PREPARATIONS OF SOME *para*-SUBSTITUTED N-ALKOXYALKYLANILINES AND N-ALKOXYACYLANILIDES*

V.JAROLÍM and F.ŠORM

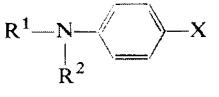
Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6

Received September 15th, 1975

As bioanalogues of the insect juvenile hormone, numerous N-alkoxyalkylanilines and N-alkoxyacylanilides have been prepared with various alkoxyalkyl or alkoxyacyl groups and various *para*-substituents.

In connection with preparation of some insect juvenile hormone bioanalogues based on N-geranyl and N-geranoyl derivatives of *para*-substituted aromatic amines in this Laboratory[1-4], attention has been now paid to the synthesis of *para*-substituted N-alkoxyalkylanilines and N-alkoxyacylanilides. Some of the substances and procedures have been reported in our patent applications[5,6].

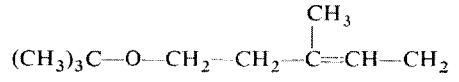
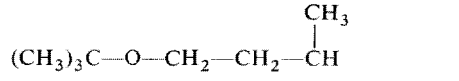
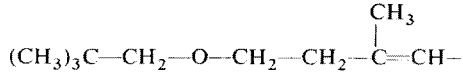
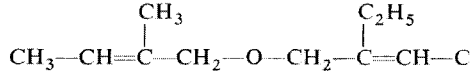
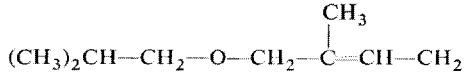
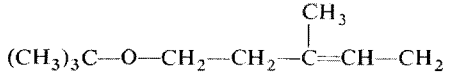
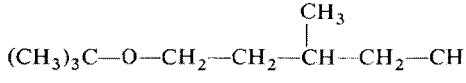
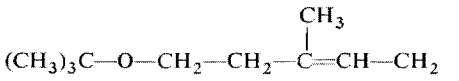
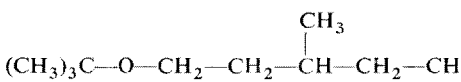
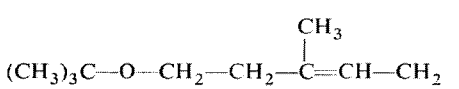
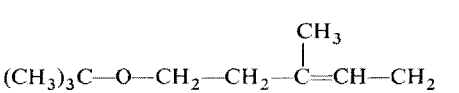
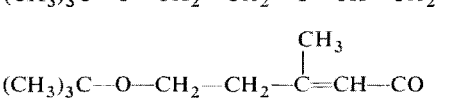
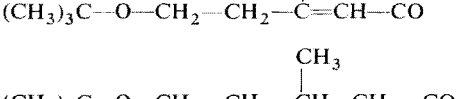
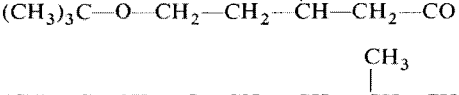
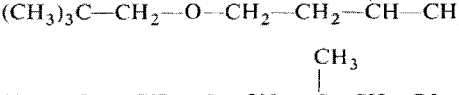
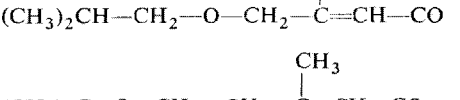
In the preparation of N-alkoxyalkylanilines, the earlier reported[7,8] branched alkoxy alcohols as starting compounds were transformed by the action of phosphorus tribromide in the presence of pyridine or on treatment[9] with bromine and triphenylphosphine** into the corresponding alkoxyalkyl bromides which afforded the analogues *I*–*XII* by reaction with the appropriate *para*-substituted aniline, N-methylaniline or trifluoroacetanilide (either directly or after saponification of trifluoroacetates). The reaction of alkoxyalkyl bromides with primary amines was accompanied by the formation of N,N-disubstituted anilines as by-products.



	R^1	R^2	X
I	$(CH_3)_3C-O-CH_2-CH_2-C(CH_3)=CH-CH_2$	$-CH_3$	$COOCH_3$

* Part XXVIII in the series Natural and Synthetic Materials with the Insect Hormone Activity; Part XXVII: This Journal *41*, 1066 (1976).

** The amount of bromine in ref.[7] is in error. The data should read 0·0202 mol of bromine and 0·0203 mol of triphenylphosphine per 0·02 mol of the appropriate alcohol.

II		—CH_3	$COOCH(CH_3)_2$
III		—CH_3	$COOCH_3$
IV		—CH_3	$COOCH_3$
V		—CH_3	$COOCH(CH_3)_2$
VI		—CH_3	$COOCH_3$
VII		H	$COOCH_3$
VIII		H	$COOCH_3$
IX		H	$CO—CH_3$
X		H	$CO—CH_3$
XI		H	CH_3
XII		H	Cl
XIII		CH_3	$COOCH_3$
XIV		CH_3	$COOCH_3$
XV		CH_3	$COOCH_3$
XVI		CH_3	$COOCH_3$
XVII		H	$COOCH_3$

XVIII $(CH_3)_3C-O-CH_2-CH_2-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-CO$ H $COOCH_3$

XIX $(CH_3)_3C-CH_2-O-CH_2-CH_2-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-CO$ H $COOCH_3$

In the preparation of N-alkoxyacylanilides, the earlier reported[7] esters of branched alkoxy acids as starting compounds were saponified and the resulting free acids converted into alkoxyacyl chlorides by the action of thionyl chloride or thionyl chloride and pyridine[10]. By reaction with appropriate *para*-substituted anilines or N-methylanilines, the alkoxyacyl chlorides afforded the analogues *XIII*–*XIX*. In the adsorption chromatography of compound *XIII*, a successful separation of the geometrical isomers *XIIIa* and *XIIIb* and a mixture of the isomers *XIIIc* and *XIIId* with shifted double bond was accomplished. Thus, methyl *cis*- and *trans*-4-(methyl-(5-(1,1-dimethylethoxy)-3-methyl-2-pentenoyl)amino)benzoate (*XIIIa* and *XIIIb*, resp.), were isolated along with a mixture of methyl 4-(methyl-(5-1,1-dimethylethoxy)-3-methylenepentanoyl)amino)benzoate (*XIIIc*) and methyl 4-(methyl-(5-(1,1-dimethylethoxy)-3-methyl-3-pentenoyl)amino)benzoate (*XIIId*).

EXPERIMENTAL

The IR spectra were taken in tetrachloromethane. The NMR spectra were measured in deuteriochloroform; tetramethylsilane was used as internal standard; chemical shifts are given in δ (p.p.m.) and coupling constants in Hz. Column chromatography was performed on the Pitra silica gel (produced by Service Laboratories of this Institute) partially deactivated by the addition of 12% water, and on neutral alumina (Reanal, Hungary) of the Brockmann activity III. Gas chromatography was carried out on a Pye Argon Chromatograph apparatus with a radioactivity ionisation detector. Samples for elemental analysis were dried at 50°C/10 Torr for one hour.

Preparation of Compounds *I*–*VI*, *XI*, and *XII*

A mixture of the corresponding alkoxyalkyl bromide (5 mmol), the appropriate amine (5 mmol), and anhydrous potassium carbonate (0·4 g) in dimethylformamide (10–15 ml) was heated at 70–80°C for 2–16 h. The reaction course was checked by thin-layer chromatography. When the starting bromide disappeared or when the composition of the reaction mixture remained constant, the mixture was poured into water, and the product extracted with ether. Usual work-up afforded the crude product which was purified by chromatography on silica gel (40–60 parts by weight) with the use of light petroleum–ether (9 : 1 with esters and 12 : 1 with compounds *XI* and *XII*). Yields, 35–55%. In chromatography of compounds *XI*, the forrun contained 4-methyl-(bis(5-(1,1-dimethylethoxy)-3-methyl-2-pentenyl)amino)benzene.

This procedure was used to prepare the methyl ester (*I*) and isopropyl ester (*II*) of 4-(methyl-(5-(1,1-dimethylethoxy)-3-methyl-2-pentenyl)amino)benzoic acid, methyl 4-(methyl-(3-(1,1-dimethylethoxy)-1-methylpropyl)amino)benzoate (*III*), methyl 4-(methyl-(5-(2,2-dimethylpropoxy)-3-methyl-2-pentenyl)amino)benzoate (*IV*), isopropyl 4-(methyl-(3-((2-methyl-2-butenyloxy)me-

thyl-2-pentenyl)amino)benzoate (*V*), methyl 4-(methyl-(4-(2-methylpropoxy)-3-methyl-2-butenyl)-amino)benzoate (*VI*), 4-methyl-(1-(5-(1,1-dimethylethoxy)-3-methyl-2-pentenyl)amino)benzene (*XI*), and 4-chloro-(1-(5-(1,1-dimethylethoxy)-3-methyl-2-pentenyl)amino)benzene (*XII*).

Preparation of Compounds *VII*—*X*

A suspension of sodium hydride (0·096 g) in dimethylformamide (5 ml) was treated with stirring at 20°C with a solution of the corresponding substituted trifluoroacetanilide (4 mmol) in dimethylformamide (10 ml) and the whole mixture stirred for 30 min. The appropriate alkoxyalkyl bromide (4·2 mmol) was then added dropwise and the resulting mixture heated at 80°C for 4—12h. The reaction course was checked by thin-layer chromatography. When the reaction was over, the mixture was poured into water, extracted with ether, and the extract processed as usual to afford the corresponding trifluoroacetyl derivative which was dissolved in methanol (20 ml). The solution was allowed to stand with 25% aqueous potassium hydroxide (1 ml) for 2—4 h at room temperature, diluted with water, extracted with ether, and the extract processed as usual to afford a crude product which was purified by chromatography on silica gel (40—50 parts by weight) with the use of light petroleum–ether (15 : 85 with esters and 25 : 75 with ketones) as eluant. Yields, 50—75%.

This procedure was used to prepare methyl 4-(5-(1,1-dimethylethoxy)-3-methyl-2-pentenyl)-aminobenzoate (*VII*), methyl 4-(5-(1,1-dimethylethoxy)-3-methylpentyl)aminobenzoate (*VIII*), 4-(5-(1,1-dimethylethoxy)-3-methyl-2-pentenyl)aminoacetophenone (*IX*), and 4-(5-(2,2-dimethylpropoxy)-3-methylpentyl)aminoacetophenone (*X*).

Preparation of Compounds *XIII*, *XIV*, *XVI*—*XVIII*

Ethyl ester of the corresponding alkoxyalkanoic acid or alkoxyalkenoic acid (0·02 mol) was refluxed with 2% ethanolic sodium hydroxide (100 ml) for 1 h, the ethanol for the most part evaporated, the residue diluted with water, and processed as usual to afford the crude acid which was directly used in the subsequent step. Yields, 95—98%.

To a precooled solution of the crude alkoxyalkanoic acid or alkoxyalkenoic acid (0·015 mol), pyridine (1·2 g), and benzene (20 ml) there was added at 10—20°C thionyl chloride (1·8 g) and the mixture kept at room temperature for 2—3 h. A solution containing the appropriate substituted amine (0·015 mol), pyridine (1·2 g), and benzene (10—20 ml) was then added, the whole mixture kept at room temperature for 5—10 h, poured into water, and extracted with ether. The extract was washed with 10% aqueous sulfuric acid, water, aqueous sodium hydrogen carbonate, and water again, and evaporated. The crude residue was purified by chromatography on silica gel (30—50 parts by weight) with the use of light petroleum–ether (1 : 1) as eluant. Yields, 65—70%.

Compound *XVII* (obtained by chromatography on silica gel) was crystallised up to the m.p. 118—119°C (ether). In chromatography of compound *XIII*, the frontal fractions afforded the homogeneous *cis*-isomer *XIIIa* while the homogeneous *trans*-isomer *XIIIb* was obtained from middle fractions. The rear fractions contained a mixture (about 15% of the purified substance) of isomers *XIIIc* and *XIIId*. For purposes of elemental analysis, all products (except for compound *XVII*) prepurified by chromatography on silica gel were rechromatographed on neutral alumina (50 parts by weight) with the use of light petroleum–ether (1 : 1) as eluant.

The above procedure was used to prepare methyl 4-(methyl-(5-(1,1-dimethylethoxy)-3-methyl--2-pentenoyl)amino)benzoate (*XIII*), methyl 4-(methyl-(5-(1,1-dimethylethoxy)-3-methylpentanoyl)amino)benzoate (*XIV*), methyl 4-(methyl-(4-(2-methylpropoxy)-3-methyl-2-butenoyl)amino)-

benzoate (*XVI*), methyl 4-(5-(1,1-dimethylethoxy)-3-methyl-2-pentenoyl)aminobenzoate (*XVII*), and methyl 4-(5-(1,1-dimethylethoxy)-3-methylpentanoyl)aminobenzoate (*XVIII*).

Preparation of Compounds *XV* and *XIX*

The corresponding esters of alkoxyalkanoic acids were saponified as stated above (Preparation of compounds *XIII*, *XIV*, *XVI*—*XVIII*). Thionyl chloride (0·9 g) was then added to the solution of the crude alkoxyalkanoic acid (5 mmol) in benzene (10 ml) and the mixture kept at 20°C for 4 h. The excess reagent and benzene were then evaporated, the residue diluted with fresh benzene (10 ml), and treated with a solution containing the appropriate aniline derivative (5 mmol), pyridine (0·4 g), and benzene (10—15 ml). The resulting mixture was then processed analogously to the above preparation. Yields, 50—60%.

This procedure was used to prepare methyl 4-(methyl-(5-(2,2-dimethylpropoxy)-3-methylpentanoyl)amino)benzoate (*XV*) and methyl 4-(5-(2,2-dimethylpropoxy)-3-methylpentanoyl)-aminobenzoate (*XIX*).

Characterisation of Compounds *I*—*XIX*

The structure of compounds *I*—*XIX* (see Table I) was confirmed by elemental analysis and in some cases by IR and ^{1}H-NMR spectra. The homogeneity was checked by thin-layer chromatography on silica gel and gas chromatography on Gas-Chrom Q impregnated with 3% SE-30 (temperature, 190—210°C).

The IR spectra of compounds *I*, *V*, *VII*, and *VIII* contained absorption bands due to an ester group attached to the aromatic ring (at about 1710, 1610, 1525, and 1280 cm^{-1}) and a band of the ethereal oxygen atom (1085—1100 cm^{-1}). The band at 3440 cm^{-1} in spectra of compounds *VII* and *VIII* indicates the presence of a —NH— group in the molecule. The IR spectra of compounds *XIII*, *XIV*, *XV*, *XVIII*, and *XIX* exhibited bands belonging to the methyl ester group attached to the aromatic ring (at about 1720—1730, 1610, 1580, 1510, 1440, and 1280 cm^{-1}). The spectra of compounds *XIII*, *XIV*, and *XV* contained a band corresponding to a N-substituted anilide (1665 cm^{-1}). In spectra of compounds *XVIII* and *XIX* bands were observed attributable to the presence of a —CO—NH— group in a non-associated state (3445, 1705, and 1520 cm^{-1}).

The structure of compounds *V*, *XIIIa*, and *XIIIb* and composition of the mixture of compounds *XIIIc* and *XIIId* were confirmed by ^{1}H-NMR spectra. Compound *V*: $C_{(4)}$—CH_3 1·1 (m) (3 H); $C_{(2'')}$ + $C_{(3''')}$ 2 × —CH_3 1·58 (m) (6 H); $H_{(1)}$ 2·1 (m) (2 H); N—CH_3 2·94 (s) (3 H); $H_{(1')}$ + + $H_{(1'')}$ 3·9 (m) (4 H); $H_{(2)}$ + $H_{(3'')}$ 5·36 (m) (2 H); aromatic 6·69 and 7·90 (4 H); isopropyl ester 2 × —CH_3 1·30 (d), J = 6·7 (6 H); —CH— 5·12 (m), J = 6·7 (1 H). The *cis*-isomer *XIIIa*: $C_{(1')}$ 3 × —CH_3 1·18 (s) (9 H); $C_{(3)}$ —CH_3 1·75 (d), J = 1·5 (3 H); $H_{(4)}$ 2·76 (bt), $J \sim 1$ and J = 6·5 (2 H); N—CH_3 3·33 (s) (3 H); $H_{(5)}$ 3·56 (t), J = 6·5 (2 H); —CH_3 (ester) 3·91 (s) (3 H); $H_{(2)}$ 5·52 (m) (1 H); aromatic 7·35 and 8·05, J = 9·0 (4 H). the *trans*-isomer *XIIIb*: $C_{(1')}$ 3 × —CH_3 1·08 (s) (9 H); $C_{(3)}$ —CH_3 2·11 (d), J = 1·5 (3 H); $H_{(4)}$ 2·17 (bt), $J \sim 1·0$ and J = = 6·0 (2 H); $H_{(5)}$ 3·32 (t), J = 6 (2 H); N—CH_3 3·33 (s) (3 H); —CH_3 (ester) 3·91 (s) (3 H); $H_{(2)}$ 5·57 (m) (1 H); aromatic 7·35 and 8·05, J = 9·0 (4 H). Methyl 4-(methyl-(5-(1,1-dimethylethoxy)-3-methylenepentanoyl)amino)benzoate (*XIIIc*): $C_{(1')}$ 3 × —CH_3 1·12 (s) (9 H); $H_{(4)}$ 2·21 (bt), $J \sim 1·0$; $H_{(2)}$ 2·97 (b); N—CH_3 3·0 (s) (3 H); $H_{(5)}$ 3·33 (t), J = 6·5; —CH_3 (ester) 3·93 (s) (3 H); $C_{(3)}$ =CH_2 4·84 (bd), J = 14·0; aromatic 7·27 and 8·09 (4 H). Methyl 4-(methyl--(5-(1,1-dimethylethoxy)-3-methyl-3-pentenoyl)amino)benzoate (*XIIId*) differed in the following data: $C_{(3)}$ —CH_3 1·74 (d), J = 1·5; $H_{(5)}$ 3·59 (d), $J \sim 6·0$; $H_{(4)}$ 5·42 (bt), $J \sim 6·0$.

TABLE I

Elemental Analyses of Compounds *I*—*XIX*

Compound	Formula (M.w.)	Calculated/Found		
		% C	% H	% N
I	$C_{19}H_{29}NO_3$	71·44	9·15	4·39
	(319·4)	71·27	8·94	4·21
II	$C_{21}H_{33}NO_3$	72·58	9·57	4·03
	(347·5)	72·48	9·65	4·06
III	$C_{17}H_{27}NO_3$	69·59	9·28	4·77
	(293·4)	69·27	9·13	4·79
IV	$C_{20}H_{31}NO_3$	72·02	9·37	4·20
	(333·5)	72·25	9·33	4·30
V	$C_{22}H_{33}NO_3$	73·50	9·25	3·90
	(359·5)	72·89	9·11	4·00
VI	$C_{18}H_{27}NO_3$	70·79	8·91	4·59
	(305·4)	70·89	8·84	4·67
VII	$C_{18}H_{27}NO_3$	70·79	8·91	4·59
	(305·4)	70·75	8·96	4·43
VIII	$C_{18}H_{29}NO_3$	70·33	9·51	4·56
	(307·4)	70·14	9·56	4·53
IX	$C_{18}H_{27}NO_2$	74·70	9·41	4·84
	(289·4)	74·61	9·50	4·70
X	$C_{19}H_{31}NO_2$	74·72	10·23	4·59
	(305·4)	75·12	10·07	4·50
XI	$C_{17}H_{27}NO$	78·11	10·41	5·36
	(261·4)	78·33	10·56	5·43
XII	$C_{16}H_{24}ClNO$[a]	68·19	8·59	4·97
	(281·8)	68·21	8·70	5·02
XIIIa	$C_{19}H_{27}NO_4$	68·44	8·16	4·20
	(333·4)	68·40	7·90	4·14
XIIIb	$C_{19}H_{27}NO_4$	68·44	8·16	4·20
	(333·4)	68·20	8·26	4·03
XIIIc,d	$C_{19}H_{27}NO_4$	68·44	8·16	4·20
	(333·4)	68·31	8·14	4·24
XIV	$C_{19}H_{29}NO_4$	68·04	8·72	4·18
	(335·4)	68·25	8·78	4·20
XV	$C_{20}H_{31}NO_4$	68·73	8·94	4·01
	(349·5)	68·59	8·83	4·14

TABLE I
(*Continued*)

Compound	Formula (M.w.)	Calculated/Found		
		% C	% H	% N
XVI	$C_{18}H_{25}NO_4$	67·69	7·89	4·39
	(319·4)	67·66	7·84	4·65
XVII	$C_{18}H_{25}NO_4$	67·69	7·89	4·39
	(319·4)	67·77	7·67	4·34
XVIII	$C_{18}H_{27}NO_4$	67·26	8·47	4·36
	(321·4)	66·94	8·58	4·44
XIX	$C_{19}H_{29}NO_4$	68·04	8·72	4·18
	(335·4)	68·26	8·67	4·17

[a] Calculated: 12·58% Cl; found: 12·67% Cl.

Biological Activity of Compounds *I*—*XIX**

The insect juvenile hormone activity of compounds *I*—*XIX* was expressed in ID-50 Morph units designating such an amount of the test substance in microgrammes per specimen which when topically applied to the last instar larvae causes formation of half-imaginal species. The N-alkoxyalkylanilines *I*—*XII* were active on *Dysdercus cingulatus* (activity range, 1·0—0·0005), weakly active or inactive on *Graphosoma italicum*, and inactive on *Tenebrio molitor*. The N-alkoxyacylanilides *XIII*—*XIX* were active on *Dysdercus cingulatus* (50·0—0·005) or inactive on *Graphosoma italicum* and *Tenebrio molitor*.

Elemental analyses were performed in the Analytical Department (Dr J. Horáček, Head) of this Institute by Mrs A. Froňková, Mrs Y. Černá, and Mr V. Štěrba. The IR spectra were measured by Mrs K. Matoušková and Mr P. Formánek, and interpreted by Dr J. Smolíková. The ^{1}H-NMR *spectra were measured and interpreted by Dr M. Masojídková and Dr M. Synáčková. The biological evaluation was performed by Dr K. Sláma, Institute of Entomology, Czechoslovak Academy of Sciences, Prague. The technical assistance was provided by Miss M. Tesaříková.*

* The biological activity of compounds *I*—*XIX* will be reported in detail elsewhere in collaboration with coworkers of the Institute of Entomology, Czechoslovak Academy of Sciences, Prague.

REFERENCES

1. Beran P., Sláma K., Šorm F.: Czech. 157 425 (1974); Czech. 157 426 (1974).
2. Sláma K., Romaňuk M., Šorm F.: *Insect Hormones and Bioanalogues.* Springer, New York 1974.
3. Kahovcová J., Arnold Z., Šorm F.: This Journal *38*, 1165 (1973).
4. Machková Z., Dolejš L., Šorm F.: This Journal *38*, 595 (1973).
5. Jarolím V., Sláma K., Šorm F.: Czech. Appl. PV 6142-74 (1974).
6. Jarolím V., Sláma K., Šorm F.: Czech. Appl. PV 6014-75 (1975).
7. Jarolím V., Šorm F.: This Journal *40*, 1059 (1975).
8. Jarolím V., Šorm F.: This Journal *40*, 1070 (1975).
9. Wiley G. A., Hershkowitz R. L., Rein B. N., Chung B. C.: J. Amer. Chem. Soc. *86*, 964 (1964).
10. Human J. P. E., Mills J. A.: Nature *158*, 877 (1946).

Translated by J. Pliml.