There was no color change, but a metallic luster appeared. The reaction mixture was allowed to stand at room temperature for 73 hr. At the end of this time the metallic luster which was present at the beginning of the reaction had disappeared but the color was still deep blue. The reaction mixture was decomposed by adding 3*N* hydrochloric acid dropwise to the reaction mixture, allowing the slight evolution of gas to subside after each addition. The mixture was then filtered, ether was added, and the layers were separated. The residue from the filtration was a small amount of an orange-red solid, insoluble in acid, base, water, acetone, and ethanol. The aqueous layer was made basic, filtered, and extracted with toluene, and the toluene extracts were dried and allowed to evaporate. The crystals which were left were recrystallized from ethanol, yielding 1.3 g. (10%) of 2-pyridyldiphenylcarbinol, m.p. 102–103°, lit. m.p. 104–105°.[14] Hydrochloride, m.p. 178–179°, mixed m.p. with an authentic sample, 177–179°.

*Procedure G. Reaction of hypophosphorous acid with pyridine and benzaldehyde.* Three reactions were set up involving $H_3PO_2$, pyridine, and benzaldehyde, in acidic, basic, and neutral (pyridine) solutions. The mixtures contained:

| | | |
|---|---|---|
| (*a*) | Pyridine, | 10 g. (0.13 mole) |
| | $C_6H_5CHO$, | 14 g. (0.13 mole) |
| | $H_3PO_2$, | 32 g. (0.5 mole) |
| (*b*) | Pyridine, | 16 g. (0.2 mole) |
| | NaOH, | 8 g. (0.2 mole) |
| | $C_6H_5CHO$, | 10.6 g. (0.1 mole) |
| | Water | 20 cc. |
| | $H_3PO_2$, | 6.6 g. (0.1 mole) |
| (*c*) | Pyridine, | 32 g. (0.4 mole) |
| | $C_6H_5CHO$, | 10.6 g. (0.1 mole) |
| | $H_3PO_2$, | 6.6 g. (0.1 mole) |

Each mixture required the addition of a little ethanol to obtain a homogeneous solution. All were refluxed for 11 hr. except for (*b*) which was allowed to stand at room temperature for 24 hr. The (*a*) was extracted with ether, while the (*b*) and (*c*) were first acidified with HCl and then ether extracted. The ether extracts were extracted with sodium bisulfite and gave, on evaporation, non-basic materials with a very wide melting range. Oxidation of these products with nitric acid gave benzoic acid as the only insoluble product.

The (*a*), (*b*), and (*c*) were basified with sodium hydroxide. Extraction of these basic solutions with ether followed by evaporation of the ether gave no basic material other than pyridine.

*Determination of the structure of the dimer of 2-isopropenylpyridine with the aid of infrared analysis.* The structure II was assigned to the dimer obtained from the attempted coreduction of 2-isopropenylpyridine and acetophenone on the basis of the following characteristic absorption peaks: (*a*) 12.73 μ and 13.40 μ-strong bands corresponding to monosubstitution at the 2-position of the pyridine nucleus,[31] and (*b*) a weak band in the region 9.52–9.62 μ corresponding to the linkage $CH_3\text{—}\overset{|}{\underset{|}{C}}H$. Bands corresponding to disubstitution on the pyridine nucleus were absent.[32] Bands corresponding to an olefinic linkage were also absent. Dimeric forms containing gem-dimethyl groups were eliminated by the absence of an absorption peak in the range 8.35–8.40 μ—a characteristic peak for this grouping.[33] Finally, any dimeric form containing a cyclobutane ring was eliminated by the absence of absorption bands in the range 10.9–11.52μ—a region which has been reported to exhibit characteristic absorption peaks for mono-alkyl-cyclobutanes (10.9–11.0 μ)[34] and more highly substituted cyclobutanes (11.28–11.52 μ).[35] Of the possible simple dimers of 2-isopropenylpyridine only II meets all of these requirements of spectral analysis. The dimers of 2-stilbazole and 2-vinylpyridine were assumed by analogy to possess structures similar to II.

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(31) W. A. Murphey, Ph. D. Thesis, Purdue University, August, 1950, has shown that 2-isopropylpyridine exhibits characteristic absorption bands at 12.73 μ and 13.38 μ originating in out-of-plane vibrations of the unsubstituted hydrogen atoms of the ring.

(32) H. E. Podall, Ph. D. Thesis, Purdue University, August, 1955.

(33) L. J. Bellamy, *The Infra-Red Spectra of Complex Molecules*, Methuen and Co., Ltd., London, 1956, p. 235.

(34) J. M. Derfer, E. E. Pickett, and C. E. Boord, *J. Am. Chem. Soc.*, 71, 2482 (1949).

(35) E. B. Reid and M. Sack, *J. Am. Chem. Soc.*, **73**, 1985 (1951).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

# Heterogeneous Bimolecular Reduction. II. Direct Acylation of Pyridine and Its Homologs and Analogs[*,1]

G. BRYANT BACHMAN AND R. M. SCHISLA[2]

*Received May 24, 1957*

Heterogeneous bimolecular reduction of pyridine and acid derivatives with metals has been found to yield *C*-acylated pyridines. The general applicability of this reaction has been studied and a series of new heterocyclic ketones has been prepared. Intermediate steps in the synthesis have been postulated.

Pyridine, quinoline, and related heterocyclic bases have never been directly and substitutively acylated.[3] Apparently the ring member =N— is sufficiently electrophylic in nature to deactivate the remainder of the ring to attack by cations. Hence the Friedel-Crafts and related reactions fail.

It occurred to us that acylation of pyridine might be achieved satisfactorily if acyl anions could be

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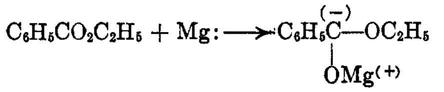
[*] This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) From the Ph.D. thesis of R. M. Schisla, June 1957, Purdue University.

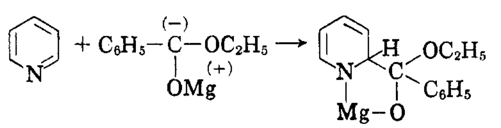
(2) Indiana Elks Fellow, 1954–55; Allied Chemical & Dye Corp. Fellow, 1955–56. Present address, Monsanto Chemical Co., Dayton, Ohio.

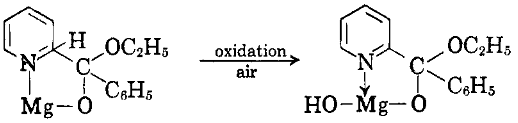
(3) R. C. Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1950, Vol. I, p. 403–410.

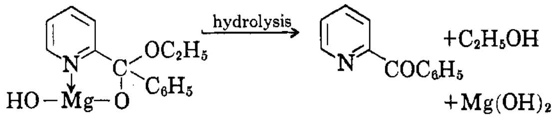
created in the presence of this heterocyclic base. Anions such as $NH_2^-$, $OH,^-$ and $(alkyl)^-$ have been shown to attack pyridine rather easily and to introduce these groups into the ring in place of hydrogen at the 2- or 4-position. Based on the hypotheses developed in the previous paper in this series,[4] a reasonable approach to the formation of acyl anions would be to treat acid derivatives with metals like magnesium and aluminum. In contrast to metals like zinc and sodium, these metals appear to be able to reduce carbonyl groups by a two-electron transfer process to form carbanions. The expected series of reactions between pyridine, ethyl benzoate, and magnesium would therefore be:

(1) 

$$C_6H_5CO_2C_2H_5 + Mg: \longrightarrow C_6H_5\overset{(-)}{C}(OMg^{(+)})—OC_2H_5$$

(2) 

(3)* 

(4) 

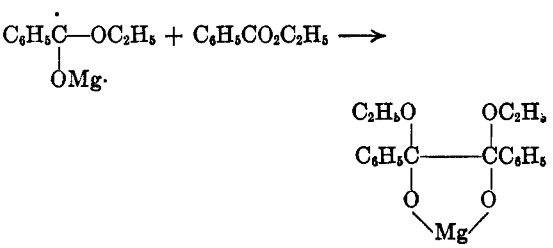
The success of this synthesis was recently announced in a Communication To The Editor of this journal.[5] The present paper describes the application of this method to pyridine homologs and analogs and to other esters. The overall synthesis is another example of heterogeneous bimolecular reduction.

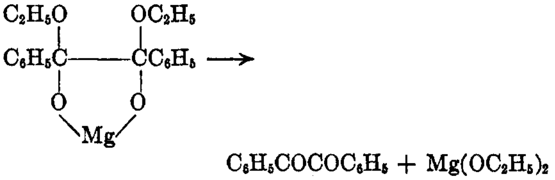
*The nature of the reaction.* A small amount of the acid derivative and pyridine mixture is heated with amalgamated aluminum until reaction starts which is made evident by the appearance of a brown coloration. The remainder of the pyridine and acid derivative is added slowly, and refluxing is continued until the metal is consumed or until no further change is noted.

The product may be worked up as described in the preceding paper or preferably by isolating the metallic complex in solid form before hydrolyzing by pouring the reaction mixture into four to five volumes of petroleum ether. This method is more convenient, more rapid, and gives a cleaner product than direct hydrolysis, although the yields are slightly (3–5%) lower. This procedure may be applied equally successfully to the preparation of pyridyl alcohols.

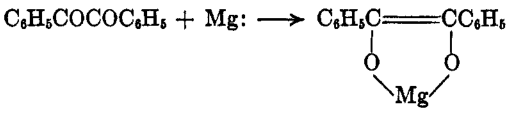
The results of a number of such reactions are summarized in Table I.

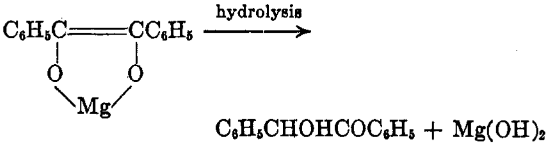
*The effects of various metals.* In the order of decreasing yields of desired mixed ketone the metals may be arranged in the series: Al > Mg > Be > other metals. This corresponds exactly to the series observed in the coreduction of pyridine and ketones and suggests that acylation of pyridine is also a two-electron transfer process. A single-electron transfer process probably occurs simultaneously, and leads, by homogeneous bimolecular reduction of the ester, to benzil and benzoin.

 (5)

 (6)

$$C_6H_5COCOC_6H_5 + Mg(OC_2H_5)_2$$

 (7)

 (8)

$$C_6H_5CHOHCOC_6H_5 + Mg(OH)_2$$

The yields of the mixture of benzil and benzoin are generally inversely proportional to the yields of benzoyl pyridine, *i.e.*, they increase as the metal becomes increasingly a single-electron transfer agent. Metals with lower reduction potentials, like zinc, do not react.

*The effects of substituents on the pyridine ring.* Only a few experiments were performed with pyridine homologs and analogs. It was found that γ-picoline gave good yields of 2-benzoyl-4-methylpyridine and that quinoline gave good yields of 2-benzoylquinoline, but none of the 4-isomer. In general it would be anticipated that pyridines substituted in the 2- and 2,6-positions would give poor yields because of steric hindrance which is also an interfering factor in coreductions of such pyridines with ketones. On the other hand pyridines substituted in the 3- or 4-positions would not be subject to such steric hindrance and yields comparable to those obtained with pyridine should be obtained.

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* This process probably involves more than one step.

(4) G. B. Bachman, M. Hamer, E. Dunning, and R. M. Schisla, *J. Org. Chem.*, 22, 1296 (1957).

(5) G. B. Bachman and R. M. Schisla, *J. Org. Chem.*, 22, 858 (1957).

TABLE I

Coreduction of Heterocyclic Compounds and Acid Derivatives

| Expt. No. | Heterocyclic Compound | Acid Derivative | Reducing Agent | Procedure Used | Products, % Yield[a] | |
|---|---|---|---|---|---|---|
| | | | | | Pyridyl ketone | Others |
| 1 | Pyridine | Acetophenone | Al | B | 2-, 31[b]<br>4-, 3.8[b] | Pinacol, 1 |
| 2 | Pyridine | Ethyl benzoate | Al | A | 2-, 23.9<br>4-, 6.4 | 2.8[x]<br>2.8[x] |
| 3 | Pyridine | Ethyl benzoate | Al | B | 2-, 32.5<br>4-, 7.1 | 12.7[x] |
| 4 | Pyridine | Ethyl benzoate | Mg | A | 2-, 10 | 19.1[x] |
| 5 | Pyridine | Ethyl benzoate | Be | A | 2-, 8.2 | 46.1[x] |
| 6 | Pyridine | Ethyl benzoate | Zn | A | 0 | 0 |
| 7 | Pyridine | Ethyl *p*-chlorobenzoate | Al | A | 2-, 26.4[d] | 6.9[e] |
| 8 | Pyridine | Ethyl *p*-nitrobenzoate | Al | A | 0 | 4,4′-bis(carbethoxy)azobenzene, 2.1[f] |
| 9 | Pyridine | Ethyl cinnamate | Al | A | 2-, 8.3[g] | tars |
| 10 | Pyridine | Ethyl phthalate | Al | A | 0 | tars |
| 11 | Pyridine | Ethyl picolinate | Al | A | 2-, 7.3[h] | tars |
| 12 | Pyridine | Ethyl formate | Al | A | 0 | [c] |
| 13 | Pyridine | Ethyl formate | Mg | A | 0 | [c] |
| 14 | Pyridine | Ethyl carbonate | Al | A[aa] | 0 | [c] |
| 15 | Pyridine | Ethyl oxalate | Al | A | 0 | Tars |
| 16 | Pyridine | Ethyl oxalate | Al | B | 0 | Tars |
| 17 | Pyridine | Ethyl malonate | Al | A[aa] | 0 | [c] |
| 18 | Pyridine | Ethyl acetoacetate | Al | A[aa] | 0 | Tars |
| 19 | Pyridine | Ethyl acetoacetate | Al | B | 0 | Tars |
| 20 | Pyridine | Ethyl acetate | Al | A | 0 | [c] |
| 21 | Pyridine | Secondary-butyl acetate | Al | A | 2- +4-, 5.5[i,j] | [c] |
| 22 | Pyridine | *n*-Amyl acetate | Al | A[aa] | 2- + 4-, 5.8[i,k] | [c] |
| 23 | Pyridine | 2-Ethyl-hexyl acetate | Al | A[aa] | 2- +4-, 13.0[i,l] | [c] |
| 24 | Pyridine | Ethyl propionate | Al | A[aa] | 2- +4-, 8.3[i,m,n] | [c] |
| 25 | Pyridine | Methyl phenylacetate | Al | A[aa] | 2-, 9.2[o] | tars |
| 26 | Pyridine | *N*,*N*-Dimethylformamide | Al | A[aa] | 0 | [c] |
| 27 | Pyridine | *N*,*N*-Dibutylacetamide | Al | A[aa] | 0 | [c] |
| 28 | Pyridine | *N*,*N*-Dimethylbenzamide | Al | A | 2-, 36<br>4-, 6 | 17.4[x] |
| 29 | Pyridine | *N*,*N*-Dimethylbenzamide | Al | B | 2-, 32<br>4-, 5.9 | 6.4[x] |
| 30 | Pyridine | *N*,*N*-Dimethylbenzamide | Mg | A | 2-, 44.5<br>4-, 4.5 | 22[x] |
| 31 | Pyridine | *N*,*N*-Dimethylbenzamide | Be | A | 2-, 4.2 | 11.7[x] |
| 32 | Pyridine | *N*,*N*-Dimethylbenzamide | Zn | A | 0 | [c] |
| 33 | Pyridine | *N*,*N*-Dimethylbenzamide | Na | D | 2-, 3.7[p] | 11.7[x]<br>2,2′-dipyridyl, 13<br>4,4′-dipyridyl, 50.3 |
| 34 | Pyridine | Acetonitrile | Al | A | 0 | [c] |
| 35 | Pyridine | Benzonitrile | Al | A | 2-, 3.4[q] | [c] |
| 36 | Pyridine | Acetic anhydride | Al | C | 0 | Acetamide, 4-ethylpyridine[u] |
| 37 | Pyridine | Acetic anhydride | Mg | C | 0 | Acetamide, 4-ethylpyridine[u]<br>Acetoin[v]<br>Biacetyl[v,w] |
| 38 | Pyridine | Butyric anhydride | Al | C | 0 | Tars |
| 39 | Pyridine | Phthalic anhydride | Al | C | 0 | Tars |
| 40 | 4-Picoline | Acetophenone | Al | B | 2-, 36[b,r] | Pinacol, 14 |
| 41 | 4-Picoline | Ethyl benzoate | Al | A | 2-, 32.9[s] | |
| 42 | Quinoline | Ethyl benzoate | Al | A | 2-, 29[t] | 12.4[x] |
| 43 | Quinoline | Ethyl benzoate | Al | B | 2-, 19.7[y] | 10.2[x] |
| 44 | Quinoline | *N*,*N*-dimethylbenzamide | Al | B | 2-, 16.1[z] | 13.2[x] |

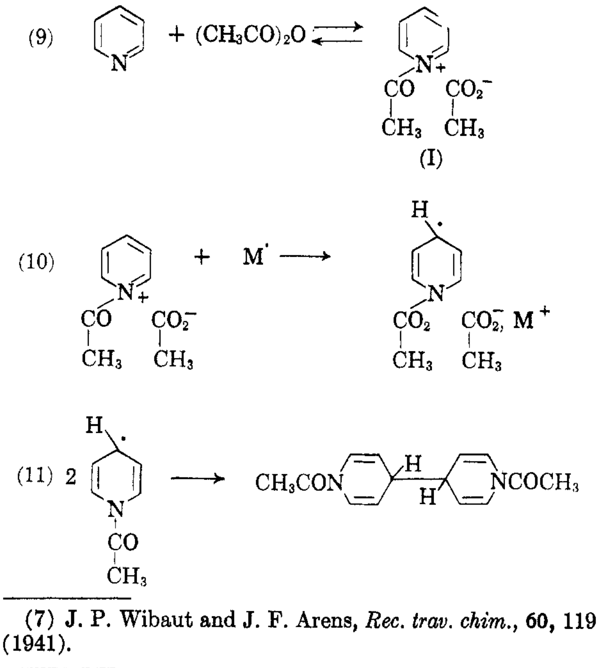
For footnotes, see opposite page →

*The effects of different acid derivatives.* Acid esters, *N*,*N*-dialkylamides, and nitriles, in the order listed, gave decreasing yields of acylated pyridines. Numerous factors, however, influence the yields in individual cases, so that variations within a class may be greater than variations between classes. Thus low-boiling acid derivatives may fail to produce good yields because of the difficulty in keeping them in the reaction mixture at the temperatures required (100° or more). Another important factor is the ease of formation or stability of the assumed intermediate carbanion which is strongly influenced by resonance interactions with the groups attached to it. Thus aliphatic esters are less satisfactory than aromatic esters probably because the carbanions produced from the former lack the resonance stabilization provided by the aryl nucleus in those from the latter.* Even esters of phenylacetic acid lack this stabilization and give yields of ketones comparable to those from unsubstituted aliphatic acid esters. Ring substituents in aromatic acid esters have varying effects; a *p*-chlorobenzoate reacted satisfactorily, a *p*-nitrobenzoate[6] and an *o*-carbethoxybenzoate did not. Ethyl picolinate gave low yields of 2,2′-dipyridyl ketone and much tar. Substituents in aliphatic esters with a single exception had a deleterious effect on the reaction. Ethyl cinnamate gave an 8% yield of the expected ketone, but ethyl carbonate, oxalate, malonate, and acetoacetate gave only tars from which the desired products could not be isolated.

Although nitriles are not carbonyl compounds they do resemble them and might be expected to acylate pyridine under reductive conditions. Benzonitrile, but not acetonitrile, gave low yields of the expected ketone.

*The coreduction of acid anhydrides with pyridines.* No ketones were obtained in attempted heterogeneous bimolecular reductions of acetic, butyric, or phthalic anhydrides and pyridine with metals. A careful study of the reaction with acetic anhydride showed that the products were instead 2,3-butanedione (biacetyl), 3-hydroxy-2-butanone (acetoin), 4-ethylpyridine, and acetamide. The first two of these products probably result from a homogeneous bimolecular reduction of the acetic anhydride. The latter two products indicate that the reaction has taken an entirely different course than it does with esters, amides, and nitriles. A further indication of this change in mechanism is the fact that similar products are obtained with zinc[7] as the reducing agent–a metal which fails to react with mixtures of pyridine and the other acid derivatives studied. Furthermore, the reaction with acid anhydrides is much more vigorous than with esters, amides, and nitriles and yields only a 4-substituted pyridine and none of the 2-isomer.

We believe the above facts can be rationalized by assuming a preliminary rapid acylation of the pyridine heterocyclic base followed by reduction proceeding by a single-electron transfer step, a pinacol-like dimerization, and subsequent changes as shown below.



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* A substituent group may, through its particular resonance effect, influence yields in opposite directions for esters and ketones, since in the one case a needed increase in reactivity of the anion may result while in the other case a needed increase in stability of the anion may result, *c.f.* the first paper in this series. Further work will be required to unravel these effects.

(6) Ethyl *p*-nitrobenzoate gave no pyridyl ketone but did give a small yield of 4,4′-bis(carbethoxy)azobenzene. This compound was previously prepared by treating the diazonium salt of ethyl *p*-aminobenzoate with an ammoniacal solution of cupric oxide, *cf.* R. Vorlander and F. Meyer, *Ann.*, **320**, 136 (1902).

(7) J. P. Wibaut and J. F. Arens, *Rec. trav. chim.*, **60**, 119 (1941).

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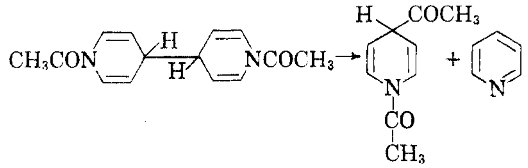
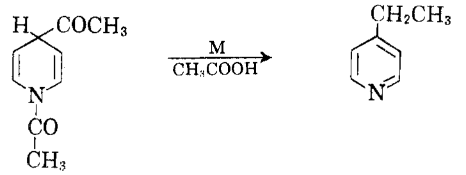
[a] Yield based on metal, see reference 4. [b] The pyridyl alcohol was isolated here instead of the pyridyl ketone.[9, 10] [c] Starting material recovered. [d] M.p. 79°, *Anal.* Calcd. for $C_{12}H_8ClNO$: Cl, 16.28; N, 6.43. Found: Cl, 16.00; N, 6.67. [e] 4,4′-Dichlorobenzil, m.p. 196–197°, lit. m.p. 200°.[11] [f] M.p. 144–145°, *Anal.* Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.55; N, 8.58. Found: C, 66.32; H, 5.61; N, 8.77. [g] 2-Cinammoylpyridine, m.p. 74–75°, lit. m.p. 74–75°.[12] [h] 2,2′-Dipyridyl ketone, m.p. 54–55°, lit. m.p. 51–53°.[13] [i] Mixture of 2- and 4-acetylpyridines (see Experimental). [j] $n_D^{25}$ 1.5182. [k] $n_D^{25}$ 1.5174. [l] $n_D^{25}$ 1.5179. [m] Mixture of 2- and 4-propionylpyridines. [n] $n_D^{20} = 1.5162$, lit, $n_D^{16.3} = 1.5166$.[14] [o] M.p. 106–107°, *Anal.* Calcd. for $C_{13}H_{11}NO$: N, 7.10. Found: N, 7.16. [p] Somewhat contaminated with 4,4′-dipyridyl. [q] Identified as 2-benzoylpyridine after hydrolysis of the imine with 6*N* HCl. [r] Only one isomer is possible in this case. [s] M.p. 89–89.5°, *Anal.* Calcd. for $C_{13}H_{11}NO$: N, 7.10. Found: N, 6.90. [t] 2-Benzoylquinoline, m.p. 111°, lit. m.p. 110–111°.[15] [u] M.p. of picrate derivative 167–168°, lit. m.p. 169.4–169.8°.[16] [v] M.p. of 2,4-dinitrophenylhydrazone derivative 309–312°, lit. m.p. 315°.[17] [w] Biacetyl gives the same 2,4-dinitrophenylhydrazone as acetoin. [x] Mixture of benzil and benzoin. [y] A 16.4% yield of 2-benzoylquinoline was also obtained from the petroleum ether filtrate. [z] A 10% yield of 2-benzoylquinoline was also obtained from the petroleum ether filtrate. [aa] Additional amounts of mercuric chloride used, 15–25 grams per mole of aluminum.

(12)


(13)


Salt (I)[8] would be expected to be even more easily reduced than pyridine itself since cations are generally better electron acceptors than the corresponding neutral molecules. Hence even zinc will cause the reaction to take place, and in this case at least the process appears likely to proceed by way of a free radical intermediate.* The products of equations (11) and (12) using zinc have been isolated by Wibaut and Arens[7] and shown to react as indicated in equations (12) and (13). The absence of 2-ethylpyridine in the products probably is conditioned by the steric requirements of the *N*-acyl group which hampers dimerization of the corresponding 2-position radical. The acetamide obtained probably arises through hydrolysis or acetolysis of the quinonoid intermediate shown as the products of reactions (10) or (11). The normal pyridine ring is too highly stabilized by resonance for such a cleavage.

*Conclusions.* The direct, substitutive acylation of pyridine, its homologs, or its analogs may be accomplished by treatment with acid derivatives and metals. From pyridine itself the 2-pyridyl ketones are the primary products, although smaller amounts of the 4-pyridyl ketones are also obtained in some cases. Suitable metals are aluminum, magnesium, and beryllium, in order of decreasing effectiveness. Suitable acid derivatives are esters, *N*,*N*-dialkylamides, and nitriles, also in decreasing order of effectiveness. Acid anhydrides react entirely differently and yield alkylated instead of acylated pyridines. The acylation process appears to involve an anionic intermediate produced by a two-electron transfer step from the metal to the acid derivative and subsequent attack by this anion at the 2- and 4-positions of the pyridine ring.

## EXPERIMENTAL

*Procedure A. Bimolecular reduction of ethyl benzoate and pyridine with aluminum.* Granular aluminum metal (27.0 g., 1.0 mole) was heated with mercuric chloride (5.0 g.) and several drops of mercury for 2 hr. at 100° in a three-necked flask fitted with an addition funnel, condenser, and stirrer. Ethyl benzoate (25 g.) and pyridine (25 g.) were added to the metallic mixture to initiate the reaction. A green color developed immediately and turned to a muddy brown within a few minutes. Pyridine (250 g., 3.5 moles total) was added dropwise over a period of 2 hr. keeping the reaction mixture at total reflux. At the end of this addition the reaction mixture was dark colored. Ethyl benzoate (425 g., 3.0 moles total) was added dropwise to the reaction mixture over a period of 24 hr. at which time all of the aluminum metal had reacted. The partially cooled reaction mixture was poured into a liter of 6*N* sodium hydroxide and the gel that developed was broken up by stirring. The oil layer was separated and extracted several times with 6*N* hydrochloric acid, and then distilled under vacuum through a 30 cm. glass-helix-packed column. The following fractions were isolated:

| Fractions | Boiling Range, °C. (Mm.) | Amount (Grams) |
|---|---|---|
| I | 78–84, (3.5–4.0) | 208.5 |
| II | 94–101, (3.4–4.0) | 3.5 |
| III | 140–146, (2.8) | 6.5 |

Fraction I was ethyl benzoate (46% recovery) while fraction II was benzoic acid. Fraction III was identified as a mixture of benzil and benzoin (2.8% yield).

The acid extracts were made basic with an excess of 6*N* sodium hydroxide and the generated oil taken up in ether, dried over potassium hydroxide pellets, and rapidly distilled, eventually under vacuum. The higher boiling distillate was refractionated through a 30 cm. glass-helix-packed column and the fraction boiling at 126–146°, (1.9 mm.) was refrigerated. The solid material which crystallized was deintified as 4-benzoylpyridine after recrystallizations from petroleum ether (90–100°). This material (17.7 g., 6.4% yield) melted at 72.5–73.0°, lit. m.p. 71.5–72.6°.[18] The picrate derivative melted at 160–161°, lit. m.p. 160.[18]

The mother liquor from this refrigeration was refractionated through a small Vigreux column to give a yellow oil, b.p. 124–126° (1.5 mm.), 65.8 g., 23.9% yield; $n_D^{20}$ 1.5940, $d_4^{20}$ 1.1458. It was identified as 2-benzoylpyridine by preparing a variety of derivatives including: (*a*) phenyl-2-pyridylmethanol hydrochloride, m.p. 180–181.5°, lit. m.p. 182–184°,[10] (*b*) phenyl-2-piperidylmethanol hydrochloride, m.p. 199.5–201°, lit. m.p. 200–202°[18] for this enantiomorphic pair, (*c*) 2,4-dinitrophenylhydrazone 196–197.5°, lit.

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(8) *cf.* Ref. 3, p. 482.

* Ionic intermediates are also conceivable of course, but the behavior of Zn in other Het BR reactions causes us to prefer the free radical type of intermediate here.

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m.p. 196.5–197.5°,[19] and (*d*) picrate, m.p. 129–130°, lit. m.p. 130°*d*,[20] 122–123°,[18] 124–127°.[13]

Anal. Calcd. for $C_{12}H_9NO$: $MR_D$, 54.47. Found: $MR_D$, 54.25.

It should be noted that larger amounts of $HgCl_2$ (0.2 mole per 1 mole of metal) were used with all the other bivalent metals (*i.e.* Zn, Mg, and Be) listed in Table 1 where Procedure A is employed.

*Procedure B. Isolation of the intermediate complex. Bimolecular reduction of ethyl benzoate and pyridine with aluminum.* The same steps were followed as in Procedure A, and the same amounts of reactants were used. The cooled reaction mixture was stripped of unreacted pyridine using an aspirator and mild heating, and then the remaining viscous oil (about 350–400 ml.) was poured into 1500 ml. of petroleum ether (90–100°). This addition resulted in the precipitation of a brown solid (286 grams) which could be filtered, dried, and allowed to stand in the presence of air without any noticeable decomposition. This complex was hydrolyzed with 6*N* hydrochloric acid and worked up in a manner similar to the techniques previously discussed for obtaining 2- and 4-benzoylpyridine. The following products were isolated and identified:

| Compounds from Complex | Grams | Yield, % |
|---|---|---|
| 2-Benzoylpyridine | 87.0 | 32.5 |
| 4-Benzoylpyridine | 19.4 | 7.1 |
| Benzil and benzoin | 26.7 | 12.7 |

After removal of the excess petroleum ether and unreacted starting material from the filtrate by mild heating under vacuum, the remaining viscous oil was hydrolyzed with 6*N* hydrochloric acid and the resulting mixture worked up using previously described techniques. The following products were found:

| Compounds from Filtrate | Grams | Yield, % |
|---|---|---|
| 2-Benzoylpyridine | 6.3 | 2.3 |
| 4-Benzoylpyridine | 2.5 | 0.9 |
| Benzil and benzoin | 10 | 4.8 |

Since the 4-isomer was found to be present in both the filtrate and the complex, no advantages of separation of the 2- and 4-isomers by isolating the complex could be found. However, the purity of the 2-isomer obtained from the hydrolysis of the complex was high as evidenced by its molecular refractivity (54.27). The presence of benzil and benzoin in the complex eliminated any possibility of studying the true composition of the pyridine component in the complex.

*Procedure C. Attempted bimolecular reduction of acetic anhydride and pyridine with aluminum.* The same reaction procedure was used as that previously described as procedure A except that the reaction was highly exothermic and only mild heating of the reaction mixture at various intervals was necessary to keep the reaction in progress. The following amounts of reactants were used; aluminum (27 g., 1 mole), mercuric chloride (5 g.), acetic anhydride (306 g., 3.0 moles), pyridine (275 g., 3.5 moles), and several drops of mercury. The cooled reaction mixture was hydrolyzed with a liter of 3*N* sodium hydroxide and the generated oil separated from the aqueous layer, which was discarded. This oil was dried, stripped of pyridine, and the distillate b.p. 30–95° (1.8 mm.), 59.5 g. was redistilled through a 30 cm. glass-helix-packed column under vacuum.

| Fractions | Boiling Range, °C. (Mm.) | Amount (Grams) |
|---|---|---|
| I | 30–42, (2.7) | 24.6 |
| II | 44–55, (2.7) | 5.3 |
| III | 73–74, (2.8) | 10.9 |

Fraction I was principally 4-ethylpyridine, picrate m.p. 167–168°, lit. m.p. 169.4–169.8°,[16] mixture m.p. 168°. Fraction II represented forerun, while fraction III gave acetamide, m.p. 81°, upon refrigeration, mixture m.p. 81° with an authentic sample. No fraction corresponding to 2- or 4-acetylpyridine could be isolated.

*Procedure D. Attempted bimolecular reduction of N,N-dimethylbenzamide and pyridine with sodium.* Sodium metal was made into a fine sand in a three-neck flask fitted with a condenser, Hershberg stirrer, nitrogen inlet, and dropping funnel, by rapidly stirring the molten metal under previously dried toluene. The cooled toluene was decanted and the reaction carried out under a slight positive pressure of nitrogen in the same manner as that previously described as Procedure A. The amounts of reactants used were; sodium (23 g., 1 mole), pyridine (158 g., 2 mole), *N,N*-dimethylbenzamide (137 g., 0.9 moles), and toluene (50–60 ml.) as a diluent. The cooled reaction mixture was filtered through a sintered-glass funnel to remove a small amount of unreacted sodium. The filtrate was decomposed with 1 l. of 6*N* hydrochloric acid and the resulting mixture washed several times with 100 ml. portions of benzene. The benzene washings were combined, dried, and stripped of benzene using an aspirator. The remaining oil was distilled under vacuum.

| Fractions | Boiling Range, °C. (Mm.) | Amount (Grams) |
|---|---|---|
| I | 67–94, (1.5) | 7.7 |
| II | 100–101, (1.6) | 10.7 |
| III | 140–151, (2.0) | 12.3 |
| IV | b.p. > 160 (2.0) | 8.3 |

Fraction I ($n_D^{20}$ 1.5470) was a mixture of benzaldehyde and N,N-dimethylbenzamide while fraction II was unreacted *N,N*-dimethylbenzamide ($n_D^{20}$ 1.5565; 7.8% recovery). Fraction III crystallized and was identified as a mixture of benzil and benzoin. Fraction IV was a non-distillable tar.

The acid soluble material obtained from the hydrolysis of the reaction mixture was made basic with excess 6*N* sodium hydroxide and the generated oil taken up in ether, dried over potassium hydroxide pellets, and stripped of ether using an aspirator. The remaining oil was distilled under vacuum. Fraction I was unreacted pyridine (29% recovery), while fraction IV was a non-distillable tar. Fractions II and III were refractionated separately through a small Vigreux column and then converted to picrates. After many recrystallizations two constant-melting picrate derivatives were obtained. One picrate derivative melted at 143–144° while the other melted at 256–257° *d*. The latter derivative corresponded to the picrate listed for 4,4′-dipyridyl, lit. m.p. 257°.[21] It is possible that the other derivative is a picrate of 2,2′-dipyridyl, (lit. m.p. 155°[22]), contaminated with a less insoluble picrate.

| Fractions | Boiling Range, °C. (Mm.) | Amount (Grams) |
|---|---|---|
| I | 25–30, (4–5) | 45.8 |
| II | 100–135, (2.0) | 61.4 |
| III | 135–155, (2.0) | 32.1 |
| IV | b.p. > 165, (2.0) | 27.8 |

All of the previously mentioned fractions were also treated with 2,4-dinitrophenylhydrazine in order to obtain any evidence for benzoylation of the pyridine nucleus. Only one fraction (b.p. 150–156°, 2.0 mm.) gave a derivative which

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melted at 196–197° after recrystallizations from 90% acetic acid and finally ethyl acetate. This derivative failed to depress the melting point of an authentic sample of a 2,4-dinitrophenylhydrazone derivative of 2-benzoylpyridine (m.p. 196–197°). However, this represents only a trace identification of 2-benzoylpyridine since the fraction from which it was obtained contained primarily 4,4′-dipyridyl.

*Discussion of infrared results.* The fractions obtained from the Het BR of *sec*-butyl acetate, *n*-amyl acetate, 2-ethylhexyl acetate, and ethyl propionate with pyridine using aluminum gave picrate and 2,4-dinitrophenylhydrazone derivatives. However the purification of these derivatives failed to yield constant melting solids, and since the yields were low, attempts to separate the isomers proved to be impractical. Therefore infrared spectra of the mixtures presumed to be 2- and 4-acetylpyridine and 2- and 4-propionylpyridine were obtained.

The characteristic absorption peak for the carbonyl band was split in these spectra, more than likely due to the presence of the 2- and 4-isomers. The absorption frequencies observed for a mixture of 2- and 4-acetylpyridine were 1655 cm.$^{-1}$ (6.04 $\mu$) and 1680 cm.$^{-1}$ (5.94 $\mu$), and for a mixture of 2- and 4-propionylpyridine 1660 cm.$^{-1}$ (6.02 $\mu$) and 1685 cm.$^{-1}$ (5.93 $\mu$). These absorption values check with those listed in the literature for carbonyl bands present in aryl alkyl ketones (1700–1680 cm.$^{-1}$).[23]

The characteristic peaks for the pyridine nucleus were also present in these spectra. Thus the mixture of 2- and 4-acetylpyridines showed absorption at 785 cm.$^{-1}$ (12.72 $\mu$) and 746 cm.$^{-1}$ (13.40 $\mu$), while the mixture of 2- and 4-propionylpyridine showed absorption at 835 cm.$^{-1}$ (11.99 $\mu$) and 760 cm.$^{-1}$ (13.18 $\mu$). These strong bands have been shown to originate in the out-of-plane vibrations of the unsubstituted hydrogen atoms of the ring.[24]

Thus we conclude from these spectra that acylation of the pyridine nucleus has occurred yielding mixtures of the 2- and 4-pyridyl substituted ketones.

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[CONTRIBUTION NO. 1454 FROM THE STERLING CHEMISTRY LABORATORY AND FROM THE BINGHAM OCEANOGRAPHIC LABORATORY, YALE UNIVERSITY]

# Contributions to the Study of Marine Products. XLV. Sponge Nucleic Acids[*,1]

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Nucleic acids have been isolated from sixteen different species of sponges, and all have been degraded to the nucleosides. All pentose nucleic acids gave the four usual ribonucleosides, and all deoxypentose nucleic acids gave the four usual deoxyribosides. There were no detectable quantities of arabinosides or other unusual nucleosides among the hydrolysis products. The nucleic acids of *Cryptotethia crypta* were exceptional in their extraordinarily low content of ribonucleic acid. The significance of these observations has been discussed.

It has been shown in previous papers of this series that extended acetone extraction of the Caribbean sponge, *Cryptotethia crypta*, affords a mixture of three unusual nucleosides which have been identified as 3-$\beta$-D-arabofuranosylthymine (spongothymidine),[3] 3-$\beta$-D-arabofuranosyluracil (spongouridine),[3] and 9-$\beta$-D-ribofuranosyl-2-methoxyadenine.[4] Some earlier observations[5] had pointed to the possibility that these new nucleosides are products of the autolysis of more complex units such as nucleic acids.

To investigate this attractive possibility we began several years ago a systematic study of sponge nucleic acids of which previous knowledge was altogether lacking. Suitable methods for the isolation and examination of the nucleic acids were developed on the common sponges of Long Island Sound rather than the more promising but less accessible Caribbean sponge, *Cryptotethia*. This sponge and other species were subsequently collected near the island of Bimini.[6] They were quickly frozen and kept in this state until shortly before their extraction. A third group of sponges was collected in the Bermudas[6] and extracted there while still quite fresh. Altogether sixteen different species were investigated which included representatives of the three well-known groups, the keratineous, siliceous, and calcareous sponges. All of these sponges had previously been investigated in this laboratory for other reasons, but with the exception of *Cryptotethia*, none of them had been observed to afford the unusual nucleosides.

The nucleic acids were isolated and characterized by modifications of procedures well described in the literature. Most of them were patterned after the

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(6) The authors express their sincere gratitude to the directors of the Lerner Marine Laboratory, Bimini, Bahamas, and of the Bermuda Biological Station for their most valuable help.