[Contribution from the Battelle Memorial Institute]

# Abnormal Condensation of Piperidinium Acetate with Aromatic Aldehydes[a]

R. H. POIRIER, R. D. MORIN, ARVETA M. McKIM[1b], and A. E. BEARSE

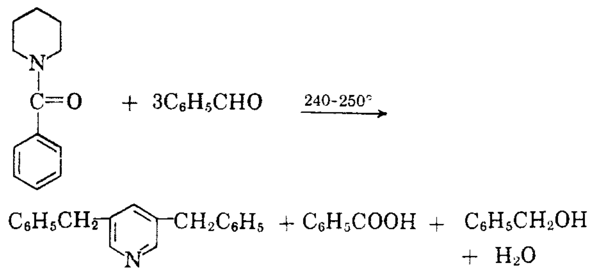
*Received April 19, 1961*

Aromatic aldehydes react with piperidine in the presence of acetic acid with azeotropic removal of water to give 3,5-dibenzylpyridines. A possible mechanism for the *beta* condensation of piperidine is suggested.

A new method for the preparation of dialkylaminostyryl derivatives of pyridine and quinoline, and their *N*-oxides was recently described by Parker and Furst.[2] Briefly, this method involves condensation of 2- or 4-methyl substituted heterocyclic bases with aromatic aldehydes in the presence of piperidinium acetate while removing the water formed azeotropically by means of toluene. Thus, the preparation of certain styryl derivatives difficultly accessible by other reported methods was achieved in our laboratory by the piperidinium acetate method (Table I). However, as noted by Parker and Furst, certain combinations of heterocyclic bases and aromatic aldehydes led to unexpected products. The identification of these anomalous products and the reactions by which they arise are discussed in this paper.

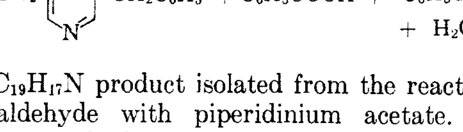
As reported by Parker and Furst, the condensation of 2-methylquinoxaline with 4-dimethylaminobenzaldehyde under azeotropic conditions in the presence of piperidinium acetate indeed gave the styryl compound in good yield (82%). However, the reaction of 2-methylpyrazine and 4-dimethylaminobenzaldehyde under similar conditions gave no styryl base, and only a small amount of unidentified product, $C_{23}H_{27}N_3$, apparently identical to "Compound A" obtained by Parker and Furst. Similarly, anisaldehyde failed to condense with either γ-picoline or lepidine under the conditions of the piperidinium acetate method. Instead, a product with the empirical formula $C_{21}H_{21}NO_2$ was isolated in both of these instances. Hence, it was concluded that the heterocyclic bases γ-picoline and lepidine were not involved in the formation of the anomalous products.

The reaction of benzaldehyde with piperidinium acetate in the absence of any other heterocyclic base was next investigated. Such a reaction yielded a product with the empirical formula $C_{19}H_{17}N$, which appeared to correspond to the parent member of the series of "Compounds A and B" of Parker and Furst, as well as the compound derived from anisaldehyde. A clue to the possible identity of these anomalous products was uncovered when it was noted that Rügheimer[3] obtained 3,5-dibenzylpyridine, $C_{19}H_{17}N$, m.p. 89°, by heating *N*-benzoylpiperidine and a slight excess of benzaldehyde at 240–250° in a sealed tube. When this reaction was repeated, the product obtained was identical with




the $C_{19}H_{17}N$ product isolated from the reaction of benzaldehyde with piperidinium acetate. Both products melted at 89–90°, and a mixture showed no melting point depression.

Rügheimer characterized his dibenzylpyridine by identification of 3,5-dibenzoylpyridine and pyridine-3,5-dicarboxylic acid from its permanganate oxidation products. We, however, verified his structure assignment *via* a synthetic route. Thus, 3,5-pyridinedicarboxylic acid was converted through the acid chloride to 3,5-dibenzoylpyridine by a Friedel-Crafts reaction, and the diketone was subsequently reduced to 3,5-dibenzylpyridine by the Clemmensen method. The synthesized product proved to be identical with the dibenzylpyridine obtained *via* the condensation of piperidinium acetate, or benzoylpiperidine, with benzaldehyde. It was then generalized that "Compounds A and B," reported by Parker and Furst, probably are 3,5-bis(4-dialkylaminobenzyl)pyridines, (I).




I

a. "Compound A," R = $CH_3$
b. "Compound B," R = $C_2H_5$

The formation of 3,5-dibenzyl- and 3,5-dipicolylpyridines by condensation of piperidine with appro-

(1) (a) Presented at the 139th Meeting of the American Chemical Society, St. Louis, Mo., March 27, 1961, Abstracts of Papers, p. 18-O. (b) Present address: Chemical Abstracts, Ohio State University, Columbus, Ohio.

(2) Elizabeth D. Parker and A. Furst, *J. Org. Chem.*, **23**, 201 (1958).

(3) Rügheimer, *Ber.*, **24**, 2186 (1891); *Ber.*, **25**, 2421 (1892); *Ann.*, **280**, 41 (1894).

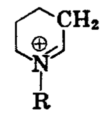
TABLE I

STYRYL DERIVATIVES *via* PIPERIDINIUM ACETATE-CATALYZED CONDENSATIONS

| Compound | Hr. Refluxed | Yield, % | M.P. | Empirical Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| 2-(4-Dimethylaminostyryl)-benzothiazole | 78 | 51 | 204–205[a] | | | | | | | |
| Benzimidazole | 48 | 50 | 259–260[b] | | | | | | | |
| 5-(or 6)Methoxybenzimidazole | 98 | 21 | 172–174 | $C_{18}H_{19}N_3O$ | 73.69 | 73.75 | 6.53 | 6.43 | 14.32 | 14.11 |
| 5-(or 6)Chlorobenzimidazole | 75 | 35 | 215–216 | $C_{17}H_{16}ClN_3$ | 68.56 | 68.37 | 5.42 | 5.72 | 14.11 | 14.48 |
| 4-(4-Dimethylaminostyryl)-6-ethoxyquinoline | 62 | 60 | 183–184 | $C_{21}H_{22}N_2O$ | 79.21 | 78.53 | 6.96 | 6.60 | 8.80 | 8.74 |
| 4-(4-Diethylaminostyryl)quinoline | 68 | 23 | 134–135[c] | $C_{21}H_{22}N_2$ | 83.40 | 83.61 | 7.33 | 7.19 | 9.27 | 9.24 |
| 1-(9-Julolidyl)-2-(4-quinolyl)-ethylene | 126 | 29 | 153–154 | $C_{23}H_{22}N_2$ | 84.62 | 84.74 | 6.79 | 6.62 | 8.58 | 8.57 |
| 2-(4-Dimethylaminostyryl)pyrazine[d] | 192 | 10 | 123–124 (b.p. 170/200/0.6 mm.) | $C_{14}H_{15}N_3$ | 74.67 | 73.69 | 6.67 | 6.33 | 18.76 | 18.55 |

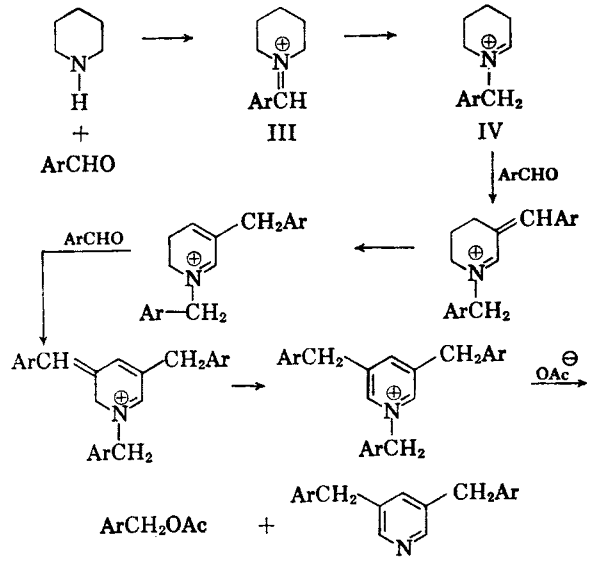
[a] L. G. S. Brooker and R. H. Sprague, *J. Am. Chem. Soc.*, **63**, 3203 (1941); m.p. 206–208° dec. [b] H. Rupe, F. Pedrini, and A. Collin, *Helv. Chim. Acta*, **15**, 1321 (1932); m.p. 256°. [c] Mary A. Clapp and R. S. Tipson, *J. Am. Chem. Soc.*, **68**, 1332 (1946); m.p. 120–122°. [d] Mixed alkane sulfonic acids as catalyst in place of piperidinium acetate.

priate aromatic and heterocyclic aldehydes can be explained *via* tertiary iminium chemistry. Studies by Schöpf *et al.*[4] and by Leonard and Hauck[5] have indicated that the $\beta$-methylene of $\Delta^1$-tetrahydropyridinium structures (II) should be sufficiently

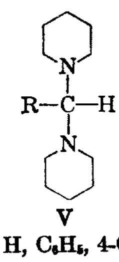


II

active for condensation with aldehydes. Therefore, the following sequence of transformations is proposed to account for $\beta$-condensation of piperidine to yield ultimately 3,5-disubstituted pyridines.



Bispiperidino products (V) also condense with



V

R = H, $C_6H_5$, 4-$C_5H_5N$

aldehydes under the influence of acetic acid and with the azeotropic removal of water to form 3,5-disubstituted pyridines. However, the acid presumably regenerates the Schiff base (III) from which the active tertiary iminium (IV) salt is derived.

## EXPERIMENTAL[6]

*Preparation of styryl bases via the piperidinium acetate azeotrope method.* The method used for these preparations

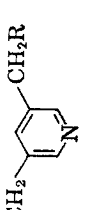
(4) C. Schöpf, F. Braun, and A. Komzak, *Chem. Ber.*, **89**, 1821 (1956).

(5) N. J. Leonard and F. R. Hauck, Jr., *J. Am. Chem. Soc.*, **79**, 5279 (1957).

(6) All melting points are uncorrected.

TABLE II

3,5-BIS(ARYLMETHYL)PYRIDINES PREPARED *via* CONDENSATION OF PIPERIDINE WITH AROMATIC ALDEHYDES




| R | Yield, %[a] | B.P. (Mm.) | M.P. Base | M.P. HCl Salt | Empirical Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found | Chlorine, % Calcd. | Chlorine, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Phenyl | 43 | 165-195 (0.55) | 89.5-90[b] | 170-171[b] | $C_{19}H_{17}N$ | 88.0 | 87.8 | 6.55 | 6.5 | 5.40 | 5.4 | — | — |
| Phenyl | 46[c,1] | 170-175 (0.3) | 87-89 | — | | | | | | | | | |
| Phenyl | 15[c,2] | 181-183 (0.6) | 86-89 | — | | | | | | | | | |
| Anisyl | 37[d] | *ca.* 240 (0.8) | 125-126 | 165-166 dec. | $C_{21}H_{21}NO_2$ | 79.0 | 78.7 | 6.58 | 6.55 | 4.39 | 4.61 | — | — |
| 4-Dimethyl-amino-phenyl | 33[d] | 200-225 (1.5) | 131-132 | 209-210 dec[e] | $C_{23}H_{29}Cl_2N_3$ | — | — | — | — | — | — | — | — |
| 4-Pyridyl | 22 | 200-225 (0.3) | — | 254-257 dec.[f] | $C_{17}H_{18}Cl_3N_3$ | 55.0 | 54.4 | 4.86 | 5.1 | 11.3 | 11.1 | 28.8 | 27.9 |
| 3-Pyridyl | 18 | 130-150 (0.15) | — | 248-253 dec.[f] | $C_{17}H_{18}Cl_3N_3$ | 55.0 | 55.4 | 4.86 | 5.0 | — | — | 28.8 | 27.0 |

[a] Based on the assumption that the stoichiometry of the reaction requires four moles of aldehyde per mole of piperidine. [b] Rugheimer, *Ber.*, **25**, 2421 (1892) gave m.p. 89° for the free base and m.p. 164.5–166° for the hydrochloride salt. [c] From reaction of benzaldehyde with (1) α,α-bispiperidinotoluene [A. T. Stewart and C. R. Hauser, *J. Am. Chem. Soc.*, **77**, 1098 (1955)]; (2) bispiperidinomethane [Knoevenagel, *Ber.*, **31**, 2586 (1898)]. [d] Isolated from attempts to prepare styryl derivatives of 2-methylpyrazine and 4-picoline. [e] Dihydrochloride. [f] Trihydrochloride.

was essentially identical to that described by Parker and Furst.[2] Thus, 0.1 mole of heterocyclic base, 0.11 mole of appropriate aldehyde, 5 ml. of piperidine, and 4 ml. of acetic acid were mixed in 150 ml. of toluene, and the solution was refluxed under a Dean-Stark trap until water was no longer liberated. Most of the toluene was then removed *via* the Dean-Stark trap. In many instances, the styryl base crystallized from the sirupy concentrate. However, it was frequently necessary to remove all the toluene under reduced pressure before crystallization could be induced. Moreover, 2-(4-dimethylaminostyryl)pyrazine required vacuum distillation before it would crystallize. In general, final purification of the styryl bases was effected by recrystallization from methanol, ethanol or ethanol-benzene. Table I summarizes the results of these preparations.

*Preparation of 3,5-dibenzylpyridine.* (a) *By condensation of benzaldehyde with piperidinium acetate.* A mixture of 31.8 g. (0.3 mole) of benzaldehyde, 15 ml. (12.9 g., 0.15 mole) of piperidine, and 12 ml. (12.6 g., 0.21 mole) of glacial acetic acid in 250 ml. of toluene was refluxed under a Dean-Stark trap. The volume of aqueous phase that accumulated in the Dean-Stark trap amounted to 9.0 ml. after 8 hr. and 9.7 ml. after 24 hr. Titration of the total aqueous phase with 0.5*N* sodium hydroxide showed an approximate composition of 3.1 ml. (3.25 g., 0.054 mole) of acetic acid and 6.6 ml. (0.37 mole) of water. These values of acetic acid and water are reasonably close to the values of 0.05 mole excess of acetic acid and 0.3 mole of water of reaction calculated according to the proposed course of reaction. The deviations from theory presumably arose from the formation of intractable tars and resins that amounted to about 20% of the reaction products.

After the removal of toluene by distillation at atmospheric pressure, distillation of the residual oil gave three main fractions and a residue:

| Fraction | Weight, G. | B.P. (Mm.) | Characteristics |
|---|---|---|---|
| A | 6.3 | 58 (0.70)–98 (0.45) | Nearly colorless oil with ester-like odor |
| B | 11.9 | 165–195 (0.55) | Yellow oil that solidified |
| C | 13.2 | 210–255 (0.45) | Yellowish brown, viscous oil |
| D | 7.2 | — | Brown, glassy residue |

Redistillation of Fraction A through a 6-in. Vigreux column yielded 3.2 g. of a colorless oil, b.p. 104° (20 mm.), $n_D^{25}$ 1.5033, with an ester-like odor. The presence of strong absorption at 5.75 μ of the infrared spectrum of this oil seemed to confirm the ester nature of the oil. Hence, it was saponified and the alcohol moiety of the ester was identified as benzyl alcohol *via* the α-naphthylurethane derivative; white silky needles from ligroin and chloroform, m.p. 131–132°. The urethane derivative did not depress the melting point of the α-naphthylurethane derivative of an authentic specimen of benzyl alcohol. A sample of benzyl acetate was then prepared and its b.p. of 104° (20 mm.), and $n_D^{25}$ 1.5031 were in excellent agreement with those recorded from the sample of redistilled Fraction A.

Crystallization of Fraction B using petroleum ether (b.p. 30–60°) with a little ethyl alcohol yielded 5.45 g. of yellowish white crystals, m.p. 86–89°. Another crystallization of this product using ligroin removed the colored impurities and gave 5.1 g. of pure 3,5-dibenzylpyridine, m.p. 88.5–89°, which was identical with the product obtained from benzoylpyridine and benzaldehyde.[3] Another 3.3 g. of dibenzylpyridine was recovered by redistillation of Fraction C. Over-all yield of 3,5-dibenzylpyridine based on the aldehyde used was 43%, assuming that four moles of aldehyde are required per mole of product.

*Anal.* Calcd. for $C_{19}H_{17}N$: C, 88.0; H, 6.55; N, 5.4. Found: C, 87.8; H, 6.5; N, 5.4.

The hydrochloride salt had a m.p. of 170–171°.

As summarized in Table II this method is applicable to other aromatic aldehydes to yield the corresponding 3,5-bis(arylmethyl)pyridines.

(b) *By condensation of N-benzoylpiperidine with benzaldehyde.* Rügheimer[3] reported a 72% yield of 3,5-dibenzylpyridine by heating a mixture of *N*-benzoylpiperidine and 2.15 mole equivalents of benzaldehyde in a sealed tube at 250° for 6 hr. However, it was necessary to employ conditions more stringent than those of Rügheimer when such a reaction was conducted in a stainless steel microbomb. Thus, in a reaction carried out at 250° for 6 hr., none of the dibenzylpyridine was isolated. Prolonging the heating time at 250° to 24 hr. gave 17.5% of the desired product. However, reaction at 300° for 12 hr. increased the yield of distilled (b.p. 177°/0.23 mm.) and recrystallized 3,5-dibenzylpyridine, m.p. 89–90° (lit.[3] m.p., 89°) to 54%. The hydrochloride salt melted at 168–171° (lit.[3] m.p., 164.5–166°) and did not depress the melting point of the product derived by reaction of benzaldehyde with piperidinium acetate.

(c) *From 3,5-pyridinedicarboxylic acid.* A mixture of 50 g. (0.3 mole) of 3,5-pyridinedicarboxylic acid and 150 ml. of thionyl chloride was refluxed for 16 hr. Excess thionyl chloride was removed by evaporation under reduced pressure; two 50-ml. portions of dry benzene were added and evaporated to remove the last of the thionyl chloride. The residual acid chloride was dissolved in 300 ml. of dry reagent benzene, and to this solution, cooled to 5 to 10°, was added 200 g. of anhydrous aluminum chloride with stirring. The reaction mixture was permitted to warm to room temperature and then refluxed with stirring for 6 hr. The dark brown mixture was poured cautiously onto ice and hydrochloric acid, and the solid 3,5-dibenzoylpyridine which formed was collected by filtration. Additional product was obtained by concentration of the benzene layer of the filtrate; yield, 78.7 g. (91%); m.p. 122.5–123.5°, unchanged after recrystallization from alcohol (lit.,[3] m.p., 123°).

A solution of 14.3 g. (0.05 mole) of 3,5-dibenzoylpyridine in 85 ml. of concd. hydrochloric acid and 100 ml. of water was added to 100 g. of amalgamated mossy zinc, and the mixture was boiled under reflux for 4 hr. in a manner similar to that described for reduction of 4-benzoylpyridine to 4-benzylpyridine.[7] A brown insoluble oil formed, and after separation by decantation, it was heated with 10% aqueous sodium hydroxide and benzene. The benzene layer was washed with water and the benzene removed by evaporation. The residual dark oil, which refused to crystallize, was distilled under reduced pressure, and the fraction boiling at 173–178° (0.2 mm.) was collected as a pale yellow oil which was crystallized and recrystallized from petroleum ether (b.p. 60–110°); yield, 5.8 g. (45%); m.p. 89–90° (reported,[3] m.p., 88.5–89°).

COLUMBUS 1, OHIO

(7) F. B. La Forge, *J. Am. Chem. Soc.*, **50**, 2484 (1928).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

# Stereoselective Synthesis of α-Substituted α,β-Unsaturated Esters

HERBERT O. HOUSE AND GARY H. RASMUSSON[1]

*Received May 10, 1961*

2-Methyl-*trans*-2,4-pentadienoic acid and its methyl ester have been prepared from acrolein and the ylid *3*. Reaction of the same ylid with acetaldehyde afforded an ester mixture composed of 96.5% methyl tiglate and 3.5% methyl angelate. Reaction of methyl pyruvate with the ylid *15* produced an ester mixture composed of 68% methyl tiglate and 32% methyl angelate.

In order to synthesize a sample of methyl 2-methyl-2,4-pentadienoate (*1*), needed for other synthetic work, we were led to consider various synthetic routes to α,β-unsaturated acids and their esters. The dienoic acid *2* has been prepared by the decarboxylative condensation of acrolein with malonic acid,[2] a reaction which is generally applicable to aldehydes forming the *trans* α,β-unsaturated acids.[3,4] Although substituted malonic acids have been successfully employed in comparable condensations with aromatic aldehydes,[5] the sensitivity[2] of the dienoic acid *2* to polymerization suggested that the direct formation of the desired ester *1* from acrolein and the Wittig reagent *3*[6–8] would be a more satisfactory route. In accord with this expectation, the ester *1* was produced in 60% yield. The liquid product, which exhibited a single peak on gas chromatography, yielded a single crystalline acid *4* on saponification; treatment of this acid *4* with diazomethane regenerated the ester *1*. Comparison of the ultraviolet spectra of the acid *4* [$\lambda_{max}$ 251 mμ (ε 23,000) ] and the ester *1* [$\lambda_{max}$ 253 mμ (ε 24,300) ] with the spectra of *2* [$\lambda_{max}$ 244 mμ (ε 24,000) ] and *5* [$\lambda_{max}$ 247 mμ (ε 20,600) ] indicated that product *4* possesses the indicated *trans* configuration.

(1) National Science Foundation Predoctoral Fellow, 1958–61.

(2) I. E. Muskat, B. C. Becker, and J. S. Lowenstein, *J. Am. Chem. Soc.*, **52**, 326 (1930).

(3) J. R. Johnson, *Org. Reactions*, **1**, 210 (1942).

(4) Cf. H. E. Zimmerman and L. Ahramjian, *J. Am. Chem. Soc.*, **81**, 2086 (1959).

(5) W. J. Gensler and E. Berman, *J. Am. Chem. Soc.*, **80**, 4949 (1958).

(6) O. Isler, H. Gutmann, M. Montavon, R. Rüegg, G. Ryser, and P. Zeller, *Helv. Chim. Acta*, **40**, 1242 (1957).

(7) U. Schöllkopf, *Angew. Chem.*, **71**, 260 (1959).

(8) S. Trippett in R. A. Raphael, E. C. Taylor, and H. Wynberg, *Advances in Organic Chemistry, Methods and Results*, Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1960, pp. 83–102.