Synthesis and Hypoglycemic Activity of Pyridyl Alcohols[1]

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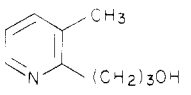
The potent hypoglycemic activity of 3-(3-methyl-2-pyridyl)propan-1-ol (**1**) prompted us to synthesize and study related structures. Some of the variables studied were the position of the methyl and alcohol side chains, the distance between the heterocyclic ring and the hydroxyl group, the effect of additional nuclear substitution, and the effects of branching and substitution on the alcohol side chain. The compounds were tested in 48-h fasted rats, usually at a dose of 150 mg/kg po. **1**, the corresponding propionic acid **12**, the acetate and methyl ether of **1** (**22** and **23**), and the 5-methyl analogue of **1** (**29**) were of comparable hypoglycemic potency. However, these compounds all caused a concomitant elevation of hepatic triglycerides and/or death in the test animals when observations were continued for 4–24 h.

The interesting and highly selective SAR seen in studying 3-mercaptopicolinic acid and its derivatives and analogues[2-5] have encouraged us to continue testing substituted pyridines for hypoglycemic activity in the 48-h fasted rat. This approach has uncovered the fact that certain thiazolo[3,2-*a*]pyridinium salts also are potent hypoglycemic agents, although of limited potential because of concomitant elevated hepatic triglyceride levels.[6] Further study in the pyridine series disclosed that 3-(3-methyl-2-pyridyl)propan-2-ol (**1**), prepared by Reinecke

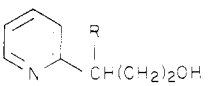


1

and Kray,[7] was a potent hypoglycemic compound in fed and fasted rats, in fasted guinea pigs, and in streptozotocin-diabetic rats.[8]

Examination of several related, commercially available compounds (**2–7**) yielded the biological findings shown in Table I. In a series of pyridylmethanols (**2–4**), only **3** was hypoglycemic. In the propanol series (**5–7**), the 2 and 4 isomers **5** and **7** were weakly hyperglycemic, while the 3 isomer **6** was weakly hypoglycemic. All compounds were studied after oral doses of 150 mg/kg in fasted rats. When glycemic levels were measured out to 7 h instead of the usual 4, **6** at 150 mg/kg had hypoglycemic activity comparable to that of **1** at 50 mg.[8]

It was also noted that two analogues of **5**, 3-ethyl-3-(2-pyridyl)propan-1-ol (A) and 3-phenyl-3-(2-pyridyl)-

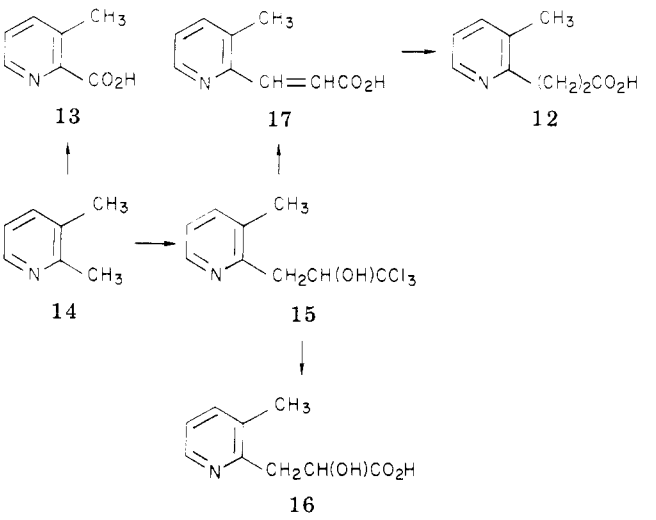


A, R = C_2H_5
B, R = C_6H_5

propan-1-ol (B),[9] were inactive in the hypoglycemic screen. However, the ring-reduced analogue of the phenyl compound had oral hypoglycemic activity at 150 mg/kg (12% decrease at 1 h, 24% at 2 h, and 28% at 4 h).[8]

Chemistry. The above findings served as a guide to the synthesis of specific compounds, designed to explore in greater detail the structural parameters in **1** that were essential for potent hypoglycemic activity. Toward this end, the piperidine analogue of **1** (**8**)[7] was prepared. The effect of side-chain length on hypoglycemic activity was determined by preparing analogues of **1** in which the C_2 side chain was shortened by one or two carbon atoms[10] (**9** and **10**) and lengthened by one carbon atom[7] (**11**) (Table I). Reflecting on the time course of the hypoglycemic activity effected by **1**, it was thought possible that a metabolite of the administered drug was really responsible for the biological response noted. If this were true, one likely candidate for such a role was propionic acid **12** (Table I). Several attempts to oxidize **1** directly to **12** were unsuccessful. One product isolated from these attempts was 3-methylpicolinic acid (**13**), also a possible metabolite of **1** resulting from β-oxidation of preliminarily formed **12**. **13** was more conveniently synthesized by oxidizing 2,3-dimethylpyridine (**14**) with selenium dioxide, according to the method of Jerchel, Bauer, and Hippchen.[11]

Scheme I



13 **17** **12** **14** **15** **16**

An alternative, successful route to **12**, as well as to other interesting structures (**15–17**), is shown in Scheme I. This route was based on the synthesis developed by Einhorn[12] for 3-(2-pyridyl)-2-propenoic acid.

Other possible metabolites of **1**, its *N*-oxide **18** and *N*-methyl quaternary salt **19**, were prepared from **1**.

To prevent possible metabolic oxidation of the hydroxyl group in **1**, the α,α,-dimethyl compound, 1,1-dimethyl-3-(3-methyl-2-pyridyl)propan-1-ol (**20**), was prepared from **14** and 2,2-dimethyloxirane. Another modification of the propanol side chain was effected by preparing 3-(3-methyl-2-pyridyl)propane-1-thiol (**21**) from **14** and ethylene sulfide. The acetate and methyl ether of **1** (**22** and **23**) were prepared to determine the importance of a free hydroxyl group in producing a hypoglycemic response. The ester was prepared from **1**. The ether, on the other hand, was synthesized by alkylating **14** with 1-bromo-2-methoxyethane.

The finding that only **3** and **6** of the unsubstituted alkanols (**2–7**) had hypoglycemic activity prompted us to prepare the corresponding 2-methyl congeners, (2-methyl-3-pyridyl)methanol (**24**) and 3-(2-methyl-3-

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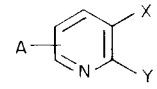
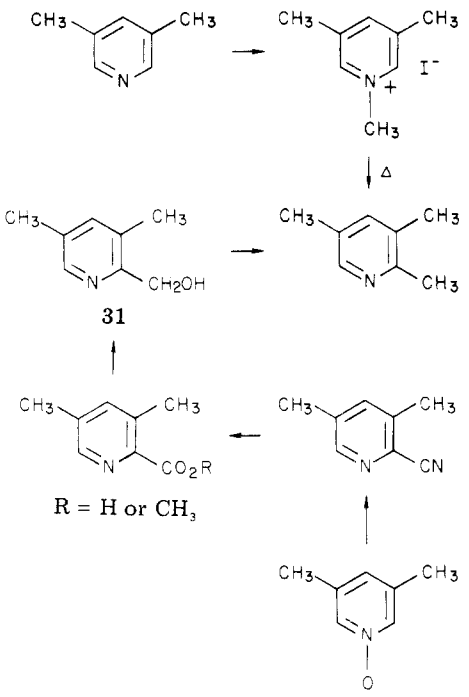
Table I. Pyridyl Alcohols



no.	X	Y	A	mp or bp (mm), °C	recrystn solvent	% yield	formula[a]	hypoglycemic act. in 48-h fasted rats[b] 1 h	2 h	4 h	5 h
1	CH_3	$(CH_2)_3OH$	H	108–110 (0.1)[c]		53	$C_9H_{13}NO$	−22[d]	−18[e]	−68[f]	−87[f]
2	H	CH_2OH	H	[g]			C_6H_7NO	4	6	2	
3	CH_2OH	H	H	[g]			C_6H_7NO	11	−3	−19[e]	
4	H	H	4-CH_2OH	[g]			C_6H_7NO	4	0	−4	
5	H	$(CH_2)_3OH$	H	[g]			$C_8H_{11}NO$		9	46[f]	42[f]
6	$(CH_2)_3OH$	H	H	[g]			$C_8H_{11}NO$	3	−12	−24[e]	
7	H	H	4-$(CH_2)_3OH$	[g]			$C_8H_{11}NO$	17[e]	14[e]	33[f]	
8		reduced 1		111–113[h]	EtOH-Et_2O	84	$C_9H_{19}NO\cdot HCl$	−15[f]	−3	−6	
9	CH_3	CH_2OH	H	222–224	MeOH-Et_2O	55	$C_7H_9NO\cdot HCl$	−9	0	3	
10	CH_3	$(CH_2)_2OH$	H	47–49[i]	pet. ether	20	$C_8H_{11}NO$[j]	−8[e]	−14[d]	8	
11	CH_3	$(CH_2)_4OH$	H	90–95 (0.8)[k]		20	$C_{10}H_{15}NO$[l]	−9	−9	0	
12	CH_3	$(CH_2)_2CO_2H$	H	83–85	$CHCl_3$-pet. ether	80	$C_9H_{11}NO_2$	5	−28	−85[d]	−90[d]
13	CH_3	CO_2H	H	117–118[m]	C_6H_6	50	$C_7H_7NO_2$	−8[e,n]	−9[n]	−15[n]	
14	CH_3	CH_3	H	173–175	EtOH-Et_2O	70	$C_7H_9N\cdot HCl$	0	−5	8	
15	CH_3	$CH_2CH(OH)CCl_3$	H	223–225[o]	MeCN	74	$C_9H_{10}Cl_3NO\cdot HCl$	−16[e]	−29[f]	−16[e]	
16	CH_3	$CH_2CH(OH)CO_2H$	H	146–148[o]	EtOH-Et_2O	25[p]	$C_9H_{11}NO_3\cdot HCl$	−9[d]	−5	−1	
17	CH_3	$CH{=}CHCO_2H$	H	183–185	MeOH	10	$C_9H_9NO_2$	−5	4	23[f]	
18		*N*-oxide of 1		95–97	CCl_4-Et_2O	75	$C_9H_{13}NO_2$	−6	−3	−8[f]	
19		methiodide of 1		82–84	*i*-PrOH	70	$C_{10}H_{16}INO$[q]	−1	3	−14[f]	
20	CH_3	$(CH_2)_2C(CH_3)_2OH$	H	114–116	EtOH-Et_2O	30	$C_{11}H_{17}NO\cdot HClO_4$	6	−7	−10[e]	
21	CH_3	$(CH_2)_3SH$	H	103–105 (0.05)		5	$C_9H_{13}NS$[r]	−9	−14[e]	−18[d]	
22	CH_3	$(CH_2)_3OAc$	H	87 (16)		80	$C_{11}H_{15}NO_2$	21[f]	−34[f]	−73[f]	
23	CH_3	$(CH_2)_3OMe$	H	75–78 (0.8)		13	$C_{10}H_{15}NO$	−15	−14	−29	−52[d]
24	CH_2OH	CH_3	H	140–142[s]	*i*-PrOH-Et_2O	49	$C_7H_9NO\cdot HCl$	−3	1	−11	
25	$(CH_2)_3OH$	CH_3	H	95–97	Me_2CO-Et_2O	53	$C_9H_{13}NO\cdot HClO_4$	−4[e]	−8	−1	
26	CH_3	$CH_2CH(OH)CH_3$	H	131–133	EtOH-Et_2O	56	$C_9H_{13}NO\cdot HCl$	3	−3	−12[e]	
27	CH_3	CH_2COCH_3	H	74–80 (1.3)[t]		38[p]	$C_9H_{11}NO$[u]	−12[d]	−14[f]	−8	
28	H	$(CH_2)_3OH$	5-CH_3	90–92	EtOH-Et_2O	90[p]	$C_9H_{13}NO\cdot HClO_4$[v]	0[w]	−1[w]	18[w]	
29	CH_3	$(CH_2)_3OH$	5-CH_3	83–84	*i*-PrOH-Et_2O	37	$C_{10}H_{15}NO\cdot HCl$	27[f]	−39[f]	−72[f]	
30	CH_3	$(CH_2)_3OH$	5,6-benzo	131–133	EtOH-Et_2O	50[p]	$C_{13}H_{15}NO\cdot HCl$[q]	16	−9	−10	
31	CH_3	CH_2OH	5-CH_3	167–168	MeOH-EtOAc	30	$C_8H_{11}NO\cdot HCl$[x]	−12	−17[f]	−1	−9
32	H	$CH_2CH(OH)CCl_3$	H	75–76[y]	EtOH	49	$C_8H_8Cl_3NO$	24[e,z]	40[f,z]	101[f,z]	
33		methiodide of 6		70–72[a,a]	*i*-PrOH	83	$C_9H_{14}INO$	−13[d]	−14[d]	−12[e]	

[a] Analyses (C, H, and N) for compounds in this table were within ±0.4% of the theoretical values unless otherwise noted. [b] Results are expressed as the percent difference between the mean change in control and treated groups after an oral dose of 150 mg/kg. [c] Lit.[7] bp 125–126 °C (0.2). [d] $p < 0.01$. [e] $p < 0.05$. [f] $p < 0.001$. [g] Available from Aldrich Chemical Co., Inc., Milwaukee, WI. [h] Lit.[7] bp 112–113 °C (2); observed bp 136–138 °C (9). [i] Lit.[9] mp 47–49 °C. [j] C: calcd, 70.04; found, 69.25. [k] Lit.[7] bp 152–153° (0.5). [l] N: calcd, 8.48; found, 9.03. [m] Lit. mp 111 °C. N. H. Cantwell and E. V. Brown, *J. Am. Chem. Soc.*, 74, 5967 (1952). [n] Results are for a dose of 300 mg/kg ip. [o] With decomposition. [p] Based on the amount of starting material actually consumed. [q] Contains 0.25 mol of H_2O. [r] Material was contaminated with polymeric impurities. C: calcd, 64.62; found, 62.72. N: calcd, 8.37; found 7.02. [s] Lit.[23] mp of free base 46–47 °C. [t] Lit. bp 61–62 °C (0.5). A. Burger and H. H. Ong, *J. Med. Chem.*, 6, 205 (1963). [u] Contains 0.125 mol of H_2O. [v] Contains 0.75 mol of H_2O. [w] Results are for a dose of 260 mg/kg po. [x] C: calcd, 55.34; found, 54.83. [y] Lit.[11] mp 201–202 °C for HCl salt. [z] Results are for a dose of 300 mg/kg po. [a,a] Lit.[22] mp 91–93 °C.

Scheme II



pyridyl)propan-1-ol (**25**). This was accomplished readily by lithium aluminum hydride or diborane reduction of the corresponding acid or ester. Variation of the position of the oxygen in the C_2 side chain of **1** was accomplished with the synthesis of 3-(3-methyl-2-pyridyl)propan-2-ol (**26**) and the corresponding ketone **27**. **27** was derived from the reaction of **14** with acetonitrile using the technique described by Büchi, Kracher, and Schmidt.[13] Borohydride reduction of **27** gave **26**.

The effect on hypoglycemic activity produced by moving the 3-methyl substituent in **1** to C_5 was noted by preparing 3-(5-methyl-2-pyridyl)propan-1-ol (**28**). The effect of additional bulk was investigated with the preparation of 3-(3,5-dimethyl-2-pyridyl)propan-1-ol (**29**) and 3-(3-methyl-2-quinolyl)propan-1-ol (**30**). These three analogues of **1** were prepared in a manner analogous to that used for the preparation of **1**, namely, allowing ethylene oxide to react with the appropriate 2-methyl heterocycle. 3,5-Dimethylpyridine was available commerically. 2,3-Dimethylquinoline was made as described by Gagan and Lloyd.[14] 2,3,5-Trimethylpyridine, the starting material for **29**, seemed to be readily available from the thermal rearrangement of 3,5-dimethylpyridine methiodide.[15]

Although a direct route, the rearrangement of the methiodide led to a mixture of isomeric alkylpyridines which were difficult to separate. Thus, the longer route from the *N*-oxide of 3,5-dimethylpyridine was carried out to ensure that the correct product could be identified and also served as an alternative route to 2,3,5-trimethylpyridine (Scheme II). The intermediate **31** prepared in this sequence was also tested, and the results were compared with those from the testing of **24** and **29**.

Test results, together with appropriate physical constants, are found in Table I.

Discussion

The presence and position of the methyl group in **1** played an important role in determining whether hypoglycemia was noted and to what extent. Compare, respectively, **1** with **25** and **28**, isomers in which the C_2 and C_3 side chains were reversed and in which the methyl group was moved from C_3 to C_5. Neither of these isomers of **1** had hypoglycemic activity. The introduction of the C_3 methyl group converted **5**, a compound with hyperglycemic activity, to **1**, a compound with potent hypoglycemic activity. The glycemic activity seen in the methanol and propanol series (**2**–**7**) was not consistent with the above data, in that **3** and **6** with C_3 alcohol side chains were most potent, whereas **1** with a C_2 propanol side chain was more potent than **25** with a C_3 propanol side chain. Similarly, introducing a C_2 methyl group into **3** led to a compound (**24**) with no hypoglycemic activity.

The length of the hydrocarbon backbone of the alcohols was important for determining hypoglycemic activity (compare **1** with **9**–**11**). Optimum activity resided in **1**; less activity was seen with **10** and none with **9** and **11**. Modification to the C_2 propanol side chain of **1** yielded compounds with divergent glycemic activities. Introduction of two α-methyl groups into **1** or replacing its hydroxyl group with a mercapto group gave the weakly hypoglycemic compounds **20** and **21**. The secondary alcohol **26** and the corresponding ketone **27** were less potent hypoglycemic agents than **1**, but the trichloro secondary alcohol **15** caused a slight elevation in glycemic levels and the corresponding nonmethylated alcohol **32** caused a marked hyperglycemic response at twice the dose of **15** (300 vs. 150 mg/kg).

Testing other derivatives and analogues of **1** produced heterogenous results. The piperidine analogue **8**, the *N*-oxide **18**, and the methiodide **19** were less potent than **1**. The acetate and methyl ether of **1** (**22** and **23**) had activity comparable to that of **1**, although both seemed more toxic (4/8 animals dead after 4 h),[8] and the peak activity seen with **23** was delayed until the 5- and 6-h sampling times. The addition of a C_5 methyl group to **1** produced a potent compound (**29**). A bulkier substituent, the 5,6-benzo group, led to the inactive congener **30**. It is interesting to note that **31**, the methanol congener of **29**, was essentially devoid of hypoglycemic activity and matched the activities of **2** and **9**.

The acids **12**, **13**, **16**, and **17** varied in the effects they elicited. **12** produced pronounced hypoglycemia 4 and 5 h after dosing, but all the animals were dead at the 6-h sampling time.[8] In contrast, **13** and **16** were essentially without effect on glycemic levels, while **17** caused a slight rise in these levels.

When test animals were dosed with the hypoglycemic compounds **1**, **12**, **22**, **23**, and **29** and observed up to 24 h, death and/or elevated hepatic triglyceride levels accompanied the hypoglycemic response. For example, hepatic triglycerides increased about tenfold (rose to 26.1 ± 10.0 mg from a control value of 2.7 ± 0.8 mg/g of tissue, $p \leq 0.001$) 4 h after treatment with 50 mg/kg of **1**. Death could be delayed but not prevented by the administration of glucose, suggesting that death may have been due to hypoglycemia. The significance of these findings is still under investigation.

Experimental Section

Melting points were determined in a Thomas-Hoover melting point apparatus or an electrically heated metal block (Mel-temp) and are uncorrected. Compounds for which formulas are given were analyzed for C, H, and N; analytical values were within ±0.4% of the calculated values unless otherwise noted. Analyses were performed by members of our Analytical and Physical Chemistry Section.

Starting Materials. 2,3-Dimethylpyridine was purchased from Columbia Organic Chemical Co., Inc., Columbia, S. C.; 2,5- and 3,5-dimethylpyridines were available from Aldrich Chemical Co. Inc., Milwaukee, Wis; 2,3-dimethylquinoline was prepared as reported by Gagan and Lloyd;[14] and 2,3,5-trimethylpyridine was prepared by the method of Oparina[15] and from **31** as described

below and in the body of the paper.

Chromatographic separations were performed using neutral alumina, activity 3, supplied by ICN Pharmaceuticals, Inc., Life Sciences Group, Cleveland, Ohio.

Pyridylmethanols and Pyridylpropanols (2–7). These compounds were purchased from Aldrich Chemical Co., Inc., Milwaukee, Wis., were examined spectroscopically, and were used in hypoglycemic screens.

Preparation of (2-Pyridyl)propanols 1, 20, 28, 29, and 30, Butanol 11, and (2-Pyridyl)propanethiol 21. Ethylene oxide, trimethylene oxide, and ethylene sulfide were commercially available. 2,2-Dimethyloxirane was prepared from 1-chloro-2-methylpropan-2-ol,[16] which was derived from methallyl chloride using the procedure described by Burgin, Hearne, and Rust.[17]

A solution of 22 mL of commercially available 1.8 M C_6H_5Li in C_6H_6–Et_2O (70–30, v/v; Alfa Products, Ventron Corp., Danvers, Mass.) was cooled to −5 °C and to it was added slowly 0.038 mol of the appropriate 2-methylpyridine in 75 mL of Et_2O. The mixture was blanketed with N_2 and stirred for 30 min, whereupon excess cyclic oxide or sulfide (0.04 mol) in 25 mL of Et_2O was added carefully. The mixture was stirred overnight while being allowed to come to room temperature. An additional 0.04 mol of oxide or sulfide was added during this time. The mixture was cooled and carefully acidified with 6 N HCl. The layers were separated and the organic phase was washed with H_2O. The combined aqueous phases were brought to pH 8 with solid Na_2CO_3. The mixture was extracted with $CHCl_3$, and the $CHCl_3$ was dried (K_2CO_3) and evaporated. The residue was purified by distillation in vacuo or by chromatography.

3,5-Dimethylpicolinic Acid. 3,5-Dimethylpyridine was converted to its *N*-oxide with *m*-chloroperoxybenzoic acid as described earlier[2] to give 52% of material melting at 91–93 °C (C_6H_5Me–petroleum ether). Anal. ($C_7H_9NO \cdot 0.25H_2O$) C, H, N. This compound has been prepared by Augustinsson and Hasselquist[18] using peroxybenzoic acid. These workers purified this hygroscopic compound by distillation and characterized it as a picrate.

The *N*-oxide (5.3 g, 0.043 mol) was converted to crude 3,5-dimethylpicolinonitrile using the method of Reissert and Kaufman, as described by Matsumara, Ariga, and Ohfuji.[19] The crude product weighed 5.6 g and was purified by chromatography using C_6H_6. The chromatographed nitrile weighed 2.8 g (60%), mp 53–58 °C.

A larger batch of nitrile (39 g, 0.3 mol) was hydrolyzed by heating with 50% H_2SO_4 for 4 h. After cooling, 60 g of $Cu(OAc)_2 \cdot H_2O$ was added and the solution was adjusted to pH 2. A magenta-colored copper salt precipitated. The mixture was stirred 1 h and filtered. The salt was washed with H_2O and suspended in 500 mL of 20% HOAc. The suspension was stirred, warmed on a steam bath, and saturated with H_2S. The resulting suspension was filtered and washed with hot H_2O. The combined filtrates were evaporated, and the residue was dried and recrystallized from CCl_4 and then from C_6H_5Me to give 60% of acid, mp 147–149 °C. Anal. ($C_8H_9NO_2$) C, H, N.

Methyl 3,5-Dimethylpicolinate. The above acid was esterified with BF_3–MeOH as described previously:[2] yield 90–95%; mp 39–41 °C (petroleum ether, bp 30–60 °C). Anal. ($C_9H_{11}NO_2$) C, H, N.

The hydrochloride melted at 128–129 °C (Me_2CO). Anal. ($C_9H_{11}NO_2 \cdot HCl \cdot 0.25H_2O$) C, H, Cl, N.

(3,5-Dimethyl-2-pyridyl)methanol (31). A solution of 3 g (0.018 mol) of methyl 3,5-dimethylpicolinate in 100 mL of Et_2O was added dropwise to a cooled, stirred suspension of 900 mg (0.023 mol) of LAH in 60 mL of Et_2O. The mixture was refluxed for 5 h and cooled, and an additional 900 mg of LAH was added. Stirring and heating were resumed for 5 h and stirring alone was continued for 60 h. The mixture was cooled, and 8 mL of H_2O, 8 mL of 10% NaOH, and 32 mL of H_2O were added dropwise in the order listed. After an additional 1 h, the granular precipitate was collected and washed with Et_2O. The filtrates were evaporated and the residue was dried by azeotropic distillation with EtOH. The residual oil was converted to a hydrochloride.

2,3,5-Trimethylpyridine. A. Using the method of Marvel et al.,[20] 5.3 g (0.039 mol) of **31** was reduced in 30 mL of HOAc by heating with 1.25 g (0.042 g-atom) of red P and 30 mL of 47% HI for 35 h. The cooled mixture was filtered; the filtrate was diluted with 50 mL of H_2O and made basic with solid NaOH. Et_2O (50 mL) was added and insoluble material was removed. The solids and aqueous phase were washed with Et_2O. The Et_2O phases were washed with H_2O, dried, and evaporated to give 2.2 g (47%) of oil whose picrate melted at 175–176 °C (lit.[21] mp 182 °C).

B. 3,5-Dimethylpyridine was redistilled, and 107 g (1 mol) was stirred and refluxed for 3.5 h with 155 g (1 mol) of MeI in 500 mL of C_6H_6. The methiodide precipitated and was left overnight at room temperature. The solid was collected and washed with Et_2O; it weighed 243.7 g (98%), mp 265–266 °C dec.

The methiodide was heated at 300–320 °C for 3 h in a bomb. The bomb was cooled, opened, and rinsed with MeOH. The mixture was concentrated and the residue was dissolved as completely as possible in 3 N HCl. The acidic mixture was washed with Et_2O five times. The aqueous mixture was made alkaline with aqueous NH_3 and then made more strongly alkaline with 10% NaOH and extracted with Et_2O. The Et_2O was filtered to remove insoluble material and washed with H_2O three times. The aqueous washes were backwashed twice with Et_2O, and the combined Et_2O extracts were dried and concentrated to leave 76 g of brown oil. The oil was fractionated at 25 mmHg using a Widmer column. The fraction boiling at 84–88 °C weighed 14 g and formed a picrate melting at 180–185 °C (lit.[20] 182 °C). The mixture melting point with material obtained from **31** was 176–178 °C.

3-(3-Methyl-2-piperidinyl)propan-1-ol Hydrochloride (8). The conversion of **1** to **8** was accomplished using the protocol of Reinecke and Kray.[7] The impure amino alcohol was distilled (bp 136–138 °C) and converted to its hydrochloride.

(3-Methyl-2-pyridyl)methanol Hydrochloride (9). The acetate of **9** was prepared as described by Ginsburg and Wilson,[22] and purified as the hydrochloride: yield 77%; mp 135–136 °C (MeCN–Et_2O). Anal. ($C_9H_{11}NO_2 \cdot HCl$) C, H, Cl, N.

The hydrochloride of 2-(acetoxymethyl)-3-methylpyridine (6.2 g, 0.031 mol) was added to a stirred suspension of 10 g (0.1 mol) of Na_2CO_3 in a mixture of 50 mL of H_2O and 200 mL of MeOH. The mixture was refluxed overnight, the MeOH was removed, and the aqueous residue was extracted with $CHCl_3$. The $CHCl_3$ was dried and evaporated. The residue was dissolved in Et_2O and saturated with HCl. The precipitate was collected, washed with Et_2O, and recrystallized.

2-(3-Methyl-2-pyridyl)ethan-1-ol (10). Allowing **14** to react with paraformaldehyde as described by Bohlmann and coworkers[10] gave **10**.

3-(3-Methyl-2-pyridyl)-1,1,1-trichloropropan-2-ol Hydrochloride (15). A solution of 53.5 g (0.5 mol) of **14** and 60 mL of chloral in 500 mL of amyl acetate was stirred and refluxed under N_2 for 20 h. The resulting mixture was cooled and distributed between C_6H_6 and 3 N HCl. The layers were separated and the organic phase was washed with 3 N HCl and H_2O. The combined aqueous phases were adjusted to pH 8 with solid Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ was washed with H_2O, dried, and evaporated. The residue was dissolved in Et_2O and saturated with dry HCl. The salt was collected and purified.

3-(3-Methyl-2-pyridyl)-2-propenoic Acid (17). A solution of 132 g (2.4 mol) of KOH in 400 mL of dry EtOH was stirred and warmed on a steam bath under N_2 as 60 g (0.21 mol) of **15** was added in small portions. Heating was continued for a total heating time of 6 h. The mixture was cooled and the precipitated KCl was removed. The filtrate was acidified by adding acidic ion-exchange resin (IRA-120). The slurry was filtered and the resin was washed with EtOH. The filtrate was concentrated to leave 7.2 g of semisolid, which was recrystallized from MeOH.

3-(3-Methyl-2-pyridyl)propionic Acid (12). A slurry of 2 g (0.012 mol) of **17** and 0.5 g of 10% Pd/C in 75 mL of MeOH was hydrogenated under an initial pressure of 3.5 kg/cm^2 of H_2. The reduction was complete in 1 h. The catalyst was removed and washed, the filtrate was concentrated, and the residue was recrystallized.

The hydrochloride of **12** melted at 157–159 °C (EtOH). Anal. ($C_9H_{11}NO_2 \cdot HCl \cdot 0.25H_2O$) C, H, Cl, N.

3-Methylpicolinic Acid (13). This acid was prepared from **14** using the experimental details supplied by Jerchel, Bauer, and Hippchen.[11]

3-(3-Methyl-2-pyridyl)lactic Acid Hydrochloride (16). A solution of 2.9 g (0.01 mol) of **15** in 7 mL of H_2O was added dropwise to a stirred, refluxing solution of 3.5 g (0.028 mol) of Na_2CO_3 in 15 mL of H_2O. The mixture was refluxed for 3 h. An oil separated, which on standing gave a solid melting about 65 °C to a cloudy melt. This proved to be 1.5 g of the free base of **15**.

To the filtrate was added 3 g of $Cu(OAc)_2 \cdot H_2O$. A powder blue-colored salt precipitated. The solid was collected in two crops and decomposed with H_2S in 20% HOAc. The precipitated CuS was removed and washed with H_2O, and the filtrates were evaporated. The residue was dried by azeotroping with EtOH and weighed ca. 1.8 g. The syrupy residue was dissolved in MeCN and treated with ethereal HCl. After trituration with Et_2O, the resulting gum hardened to give 0.7 g of solid. This was recrystallized to give pure **16**.

3-(3-Methyl-2-pyridyl)propan-1-ol *N*-Oxide (18). A solution of **1** in $CHCl_3$ was stirred under reflux with a slight excess of *m*-chloroperoxybenzoic acid. Conditions for the isolation and purification of the *N*-oxide were similar to those reported earlier.[2]

Methiodides of 1 and 7 (19 and 33). The synthetic directions of Weber[23] used to prepare **33** were also used to obtain **19**.

1-Acetoxy-3-(3-methyl-2-pyridyl)propane (22). A solution of 4 g (0.027 mol) of **1** and 40 mL of Ac_2O was refluxed for 1 h and left overnight at room temperature. Evaporation of the excess Ac_2O left an oil which was dissolved in Et_2O. The Et_2O was washed with 5% $NaHCO_3$ and H_2O, dried, and evaporated. The residue was fractionated in vacuo.

1-Methoxy-3-(3-methyl-2-pyridyl)propane (23). **14** (0.1 mol) was alkylated with 0.15 mol of 1-bromo-2-methoxyethane under conditions comparable to those used in the preparation of **1**.

(2-Methyl-3-pyridyl)methanol Hydrochloride (24) and 3-(2-Methyl-3-pyridyl)propan-1-ol Perchlorate (25). LAH reduction of ethyl 2-methylnicotinate[24] gave **24**[25] which was converted to the corresponding known nicotinaldehyde in 74% yield by oxidation with activated MnO_2. The sequential conversion of the aldehyde to the corresponding acrylic and propionic acids was effected as described by Dornow and Bormann.[26]

A solution of 0.9 M diborane in THF (75 mL, Alfa Products of Ventron Corp., Danvers, Mass.) was added dropwise to a cooled, stirred suspension of 8.2 g (0.05 mol) of 3-(2-methyl-3-pyridyl)propionic acid[26] under N_2. After one-half the diborane had been added, the starting material dissolved. When the diborane addition had been completed, the solution became cloudy. The mixture was stirred for 1 h in the cold and for 2 h at room temperature and cooled again. The boron complexes were decomposed by the careful addition of 100 mL of a THF–H_2O (1:1, v/v) mixture. The resulting clear solution was concentrated and the residue was dried by azeotropic distillation with EtOH. The resulting glass was dissolved in 100 mL of 3 N HCl and warmed for 15 min on a steam bath. The solution was cooled, made alkaline, and extracted with $CHCl_3$. The $CHCl_3$ was washed with H_2O, dried, and removed. The residual oil weighed 5.3 g. It was dissolved in Et_2O and carefully acidified with 70% $HClO_4$. The Et_2O was decanted from the settled oil and the oil was triturated with Me_2CO to induce crystallization. The mixture was diluted with Et_2O and filtered, and the solid was washed with Et_2O and recrystallized.

3-(3-Methyl-2-pyridyl)propan-2-one (27). Employing the method and conditions described by Büchi, Kracher, and Schmidt for the preparation of the nonmethylated propanone,[13] 26.8 g (0.25 mol) of **14** was allowed to react with MeCN in the presence of C_6H_5Li. The intermediate ketimine was decomposed with 2 N H_2SO_4. After liberation of the free base with 40% NaOH, the crude, brown product mixture weighed 30 g. Fractionation through a small Vigreaux column gave 11.1 g of recovered **14** and 8.5 g of **27**.

3-(3-Methyl-2-pyridyl)propan-2-ol Hydrochloride (26). To a solution of 8.8 g (0.059 mol) of **27** in 90 mL of absolute EtOH was added 3 g (0.084 mol) of $NaBH_4$. The solution was stirred for 1 h and the EtOH was removed. The residue was dissolved in H_2O and the aqueous solution was extracted with Et_2O. The Et_2O was dried and distilled. The residue was chromatographed with EtOAc–cyclohexane (1:1, v/v) to give 5.0 g (56%) of purified **26**, which was converted to 4.3 g of hydrochloride.

3-(2-Pyridyl)-1,1,1-trichloropropan-2-ol (32). 2-Methylpyridine was converted to **32** using the experimental protocol set forth in the preparation of **15**.

Biochemistry. Hypoglycemic testing was carried out in 48-h fasted male rats.[2,27] Tolbutamide, after an oral dose of 200 mg/kg, lowered blood glucose levels in this test system 28% at 1 h, 47% at 2 h, and 48% at 4 h after treatment. In vitro studies were carried out using rat kidney cortex slices. Both procedures have been described.[2,27] Hepatic triglycerides were determined by extracting livers according to the method of Folche, Lees, and SloaneStanley[28] and analyzing the material in the $CHCl_3$ fractions as described by van Handel and Zilversmit.[29]

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References and Notes

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