[Contribution from the Department of Chemistry of Purdue University]

# Heterogeneous Bimolecular Reduction. III. The Coreduction of Pyridine with Imines and the Preparation of Pyridylmethylamines[1]

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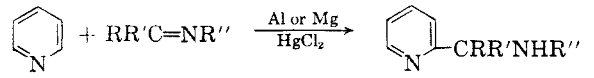
*Received June 24, 1959*

The coreduction of mixtures of pyridine and imines with magnesium or aluminum amalgams has been shown to lead to substituted α-pyridylmethylamines in accord with the mechanism previously proposed for closely related reactions involving pyridine and carbonyl compounds or esters. Aromatic imines give considerably better yields than aliphatic imines. The electronic effects of substituent groups have been studied and the variations in yields of products discussed.

Previous reports on heterogeneous bimolecular reduction have served to define the scope of the reaction and to determine conditions necessary for the coreduction of pyridine with carbonyl compounds and acid derivatives.[3,4] We wish now to describe the extension of these reactions to the coreduction of pyridine with imines and the development of a one-step synthesis of substituted α-pyridylmethylamines. During the course of this investigation we have also attempted to study the electronic effects of substituent groups and to relate the yields of products obtained with the mechanisms previously proposed for these reactions.

It has been found that imines, obtained by condensation of primary amines with aldehydes and ketones, react with pyridine in the presence of aluminum or magnesium amalgams to form the expected coupled products in yields ranging up to 75% based on the imine or the metal. The results of these experiments are summarized in Table I. It will be noted that far better yields are generally obtained with aromatic imines than with aliphatic imines. The replacement of aromatic groups by aliphatic groups in R or R′ is especially detrimental to the yields. The influences of substituent groups in the ortho- or para- positions of the aromatic nuclei seem to depend upon the inductive effects of these groups, being favorable for those groups which show a +I effect (electron supply) and detrimental for those groups which show a −I effect (electron withdrawal). In accord with previously observed inductive effects, the influence of substituent groups is generally greater in the ortho-position than the para- position.[5] In addition to their electronic effects, ortho substituents probably exhibit steric effects[4,5] although not enough data is available from our experiments to determine the relative importance of this effect.



The relative results obtained with aluminum and magnesium amalgam are confusingly erratic. All that can be said about them is that in some cases aluminum amalgam gives better yields while in other cases magnesium amalgam gives better yields. There is no apparent basis for predicting in advance which amalgam will be preferable, although the more aromatic imines appear to work better with magnesium while the more aliphatic amines work better with aluminum. No γ-substituted pyridylmethylamines were isolated from our experiments using either aluminum amalgam or magnesium. This is in contradistinction to the results obtained in the coreduction of pyridine with carbonyl compounds and acid derivatives where aluminum amalgam (but not magnesium amalgam) gives small yields of the γ-isomer.[3,4] The reason for this difference may lie in the very high boiling points of the pyridylmethylamines obtained. The γ-isomers normally boil higher than the α-isomers in these series and may decompose before they reach their boiling points. It is also possible of course that they are not formed in the reaction.

The poor yields obtained with aliphatic imines are probably the results of self-condensations of these substances before they can condense with the pyridine nucleus. Thus Emerson and co-workers[6] have observed that *N*-butylidenebutylamine rapidly forms 2-ethyl-2-hexylidenebutylamine under the catalytic influence of bases. This hypothesis is also in accord with the fact that aluminum amalgam gives better yields with aliphatic amines than does magnesium amalgam. The latter of these metals forms the more basic intermediates in the reaction. It is also in accord with the fact that it is difficult to obtain aliphatic imines in good yields since, in the process of their formation from carbonyl com-

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[1] Taken from a thesis submitted by M. Karickhoff to the faculty of the Graduate School of Purdue University in partial fulfillment of the requirements for the Ph.D. degree, January 1959.

[2] Continental Oil Co. Fellow, 1956–58.

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

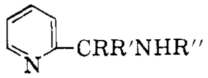
[4] G. B. Bachman and R. M. Schisla, *J. Org. Chem.*, **22**, 1302 (1957).

[5] These observations are also in accord with the results obtained by C. H. Tilford, R. S. Shelton, and M. G. Van Campen, Jr., *J. Am. Chem. Soc.*, **70**, 4001 (1948).

[6] W. S. Emerson, S. M. Hess, and F. C. Uhle, *J. Am. Chem. Soc.*, **63**, 782 (1941).

TABLE I

SUBSTITUTED 2-PYRIDYLMETHYLAMINES AND THEIR DERIVATIVES



| No. | R | R' | R'' | Yield, % |  | B.P. |  | M.P. |  |
|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  | Al | Mg | °C. | (Mm.) | Product | Picrate |
| 1 | Phenyl | Phenyl | Phenyl | 10.6 | 75.0 | 156 | (0.08) | 53 | ... |
| 2 | Phenyl | Hydrogen | Phenyl | 18.8 | 48.5 | 158 | (0.01) | 78 | 175 |
| 3 | Phenyl | Hydrogen | *p*-Chlorophenyl | Trace | 12.7 | 171 | (0.08) | 113 | 158 |
| 4 | Phenyl | Hydrogen | *o*-Chlorophenyl | 0 | 18.1 | 168 | (0.05) | 100 | 154 |
| 5 | Phenyl | Hydrogen | *p*-Tolyl | 34.5 | 34.5 | 166 | (0.03) | 81 | 128 |
| 6 | Phenyl | Hydrogen | *o*-Tolyl | 19.2 | 70.0 | 161 | (0.01) | Oil | 156 |
| 7 | Phenyl | Hydrogen | *p*-Anisyl | ... | 34.2 | 185 | (0.03) | 91 | 131 |
| 8 | Phenyl | Hydrogen | *o*-Anisyl | ... | 27.2 | 176 | (0.02) | Oil | 146 |
| 9 | *p*-Chlorophenyl | Hydrogen | Phenyl | 20.0 | 27.0 | 163 | (0.03) | 80 | 169 |
| 10 | *o*-Chlorophenyl | Hydrogen | Phenyl | 17.8 | 0 | 183 | (0.09) | 96 | 163 |
| 11 | *p*-Tolyl | Hydrogen | Phenyl | 20.0 | 47.5 | 167 | (0.02) | Oil | 163 |
| 12 | Phenyl | Hydrogen | Benzyl | 38.4 | 0 | 184 | (0.03) | Oil | 131 |
| 13 | Phenyl | Hydrogen | Ethyl | 36.8 | 14.9 | 106 | (0.50) | Oil | 150 |
| 14 | Phenyl | Hydrogen | Methyl | 30.0 | ... | 122 | (0.50) | Oil | 195 (d) |
| 15 | Methyl | Isobutyl | Phenyl | 10.3 | 0 | 145 | (0.08) | Oil | Oil |
| 16 | Methyl | Hexyl | Phenyl | 0 | 13.8 | 141 | (0.03) | Oil | Oil |
| 17 | Butyl | Hydrogen | Butyl | 0 | 0 |  |  |  |  |

pounds and primary amines, they tend to condense with themselves and form high molecular weight tars.

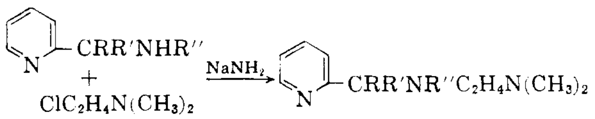
We have also observed that aliphatic acid derivatives give much poorer yields of acylated pyridines than do aromatic acid derivatives. In this case, however, the self-condensation undoubtedly occurs after the formation of the pyridyl ketone since oxidation of the large amounts of high-boiling nitrogeneous byproducts leads to considerable amounts (40% yields) of picolinic acid. Similar oxidations on the tarry byproducts obtained in the coreduction of pyridine and *N*-butylidenebutylamine did not yield picolinic acid, suggesting that in this case self condensation occurs before condensation with the pyridine nucleus can occur.

The structure of the *N*-methyl-1-phenyl-1-(2'-pyridyl)methylamine obtained by the heterogeneous bimolecular reduction of pyridine with *N*-benzylidenemethylamine was established by comparison with the known physical constants for this pyridylmethylamine.[5]

A by-product of these reactions is the homogeneous monomolecular reduction product of the imine. These secondary amines were usually obtained in 10 to 20% yields. Their compositions were confirmed by analyses or by comparison with previously published physical constants.

$$RR'C{=}NR'' \xrightarrow{H_2} RR'CH{-}NHR''$$

The heterogeneous bimolecular reduction of pyridine with imines makes available a series of compounds of potential interest as intermediates in the preparation of pharmaceutically active compounds. As a preliminary step in a proposed study of such preparations we have accomplished the following condensation:



where R = R'' = phenyl and R' = hydrogen.

The product is closely related in structure to compounds known to possess antihistaminic activity.[5]

## EXPERIMENTAL

The following experiments illustrate the procedures used in this investigation:

*Preparation of 1-methylhexylideneaniline.* Methyl hexyl ketone, 256.0 g. (2.0 mol.), aniline, 186.0 g. (2.0 mol.), and benzene, 50 ml., were refluxed together for 24 hr., the water produced (35 ml.) being separated by azeotropic distillation. Distillation of the crude anil through a 30-cm. glass-helix packed column gave the previously undescribed 1-methylhexylideneaniline, 266.0 g. (60% theory), b.p. 96° (1.0 mm.).

*Anal.* Calcd. for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.90; H, 10.40; N, 7.20.

The other imines were prepared similarly. They are adequately described in the literature.

*Preparation of N-phenyl-1-phenyl-1-(2'-pyridyl)methylamine using magnesium amalgam.*[7] Magnesium turnings,

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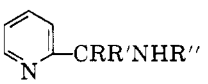
[7] When aluminum was used as the reducing agent, smaller amounts of mercuric chloride, 5.0 g. (0.018 mol.), were used in preparing the amalgam, but the same molar amount of aluminum was used, 13.5 g. (0.5 mol.).

TABLE II



SUBSTITUTED 2-PYRIDYLMETHYLAMINES AND THEIR DERIVATIVES

| No. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|
| 1 | $C_{24}H_{20}N_2$ | 85.68 | 85.63 | 5.99 | 6.01 | 8.33 | 7.98 |
| 2 | $C_{18}H_{16}N_2$ | 83.04 | 83.10 | 6.20 | 6.47 | 10.76 | 10.65 |
| 3 | $C_{18}H_{15}N_2Cl$ | 73.34 | 73.41 | 5.14 | 5.30 | 9.51 | 9.35 |
| 4 | $C_{18}H_{15}N_2Cl$ | 73.34 | 73.63 | 5.14 | 5.40 | 9.51 | 9.48 |
| 5 | $C_{19}H_{18}N_2$ | 83.17 | 82.90 | 6.61 | 6.76 | 10.21 | 10.25 |
| 6 | $C_{19}H_{18}N_2$ | 83.17 | 83.00 | 6.61 | 6.38 | 10.21 | 10.36 |
| 7 | $C_{19}H_{18}N_2O$ | 78.59 | 78.76 | 6.25 | 6.48 | 9.65 | 9.79 |
| 8 | $C_{19}H_{18}N_2O$ | 78.59 | 78.73 | 6.25 | 6.25 | 9.65 | 9.57 |
| 9 | $C_{18}H_{15}N_2Cl$ | 73.34 | 73.60 | 5.14 | 5.40 | 9.51 | 9.61 |
| 10 | $C_{18}H_{15}N_2Cl$ | 73.34 | 73.44 | 5.14 | 4.99 | 9.51 | 9.54 |
| 11 | $C_{19}H_{18}N_2$ | 83.17 | 83.00 | 6.61 | 6.40 | 10.21 | 10.36 |
| 12 | $C_{19}H_{18}N_2$ | 83.17 | 82.90 | 6.61 | 6.45 | 10.21 | 10.04 |
| 13 | $C_{14}H_{16}N_2$ | 79.21 | 79.51 | 7.60 | 7.44 | 13.20 | 13.12 |
| 14 | $C_{13}H_{14}N_2$ | 78.75 | 78.59 | 7.12 | 7.26 | 14.13 | 13.99 |
| 15 | $C_{17}H_{22}N_2$ | 80.27 | 80.42 | 8.72 | 8.95 | 11.01 | 11.09 |
| 16 | $C_{19}H_{26}N_2$ | 80.80 | 81.08 | 9.28 | 9.11 | 9.92 | 10.02 |

12.0 g. (0.5 mol.), mercuric chloride, 50.0 g. (0.18 mol.), and 10 drops of mercury were heated together for 2 hr. at 100°. A mixture of pyridine, 25.0 g., and *N*-benzylideneaniline, 25.0 g., was added to initiate the reaction. A deep violet color developed almost immediately and gradually turned to red-brown over a period of time. Pyridine, 91.0 g. (1.15 mol.), was added and the reaction mixture stirred for 20 min. The remainder of the *N*-benzylideneaniline, 90.5 g. (0.5 mol. total), was added dropwise over a 4-hr. period. During this period it was necessary to add more pyridine, 276.0 g. (3.5 mol.) in order to prevent caking in the reaction flask. During the anil addition and for 6 hr. thereafter heat was supplied so that the pyridine refluxed gently. The partially cooled reaction mixture was poured into a mixture of 500 ml. of 3*N* sodium hydroxide and ice, stirred for 5 hr. at room temperature, and then filtered through Celite. The dark organic layer was separated, and the aqueous layer extracted several times with benzene. The combined extracts and organic layer were dried and the excess pyridine and other volatile materials were removed by distillation at aspirator pressure. The resulting red viscous material was distilled rapidly and gave the following fractions:

| Fraction | B.P. (Mm.) | Amount, G. |
|---|---|---|
| 1 | 70–118 (1.5) | 2.0 |
| 2 | 118–140 (0.5) | 30.0 |
| 3 | 168–210 (0.5) | 52.0 |
| 4 | Residue | 4.0 |

Redistillation of Fraction 2 through a 30-cm. glass-helix packed column yielded *N*-benzylaniline, 15.0 g., b.p. 169–171° (11.0 mm.), $n_D^{25}$ 1.6115, m.p. of hydrochloride 210–212°. Reported values, b.p. 171.5° (10.0 mm.),[8] $n_D^{24.8}$ 1.6118,[9] m.p. of hydrochloride 214–216°.[10] Fraction 3 was redistilled and identified as *N*-phenyl-1-phenyl-1-(2'-pyridyl) methylamine, b.p. 155–162° (0.1 mm.), m.p. of picrate 175°. The yield of yellow viscous material was 40.0 g. or 48.1%. On trituration with petroleum ether this oil slowly solidified. It then recrystallized readily from petroleum ether, m.p. 78–79°.

*Anal.* Calcd. for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 83.10; H, 6.47; N, 10.65.

The coreduction of pyridine with 1-methylhexylideneaniline gave the previously undescribed *N*-(1-methylhexyl)-aniline, b.p. 116–117° (3.0 mm.).

*Anal.* Calcd. for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82. Found: C, 82.13; H, 11.01; N, 6.84.

Similarly 1,3-dimethylbutylideneaniline gave *N*-(1,3-dimethylbutyl)aniline, b.p. 110° (12.0 mm.).

*Anal.* Calcd. for $C_{12}H_{19}N$: C, 81.30; H, 10.80; N, 7.90. Found: C, 81.58; H, 10.51; N, 8.20.

*Preparation of 2-{α-[N-(2-dimethylaminoethyl)-N-phenylamino]benzyl}pyridine or 1-(α-pyridyl)-1,2-diphenyl-5-methyl-2,5-diazahexane.* A solution of *N*-phenyl-1-phenyl-1-(2'-pyridyl)methylamine, 26.0 g. (0.1 mole), in dry toluene, 50 ml., was added to a stirred solution of sodamide, 7.8 g. (0.2 mole) in toluene, 50 ml., at 100°. The mixture was heated on a steam bath for 3 hr. and then treated with a toluene solution of β-dimethylaminoethyl chloride, 27.4 g. (0.19 mole). The reaction mixture was heated and stirred for an additional 24 hr. The cooled reaction mixture was washed with water and the toluene layer separated. The aqueous layer was saturated with potassium carbonate and then extracted with toluene. The combined toluene fractions were dried and distilled. After an initial rapid distillation the crude product was twice distilled using a 12-in. unpacked column. The desired pyridyl derivative boiled at 160–163° (0.03 mm.); yield 10 g. (33.3% theory).

*Anal.* Calcd. for $C_{22}H_{25}N_3$: C, 79.77; H, 7.55; N, 12.69. Found: C, 79.83; H, 7.60; N, 12.48.

*Reaction of pyridine and phenyl hexanoate using aluminum amalgam (nitrogen atmosphere).* The general procedure of Bachman and Schisla[4] was followed in this experiment. Reactants employed were:

| | Grams | Moles |
|---|---|---|
| Aluminum metal | 13.5 | 0.5 |
| Mercuric chloride | 10.0 | 0.032 |
| Phenyl hexanoate | 96.0 | 0.5 |
| Pyridine | 120.0 | 1.5 |

A total reflux period of 43 hr. and additional amounts of mercuric chloride, 5.0 g., were required before most of the

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(8) C. Courtot and P. Petitcolas, *Bull. Soc. Chem.*, [4], **39**, 452 (1926).

(9) P. Groth, *Chem. Krystallographie*, 5th part, Leipzig (1906–19).

(10) K. Brand, *Ber.*, **42**, 3462 (1909).

metal had reacted. Work-up and distillation of the nitrogeneous material gave the following fractions:

| Fraction | B.P. (Mm.) | $n_D^{20}$ | Amount, G. |
|---|---|---|---|
| 1 | 75–84 (2.5) | 1.4624 | 1.6 |
| 2 | 94–104 (2.5) | 1.4832 | 1.9 |
| 3 | 108–110 (2.5) | 1.5010 | 10.5 |
| 4 | Residue | | 5.0 |

Fraction 3 did not give classification tests for a carbonyl compound or a tertiary nitrogen atom. Permanganate oxidation[11] of a 5.0-g. sample of fraction 3 yielded picolinic acid, 1.2 g. (40% based on sample alone, 28.1% based on phenyl hexanoate), m.p. 135°. Reported m.p. 133–134°.[11] Work-up of the neutral fraction gave phenol, 80.0 g.

LAFAYETTE, IND.

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[11] G. R. Clemo and G. R. Ramage, *J. Chem. Soc.*, 440 (1931).

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[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

# β-Cyanoethylation of Phenoxazine and 7*H*-Benzo[c]phenothiazine

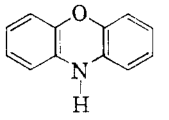
PAULETTE MÜLLER, N. P. BUU-HOÏ, and R. RIPS

*Received June 15, 1959*

Phenoxazine and 7*H*-benzo[c]phenothiazine have been found to condense smoothly with acrylonitrile in the presence of organic alkaline catalysts; α-methylacrylonitrile failed to react. Friedel-Crafts cyclization of β-(10-phenoxazinyl)propionic acid has been performed, and its reaction products are investigated.

From the triad formed by phenoxazine, phenothiazine, and phenoselenazine, the behavior of the last two in β-cyanoethylation reactions has already been investigated, and both phenothiazine[1] and phenoselenazine[2] were found to give the corresponding *N*-propionic acid in good yields.

It is now shown that phenoxazine (I) likewise undergoes smooth β-cyanoethylation with acrylonitrile in the presence of benzyltrimethylammonium methoxide, to give β-(10-phenoxazinyl)propionitrile (II), the reaction being even more energetic than in the case of phenothiazine and phenoselenazine, probably because of its higher solubility in acrylonitrile. In similar and even more drastic experimental conditions, α-methylacrylonitrile failed to undergo condensation. Alkaline hydrolysis afforded β-(10-phenoxazinyl)propionic acid (III); cyclization of this acid could be effected, as in the case of the corresponding propionic acids derived from phenothiazine[1] and phenoselenazine,[2] with phosphorus pentoxide, but afforded two products, both of them yellow, the lower-melting one being 2,3-dihydro-3-keto-1H-pyrido[3,2,1-kl]phenoxazine (IV), as it possessed a reactive keto group and readily gave a phenylhydrazone. The higher-melting product, which did not form a phenylhydrazone in the same conditions, and which contained two atoms less of hydrogen, could be tentatively formulated as the *dehydro* derivative (V) of the former ketone. The differences in the degree of saturation of the two compounds are reflected in their infrared spectra (see Figure 1); in the case of ketone IV, the absorption band characterizing the ketone function is located at 1655 cm.$^{-1}$, while for compound V there are two ketone bands, one at 1630 cm.$^{-1}$ and the other at 1640 cm.$^{-1}$, a splitting resembling that observed with quinones. The infrared spectrum of ketone IV is similar to those of 2,3-dihydro-3-keto-1H-pyrido-[3,2,1-kl]phenoselenazine and its 10-chloro- derivative (see Figure 2).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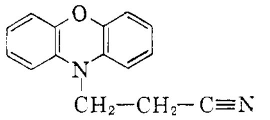
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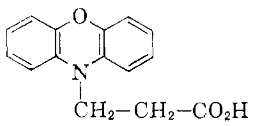
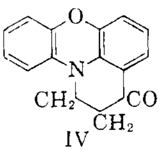
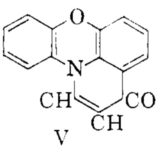
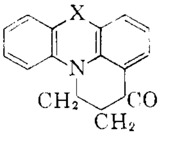
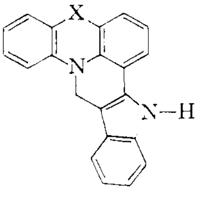

III


IV


V

In the framework of our investigations on potential carcinogenic nitrogen-containing heterocycles, the phenylhydrazones of ketone IV and of its analogs 2,3-dihydro-3-keto-1H-pyrido[3,2,1-kl]phenothiazine (VI; X = S) and 2,3-dihydro-3-keto-1H-pyrido[3,2,1-kl]phenoselenazine (VI; X = Se) were converted by Fischer cyclizations into indolo[3′,2′-2,3]-1H-pyrido[3,2,1-kl]phenoxazine (VII) and its phenothiazine and phenoselenazine analogs (VIII) and (IX). The Pfitzinger reaction of ketone (VI; X = S) with isatin afforded 4′-carboxyquinoleino[3′,2′-2,3]-1H-pyrido[3,2,1-kl]phenothiazine (X; X = S), which underwent


VI


{VII; X = O
VIII; X = S
XI; X = Se

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[1] N. L. Smith, *J. Org. Chem.*, **15**, 1125 (1950).

[2] P. Müller, N. P. Buu-Hoï, and R. Rips, *J. Org. Chem.*, **24**, 37 (1959).