charred above 250°. *Anal.* Calcd. for $C_5H_5O_2N_3$: C, 42.65; H, 4.99; N, 29.78. Found: C, 42.49; H, 5.05; N, 29.61.

2-Methyl-4(5)-amino-5(4)-imidazolecarboxamide (XI).—This substance was obtained by the condensation of aminocyanoacetamide (IX) with ethyl acetiminoester in ice-cold methanol for 24 hours.[3] After removal of the methanol *in vacuo*, the residue was dissolved in water, acidified to congo red with dilute HCl and decolorized with charcoal. The compound was recovered as the picrate which was repeatedly recrystallized from hot water and 50% aqueous acetic acid (yield 37%), m.p. 240° dec. *Anal.* Calcd. for $C_{11}H_{11}O_8N_7$: C, 35.78; H, 3.00; N, 26.56. Found: C, 36.02; H, 3.14; N, 26.57.

Biological.—"Nucleotide" adenine as well as the "nucleic acid" adenine, guanine, uracil and thymine were isolated by the methods previously employed in this Laboratory.[15,3] Urinary allantoin was isolated as described previously.[8]

(15) M. R. Heinrich and D. W. Wilson, *J. Biol. Chem.*, **186**, 447 (1950).

PHILADELPHIA, PENNA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

Preparation of 4-Alkylpiperidines[1]

BY S. WAWZONEK, M. F. NELSON, JR., AND P. J. THELEN

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4-Alkylpiperidines can be prepared in good yields from 4-alkylpyridines by a sodium and 1-butanol reduction followed by a catalytic reduction in the presence of activated palladium. Sodium and 1-butanol alone give mainly the tetrahydropyridine. Yields are reported for 4-ethyl-, 4-(β-hydroxyethyl)-, 4-*n*-propyl-, 2-methyl-4-ethyl-, 2-*n*-butyl-, 3-methyl-4-ethyl- and 2,6-dimethyl-4-ethylpiperidines.

Piperidines are reported to be formed by the reduction of the corresponding pyridines with tin and hydrochloric acid,[2] or sodium and ethanol.[3] The latter combination, when used with 3-alkyl- and 4-alkylpyridines gives a product in which varying amounts of the tetrahydropyridine are present.[4] In the earlier literature such mixtures were often reported as the piperidines.

In the present work it has been found that sodium and 1-butanol reduction followed by catalytic reduction in the presence of activated palladium will convert 4-alkylpyridines into 4-alkylpiperidines in good yields. A list of the piperidines made in this way together with the yields obtained is given in Table I.

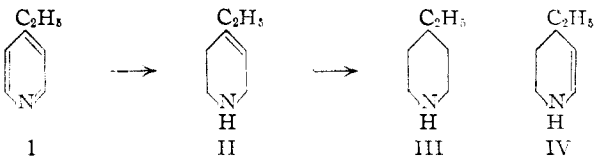
TABLE I

REDUCTION OF PYRIDINES

Pyridine	Yield of tetrahydropyridine	B.p. of tetrahydropyridine °C.	Mm.	Yield of piperidine, %	B.p. of piperidine °C.	Mm.	$n^{23}D$	d^{23}_4
4-Ethyl-	64	158–158.5	749	94.5	151–151.5	753[a]	1.4519	0.862
4-*n*-Propyl-[6]	75	178–179.5	742	95.5	172–172.5	748[b]	1.4465	.864
4-*n*-Butyl-[6]	70.5	196–197	741	94	193–194	745	1.4472	.879
2-Methyl-4-ethyl-	57.5	162–163	747	87	155–156	750[c]	1.4512	.853
3-Methyl-4-ethyl-	87	175–185		85.5	171.5–173	748	1.4530	.901
2,6-Dimethyl-4-ethyl-[10]	72[d]	173–175		71	167–168[e]		1.4433[f]	.831[g]
4-(β-Hydroxyethyl)-	59	140–145	16	85	131–136	17[h]	1.4902	....

[a] Ladenburg using solely a sodium and ethanol reduction on 4-ethylpyridine reports a boiling point of 156–158°. [b] Ahrens[7] lists the boiling point as 178–180°. [c] Schultz[8,9] lists the boiling point as 155–160°. [d] Sodium and ethanol reduction. [e] The literature[17] reports 165–167° (725 mm.). [f] At 30°. [g] At 34°. [h] Meisenheimer[5b] reports a boiling point of 140–141° (13–14 mm.).

Reduction with sodium and butanol was found to give better yields of the tetrahydro compound than reduction with sodium and ethanol. The structure of the product from this reaction was established only in the case of the compound obtained from 4-ethylpyridine; the product was 1,2,5,6-tetrahydro-4-ethylpyridine (II) since it formed a benzenesulfonamide which was stable to alkali. The only other possibility (IV) with the unsaturation in the 2,3-position would be expected to open to an amino-aldehyde under these conditions because of its vinyl amine structure (IV). The unsaturation is probably present in the 3,4-position in all other examples with the exception of the products from 2-methyl-4-ethylpyridine and 3-methyl-4-ethylpyridine. In these two compounds, because of their unsymmetrical structures, the unsaturation is either in the 3,4- or 4,5-positions.



1 II III IV

The reduction of the tetrahydro compounds to the piperidines was found to proceed in good yield in the presence of palladium. 4-(β-Hydroxy-

(1) Abstracted in part from the Ph.D. thesis (1949) of M. F. Nelson, Jr., and the Ph.D. thesis (1948) of P. J. Thelen. Presented before the Organic Division of the American Chemical Society, Milwaukee, Wisconsin, March 31, 1952.

(2) W. Koenigs, *Ber.*, **14**, 1852 (1881).

(3) A. Ladenburg, *ibid.*, **17**, 156, 388 (1884).

(4) W. Koenigs, *ibid.*, **40**, 3199 (1907).

(5) A. Ladenburg, *Ann.*, **247**, 72 (1878).

(6) J. F. Arens and J. P. Wibaut, *Rec. trav. chim.*, **61**, 59 (1942).

(7) F. B. Ahrens, *Ber.*, **38**, 155 (1905).

(8) M. Schultz, *ibid.*, **20**, 2720 (1887).

(9) F. Engelmann, *Ann.*, **231**, 378 (1885).

(10) A. Jaeckle, *ibid.*, **246**, 45 (1888).

TABLE II

ANALYSES AND PROPERTIES OF PIPERIDINES AND THEIR DERIVATIVES

Piperidine	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Benzenesulfonamide	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
4-Ethyl	$C_7H_{15}N$	74.33	74.43	13.27	13.54	$C_{13}H_{19}O_2SN$	74–75	61.63	61.90	7.56	7.42
4-*n*-Propyl	$C_8H_{17}N$	75.52	75.48	13.47	13.34	$C_{14}H_{21}O_2SN$	72–73	62.92	62.80	7.86	8.46
4-*n*-Butyl	$C_9H_{19}N$	76.52	76.08	13.56	13.37	$C_{15}H_{23}O_2SN$	57–58	64.04	63.82	8.18	8.07
3-Methyl-4-ethyl	$C_8H_{17}N$	75.52	75.82	13.47	13.30	$C_{14}H_{21}O_2SN$	73–75	62.92	62.46	7.86	7.73
2-Methyl-4-ethyl	$C_8H_{17}N$	75.52	75.57	13.47	13.48	$(C_8H_{17}N)_2$–H_2PtCl_6[a]	187–190	28.91	29.03	5.42	5.56
2,6-Dimethyl-4-ethyl	$C_9H_{19}N$	76.52	76.35	13.56	14.02	$(C_9H_{19}N)_2$–H_2PtCl_6[a,b]	235 dec.	31.35	31.19	5.80	5.75

[a] The benzenesulfonamide was an oil. The chloroplatinate was recrystallized twice from water. [b] Jaeckle[17] gives no data on his chloroplatinate.

ethyl)-piperidine prepared in this manner could be converted successfully by hydrogen bromide and alkali into quinuclidine in a 58% yield. The tetrahydro compound in this case, even though prepared after Koenig's work,[4] is reported in the literature as a piperidine since it was converted by hydriodic acid and alkali into quinuclidine.[11] Hydrobromic acid when used in a similar way on this compound gives no quinuclidine.

In the course of this work, several new substituted pyridines were prepared. 3-Methyl-4-ethylpyridine was obtained from the action of zinc and acetic anhydride on β-picoline following the method used for 4-ethylpyridine.[12] The structure of the product was demonstrated by its oxidation to cinchomeronic acid. This method was also found suitable for preparing 2-methyl-4-ethylpyridine from α-picoline.

3-Cyano-4-ethylpyridine was prepared by treating 4-ethylpyridine-3-sulfonic acid with a mixture of sodium and potassium cyanide following the directions used for 3-cyano-4-methylpyridine.[13] The structure of the product was demonstrated by hydrolysis to 4-ethylnicotinic acid. The latter acid was also prepared by fusing sodium 4-ethylpyridine-3-sulfonate with sodium formate in a manner similar to that used for aromatic acids.[14] The yield of product in both cases was too small to study the reduction of these compounds to the corresponding piperidine.

Experimental[15]

Preparation of 4-Alkylpiperidines.—The 4-alkylpiperidines were prepared by the directions which are given for 4-ethylpiperidine with the exception of 4-(β-hydroxyethyl)-piperidine and 2,6-dimethyl-4-ethylpiperidine. A solution of 4-ethylpyridine[16] (100 g.) in 1-butanol (1200 ml.) was heated to 50–60° in a flask fitted with a stirrer and an efficient condenser to which two gas traps were attached. The first of these was empty while the second contained 6 *N* hydrochloric acid (250 ml.). To the butanol solution, sodium (200 g.) was added at such a rate that the solution refluxed moderately. After the addition, the reaction flask was heated until the solution of the sodium was complete, then cooled to 80° and cold water (500 ml.) was slowly added. The reaction mixture was stirred for 20 minutes, then cooled to 20° and the aqueous layer drawn off. The alcohol–amine layer was mixed with the acid from the trap and then made acid to litmus by the addition of more hydrochloric acid. The alcohol was removed by steam distillation and the contents of the flask cooled, made strongly alkaline with 40% sodium hydroxide and steam distilled again until the distillate was no longer basic to litmus. The amine was separated by saturating the distillate with potassium carbonate, dried over potassium hydroxide pellets and then fractionated. The yield of liquid boiling from 151–159° was 67 g. Careful refractionation of this liquid gave a small amount of 4-ethylpiperidine boiling at 151–151.5° and mainly 4-ethyl-1,2,5,6-tetrahydropyridine boiling at 158–158.5°. The amount of these substances seems to vary with the speed of addition of the sodium. Rapid addition favored the tetrahydropyridine. The tetrahydropyridine had the following constants: $n^{25}D$ 1.4699, d^{24} 0.881.

Anal. Calcd. for $C_7H_{13}N$: C, 75.67; H, 10.72. Found: C, 75.81, H, 10.78.

The benzenesulfonamide prepared by shaking the amine in alkali with benzenesulfonyl chloride was insoluble in alkali and melted at 50–52° after three crystallizations from ethanol. This compound adds bromine and liquefies upon standing after a period of time.

Anal. Calcd. for $C_{13}H_{17}SO_2N$: C, 62.15; H, 6.77. Found: C, 62.00; H, 6.58.

To the product (50 g.) from the sodium and 1-butanol reduction was added palladium–norite[17] catalyst (12 g.) in glacial acetic acid (100 ml.) and the resulting mixture shaken with hydrogen at 40 pounds pressure until absorption ceased (40–48 hours). The reduction product was filtered, the residue washed with 400 ml. of water, and the filtrate made strongly alkaline and steam distilled until the distillate coming over was no longer basic to litmus. The filtrate was saturated with anhydrous potassium carbonate and the organic layer was drawn off, dried for three to five hours with solid potassium hydroxide and fractionated. The yields of 4-ethylpiperidine were 47–48 g.

The benzenesulfonamide prepared by shaking the amine in alkali with benzenesulfonyl chloride melted at 74–75° after two recrystallizations from an acetone–ligroin mixture. This sulfonamide does not decolorize bromine and is stable toward air. It lowers the melting point of the sulfonamide of the tetrahydropyridine when mixed with this compound. This procedure was followed for the other examples.

Sodium–Ethanol Reduction.—4-Ethylpyridine (100 g.) when reduced in absolute ethanol (1000 ml.) with sodium (170 g.) gave, after working up as in the above, 25 g. of the tetrahydropyridine and 30 g. of starting material.

2-Methyl-4-ethylpyridine.—This material was prepared from α-picoline using the directions given for preparing 4-ethylpyridine from pyridine.[10] From 120 g. of α-picoline 19.0 g. of 2-methyl-4-ethylpyridine, b.p. 177–178° (752 mm.) and 45 g. of unreacted α-picoline were obtained.

3-Methyl-4-ethylpyridine.—This amine was prepared by the procedure devised for 4-ethylpyridine.[10] From 50 g. of β-picoline, 13 g. of 3-methyl-4-ethylpyridine was obtained; b.p. 195.5–197°; $n^{23}D$ 1.4992; d^{23} 0.942.

Anal. Calcd. for $C_8H_{11}N$: C, 79.31; H, 9.18. Found: C, 79.28; H, 9.27.

The picrate melted at 144–146° after three crystallizations from ethanol.

(11) (a) K. Loffler and F. Stietzel, *ibid.*, **42**, 124 (1909); (b) J. Meisenheimer, *Ann.*, **420**, 196 (1920).

(12) J. P. Wibaut and J. F. Arens, *Rec. trav. chim.*, **60**, 119 (1941).

(13) J. L. Webb and A. H. Corwin, THIS JOURNAL, **66**, 1456 (1944).

(14) V. Meyer, *Ann.*, **156**, 273 (1870).

(15) Melting points and boiling points are not corrected.

(16) R. L. Frank and P. V. Smith, *Org. Syntheses*, **27**, 88 (1947).

(17) R. Mozingo, *ibid.*, **26**, 77 (1946).

Anal. Calcd. for $C_{14}H_{14}N_4O_6$: C, 48.00; H, 4.00. Found: C, 47.81; H, 4.00.

Oxidation of 3-Methyl-4-ethylpyridine.—3-Methyl-4-ethylpyridine (15 g.) in water (100 ml.) was treated at 60° with a 5% potassium permanganate solution until the pink color was permanent. The solution was cooled and filtered from the manganese dioxide. The filter cake was washed twice with 100-ml. portions of water and the washings combined with the original filtrate. Acidification of the filtrate to *p*H 6–6.5 followed by the addition of 40 ml. of 5% copper sulfate solution precipitated the cinchomeronic acid as the copper salt. The free acid was obtained by decomposing the copper salt with hydrogen sulfide and evaporating the solution. Recrystallization from ethanol gave crystals melting at 262–264° which did not lower the melting point of a sample prepared from isoquinoline.[18]

4-(β-Hydroxyethyl)-piperidine.—4-(β-Hydroxyethyl)-pyridine (100 g.) was reduced in 1-butanol (900 ml.) with sodium (150 g.) in a similar manner to that used for 4-ethylpyridine. The reduction mixture was diluted with 400 ml. of water and the sodium hydroxide layer discarded. The alcohol–amine layer was acidified with 6 *N* hydrochloric acid and the 1-butanol removed by steam distillation. The residue was made strongly alkaline with 20% sodium hydroxide solution and extracted with ether using a continuous extractor. The yield of product was 60 g.; b.p. 140–145° (16 mm.). This product did not cyclize to quinuclidine when treated with anhydrous hydrogen bromide and thionyl bromide or with aqueous hydrobromic acid (sp. gr. 1.42).

The above product (30 g.) upon catalytic reduction in glacial acetic acid gave a solution which was made strongly alkaline with 20% sodium hydroxide. Extraction with ether using a continuous extractor gave 26 g. of 4-(β-hydroxyethyl)-piperidine; b.p. 131–136° (16–18 mm.).

Refluxing this amine with hydrobromic acid (sp. gr. 1.42) for two hours followed by treatment with alkali gave quinuclidine melting at 155–156°.

Sodium 4-Ethylpyridine-3-sulfonate.—This salt was prepared from 4-ethylpyridine (90 g.) following the directions[7] used for sodium 4-methylpyridine-3-sulfonate. The yield of sodium salt varied from 50–90 g. The salt was not purified further but used as such in the next reaction.

3-Cyano-4-ethylpyridine.—This compound was prepared in a manner similar to that used for 4-methylnicotinonitrile.[7] Yields based on 40 g. of sodium-4-ethylpyridine-3-sulfonate were 2.4–3.2 g.; b.p. 72–74° (2 mm.).

Anal. Calcd. for $C_8H_8N_2$: C, 72.65; H, 6.06. Found: C, 72.48; H, 6.19.

Hydrolysis of 3-cyano-4-ethylpyridine (4 g.) in 75% sulfuric acid gave 3.2 g. of 4-ethylnicotinic acid; m.p. 137–138°. Gabriel and Colman[19] report a melting point of 135.5–136°.

This acid was also obtained by treating sodium 4-ethylpyridine-3-sulfonate (21 g.) with sodium formate (34 g.) according to the directions used for aromatic acids.[8] The yield of product was 1.4 g.; m.p. 133–135°. No lowering in melting point was observed when the two different preparations were mixed.

(18) L. Ternajgo, *Monatsh.*, **21**, 446 (1900).

(19) S. Gabriel and J. Colman, *Ber.*, **35**, 1358 (1902).

IOWA CITY, IOWA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Reactivity of the Heterocyclic Nuclear Halogen in the Friedel–Crafts Reaction: The Preparation of Some Dihydroxyphenylquinoline and -benzothiazole Derivatives

BY GABRIELLO ILLUMINATI AND HENRY GILMAN

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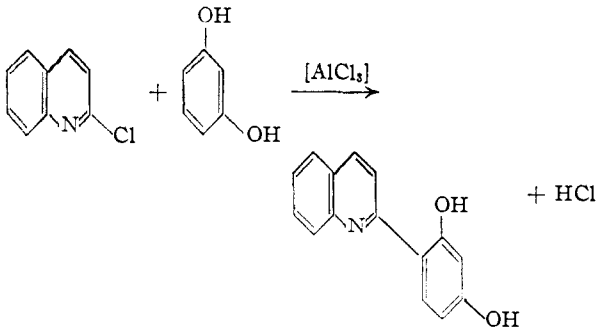
The active nuclear halogens in 2-chloroquinoline, 4,7-dichloroquinoline and 2-chlorobenzothiazole undergo Friedel–Crafts reactions with resorcinol and 4-chlororesorcinol to give dihydroxyphenyl- or chlorodihydroxyphenylquinoline and benzothiazole derivatives. The products obtained are colored. A suitable solvent for these reactions is dry quinoline. Such a medium, in many respects similar to nitrobenzene, was profitably used in reactions which either had been unsuccessful or had resulted in somewhat lower yields when carried out in nitrobenzene. The molecular compounds of 4-chlororesorcinol with 2-chloroquinoline and 4,7-dichloroquinoline are also described.

Friedel–Crafts reactions involving the use of chloroquinoline and chlorobenzothiazole derivatives as the organic halogen components do not appear in the literature. More generally, Friedel–Crafts reactions involving nuclear halogen have been observed only in a few cases.[1] Since the chlorine atom attached to the positions 2 and 4 of quinoline and to the position 2 of benzothiazole shows high reactivity in many instances such as its ready displacement by sodium alkoxides, a condensation of 2-chloroquinoline and the other similarly reactive heterocyclic compounds with some aromatic nuclei in the presence of aluminum chloride seemed to be likely to occur.

The present investigation deals with the condensation of 2-chloroquinoline, 4,7-dichloroquinoline and 2-chlorobenzothiazole with resorcinol or 4-chlororesorcinol. The typical reaction takes place according to the equation



Evidence that the product was a dihydroxyphenyl- or chlorodihydroxyphenylquinoline or -benzothiazole derivative, and not the monohydroxyphenoxy- or chloromonohydroxyphenoxy- isomer, was obtained in the case of 2-(2,4-dihydroxyphenyl)-quinoline (1) by infrared absorption measurements, (2) by unsuccessful attempts at ether-cleavage, and (3) analyses for active hydrogen.

The reactivity of 4-chlororesorcinol is appreciably lower than that of resorcinol, the yields of the prod-

(1) See, for example, A. W. Weston and C. M. Suter, THIS JOURNAL, **61**, 2556 (1939); F. D. Chattaway, *J. Chem. Soc.*, **63**, 1185 (1893); E. Clar, *Ber.*, **65**, 846 (1932); E. B. Barnett and J. W. Cook, *J. Chem. Soc.*, **123**, 2631 (1923).