TABLE I

HYDROGENATION OF UNSATURATED ESTERS AT ROOM TEMPERATURES OVER RANEY NICKEL

(M is malonate, S succinate and A acetoacetate)

Ethyl ester of	G.	Time, hrs.	Yield of ethyl ester of	B. p. of ester, °C.	M. p. of acid, °C.
Methyliden M[5]	43	3	95% Me M	196–199	124–125[9]
Ethyliden M[6]	46	5	93% Et M	205–208	110–111[10]
Butyliden M[7]	21	3	95% Bu M	128–130 (17)	101–102[11]
Heptyliden M[1]	43	4	97% Heptyl M	136–138 (3)	95–96
Benzyliden M[7]	61	5	97% Benzyl M	158 (8)	117–118[12]
Furfuryliden M[7]	79		94% Furfuryl M	138–140 (6)	124–125[13]
Methyliden S[8] (itaconate)	100	4	98% Me S	108–110 (16)	
Isopropylidene S[2]	35	3	97% *i*-Pr S	110–112 (8)	
Me-Ph carbinylidene S[2]	28	8	95% (Me-Ph-carbinyl) S	165–167 (8)	
α-Heptyliden A[1]	75	6	97% α-Heptyl A	130–132 (7)[14]	
α-Cinnamyliden A[1]	50	9	78% α-Acetyl Δ Ph valerate	163–170 (8)[15]	

and the ether layer separated. The aqueous layer was extracted with 100 cc. of ether. The ether solution of the ester was washed with 100 cc. of 5% solution of sodium bicarbonate, then with water, dried over anhydrous sodium sulfate and fractionated through a Widmer column. The yield (44 g., b. p. 115–122°, 7 mm.) was 41% of the theoretical.

The hydrogenations summarized in Table I were, with one exception, carried out under a pressure of 100–130 atm. with an amount of Raney nickel[3] corresponding to 10 to 15% of the weight of ester. This proportion of catalyst to ester was unnecessarily high as 2 g. of nickel was found sufficient for 100 g. of diethyl itaconate. In a larger preparation in which 12 g. of nickel was used with 282 g. of that ester, the hydrogenation went to completion within three minutes, the heat of reaction being sufficient to raise the temperature from 23 to 123°. An amount of ether equal to the volume of the ester was ordinarily used as the reaction medium. Ethanol was also used for this purpose and with diethyl itaconate no solvent was used. The malonic esters were characterized by converting them to the free acids whose melting points are given in Table I. The keto esters were hydrolyzed by the method recently described[4] and the ketones, decanone-2 and 6-phenylhexanone-2, obtained and characterized.

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(4) Connor and Adkins, THIS JOURNAL, **54**, 3424 (1932).

(5) Welch, *J. Chem. Soc.*, **553**, 673 (1931).

(6) Komnenos, *Ann.*, **218**, 156 (1883).

(7) Knoevenagel, *Ber.*, **31**, 2585, 2895 (1898).

(8) Anschütz, *ibid.*, **14**, 1638 (1881).

(9) Lucas and Young, THIS JOURNAL, **51**, 2537 (1929).

(10) Conrad, *Ann.*, **214**, 134 (1880).

(11) Hell and Lumpp, *Ber.*, **17**, 2219 (1884).

(12) Claisen and Crismer, *Ann.*, **218**, 139 (1883).

(13) Marckwald, *Ber.*, **21**, 1083 (1888).

(14) Jourdan, *Ann.*, **200**, 105 (1880).

(15) Borsche and Peitzsch, *Ber.*, **62**, 372 (1929).

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, UNIVERSITY OF WISCONSIN]

Hydrogenation of Derivatives of Pyridine

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The pyridinoid ring may be saturated with hydrogen over catalytic nickel at temperatures and pressures of hydrogen which are a function of the substituents in the ring, the nature of the solvent and the type of nickel catalyst. There is a very wide variation with respect to the effect of these factors upon the temperature required for hydrogenation. The control of the temperature of hydrogenation is particularly important in the hydrogenation of pyridine derivatives because of the side reactions that occur. These reactions are apparently of three types, cleavage of a nitrogen to carbon linkage, alkylation of the secondary amine formed by hydrogenation, and condensation of various intermediate products. Since Raney nickel[1] is characterized by its activity at relatively low temperatures, it is particularly suited for use with pyridine compounds. For example, 2-benzylpyridine which required 160° with a nickel-on-kieselguhr catalyst was hydrogenated completely at 100° with Raney nickel in less than one-half the time required at 160° with the supported catalyst. Quinolinic ester (2,3-dicarbethoxypyridine) was hydrogenated over Raney nickel at a temperature 50° lower than was feasible with the supported catalyst.

Incidental to the study of another problem Folkers prepared ethyl nipecotate (3-carbethoxy-

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(1) Adkins and Covert, THIS JOURNAL, **54**, 4116 (1932).

piperidine) by the hydrogenation of ethyl nicotinate at 165° in ethanol over a nickel-on-kieselguhr catalyst.[2,3] A study of this transformation has shown that ethyl nipecotate so prepared invariably contained 3 to 6% of ethyl nicotinate from which the nipecotate could not be separated by fractionation. When ethyl nicotinate was hydrogenated in ethanol solution at 165° over Raney nickel, the ethyl nipecotate fraction obtained after very careful fractionation also contained both ethyl nicotinate (2–3%) and ethyl N-ethylnipecotate (20%).

No ethyl N-ethylnipecotate was produced when ether, methylcyclohexane or dioxane was used as solvent during the hydrogenation of ethyl nicotinate over Raney nickel. The two latter solvents were preferable because the hydrogenation proceeded much more rapidly than in ether. In none of these solvents was the amount of residual ethyl nicotinate after the hydrogenation greater than 0.5%. Folkers obtained a considerable yield of 3-methylpiperidone-2 in the hydrogenation of ethyl nicotinate over nickel-on-kieselguhr. Under the conditions described above the yield of this compound has never been higher than 5%. Other high boiling but unidentified materials were produced in 15 to 20% yields in ethanol. The yields of these materials in methylcyclohexane or ether were about 5%.

The catalytic hydrogenation of the pyridine ring of quinolinic ester (2,3-dicarbethoxypyridine) has apparently never been reported. The hydrogenation is a difficult one because of the formation of high molecular weight compounds especially at higher temperatures. These condensation products are quite effective poisons for nickel and the hydrogenations became very slow while there were yet considerable quantities of the original ester in the reaction mixture. When the hydrogenation was pressed to completion the yield of dicarbethoxypiperidine was not increased but a larger proportion of higher boiling products was obtained. However, it was ultimately ascertained that over Raney nickel in dioxane at 125° the desired ester could be obtained in a 77% yield.

The hydrogenation of 3-pyridyl methyl ketone to 3-piperidylmethylcarbinol has occasioned considerable difficulty[4] because of the tendency for the formation of 3-ethylpiperidine. However, through the use of Raney nickel in methylcyclohexane at 145° the mixture of isomeric alcohols was obtained in a 60% yield accompanied by a 28% yield of 3-ethylpiperidine. In all probability dioxane would be an even better reaction medium for this hydrogenation since it is particularly useful for those reactions in which water is formed.

The introduction of substituents in pyridine, especially in the 2 and 6 positions, has a rather surprising effect upon the readiness of hydrogenation, as measured by the temperature required for a reasonably rapid rate of reaction. The pyridine compounds having benzyl, β-phenylethyl or carbethoxy groups in the 2 or 2,6 positions were hydrogenated rapidly at lower temperatures than was pyridine itself. While this lability toward hydrogenation is referred to as "surprising" it is no doubt due to the effect of the substituents in lowering the tendency of the nitrogen to "poison," *i. e.*, combine with the catalyst. It seems unnecessary to add anything further to the data tabulated in Table I which discloses conditions for the successful hydrogenation of a number of substituted pyridines.

Hydrogenation of Piperidino Esters.—Folkers obtained no appreciable amount of a carbinol by the hydrogenation of ethyl N-ethylnipecotate or of β-piperidinopropionate over copper–chromium oxide, hence he concluded that a carbinol β to a nitrogen was unstable just as it is in the compounds where a carbinol group is β to an oxygen. It seemed advisable to determine whether or not a carbethoxy group α, γ or Δ to a nitrogen could be converted to the carbinol. To that end the ethyl esters piperidinoacetate, γ-piperidinobutyrate and Δ-piperidinovalerate[5] (25–43 g.) in ethanol (25–50 ml.) were submitted to the action of hydrogen under 200–300 atmospheres at 250° over copper–chromium oxide (5–8 g.).[2] The reactions went to completion in from 1.5 to 3 hours. The 2-piperidinoethanol and 5-piperidinopentanol-1 were obtained in yields of 80 to 82%. The γ-piperidinobutyrate gave only a 16% yield of 4-piperidinobutanol-1, accompanied by N-*n*-butylpiperidine (35%), N-ethylpiperidine (24%) and butanol (24%). It thus appears that the labilizing effect of a nitrogen in the β or γ position with respect to a carbinol is very similar to that exerted by an oxygen atom, as has been shown in the hydrogenation of β-

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[2] Folkers and Adkins, This Journal, **54**, 1147 (1932).

[3] Covert, Connor and Adkins, *ibid.*, **54**, 1651 (1932).

[4] *Cf.* Strong and McElvain, *ibid.*, **55**, 816 (1933).

[5] For preparation of these esters see Thomas and McElvain, *ibid.*, **56**, 1808 (1934).

hydroxy butyric, malonic and succinic esters. With both oxygen and nitrogen the effect of the position of the substituent is, in the order of decreasing effectiveness, β, γ, α, Δ.

Preparation of Compounds and Analysis of Products.—Ethyl nicotinate was prepared as follows: *Finely pulverized* nicotinic acid hydrochloride (200 g.) and thionyl chloride (612 g.) were refluxed until the solid was *completely* in solution (five to seven hours). The excess thionyl chloride was removed at 15 mm. by distillation on a steam-bath. Ethanol (300 ml.) was then added slowly through a reflux condenser and the mixture refluxed for two hours. The mixture was then poured into a 2-liter beaker surrounded by ice and covered with a layer of ether 1.5 cm. deep. The acid was neutralized with a saturated solution of sodium carbonate or 20% solution of sodium hydroxide during the course of five to ten minutes, the reaction mixture being kept well stirred and cool. The ether layer was removed and later combined with 100 ml. of ether which had been used for a second extraction. The ester was obtained by fractionation through a Widmer column at 78–80° (4 mm.), or 100–101° (11 mm.), in 75–85% yield. Butyl nicotinate was similarly obtained in 75% yield.

TABLE I

HYDROGENATION OF PYRIDINE TO PIPERIDINE DERIVATIVES[a]

Substituent(s)	Ni catalyst, g.	Temp., °C.	Time, hrs.	Product			
				G.	Yield, %	B. p., etc., °C.,	mm.
None	25 R	200	7	610	83	103–105	740
2-Methyl	3 R	200	0.6	30	90	117–119	740
2-Phenyl	3 K(a)	160	4	31	80	110–112	9
4-Phenyl	5 R(b)	175	10	29	85	M. p. 50°	
2-Benzyl	5 R	100	3	25	96	131–132	13
2-(β-Phenylethyl)	5 R(b)	125	4	25	95	103.5–104	1.5
3-Carbo-*n*-butoxy	R(b)	165	2		84	83–86	2
3-Carbethoxy	6 K(a)	165	8		58	79–80	4
3-Carbethoxy	10 R(b)	165	1.5	38	80	83–85	5
3-Carbethoxy	10 R(c)	165	5	44	80	79–80	4
3-Carbethoxy	6 R(d)	165	1	30	77	79–80	4
2,6-Dimethyl	6 R(b)	175	2	23	92	128–129	740
2,6-Diphenyl	7 R(b)	175	1	11	66	193–194	10
2,6-Di-(β-phenylethyl)	3 K(a)	175	12	52	93	223	9
2-Methyl-6-phenyl	7 R(b)	200	2.5	10	60	112–114	12
2-(γ-Phenylpropyl)	3 K(a)	160	2	19	89	160–163	10
2-(Δ-Phenylbutyl)	5 K(c)	160	1.2	17	81	164–166	9
2,6-Dicarbethoxy	R(a)	137	0	15	66	155–156	11
2,6-Dimethyl-3-carbethoxy	5 R(b)	125	7	26	88	93–95	10
2,3-Dicarbethoxy	5 K(b)	150	0.5	26	51	119–121	3
2,3-Dicarbethoxy	5 R(b)	100	1	15	49	119–121	3
2,3-Dicarbethoxy	5 R(d)	125	0.2	23	77	119–121	3
3-Acetyl	8 R(b)	145	4.5	19	61(f)	102–104	4
				7	28(e)	150–155	740

[a] "R" refers to Raney nickel, "K" to nickel-on-kieselguhr. The solvents are indicated as: (a) ethanol, (b) methylcyclohexane, (c) ether and (d) dioxane. The pressure of hydrogen was 150–300 atmospheres. With two exceptions the piperidine derivatives had the same substituent as the pyridine. These are indicated as (e) 3-ethylpiperidine, and (f) 3-piperidylmethylcarbinol.

3-Acetylpyridine was prepared as by Strong and McElvain.[6] However, a better grade of sodium ethoxide[7] was used for the condensation of ethyl nicotinate and ethyl acetate so that the yield of 3-acetylpyridine, in five preparations, was 85–87% of the theoretical based upon the ethyl nicotinate, as compared with 50–70% previously reported. A continuous extractor was used.

Quinolinic ester (2,3-dicarbethoxypyridine) was prepared by the esterification of the acid by the method given for β-chloropropionic acid.[8] From 153 g. of the acid 20 g. of ethyl nicotinate and 100 g. (49% yield) of the desired ester (b. p. 168–170 (8 mm.)) were obtained.[9]

The pyridine derivatives not discussed in detail above were prepared and the products of hydrogenation utilized by Messrs. Walter and Singer in studies reported elsewhere in collaboration with Dr. S. M. McElvain.

A number of methods were resorted to for the analysis of mixtures of ethyl nicotinate, ethyl nipecotate, and ethyl N-ethylnipecotate. The ethyl nicotinate was determined by noting the amount of hydrogen absorbed by the mixture in a bomb especially designed for quantitative hydrogenation.[10] This ester was also determined by allowing the mixture of esters to react with acetophenone and weighing the pyridoylbenzoylmethane so formed. The two piperidine esters do not undergo the Claisen reaction and do not interfere with the reaction of ethyl nicotinate. For example, a mixture of ethyl nicotinate (0.75 g.), ethyl nipeco-

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[6] Strong and McElvain, THIS JOURNAL, 55, 816 (1933).

[7] Bruhl, "Houben–Weyl," 1922, Vol. II, p. 578.

[8] "Organic Syntheses," John Wiley and Sons, Inc., New York, Coll. Vol. I, p. 241.

[9] *Cf.* Engler, *Ber.*, 27, 1788 (1894).

[10] Adkins, THIS JOURNAL, 55, 4272 (1933).

TABLE II

PROPERTIES AND ANALYSES OF ESTERS

Name	Mole formula	B. p. (or m. p.)				MR'D		Analyses, %		
		°C.	Mm.	d^{25}	n^{25}_D	Calcd.	Found	Element	Calcd.	Found
3-Carbethoxypiperidine[12]		79–80	4	1.0279	1.465	42.4	42.3			
2,3-Dicarbethoxypiperidine[13]	$C_{11}H_{19}O_4N$	119–121	3	1.0933	1.4612	57.7	57.7	C	57.6	57.5
								H	8.36	8.26
2,3-Dicarbethoxypiperidine HCl	$C_{11}H_{20}O_4NCl$	M. p. 200–2 (dec.)						Cl	13.37	13.60
2,6-Dimethyl-3-carbethoxypiperidine	$C_{10}H_{19}O_2N$	93–95	10	0.9637	1.4492	51.4	51.6	C	64.9	64.8
								H	10.35	10.35
2,6-Dimethyl-3-carbethoxypiperidine HCl	$C_{10}H_{20}O_2NCl$	M. p. 162–163						Cl	16.0	16.2
3-Carb-*n*-butoxypyridine	$C_{10}H_{13}O_2N$	119–120	8	1.0496	1.4930	50.8	49.6	N	7.82	7.77
3-Carb-*n*-butoxypiperidine	$C_{10}H_{19}O_2N$	83–86	2	0.9838	1.4580	51.6	51.4	N	7.57	7.62
								C	64.8	65.3
								H	10.33	10.37
1-Ethyl-3-carbethoxypiperidine	$C_{10}H_{19}O_2N$	113–116	19	.9813	1.4536	51.9	51.7	C	64.81	65.14
								H	10.34	10.63
1-Ethyl-3-carbethoxypiperidine HCl	$C_{10}H_{20}O_2NCl$	M. p. 143						Cl	16.0	16.01

tate (15 g.), acetophenone (3.0 g.), and sodium ethoxide (3.4 g.) was heated on a water-bath for an hour, cooled, water added until the solution was homogeneous, the solution extracted with ether, and the aqueous solution acidified with acetic acid. The solid diketone so obtained was filtered off, dried and found to weigh 0.79 g. This corresponds to a 70% yield and is the same as that obtained from ethyl nicotinate and acetophenone under the same conditions.

The piperidine nitrogen was also determined by titrating rapidly with a standard solution of hydrochloric acid (0.1 *N*) using a mixture of methyl red and methylene blue as an indicator.[11] The acid had been standardized against a piperidine derivative of known purity, for example, N-*n*-duodecylpiperidine or 3-piperidylmethylcarbinol.

The average molecular weight was ascertained from the saponification value for the mixture of esters. From the data obtained by these various operations the percentages of each of the three esters present may be calculated. The ethyl N-ethylnipecotate was also estimated by acetylating the mixture of esters, and isolating the unchanged ester. These various methods of analysis gave results which were in agreement.

Summary

The catalytic hydrogenation over nickel of various carbethoxy and other substituted pyridines in good yields to the corresponding piperidine derivatives has been described. Raney nickel has been shown to be particularly satisfactory for this type of hydrogenation. The pyridines having substituents in the 2,6-positions could be hydrogenated under milder conditions than pyridine itself or pyridines substituted in other positions.

It has been found that with esters of the type $C_5H_{10}N(CH_2)_nCOOEt$ the ester group could be hydrogenated satisfactorily to a carbinol group where *n* was 1 or 4, very much lower yields were obtained when *n* was 3 while no carbinol was obtained when *n* was 2.

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[11] Johnson and Green, *Ind. Eng. Chem., Anal. Ed.*, **2**, 2 (1930).

[12] *Cf.* McElvain and Adams, THIS JOURNAL, **45**, 2738 (1923).

[13] *Cf.* Besthorn, *Ber.*, **28**, 3159 (1895); Clemo, Ramage and Raper, *J. Chem. Soc.*, 3196 (1931).