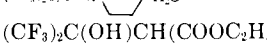
Table II
Known Compounds

No.	Structure	Formula	LD50[a] Oral	LD50[a] Ip	Antitrypanosomal effect[b] Oral	Antitrypanosomal effect[b] Ip	Anti-inflammatory effect[c]	CNS effects[d]	Endocrine effects[e] T	Th	S.V.	B wt
10	$(CF_3)_2C{=}O \cdot 1.5H_2O$	$C_3F_6O \cdot 1.5H_2O$[f]	300	250	5	55	21	Depression	81	77	53	88
11	$(CF_3)_2C(OCH_3)_2$	$C_5H_6F_6O_2$[g]	>800	>800	0	0		Depression	x	x	x	x
12		$C_8H_{11}F_6NO \cdot H_2O$[h]	300	300	37	40	0	Depression	...	...	...	...
13	$(CF_3)_2C(OH)CH(COOC_2H_5)_2$	$C_{10}H_{12}F_6O_5$[i]	1600	800	0	0	0	Mild depression	...	...	...	...
14	$(CF_3)_2C(OH)CH(COCH_3)COOC_2H_5$	$C_9H_{10}F_6O_4$[i]	800	500	68	66	0	Depression	...	...	...	...
15	$(CF_3)_2C(OH)CH(COCH_3)_2$	$C_8H_8F_6O_3$[i]	400	300	55	87	0	Depression	...	...	...	...
16	$(CF_3)_2C(OH)CH_2COOH$	$C_5H_4F_6O_3$[i]	1600	600	0	0	22	Depression	x	x	x	x
17	$(CF_3)_2CHOH$	$C_3H_2F_6O$[j]	600	300	0	0	0	Depression	x	x	x	x

[a] The LD_{50} was determined in mice. [b] Compounds were tested against *Trypanosoma rhodesiense* infection in mice. Doses were 4 daily doses of 100 mg/kg by the oral route and 4 daily doses of 0.2 of the ip LD_{50} by the ip route. Figures given refer to the per cent survival of the animals—controls have 0% survival. [c] The figures refer to the per cent reduction of edema produced by carrageenin relative to controls. Doses were 100 mg/kg (0.5 and 2 hr before carrageenin) in the rat. [d] CNS effects were observed in mouse behavior test. [e] 50 mg/kg per day given sc for 12 days to Wistar rats weighing 80 g: T = testes; S.V. = seminal vesicles; Th = thymus; B wt = body weight; % weight relative to controls; ... results not available; x not significantly different from control. [f] See ref 2. [g] J. J. Drysdale, U. S. Patent, 2,901,514 (1959); *Chem. Abstr.* **54,** 1320*f* (1960). [h] N. P. Gambaryan, E. M. Rokhlin, Yu, V. Ziefman, Cheng, Ching-Yun, and I. L. Knunyants, *Angew. Chem. Int. Ed. Engl.*, **5,** 947 (1966). [i] I. L. Knunyants, Tsin-Yun Chen, and N. P. Gambaryan, *V. Khim. Obshchest. D. I., M.*, **5,** 112 (1960); *Chem. Abstr.*, **54,** 20872*g* (1960). [j] I. K. Knunyants and M. P. Krasuskaya, U.S.S.R. Patent 138,604 (1960), *Chem. Abstr.*, **56,** 8563*g* (1962).

Experimental Section

Microanalytical figures for new compounds given in Table I agree with theoretical values to within 0.4%. The structures of all new compounds were confirmed by ir and nmr spectroscopy. Known compounds listed in Table II were prepared by established methods. Melting points are uncorrected and were measured in sealed capillary tubes. All compounds were prepared by similar methods, two representative preparations are given below.

2,2-Bis(trifluoromethyl)imidazolidine Monohydrate (1).—HFAS (5.8 g, 0.03 mole) and ethylenediamine (1.8 g, 0.03 mole) were mixed in C_6H_6 (150 ml). The mixture was refluxed for 0.5 hr, then for 6 hr under a Dean–Stark trap. During this period 1 ml of H_2O was collected. The C_6H_6 was removed by evapn leaving a white solid which was recrystd from Et_2O. The material was further purified by sublimation at 0.5 mm. The product, 4.0 g (59%), was a white crystalline solid, mp 109–111°.

2,2-Bis(trifluoromethyl)thiazolidine Monohydrate (4).—2-Mercaptoethylamine·HCl (10 g, 0.088 mole) in EtOH (100 ml) was deoxygenated by passage of dry N_2. The solution was neutralized by NaOEt. HFAS (17 g, 0.088 mole) was added and the mixture was boiled for 2 hr with passage of N_2. Solvent was removed and the residue was extracted with dry Et_2O. The ethereal extract was concd to give a crystalline solid, which was purified by recrystn from Et_2O. The product, 10.9 g (51%), was a white crystalline solid, mp 115–117°.

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Structure–Taste Relationships of Aspartic Acid Amides

Robert H. Mazur,* Arthur H. Goldkamp, Patricia A. James, and James M. Schlatter

Chemical Research Department, G. D. Searle & Co., Skokie, Illinois 60076

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It has been discovered that many α-amides of L-aspartic acid are sweet. The most potent products are derived from L-1-methyl-2-substituted-ethylamines where the substituent is Ph, cyclohexyl, *n*-Pr, *n*-Bu, or *i*-Bu.

During the synthesis of gastrin C-terminal tetrapeptide, tryptophylmethionylaspartylphenylalaninamide, one of us (J. M. S.) discovered that an intermediate, L-Asp-L-Phe Me ester, was intensely sweet.[1] Subsequent organoleptic evaluation has shown that the compound is 100–150 times as sweet as sucrose and free of unpleasant aftertaste.[2] Structural variations[1] in the Asp, Phe, and Me ester parts of the molecule were made. The presence of both the free, unsubstituted NH_2 and one CO_2H of Asp as well as the distance between them and the absolute configuration of the asymmetric C were completely critical for sweetness; the requirement of absolute L configuration also held for Phe. Sweetness fell off rapidly with increasing size of the ester radical. For example, the *n*-Pr ester had about 1% the potency of the Met ester. It was also found that Phe could be replaced by Met or Tyr to give dipeptide esters retaining substantial sweetening power.

At the present time the phenomenon of taste seems best explained by selective adsorption of chemical compounds onto a taste receptor.[3] The receptor is probably a site on the surface of a cell and is therefore a

* To whom correspondence should be addressed.

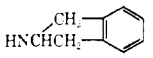
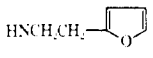
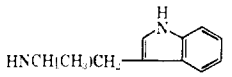
(1) R. H. Mazur, J. M. Schlatter, and A. H. Goldkamp, *J. Amer. Chem. Soc.*, **91,** 2684 (1969).

(2) R. H. Mazur, J. M. Schlatter, and L. Jokay, Program of the Institute of Food Technologists 29th Meeting, Chicago, Ill., May 1969, p 58.

(3) L. M. Beidler, *Advan. Chem. Ser.*, **56,** 1 (1966). We would like to thank a referee for calling our attention to Dr. Beidler's work.

TABLE I
PROTECTED ASPARTIC ACID AMIDES

OBzl
Z—Asp—X[a]

No.	X	Yield, %	Mp, °C	$[\alpha]_D$, deg	Formula[i]
1	HNCH(CH$_3$)CH$_2$C$_6$H$_5$; L[b]	99 A[c]	120–121 PA[d]	−24 M[e]	$C_{28}H_{30}N_2O_5$
2	HNCH(CH$_3$)CH$_2$C$_6$H$_5$; D	98 A	110–111 PA	+4 M	$C_{28}H_{30}N_2O_5$
3	HNCH(CH$_3$)CH$_2$C$_6$H$_5$[f]	98 M	133–141 P	−11 M	$C_{29}H_{32}N_2O_5$
4	HNCH$_2$CH$_2$C$_6$H$_5$	73 A	112–114 C	−11 M	$C_{27}H_{28}N_2O_5$
5	HNCH(C$_2$H$_5$)CH$_2$C$_6$H$_5$	91 A	105–115 PA–CY	−11 M	$C_{29}H_{32}N_2O_5$
6	HNC(CH$_3$)$_2$CH$_2$C$_6$H$_5$	24 A	96–99 CY	−1 M	$C_{29}H_{32}N_2O_5$
7		98 M	122–126 P	−5 M	$C_{28}H_{28}N_2O_5$
8	HN-*c*-C$_3$H$_4$CHCHC$_6$H$_5$; *t*-	95 A	80–92 P	−13 M	$C_{28}H_{28}N_2O_5$
9	HNCH$_2$CH(CH$_3$)C$_6$H$_5$	99 A	72–81	−16 M	$C_{28}H_{30}N_2O_5$
10	HNCH(CH$_3$)CH$_2$CH$_2$C$_6$H$_5$	85 A	97–115 ET–PN	−6 M	$C_{29}H_{32}N_2O_5$
11	HNCH(CH$_3$)CH$_2$OC$_6$H$_5$	99 A	76–88	+14 CH	$C_{28}H_{30}N_2O_6$
12	HNCH$_2$CH$_2$OC$_6$H$_5$	88 A	101–103 PA	−6 M	$C_{27}H_{28}N_2O_6$
13	HNCH(CH$_3$)CH$_2$C$_6$H$_3$(OCH$_2$O)-3,4	80 A	119–122 PA	+10 CH	$C_{29}H_{30}N_2O_7$
14	HNCH(CH$_2$OH)CH$_2$C$_6$H$_5$; L	85 A	140–142 P	−36 M	$C_{28}H_{30}N_2O_6$
15	HNCH(CH$_3$)CH(OH)C$_6$H$_5$	99 A	72–84 P–W	−9 M	$C_{28}H_{30}N_2O_6$
16	HNCH(CH$_3$)CH$_2$C$_6$H$_4$OH-4	98 A	106–117	−10 M	$C_{28}H_{30}N_2O_6$
17	HNCH$_2$CH$_2$C$_6$H$_4$OH-4	88 A	148–149 PA–CH	−12 M	$C_{27}H_{28}N_2O_6$
18	HNCH(CH$_2$OH)CH$_2$C$_6$H$_4$OH-4; L-	30 A	73–77 MC–ET	−33 M	$C_{28}H_{30}N_2O_7$
19	HNCH(CH$_3$)CH$_2$C$_6$H$_4$NHSO$_2$CH$_3$-4; L-	97 M	144–155 P–W	−24 M	$C_{29}H_{33}N_3O_7S$
20	HNCH(CH$_3$)CH$_2$C$_6$H$_4$F-4	69 M	83–87 EA–CY	−13 M	$C_{28}H_{29}FN_2O_5$
21	HNCH$_2$CH$_2$C$_6$H$_4$F-4	79 A	106–108 T	−9 M	$C_{27}H_{27}FN_2O_5$
22		86 A	113–114 P	−10 M	$C_{25}H_{26}N_2O_6$
23		46 A	102–108 P	−15 M	$C_{30}H_{31}N_3O_5$
24	HNCH(CH$_3$)CH$_2$-*c*-C$_6$H$_{11}$; L	91 M	65–70 S	−18 M	$C_{28}H_{36}N_2O_5$
25	HNCH(CH$_3$)CH$_2$-*c*-C$_6$H$_{11}$; D-	90 A	69–81 S	+2 M	$C_{28}H_{36}N_2O_5$
26	HNCH$_2$CH$_2$-*c*-C$_6$H$_{11}$	85 A	129–130 PA	−3 M	$C_{27}H_{34}N_2O_5$
27	HN-*c*-C$_6$H$_{11}$	81 M	140–142 P	−7 M	$C_{25}H_{30}N_2O_5$
28	HNCH(CH$_3$)CH$_2$CH$_2$CH$_3$	94 M	91–99 P–W	−4 M	$C_{24}H_{30}N_2O_5$
29	HN(CH$_2$)$_3$CH(CH$_3$)CH$_3$[g]	92 M	78–80 P–W		$C_{28}H_{32}N_2O_5$
30	HNCH(CH$_3$)CH$_2$CH(CH$_3$)CH$_3$; L-	75 A	104–105 P–W	−16 M	$C_{25}H_{32}N_2O_5$
31	HNCH(CH$_3$)CH$_2$CH(CH$_3$)CH$_3$; D-	72 A	94–96 P–W	+47 M	$C_{25}H_{32}N_2O_5$
32	HNCH(C$_2$H$_5$)CH$_2$CH$_2$CH$_3$	94 M	96–98 P–W	−6 M	$C_{25}H_{32}N_2O_5$
33	HN(CH$_2$)$_5$CH$_3$	97 M	72–75 P–W	−10 M	$C_{25}H_{32}N_2O_5$
34	HNCH(CH$_3$)(CH$_2$)$_3$CH$_3$	94 M	70–75	−7 M	$C_{25}H_{32}N_2O_5$
35	HN(CH$_2$)$_6$CH$_3$	96 M	92–93 P	−6 M	$C_{26}H_{34}N_2O_5$
36	HNCH(CH$_3$)(CH$_2$)$_4$CH$_3$	85 M	65–69	−6 M	$C_{26}H_{34}N_2O_5$
37	HNCH(CH$_3$)CH$_2$CH(CH$_3$)C$_2$H$_5$	89 M	61–71	+11 M	$C_{26}H_{34}N_2O_5$
38	HNCH(CH$_3$)CH$_2$CH$_2$CH(CH$_3$)CH$_3$	98 M	90–103	−8 M	$C_{26}H_{34}N_2O_5$
39	HNCH(C$_2$H$_5$)(CH$_2$)$_3$CH$_3$	94 M	91–98	−9 M	$C_{26}H_{34}N_2O_5$
40	HNCH(CH$_3$)(CH$_2$)$_4$CH$_3$; L-	94 M	96–99 P–W	−11 M	$C_{26}H_{34}N_2O_5$
41	HNCH(CH$_3$)(CH$_2$)$_4$CH$_3$; L[h]	94 M	99–101 P–W	+3 M	$C_{26}H_{34}N_2O_5$
42	HNCH(CH$_3$)(CH$_2$)$_4$CH$_3$; D-	98 M	98–100 P–W	−4 M	$C_{26}H_{34}N_2O_5$
43	HNCH(CH$_3$)(CH$_2$)$_4$CH$_3$; D[h]	97 M	95–97 P–W	+12 M	$C_{26}H_{34}N_2O_5$
44	HNCH(CH$_3$)CH$_2$CH$_2$CH(CH$_3$)CH$_3$; L-	89 M	104–106 P–W	−13 M	$C_{26}H_{34}N_2O_5$
45	HNCH(CH$_3$)CH$_2$CH$_2$CH(CH$_3$)CH$_3$; L[h]	83 M	117–119 P–W	+3 M	$C_{26}H_{34}N_2O_5$
46	HNCH(CH$_3$)CH$_2$CH$_2$CH(CH$_3$)CH$_3$; D-	77 M	117–119 P–W	−4 M	$C_{26}H_{34}N_2O_5$
47	HNCH(CH$_3$)CH$_2$CH$_2$CH(CH$_3$)CH$_3$; D[h]	99 M	106–107 P–W	+13 M	$C_{26}H_{34}N_2O_5$
48	HNCH(CH$_3$)CH$_2$CH$_2$OC$_2$H$_5$	93 M	64–81	−8 M	$C_{25}H_{32}N_2O_6$
49	HNCH(CH$_3$)(CH$_2$)$_5$CH$_3$	89 M	80–86 P–W	−5 M	$C_{27}H_{36}N_2O_5$

[a] Asp = L-Aspartic acid, Z = $C_6H_5CH_2OCO$, Bzl = $C_6H_5CH_2$. [b] Amines are DL unless the configuration is specified. [c] Coupling procedure: A, active ester; M, mixed anhydride. [d] Crystallization solvent: A, Me_2CO; AC, AcOH; C, CCl_4; CH, $CHCl_3$; CY, cyclohexane; E, EtOH; EA, EtOAc; ET, Et_2O; H, 1 *N* HCl; M, MeOH; MC, CH_2Cl_2; P, *i*-PrOH; PA, *i*-PrOAc; PN, pentane; S, Skellysolve B; T, PhMe; W, H_2O. Where no solvent is indicated, the melting point was taken on crude product. [e] Rotations were measured at room temperature at 1% concentration in the solvent shown. [f] L-Z-Glu (OBzl) was used. [g] DL-Z-Asp(OBzl) was used. [h] D-Z-Asp(OBzl) was used. [i] All compounds were analyzed for C, H, N.

protein. Adsorption changes the local geography of the surface membrane which in some way initiates a response that we call taste. Our earlier work left little doubt that the ionic properties of the NH_2 and CO_2H groups of Asp were responsible for their binding to the taste receptor, but the role of the Ph and CO_2Me groups of Phe Me ester was uncertain. Their function could be explained equally well on the basis of either electrophilic or hydrophobic components of the receptor site. We wish to present evidence that the taste receptor has

hydrophobic components and that a remarkable property of many α-amides of L-Asp is their sweet taste.

Initial tasting was carried out with 1% solutions and the results expressed as + (sweet), 0 (tasteless), and − (bitter). The sweet compounds were tasted at successively greater dilutions to determine an approximate potency with reference to sucrose as 1. Table II gives the data; substances that are only 1–2 times as sweet as sucrose are reported as +. The potencies are based on ratios of threshold values—the threshold concentration of sucrose for most subjects is 1–1.5%—and might be different at sucrose concentrations typical of foods and beverages.

Replacement of the CO_2Me group of Phe by Me gives the well-known CNS stimulant and appetite inhibitor, amphetamine. When this change was applied to AspPhe Me ester, the resulting Asp-L-amphetamine[4] (**50**) was quite sweet, about 50 times sucrose. The corresponding D isomer, Asp-D-amphetamine (**51**), was tasteless. As a further check on parallelism with AspPhe Me ester, L-Glu-DL-amphetamine (**52**) was synthesized and tasted bitter. Thus, for the biological activity we are considering, the CO_2Me and Me groups produce an equivalent effect within about a factor of 2. Furthermore, structure–taste specificity has not been changed. This strongly suggests that for sweetness, the size of the group on C-1 of phenethylamine determines the binding effectiveness of the molecule. We have studied the point in considerable detail.

AspPhe was bitter so that an ionic group at C-1 of phenethylamine will not do. Removing the C-1 substituent [Asp-phenethylamine (**53**)] gave a tasteless compound. The 1-ethyl-2-phenethylamide **54** was slightly sweet, about equal to sucrose. It was surprising to us that Asp-1,1-dimethylphenethylamine (**55**) was about 20 times as sweet as sucrose. Apparently, an asymmetric C is not absolutely necessary and the correct substitution on C-1 is enough by itself to produce a sweet taste. Another example of a sweet amide of a symmetrical amine was Asp-2-aminoindane (**56**), about 10 times sucrose in potency. However, closing a ring on C-2 [Asp-*trans*-2-phenylcyclopropylamine (**57**)] gave a bitter product. Moving the Me along the chain [Asp-2-methylphenethylamine (**58**)] resulted in a bitter substance. Asp-*N*-methylamphetamine (**59**) was also bitter. The higher homolog, Asp-1-methyl-3-phenylpropylamine (**61**), was somewhat sweet, about 5 times sucrose.

To summarize, the structural requirements for sweetness in Asp-phenethylamides seem to be substitution on C-1 and absolute L configuration when the amine is asymmetric. An apparent exception [Asp-*trans*-phenylcyclopropylamine (**57**)] may be due to the rigid configuration of the amine preventing approach to the taste receptor.

Introduction of heteroatoms gave compounds **62–72** with reduced potency and also altered structural specificity in that a number of phenethylamides without substitution at C-1 were slightly sweet. The benzene ring was replaced by furan in **73** and **74** with similar results. However, the aspartic amide of α-methyltryptamine (**75**) was bitter.

When hexahydro-L-amphetamine was substituted for L-amphetamine, the product, Asp-L-1-methyl-2-cyclohexylethylamine (**76**) suffered no diminution in sweetness being about 50 times sucrose. Also, the D isomer **77** gave an amide that was slightly sweet in contrast to D-amphetamine.

Asp-2-cyclohexylethylamine (**78**) was also slightly sweet, but both L and D isomers **79** and **80** of Asp-*N*,-1-dimethyl-2-cyclohexylethylamine were bitter as was aspartylcyclohexylamine (**81**).

The fact that an aromatic ring was not necessary for sweetness was completely unexpected and probably means that the corresponding binding site is not only hydrophobic but can accept a wide variation of shapes. This speculation led us to synthesize aspartic acid amides of a number of homologous and isomeric aliphatic amines.

It was found that aliphatic amines will give sweet aspartic acid amides but that the structural requirements for good activity are quite specific. A 5-C amine, 1-methylbutylamine, gave a tasteless amide (**82**). Six-C amines yielded amides that were tasteless (4-methylpentylamine) (**83**), bitter (1,3-dimethylbutylamine) (**84**, **85**), 1-ethylbutylamine (**86**), and sweet (hexylamine) (**87**), (1-methylpentylamine) (**88**). All 7-C amides (**89–93**) tested were sweet, and the two best compounds [Asp-1-methylhexylamine (**90**) and Asp-1,4-dimethylpentylamine (**92**)] were prepared in all four possible configurations (**94–101**). As in the case of AspPhe Me ester, the sweet isomer was found to be LL. The 1-methylhexylamide **94** was about 50 times sucrose while the 1,4-dimethylpentylamide **98** was about 100 times sucrose. Actually, our sweet amides were derived from D-amines according to absolute configurations previously assigned.[5] In this case, taste was a reliable method for determining absolute configuration and we were able to show that the literature work had been incorrectly interpreted.[6] Asp-1-methylheptylamine (**103**) was only slightly sweet.

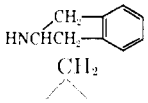
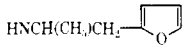
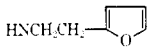
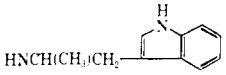
The above data may be correlated to a first approximation by assuming that the basic structure necessary for sweetness is L-isoasparagine with the amide N attached to a straight chain of 6 C at C-2. The compound described is Asp-1-methylpentylamine (**88**). In addition, the amine must have the L configuration. Models show that apparently dissimilar amines (1-methylhexylamine, 1-methyl-2-cyclohexylethylamine, 1-methyl-phenethylamine) actually have almost exactly the same overall length. A shorter chain (1-methylbutylamine) gives a tasteless amide **82** while longer chains (1-methylhexylamine and 1-methylheptylamine) give progressively less sweet amides (**90**, **103**). Among the sweet compounds there is at least a 100-fold range in potency so that obviously the nature and position of substituents is of great importance. Although it would be possible within the present series to design additional compounds that would certainly be sweet, the prediction of potency is much more difficult. Compounds reported as sweet also have a pleasant taste. No particular effort was made to determine qualitative aspects of taste or similarity to sucrose.

(4) In order to emphasize that the present products are amides of aspartic acid, Chemical Abstracts nomenclature is not followed. For example, L-Asp-L-amphetamine would be indexed as L-3-amino-*N*-L-1′-methyl-2′-phenethylsuccinamic acid. Asp has the L configuration unless otherwise noted. The amines are DL if the absolute configuration is not specified.

(5) B. Halpern, J. Ricks, and J. W. Westley, *Chem. Commun.*, 679 (1966).

(6) R. H. Mazur, *J. Org. Chem.* **35**, 2050 (1970).

TABLE II
ASPARTIC ACID AMIDES
Asp-X[a]

No.	X	Yield, %	Mp, °C	[α]D, deg	Formula[c]	Taste
50	HNCH(CH$_3$)CH$_2$C$_6$H$_5$; L-	88 AC	197–198 W	−12 M	C$_{13}$H$_{18}$N$_2$O$_3$	50
51	HNCH(CH$_3$)CH$_2$C$_6$H$_5$; D-	98 AC	222–225 E–W	+14 W	C$_{13}$H$_{18}$N$_2$O$_3$	0
52	HNCH(CH$_3$)CH$_2$C$_6$H$_5$[b]	79 M	164–166 A–W	+34 M	C$_{14}$H$_{20}$N$_2$O$_3$	-
53	HNCH$_2$CH$_2$C$_6$H$_5$	70 AC	212–214 P–W	−15 W	C$_{12}$H$_{16}$N$_2$O$_3$	0
54	HNCH(C$_2$H$_5$)CH$_2$C$_6$H$_5$	91 AC	158–163 M–ET	+8 M	C$_{14}$H$_{20}$N$_2$O$_3$·0.25H$_2$O	5
55	HNC(CH$_3$)$_2$CH$_2$C$_6$H$_5$	96 AC	159–161 W	−16 M	C$_{14}$H$_{20}$N$_2$O$_3$	20
56		91 M	223–224 M–W	−6 H	C$_{13}$H$_{16}$N$_2$O$_3$	10
57	HNCHCHC$_6$H$_5$; *t*-	95 M	175–178	+5 M	C$_{13}$H$_{16}$N$_2$O$_3$·H$_2$O	-
58	HNCH$_2$CH(CH$_3$)C$_6$H$_5$	70 AC	182–188 W	−20 W	C$_{13}$H$_{18}$N$_2$O$_3$	-
59	N(CH$_3$)CH(CH$_3$)CH$_2$C$_6$H$_5$; L-	84 M	164–166	+47 W	C$_{14}$H$_{20}$N$_2$O$_3$·0.5H$_2$O	-
60	N(CH$_3$)CH(CH$_3$)CH$_2$C$_6$H$_5$; D-	82 M	185–187	+12 W	C$_{14}$H$_{20}$N$_2$O$_3$·0.5H$_2$O	-
61	HNCH(CH$_3$)CH$_2$CH$_2$C$_6$H$_5$	95 AC	190–196 M–W	+16 H	C$_{14}$H$_{20}$N$_2$O$_3$	5
62	HNCH(CH$_3$)CH$_2$OC$_6$H$_5$	68 M	180–184 M–W	+11 H	C$_{13}$H$_{18}$N$_2$O$_4$	10
63	HNCH$_2$CH$_2$OC$_6$H$_5$	85 AC	184–185 W	−13 H	C$_{12}$H$_{16}$N$_2$O$_4$	+
64	HNCH(CH$_3$)CH$_2$C$_6$H$_3$(OCH$_2$O)-3,4	95 M	189–192	+6 M	C$_{14}$H$_{16}$N$_2$O$_5$	-
65	HNCH(CH$_2$OH)CH$_2$C$_6$H$_5$; D-	95 AC	237–238 W	−26 AC	C$_{13}$H$_{18}$N$_2$O$_4$	+
66	HNCH(CH$_3$)CH(OH)C$_6$H$_5$	98 M	188–190 M	+10 M	C$_{13}$H$_{18}$N$_2$O$_4$·0.5H$_2$O	+
67	HNCH(CH$_3$)CH$_2$C$_6$H$_4$OH-4	95 M	160–185	+5 W	C$_{13}$H$_{18}$N$_2$O$_4$	+
68	HNCH$_2$CH$_2$C$_6$H$_4$OH-4	72 AC	209–210 W	−21 W	C$_{12}$H$_{16}$N$_2$O$_4$	+
69	HNCH(CH$_2$OH)CH$_2$C$_6$H$_4$OH-4; L-	44 M	212–213 M	−10 H	C$_{13}$H$_{18}$N$_2$O$_5$	+
70	HNCH(CH$_3$)CH$_2$C$_6$H$_4$NHSO$_2$CH$_3$-4; L-	96 M	199–208 W	+14 H	C$_{14}$H$_{21}$N$_3$O$_5$S	-
71	HNCH(CH$_3$)CH$_2$C$_6$H$_4$F-4	87 M	203–209 M–ET	+9 H	C$_{13}$H$_{17}$FN$_2$O$_3$	20
72	HNCH$_2$CH$_2$C$_6$H$_4$F-4	74 M	208–209 W	−6 M	C$_{12}$H$_{15}$FN$_2$O$_3$	5
73		85 M	168–180 M–ET	+6 H	C$_{11}$H$_{16}$N$_2$O$_4$·0.333H$_2$O	10
74		71 M	195–196 M	−17 M	C$_{10}$H$_{14}$N$_2$O$_4$	+
75		96 AC	203–205 M	−22 M	C$_{15}$H$_{19}$N$_3$O$_3$	-
76	HNCH(CH$_3$)CH$_2$-*c*-C$_6$H$_{11}$; L-	84 AC	184–185 M–W	−19 M	C$_{13}$H$_{24}$N$_2$O$_3$	50
77	HNCH(CH$_3$)CH$_2$-*c*-C$_6$H$_{11}$; D-	60 M	207–208 M–W	+16 M	C$_{13}$H$_{24}$N$_2$O$_3$	5
78	HNCH$_2$CH$_2$-*c*-C$_6$H$_{11}$	94 AC	193–202 M–W	+7 AC	C$_{12}$H$_{22}$N$_2$O$_3$	10
79	N(CH$_3$)CH(CH$_3$)CH$_2$-*c*-C$_6$H$_{11}$; L-	78 M	179–180 P–ET	−14 W	C$_{14}$H$_{26}$N$_2$O$_3$·0.25H$_2$O	-
80	N(CH$_3$)CH(CH$_3$)CH$_2$-*c*-C$_6$H$_{11}$; D-	64 M	194–196	+1 W	C$_{14}$H$_{26}$N$_2$O$_3$	-
81	HN-*c*-C$_6$H$_{11}$	91 M	224–225 W	+16 H	C$_{10}$H$_{18}$N$_2$O$_3$	-
82	HNCH(CH$_3$)CH$_2$CH$_2$CH$_3$	92 M	190–194 A–W	+9 AC	C$_9$H$_{18}$N$_2$O$_3$·0.5H$_2$O	0
83	HN(CH$_2$)$_3$CH(CH$_3$)CH$_3$[c]	89 M	222–223 M–W		C$_{10}$H$_{20}$N$_2$O$_3$	0
84	HNCH(CH$_3$)CH$_2$CH(CH$_3$)CH$_3$; L-	91 AC	166–168 W	−17 M	C$_{10}$H$_{20}$N$_2$O$_3$·0.5H$_2$O	-
85	HNCH(CH$_3$)CH$_2$CH(CH$_3$)CH$_3$; D-	92 AC	201–202 W	+9 M	C$_{10}$H$_{20}$N$_2$O$_3$·0.25H$_2$O	-
86	HNCH(C$_2$H$_5$)CH$_2$CH$_2$CH$_3$	93 M	196–200 A–W	+12 AC	C$_{10}$H$_{20}$N$_2$O$_3$·H$_2$O	-
87	HN(CH$_2$)$_5$CH$_3$	88 M	200–201 W	+9 AC	C$_{10}$H$_{20}$N$_2$O$_3$·0.25H$_2$O	+
88	HNCH(CH$_3$)(CH$_2$)$_3$CH$_3$	98 M	188–193 A–W	+11 AC	C$_{10}$H$_{20}$N$_2$O$_3$·0.5H$_2$O	30
89	HN(CH$_2$)$_6$CH$_3$	89 M	200–201 W	+8 AC	C$_{11}$H$_{22}$N$_2$O$_3$·0.25H$_2$O	+
90	HNCH(CH$_3$)(CH$_2$)$_4$CH$_3$	95 M	190–194	+7 AC	C$_{11}$H$_{22}$N$_2$O$_3$	20
91	HNCH(CH$_3$)CH$_2$CH(CH$_3$)CH$_2$CH$_3$	94 M	162–166 W	−2 M	C$_{11}$H$_{22}$N$_2$O$_3$·0.25H$_2$O	+
92	HNCH(CH$_3$)CH$_2$CH$_2$CH(CH$_3$)CH$_3$	94 M	181–188 A–W	+9 AC	C$_{11}$H$_{22}$N$_2$O$_3$·0.25H$_2$O	50
93	HNCH(C$_2$H$_5$)(CH$_2$)$_3$CH$_3$	98 M	190–195	+9 AC	C$_{11}$H$_{22}$N$_2$O$_3$·0.5H$_2$O	+
94	HNCH(CH$_3$)(CH$_2$)$_4$CH$_3$; L-	94 M	187–189 W	−5 M	C$_{11}$H$_{22}$N$_2$O$_3$·H$_2$O	50
95	HNCH(CH$_3$)(CH$_2$)$_4$CH$_3$; L-[d]	97 M	213–214 M–W	−5 M	C$_{11}$H$_{22}$N$_2$O$_3$·0.5H$_2$O	-
96	HNCH(CH$_3$)(CH$_2$)$_4$CH$_3$; D-	96 M	217–218 M–W	+5 M	C$_{11}$H$_{22}$N$_2$O$_3$	0
97	HNCH(CH$_3$)(CH$_2$)$_4$CH$_3$; D-[d]	97 M	189–192 W	+6 M	C$_{11}$H$_{22}$N$_2$O$_3$	-
98	HNCH(CH$_3$)CH$_2$CH$_2$CH(CH$_3$)CH$_3$; L-	84 M	187–190 W	+23 H	C$_{11}$H$_{22}$N$_2$O$_3$·0.5H$_2$O	100
99	HNCH(CH$_3$)CH$_2$CH$_2$CH(CH$_3$)CH$_3$; L-[d]	99 M	215–216 M–W	+2 M	C$_{11}$H$_{22}$N$_2$O$_3$	0
100	HNCH(CH$_3$)CH$_2$CH$_2$CH(CH$_3$)CH$_3$; D-	96 M	210–213 M–W	−3 M	C$_{11}$H$_{22}$N$_2$O$_3$·0.5H$_2$O	+
101	HNCH(CH$_3$)CH$_2$CH$_2$CH(CH$_3$)CH$_3$; D-[d]	91 M	192–195 W	−26 H	C$_{11}$H$_{22}$N$_2$O$_3$·0.25H$_2$O	-
102	HNCH(CH$_3$)CH$_2$CH$_2$OCH$_2$CH$_3$	77 M	166–170 M–ET	+3 M	C$_{10}$H$_{20}$N$_2$O$_4$·0.25H$_2$O	10
103	HNCH(CH$_3$)(CH$_2$)$_5$CH$_3$	85 M	180–190	−8 M	C$_{12}$H$_{24}$N$_2$O$_3$·0.5H$_2$O	10

[a] See Table I for abbreviations and explanations. [b] The amide was derived from L-Glu. [c] The amide was derived from DL-Asp. [d] The amide was derived from D-Asp. [e] All compounds were analyzed for C, H, N.

Experimental Section

Melting points were determined in open capillaries in a stirred bath and are uncorrected. Analyses were done under the direction of E. Zielinski; where analyses are indicated only by symbols of the elements, analytical results were within ±0.4% of the theoretical values. We would like to thank W. M. Selby, J. Seranskas, and M. C. Scarro for many hydrogenations.

All intermediates and products were controlled by tlc on silica. Protected compounds were run in a suitable mixture of MeOH and chloroform. Deprotected compounds were run in *n*-BuOH–HOAc–H_2O, 7:1:2. Spots were detected by the *tert*-butyl hypochlorite–starch–iodide method.[7] All compounds reported here were essentially homogeneous on tlc.

The *N*-carbobenzoxy-β-benzyl aspartate was prepared in our pilot plant by T. J. Telinski, L. J. Sacco, and R. Shubart. The crude product was crystallized from 3 parts of HOAc and 6 parts of H_2O to give homogeneous material, mp 110–111° (lit.[8] 107–109°). It was not possible to achieve this melting point using other solvent combinations.

Most amines were commercially available. It was necessary to synthesize the following: 1-ethylphenethylamine,[9] 2-methylphenethylamine,[10] 1-methyl-2-phenoxyethylamine,[11] 2-phenoxyethylamine,[12] 1-hydroxymethylphenethylamine (phenylalaninol).[13] 1-hydroxymethyl-2-(4-hydroxyphenyl)ethylamine (tyrosinol),[13] 1-methyl-2-(4-fluorophenyl)ethylamine,[14] 2-(4-fluorophenyl)-ethylamine,[15] 1-methyl-2-(2-furyl)ethylamine,[15] 1-methyl-2-cyclohexylethylamine,[16] *N*,1-dimethyl-2-cyclohexylethylamine,[16] 1-methyl-3-ethoxypropylamine,[17] 1-methyl-2-(4-methanesulfonylaminophenyl)ethylamine.[18]

Amides were prepared by the *p*-nitrophenyl ester[19] or mixed anhydride procedure.[20] Hydrogenations of protected amides were carried out in either 90% HOAc or MeOH over 10% by weight of Pd at room temperature and up to 4 atm pressure.

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12-Carboxyeudesma-3,11(13)-diene. A Novel Sesquiterpenic Acid with a Narrow Antifungal Spectrum[1]

GAD SHTACHER AND YOEL KASHMAN

Department of Physiology and Pharmacology, Tel-Aviv University Medical School, and the Department of Chemistry, Tel-Aviv University, Tel-Aviv, Israel

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An antifungal sesquiterpenic acid, 12-carboxyeudesma-3,11(13)-diene, has been isolated from the leaves of a Mediterranean herb *Inula viscosa* Ait. *In vitro* evaluation of its potential antifungal and antibacterial properties revealed a selective antidermatophytic activity and scarcely any activity against Gram-positive and Gram-negative bacteria and mycobacteria. The presence of a free CO_2H and two olefinic bonds in the molecule is essential for its antidermatophytic activity. The *in vitro* antidermatophytic efficacy of 12-carboxyeudesma-3,11(13)-diene is very low, in the order of 1 mg/ml; however, when tested orally in mice it showed a favorable therapeutic index in the order of 10^2. These findings warrant further investigation of compounds structurally related to 12-carboxyeudesma-3,11(13)-diene, as potential antidermatophytic agents.

The isolation and partial chemical and pharmacological characterisation of a novel sesquiterpene 12-carboxyeudesma-3,11(13)-diene from the dried leaves of *Inula viscosa* Ait. are reported.

I. viscosa Ait. is a wild-growing perennial plant belonging to the family Compositae and is found abundantly along the Mediterranean shores. Folk medical tradition has ascribed antiinflammatory and antipyretic properties to this plant[2] and therefore, a search for potential medicinal products present in it was carried out. In the course of this search, attention was focussed on the selective *in vitro* antidermatophytic activity of petroleum ether extracts of the dried leaves. Consequently, the active extracts were fractionated, an active component was isolated, and its structure elucidated. To our knowledge, 12-carboxyeudesma-3,11(13)-diene is the first sesquiterpene exhibiting a specific antifungal activity.

Chemistry.—12-Carboxyeudesma-3,11(13)-diene (I) was obtained as a colorless, low-melting point compound from the petroleum ether extracts of the dried leaves of *I. viscosa* following alkaline extraction and column chromatography in a total yield of *ca.* 0.5%. Analytical results and molecular weight determination ($M^+ = 234$) by mass spectrometry established the molecular formula of I as $C_{15}H_{22}O_2$. Further support for this molecular formula was obtained from the analytical results on the cyclohexylamine salt of I, $C_{21}H_{35}NO_2$(I + $C_6H_{13}N$). The presence of an α,β-unsaturated CO_2H in I was evident from its ir spectrum as well as its uv spectrum. The nmr spectrum of I clearly indicated the presence of the following groups: $CH_3C<$, $CH_3C{=}CH$, $>C{=}CH_2$, and $-CO_2H$.

The analytical and spectral data of I presented so far strongly suggested a bicyclic sesquiterpene structure. Further support for this structure was obtained by Se dehydrogenation of I which gave, in *ca.* 25% yield, a naphthalenic hydrocarbon identified as 1-methyl-7-ethylnaphthalene (II) a compound identical in every respect with that obtained by dehydrogenation of isoalantolactone (IV). The formation of II accounts for 13 of the 15 C atoms present in I. Of the remaining two, one can be accounted for as the angular Me group which is eliminated as CH_4 during dehydrogenation, and the other as the CO_2H which is lost due to decar-

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