340 mg (59%); mp 238–240°; $[\alpha]^{19}D$ +41.5° (c 1, DMF); lit.[4] (L isomer) mp 239–240°; $[\alpha]^{20}D$ −42° (c 1, DMF).

Procedure B.—Octapeptide·HBr, obtained in a run identical with the one described in procedure A, was dissolved in 60 ml of MeOH and treated with 100 mg of imidazole. The resulting soln was evapd to a solid residue which was dried over P_2O_5 under vacuum. The dry residue was dissolved in 2 ml of DMF and condensed with *p*-nitrophenyl *S*-benzyl-β-mercaptopropionate as described in procedure A: yield 485 mg (84%); mp 241–243°; $[\alpha]^{19}D$ +41.6° (c 1, DMF). *Anal.* ($C_{57}H_{79}N_{11}O_{12}S_2$) C, H, N.

Deamino-D-oxytocin.—The debenzylation of 200 mg of amide I was performed with Na in 400 ml of liq NH_3 freshly distd from Na.[5] The soln was concd, and the last 30 ml of liq NH_3 was lyophilized. The residual white powder was dissolved in 150 ml of 0.25% AcOH, the pH was adjusted to 6.8 with 1 *N* NH_4OH, and the resulting clear soln was titrated with 0.011 *M* $K_3Fe(CN)_6$ until a yellow color began to appear (27 ml). Then excess ferricyanide (8 ml) was added. After 30 min the soln gave a negative Ellman test, and it was passed through a column of AG3-X4 (Cl^-). The soln of the crude product thus obtained was divided into 2 equal portions, each of which was purified by a different method. One half of the soln was concd to 15 ml and subjected to countercurrent distribution in the solvent system *n*-BuOH–*n*-PrOH–0.5% AcOH contg 0.1% pyridine (6:1:8). After 200 transfers a main peak (K = 4.4) was obtained, as detd by measurement of the Folin–Lowry color values.[14] The contents of tubes 155–170 were combined, concd, and lyophilized to yield 25 mg of a white fluffy powder. A sample was hydrolyzed in 6 *N* HCl at 120° for 20 hr for amino acid analysis,[15] and the following molar ratios were found, with the value of Gly taken as 1.0: Gly, 1.0; Leu, 1.0; Pro, 1.0; Asp, 1.0; Glu, 1.1; Ile, 0.93; aIle, 0.07; Tyr, 1.0; Cys, 0.24; the mixed disulfide of cysteine and β-mercaptopropionic acid, 0.67; NH_3, 2.9.

The other half of the crude soln of deamino-D-oxytocin was concd to a low vol and purified by partition chromatography by the method of Yamashiro.[8] A Sephadex G-25 column (2.15 × 113 cm) was employed with the solvent system *n*-BuOH–C_6H_6–3.5% AcOH contg 1.5% pyridine (1:1:2). Elution with the upper phase was performed at a rate of 30 ml/hr. The Folin–Lowry color values showed a main peak with R_f 0.19. The correspg value for deamino-L-oxytocin is 0.19.[11] Fractions correspg to the main peak were combined, concd, and lyophilized: yield 37 mg of white fluffy powder; $[\alpha]^{20}D$ +104° (c 0.5, 1 *N* AcOH); lit.[4] (amorphous L isomer) $[\alpha]^{21}D$ −107° (c 0.5, 1 *N* AcOH). A sample of deamino-D-oxytocin was hydrolyzed in 6 *N* HCl at 120° for 20 hr for amino acid analysis. The following molar ratios were obtd, with the value of Gly taken as 1.0: Gly, 1.0; Leu, 1.0; Pro, 1.0; Asp, 1.0; Glu, 1.0; Ile, 1.0; aIle, 0.02; Tyr, 1.0; Cys, 0.34; the mixed disulfide of cysteine and β-mercaptopropionic acid, 0.62; NH_3, 2.9. *Anal.* ($C_{43}H_{65}N_{11}O_{12}S_2$) C, H, N.

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New Compounds

α-Bromo- and α-Chloropyridylalanines[1]

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Phenylalanine analogs have exhibited biological activity in certain mammalian phenylalanine, tryptophan, and tyrosine hydroxylase systems.[2–5] *p*-Chlorophenylalanine depletes brain serotonin in the rat[6] thus causing an abnormal psychic behavior of the animal.[7] The synthesis of the α-fluoro- and α-hydroxypyridylalanines has been described in an earlier study and certain of these compounds are toxic to the growth of various microorganisms.[8] In this report the synthesis of the bromo and chloro analogs is described.

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Experimental Section

A Thomas-Hoover capillary melting point apparatus was employed for all mp determinations, and the melting points reported are uncorr. Uv spectra were determined with a Beckman DBG recording spectrophotometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ± 0.4% of the theoretical values unless otherwise specified. The aminopicolines were obtained from Aldrich Chemical Co., Inc. and J. T. Baker Laboratory Chemicals.

The following reaction procedures are given for specific compds; compds indicated by reference to the particular table were prepared in like manner.

α-Bromopicolines.—The appropriate aminopicoline was diazotized as previously reported[9] utilizing HBr, Br_2, and $NaNO_2$. The boiling points and melting points agreed in all cases with those reported above.

α-Chloropicolines.—The appropriate aminopicoline was diazotized as reported[10] employing HCl and $NaNO_2$. The boiling points were in agreement with those reported in the literature.

2-Bromo-3-bromomethylpyridine·HBr (Table I, 1–8).—2-Bromo-3-methylpyridine (29.2 g, 0.17 mole), NBS (30.2 g, 0.17 mole), and 1.5 g of benzoyl peroxide in 500 ml of $MgSO_4$-dried CCl_4 were refluxed several hours. The succinimide was removed by filtration, and the filtrate was concd *in vacuo* to about 100 ml. The soln was washed with 100 ml of each of the following: 4% NaOH, H_2O, and 2% aq HBr. Et_2O was added to the org layer to make a total of 175 ml, and the dried soln was satd with anhyd

(9) For syntheses and physical constants of the α-bromopicolines see F. A. Case, *J. Amer. Chem. Soc.*, **68**, 2574 (1946); P. Adams and S. Miyano, *ibid.*, **76**, 3168 (1954).

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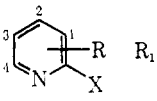
TABLE I
SYNTHETIC INTERMEDIATES

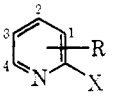


$R_1 = CH_2Br \cdot HBr$; $R_2 = CH_2C(COOC_2H_5)_2NHCOCH_3$

No.	X	R	Position	Mp, °C	Recrystn[b] solvent	Yield[d]	Formula[a]
1	Br	R_1	1	135–143 dec	*c*	15	$C_6H_6Br_3N$[e]
2	Br	R_1	2	120–124 dec	*c*	59	$C_6H_6Br_3N$
3	Br	R_1	3	160–170 dec	*c*	33	$C_6H_6Br_3N$
4	Br	R_1	4	150–157 dec	*c*	53	$C_6H_6Br_3N$[f]
5	Cl	R_1	1	98–110 dec	*c*	47	$C_6H_6Br_2ClN$
6	Cl	R_1	2	113–119 dec	*c*	71	$C_6H_6Br_2ClN$
7	Cl	R_1	3	92–98 dec	*c*	62	$C_6H_6Br_2ClN$
8	Cl	R_1	4	95–111 dec	*c*	58	$C_6H_6Br_2ClN$
9	Br	R_2	1	107–180	W	33	$C_{15}H_{19}BrN_2O_5$
10	Br	R_2	2	103–104	E–P	19	$C_{15}H_{19}BrN_2O_5$
11	Br	R_2	3	119–120	W	19	$C_{15}H_{19}BrN_2O_5$[g]
12	Br	R_2	4	81–82	W–A	30	$C_{15}H_{19}BrN_2O_5$
13	Cl	R_2	1	112–114	E	29	$C_{15}H_{19}ClN_2O_5$
14	Cl	R_2	2	106–107	E	13	$C_{15}H_{19}ClN_2O_5$
15	Cl	R_2	3	114–116	W	32	$C_{15}H_{19}ClN_2O_5$
16	Cl	R_2	4	114–115	W	45	$C_{15}H_{19}ClN_2O_5$

[a] All compds were analyzed for C, H, N. [b] A = Me_2CO, E = Et_2O, P = petr ether, W = H_2O. [c] Unstable to recrystn. [d] Yield of crude product for **1–8**; yield of purified product for **9–16**. [e] C: calcd, 21.71; found, 23.55. [f] C: calcd, 21.71; found, 22.72. [g] C: calcd, 46.52; found, 47.02.

TABLE II
BROMO- AND CHLORO-SUBSTITUTED PYRIDYLALANINES



$R = CH_2CHCOOH$ (NH$_2$)

No.	X	R (position)	Mp, °C dec	Uv (λ_{max})	Recrystn[b] solvent	Yield purified, %	Formula[a,c]
17	Br	1	200–201	271	W–A	47	$C_8H_9BrN_2O_2$
18	Br	2	187–189	269	W–A	42	$C_8H_9BrN_2O_2$
19	Br	3	253–255	272	W	68	$C_8H_9BrN_2O_2$
20	Br	4	230–232	271	W	51	$C_8H_9BrN_2O_2$
21	Cl	1	200–201	270	W–A	31	$C_8H_9ClN_2O_2$
22	Cl	2	203–206	267	W–A	38	$C_8H_9ClN_2O_2$
23	Cl	3	260–262	271	W	47	$C_8H_9ClN_2O_2$
24	Cl	4	182–184	271	W–A	50	$C_8H_9ClN_2O_2$

[a] See footnote *a*, Table I. [b] See footnote *b*, Table II. [c] The bromopyridylalanines (**17–20**) did not give consistently acceptable C analyses. However, the N analyses were acceptable in every case except for **18** for which, N: calcd, 11.43; found, 11.92.

HBr at 0°. The pptd salt was rapidly filtered by suction, washed with several portions of anhyd Et_2O, and stored over P_2O_5. The product was unstable to recrystn, but was sufficiently pure (Table I) for further synthetic work.

Ethyl 2-Acetamido-2-(2-bromo-3-pyridylmethyl)malonate (Table I, 9–16).—To 1.15 g (0.050 g-atom) of Na in 150 ml of Mg-dried EtOH was added 5.43 g (0.025 mole) of ethyl acetamidomalonate. To this soln was added 8.3 g (0.025 mole) of 2-bromo-3-bromomethylpyridine·HBr and the soln refluxed until the pH of an aliquot dissolved in distd H_2O had decreased to approximately pH 5–6. The reaction mixt was taken to dryness *in vacuo*, and the product was extd (Et_2O). It was then crystd from Et_2O–petr ether and recrystd from H_2O. The condensation leading to **10**, **12**, **14**, and **16** was carried out in the same vol (as above) of 1:1 C_6H_6–EtOH. For **12** and **16** a molar excess of ethyl acetamidomalonate and Na was used, and the halide was added portionwise over a period of 1 hr. Physical constants and analyses are given in Table I.

β-(2-Bromo-3-pyridyl)-DL-alanine (Table II, 17–24).—Compound **9** (3.86 g, 0.010 mole) was hydrolyzed in the presence of 50 ml of refluxing 6 *N* HCl for 9 hr. The soln was evapd to dryness *in vacuo*, and the residue was dissolved in 100 ml of H_2O and neutralized (Amberlite IR-45). The neutralized soln was decolorized (Darco G-60) and concd to dryness *in vacuo*. The amino acid was recrystd from H_2O–Me_2CO. Physical constants and analyses are reported in Table II.

Quaternary Ammonium Salts of Tertiary Aminoalkyl Amides

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Quaternary ammonium salts derived from long-chain fatty acids are known to possess antimicrobial activity.[2] Many N-substituted amides of long-chain fatty acids have been reported to have antimycotic activity.[3–5]

(1) A laboratory of the Southern Utilization Research and Development Division, ARS, U. S. Department of Agriculture. Naming of a company or product does not imply approval or recommendation by the Department over others which may also be suitable.

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