After the catalyst was filtered off about 25 ml. of ether was added to the filtrate which was then washed with two 50-ml. portions of water and dried over calcium chloride. An 81% yield of 3-benzylindole (m.p. 105–106°) was filtered from the cooled solution. Recrystallization from methylcyclohexane and then from methanol raised the m.p. only to 106.5–107° and lowered the yield to 76%. Further recrystallization failed to change the m.p.; lit. values are 103–105°[15] and 111°.[5] The picrate melted at 114° (lit.[5] m.p. 113°).

The foregoing isolation and recrystallization procedure was used unless otherwise noted for all solid products. For liquids and a few low-melting solids the ether was volatilized from the washed and dried solution at the water-pump and the crude product isolated by distillation through a vacuum jacketed still-head at about 0.2 mm. pressure. The pure product for which yields are tabulated was obtained by redistillation through an 8-in. Vigreux column.

New Compounds.—Five of the seven products obtained with primary alcohols are new. The **3-(*p*-methoxybenzyl)-indole** isolated in the standard fashion was obtained in 36% yield with m.p. 84.0–84.5° and in 26% yield with m.p. 87.0–88.0°. *Anal.* Calcd. for $C_{15}H_{15}NO$: C, 80.98; H, 6.37. Found: C, 80.90, H, 6.14. The **3-(*p*-methylbenzyl)-indole** melted at 95.0–95.5°. Since results of analysis for carbon were erratic, the picrate was prepared. *Anal.* Calcd. for $C_{16}H_{15}N \cdot C_6H_3N_3O_7$: C, 60.03; H, 4.03. Found: C, 59.75; H, 3.86. The standard distillation procedure for liquids was used for the **3-octylindole**. It boiled at 125–127° (0.2 mm.) and solidified in the receiver (m.p. 33–34°). *Anal.* Calcd. for $C_{16}H_{23}N$: C, 83.78; H, 10.11. Found: C, 83.24; H, 10.18. The **3-(cyclohexylmethyl)-indole** distilled at 140–149° (0.1 mm.). Recrystallization of the solidified distillate from methanol gave 20.2 g. (76%) which melted at 70.5–71.5°; further recrystallization raised the m.p. to 72.0–72.5°. *Anal.* Calcd. for $C_{15}H_{19}N$: C, 84.45; H, 8.97. Found: C, 84.11; H, 8.70. Under the standard distillation conditions **3-(2-ethylhexyl)-indole** was obtained at 138–142° (0.5 mm.). The $n^{25}D$ value of 1.5415 was raised to 1.5422 upon redistillation to obtain the analytical sample. *Anal.* Calcd. for $C_{16}H_{23}N$: C, 83.78; H, 10.11. Found: C, 84.13; H, 9.65. The **3-(2-butyloctyl)-indole** described in the following section is also new.

All four of the alkylated indoles obtained with the secondary alcohols are new. The **3-(1-phenylethyl)-indole** was isolated by rapid distillation (up to 170° at 0.1 mm.) followed by two recrystallizations from methylcyclohexane. The m.p. of the product, obtained in 45% yield, was raised from 75.5–76.0° to 76.5–77.5° by further recrystallization. *Anal.* Calcd. for $C_{16}H_{15}N$: C, 86.84; H, 6.83. Found: C, 86.90; H, 6.53. From benzhydrol an 89% yield of **3-(diphenylmethyl)-indole** which melted at 120–124° was obtained upon recrystallization from methanol; the yield fell to 67% and the m.p. rose to 127–128° upon recrystallization from methylcyclohexane. *Anal.* Calcd. for $C_{21}H_{17}N$: C, 89.01; H, 6.05; N, 4.95. Found: C, 89.07; H, 6.11; N, 4.65. The **3-(2-octyl)-indole** which distilled at about 148–153° (0.3 mm.) had $n^{25}D$ 1.5329. *Anal.* Calcd. for $C_{16}H_{23}N$: C, 83.78; H, 10.11. Found: C, 83.83; H, 10.39. Distillation up to 145° (0.5 mm.) followed by recrystallization from methyl alcohol gave the pure **3-cyclohexylindole** which melted at 92.0–92.5°. *Anal.* Calcd. for $C_{14}H_{17}N$: C, 84.36; H, 8.60. Found: C, 84.26; H, 8.36.

The tabulated data suffice for the 3-benzyl-,[5,15] the 3-(3-phenylpropyl)-,[5] the 2-methyl-3-benzyl-[18] and the 2-phenyl-3-benzylindoles,[19] all of which are known compounds melting very close to the reported temperatures.

Guerbet Condensations.—In order to determine the extent of interference of the Guerbet reaction, expt. 11 was repeated, except the indole was omitted. A 90% yield of water collected in about 19 hr. and a 101% yield in about 25 hr. at 181–185°. The reaction mixture was washed free of base, dried and distilled through an 8-in. Vigreux column to give a 66% yield of 2-hexyldecanol-1 at 133–137° (0.8 mm.); $n^{25}D$ was 1.4476 as compared to the lit. value of 1.4472.[13]

In a similar experiment in which 0.50 mole of *n*-hexyl alcohol was used in place of the 0.25 mole of *n*-octyl alcohol, water evolution practically ceased after 80 hr. of refluxing at 165–188° at which time a 90% yield had collected. One-eighth mole of indole was then added and refluxing continued. Since only 0.40 ml. of water collected after 46 hr. at 193–194°, another 0.04 mole of potassium hydroxide was added. After refluxing for 80 hr. more at 191–192°, water evolution ceased at 121%, calculated for complete alkylation of the indole by the 2-butyloctanol-1. After washing the reaction mixture with water, it was dried and distilled through an 8-in. Vigreux column. A 60% yield of **3-(2-butyloctyl)-indole** distilled at about 155–170° (0.3 mm.), $n^{25}D$ 1.5180. The $n^{25}D$ for an analytical sample (b.p. 170° at 0.3 mm.) was 1.5214. *Anal.* Calcd. for $C_{20}H_{31}N$: C, 84.11; H, 10.95. Found: C, 84.49; H, 11.11.

Supplementary Experiments.—The standard expt. 1 was repeated with a gas buret connected to the top of the reflux condenser. On the assumption that the gas collected throughout the reflux period was a mixture of hydrogen and air it was calculated, from the volume and density, that 0.035 mole of hydrogen was evolved. By acidification of the 100 ml. of aqueous extracts of the reaction mixture, obtained in the standard isolation procedure, 1.2 g. of a white solid was obtained which melted at 121–122° both alone and when mixed with authentic benzoic acid.

In an expt. identical with no. 11 except that no excess of *n*-octyl alcohol was used a 98% yield of water was obtained in 75 hr. The yield of 3-octylindole was 37% showing that here, as with benzyl alcohol, an excess of alcohol markedly improves the yield.

(18) T. Hoshino, *Ann.*, **500**, 40 (1932).

(19) P. L. Julian, E. W. Meyer, A. Magnani and W. Cole, THIS JOURNAL, **67**, 1210 (1945).

COLLEGE PARK, MARYLAND

[CONTRIBUTION FROM MCNEIL LABORATORIES, INC.]

Dihydroergot Analogs. 1-(3-Indolylmethyl)-piperidinecarboxamides[1]

BY ANSEL P. SWAIN AND SARA K. NAEGELE

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The preparation of N-mono- and N,N-disubstituted-1-(3-indolylmethyl)-isonipecotamides, nipecotamides and pipecolamides, structural analogs of the hydrogenated ergot alkaloids, is described. Many of the new compounds when administered intravenously cause a decrease in blood pressure at about 2–16 mg./kg. in dogs anesthetized with α-chloralose. Several of the indolylmethyl nipecotamides and pipecolamides, but not the 4-isomers, also cause a typical apnea. The synthesis of a series of 1-alkyl-, 1-aralkyl- and 1-acyl-N,N-diethylisonipecotamides, prepared for a study of the effects of alterations in structure of the 1-indolylmethyl compound upon hypotensive activity, is also described.

As part of a search for new synthetic hypotensive agents we have prepared a number of substituted piperidinecarboxamides of formula I. Compounds in which R_3 is an indolylmethyl group (II) resemble amides of dihydrolysergic acid (III).

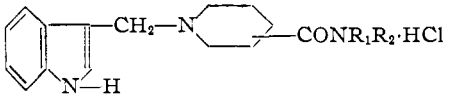
Stoll has reviewed the chemistry and pharmacology of the ergot alkaloids.[2] The most potent hypotensive agents of this group are the dihydro-

(1) Presented before the Division of Medicinal Chemistry at the 126th Meeting of the American Chemical Society, New York, September 17 1954.

(2) A. Stoll, *Chem. Revs.*, **47**, 197 (1950).

TABLE I

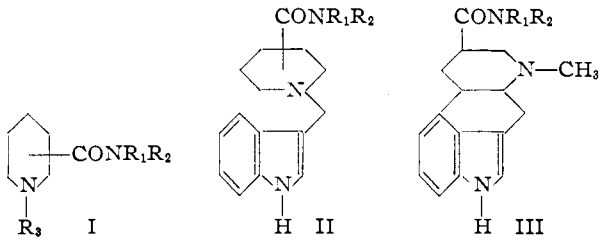
1-(3-INDOLYLMETHYL)-PIPERIDINECARBOXAMIDE HYDROCHLORIDES



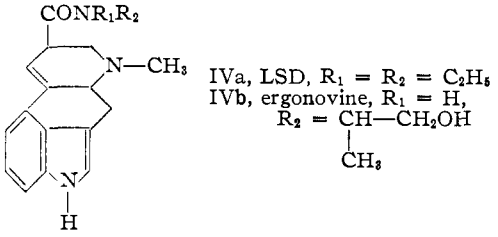
R_1	R_2	Isomer	Yield, %[a]	M.p., °C.[b]	Formula	Nitrogen, %[c] Calcd.	Found	B.p.,[d] mg./kg.	S,[e] mg./kg.	C.O.,[f] mg./kg.	LD_{50},[g] mg./kg.
H	H	4	75	196–197	$C_{15}H_{19}N_3O\cdot HCl$	14.3	14.3	NE32	NE32	NE32	350
H	H	3	71	194.5–195	$C_{15}H_{19}N_3O\cdot HCl$	14.3	14.3[h]	NE	NE	NE	280
CH_3	CH_3	4	93	166–167	$C_{17}H_{23}N_3O\cdot HCl$	13.1	13.2	32	NE64	16	280
H	C_2H_5	4	70	188–189	$C_{17}H_{23}N_3O\cdot HCl$	13.1	12.9	16	64	8	280
C_2H_5	C_2H_5	4	70	170–172	$C_{19}H_{27}N_3O\cdot HCl$	12.0	11.9[i]	16	NE32	8	180
C_2H_5	C_2H_5	3	62	188–189	$C_{19}H_{27}N_3O\cdot HCl$	12.0	12.1[j]	10	NE	9	80
C_2H_5	C_2H_5	2	52	169–171	$C_{19}H_{27}N_3O\cdot HCl$	12.0	12.0	24	NE	24	180
C_2H_5	C_2H_5	4	45	246–247 d.	$C_{20}H_{29}N_3O\cdot HCl$[k]	11.5	11.5	8	8	4	150
$(CH_3)_2CH$	$(CH_3)_2CH$	4	55	217–218 d.	$C_{21}H_{31}N_3O\cdot HCl$	11.1	11.2[l]	NE26	8	8	100
$(CH_3)_2CH$	$(CH_3)_2CH$	3	66[m]	177–179	$C_{21}H_{31}N_3O\cdot HCl$	11.1	11.1	12	NE	12	420
H	$C_6H_5CH_2$	4	85	192–193	$C_{22}H_{25}N_3O\cdot HCl$	10.9	10.8	NE32	NE16	NE16	100
C_2H_5	$C_6H_5CH_2$	4	90	195–196	$C_{24}H_{29}N_3O\cdot HCl$	10.2	10.3	NE32	NE32	NE16	333
H	$CH_3CHCOOC_2H_5$	4	51	176–177	$C_{20}H_{27}N_3O\cdot HCl$	10.7	10.6	8[n]	NE64	NE64	940

[a] Recrystallized yield. [b] Uncorrected. [c] Semimicro-Kjeldahl. [d] I.v. dose required for 25% decrease in blood pressure for 15 minutes or longer in chloralosed dogs. (NE means no significant hypotensive effect in the highest tolerated dose.) [e] I.v. dose required to prevent 50% of the pressor response (30–60 mm.) to small doses of epinephrine in chloralosed dogs. [f] I.v. dose required to prevent 50% of the pressor rise resulting from bilateral carotid occlusion in chloralosed dogs. [g] Following i.p. injection in white mice. [h] *Anal.* Calcd.: Cl, 12.1. Found: Cl, 12.5. [i] *Anal.* Calcd.: C, 65.22; H, 8.07; Cl, 10.1. Found: C, 65.64; H, 8.08; Cl, 9.8. M.p. of picrate: 171–172°. [j] *Anal.* Calcd.: Cl, 10.1. Found: Cl, 10.2. [k] Has CH_3 in 2-position of indole ring. [l] Picrate: m.p. 187–188°. [m] Crude yield. [n] Blood pressure decrease of brief duration.

genated alkaloids of the ergotoxine type in which R_2 (III, R_1 = H) is a cyclic polypeptide group.[3]

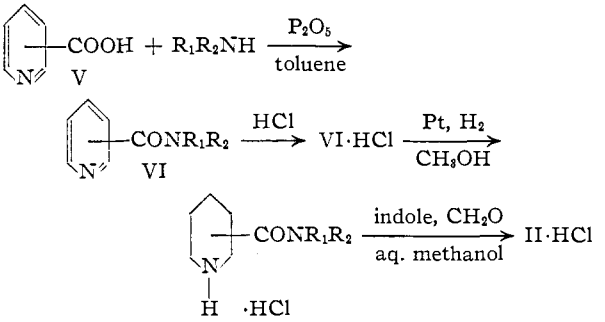


The compounds whose preparation is described in this paper are more closely related in structure to lysergic acid diethylamide (LSD, formula IVa), or to the oxytocic alkaloids, represented by ergonovine (IVb).



IVa, LSD, $R_1 = R_2 = C_2H_5$
IVb, ergonovine, R_1 = H, $R_2 = CH(CH_3)CH_2OH$

The indolylmethylpiperidine amides were prepared by the series of reactions shown. Alternatively, the acids V were converted to the acid chlorides which were allowed to react with an excess of the amine, but the phosphoric anhydride method was preferred because of its simplicity of operation. The 1-aralkyl- and 1-acyl-diethylisonipecotamides were prepared by reaction of the piperidine derivative with the corresponding halides. The 1-methyl- and 1-ethyl-N,N-diethylisonipecotamides were obtained by reduction of the isonicotinamide quaternary iodides. Pertinent data appear in the tables.



Many of these substituted piperidine amides cause a decrease in blood pressure after intravenous injection into dogs anesthetized with α-chloralose. The N,N-diethylamide of 1-(3-indolylmethyl)-isonipecotic acid (Table I) lowers the blood pressure, decreases the heart rate and blocks the pressor rise resulting from bilateral carotid occlusion at dose levels ranging from 2 to 16 mg./kg. The isomers having the diethylamide group in the 2- or 3-position produce, in addition, a typical apnea of short duration. Representative data appear in the tables.

In addition, several 1-(3-indolylmethyl)-piperidinecarboxylic acids and esters were prepared. They were either inactive or produced irregular lowering of blood pressure.

Akkerman and Veldstra[4,5] reported the synthesis and oxytocic activities of a series of 3-(1- and 2-[piperidylmethyl])-indoles carrying alkyl, carboxyl, ester or hydroxyalkylamide groups on the piperidine ring. The 2-piperidylmethyl indoles were

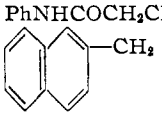
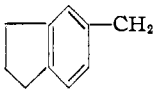
(3) A. Stoll, A. Hofmann and Th. Petrzilka, *Helv. Chim. Acta*, **34**, 1544 (1951).

(4) A. M. Akkerman and H. Veldstra, *Rec. trav. chim.*, **73**, 629 (1954).

(5) A. M. Akkerman, D. K. de Jongh and H. Veldstra, *ibid.*, **70**, 899 (1951).

TABLE II

1-SUBSTITUTED-N,N-DIETHYLISONIPECOTAMIDES, HYDRIODIDES AND HYDROCHLORIDES R—N⟨⟩—CON(C_2H_5)$_2$

R	Yield, %[a]	M.p., °C.[b]	Formula	Nitrogen, % Calcd.[c]	Nitrogen, % Found[c]	B.p.,[d] mg./kg.	S,[e] mg./kg.	C.O.,[f] mg./kg.	LD_{50},[g] mg./kg.
CH_3	100	141–142	$C_{11}H_{22}N_2O$·HI	8.6	8.3	NE64	NE64	NE64	940
C_2H_5	91	124–126	$C_{12}H_{24}N_2O$·HI	8.2	8.3	NE64	NE64	NE64	780
CH_3CO	54[h]	[i]	$C_{12}H_{22}N_2O_2$	12.4	12.4	16	8	32	>940[j]
$PhCH_2$	77[k]	221–222	$C_{17}H_{26}N_2O$·HCl	9.0	9.1	2	16	4	165
$PhCH_2CH_2$	89	251.5–252.2	$C_{18}H_{28}N_2O$·HCl	8.6	8.5	4	4	8	730
$PhOCH_2CH_2$	47[k]	160–161	$C_{18}H_{28}N_2O_2$·HCl	8.2	8.1	4	8	8	80
PhCO	70[h]	96–97	$C_{17}H_{24}N_2O_2$	9.7	9.7	NE64	NE64	32	280
$PhCOCH_2$	100	201–202	$C_{18}H_{26}N_2O_2$·HCl	8.3	8.2	4	8	16	230
$PhNHCOCH_2CH_2$	27	214–215	$C_{19}H_{29}N_3O_2$·HCl	11.4	11.2				
	83	224–225	$C_{21}H_{28}N_2O$·HCl	7.8	7.8	8	8	8	67
	82	202–203	$C_{20}H_{30}N_2O$·HCl	8.0	8.0				

[a] These yields represent those of crude products. [b] All melting points are uncorrected. [c] Semimicro-Kjeldahl. [d] I.v. dose required for 25% decrease in blood pressure for 15 minutes or longer in chloralosed dogs. (NE means no significant hypotensive effect in the highest tolerated dose.) [e] I.v. dose required to prevent 50% of the pressor response (30–60 mm.) to small doses of epinephrine in chloralosed dogs. [f] I.v. dose required to prevent 50% of the pressor rise resulting from bilateral carotid occlusion in chloralosed dogs. [g] Following i.p. injection in white mice. [h] Yield after distillation. [i] B.p. 168–170° (0.5 mm.). [j] Did not produce deaths at this dose, the highest tested. [k] Yield after recrystallization. [l] B.p. 222–225° (0.5 mm.).

TABLE III

PIPERIDINECARBOXAMIDES AND HYDROCHLORIDES H—N⟨⟩—$CONR_1R_2$

R_1	R_2	Isomer	Yield, %[a]	M.p., °C.[b]	Formula	Nitrogen, % Calcd.[c]	Nitrogen, % Found[c]
CH_3	CH_3	4	84[d]	169–170	$C_8H_{16}N_2O$·HCl	14.5	14.2
H	C_2H_5	4	88	162–163	$C_8H_{16}N_2O$·HCl	14.5	14.7
C_2H_5	C_2H_5	4	69[d]	260–261	$C_{10}H_{20}N_2O$·HCl	12.7	12.6
C_2H_5	C_2H_5	2	81	239–240	$C_{10}H_{20}N_2O$·HCl	12.7	12.7[e]
$(CH_3)_2CH$	$(CH_3)_2CH$	4	72[d]	300–301 d.	$C_{12}H_{24}N_2O$·HCl	11.3	11.2
$(CH_3)_2CH$	$(CH_3)_2CH$	3	54	97–99	$C_{12}H_{24}N_2O$	13.2	13.3
H	$CH_3CHCOOC_2H_5$	4	81	180–180.5	$C_{11}H_{20}N_2O_3$·HCl	10.6	10.7
H	$C_6H_5CH_2$	4	80	110–112	$C_{13}H_{18}N_2O$	12.8	12.8
C_2H_5	$C_6H_5CH_2$	4	95	229–230	$C_{15}H_{22}N_2O$·HCl	9.9	9.8

[a] Crude yield. [b] Uncorrected. [c] Semimicro-Kjeldahl. [d] Recrystallized yield. [e] Calcd.: C, 54.42; H, 9.59. Found: C, 54.62; H, 9.22.

TABLE IV

PYRIDINECARBOXAMIDES AND HYDROCHLORIDES N⟨⟩—$CONR_1R_2$

R_1	R_2	Isomer	Yield, %[a]	M.p., °C.[b]	Formula	Nitrogen, % Calcd.[c]	Nitrogen, % Found[c]
CH_3	CH_3	4	70	60–60.5	$C_8H_{10}N_2O$	18.7	18.3[d]
CH_3	CH_3	4		145–146	$C_8H_{10}N_2O$·HCl	15.0	14.8
$(CH_3)_2CH$	$(CH_3)_2CH$	4	86	102–103	$C_{12}H_{18}N_2O$	13.6	13.5[e]
$(CH_3)_2CH$	$(CH_3)_2CH$	3	71	100–101	$C_{12}H_{18}N_2O$	13.6	13.7[f]
$(CH_3)_2CH$	$(CH_3)_2CH$	3		182–183	$C_{12}H_{18}N_2O$·HCl	11.5	11.5
H	$CH_3CHCOOC_2H_5$	4	64	67–68	$C_{11}H_{14}N_2O_2$	12.6	12.7
C_2H_5	$C_6H_5CH_2$	4	79[g]	156–157	$C_{15}H_{16}N_2O$·HCl	10.1	10.2

[a] These yields represent those of crude products. [b] All melting points are uncorrected. [c] Semimicro-Kjeldahl. [d] *Anal.* Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.22. Found: C, 64.08; H, 6.38. [e] *Anal.* Calcd. for $C_{12}H_{18}N_2O$: C, 69.86; H, 8.79. Found: C, 69.79; H, 8.75. [f] B.p. 131–134° (1 mm.). *Anal.* Calcd.: C, 69.86; H, 8.79. Found: C, 70.06; H, 8.47. [g] Yield of base.

found to be in general less active and less specific than the 1-piperidylmethylindoles. Their most active compounds were one-third to one-half as potent as ergonovine.[6,7] No information is available on the possible oxytocic or LSD-like activities of the 3-(1-piperidylmethyl)-indoles reported in the present paper.

(6) E. G. van Proosdij-Hartzema and D. K. de Jongh, *Arch. intern. pharmacodynamie*, **98**, 335 (1954).

(7) D. K. de Jongh and E. G. van Proosdij-Hartzema, *J. Pharmcol. Exptl. Therap.*, **105**, 130 (1952).

Experimental[8]

The following examples illustrate the general methods used.

N,N-Diethylpicolinamide Hydrochloride.—A hot solution of 24.5 g. (0.2 mole) of picolinic acid and 74 ml. (0.7 mole) of N,N-diethylamine in 100 ml. of toluene was treated

(8) Melting points are uncorrected.

with 31.2 g. (0.22 mole) of phosphoric anhydride in portions. When the mixture had been refluxed for four hours, it was chilled in an ice-bath while an excess of aqueous 10% sodium hydroxide was added. The toluene layer was separated, and the aqueous layer was extracted with a mixture of ether and toluene. The residue from evaporation of the combined dried organic layers was distilled, b.p. 102–110° at less than 1 mm.[9] Addition of anhydrous hydrogen chloride to an ether solution of the distillate yielded 20.0 g. (46%) of a white solid, m.p. 125–126°. Recrystallization from 95% ethanol gave 15.8 g., m.p. 128–128.5°.

Anal. Calcd. for $C_{16}H_{14}N_2O\cdot HCl$: N, 13.0. Found: N, 13.0.

N,N-Diisopropylnicotinamide and its Hydrochloride.—Nicotinyl chloride hydrochloride prepared from 19.7 g. (0.16 mole) of nicotinic acid and thionyl chloride was suspended in a mixture of 100 ml. of dry benzene and 27 ml. (0.32 mole) of pyridine; 74 ml. (0.49 mole) of diisopropylamine was added. The mixture was refluxed for 15 minutes and was then allowed to stand at room temperature overnight. The solid which separated was removed and washed with benzene. The combined benzene filtrate and washings were chilled in an ice-bath and treated with an excess of 50% aqueous sodium hydroxide solution. The benzene layer was separated and the alkaline solution was extracted with ether. The combined benzene and ether layers were dried over sodium sulfate and the solvents were removed by distillation. The residue (23.7 g., 71%) was distilled under reduced pressure. The yellow distillate, b.p. 131–134° at 1 mm., solidified on cooling; yield 19.7 g. (60%). Recrystallization from water containing a little methanol gave 11.2 g. (34%), m.p. 101°. Recrystallization of this material from 45 ml. of *n*-heptane gave large white crystals; yield 11.0 g., m.p. 101°. The analysis was carried out on a sample which was dried to constant weight.

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.79; N, 13.6. Found: C, 70.06; H, 8.47; N, 13.7.

N,N-Diethylpipecolamide Hydrochloride.—A solution of 14.0 g. (0.065 mole) of N,N-diethylpicolinamide hydrochloride in 75 ml. of methanol was reduced at 3–4 atm. of hydrogen and room temperature with 0.4 g. of platinum oxide catalyst. After removal of the catalyst, the solution was concentrated until solid began to separate; 11.6 g. (81%) of product was obtained. Three recrystallizations from a mixture of methanol and ether gave a product, m.p. 239–240° dec., which was a hydrate.

Anal. Calcd. for $C_{10}H_{20}N_2O\cdot HCl\cdot H_2O$: N, 11.7. Found: N, 11.9.

1-(3-Indolylmethyl)-N,N-diethylpipecolamide Hydrochloride.—A solution of 10.2 g. (0.043 mole) of N,N-diethylpipecolamide hydrochloride hydrate, 5.2 g. (0.044 mole) of recrystallized indole and 1.3 g. (0.044 mole) of formaldehyde (3.35 ml. of 37% aqueous formaldehyde) in 30 ml. of methanol was allowed to stand at room temperature in the dark for three days. The orange solution was treated with ether, chilled and scratched so that 15.9 g. (100%) of a light yellow solid, m.p. 136–142°, separated. After four recrystallizations from a mixture of methanol and ether, 8.4 g. (52%) of shiny, hard crystals, m.p. 169–171°, was obtained. The melting point varies with the rate of heating.

1-(2-Phenoxyethyl)-N,N-diethylisonipecotamide Hydrochloride.—A mixture of 11.1 g. (0.05 mole) of N,N-diethylisonipecotamide hydrochloride, 10.1 g. (0.05 mole) of phenoxyethyl bromide, 8.0 g. (0.075 mole) of anhydrous sodium carbonate and 50 ml. of methanol was refluxed for 26 hours. Ether (300 ml.) was added and the mixture was filtered. Addition of anhydrous hydrogen chloride to the filtrate caused separation of an oil which solidified readily on stirring. The precipitate was recrystallized twice from a mixture of methanol and ether. The product separated as white crystals weighing 7.9 g. (47%), m.p. 160–161°.

4-Diethylcarbamyl-1-ethylpyridinium Iodide.—A mixture of 35.7 g. (0.2 mole) of N,N-diethylisonicotinamide, 31.2 g. (0.2 mole) of ethyl iodide and 300 ml. of benzene was refluxed for 16 hours. The yellow crystals which separated weighed 37.0 g. (55%). After two recrystallizations from a mixture of methanol and ether, 35.5 g. of product, m.p. 105–106°, was obtained.

Anal. Calcd. for $C_{12}H_{19}IN_2O$: N, 8.4. Found: N, 8.1.

Heating the benzene filtrate with an additional 0.2 mole of ethyl iodide gave another 13.5 g. (20%) of product; total yield 75%.

1-Ethyl-N,N-diethylisonipecotamide Hydriodide.—Reduction of 20.5 g. (0.06 mole) of 4-diethylcarbamyl-1-ethylpyridinium iodide in methanol with platinum oxide catalyst and hydrogen at room temperature and 50 p.s.i. gave 18.5 g. (91%) of solid which was recrystallized three times from a mixture of methanol and ether to give 15.0 g. of product, m.p. 124–126°.

1-(3-Indolylmethyl)-nipecotic and isonipecotic acids were prepared from nipecotic and isonipecotic acids by the general method already described in yields of 90–95%. The compound obtained from nipecotic acid, indole and formaldehyde had m.p. 165–166° dec.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: N, 10.8. Found: N, 10.6.

The product obtained from isonipecotic acid, 1-(3-indolylmethyl)-isonipecotic acid, melted at 228° dec.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: N, 10.8. Found: N, 10.8.

Attempts to use the hydrochlorides of nipecotic and isonipecotic acids in the Mannich reaction were unsuccessful, apparently because of the instability of indole at the *p*H of the reaction mixture.

2-Ethoxycarbonyl-1-(3-indolylmethyl)-piperidine Hydrochloride was prepared from ethyl pipecolate hydrochloride by the general method in almost quantitative yield; m.p. 150–151°.

Anal. Calcd. for $C_{17}H_{22}N_2O_2\cdot HCl$: N, 8.7. Found: N, 8.4.

1-(3-Indolylmethyl)-3-methoxycarbonylpiperidine Hydrochloride.[10]—This methyl ester was obtained in 73% yield (recrystallized), m.p. 169–170°.

Anal. Calcd. for $C_{16}H_{20}N_2O_2\cdot HCl$: N, 9.1; Cl, 11.5. Found: N, 9.1; Cl, 11.7.

1-(3-Indolylmethyl)-4-methoxycarbonylpiperidine Hydrochloride.—The reaction of indole, formaldehyde and methyl isonipecotate hydrochloride yielded this compound, m.p. 188.5–189°.

Anal. Calcd. for $C_{16}H_{20}N_2O_2\cdot HCl$: N, 9.1; Cl, 11.5. Found: N, 9.0; Cl, 11.4.

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(9) Literature value 122–125° (3 mm.); E. Gryszkiewicz-Trochimowski, *Roczniki Chem.*, **11**, 193 (1931); *C. A.*, **26**, 144 (1932).

(10) The corresponding ethyl ester was reported by F. C. Wheeler, G. L. Jenkins and G. E. Cwalina, *J. Am. Pharm. Assoc., Sci. Ed.*, **40**, 589 (1951).