad, 13H).

*Reaction of* **1** *with acetyl chloride*. A solution of 2.8 ml (2.0 g, 20 mmol) of triethylamine in 5 ml of ether was added dropwise to a stirred solution of 1.14 g (10 mmol) of 1-methylcyclohexanol **1**, 1.43 ml (1.57 g, 20 mmol) of acetyl chloride and 1.0 mmol of **4**. The reaction was followed by GC as described above. After 2 h, the ratio of alcohol **1** to acetate **2** was *ca.* 1:3. This ratio was not appreciably different after 24 h. When this reaction was repeated without the addition to 4-pyrrolidinopyridine **4**, the results were the same. When triethylamine was omitted from these reactions, 10% acetylation of **1** was observed.

*Acetylation of* 1,1-*diphenylethanol* **10**. To a mixture of 0.20 g (1.0 mmol) of 1,1-diphenylethanol **10**,[33] 0.28 ml (0.20 g, 2.0 mmol) of triethylamine, and 0.19 ml (0.02 g, 2.0 mmol) of acetic anhydride was added 0.1 mmol of the acylation catalyst. To compare the effects of the different catalysts, the reaction was quenched after 4 h by the addition of a few drops of methanol. The reaction mixture was then taken up in 35 ml of hexane and the solution washed with a 5% HCl solution, a saturated $NaHCO_3$ solution and brine, and dried over $K_2CO_3$. The solvent was removed *in vacuo* to afford a mixture of the alcohol and acetate. The ratio of alcohol to acetate was determined by integration of the methyl peaks in the NMR spectrum of the mixture. With 4-pyrrolidinopyridine **4** as the catalyst, acetylation of 1,1-diphenylethanol was complete after *ca.* 40 h to afford 0.22 g (92%) of the acetate, IR ($CCl_4$) 1745 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.2 (s, 5H), 2.02 (s, 3H) and 1.97 (s, 3H). Attempted distillation or chromatography of this acetate led to partial decomposition to diphenylethylene.

2-*Acetyl*-1-*methylcyclohexanol* **25**. To a mixture of 0.50 g (3.85 mmol) of diol **24**,[34] 0.37 ml (0.39 g, 3.9 mmol) of acetic anhydride, and 0.54 ml (0.39 g, 3.9 mmol) of triethylamine in 2 ml of methylene chloride was added 15 mg (0.1 mmol) of 4-pyrrolidinopyridine **4**. The mixture was stirred for 2 min, poured into 35 ml of hexane and washed with a 5% HCl solution, a saturated $NaHCO_3$ solution and brine. The solution was dried over $K_2CO_3$ and the solvent removed *in vacuo* to afford 0.57 g (86%) of **25**, IR (neat) 3550–3250 and 1715 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 4.8 (m, 1H), 2.3–1.3 (9H), 2.08 (s, 3H) and 1.25 (s, 3H).

The reaction of 1.5 mmol of diol **24** and 7.5 mmol each of acetic anhydride and triethylamine required 2 h to completion to afford **25** in 73% yield. Acetate **25** did not react further under these conditions.

2 - *Acetyl* - 1 - *methylcyclohexyl acetate* **26**. To a mixture of 0.20 g (1.54 mmol) of diol **24**, 0.70 ml (0.76 g, 7.5 mmol) of acetic anhydride and 1.05 ml (0.76 g, 7.5 mmol) of triethylamine was added 15 mg (0.1 mmol) of 4-pyrrolidinopyridine **4**. Upon addition of **4**, the reaction mixture became warm. Immediate analysis by GC (a 15 ft × 3/8 in. 10% QF-1 column at 200° was used) indicated that diol **24** (retention time 3.3 min) had been completely converted to **25** (retention time 5.3 min). After 24 h, the reaction was worked up as before to afford 0.32 g of an oil which was purified by bulb to bulb distillation (oven 100°, 0.5 mm) to afford 0.31 g (94%) of **26**,[35] IR (neat) 1730 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 5.1 (m, 1H), 2.1–1.2 (8H), 2.08 (s, 3H), 2.0 (s, 3H) and 1.50 (s, 3H).

2 - *Acetyl* - 2 - *methylcyclohexanone* **30**. To a mixture of 5.0 g (39.0 mmol) of hydroxy ketone **27**,[36] 7.35 ml (7.95 g, 78.0 mmol) of acetic anhydride and 10.8 ml (7.87 g, 78.0 mmol) of triethylamine was added 60 mg (0.40 mmol) of 4-pyrrolidinopyridine **4**. The mixture was stirred at room temperature for 45 min, then 4.0 ml of methanol was added slowly. The reaction mixture was taken up in 100 ml of hexane and worked up as described above. Distillation of the residue afforded 5.80 g (87%) of **30**, b.p. 81–83° (2 mm) (lit.[37] 105–107° (6 mm)), IR (neat) 1730 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 2.8–1.2 (8H), 2.02 (s, 3H) and 1.35 (s, 3H).

2-*Acetyl*-2-*methylbutan*-3-*one* **31**. To a mixture of 1.5 g (14.9 mmol) of 2-hydroxy-2-methylbutan-3-one **28**,[22] 2.83 ml (3.06 g, 30.0 mmol) of acetic anhydride and 4.18 ml (3.04 g, 30.0 mmol) of triethylamine was added 30 mg (0.2 mmol) of 4-pyrrolidinopyridine **4**. The mixture was stirred at room temperature for 30 min, then worked up as described above. Bulb to bulb distillation (oven 70°, 0.5 mm) of the residue afforded 1.96 g (92%) of **31**,[38] IR (neat) 1725 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 2.05 (s, 6H) and 1.43 (s, 6H).

*Acetylation of alcohol* **29**. A mixture of 100 mg (0.40 mmol) of alcohol **29**,[21] 0.14 ml (1.5 mmol) of acetic anhydride and 0.21 ml (1.5 mmol) of triethylamine was allowed to stand at room temperature for 24 h. Work up as described above afforded 115 mg of a yellow oil, determined by NMR to contain *ca.* 80% of acetate **32**, a trace of unreacted alcohol **29** and unidentified material. Attempted crystallization or chromatography of **32** led to elimination of acetic acid to the olefin. Acetate **32** had IR (neat) 1730 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 7.1 (m, 8H), 4.3 (broad d, J = 5 Hz, 1H), 2.3 (m, 2H), 2.0 (s, 3H) and 1.8 (s, 6H).

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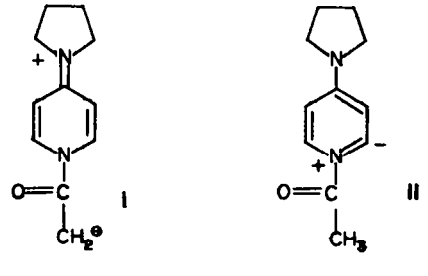

form zwitter ion I was discounted since no D-incorporation was observed into the methyl group of *t*-butyl acetate when *t*-BuOD was used in the catalyzed acetylation. Similarly, intermediate II can be ruled out by the absence of D-incorporation into 4.

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