AMINO ACID DERIVATIVES WITH ACYL AND CHLOROACYL PROTECTING GROUPS-SYNTHESIS AND INSECT JUVENILE HORMONE ACTIVITY

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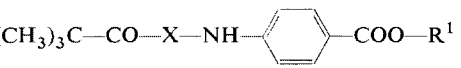
The synthesis and some biological properties of the derivatives of L-amino acids with an aliphatic side-chain, with the esters of 4-aminobenzoic acid or aromatic amines are described. These substances were substituted at the amino terminus with branched acyl groups derived from carboxylic or mono-, di- and trichlorocarboxylic acids. Many of these substances appeared to be very potent and selective analogues of juvenile hormone for an insect family *Pyrrhocoridae*. The most active substance of this series was ethyl 2-chloroisobutyryl-L-valyl-4-aminobenzoate; 2 pg of which produced a 50 per cent morphological inhibition of metamorphosis in *Dysdercus cingulatus*.

Previous reports[1-3] have shown that some derivatives of amino acids with esters of 4-aminobenzoic acid or aromatic amines inhibit metamorphosis in the insect family *Pyrrhocoridae*, and can be considered as analogues of juvenile hormone. These substances had in most cases an amino terminus substituted with urethane groups, tert-butyloxycarbonyl in particular. The most effective was the ethyl ester of tert-butyloxycarbonyl-L-valyl-4-aminobenzoic acid with the 700 pg ID-50 Morph. unit of biological activity (dose required for 50 per cent inhibition of metamorphosis in topical application) in the red cotton staining bug *Dysdercus cingulatus*.

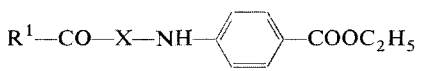
In the present report the preparation and activities of a further series of substances are described, in which branched acyl groups derived from pivalic, propionic, isobutyric and isovaleric acids replaced the urethane protecting group. Shortening of the chain by one oxygen atom resulted in some analogues in an increase in biological activity by 2–3 orders of ten.

N-Pivaloylamino acid was prepared by acylation of the corresponding amino acid with pivaloyl chloride in 1M-NaOH. Condensation of pivaloyl derivatives of L-alanine, L-valine, L-isoleucine and L-methionine with ethyl 4-aminobenzoate produced substances *I–IV*. Condensation of pivaloyl-L-alanine with the tert-butyl 4-aminobenzoate, 4-chloroaniline or 3,4-methylenedioxyaniline[4] gave compounds *VII–IX*. Reaction of pivaloyl-L-isoleucine with 3,4-methylenedioxyaniline gave substance *X*, and of pivaloyl-D,L-3-aminobutyric, acid with 3,4-methylenedioxy-

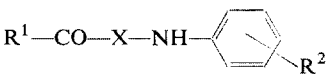
aniline or with 3-methoxyaniline gave substances *XI* and *XII*. The condensation reagent in the above reactions was dicyclohexylcarbodiimide in the presence of 1-hydroxybenzotriazole in dimethylformamide[5]. Substances *V* and *VI* were obtained by condensation of pivaloyl-L-proline and pivaloyl-2-aminoisobutyric acid with ethyl 4-aminobenzoate by the action of PCl_3 in pyridine[6]. Reaction of pivaloyl chloride in the presence of N-ethylpiperidine with the ethyl L-leucyl-4-aminobenzoate in diethyl ether gave compound *XIII*. Ethyl L-leucyl-4-aminobenzoate was obtained by the action of 36% HBr in acetic acid on the ethyl tert-butyloxycarbonyl-L-leucyl-4-aminobenzoate[3], and base was freed up from the resulting hydrobromide in a chloroformic solution of ammonia. In the syntheses of substances *XIV*–*XVI*, using dicyclohexylcarbodiimide in the presence of 1-hydroxybenzotriazole, propionic, isobutyric and isovaleric acids were condensed with the ethyl L-alanyl-4-aminobenzoate, prepared from the ethyl tert-butyloxycarbonyl-L-alanyl-4-aminobenzoate[2] by the action of trifluoroacetic acid, and freeing up of the base from the trifluoroacetate using N-ethylpiperidine.



I, $R^1 = C_2H_5$, X = Ala
II, $R^1 = C_2H_5$, X = Val
III, $R^1 = C_2H_5$, X = Ile
IV, $R^1 = C_2H_5$, X = Met
V, $R^1 = C_2H_5$, X = Pro
VI, $R^1 = C_2H_5$, X = 2-Aib
VII, $R^1 = (CH_3)_3C$, X = Ala
XIII, $R^1 = C_2H_5$, X = Leu



XIV, $R^1 = CH_3CH_2$, X = Ala
XV, $R^1 = (CH_3)_2CH$, X = Ala
XVI, $R^1 = (CH_3)_2CHCH_2$, X = Ala
XVII, $R^1 = Cl_2CH$, X = Ala
XVIII, $R^1 = Cl_3C$, X = Ala
XIX, $R^1 = CH_3ClCH$, X = Ala
XX, $R^1 = CH_3Cl_2C$, X = Ala
XXI, $R^1 = (CH_3)_2ClC$, X = Ala
XXIII, $R^1 = Cl_3C$, X = Val
XXIV, $R^1 = CH_3Cl_2C$, X = Val
XXV, $R^1 = (CH_3)_2ClC$, X = Val
XXVI, $R^1 = Cl_3C$ X = Ile



VIII, $R^1 = (CH_3)_3C$, R^2 = 4-Cl, X = Ala
IX, $R^1 = (CH_3)_3C$, R^2 = 3,4-OCH_2O, X = Ala
X, $R^1 = (CH_3)_3C$, R^2 = 3,4-OCH_2O, X = Ile
XI, $R^1 = (CH_3)_3C$, R^2 = 3,4-OCH_2O, X = DL-3-Abu
XII, $R^1 = (CH_3)_3C$, R^2 = 3-CH_3O, X = DL-3-Abu
XXII, $R^1 = Cl_3C$, R^2 = 3,4-OCH_2O, X = Ala
XXVII, $R^1 = Cl_3C$, R^2 = 3,4-OCH_2O, X = Ile

A further increase in juvenile hormone activity was obtained in many of the above analogues by substitution of their N-acyl groups by chloroacyl, derived from di- and trichloroacetic, 2-chloropropionic and 2,2'-dichloropropionic acids, and in particular from 2-chloroisobutyric acid. These compounds were prepared by condensation of the corresponding acid and amino-component by the action of $POCl_3$ in tetrahydrofurane and pyridine, through the salt stage resulting before the condensation reaction when both components are mixed in diethyl ether[7]. All amino components were freed up from their N-tert-butyloxycarbonyl derivatives, as described elsewhere[2,3], in the same manner as ethyl L-leucyl-4-aminobenzoate in the preparation of substance *XIII*. An exception was L-isoleucine-3,4-methylenedioxyanilid, which was freed up analogously from the N-benzyloxycarbonyl derivative. This intermediate product was prepared by condensation of benzyloxycarbonyl-L-isoleucine[8] with 3,4-methylenedioxyaniline by the action of dicyclohexylcarbodiimide in dimethylformamide.

Condensation of di- and trichloroacetic, 2-chloropropionic, 2,2'-dichloropropionic and 2-chloroisobutyric acids with ethyl L-alanyl-4-aminobenzoate yielded

TABLE I
Pivaloylamino Acid Derivatives

Substance (% yield)	M.p., °C solvent	Formula (m.w.)	Calculated/Found % C	% H	% N	$[\alpha]_D$ (c)
Piv-L-Ala[a]	130–132	$C_8H_{15}NO_3$	55·47	8·73	8·09	−22·3
(55)	[b]	(173·2)	55·72	8·80	7·83	(0·50)
Piv-L-Val	138–140	$C_{10}H_{19}NO_3$	59·68	9·52	6·96	−9·3
(59)	[b]	(201·3)	59·79	9·43	6·68	(0·31)
Piv-L-Ile	93–95	$C_{11}H_{21}NO_3$	61·37	9·83	6·51	−5·8
(56)	[c]	(215·3)	61·61	9·61	6·72	(0·50)
Piv-L-Met	71–73	$C_{10}H_{19}NO_3S$	51·48	8·21	6·00	−32·3
(61)	[b]	(233·3)	51·27	8·29	6·18	(0·52)
Piv-L-Pro	128–130	$C_{10}H_{17}NO_3$	60·28	8·60	7·03	−54·9
(55)	[b]	(199·3)	60·37	8·61	6·91	(0·51)
Piv-DL-3-Abu	123–125	$C_9H_{17}NO_3$	57·73	9·15	7·48	—
(38)	[b]	(187·2)	57·45	9·27	7·52	
Piv-2-Aib	178–180	$C_9H_{17}NO_3$	57·73	9·15	7·48	—
(25)	[c]	(187·2)	58·01	9·12	7·31	

[a] Symbols for amino acids according to IUPAC-IUB (ref.[9]), Aib amino isobutyric acid, Piv pivaloyl; [b] ethyl acetate–light petroleum; [c] aqueous ethanol.

TABLE II
Substances *I*—*XXVII*

Substance (% yield) methods	Acyl component amino component	M.p., °C solvent	Formula (m.w.)	Calculated/Found % C	% H	% N	% Cl	$[\alpha]_D$ (*c*)
I (48)	Piv[a]-L-Ala	166—168	$C_{17}H_{24}N_2O_4$	63·73	7·55	8·75	—	−1·0
A	PABE	*b*	(320·4)	63·65	7·77	8·75		(0·50)
II (30)	Piv-L-Val	162—164	$C_{19}H_{28}N_2O_4$	65·49	8·10	8·04	—	−0·5
A	PABE	*b*	(348·4)	65·78	8·16	7·95		(0·48)
III (40)	Piv-L-Ile	149—151	$C_{20}H_{30}N_2O_4$	66·27	8·34	7·73	—	−1·0
A	PABE	*c*	(362·5)	66·36	8·11	7·97		(0·50)
IV (48)	Piv-L-Met	145—147	$C_{19}H_{28}N_2O_4S$	59·79	7·40	7·34	—	−1·0
A	PABE	*b*	(380·5)	60·01	7·35	7·22		(0·51)
V (49)	Piv-L-Pro	115—117	$C_{19}H_{26}N_2O_4$	65·84	7·66	8·01	—	−2·0
C	PABE	*d*	(346·4)	65·87	7·77	8·07		(0·50)
VI (75)	Piv-2-Aib	91—93	$C_{18}H_{26}N_2O_4$	64·65	7·84	8·38	—	—
C	PABE	*b*	(334·4)	64·24	7·87	8·18		
VII (30)	Piv-L-Ala	149—151	$C_{19}H_{28}N_2O_4$	65·49	8·10	8·04	—	−1·7
A	PABBu[t]	*d*	(348·4)	65·26	8·09	7·89		(0·50)
VIII (43)	Piv-L-Ala	157—160	$C_{14}H_{19}ClN_2O_2$	59·46	6·77	9·91	12·54	+0·4
A	4-ClA	*c*	(282·8)	59·85	6·96	9·78	12·74	(0·51)
IX (48)	Piv-L-Ala	121—123	$C_{15}H_{20}N_2O_4$	61·63	6·90	9·58	—	+0·2
A	3,4-MDA	*d*	(292·3)	61·62	7·10	9·52		(0·50)
X (78)	Piv-L-Ile	173—175	$C_{18}H_{26}N_2O_4$	64·65	7·84	8·38	—	+8·1
A	3,4-MDA	*b*	(334·4)	64·76	7·91	8·29		(0·50)
XI (30)	Piv-DL-3-Abu	165—166	$C_{16}H_{22}N_2O_4$	62·73	7·24	9·15	—	—
A	3·4-MDA	*b*	(306·4)	63·02	7·43	9·25		
XII (59)	Piv-DL-3-Abu	150—153	$C_{16}H_{24}N_2O_3$	65·73	8·27	9·58	—	—
A	3-MOA	*b*	(292·4)	65·83	8·42	9·71		
XIII (87)	PivCl	180—182	$C_{20}H_{30}N_2O_4$	66·27	8·34	7·73	—	+17·2
D	L-Leu-PABE	*b*	(362·5)	66·25	8·45	7·73		(0·52)

XIV (69)	$CH_3CH_2CO_2H$	145—147	$C_{15}H_{20}N_2O_4$	61·63	6·90	9·58	—	−16·4
A	L-Ala-PABE	*c*	(292·3)	61·90	6·90	9·53		(0·50)
XV (43)	$(CH_3)_2CHCO_2H$	178—181	$C_{16}H_{22}N_2O_4$	62·72	7·24	9·15	—	−16·9
A	L-Ala-PABE	*c*	(306·4)	62·96	7·44	9·35		(0·51)
XVI (38)	$(CH_3)_2CHCH_2CO_2H$	148—150	$C_{17}H_{24}N_2O_4$	63·72	7·55	8·75	—	−9·4
A	L-Ala-PABE	*c*	(320·4)	63·86	7·65	8·91		(0·50)
XVII (63)	Cl_2CHCO_2H	197—200	$C_{14}H_{16}Cl_2N_2O_4$	48·43	4·65	8·07	20·42	−13·4
B	L-Ala-PABE	*b*	(347·2)	48·56	4·95	8·27	20·34	(0·50)
XVIII (44)	Cl_3CCO_2H	185—187	$C_{14}H_{15}Cl_3N_2O_4$	44·06	3·96	7·38	27·87	−2·3
B	L-Ala-PABE	*b*	(381·7)	44·18	3·99	7·05	27·25	(0·31)
XIX (57)	$CH_3ClCHCO_2H$	152—155	$C_{15}H_{19}ClN_2O_4$	55·13	5·86	8·58	10·85	−29·5
B	L-Ala-PABE	*c*	(326·8)	55·42	6·08	8·90	10·67	(0·20)
XX (52)	$CH_3Cl_2CCO_2H$	146—147	$C_{15}H_{18}Cl_2N_2O_4$	49·87	5·02	7·76	19·63	−0·2
B	L-Ala-PABE	*b*	(361·2)	50·12	5·01	7·85	19·63	(0·31)
XXI (48)	$(CH_3)_2ClCCO_2H$	112—114	$C_{16}H_{21}ClN_2O_4$	56·39	6·21	8·22	10·40	−2·5
B	L-Ala-PABE	*e*	(340·8)	56·62	6·07	8·12	10·05	(0·50)
XXII (75)	Cl_3CCO_2H	96—98	$C_{12}H_{11}Cl_3N_2O_4$	40·76	3·14	7·92	30·08	−7·3
B	L-Ala-3,4-MDA	*d*	(353·6)	41·03	3·03	7·94	29·89	(0·36)
XXIII (48)	Cl_3CCO_2H	82—85	$C_{16}H_{19}Cl_3N_2O_4$	46·90	4·67	6·84	25·96	+20·2
B	L-Val-PABE	*d*	(409·7)	47·21	4·93	6·64	25·48	(0·55)
XXIV (42)	$CH_3Cl_2CCO_2H$	107—110	$C_{17}H_{22}Cl_2N_2O_4$	52·43	5·70	7·20	18·23	+23·5
B	L-Val-PABE	*d*	(389·3)	52·70	5·71	7·25	18·14	(0·50)
XXV (34)	$(CH_3)_2ClCCO_2H$	73—75	$C_{18}H_{25}ClN_2O_4$	58·61	6·83	7·59	9·61	+30·0
B	L-Val-PABE	*f*	(368·9)	58·64	6·86	7·50	9·53	(0·28)
XXVI (51)	Cl_3CCO_2H	sirup[g]	$C_{17}H_{21}Cl_3N_2O_4$	48·18	5·00	6·61	25·10	+8·2
B	L-Ile-PABE		(423·7)	48·02	5·17	6·41	24·81	(0·52)
XXVII (68)	Cl_3CCO_2H	163—166	$C_{15}H_{17}Cl_3N_2O_4$	45·53	4·33	7·08	26·88	+10·1
B	L-Ile-3,4-MDA	*b*	(395·7)	45·81	4·29	6·96	26·93	(0·50)

[a] Symbols: Piv pivaloyl, Aib amino isobutyric acid, PABE ethyl 4-aminobenzoate, PABBu[t] tert-butyl 4-aminobenzoate, ClA chloroaniline, MDA methylenedioxyaniline, MOA methyloxyaniline; [b] aqueous ethanol; [c] ethyl acetate; [d] ether–light petroleum; [e] ethyl acetate–light petroleum; [f] light petroleum; [g] purified by silica gel TLC (30 μ in ether–benzene system 1 : 1), structure confirmed by mass spectrometry.

substances *XVII*–*XXI*. Substance *XXII* resulted from the reaction of trichloroacetic acid with the 3,4-methylenedioxyanilide of L-alanine. Condensation of trichloroacetic, 2,2'-dichloropropionic and 2-chloroisobutyric acids with the ethyl L-valyl-4-aminobenzoate gave substances *XXIII*–*XXV*, and of trichloroacetic acid with the ethyl L-isoleucyl-4-aminobenzoate or with the 3,4-methylenedioxyanilide of L-isoleucine gave substances *XXVI*–*XXVII*.

All the compounds listed were bioassayed for juvenile hormone activity on the freshly ecdysed last instar larvae of *Pyrrhocoris apterus* L., *Dysdercus cingulatus* F. (*Pyrrhocoridae*), and *Graphosoma italicum* (MÜLL.) (*Pentatomidae*); further assays were carried on with the freshly ecdysed pupae of *Tenebrio molitor* L. The samples were applied topically in 1 μl of acetone and the activity was evaluated according to the degree of morphological inhibition of metamorphosis (ID-50 Morph. units). As all the substances were completely inactive in doses up to 500 μg per spec. on *Graphosoma* and *Tenebrio* we have quoted in Table III only their activity on the *Pyrrhocorid* bugs.

The most active substance was ethyl 2-chloroisobutyryl-L-valyl-4-aminobenzoate which caused appearance of malformed adultoid intermediates in doses as small as 2 pg per spec. in *Dysdercus*. This is the highest hormonal activity ever recorded in this relatively sensitive insect species.

TABLE III

Juvenile Hormone Activity of Compounds *I* to *XXVI* Assayed on Two Species of *Pyrrhocoridae*
The values indicate ID-50 Morph. units of activity in μg per spec.

Compound	*Pyrrhocoris apterus*	*Dysdercus cingulatus*	Compound	*Pyrrhocoris apterus*	*Dysdercus cingulatus*
I	0·00004	0·00004	*XV*	—	0·008
II	0·00004	0·00004	*XVI*	—	0·03
III	0·003	0·0001	*XVII*	—	>50
IV	—	0·1	*XVIII*	0·001	0·0008
V	0·008	0·001	*XIX*	10	10
VI	10	10	*XX*	—	0·0001
VII	—	10	*XXI*	0·0001	0·00001
VIII	100	1—100	*XXIII*	—	0·000009
XI	—	30	*XXIV*	—	0·000005
XIII	—	0·01	*XXV*	—	0·000002
XIV	—	10	*XXVI*	—	0·001

EXPERIMENTAL

Melting points were determined on a Kofler block. Samples for elemental analysis were dried for several hours over P_2O_5 at room temperature and 1 Torr. Evaporation was done in a rotating apparatus (water pump, bath temperature about 35°C). Mixtures containing dimethylformamide were evaporated at 1 Torr. Optical rotations in dimethylformamide were determined on a photoelectric polarimeter at 23°C. Electrophoresis of intermediary products was carried out after removal of tert-butyloxycarbonyl protecting group with trifluoroacetic acid or 36% HBr in acetic acid, on Whatman 3 MM paper for 45 min at a potential drop of 20 V/cm, in 1M acetic acid (pH 2·4) and pyridine–acetate (pH 5·7) buffer, with ninhydrin detection. The mass spectrogram of substance *XXVI* was obtained on the MS 902 AEI instrument.

Preparation of Pivaloylamino Acids (Table I)

To a solution of amino acid (10 mM) in 1M-NaOH (10 ml) pivaloyl chloride (2·4 ml; 20 mM) and 1M-NaOH (20 ml) were added dropwise simultaneously under mixing at 0°C. The mixture was stirred for 1 h at 0°C, 1 h at room temperature, washed with diethyl ether (2 × 50 ml) and acidified with 1M-HCl. If a crystalline product separated out, it was filtered and washed with water (3 × 100 ml), if an oil separated out, it was extracted with ethyl acetate (3 × 50 ml), pooled extracts were washed with water (3 × 100 ml) and after drying with sodium sulphate the solvent was distilled off. The remaining oil crystallised from light petroleum.

Preparation of Substances *I*—*XXVII* (Table II)

Method A (ref.[5]): 1-Hydroxybenzotriazol (11 mM) and dicyclohexylcarbodiimide (11 mM) were added at −7°C, with stirring, to a solution of the acyl component (10 mM) in dimethylformamide (10 ml). After 30 min, with no change in temperature, the amino component was added (10 mM) and the mixture was maintained at 0°C for 24 h. The dicyclohexylurea which separated out was then filtered and the filtrate was concentrated under reduced pressure. The dried substance was dissolved in ethyl acetate (50 ml) and the solution was washed with 1M-HCl (in the case of tert-butyl ester *VII*, with 10% citric acid), water, 5% Na_2CO_3 and water, and after drying with sodium sulphate ethyl acetate was distilled off under reduced pressure. The raw product was either crystalline or a syrup which crystallised at 3°C under light petroleum.

Method B (ref.[7]): To a solution of the amino component (10 mM) in ether (25 ml) (in the case of ethyl L-valyl-4-aminobenzoate, 100 ml ether) a solution of the acid (10 mM) in ether (5 ml) was added dropwise. Only rarely did the salt separate out in crystalline state, so that the solvent was distilled off and the remainder was dissolved in tetrahydrofurane (30 ml) and $POCl_3$ (1 ml) was added. After cooling to −15°C, pyridine (2·4 ml) was added with stirring and temperature was allowed gradually to reach the room temperature, at which the mixture was left for 1 h. The tetrahydrofurane was then distilled off and the oily residue was extracted with ethyl acetate (3 × 50 ml). After washing the pooled extracts with 5% Na_2CO_3, 1M-HCl and water and drying with sodium sulphate, ethyl acetate was distilled off and the resulting syrup crystallized on adding to light petroleum.

Method C (ref.[6]): PCl_3 (0·45 ml) was added at −20°C to a solution of the amino-component (10 mM) in pyridine (25 ml) and after 30 min at −20°C and 30 min at room temperature the acyl component was added (10 mM). The mixture was refluxed for 3 h and after cooling and filtration with charcoal pyridine was distilled off under reduced pressure. The residue was dissolved in ethyl acetate and the solution was shaken up with 1M-HCl, water, 5% Na_2CO_3, and water. After drying with sodium sulphate, ethyl acetate was distilled off and crude crystals resulted.

Method D: N-Ethylpiperidine (1·37 ml) was added to a solution of the amino-component (10 mM) in dioxane (14 ml) and ether (7 ml), and with stirring at 0°C pivaloyl chloride (10 mM) was dropped in. The mixture was left 30 min at 3°C, the N-ethylpiperidine hydrochloride was filtered off and washed with diethyl ether. The filtrate was diluted with ethyl acetate and washed with 1M-HCl, 5% Na_2CO_3 and water, and dried with sodium sulphate. After distilling off the solvent a crystalline product resulted.

Benzyloxycarbonyl-L-isoleucine-3,4-methylenedioxyanilide

A solution of the dicyclohexylammonium salt of benzyloxycarbonyl-L-isoleucine (7·40 g) in 50% ethanol (100 ml) was shaken up for 30 min with Dowex 50W (50 ml) and after filtration of the resin, the solvent was distilled off, the remnant dissolved 3 × in benzene which was distilled off, and an oily benzyloxycarbonyl-L-leucine resulted. It was dissolved in dimethylformamide (45 ml) and at −7°C, with stirring, dicyclohexylcarbodiimide (2·47 g) and after 30 min at this temperature, 3,4-methylenedioxyaniline (2·25 g) were added. The mixture was left overnight at 0°C. Dicyclohexylurea was filtered off and dimethylformamide was distilled off. The residue was washed with water, 20% citric acid, 5% Na_2CO_3 and water, and after drying over P_2O_5 there was a yield of 4·82 g of crude product, m.p. 195–201°C. Recrystallization from aqueous ethanol gave a yield of 4·75 g (75%), m.p. 200–203°C. For $C_{21}H_{24}N_2O_5$ (384·4) calculated: 65·61% C, 6·29% H, 7·28% N; found: 65·59% C, 6·25% H, 7·32% N.

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