(*i.e.*, $ED_{50} \leq 4$ γ/ml.). These results are included in Table IV for comparison.

Experimental Section[8]

The preparation of the individual compounds listed below illustrates the general procedure for each class of compounds.

2-Acyloxyacetophenones (Table I). 5-Chloro-2-(2-quinolinecarboxy)acetophenone (III).—Quinaldoyl chloride (10.0 g., 0.052 mole) in dry benzene (80 ml.) was added gradually to a well-stirred ice-cold solution of 5-chloro-2-hydroxyacetophenone (8.9 g., 0.052 mole) in pyridine (70 ml.). After 24 hr. the mixture was added to excess dilute acetic acid. The product, which separated, crystallized from ethanol–acetone in needles. Melting points, per cent yields, and analyses are summarized in Table I. In the preparation of the esters IV–VII, the acid chloride was added dropwise to the pyridine solution of the acetophenone.

1-(2-Hydroxyphenyl)propane-1,3-diones (Table II). 1-(5-Chloro-2-hydroxyphenyl)-3-(2-quinolyl)propane-1,3-dione (IX).—Powdered KOH (2.5 g.) was added to a solution of 5-chloro-2-(2-quinolinecarboxy)acetophenone (5.0 g.) in dry pyridine (100 ml.). The mixture was shaken vigorously for 20 min. and set aside for 12 hr. The crude product, liberated by the addition of cold dilute acetic acid, was washed with water. It crystallized from ethanol–acetone in yellow needles. Melting points, etc., are recorded in Table II.

Chromones (Table III). 6-Chloro-2-(2-quinolyl)chromone (XV).—1-(5-Chloro-2-hydroxyphenyl)-3-(2-quinolyl)propane-1,3-dione (3.6 g.) in acetic acid (40 ml.) and H_2SO_4 (1 ml.) was heated on a steam bath for 15 min., poured onto crushed ice, and neutralized with 10% NaOH. The product which separated crystallized from ethanol–acetone in needles. Melting points, etc., are recorded in Table III.

Acrylophenones. 5-Chloro-2-hydroxy-3-(4-pyridyl)acrylophenone (XXII).—Aqueous KOH (50%, 10 ml.) was added to a solution of 5-chloro-2-hydroxyacetophenone (3.4 g., 0.02 mole) and pyridine-4-aldehyde (2.1 g., 0.02 mole) in ethanol (50 ml.). After being stirred at room temperature for 12 hr., the solution was neutralized with dilute acetic acid. The product, which separated, crystallized from alcohol in yellow needles, m.p. 143–144°, yield 40%.

Anal. Calcd. for $C_{14}H_{10}ClNO_2$: C, 64.7; H, 3.9; N, 5.4. Found: C, 64.5; H, 4.0; N, 5.5.

(8) Microanalyses were carried out by Mrs. E. M. Carey of the Department of Chemistry, University College, Dublin, and by Drs. Weiler and Strauss, Analytical Laboratory, Oxford, England.

Synthetic Spasmolytic Amines

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A study of some isomeric hexyl- and heptylamines by Marsh, *et al.*,[2] indicated that N-methyl substitution of these primary amines enhanced spasmolytic action and increased muscle relaxant activity while having no effect on the pressor activity of the amine. One of the more potent spasmolytic amines is 2-(3-methylbutyl)-amino 6-methylheptane (Octinum-D).[3] A more recent study[4] of N-alkyl-1,5-dimethylhexylamines has shown that these compounds exhibit some activity against acetylcholine-induced spasms and against blood pressure lowering.

The pharmacodynamic action of these amines has been conveniently compared with that of the natural alkaloids, atropine and papaverine, in their ability to prevent spasms of isolated muscle when activated by acetylcholine or barium chloride solutions, respectively. More often than not, these amines possess both actions. The rather interesting pressor activity data of simple amines and the properties of such a compound as 2-(3-methylbutyl)amino-6-methylheptane[5] prompted the synthesis of the compounds listed in Table I.

The secondary and tertiary amines were conveniently prepared by alkylating amines such as pyrrolidine, piperidine, morpholine, furfurylamine, and 2-amino-methyl-1,4-benzodioxane with the appropriate alkyl bromides, *e.g.*, isoamyl bromide 2-bromo-6-methylheptane, and 2-bromo-6-methylhept-5-ene.

The preparation of alkyl bromides was achieved by the reduction of the corresponding methyl ketone with potassium borohydride to give the secondary alcohol. Subsequent bromination of the alcohol with phosphorus tribromide gave the bromide.

The spasmolytic activity on isolated muscle tissue of the most active amines is listed in Table II. None of the amines tested were superior to either atropine or papaverine in spasmolytic activity.

Experimental Section[6]

Reduction of 6-Methylhept-5-en-2-one.—A solution of 16.2 g. (0.3 mole) of KBH_4 in 100 ml. of water[7] was added dropwise to a solution of 100 g. (0.8 mole) of 6-methylhept-5-en-2-one[8] in 200 ml. of methanol. The addition was made slowly to keep the temperature below 40°. After all the borohydride solution was added, the mixture was heated on a steam bath for 2 hr. and then cooled in an ice bath. A 1:1 solution of concentrated HCl and water (250 ml.) was then added to the reaction and the mixture was allowed to separate. The aqueous layer was extracted with three 100-ml. portions of ether and the combined organic layers were dried (Na_2CO_3). Distillation of the combined organic layers yielded 80 g. of 6-methylhept-5-en-2-ol, b.p. 76–78° (11 mm.).

Anal. Calcd. for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 75.11, 74.89; H, 12.74, 12.48.

Reduction of 6-Methylheptan-2-one.—A similar procedure as that described above gave 75% of 6-methylheptan-3-ol, b.p. 74° (15 mm.).

Anal. Calcd. for $C_8H_{18}O$: C, 73.78; H, 13.99. Found: C, 74.04, 74.38; H, 14.21, 14.51.

Bromination of 6-Methylhept-5-en-2-ol.—A mixture of 117 g. (0.91 mole) of 6-methylhept-5-en-2-ol and 35 g. (0.44 mole) of dry pyridine was cooled to −40° and kept at that temperature as 147 g. (0.52 mole) of PBr_3 was added dropwise over a period of 3 hr. The mixture was allowed to stand overnight at room temperature and then distilled under reduced pressure. A fraction boiling at 66–85° (17 mm.) was washed with cold saturated $NaHCO_3$ solution and extracted with 200 ml. of ether. The extract was dried (Na_2SO_4) and distilled to yield 134 g. of 2-bromo-6-methylhept-5-ene, b.p. 85–86° (27 mm.), $n^{20}D$ 1.4922.

Anal. Calcd. for $C_8H_{15}Br$: C, 50.27; H, 7.91; Br, 41.81. Found: C, 50.84; H, 8.12; Br, 41.36.

Bromination of 6-methylheptan-2-ol.—Phosphorus tribromide (380 g., 1.40 moles) was added over a period of 3 hr. to 177 g.

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(2) D. F. Marsh, A. Howard, and D. A. Herring, *J. Pharmacol. Exptl. Therap.*, **103**, 325 (1951).

(3) H. Hass, *Arch. Exptl. Pathol. Pharmakol.*, **227**, 71 (1955).

(4) (a) Y. Ota, G. Otani, and R. Enomoto, *Yakugaku Zasshi.*, **80**, 1153 (1960); (b) Y. Ota, *ibid.*, **81**, 403 (1961).

(5) (a) J. Paris and J. Vanlerenberghe, *Compt. rend. soc. biol.*, **146**, 265 (1950); (b) E. Savini, *Arch intern. pharmacodyn.*, **82**, 127 (1950).

(6) Melting points were taken in a mineral oil bath with an open capillary and are corrected. The authors are indebted to Mr. Sidney Alpert and his associates of the Analytical section for carrying out the nitrogen (Dumas method) analyses.

(7) Potassium borohydride solution was stabilized by the addition of a few drops of 1 *N* NaOH solution.

(8) Obtained from Givaudan-Delawanna, Inc., Phila., Pa., as methylheptenone.

TABLE I
AMINES

No.	Alkyl fragment	Parent amine	% yield	B.p. of free base, °C. (mm.)	M.p. of HCl salt, °C.	Formula	% nitrogen Calcd.	% nitrogen Found
1	$(CH_3)_2CHCH_2CH_2$	C_4H_9N[a]	94	56–58 (12)	203–205[b]	$C_9H_{20}ClN$	7.90	7.97, 8.04
2	$(CH_3)_2CHCH_2CH_2$	$C_5H_{11}N$[c]	75	68–60 (12)	254–256[b]	$C_{10}H_{22}ClN$	7.31	7.33, 7.36
3	$(CH_3)_2CHCH_2CH_2$	C_4H_9NO[d]	95	74–75 (12)	228–229[b]	$C_9H_{20}ClNO$	7.23	7.47, 7.41
4	$(CH_3)_2CHCH_2CH_2$	C_5H_9NO[e]	72	103–105 (19)	218–220	$C_{16}H_{18}ClNO$	6.88	6.94, 6.96
5	$(CH_3)_2CHCH_2CH_2$	$CH_3(CH_2)_7NH$	73	115–117 (6)	230–230[f]	$C_{13}H_{30}ClN$	5.94	5.95, 5.97
6	$(CH_3)_2CHCH_2CH_2$	$CH_3(CH_2)_9NH$	53	137–142 (6)	229–232[g]	$C_{15}H_{34}ClN$	5.31	5.47, 5.39
7	$(CH_3)_2CHCH_2CH_2$	C_7H_8N[h]	70	109–111 (6)	248–252[f]	$C_{12}H_{20}ClN$	6.55	6.75, 6.64
8	$(CH_3)_2CHCH_2CH_2$	$(C_2H_5)_2N$	83	42 (13)	112–115[i]	$C_9H_{22}ClN$	7.79	7.69, 7.75
9	$(CH_3)_2CHCH_2CH_2$	$C_{10}H_{15}NO_2$[j]	51	136 (0.5)	166–170[g]	$C_{15}N_{26}ClNO_2$	4.87	5.01, 5.00
10	$(CH_3)_2CHCH_2CH_2$	$C_6H_{13}NO$[k]	97	82–85 (8)	203–205[f]	$C_{11}H_{24}ClNO$	6.32	6.36, 6.38
11	$(CH_3)_2CHCH_2CH_2$	$C_{10}H_{13}NO$[l]	90[m]	110–115 (0.05)	133–135[f]	$C_{15}H_{24}ClNO$	5.19	5.14, 5.13
12	$(CH_3)_2CHCH_2CH_2$	$C_6H_{17}N_2O$[n]	56[m]	120 (6)	258–260[o]	$C_{11}H_{26}Cl_2N_2O$	10.25	10.10,10.13
13	$(CH_3)_2CHCH_2CH_2$	$C_9H_{11}NO_2$[p]	62[m]	105–106 (0.1)	208–210[f]	$C_{17}H_{22}ClNO_2$	8.55	8.42, 8.49
14	$(CH_3)_2CH(CH_2)_3C(CH_3)H$	C_4H_9N[a]	70	97–98 (10)	[q]	$C_{12}H_{26}ClN$	6.37	6.49, 6.53
15	$(CH_3)_2CH(CH_2)_3C(CH_3)H$	$C_5H_{11}N$[c]	66	106–108 (12)	184–186[r]	$C_{13}H_{28}ClN$	5.99	6.11, 6.12
16	$(CH_3)_2CH(CH_2)_3C(CH_3)H$	C_4H_9NO[d]	83	110–112 (12)	166–168[b]	$C_{12}H_{26}ClNO$	5.94	6.07, 6.12
17	$(CH_3)_2CH(CH_2)_3C(CH_3)H$	C_5H_8NO[e]	60	132 (18)	[s]	$C_{13}H_{23}NO$	6.69	6.84, 6.72
18	$(CH_3)_2CH(CH_2)_3C(CH_3)H$	$CH_2{=}CHCH_2NH$	63	70–80 (10)	97–99	$C_{11}H_{24}ClN$	6.81	6.87, 6.83
19	$(CH_3)_2CH(CH_2)_3C(CH_3)H$	$C_9H_{11}NO_2$[p]	58[m]	140–145 (0.3)	180–184[f]	$C_{17}H_{28}ClNO_2$	4.46	4.45, 4.45
20	$(CH_3)_2C{=}CH(CH_2)_2C(CH_3)H$	C_4H_9N[a]	61	115–119 (22)	104–108[b]	$C_{12}H_{24}ClN$	6.43	6.38, 6.43
21	$(CH_3)_2C{=}CH(CH_2)_2C(CH_3)H$	$C_5H_{11}N$[c]	67	125–127 (18)	171–174[f]	$C_{13}H_{26}ClN$	6.04	6.02, 6.02
22	$(CH_3)_2C{=}CH(CH_2)_2C(CH_3)H$	C_4H_9NO[d]	61	145–146 (20)	137–140[b]	$C_{12}H_{24}ClNO$	5.99	6.00, 5.99
23	$(CH_3)_2C{=}CH(CH_2)_2C(CH_3)H$	C_5H_8NO[e]	57	127–128 (10)	[s]	$C_{13}H_{21}NO$	6.76	6.76, 6.83
24	$(CH_3)_2C{=}CH(CH_2)_2C(CH_3)H$	$CH_2{=}CHCH_2NH$	74	103 (20)	83–86	$C_{11}H_{22}ClN$	6.87	6.84, 6.89
25	$(CH_3)_2C{=}CH(CH_2)_2C(CH_3)H$	$C_6H_{13}N_2O$[n]	58[m]	108–110 (0.03)	229–231[c,o]	$C_{14}H_{30}Cl_2N_2O$	8.94	8.94, 8.96
26	$(CH_3)_2C{=}CH(CH_2)_2C(CH_3)H$	$(CH_3)_2CHCH_2CH_2NH$	66	119–120 (20)	111–112[b]	$C_{13}H_{28}ClN$	5.99	6.02, 6.08
27	$(CH_3)_2C{=}CH(CH_2)_2C(CH_3)H$	$C_9H_{11}NO_2$[p]	85[m]	135–136 (0.05)	156–157[f]	$C_{17}H_{26}ClNO_2$	4.49	4.44, 4.45
28	$(CH_3)_2C{=}CH(CH_2)_2C(CH_3)H$	$C_7H_{16}N_2O$[t]	54	110–113 (0.05)	208–210[f,o]	$C_{15}H_{32}Cl_2N_2O$	8.56	8.42, 8.49

[a] Pyrrolidine. [b] Recrystallized from acetone–ethanol (15:1). [c] Piperidine. [d] Morpholine. [e] Furfurylamine. [f] Recrystallized from ethanol–ether. [g] Recrystallized from ethanol. [h] Benzylamine. [i] Recrystallized from benzene–petroleum ether (30–60°). [j] 3,4-Dimethoxyphenethylamine. [k] 2,6-Dimethylmorpholine. [l] 6-Methoxy-1,2,3,4-tetrahydroquinoline. [m] Reaction carried out in presence of 1 equiv. of triethylamine. [n] 4-β-Hydroxyethylpiperazine. [o] Di-HCl salt. [p] 2-Aminomethyl-1,4-benzodioxane. [q] Highly hygroscopic solid, m.p. 70–80°. [r] M.p. 186–187° see ref. 4a. [s] HCl salt precipitated as an oil. [t] 3-(4-Morpholinyl)propylamine.

TABLE II
SPASMOLYTIC ACTIVITY

Spasmolytic amine[a]	$BaCl_2$-induced spasms (1:10,000) Concn. of amine, g./ml.	% inhib.	Acetylcholine-induced spasms (1:50,000,000) Concn. of amine, g./ml.	% inhib.
5	1:50,000	75–100	1:500,000	75–100
6	1:100,000	75–100	1:500,000	75–100
21	1:50,000	10	...	...
24	1:50,000	50	...	...
	1:100,000	10–30	...	...
27	1:50,000	75–100	...	...
	1:100,000	50	...	...
Papaverine	1:100,000	100	...	...
Atropine	...	...	1:50,000,000	100
Octinum-D	1:1,000,000	100	1:40,000	100

[a] Numbers correspond to the amines in Table I. [b] All other amines in Table I had no effect in relieving spasms.

(1.36 moles) of 6-methylheptan-2-ol during which time the temperature of the reaction mixture was kept at 5°. The mixture was then poured into 300 g. of ice water. The organic layer was separated and the aqueous layer was extracted with 150 ml. of ether. The organic layers were combined and washed with a solution of Na_2CO_3 and then dried (Na_2SO_4). Distillation of the dried ethereal solution yielded 228 g. of 2-bromo-6-methylheptane, b.p. 62–63° (23 mm.), $n^{20}D$ 1.4482.

Anal. Calcd. for $C_8H_{17}Br$: C, 49.75; H, 8.87; Br, 41.38. Found: C, 49.96; H, 8.91; Br, 41.23.

Alkylation of Amines.—The following procedure was the general method employed in preparing the secondary and tertiary amines whose physical properties and analytical results are listed in Table I.

A mixture of 0.1 mole of the alkyl bromide and 0.25 mole[9] of the

(9) When the primary or secondary amine was not readily available only 0.02 mole excess of this amine was used and in addition 0.1 mole of triethylamine was included in the reaction mixture. The reaction mixture was worked up in a manner similar to that described above.

primary or secondary amine was heated on an oil bath at 130–140° for 3 hr. with constant stirring. The mixture was then cooled and 20 g. of a 50% aqueous NaOH solution was added. The mixture was extracted with 200 ml. of ether and the extract was dried overnight. The dried extract was then distilled to yield the desired product.

Spasmolytic Activity.—Anticholinergic activity was determined on isolated guinea pig ileum suspended in Locke–Ringer's solution in a water bath at 37°. Acetylcholine (1:50 p.p.m.) was used as the spasmogenic agent. The compounds being tested were added to the medium 30 sec. before the addition of acetylcholine, and the inhibition of the acetylcholine-induced contraction was measured by comparison with control values.

The procedure used to determine the inhibition of $BaCl_2$-induced contractions was the same, except that the final concentration of $BaCl_2$ was 1:10,000 and rabbit ileum was the test tissue. The results are shown in Table II.

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Amino Acid Analogs. I. Analogs of the Glutamic Acid–Proline Interconversion. III. Substituted 2-Acetamido-4-benzoylbutyric Acids and 5-Phenylprolines

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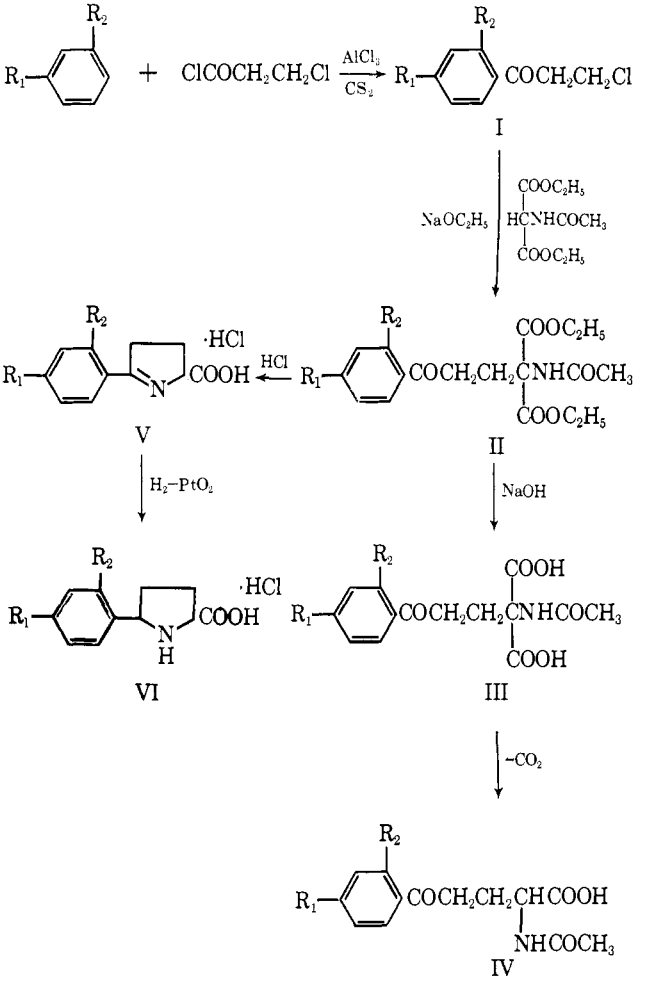
In a previous paper,[2] a rationale for our interest in the preparation of proline and glutamic acid analogs was presented. In that work, the syntheses of 2-acetamido-4-benzoylbutyric acid and 5-phenylproline were reported, and the methods were thought to be suitable for the preparation of aromatic substitution products which were desired for biological study.

In this study, 10 glutamic acid and 10 proline analogs and the necessary intermediates[3] will be described.

The β-chloropropiophenones (I) were prepared by acylation of the appropriate benzene derivative with β-chloropropionyl chloride by means of aluminum chloride in carbon disulfide, according to Allen, Cressman, and Bell.[4] The chloro ketones were used without further purification in the condensation with ethyl acetamidomalonate using sodium ethoxide in anhydrous ethyl alcohol as the condensing medium. Upon hydrolysis of the acetamidomalonates (II) with alkali, malonic acids (III) were obtained which were decarboxylated to the acetylated glutamic acid analogs (IV). Acid hydrolysis of II yielded 2-(substituted phenyl)-1-pyrroline-5-carboxylic acids (V). Subsequent hydrogenation of the pyrrolines (V) over Adams' catalyst at 3–4 atm. of hydrogen yielded the corresponding proline analogs (VI). These reactions are summarized in Scheme I, and the physical and analytical data on compounds of types II–VI are listed in Tables I–V, respectively.

SCHEME I



a, R_1 = F; R_2 = H
b, R_1 = Cl; R_2 = H
c, R_1 = Br; R_2 = H
d, R_1 = CH_3; R_2 = H
e, R_1 = C_6H_5; R_2 = H
f, R_1 = CH_3O; R_2 = H
g, R_1 = C_6H_5O; R_2 = H
IIh–IVh, R_1 = CH_3CONH; R_2 = H
Vh, VIh, R_1 = R_1 = $NH_2 \cdot HCl$; R_2 = H
i, R_1 = F; R_2 = F
j, R_1 = Cl; R_2 = Cl

The genus *Leuconostoc* is composed of streptococcus-like bacteria that secrete large quantities of gum. These organisms which are prevalent in sugar refineries interfere with the processing of cane sugar.[5] *Leuconostoc mesenteroides* P-60 is a species that has been used as an assay organism for 18 amino acids.[6] Among these are glutamic acid and proline.

To learn whether these glutamic acid and proline analogs possess differences in biological activity from the unsubstituted analogs and to learn whether such compounds could be useful in the cane sugar industry,

(1) To whom requests for reprints should be made: Boyce Thompson Institute for Plant Research, Yonkers, N. Y. 10701.

(2) H. Gershon and A. Scala, *J. Org. Chem.*, **26**, 2347 (1961).

(3) Three of the intermediates prepared in this study, 2-(4-chlorophenyl)-, 2-(4-methoxyphenyl)-, and 2-(4-aminophenyl)-1-pyrroline-5-carboxylic acid, were claimed in a recent patent [F. Leonard, British Patent 977,097 (1964)] but were not characterized. The method of synthesis described in the patent is analogous to that reported by Gershon and Scala[2] for the preparation of 2-phenyl-1-pyrroline-5-carboxylic acid.

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