dine, acetic anhydride, acetic acid, and zinc lead to low yields of 35–41% based on the pyridine charged. Because of the increased interest in 4-substituted pyridines, particularly derivatives of isonicotinic acid, an investigation was undertaken to develop an improved synthesis of 4-ethylpyridine.

Theoretically, one half of the charged pyridine is regenerated in the course of the reaction so the maximum yield of 4-ethylpyridine is only 50%.[6] In the present modified procedure the regenerated pyridine, in the reaction mixture, was subjected to further treatment in this same reaction mixture, was subjected to further treatment in this same reaction mixture, to increase the overall yield to 75%. Without using the regenerated pyridine, crude yields were increased from previously reported 35.5–41% to 48–50%. By using the regenerated pyridine, in what is referred to as the cyclic process, crude yields up to 78% were obtained. Yields of over 80% were obtained, based upon recovered pyridine. Less expensive iron powder (Belmont 98%) was substituted for activated zinc.[7] (It was found that regular zinc powder gave yields similar to those obtained employing activated zinc). Iron filings and impure iron powder resulted in lower yields compared to pure powder. It was also determined that the violent exothermic reactions that occurred during certain stages of the original procedure were more readily controlled by running the reaction at higher temperatures and adding the iron at about 80–100° C. instead of 35–40° C. Water was used to replace acetic acid at one stage of the reaction, and benzene was substituted for chloroform in the extraction of the product.

A study of the influence of the initial concentration of acetic acid was also made. The experimental results indicated that this is important, and in the cyclic process a large initial quantity of the acid has an adverse effect, probably because the unreacted acid competes with acetic anhydride by forming a salt with pyridine in the second phase of the process.

Where the maximum theoretical yield of 4-ethylpyridine is 50%, the process is referred to as phase and where the regenerated pyridine is further treated, without prior separation from the reaction mixture, the process is referred to as cyclic.

EXPERIMENTAL

Phase process (*optimum conditions*). To 200 g. of pyridine, in a flask equipped with a thermometer, a $^1/_{15}$ h.p. motor and a sealed stainless steel stirrer, was added 600 ml. of acetic anhydride. The temperature was raised to 80° C., and 165 g. of iron powder (Belmont Grade 98.5%) was added, in portions, over a 1-hr. period, maintaining the same temperature. Over a 0.5-hr. period 30 ml. of water was added and the temperature was not permitted to exceed 97° C. The mixture was cooled to 90° C. and 103 g. of iron powder was added, in portions, over a 0.5-hr. period, the temperature being maintained between 80–90° C. The temperature of the reaction mixture was raised to 136° C. over a 0.5-hr. period and reflux maintained for 1.5 hr. With provisions for cooling, 500 ml. of water was slowly and carefully added, not permitting the temperature to exceed 110° C. After the water was added, the *p*H of the mixture was adjusted to 9.5–10 with 50% caustic and then steam distilled. The oily layer of the steam distillate was separated and the lower aqueous phase was saturated with potassium carbonate and then extracted with three 175 ml. portions of benzene. The benzene extracts were combined with the oily layer, dried over anhydrous potassium carbonate, and fractionated at atmospheric pressure. The fraction, b.p. 145–167° C., n_D^{23} 1.500 was collected, 131.0 g. (49.5%). Redistillation of the product gave 120.3 g., b.p. 160–167° C., yield, 45.5%. By titration of the lower boiling fractions with standard alkali, 92 g. as pyridine was accounted for.

Cyclic process. From a series of 12 runs, the following procedure was found to give optimum yields. Employing the same apparatus, as previously described for the phase process, 100 g. of pyridine and 300 ml. of acetic anhydride were heated to 80° C. and 84 g. of iron powder was gradually added over a 0.5-hr. period. The temperature was maintained at 80° C. for 1.5 hr., 30 ml. of acetic acid was added followed by the gradual addition of 42 g. of iron powder over 0.5-hr. Then 150 ml. of acetic anhydride was added and the temperature raised to 137° C. and maintained there for 1 hr. An additional 100 ml. of acetic anhydride was then added, permitting the temperature to fall to 127° C. Over the next 0.5-hr., 50 g. of iron powder was gradually added and the temperature rose to 136° C. The very viscous reaction mixture was stirred vigorously for 0.5 hr. and 60 ml. of acetic acid were added, producing a more fluid reaction mixture. At 136° C., a fourth gradual addition of 25 g. of iron powder was made over a 0.5-hr. period, and reflux maintained for 0.5 to 1 hr. Water and 50% caustic were then carefully added, permitting the temperature to remain above 100° C., while applying cooling. The reaction mixture was then treated as previously described. The crude yield was 102 g. of product, b.p. 145–170° C., n_D^{23} 1.500 (78%). Four grams of product boiling above 170° C. were also obtained, n_D^{23} 1.499. Fractionation of the crude resulted in a product, b.p. 160–167° C., n_D^{23} 1.500, neutralization equivalent 109, yield 70.5% of theory.

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Derivatives of (1-Aminocyclohexyl)methanol

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Nitrocyclohexane undergoes base-catalyzed condensations with formaldehyde to give (1-nitro-

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cyclohexyl)methanol (I) in 93% yield,[2,3] and with acetaldehyde to give 1-(1-nitrocyclohexyl)ethanol in unstated yield.[4] High pressure catalytic hydrogenation of I gives (1-aminocyclohexyl)methanol (II) in 43[3]–80[2]% yield. High pressure hydrogenation is unnecessary, however, since we have obtained II in 50–60% yield by hydrogenation of I over a Raney nickel catalyst at an initial pressure of 2 atm. in methanol, absolute ethanol, or 1,4-dioxane solutions, or without solvent. II was first prepared, in excellent yield,[5] from cyclohexanone through a Strecker synthesis,[6] followed by high-pressure catalytic hydrogenation of the ethyl ester of the α-aminoacid.

The amino alcohol II yielded dibenzoyl and diacetyl derivatives having both ester and amide groups, as shown by the presence in their infrared spectra of both ester and amide (amide I) carbonyl bands and NH stretching and amide NH deformation (amide II) bands. Refluxing of the diacetyl derivative with ethanol in the presence of sulfuric acid removed an acetyl group, yielding the acetamide of II.[7] The corresponding formamide of II was obtained by refluxing II with formic acid. That the formamide and acetamide of II are amide-alcohols and not amino-esters is shown by their neutrality and by the presence in their infrared spectra of amide I and II bands and the absence of ester carbonyl bands.

The 2-oxazolidone (III) of the amino alcohol II has previously been obtained in 89% yield by heating II with diethyl carbonate in the presence of sodium methoxide.[2] We have also obtained III in 34% yield by heating II with urea at 185° without a catalyst. It was hoped that II could likewise be converted to the heterocyclic spiranes IV and V. Precedent exists for the formation from ethanolamines and acetic acid of 2-oxazolines[8] containing the heterocyclic ring of IV (see Fig. 1). Models indicate, however, that the presence of unsaturation in the 2-oxazoline ring of the 5-6 spirane IV would impose a very considerable strain. Compound IV was not obtained. Refluxing of II with excess diethyl oxalate also did not yield the saturated heterocyclic 6-6 spirane V (see Fig. 1), but rather the oxamide of II, indicating that in this case the preferred reaction course is *inter*molecular amine-ester interchange. That this oxalyl derivative is the diamide and not the diester with free amino groups is shown by its neutrality and by the presence in its infrared spectra of amide I and II bands and the absence of the ester carbonyl-band. The formation of the oxamide of II is consistent with the fact that the normal products of ester-ethanolamine reactions, isolated without acid treatment, are the corresponding ethanolamides.[9]

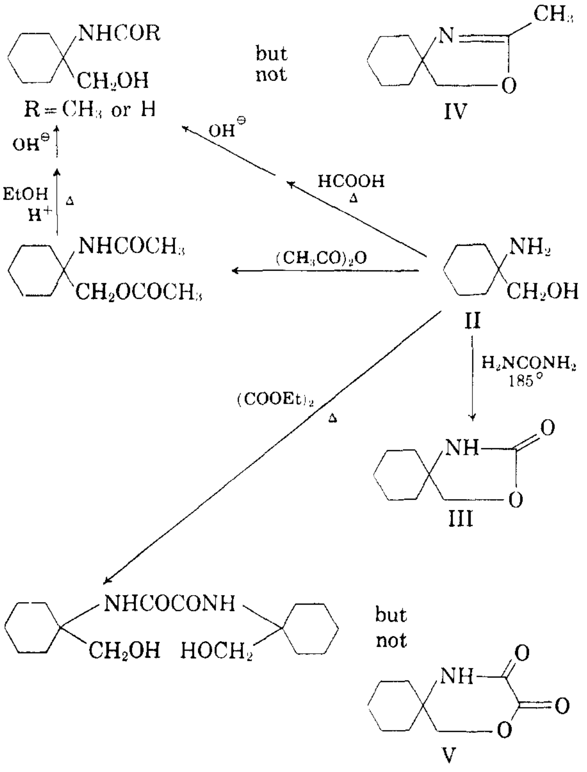

Fig. 1. Some Reactions of (1-Aminocyclohexyl)methanol (II)

EXPERIMENTAL

Melting points were determined on a calibrated Kofler micro hot stage.

(*1-Nitrocyclohexyl)methanol* (I). The compound was obtained in about 80% yield by a modification of the method of Newman and Edwards[2] in which 20% methanolic potassium hydroxide (50 cc.) was added slowly, with occasional shaking, to a mixture of nitrocyclohexane[10] (1 mole) and paraformaldehyde (1 mole of CH_2O) containing 250 cc. of methanol to moderate the reaction. After the paraformaldehyde had dissolved slowly as the temperature rose to 52°, the solution was refluxed for 1 hr. and let stand overnight. Our analytical sample had the following properties: n_D^{25} 1.4845; ν_{OH} (cm.$^{-1}$) 3390, ν_{NO_2} 1542, 1352; m.p. ~ 0–4°; b.p. 136–137° (5.5 mm.). Reported:[2] n_D^{20} 1.4853; b.p. 113–114° (3 mm.).

Anal. Calcd. for $C_7H_{13}NO_3$: C, 52.81; H, 8.23; N, 8.80. Found: C, 52.91; H, 8.46; N, 9.00.

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(2) M. S. Newman and W. M. Edwards, *J. Am. Chem. Soc.*, **76**, 1840 (1954).

(3) W. B. Wheatley, *J. Am. Chem. Soc.*, **76**, 2832 (1954).

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(7) A referee has kindly pointed out that the acid hydrolysis of the diacetyl derivative of II probably yielded a salt of the aminoacetate of II, which then rearranged under the alkaline conditions of the workup procedure to the acetamide of II. Such rearrangements are normal for ethanolamines: A. P. Phillips and R. Baltzly, *J. Am. Chem. Soc.*, **69**, 200 (1947).

(8) S. H. Shapiro, "Nitroparaffin Symposium," Commercial Solvents Corp., New York, N. Y., 1956, p. 21.

(9) See reference in note 7.

(10) We are grateful to the E. I. du Pont de Nemours & Co., Inc., Explosives Department, for a one-gallon sample of nitrocyclohexane.

(1-Nitrocyclohexyl)methyl 3,5-dinitrobenzoate (3,5-dinitrobenzoate of I). From benzene–light petroleum (b.p. 60–68°), white platelets, m.p. 131–132.5°. $\nu_{\text{C=O}}$ (cm.$^{-1}$) 1733 in Nujol, 1742 in CS_2; ν_{NO_2} 1545, 1347 in Nujol, 1339 in CS_2.

Anal. Calcd. for $C_{14}H_{15}N_3O_8$: C, 47.59; H, 4.28; N, 11.90. Found: C, 47.49; H, 4.19; N, 12.06.

(1-Aminocyclohexyl)methanol (II). (1-Nitrocyclohexyl)methanol was hydrogenated in methanol with Raney nickel catalyst at an initial pressure of 2 atm. at room temperature in a Parr low pressure hydrogenation apparatus, causing the mixture to become quite warm. After removal of the catalyst and solvent, the crude product was taken up in ether and extracted with dilute hydrochloric acid. The acid extract was washed with ether, strongly basified with concentrated potassium hydroxide solution, salted out with sodium chloride, and extracted repeatedly with ether. Drying and evaporation of the ether extracts, followed by vacuum distillation of the residue, gave colorless, syrupy (1-aminocyclohexyl)methanol (60% yield), having a potent sperm-like odor. Our analytical sample had the following properties: n_D^{25} 1.4959; ν_{OH} (cm.$^{-1}$) ~3260 (broad), ν_{NH} 1589; m.p. ~37–39.5° (but readily supercools); b.p. 84° (1 mm.). Reported: n_D^{20} 1.4970,[5] 1.4964[3]; b.p. 117–118° (27 mm.),[5] 114–118° (14 mm.),[3] 111–114° (13 mm.).[2]

Anal. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.99; H, 11.45; N, 10.85.

(1-Aminocyclohexyl)methanol hydrochloride (hydrochloride of II).[11] From chloroform-petroleum (b.p. 90–100°), white crystals, m.p. 161.5–163.5°. Reported:[5] m.p. 158–159°, but no analyses were given.

Anal. Calcd. for $C_7H_{16}ClNO$: C, 50.75; H, 9.74; N, 8.46. Found: C, 51.05; H, 9.71; N, 8.43.

(1-Aminocyclohexyl)methanol sulfate (sulfate of II). White needles, m.p. 237.5–240.5°, from ethanol.

Anal. Calcd. for $C_{14}H_{32}N_2O_6S$: C, 47.17; H, 9.05; N, 7.86. Found: C, 46.71; H, 9.01; N, 8.08. Qualitative analysis showed sulfur to be present.

(1-Benzamidocyclohexyl)methyl benzoate (dibenzoyl derivative of II). The compound was prepared by the Schotten-Baumann reaction. From methylene chloride–light petroleum (b.p. 60–68°), white featherlets, m.p. 100–102°. ν_{NH} (cm.$^{-1}$) 3330, 1537 in Nujol, 3420 in CS_2; $\nu_{\text{C=O}}$ 1720, 1643 in Nujol, 1719, 1671 in CS_2.

Anal. Calcd. for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.76; H, 6.81; N, 4.16.

(1-Acetamidocyclohexyl)methyl acetate (diacetyl derivative of II). The ester was obtained by warming (1-aminocyclohexyl)methanol with acetic anhydride on the steam bath for 4.5 hr. From methylene chloride-light petroleum (b.p. 60–68°), thick, white needles, m.p. 63–66.5°. ν_{NH} (cm.$^{-1}$) 3290, 3190, 1552 in Nujol solution, 3410, 3300 in CS_2, 3410, 3310 in $CHCl_3$; $\nu_{\text{C=O}}$ 1745, 1644 in Nujol solution, 1736, 1654 in CS_2, 1725, 1651 in $CHCl_3$.

Anal. Calcd. for $C_{11}H_{19}NO_3$: C, 61.94; H, 8.98; N, 6.57. Found: C, 62.21; H, 8.98; N, 6.58.

(1-Acetamidocyclohexyl)methanol (acetamide of II). A solution of (1-acetamidocyclohexyl)methyl acetate (1.00 g., 0.00469 mole) and concentrated sulfuric acid (0.25 cc.) in 95% ethanol (15 cc.) was refluxed for 2.5 hr. After distillation of the ethanol, the residue was made slightly basic with sodium bicarbonate solution and extracted repeatedly with ether. Evaporation of the ether extracts, solution of the residual oil in methylene chloride and light petroleum (b.p. 60–68°), concentration, and cooling in an ice bath caused precipitation of small white needles (0.23 g., 0.00134 mole, 29%). Several recrystallizations from methylene chloride-light petroleum gave small white needles of (1-acetamidocyclohexyl)methanol, m.p. 121–123°. ν_{NH} (cm.$^{-1}$) 3300, 1548 in Nujol, 3430, 3310 in $CHCl_3$; $\nu_{\text{C-O}}$ 1646 in Nujol, 1653 in $CHCl_3$.

Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.13; H, 10.00; N, 8.18. Found: C, 63.16; H, 9.97; N, 8.15.

(1-Formamidocyclohexyl)methanol (formamide of II). (1-Aminocyclohexyl)methanol (3.9 g., 0.030 mole) and anhydrous formic acid (10 cc., 0.26 mole) were refluxed for 4 hr. When the reactants were mixed, considerable heat was evolved and a white precipitate formed, probably the formic acid salt, but this dissolved as the reactants were warmed to reflux. The cooled solution was poured into water (30 cc.), neutralized, and saturated with solid sodium carbonate and allowed to evaporate to dryness at room temperature. The crystalline residue was extracted repeatedly with methylene chloride. Evaporation of the methylene chloride and recrystallization from methylene chloride-light petroleum (b.p. 60–68°) gave white crystals (1.01 g., 0.0064 mole, 21%). Three more recrystallizations yielded dense, granular white crystals of (1-formamidocyclohexyl)methanol (0.73 g., 0.0046 mole, 15%), m.p. 124–125.5°. ν_{NH} (cm.$^{-1}$) 1548 in Nujol, 3400 in $CHCl_3$; ν_{OH} ~3180 (broad) in Nujol; $\nu_{\text{C=O}}$ 1659 in Nujol, 1674 in $CHCl_3$.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.13; H, 9.73; N, 8.94.

3-Oxa-1-azaspiro[4,5]decan-2-one (III) (*2-oxazolidone of II*). The compound was obtained in 34% yield by heating (1-aminocyclohexyl)methanol with a 100% molar excess of urea at 185° for 1 hr. without catalyst. From methylene chloride-light petroleum, white, chunky crystals, m.p. 82–84.5°. ν_{NH} (cm.$^{-1}$) 3210, 1544 in Nujol, 3240 in CCl_4; $\nu_{\text{C=O}}$ 1748 in Nujol and in CCl_4. Reported:[2] m.p. 81–82°.

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.22; H, 8.26; N, 9.01.

N,N′-Bis(1-hydroxymethylcyclohexyl)oxamide (oxamide of II). (1-Aminocyclohexyl)methanol (4.4 g., 0.034 mole), diethyl oxalate (9.9 g., 0.068 mole), and 1,4-dioxane (125 cc.) were refluxed for 15 hr. The mixture was poured into water, causing the precipitate to dissolve, giving an acidic solution. The solution was made slightly basic with sodium bicarbonate and extracted several times with ether. The ether extracts were dried, distilled, and the residual dioxane solution was evaporated on the steam bath in a current of air, leaving a brown oil, which crystallized on standing. Four recrystallizations, one with charcoal, from methylene chloride-light petroleum (b.p. 60–68°) yielded white platelets of *N,N′*-bis(1-hydroxymethylcyclohexyl)oxamide (0.75 g., 0.0024 mole, 14%), m.p. 174.5–176.5°. ν_{NH} (cm.$^{-1}$) 3420, 3350, 1518 in Nujol, 3370, 1516 in $CHCl_3$; $\gamma_{\text{C=O}}$ 1664 in Nujol, 1672 in $CHCl_3$.

Anal. Calcd. for $C_{16}H_{28}N_2O_4$: C, 61.51; H, 9.03; N, 8.97. Found: C, 61.46; H, 8.82; N, 8.92.

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[11] Prepared by James H. Cooley.

Urea Complexes of Some Higher Methylalkanes

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The principal requirement for the formation of crystalline channel inclusion complexes by urea and a hydrocarbon is the presence of a sufficiently long normal carbon chain in the hydrocarbon molecule. While studying the requirement for the for-

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