spectrophotometer on 70% ethyl alcohol solutions of the dried material.

Figure 2A shows the distribution pattern obtained in the *n*-BuOH (4), 20% HOAc (5) system on a 138-mg. sample from the central section of the subtilin A peak of a silica gel partition chromatogram corresponding to that of Fig. 1. The sample was loaded in two tubes. Figure 2B shows an analytical redistribution from a single tube of a 50-mg. sample of subtilin A in the system isobutyl alcohol (2), 20% HOAc (3). The sample had been chromatographed as above and distributed for 130 transfers in system 2 and for 200 transfers in system 3 where a skewed distribution pattern was obtained at a higher concentration.

Theoretical curves for both single and multiple tube loadings were constructed from a table of the cumulative binomial.[15]

Optical Rotation.—Optical rotation was determined with sodium light in 1% aqueous HOAc at 25° in Rudolph polarimeter with photoelectric field matcher. The newly grown preparation no. 2 showed $[\alpha]^{25}D$ −35.2° (*c* 0.186). For a cut from the center of the subtilin B peak from a chromatogram like that of Fig. 1 $[\alpha]^{25}D$ −44.3° (*c* 0.0524). Chromatographed subtilin A had $[\alpha]^{25}D$ −34.4° (*c* 0.228).

Stability Tests.—Subtilin A isolated by partition chromatography from preparation no. 2 was exposed for 3 days at 400 μg./ml. to the solvents and conditions of light and temperature listed in Table II. After exposure the samples were evaporated to dryness under oil-pump vacuum and assayed for antibiotic activity.

Antibiotic Activity Measurement.—Antibiotic activity of subtilin fractions was measured by cylinder-plate assay with *Arthrobacter citreus*, ATCC 11,624, a bacterium used for some time in this Laboratory for assay purposes. Cells from Nutrient Agar (Difco) slants incubated 20 to 24 hours at 27° were suspended in 0.8% NaCl to an optical density of 0.4 at 650 mμ in 18-mm. test-tubes in a Coleman model 11 spectrophotometer. Assay plates (9-cm. diameter), prepared fresh for each assay, contained two 10-ml. layers of Nutrient Agar (1.5 and 1% agar, respectively, in lower and upper layers) with 3% NaCl added. The upper layer was inoculated immediately before dispensing, 1 ml. to 50 ml., with the 0.8% NaCl suspension of the test organism.

Subtilin was tested in aqueous solution in 8-mm. diameter stainless-steel cylinders. Assays were incubated 16 to 20 hours at 35°. For the most part the assays followed established procedures which have been discussed adequately in the literature.[16] A helpful variation was use of only 1% agar in the upper layer of plate medium, permitting slight sinking and improved sealing of cylinders. Assay sensitivity was increased by retarding growth of the test organism with inclusion of 3% NaCl in the medium and with incubation at higher than optimum temperature. Caution is required in the use of stainless-steel cylinders. We observed considerable destruction of subtilin activity in blackened or in very slightly corroded cylinders. Cylinders discolored by sulfuric acid–dichromate cleaning solution, even after subsequent repeated and prolonged washings, caused reductions in activity as great as 50% when used in assays. Contact with such cylinders for 24 hours preceding assay destroyed almost all the activity in weak aqueous solutions of subtilin. Excessive replication was necessary in assays until this factor was discovered.

Infrared Spectra.—The infrared spectrum of 0.98 mg. of chromatographed subtilin A in a 12.5-mm. (247 mg.) KBr pellet was scanned in a Beckman IR-3 instrument with rock salt optics. Strong bands were found at 3.05, 6.01 and 6.57 μ; medium at 7.21, 7.48, 7.78 and 8.13 μ; weak at 9.55 and 13.40 μ.

Acknowledgment.—We are indebted to Glen Bailey and Edith Gong for many ultraviolet spectra and the infrared spectrum, and to L. E. Sacks for paper electrophoresis.

(15) Harvard University Staff of the Computation Laboratory, "Tables of the Cumulative Binomial Probability Distribution," Harvard University Press, Cambridge, Mass., 1955.

(16) J. J. Gavin, *Appl. Microbiol.*, **5**, 25 (1957).

ALBANY, CALIF.

[CONTRIBUTION FROM THE MEDICINAL CHEMICAL RESEARCH DEPARTMENT OF THE SCHERING CORPORATION]

Parasympathetic Blocking Agents. III. N-Alkylpiperidinecarboxylic Esters[1]

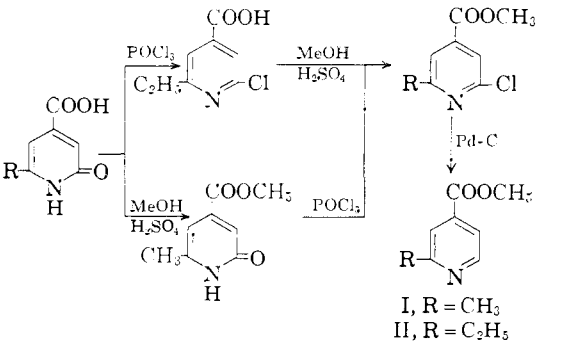
BY NATHAN SPERBER, MARGARET SHERLOCK, DOMENICK PAPA AND DOROTHY KENDER

RECEIVED JULY 28, 1958

A number of pyridinecarboxylic esters have been prepared and quaternized with alkyl *p*-toluenesulfonates and alkyl halides. The hydrogenation of the crude quaternary salts with platinum oxide or Raney nickel yielded N-alkylpiperidinecarboxylates, intermediates in the synthesis of compounds of potential pharmacological interest.

As part of a program on the synthesis of parasympathetic blocking agents related to N-methyl-4-benzhydrylidenepiperidine,[1a] a number of ring substituted N-alkylpiperidinecarboxylates were required for the synthesis of the intermediate N - alkyl - α,α - diphenylpiperidinemethanols. Although the lower N-alkylpiperidine esters have been described previously, the ring substituted and higher N-alkylpiperidine esters have not been reported.

In general, the requisite pyridine ester (Table I) were prepared according to known procedures with slight modifications. The preparation of methyl 2-methylisonicotinate (I) and methyl-2-ethylisonicotinate (II) is illustrated by a series of reactions similar to those employed by Tracy and Elderfield,[2] for the preparation of 2-ethylisonicotinic acid. In a similar manner ethyl 6-isobutylnicotinate and ethyl 2-chloro-6-isopropylnicotinate were



prepared from the corresponding 3-carboxy-6-isobutylpyridone-2[3] and 3-carboxy-6-isopropylpyridone-2, respectively. The requisite pyridones

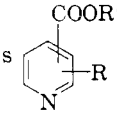
(1) (a) Part I, N. Sperber, F. J. Villani, M. Sherlock and D. Papa, THIS JOURNAL, **73**, 5010 (1951); (b) Part II, S. Coan and D. Papa, *J. Org. Chem.*, **20**, 774 (1955).

(2) A. H. Tracy and R. C. Elderfield, *ibid.*, **6**, 70 (1941).

(3) R. P. Mariella, THIS JOURNAL, **69**, 2670 (1947).

TABLE I

SUBSTITUTED PYRIDINE ESTERS

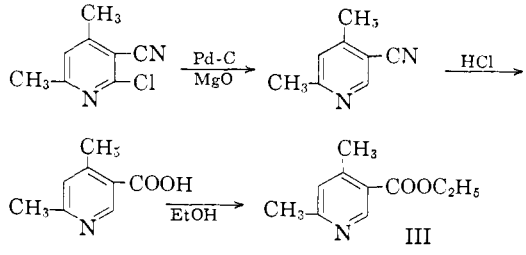


R	R'	B.p. °C.	B.p. Mm.	$n^{t}D$	t, °C.	Yield,[a] %	Formula	Nitrogen, % Calcd.	Found
2-CH_3	4-$COOCH_3$	109–112	15.0	1.5060	25	74[b]	$C_8H_9NO_2$	9.27	9.23
2-CH_3	4-$COOC_2H_5$	120–122[c]	14.0	1.4938	30	67	$C_9H_{11}NO_2$	8.48	8.13
3-CH_3	4-$COOC_2H_5$	98–100	6.0	1.5010	25	84	$C_9H_{11}NO_2$	8.48	8.67
2-C_2H_5-6-Cl	4-$COOCH_3$	104–105	2.5	1.5198	25	75	$C_9H_{10}NO_2Cl$	7.02	7.47
2-C_2H_5	4-$COOCH_3$	107–108	9.0	1.5030	27	69[d]	$C_9H_{11}NO_2$	8.48	8.52
2,6-$(CH_3)_2$	4-$COOC_2H_5$	115–118	11.0	M.p. 38–39°		82	$C_{10}H_{13}NO_2$	7.82	7.98
H	4-$(CH_2)_2COOEt$	118–125	4.0	1.4936	25	64	$C_{10}H_{13}NO_2$	7.82	7.74
2-CH_3	3-$COOC_2H_5$	115–117[e]	15.0	1.5008	25	73			
6-CH_3	3-$COOC_2H_5$	102–104[f]	5.0	1.4980	32	78			
2,6-$(CH_3)_2$	3-$COOC_2H_5$	111–120[g]	7.0	1.5009	28	91[h]			
4,6-$(CH_3)_2$	3-$COOC_2H_5$	111–113	5.0	1.5058	24	57[i]	$C_{10}H_{13}NO_2$	7.82	7.98
2,4-$(CH_3)_2$	3-$COOC_2H_5$	110–114[j]	6.0	1.4960	24	6.5	$C_{10}H_{13}NO_2$	7.82	7.74
2,6-$(C_2H_5)_2$-4-Cl	3-$COOC_2H_5$	109–112	2.0	1.4980	27	75[k]	$C_{12}H_{16}NO_2Cl$	5.80	5.71
2,6-$(C_2H_5)_2$	3-$COOC_2H_5$	121–124	7.0	1.4948	27	75[l]	$C_{12}H_{17}NO_2$	6.76	6.62
2,6-$(CH_3)_2$-4-OC_2H_5	3-$COOC_2H_5$	122–127	1.0	1.4942	30	89[m]	$C_{12}H_{17}NO_3$	6.28	6.15
6-$CH(CH_3)_2$-2-Cl	3-$COOC_2H_5$	109–114	1.0	1.5102	29	24[m]	$C_{11}H_{14}NO_2Cl$	6.15	5.72
6-$CH_2CH(CH_3)_2$-2-Cl	3-$COOC_2H_5$	120–126	0.5	1.5107	27	45[n]	$C_{12}H_{16}NO_2Cl$	5.79	5.72
6-$CH_2CH(CH_3)_2$	3-$COOC_2H_5$	103–105	2.0	1.4882	24	79[o]	$C_{12}H_{17}NO_2$	6.76	6.41
2,4,6-$(CH_3)_3$	3-$COOC_2H_5$	121–123[p]	7.0	1.4930	27	40[q]	$C_{11}H_{15}NO_2$	7.25	7.39
6-CH_3	3-CH_2COOEt	101–107	4.0	1.4969	26	45[r]	$C_{10}H_{13}NO_2$	7.82	7.42

[a] Unless otherwise noted the yields refer to esterification of the corresponding acid. [b] From the catalytic dehalogenation of methyl 2-chloro-6-methylisonicotinate. [c] O. Efimovsky and P. Rumpf, *Bull. soc. chim. France*, 648 (1954), report a b.p. of 139–143° (17.0 mm.). [d] From the catalytic dehalogenation of methyl 2-chloro-6-ethylisonicotinate. [e] A. Dornow and H. Bormann, *Ber.*, **82**, 216 (1949), report a b.p. of 105° (12.0 mm.). [f] Reference 21 reports a b.p. of 130° (15 mm.). [g] P. Rabe, *Ber.*, **45**, 2163 (1912), reports a b.p. of 129–130° (18 mm.). [h] From the catalytic dehalogenation of ethyl 2,6-dimethyl-4-chloronicotinate; after this work was completed K. Tsuda, N. Ikekawa, A. Iino, M. Furukawa and T. Hattori, *Pharm. Bull. (Japan)*, **1**, 126 (1953); *C. A.*, **49**, 3190*b* (1955), reported the same dehalogenation. [i] Over-all yield from 4,6-dimethylnicotinonitrile. [j] Ref. 16 reports a b.p. of 246–247°. [k] From the cyclization of ethyl 3-amino-2-pentenoate. [l] From the catalytic dehalogenation of ethyl 2,6-diethyl-4-chloronicotinate. [m] See Experimental section. [n] From 3-carboxy-6-isobutylpyridone-2. [o] From the catalytic dehalogenation of ethyl 2-chloro-6-isobutylnicotinate. [p] Reference 17 reports a b.p. of 255–256°. [q] From the hydrolysis of 3,5-dicarbethoxycollidine according to ref. 17. [r] From the crude 6-methyl-3-pyridylthioacetmorpholide; see Experimental section.

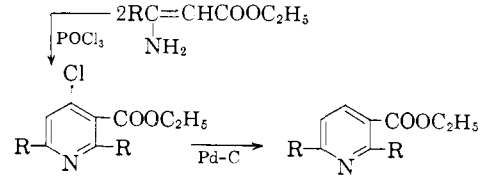
were prepared by procedures described in the literature.

Catalytic dehalogenation of 4,6-dimethyl-2-chloronicotinonitrile[4] with palladium-on-carbon and magnesium oxide yielded 4,6-dimethylnicotinonitrile which upon hydrolysis to the acid followed by esterification gave the desired ester, ethyl 4,6-dimethylnicotinate (III).



III

Ethyl 2,6-dimethyl (IV) and 2,6-diethylnicotinates (V) were prepared by the cyclization of ethyl β-aminocrotonate and ethyl 3-amino-2-pentenoate, respectively, with phosphorus oxychloride to the ethyl 2,6-dialkyl-4-chloronicotinates according to the procedure described by Bachman and Barker[5] followed by catalytic dehalogenation with palladium-on-carbon catalyst.



IV, R = CH_3
V, R = C_2H_5

The hydrogenation of N-methylpyridiniumcarboxylic ester chlorides[6] and iodides[7,8] with platinum oxide and with Raney nickel[9] catalysts to the corresponding N-methylpiperidinecarboxylic esters has been reported. Although the reduction of the lower N-alkylpyridinium halide esters yielded the desired N-alkylpiperidine esters in good yields, we have found that the use of branched alkyl halides in the quaternization step followed by catalytic reduction gave anomalous results. When methyl isonicotinate was heated with an excess of isopropyl iodide and the resulting crude quaternary salt reduced in ethanol with platinum oxide catalyst, poor yields of impure esters were obtained.

(4) R. P. Mariella and J. L. Leech, THIS JOURNAL, **71**, 331 (1949).

(5) G. B. Bachman and R. S. Barker, *J. Org. Chem.*, **14**, 97 (1949).

(6) N. Sugimoto and H. Kugita, *J. Pharm. Soc. Japan*, **73**, 66 (1953); *C. A.*, **47**, 10532 (1953).

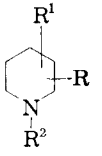
(7) J. V. Supniewski and M. Serafinówna, *ibid.*, **33**, 730 (1939).

(8) J. Schmutz, F. Kungle and R. Hirt, *Helv. Chim. Acta*, **37**, 1762 (1954).

(9) C. A. Grob and E. Renk, *ibid.*, **37**, 1672 (1954).

TABLE II

SUBSTITUTED PIPERIDINE ESTERS



R	R_1	R_2	B.p. °C.	B.p. Mm.	n_D	t, °C.	Method	Alkylating agent[a]	Time, hr.	Temp.,[b] °C.	Yield,[c] %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
H	4-$COOC_2H_5$	CH_3	103–105[d]	18.0	1.4460	34	A	R_2PTS	1.5	95	84			
H	4-$COOCH_3$	CH_3	82–86[e]	10.0	1.4539	24	A	$(R_2)_2SO_4$	1.0[f]		92[g]			
								R_2PTS	1.0[f]		82			
H	4-$COOC_2H_5$	C_2H_5	120–124	20.0	1.4515	24	A	R_2PTS	5	95	86	$C_{10}H_{19}NO_2$	7.56	7.12
								R_2I	8[f]		98			
H	4-$COOCH_3$	C_2H_5	103–106	18.0	1.4510	24	A	R_2I	1.5[f]		30	$C_9H_{17}NO_2$	8.18	8.16
								R_2PTS	1.5[h]		83[g]			
H	4-$COOCH_3$	n-C_3H_7	118–125	21.0	1.4496	31	A	R_2PTS	3	95	90	$C_{10}H_{19}NO_2$	7.56	7.66
H	4-$COOC_2H_5$	n-C_3H_7	123–127	16.0	1.4498	25	A	R_2PTS	2.5	95	83	$C_{11}H_{21}NO_2$	7.03	6.52
H	4-$COOCH_3$	$CH(CH_3)_2$	127–130	30.0	1.4550	26	A	R_2PTS	3	95	76	$C_{10}H_{19}NO_2$	7.56	7.70
H	4-$COOCH_3$	n-C_4H_9	128–135	24.0	1.4513	28	A	R_2PTS	3.5	95	81	$C_{11}H_{21}NO_2$	7.03	6.74
H	4-$COOCH_3$	$(CH_2)_2OH$	124–126	3.0	1.4696	32	A	R_2Br	2	85	67	$C_{10}H_{19}NO_3$	6.96	6.89
H	4-$COOC_2H_5$	$(CH_2)_2N(CH_3)_2$	98–100	1.0	1.4648	25	B	R_2Cl	16[f]		32	$C_{11}H_{22}N_2O_2$	13.07	13.20
H	4-$COOCH_3$	$CH_2C_6H_5$	190–192	21.0	1.5177	24	A	R_2Cl	2	95	28	$C_{14}H_{19}NO_2$	6.01	6.39
H	4-$COOCH_3$	CH_2-m-$CH_3C_6H_4$	141–142	2.0	1.5172	25	A	R_2Br	6[f]		94	$C_{15}H_{21}NO_2$	5.66	5.64
							B		2[f]		28			
H	4-$CH_2COOC_2H_5$	CH_3	106–108	11.0	1.4509	24	A	R_2PTS	1	95	86	$C_{10}H_{19}NO_2$	7.56	7.64
H	4-$(CH_2)_2COOC_2H_5$	CH_3	101–105	4.0	1.4508	26	A	R_2PTS	1	95	85	$C_{11}H_{21}NO_2$	7.03	7.29
2-CH_3	4-$COOCH_3$	CH_3	93–95	7.5	1.4522	29	A	R_2PTS	1	95	87	$C_9H_{17}NO_2$	8.18	8.19
2-CH_3	4-$COOC_2H_5$	C_2H_5	91–93	3.5	1.4532	25	A	R_2PTS	4	130–140	54	$C_{11}H_{21}NO_2$	7.03	7.18
3-CH_3	4-$COOC_2H_5$	CH_3	89–94	6.0	1.4492	26	A	R_2PTS	1	95	84	$C_{10}H_{19}NO_2$	7.56	7.59
3-CH_3	4-$COOC_2H_5$	C_2H_5	82–84	2.0	1.5085	28	A	R_2PTS	3	150	75	$C_{11}H_{21}NO_2$	7.03	6.93
2,6-$(CH_3)_2$	4-$COOC_2H_5$	CH_3	98–100	4.0	1.4551	25	A	R_2PTS	4	95	88	$C_{11}H_{21}NO_2$	7.03	7.07
2,6-$(CH_3)_2$	4-$COOC_2H_5$	C_2H_5	130–134	16.0	1.4601	30	A	R_2PTS	1	160	82	$C_{12}H_{23}NO_2$	6.57	6.16
H	3-$COOC_2H_5$	CH_3	94–96[d]	12.0	1.4460	30	A	R_2PTS	0.5	95	96			
H	3-$COOCH_3$	CH_3	83–84[i]	12.0	1.4520	25	B[j]				85			
H	3-$COOC_2H_5$	C_2H_5	109–112[k]	15.0	1.4510	25	A	R_2PTS	1.5	95	87	$C_{10}H_{19}NO_2$	7.56	7.80
							B	R_2I	10.0[f]		81			
H	3-$COOC_2H_5$	n-C_3H_7	118–121	15.0	1.4480	29	B	R_2Br	16[f]		88	$C_{11}H_{21}NO_2$	7.03	6.48
H	3-$COOC_2H_5$	$CH(CH_3)_2$	111–113	9.0	1.4519	25	B	R_2I	22[f]		89	$C_{11}H_{21}NO_2$	7.03	6.99
H	3-$COOC_2H_5$	$CH_2CH{=}CH_2$	103–105	4.5	1.4621	25	B	R_2Br	18[f]		74	$C_{11}H_{19}NO_2$	7.10	7.44
6-CH_3	3-$COOC_2H_5$	CH_3	94–96	9.0	1.4506	26	A	R_2PTS	0.5	95	87	$C_{10}H_{19}NO_2$	7.56	7.50
6-CH_3	3-$COOC_2H_5$	C_2H_5	93–95	5.0	1.4512	26	A	R_2PTS	6	95	85	$C_{11}H_{21}NO_2$	7.03	7.28
2-CH_3	3-$COOC_2H_5$	C_2H_5	121–122	15.0	1.4565	26	A	R_2PTS	18	95	70	$C_{11}H_{21}NO_2$	7.03	6.91
							B	R_2I	16[f]		83			
6-$CH_2CH(CH_3)_2$	3-$COOC_2H_5$	CH_3	129–133	7.0	1.4500	33	A	R_2PTS	3	95	79	$C_{13}H_{25}NO_2$	6.16	6.55
2,6-$(CH_3)_2$	3-$COOC_2H_5$	CH_3	100–102	7.0	1.4510	27	A	R_2PTS	6	95	94	$C_{11}H_{21}NO_2$	7.03	7.11

TABLE II (*Continued*)

R	R_1	R_2	B.p., °C.	Mm.	$n^{25}D$	t, °C.	Method	Alkylating[a] agent	Time, hr.	Temp.,[a] °C.	Yield[c] %	Formula	Nitrogen, % Calcd.	Found
2,6-$(CH_3)_2$	3-$COOC_2H_5$	C_2H_5	104–110	7.0	1.4590	20	A	R_2PTS	2	180–190	72	$C_{12}H_{23}NO_2$	6.57	7.01
2,6-$(CH_3)_2$-4-OC_2H_5	3-$COOC_2H_5$	CH_3	97–103	1.0	1.4522	28	A	R_2PTS	1	95	75	$C_{13}H_{25}NO_3$	5.76	5.71
2,4-$(CH_3)_2$	3-$COOC_2H_5$	CH_3	91–95	4.0	1.4531	26	A	R_2PTS	0.5	95	88	$C_{11}H_{21}NO_2$	7.03	7.14
4,6-$(CH_3)_2$	3-$COOC_2H_5$	CH_3	95–102	8.0	1.4470	25	A	R_2PTS	0.5	95	88	$C_{11}H_{21}NO_2$	7.03	7.17
2,6-$(C_2H_5)_2$	3-$COOC_2H_5$	CH_3	108–111	3.0	1.4472	26	A	R_2PTS	0.5	160–180	90	$C_{13}H_{25}NO_2$	6.16	6.32
2,4,6-$(CH_3)_3$	3-$COOC_2H_5$	CH_3	99–105	5.0	1.4573	25	A	R_2PTS	2	95	76	$C_{12}H_{23}NO_2$	6.57	6.80
6-CH_3	3-$CH_2COOC_2H_5$	CH_3	103–107	3.0	1.4535	21	A	R_2PTS	1	95	87	$C_{11}H_{21}NO_2$	7.03	7.05
H	2-$COOC_2H_5$	CH_3	114–115[d]	36.0	1.4471	28	A	R_2PTS	3[f]		67			
H	2-$COCH_3$	CH_3	90–95[i]	16.0	1.4500	22	A	R_2PTS	0.5		57			
							B[j]				83			
H	2-$COOC_2H_5$	C_2H_5	110–113	20.0	1.4512	21	A	R_2PTS	24	95	79	$C_{10}H_{19}NO_2$	7.56	7.68
							B	R_2I	12[f]		89			
H	2-CH_2COOCH_3	CH_3	119–121[l]	29.0	1.4590	26	A	R_2PTS	4	95	45			
H	2-$CH_2COOC_2H_5$	CH_3	136–138	35.0	1.4557	26	A	R_2PTS	2	95	72	$C_{10}H_{19}NO_2$	7.56	8.00
H	2-$(CH_2)_2COOCH_3$	CH_3	83–87	2.0	1.4598	24	A	R_2PTS	0.5	95	81	$C_{10}H_{19}NO_2$	7.56	7.44
H	2-$(CH_2)_2COOC_2H_5$	C_2H_5	108–110	3.0	1.4578	30	A	R_2PTS	2	160	78	$C_{12}H_{23}NO_2$	6.57	6.63

[a] PTS = *p*-Toluenesulfonate. [b] Unless otherwise noted the quaternizations were effected without solvents. [c] In method A yields are based on the pyridine esters and unless otherwise noted reductions were carried out with platinum oxide catalyst. [d] Ref. 12. [e] Ref. 9. [f] Refluxing benzene. [g] Raney nickel catalyst. [h] Refluxing xylene. [i] K. Hess and F. Leibbrandt, *Ber.*, **51**, 806 (1918). [j] Catalytic N-methylation; see ref. 13. [k] This compound has been reported by H. Adkins, L. F. Kuick, M. Farlow and B. Wojcik, THIS JOURNAL, **56**, 2425 (1934), by the Raney nickel reduction of ethyl nicotinate in ethanol in a 20% yield. [l] C. Tilford and M. G. Van Campen, Jr., *ibid.*, **76**, 2431 (1954), described the hydrobromide of this compound from the catalytic reduction of methyl-N-methylpyridinium-2-acetate bromide.

The reaction of the latter with phenylmagnesium bromide yielded N-methyl-α,α-diphenyl-4-piperidinemethanol as the only identifiable product. A similar experience was encountered when isobutyl bromide was used as the quaternizing agent. The reaction of phenylmagnesium bromide with the presumed N-isobutylisonipecotic ester afforded N-methyl-α, α-diphenyl-4-piperidinemethanol which upon dehydration yielded N-methyl-4-benzhydrylidenepiperidine.[1a] In contrast to the results obtained with branched alkyl halides, it is interesting to note that quaternization of methyl isonicotinate with isopropyl *p*-toluenesulfonate followed by catalytic reduction of the crude quaternary salt gave the desired methyl N-isopropylisonipecotate in good yield (Table II).

Since N-methyl-2,6-diphenacylpyridinium *p*-toluenesulfonate on hydrogenation with platinum oxide has been reported to give the corresponding piperidine,[10] we have chosen this procedure, method A, for the preparation of most of the N-alkylpiperidinecarboxylic esters (Table II).[11] Quaternization of the pyridinecarboxylic ester with

X = halogen, *p*-toluenesulfonate;
R = alkyl, aralkyl;
R' = alkyl

an alkyl *p*-toluenesulfonate gave good yields of the crude quaternary salts. In most cases steam bath temperatures were sufficient to effect quaternization although the more hindered esters required temperatures up to 180°. The crude N-alkylpyridiniumcarboxylic ester *p*-toluenesulfonates VI were hydrogenated with platinum oxide or Raney nickel to give good yields of the reduced esters VIII. As an alternate procedure, for the preparation of VIII (method B), the appropriate piperidinecarboxylic ester VII[12] was alkylated with an alkyl halide and sodium carbonate or catalytically N-methylated with formaldehyde and palladium catalyst according to the procedure described by Albertson.[13]

Experimental

All melting points are corrected. All boiling points are uncorrected.

(10) G. Scheuing and L. Winterhalder, *Ann.*, **473**, 126 (1929).

(11) After this work had been completed R. Lukeš, J. Kloubek, K. Bláha and J. Kovář, *Chem. Listy*, **50**, 1466 (1956); *C. A.*, **51**, 2775[b] (1957), reported the preparation of ethyl N-methylpipecolate by hydrogenation of the ethyl N-methyl-2-carbethoxypyridinium *p*-toluenesulfonate with platinum oxide.

(12) R. F. Feldkamp, J. A. Faust and A. J. Cushman, THIS JOURNAL, **74**, 3831 (1952).

(13) N. F. Albertson, *ibid.*, **72**, 2594 (1950).

Pyridine Acids.—2-Methyl-, 3-methyl-, 2,6-dimethylisonicotinic and 6-methyl- and 2-methylnicotinic acids were obtained from the Reilly Tar and Chemical Co. β-4-Pyridylpropionic acid[14] and β-2-pyridylpropionic acid were prepared by the oxidation of the appropriate β-pyridinepropanol.[15]

Pyridine Esters (Table I).—Ethyl 2,4-dimethylnicotinate[16] and ethyl 2,4,6-trimethylnicotinate[17] were prepared according to known procedures. Ethyl 4-pyridylacetate,[18] methyl and ethyl 2-pyridylacetate were prepared as described in reference[19] or by the procedure of Weiss and Hauser.[20]

Ethyl 6-Methylnicotinate.[21]—The esterification of 6-methylnicotinic acid illustrates the general method of preparation. A solution of 30 g. of 6-methylnicotinic acid, 68 ml. of absolute ethanol and 47 ml. of concentrated sulfuric acid was refluxed on a steam-bath for 4 hours. The solution was poured on ice and made basic with potassium carbonate, the oil extracted with ether, the ether extracts dried over sodium sulfate, concentrated, and the residue fractionated *in vacuo*.

Methyl 2-Methylisonicotinate (I, **R** = CH_3).—To a solution of 25 g. of 6-methyl-4-carbomethoxy-2-pyridone[22] in 80 ml. of phosphorus oxychloride, there was added, in portions, 60 g. of phosphorus pentachloride. The reaction mixture was refluxed and stirred for 2 hours, the excess phosphorus oxychloride removed *in vacuo* and the residual oil decomposed with ice and water; yield 21 g., m.p. 57–60°. Recrystallization from methanol–water gave 15.5 g. of white needles, m.p. 61–63°. (Hydrolysis of the ester with alcoholic potassium hydroxide yielded the known acid, 2-chloro-6-methylisonicotinic acid, m.p. 214–216° (lit.[22] m.p. 214°).) A solution of 14 g. of crude methyl 2-chloro-6-methylisonicotinate, 115 ml. of absolute ethanol and 2 ml. of concentrated hydrochloric acid was dehalogenated with 5 g. of 5% palladium-on-charcoal and hydrogen at 4 atm. The catalyst was filtered, the filtrate concentrated, the residue dissolved in 150 ml. of water and made basic with solid sodium bicarbonate. The oily layer was extracted with ether, the ether dried over sodium sulfate, concentrated, and the residue fractionated *in vacuo*.

Ethyl 2-Chloro-6-isopropylnicotinate.—3-Cyano-6-isopropyl-pyridone-2[23] was prepared from the condensation of sodium hydroxy-methylene methyl isopropyl ketone and cyanoacetamide according to the procedure described for the corresponding isobutyl compound[3]; yield 84%, m.p. 207–208° after two recrystallizations from ethanol.

Anal. Calcd. for $C_9H_{10}N_2O$: N, 17.27; Found: N, 17.00.

A mixture of 63.5 g. of 3-cyano-6-isopropylpyridone-2 and 125 g. of phosphorus pentachloride was stirred and refluxed for 90 minutes at 120°. The excess phosphorus oxychloride was removed *in vacuo* the residue poured on ice, made alkaline with 50% sodium hydroxide solution and extracted with ether. The ether extracts were dried over sodium sulfate, concentrated and fractionated; yield 48 g., b.p. 105–115° (1 mm.). A solution of 20 g. of crude 6-isopropyl-2-chloronicotinonitrile and 125 ml. of 75% sulfuric acid was refluxed for 6 hours, poured on ice, neutralized with solid calcium hydroxide and filtered. The filtered solids were boiled twice with water, the combined filtrates concentrated to dryness *in vacuo* to a brown residue. The crude 6-isopropyl-2-chloronicotinic acid was esterified with 115 ml. of absolute ethanol and 60 ml. of concentrated sulfuric acid for 10 hours on the steam-bath and processed in the usual manner.

Ethyl 6-Isobutylnicotinate.—To a stirred mixture of 19.5 g. of 3-carboxy-6-isobutylpyridone-2[3] and 32 ml. of phosphorus oxychloride, there was added, in portions, 60 g. of phosphorus pentachloride. The reaction mixture was stirred and heated for 45 minutes at 110°, the excess phosphorus oxychloride removed *in vacuo* and the residual oil poured onto ice. The mixture was extracted with ether, the ether extracts concentrated and the residue heated and stirred on a steam-bath for 3 hours with 5% sodium hydroxide solution to hydrolyze any remaining acid chloride. The solution was cooled, acidified with concentrated hydrochloric acid and the brown oil extracted with benzene. The benzene extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude, viscous brown oil was esterified with 68 ml. of absolute ethanol and 47 ml. of concentrated sulfuric acid yielding ethyl 2-chloro-6-isobutylnicotinate.

A mixture of 18.5 g. of ethyl 2-chloro-6-isobutylnicotinate, 150 ml. of absolute ethanol, 5 ml. of concentrated hydrochloric acid and 4 g. of 5% palladium-on-carbon catalyst was dehalogenated according to the procedure described previously.

Ethyl 4,6-Dimethylnicotinate (III).—A mixture of 25 g. of 4,6-dimethyl-2-chloronicotinonitrile,[4] 150 ml. of absolute ethanol, 100 ml. of water, 25 g. of magnesium oxide[24] and 6 g. of 5% palladium-on-carbon was hydrogenated at 4 atm. The catalyst was filtered, the filtrate concentrated *in vacuo*, the residue treated with 60 ml. of water, extracted with ether, the ether extracts dried over sodium sulfate, and concentrated; yield 16 g. of a colorless solid, m.p. 53–55°. Recrystallization from petroleum ether raised the melting point to 58–59°, but on repeated analyses the 4,6-dimethylnicotinonitrile gave consistently low nitrogen values. The compound was used without further purification.

A solution of 10 g. of crude 4,6-dimethylnicotinonitrile was hydrolyzed to the corresponding acid with 100 ml. of 75% sulfuric acid for 7 hours. Isolation of the crude acid followed by esterification was carried out according to the procedure previously described for the preparation of ethyl 2-chloro-6-isopropylnicotinate.

Ethyl 2,6-Diethyl-4-chloronicotinate, (V) (R = C_2H_5).—Ethyl 2,6-diethyl-4-chloronicotinate was prepared by the cyclization of ethyl 3-amino-2-pentenoate[25] with phosphorus oxychloride according to the procedure described for the preparation of ethyl 2,6-dimethyl-4-chloronicotinate.[5] Catalytic dehalogenation of ethyl 2,6-diethyl-4-chloronicotinate yielded V.

Ethyl 2,6-Dimethyl-4-ethoxynicotinate.—To a solution of sodium ethoxide (from 5.1 g. of sodium) in 130 ml. of absolute ethanol there was added dropwise 43 g. of ethyl 2,6-dimethyl-4-chloronicotinate. The reaction mixture was stirred and refluxed for 6 hours, cooled and filtered. The filtrate was concentrated *in vacuo*, the residue treated with 200 ml. of water, extracted with ether and the ether extracts dried over sodium sulfate, concentrated and distilled; yield 40 g.

Ethyl 6-Methyl-3-pyridylacetate.[26]—A mixture of 99.3 g. of 3-acetyl-6-methylpyridine,[27] 110 g. of morpholine and 38.2 g. of sulfur was refluxed for 6 hours. The solution was cooled, poured into water, extracted with benzene, the benzene extracts treated with charcoal, filtered and concentrated to dryness. Upon the addition of petroleum ether, a yellow solid crystallized; yield 130 g., m.p. 78–85°. The crude 6-methyl-3-pyridylthioacetmorpholide, 620 ml. of 95% ethanol and 106 ml. of 60% sodium hydroxide solution was refluxed for 16 hours. The solution was concentrated *in vacuo*, the residual mixture acidified with 350 ml. of concentrated hydrochloric acid and the solution then concentrated *in vacuo* to dryness. The residue was boiled with 300 ml. of absolute ethanol, treated with charcoal, filtered and diluted with anhydrous ether, to yield a tacky semi-solid material. A small portion of the 6-methyl-3-pyridineacetic acid hydro-

(14) W. E. Doering and R. A. N. Weil, THIS JOURNAL, **69**, 2461 (1947).

(15) F. H. McMillan and J. A. King, *ibid.*, **73**, 3165 (1951).

(16) R. Michael, *Ber.*, **18**, 2020 (1885).

(17) R. Michael, *Ann.*, **225**, 121 (1884).

(18) R. Malan and P. M. Dean, THIS JOURNAL, **69**, 1797 (1947).

(19) C. S. Hamilton, Editor, *Org. Syntheses*, **29**, 44 (1949).

(20) M. J. Weiss and C. R. Hauser, THIS JOURNAL, **71**, 2023 (1949).

(21) R. Graf, *J. prakt. Chem.*, **133**, 19 (1932).

(22) J. C. Bardhan, *J. Chem. Soc.*, 2223 (1929).

(23) After this work had been completed, N. K. Kochetkov, *Doklady Akad. Nauk. S. S. S. R.*, **84**, 289 (1952); *C. A.*, **47**, 3309 (1953), described the preparation of this compound in a 77% yield by the condensation of 4-methyl-3-keto-valeraldehyde diethyl-acetal with cyanoacetamide and reported a melting point of 203–204°

(24) N. Whittaker, *J. Chem. Soc.*, 1565 (1951).

(25) V. Prelog and S. Szpilfogel, *Helv. Chim. Acta.*, **25**, 1306 (1942).

(26) Prepared essentially by the procedure described by E. Schwenk and D. Papa, *J. Org. Chem.*, **11**, 798 (1946), for the preparation of methyl 3-pyridylacetate.

(27) Prepared in a yield of 37% by the Claisen ester condensation of ethyl 6-methylnicotinate and ethyl acetate; b.p. 107–108° (11 mm.), $n^{22}D$ 1.5303. *Anal.* Calcd. for C_8H_9NO: N, 10.36. Found: N, 10.08. See C. D. Hurd and C. N. Webb, THIS JOURNAL, **49**, 546 (1927); F. M. Strong and S. M. McElvain, *ibid.*, **55**, 816 (1953).

chloride was crystallized several times from ethanol–ether, m.p. 170–172°.

Anal. Calcd. for $C_8H_{10}NO_2Cl$: N, 7.47. Found: N, 7.40.

The crude residue was dissolved in 150 ml. of absolute ethanol and treated with 120 g. of concentrated sulfuric acid. After refluxing for 12 hours, the ethanol was distilled off, the residue poured on ice, the solution saturated with potassium carbonate and extracted several times with ether. The ether extracts were dried over sodium sulfate, filtered, concentrated and the residue distilled.

N-Alkylpiperidine Esters. (Table II) Method A. Quaternization.—The quaternization of a pyridine ester with the appropriate alkyl *p*-toluenesulfonate[28] or alkyl halide was carried out under varying conditions of time and temperature as noted in Table II. The ester was heated with a slight excess of the alkylating agent with or without a solvent. In general the quaternary salts were low melting, hygroscopic solids or viscous oils which were not purified but dissolved directly in ethanol and reduced catalytically. When the quaternization was carried out in a solvent, the quaternary salt was either filtered or separated by decantation of the solvent. The following preparations illustrate the general procedures.

Methyl N-Methylisonicotinate Methyl Sulfate.—To a stirred, refluxing solution of 28 g. of methyl isonicotinate in 150 ml. of benzene, there was added dropwise 28 g. of dimethyl sulfate. After refluxing the mixture for 1 hour, 100 ml. of petroleum ether was added and an oil separated which solidified on cooling. The hygroscopic solid was filtered, dried under a rubber dam, m.p. 76–82°, yield 48.6 g. (91%), and was used directly without further purification.

Ethyl N-Ethyl-2,6-dimethylisonicotinate *p*-Toluenesulfonate.—A mixture of 74 g. of ethyl 2,6-dimethylisonicotinate and 90 g. of ethyl *p*-toluenesulfonate was heated in a metal-bath for 1 hour at 160°. The dark brown viscous oil was dissolved in ethanol and hydrogenated directly.

Reduction.—In general the reductions were carried out in a Parr hydrogenation bottle at 4 atm. using a platinum oxide catalyst. However, for large scale reductions it was found convenient to use high pressure equipment with Raney nickel catalyst.

Platinum Oxide: Ethyl N-Ethyl-2,6-dimethylisonipecotate.—The crude ethyl N-ethyl 2,6-dimethylisonicotinate *p*-toluenesulfonate described above was dissolved in 200 ml. of ethanol in a Parr shaker and 1 g. of platinum oxide added. The initial pressure of hydrogen was 60 p.s.i. and after 12 hours the theoretical amount of hydrogen had been absorbed. The catalyst was filtered, the filtrate concentrated *in vacuo*, the residue dissolved in 250 ml. of water, and treated with potassium carbonate until an oil had separated. The oil was extracted several times with ether, the ether extracts dried over sodium sulfate, concentrated and distilled *in vacuo;* yield 72 g.

Raney Nickel: Methyl N-Methylisonipecotate.—A mixture of 79 g. of crude methyl N-methylisonicotinate methyl sulfate, 800 ml. of ethanol and 20 g. of Raney nickel catalyst was charged into a 1700-ml. steel bomb. The bomb was shaken at 110 atm. of hydrogen at 50–60° for 2 hours when no further hydrogen was absorbed. The catalyst was filtered and the filtrate processed in the manner described in the preceding example; yield 43.3 g.

Method B. Ethyl N-Ethyl 2-methylnipecotate.—To a stirred mixture of 51.3 g. of ethyl 2-methylnipecotate,[13] 18 g. of anhydrous sodium carbonate and 300 ml. of anhydrous benzene there was added dropwise 51.5 g. of ethyl iodide. The reaction mixture was stirred and refluxed for 16 hours, decomposed with water, the benzene layer separated, concentrated and the residue distilled *in vacuo;* yield 49 g.

Attempts to Prepare Methyl N-Isoalkylisonipecotates. 1. From Isopropyl Iodide and Methyl Isonicotinate.—A solution of 70 g. of isopropyl iodide and 35 g. of methyl isonicotinate was heated for 2 hours on a steam-bath. The deep red solutions was diluted with 500 ml. of anhydrous ether, the ether layer decanted, the semi-solid residue dissolved in absolute ethanol and hydrogenated in the presence of platinum oxide. The reaction mixture was processed and the ester distilled; b.p. 101–115° (15 mm.), wt. 27.5 g., $n^{24}D$ 1.4498. An analytical sample was collected at 103° (15.0 mm.), $n^{24}D$ 1.4503.

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 63.03; H, 10.37; N, 8.22, 8.18.

To a Grignard solution prepared from 17 g. of magnesium and 110 g. of bromobenzene in 400 ml. of ether there was added 25 g. of the above ester. After refluxing for 10 hours, the reaction mixture was decomposed with dilute hydrochloric acid and the solid which separated was filtered and suspended in 200 ml. of water. The addition of dilute sodium hydroxide solution to the suspension caused a gummy material to separate which was extracted with benzene. The benzene was removed *in vacuo*, and the residual oil which solidified was crystallized from benzene–petroleum ether; yield 13.5 g. of a colorless solid, m.p. 126–129°. The latter was recrystallized from benzene–petroleum ether, m.p. 132–133°, and did not depress the melting point of an authentic sample of **N-methyl-α,α-diphenyl-4-piperidinemethanol**[1a] (m.p. 133–134°).

2. From Isobutyl Bromide and Methyl Isonicotinate.—A solution of 20 g. of methyl isonicotinate and 40 ml. of isobutyl bromide was refluxed for 20 hours. The semi-solid reaction mixture was triturated with benzene, dissolved in absolute ethanol and hydrogenated with platinum oxide. After removal of the catalyst and processing in the usual manner there was obtained 10 g. of an oil, b.p. 129–135° (18 mm.), $n^{31}D$ 1.4452.

Anal. Calcd. for $C_{11}H_{21}NO_2$: N, 7.03. Found: N, 6.87.

The above ester, 25 g., was treated with phenylmagnesium bromide in the same manner as described previously. After processing, a viscous oil was obtained which slowly crystallized. A small portion of the solid was recrystallized from benzene–petroleum ether, m.p. 131–133°, and did not depress the melting point of an authentic sample of **N-methyl-α,α-diphenyl-4-piperidinemethanol.**[1a] The crude carbinol was heated on a steam-bath for 8 hours in 300 ml. of 60% sulfuric acid. The solution was poured on ice, made basic with 50% sodium hydroxide solution and the oil extracted with ether. The ether extracts were dried over sodium sulfate, concentrated and the residue distilled; yield 13 g., b.p. 149–157° (0.5 mm.).

Anal. Calcd. for $C_{19}H_{21}N$: C, 86.67; H, 8.04. Found: C, 86.03; H, 8.05.

A portion of the free base was converted to the methiodide salt and melted at 256–258° after one recrystallization from methanol. A mixed melting point with an authentic sample of N,N-dimethyl-4-benzhydrylidenepiperidinium iodide,[29] m.p. 261–262° (from methanol) prepared from **N-methyl-4-benzhydrylidenepiperidine**[1a] gave no depression.

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(28) The alkyl *p*-toluenesulfonates were obtained from Distillation Products industries with the exception of isopropyl *p*-toluenesulfonate. This compound was prepared from isopropyl-alcohol and *p*-toluenesulfonyl chloride according to the procedure described by H. Gilman and N. J. Beaber, THIS JOURNAL, **47**, 518 (1925). Due to decomposition on attempted distillation, the isopropyl *p*-toluenesulfonate was used in the crude state for the quaternization step.

(29) *Anal.* Calcd. for $C_{19}H_{21}N.CH_3I$: C, 59.26; H, 5.96. Found: C, 59.40; H, 6.26.