zation from methanol afforded 10.5 g. (69% yield) of the hydrochloride salt of XX as small, colorless crystals, m.p. 233–235°.

Decomposition of the salt provided XX, colorless needles from benzene-petroleum ether, m.p. 119–120° (lit.[8] gives m.p. 119°).

Acknowledgment. The authors are grateful to Mr. D. F. Cortright and Miss Mary Unroe for the ionic halogen and basic nitrogen determinations and for measurements of ultraviolet spectra, and to Mr. R. H. Shiley of these laboratories for preparing one of the compounds. Special thanks are also due Dr. T. B. O'Dell and his associates for furnishing the biological data.

DECATUR, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HOPE COLLEGE]

Synthesis of a Series of Derivatives of Ethyl 2-Pyridylacetate

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Monosubstitution on the methylene group of ethyl 2-pyridylacetate (I) was effected by allowing its sodium derivative to react with alkyl, allyl, and aryl halides. Substitution was shown to be on the methylene group by hydrolyzing and decarboxylating the butyl derivative of (I) to give α-amylpyridine. Benzoyl chloride reacted with I to give α-dibenzoyl-α-(2-pyridyl)-acetate. The aldehyde functions of benzaldehyde and of hexaldehyde were condensed with the methylene group in the presence of a basic catalyst. Acrolein underwent a Michael addition with I in the presence of sodium ethoxide. Nitrosation yielded the oxime.

A number of reactions of I have been reported by previous investigators: the Michael condensation[1] with acrylonitrile to form γ-carbethoxy-γ-(2-pyridyl)butyronitrile (II), the reactions[2] with ethyl chloroacetate and potassium ethoxide to form ethyl 2-pyridyinsuccinate (III), with ethyl formate and potassium to form ethyl hydroxymethylene(2-pyridyl)acetate (IV), and with γ-phenoxypropyl bromide and potassium in diethyl ether to for ethyl phenoxy-α-(2-pyridyl)valerate (V), the condensation[3] with β-phenoxyethyl bromide to form ethyl α-(2-pyridyl)-γ-phenoxy-*n*-butyrate (VI), and the preparation of ethyl α-bromo-2-pyridylacetate[4] (VII) by the addition of I to a solution of bromine in carbondisulfide.

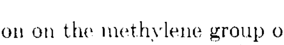
In our laboratory the sodium derivative of I, prepared in benzene, reacted with butyl bromide giving a 50% yield of ethyl α-(2-pyridyl)caproate (VIII). By using hexyl bromide, a similar yield of ethyl α-(2-pyridyl)caprylate (IX) was obtained. Lesser yields were obtained when such basic reagents as sodium hydride, sodium amide, sodium ethoxide, phenyllithium, or butyllithium were employed. The butyl derivative of I was converted to amylpyridine by hydrolysis and decarboxylation according to the method described by Doering and Pasternak.[5] The sodium derivative of I, prepared by using sodium ethoxide, reacted with benzyl chloride to give ethyl α-(2-pyridyl)-β phenylpropionate (X) in 52% yield. X was hydrolized and decarboxylated to 2-phenylethylpyridine (dihydro-α-stilbazole).

As a representative aliphatic unsaturated compound, allyl bromide was added to the sodium salt of I and gave a 27% yield of ethyl α-(2-pyridyl)-Δ^4-pentenoate (XI). Sodium in benzene when used as a basic catalyst provided a better yield than sodium ethoxide in ethanol.

Benzoyl chloride was found to react spontaneously with I to give what proved to be ethyl α-dibenzoyl-α-(2-pyridyl)acetate (XII) in 38%

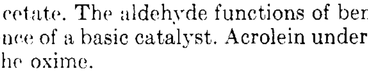
Chart 1

Reaction Products of Ethyl(2-Pyridyl)acetate



I. $R_1 = H; R_2 = H$

II. $R_1 = H; R_2 = CH_2CH_2CH_2CN$



III. $R_1 = H; R_2 = CH_2{-}\underset{\underset{O}{\|}}{C}{-}OC_2H_5$

IV. $R_1R_2 = {=}CHOH$

V. $R_1 = H; R_2 = CH_2CH_2CH_2OC_6H_5$

VI. $R_1 = H; R_2 = CH_2CH_2OC_6H_5$

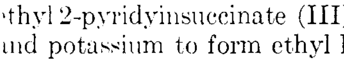
VII. $R_1 = H; R_2 = Br$

VIII. $R_1 = H; R_2 = CH_2CH_2CH_2CH_3$

IX. $R_1 = H; R_2 = CH_2CH_2CH_2CH_2CH_2CH_3$

X. $R_1 = H; R_2 = CH_2C_6H_5$

XI. $R_1 = H; R_2 = CH_2CH{=}CH_2$



XII. $R_1 = \underset{\underset{O}{\|}}{C}C_6H_5; R_2 = \underset{\underset{O}{\|}}{C}C_6H_5$

XIII. $R_1R_2 = {=}CHC_6H_5$

XIV. $R_1R_2 = {=}CH(CH_2)4CH_3$

XV. $R_1 = H; R_2 = CH_2CH_2CHO$

XVI. $R_1R_2 = {=}NOH$

XVII. $R_1 = H; R_2 = NH_2$

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(1) V. Boekelheide, W. J. Linn, P. O'Grady, and M. Lamborg, *J. Am. Chem. Soc.*, **75**, 3243 (1953).

(2) G. R. Clemo, W. McG. Morgan, and R. Raper, *J. Chem. Soc.*, 965 (1937).

(3) K. Winterfield and J. Augstein, *Naturwissenschaften*, **40**, 362 (1953).

(4) O. E. Edwards, M. Chaput, F. H. Clarke, and T Singh, *Can. J. Chem.*, **32**, 785 (1954).

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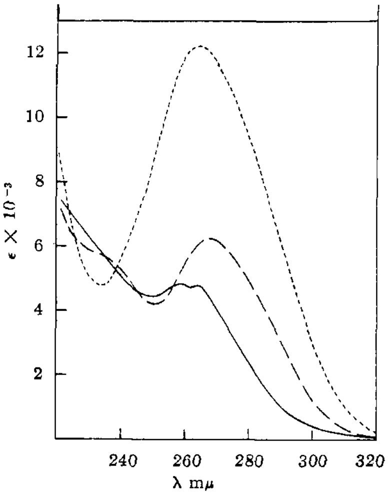


Fig. 1. The ultraviolet absorption of XVI. Solid line, in 0.1*N* hydrochloric acid; dashed line, in *p*H 7; dotted line, in 0.1*N* sodium hydroxide. Cary-11 Spectrophotometer

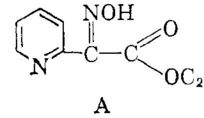
yield. No monosubstituted compound was isolated, either through the use of I or its sodium salt. Several attempts to isolate a similar compound using acetyl chloride failed.

The procedure by Cope and Hofmann[6] was found to be the most satisfactory for the condensation of aldehydes with I. Benzaldehyde condensed to give a 41% yield of ethyl α-(2-pyridyl)-β-phenylacrylate (XIII), while *n*-hexaldehyde gave a 35% yield of ethyl α-(2-pyridyl)-Δ²-octenoate (XIV).

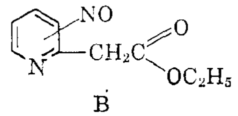
Acrolein was found to add to I in absolute ethanol in the presence of a catalytic amount of sodium ethoxide to give a 24% yield of γ-carbethoxy-γ-(2-pyridyl)butyraldehyde (XV).[7]

The procedure of Adkins and Reeve[8] was used to convert I to ethyl α-oximino-β-(2-pyridyl)acetate (XVI) in 84% yield. The reduction of XVI in a Parr hydrogenator yielded the corresponding amino compound (XVII).

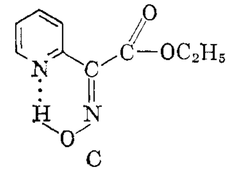
Physical methods[9] were used to show that the nitrosation took place on the α-carbon atom (A) rather than on the ring (B). The infrared spectrum determined with a Beckman IR-7 Spectrophotometer in a potassium bromide plate, showed a C=N group at 1640 cm.⁻¹ The broad low intensity band in the infrared around 2600 cm.⁻¹ could arise from hydrogen bonding of the oxime, as in (C).



A



B



C

Of course, the oxime could also be bonded to the carbonyl of the ester, although the wave length of the ester band does not indicate this. The ultraviolet curves showed no evidence for the nitroso group (B). The increased absorption in alkaline solution was consistent with the ionization of the hydroxyl group attached to a chromophore. Dissociation constants,[10] pK_a 2.5 and pHk_a 9.5 were obtained in a 50% methanol-50% water mixture. Yields were generally smaller than those obtained in similar reactions with ethylacetoacetate or malonic ester. Various amounts of I (up to 30% of the original amount used) were recovered. In general, there was considerable decomposition during the preparation and isolation of the products.

EXPERIMENTAL[11]

Ethyl (2-pyridyl)acetate (I). This compound was prepared from ethyl chloroformate and 2-picollithium according to a modification of the method by Zimmer and George[12] who synthesized 4-picollithium. After the reaction of the two compounds, 200 ml. of water was added to dissolve the solid, followed by an aqueous paste of 50 g. of sodium carbonate. The ether layer was dried over anhydrous sodium sulfate and distilled under reduced pressure. A 30% yield was obtained.

Ethyl α-(2-pyridyl)caproate (VIII). To a solution of 33 g. (0.2 mole) of I in 250 ml. of dry benzene was added 4.6 g. (0.2 mole) of sodium. This mixture was kept at 50° for 6 hr. after which 24 g. (0.23 mole) of butyl bromide was added over a period of 10 min. and the solution refluxed, with stirring, for 12 hr. The benzene solution was washed with six 50-ml. portions of water. The water washes were neutralized with dilute hydrochloric acid and extracted three times with 50-ml. portions of benzene. The combined benzene solutions were dried over anhydrous magnesium sulfate, distilled under reduced pressure to remove the benzene, and separate the remaining liquid from a black residue which was formed during the reaction. Redistillation yielded 22 g. (50%) b.p. 117-121° (2.5 mm.), n_D^{25} 1.4906.

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.54; H, 8.67; N, 6.33. Found: C, 70.68; H, 8.51; N, 6.27.

Picrate of α-amylpyridine. A 5-g. sample of (XIII) was hydrolized and decarboxylated by refluxing with hydrochloric acid for 8 hr. The resulting solution was neutralized with 10% sodium hydroxide. The ether extractable material yielded the picrate the melting point of which compared favorably with the known melting point of α-amylpicrate, 73°.

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(6) A. C. Cope and C. M. Hofmann, *J. Am. Chem. Soc.*, **63**, 3456 (1941).

(7) O. A. Moe and D. T. Warner (to General Mills, Inc.), U. S. Patent **2,599,653**, June 10, 1952; *Chem. Abstr.*, **47**, 3339h (1952).

(8) H. Adkins and E. W. Reeve, *J. Am. Chem. Soc.*, **60**, 1328 (1938).

(9) Determinations and interpretations: J. M. Vandenbelt, Parke-Davis Research Laboratories, Ann Arbor, Mich.

(10) T. V. Parke and W. W. Davis, *Anal. Chem.*, **26**, 642 (1954).

(11) All melting points uncorrected.

(12) H. Zimmer and D. K. George, *Chem. Ber.*, **89**, 2285 (1956).

Ethyl α-(2-pyridyl)caprylate (*IX*). The procedure for VIII was employed except that hexyl bromide was used instead of butyl bromide. Twenty-four grams (50%) was obtained, b.p. 181–184° (21 mm.), n_D^{25} 1.4855.

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.24; H, 9.32; N, 5.62. Found: C, 72.35; H, 9.10; N, 5.45.

Ethyl α-(2-pyridyl)-β-phenylpropionate (X). Four and six-tenths grams (0.2 mole) of sodium was dissolved in 200 ml. of absolute ethanol, followed by the addition of 33 g. (0.2 mole) of I, stirring for 1 hr., dropwise addition of 48 g. (0.29 mole) of benzyl chloride in 50 ml. of absolute ethanol, and refluxing with stirring for 6 hr. The alcohol was removed under reduced pressure and the residue was dissolved in 100 ml. of ether. The ether solution was washed with two 50-ml. portions of 10% sodium carbonate solution and dried over anhydrous sodium sulfate. Distillation yielded 26 g. (52%), b.p. 204–209° (18 mm.), n_D^{20} 1.5451.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27, H, 6.71; N, 5.49. Found: C, 75.40; H, 6.93; N, 5.44.

2-Phenylethylpyridine (*dihydro-α-stilbazole*). Twenty-five grams of X was hydrolized and decarboxylated to yield 15 g. (86%) of the product, b.p. 157–158° (18–20 mm.). The melting points of the picrate (125–127°) and hydrochloride (102–103°) agree with those found by Bergstrom and co-workers.

Ethyl α-(2-pyridyl)-Δ^4-pentenoate (XI). Twenty-eight grams (0.23 mole) of allyl bromide was added dropwise to the sodium salt of 33 g. (0.2 mole) of I in benzene. After stirring for 2 hr. the solution was refluxed for 6 hr. The benzene solution was washed with two 50-ml. portions of water and dried over anhydrous sodium sulfate. Fractional distillation yielded 11 g. (27%) of the compound, b.p. 163–168° (18 mm.).

Anal. Calcd. for $C_{12}H_{15}NO_2$: N, 6.83, Found: *N*, 6.46.

Ethyl α-dibenzoyl-α-(2-pyridyl)acetate (XII). Fourteen and one-half grams (0.1 mole) of benzoyl chloride was stirred with 8 g. (0.05 mole) of I for 1 hr. One hundred milliliters of ether was added to the viscous material. After stirring for 12 hr. the crystalline compound was recrystalized from a methanol-water mixture, yield 10 g. (53%), m.p. 120–122°.

Anal. Calcd. for $C_{25}H_{19}NO_4$: C, 73.93; H, 5.10; N, 3.75. Found: C, 73.93; H, 4.67; N, 3.80.

Ethyl α-(2-pyridyl)-β-phenylacrylate (XIII). Thirty-three grams (0.2 mole) of I, 28 g. (0.23 mole) of benzaldehyde, 0.7 g. of piperidine, 2.5 g. of acetic acid, and 100 ml. of benzene were mixed and refluxed on a constant water-separating distilling apparatus for 7 hr. Fractional distillation yielded 21 g. (41%), b.p. 145° (0.3 mm.), n_D^{25} 1.5965.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.66; H, 6.35; N, 5.44.

Ethyl α-(2-pyridyl)-Δ^2-octenoate (XIV). Twenty-three grams (0.23 mole) of *n*-hexaldehyde was used in place of benzaldehyde in the previous experimental procedure, yield 17 g. (35%), b.p. 194–196° (25 mm.).

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.83; H, 8.57; N, 5.66. Found: C, 72.67; H, 8.48; N, 5.72.

γ-Carbethoxy-γ-(2-pyridyl)butyraldehyde (XV). At a temperature of 0°, 100 ml. of absolute ethanol, 0.03 g. of finely cut sodium, and 33 g. of I, protected by an atmosphere of nitrogen, was stirred constantly while 11.8 g. (0.21 mole) of acrolein was added. The mixture was stirred at 0° for 3 hr. followed by refrigeration for 12 hr. The solution was neutralized with a few drops of acetic acid and was fractionally distilled to yield 9 g. (24%) of product, b.p. 115–116° (0.3 mm.), n_D^{25} 1.5073. The compound gave a positive aldehyde test with Fuchsin reagent.

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.13; H, 6.85; N, 6.33. Found: C, 64.93; H, 6.70; N, 6.35.

Ethyl α-oximino-α-(2-pyridyl)acetate (XVI). A solution of 33 g. (0.2 mole) of I in 50 ml. of glacial acetic acid was cooled in an ice bath and 15.9 g. (0.23 mole) of sodium nitrite in 40 ml. of water was added over a period of 30 min., keeping the temperature between 15 and 25°. The mixture was stirred for an additional 30 min., 120 ml. of water was added, and the stirring continued for two more hours. The crystals were washed with water, washed four times with 5% sodium bicarbonate solution, and again with water. Recrystallization from methanol yielded 32 g. (84%) of white needles, m.p. 149–150°.

Ethyl α-amino-α-(2-pyridyl)acetate (XVII). Nine and seven-tenths grams (0.05 mole) of XVI, 150 ml. of absolute ethanol, and 1 g. of 5% palladium on charcoal catalyst were placed in a Parr hydrogenator for 3 hr. at an initial pressure of 50 lbs. After the removal of the catalyst, fractional distillation resulted in 6 g. (75%) of the amino compound, b.p. 103° (0.3 mm.), n_D^{25} 1.5163.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.89; H, 6.71; N, 15.55. Found: C, 60.26; H, 6.76; N, 15.60.

Physical methods for identification of the oxime (XVI). Infrared analysis indicated a C=N bond at 1660 cm.$^{-1}$ Ultraviolet analysis showed no indication of a nitroso group. Increased absorption in alkaline solution was observed. Two ionization constants, pK_a 2.5 and pK_a 9.5 were obtained for the oxime in a 50% methanol-50% water solution.

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HOLLAND, MICH.

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