SYNTHESIS OF JUVABIONE ANALOGUES

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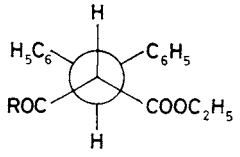
Received May 12th, 1987

Alkylation of various β-ketoesters *IIIa—d* with bis(*p*-methoxycarbonylphenyl)bromomethane (*II*) and bis(*p*-chlorophenyl)bromomethane (*VI*) followed by cleavage of ethoxycarbonyl group or hydrolysis and esterification gave methoxycarbonylphenyl and chlorophenyl analogues of ar--juvabione, respectively. Condensation of bis(*p*-methoxycarbonylphenyl)methanol (*IX*) with isovaleryl and trichloroacetyl chloride gave isovalerate *X* and trichloroacetate *XI*, respectively, while the condensation of bis(*p*-chlorophenyl)methanol (*XII*) with isovaleryl chloride and citronellyl bromide yielded isovalerate *XIII* and citronellyl ether *XIV*, respectively. The methoxycarbonylation of aryl-alkyl ketones *XVa—d* with oxalyl chloride and treatment with methanol furnished various ar-juvabione analogues *XVIa—d*. The compounds *Vb*, *Vc*, *Vd*, *XVIb*, and *XVIc* showed high activity against *Dysdercus koenigii* at 1 μg concentration.

One of the challenges that scientists face today is the protection of food crops from insect pests by safer and specific methods. Juvenile hormone analogues are quite promising as third generation pesticides[1]. The search for new compounds continues and we present here our work on the synthesis of juvabione analogues.

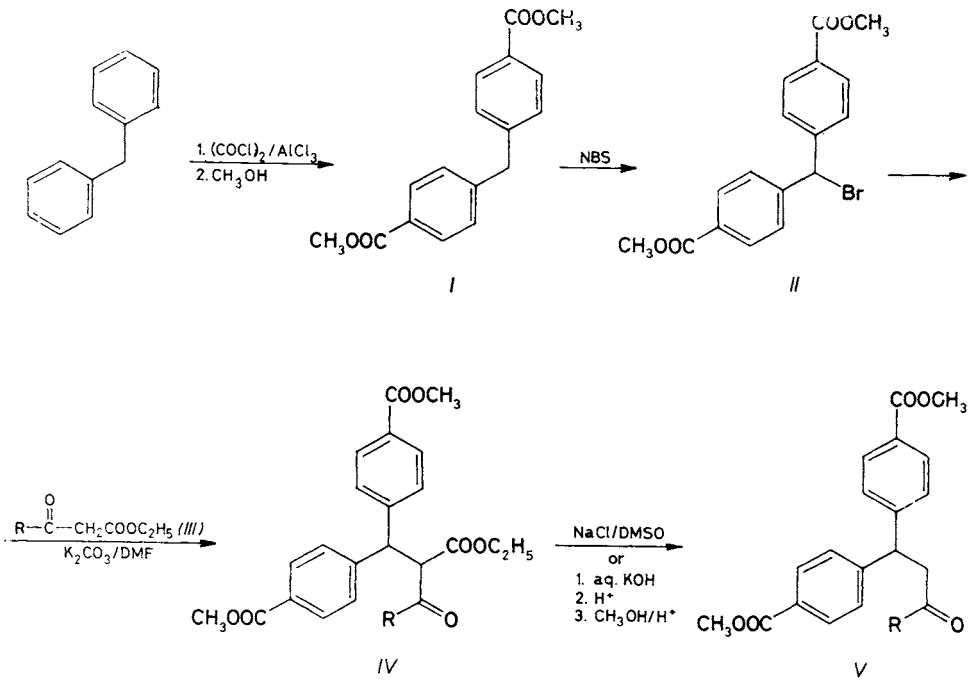
Amongst the juvabione analogues synthesized by Mane and Rao[2], it was found that 1,1-bis(*p*-methoxycarbonylphenyl)-5-methylhexan-3-one (*Vd*) had exceptionaly high activity. This fact led us to synthesize more compounds of diphenyl type. We have also synthesized various juvabione analogues in order to study the effect of variation of the side chain on its activity.

The starting material, bis(*p*-methoxycarbonylphenyl)methane (*I*) was prepared in one step by Friedel–Crafts acylation of diphenylmethane with oxalyl chloride followed by work-up with dry methanol. The ester *I*, on treatment with N-bromosuccinimide (NBS) gave bis(*p*-methoxycarbonylphenyl)bromomethane (*II*). The alkylation of various β-ketoesters *IIIa—d* with the bromoester *II* in dimethylformamide



A

(DMF) using potassium carbonate gave the desired keto-triesters *IVa–d*. A high coupling constant of 12 Hz for the methine protons in triesters *IV* indicate that they exist in a fixed conformation *A*, in which two methine protons are *trans* to each other. The cleavage of ethoxycarbonyl group of *IV* with sodium chloride–dimethyl sulfoxide (DMSO), (ref.[3]), gave the required diphenyl analogues *Va–d*. Mild alkaline hydrolysis of *IV* followed by acidification and esterification also gave the required analogues *Va–d* (Scheme 1).



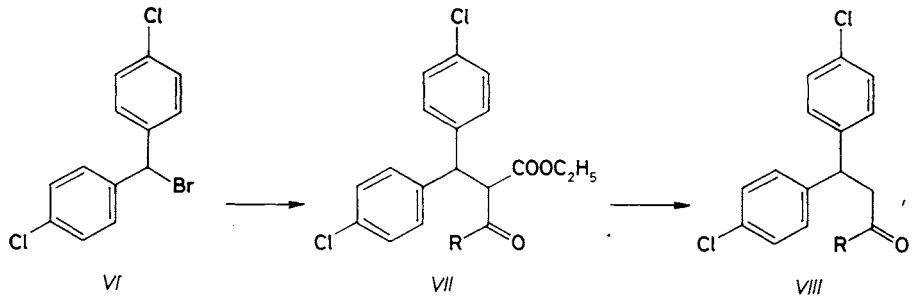
In formulae *III–V*: *a*, R = CH_3 *b*, R = C_2H_5 *c*, R = n-C_3H_7 *d*, R = i-C_4H_9

SCHEME 1

DDT is a powerful insecticide and has a *p,p'*-dichlorodiphenyl structural unit. We were interested in investigating the effect of substituting methoxylcarbonyl group in diphenyl analogues *V* by chlorine so that these compounds will have a dichlorodiphenyl unit similar to DDT.

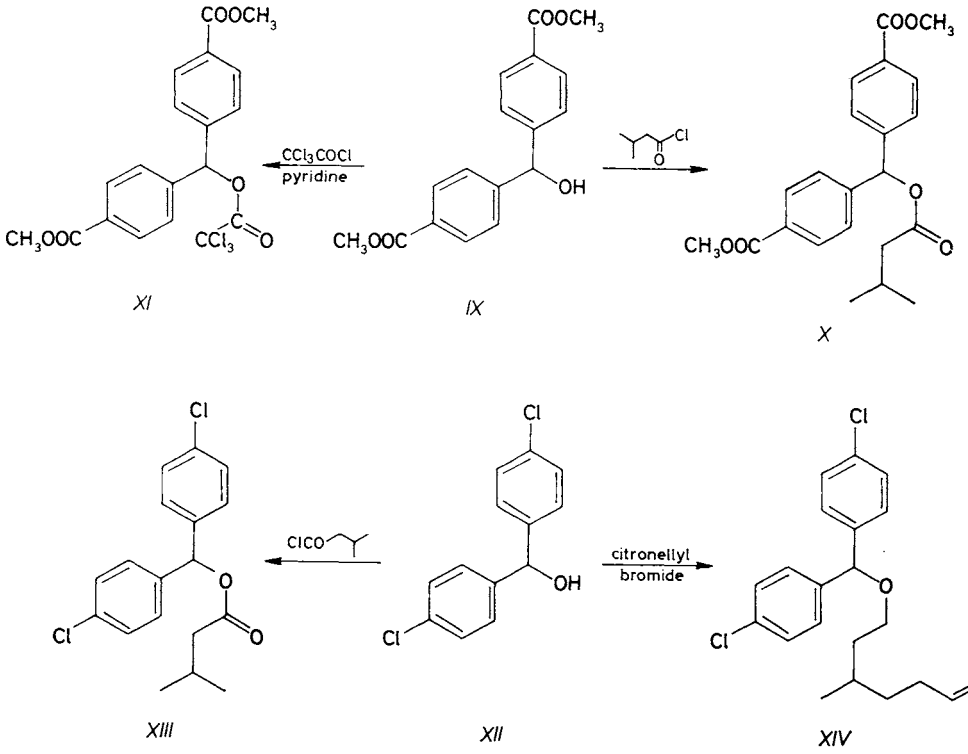
The starting bis(*p*-chlorophenyl)bromomethane (*VI*) was prepared from *p,p'*-dichlorobenzophenone[4] by sodium borohydride reduction in ethanol–dioxane system[5] followed by the treatment of the alcohol with phosphorus tribromide. The bromide was condensed with various β-ketoesters *IIIa–d* to yield the keto-esters *VIIa–d*

which were converted into the required analogues *VIIIa–d* as descibred for *V* (Scheme 2).



In formulae *VII* and *VIII*: *a*, R = CH_3 *b*, R = C_2H_5 *c*, R = n-C_3H_7 *d*, R = i-C_4H_9

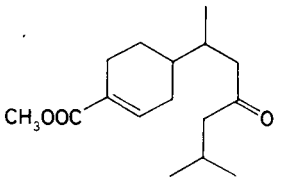
SCHEME 2



SCHEME 3

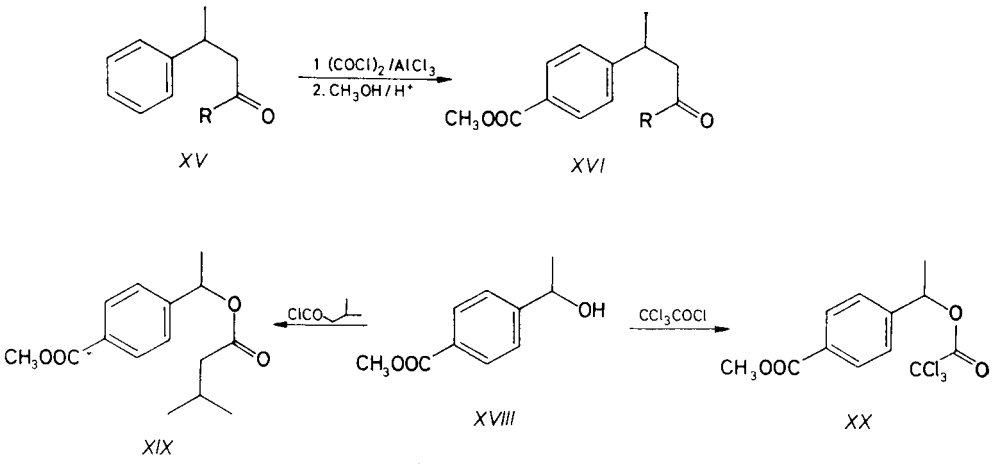
Further we have studied the effect of substituting a methylene group by oxygen in *V* and *VIII*. The terminal trichlorosubstituted groups enhance the activity of certain compounds[6,7], so it was decided to prepare the trichloroacetate derivative. The bromide *II* was hydrolyzed to yield bis(*p*-methoxycarbonylphenyl)methanol (*IX*) which was treated with isovaleryl chloride in presence of pyridine to give the isovalerate *X*. Similarly condensation of *IX* with trichloroacetyl chloride yielded trichloroacetate *XI*. Condensation of bis(*p*-chlorophenyl)methanol (*XII*) with isovaleryl chloride and citronellyl bromide yielded the isovalerate *XIII* and citronellyl ether *XIV*, respectively (Scheme 3).

ar-Juvabione (*XVId*) is a methyl ester of naturally occurring ar-todomatuic acid and exhibits juvenile hormone activity similar to juvabione[2] (*XVII*). The synthesis



XVII

of ar-juvabione has been reported by Rao and Iyer[8] and Mane and Rao[9] as well as Mane and coworkers[10]. Synthesis of the modified side chain analogues was undertaken in view of studying its effect on its activity.



In formulae *XV* and *XVI*: *a*, R = C_2H_5 *b*, R = n-C_3H_7 *c*, R = n-C_4H_9 *d*, R = i-C_4H_9

SCHEME 4

Carbonylation of the suitable aryl-alkyl ketone *XV* with oxalyl chloride and anhydrous aluminium chloride followed by esterification yielded the various side chain analogues *XVIa–d* of ar-juvabione (Scheme 4). Condensation of hydroxyester *XVIII* with isovaleryl chloride and trichloroacetyl chloride gave the isovalerate *XIX* and trichloroacetate *XX*, respectively.

The activity was tested against *Dysdercus koenigii* (freshly moulted fifth instar nymphs) at dose levels 10 and 1 μg/nymph. The results are given in Table I.

In the phenyl analogues of juvabione, the activity depends on the chain length. The compound with a three-carbon chain (*Va*) is less active than the compound with a four- (*Vb*) or five- (*Vc*) carbon chain.

In the juvabione series, the compound with eight-carbon chain *XVIc* has the highest activity and the activity decreases as the chain length decreases (*XVIc* > *XVIb* > *XVIa*). It is interesting to note that ar-juvabione (*XVId*) has an isopropyl at the end of chain but the compound with a straight chain *XVIc* and containing the same number of carbon atoms as *XVId* is also highly active.

Substitution of a methylene group by oxygen decreases the activity as indicated by the low activity of the isovalerate *XIX*. The chloro compounds have no activity against *Dysdercus koenigii*.

EXPERIMENTAL

All the melting points determined are uncorrected. The IR spectra were recorded using Beckman R-32 or Perkin–Elmer-infracord model-538 instruments and NMR spectra using Varian XL-100 with TMS as internal standard.

The β-ketoester *IIIb* was prepared by ethoxycarbonylation of ethyl methyl ketone with diethyl carbonate essentially according to the procedure reported earlier[11], while the β-ketoester *IIIc*

TABLE I

Morphological inhibition at μg/nymph of *Dysdercus koenigii*

Compound	% of Morphological inhibition at	
	10 μg/nymph	1 μg/nymph
Va	5·45	0
Vb	100	100
Vc	100	100
Vd	100	100
XVIa	4·58	0
XVIb	100	17
XVIc	100	100
XIX	30	0

and *IIId* were prepared by acylation of Meldrum's acid followed by ethanolysis as reported by Oikawa[12].

Bis(*p*-methoxycarbonylphenyl)methane (*I*)

To a stirred solution of diphenylmethane (22 ml; 0·13 mol) and oxalyl chloride (25 ml; 0·30 mol) in dry carbon disulphide (200 ml) cooled to −5°C, anhydrous aluminium chloride (36 g; 0·26 mol) was added in small portions during 1 h. The reaction mixture was further stirred at 0°C for 4 h and at room temperature for 2 h. To this reaction mixture cooled in ice, dry methanol (200 ml) was added dropwise. The reaction mixture was allowed to attain the room temperature, stirred for additional 4 h and left overnight. Ice cold hydrochloric acid (3 : 1, 200 ml) was added and the mixture was extracted with ether. The ether extract was successively washed with water, aqueous Na_2CO_3 and dried. Removal of ether gave *I* (20·3 g, 54%), m.p. 80—81°C (petroleum ether) (ref.[13] m.p. 81—82°C).

Bis(*p*-methoxycarbonylphenyl)bromomethane (*II*)

A mixture of *I* (11·4 g; 0·04 mol), N-bromosuccinimide (8 g; 0·045 mol), and catalytic amount of benzoyl peroxide in carbon tetrachloride (70 ml) was refluxed on water bath. On completion of reaction (3 h) succinimide formed was filtered and washed with carbon tetrachloride. The solvent was distilled off to give *II* (13 g, 89%), m.p. 95—96°C (petroleum ether) (ref.[2] m.p. 94—95°C).

1,1-Bis(*p*-methoxycarbonylphenyl)-2-ethoxycarbonyl-butan-3-one (*IVa*)

To a stirred mixture of ethyl acetoacetate (*IIIa*) (1·3 g; 0·01 mol) and anhydrous potassium carbonate (2 g) in dry dimethylformamide (15 ml) was added the solution of bromide *II* (2·5 g; 0·007 mol) in dry dimethylformamide (10 ml) during 1/2 h. The reaction mixture was stirred at room temperature for 36 h and at 85—90°C for 3 h, then it was cooled, diluted with water, acidified with dilute acetic acid and extracted with ether. The ethereal extract was washed with water, dried over Na_2SO_4 and ether distilled off to give 2·2 g (77%) of the keto-triester *IVa*, m.p. 118—120°C (chloroform–petroleum ether) IR spectrum (cm^{-1}): 2 940, 1 715 (non-enolic β-ketoester) and 1 615. ^1H NMR (C^2HCl_3): 1·04 t, 3 H (J = 7 Hz, —COO—CH_2—CH_3); 2·14 s, 3 H (—CO—CH_3); 3·88 s, 2 × 3 H (Ar—$COOCH_3$); 4·2 q, 2 H (—COO—CH_2—CH_3); 4·60 d, 1 H (J = 12 Hz, —CH—$COOC_2H_5$); 4·9 d, 1 H (Ar—CH—Ar); 7·36, 7·38 two doublets, 4 H (J = 8 Hz, Ar—H *ortho* to side chain) and 7·96 d, 4 H (Ar—H *ortho* to —$COOCH_3$). For $C_{23}H_{24}O_7$ (412·4) calculated: 66·98% C, 5·87% H; found 66·68% C, 5·70% H.

1,1-Bis(*p*-methoxycarbonylphenyl)butan-3-one (*Va*)

A) A mixture of keto-triester *IVa* (0·6 g), sodium chloride (0·09 g), and a drop of water in dimethyl sulphoxide (10 ml) was heated with stirring in a paraffin bath. A trap of barium hydroxide solution was attached to absorb evolved gases. The reaction mixture was heated rapidly to 130°C and thereafter very slowly. The evolution of CO_2 was recorded at a temperature of 158—162°C and it was maintained for 1/2 h. The mixture was further heated to 170°C and allowed to cool. The cooled solution on dilution with water was extracted with ether. The etheric extract was washed repeatedly with water, dried and ether removed to give crude *Va*, which was chromatographed over silica gel to get 0·32 g (64%) of pure *Va*, m.p. 78—79°C (benzene–petroleum ether). IR spectrum (cm^{-1}): 1 725 (ketone and ester —C=O). ^1H NMR (C^2HCl_3):2·12 s, 3 H (—CO—

—CH_3); 3·24 d, 2 H (J = 7 Hz, —CO—CH_2); 3·92 s, 2 × 3 H (Ar—$COOCH_3$); 4·74 t, 1 H (Ar—CH—Ar); 7·3 d, 4 H (J = 8 Hz, Ar—H *meta* to —$COOCH_3$) and 7·98 d, 4 H (Ar—H *ortho* to —$COOCH_3$). For $C_{20}H_{20}O_5$ (340·2) calculated: 70·58% C, 5·88% H; found 70·47% C, 5·98% H.

B) The keto-triester *IVa* (1·5 g) was refluxed with aqueous methanolic potassium hydroxide solution (50 ml, 5%) for 6 h. It was diluted with water (10 ml) and methanol was distilled off. The resulting alkaline solution was cooled, acidified with sulphuric acid (50%) and left overnight. The crude solid acid, 1,1-bis(*p*-carboxyphenyl)butan-3-one, was filtered off, washed with water and dried; 0·720 g (63%), m.p. 176—177°C (ethyl acetate–petroleum ether). IR spectrum (cm^{-1}): 3 340 (—COOH), 2 920, 1 720, 1 685. ^{1}H NMR (($C^2H_3)_2SO$ + C^2HCl_3): 2·1 s, 3 H (—CO—CH_3); 3·38 d, 2 H (J = 6 Hz, —CH—CH_2—CO); 4·65 t, 1 H (Ar—CH—Ar); 7·4 d, 4 H (J = 8 Hz, Ar—H *ortho* to side chain) and 7·86 d, 4 H (Ar—H *ortho* to —COOH). For $C_{18}H_{16}O_5$ (312·2) calculated: 69·23% C, 5·12% H; found 68·97% C, 4·83% H. The above acid (0·48 g) was refluxed with methanol (10 ml) and concentrated sulphuric acid (2 drops) for 6 h. The routine work-up gave the crude diester *Va* (0·42 g) which was purified by TLC (0·290 g, 55%). This compound was found to be identical in all respects with the product obtained by procedure *A*.

Alkylated β-Ketoesters *IVb* and *IVc*

The relevant spectral data for the alkylated β-ketoesters are summarized below. The procedure followed for the preparation is essentially the same as the one already described for preparation of *IVa*.

IVb: 71%; m.p. 121—122°C. For $C_{24}H_{26}O_7$ (426·3) calculated: 67·60% C, 6·10% H; found: 67·45% C, 5·93% H. ^{1}H NMR (C^2HCl_3): 0·88 t, 3 H (J = 7 Hz, —CO—CH_2—CH_3); 1·02 t, 3 H (J = 7 Hz, —COO—CH_2—CH_3); 2·42 m, 2 H (—CO—CH_2—CH_3); 3·9 s, 2 × 3 H (Ar—$COOCH_3$); 4·02 q, 2 H (—COO—CH_2—CH_3); 4·58 d, 1 H (J = 12 Hz, —CH—COO.C_2H_5); 4·96 d, 1 H (Ar—CH—Ar); 7·4 two doublets, 4 H (J = 8 Hz, Ar—H *ortho* to side chain) and 7·96 d, 4 H (Ar—H *meta* to side chain).

IVc: 68%; m.p. 122—123°C. For $C_{25}H_{28}O_7$ (440·3) calculated: 68·10% C, 6·36% H; found 67·92% C, 6·36% H. ^{1}H NMR (C^2HCl_3): 0·70 t, 3 H (J = 7 Hz, —CO—$(CH_2)_2$—CH_3); 1·02 t: 3 H (J = 7 Hz, —COO—CH_2—CH_3); 1·42 sextet, 2 H (—CO—CH_2—CH_2); 2·40 m, 2 H, (—CO—CH_2—CH_2); 3·90 s, 2 × 3 H (Ar—COO—CH_3); 4·02 q, 2 H (—COO—CH_2—CH_3); 4·60 d, 1 H (J = 12 Hz, —CH—$COOC_2H_5$); 4·94 d, 1 H (Ar—CH—Ar); 7·36 d, 4 H (J = 8 Hz, Ar—H *ortho* to side chain) and 7·96 d, 4 H (Ar—H *ortho* to —$COOCH_3$).

Ketoesters *Vb* and *Vc*

Vb: 53%; m.p. 83—84°C. For $C_{21}H_{22}O_5$ (354·2) calculated: 71·18% C, 6·21% H; found 70·85% C, 5·98% H. ^{1}H NMR (C^2HCl_3): 0·98 t, 3 H (J = 7 Hz, —CO—CH_2—CH_3); 2·38 q, 2 H (—CO—CH_2—CH_3); 3·24 d, 2 H (J = 7 Hz, —CO—CH_2—CH); 3·92 s, 2 × 3 H (Ar—$COOCH_3$); 4·78 d, 1 Hz (Ar—CH—Ar); 7·3 d, 4 H (J = 8 Hz, Ar—H *ortho* to side chain) and 7·98 d, 4 H (Ar—H *ortho* to —$COOCH_3$).

Vc: 56%; m.p. 84°C. For $C_{22}H_{24}O_5$ (368·2) calculated: 71·13% C, 6·52% H; found: 71·11% C, 6·31% H. ^{1}H NMR (C^2HCl_3): 0·82 t, 3 H (J = 7 Hz, —CO—$(CH_2)_2$—CH_3); 1·54 sextet, 2 H (—CO—CH_2—CH_2); 2·34 t, 2 H (—CO—CH_2—); 3·20 d, 2 H (J = 7 Hz, —CO—CH_2—CH); 3·92 s, 2 × 3 H (Ar—$COOCH_3$); 7·30 d, 4 H (J = 8 Hz, Ar—H *ortho* to side chain) and 7·96 d, 4 H (Ar—H *ortho* to —$COOCH_3$).

Bis(*p*-chlorophenyl)methanol (*XII*)

To the solution of *p,p'*-dichlorobenzophenone (10 g; 0·04 mol) in ethanol–dioxane mixture (1 : 2, 60 ml) was added sodium borohydride (0·6 g; 0·016 mol) in small portions with stirring and cooling. The reaction mixture was stirred at room temperature for 4 h, left overnight, decomposed by saturated ammonium chloride solution and extracted with ether. The ethereal extract was repeatedly washed with water, dried and ether removed to give 8·56 g (85%) of *XII*, m.p. 87–89°C (petroleum ether) (ref.[14], m.p. 90–91°C). IR spectrum (cm^{-1}): 3 350, 2 920, and 1 770.

Bis(*p*-chlorophenyl)bromomethane (*VI*)

The above alcohol (5·7 g) was refluxed with phosphorus tribromide (2·1 g) in dry benzene (30 ml) for 4 h. After cooling the reaction mixture was diluted with water and extracted with benzene. The benzene extract was washed with water, dried and benzene removed to yield bromide *VI* (7·1 g) as a liquid.

1,1-Bis(*p*-chlorophenyl)-2-ethoxycarbonyl-5-methylhexan-3-one (*VIId*)

To a magnetically stirred solution of ethyl 3-oxo-5-methylhexanoate (*IIId*) (1·7 g) and anhydrous potassium carbonate (3·0 g) in dry dimethylformamide (20 ml) the solution of bromide *VI* (3·2 g) in dry dimethylformamide (10 ml) was added during 1/2 h. The reaction mixture was stirred at room temperature for 48 h and at 85–90°C for 4 h. It was cooled, diluted with water and extracted with ether. The ethereal extract was washed with water, dried and ether removed to furnish 2·8 g (68%) of β-ketoester *VIId*, m.p. 122°C (chloroform–petroleum ether). IR spectrum (cm^{-1}): 1 745 and 1 715; ^{1}H NMR (C^2HCl_3): 0·92 d, 6 H (J = 7 Hz, —CH—$(CH_3)_2$); 1·06 t, 3 H (J = 7 Hz, —COO—CH_2—CH_3); 2·01 m, 1 H (—CH—$(CH_3)_2$); 2·26 m, 2 H (—CO—CH_2—CH); 4·02 q, 2 H (—COO—CH_2—CH_3); 4·44 d, 1 H (J = 12 Hz, —CH—COOC_2H_5); 4·78 d, 1 H (Ar—CH—Ar); 7·22 m, 8 H (Ar—H).

1,1-Bis(*p*-chlorophenyl)-5-methylhexan-3-one (*VIIId*)

The above β-ketoester *VIId* (2·45 g) was hydrolyzed by refluxing with methanolic aqueous potassium hydroxide (5%, 30 ml) for 4 h. The reaction mixture was diluted with water, methanol distilled off and on cooling it was acidified with sulphuric acid (50%). It was left aside for 2 h and worked up as usual to give *VIIId* (1·40 g). This was chromatographed over silica gel (30 g) when elution with petroleum ether–chloroform (80 : 20) gave 0·71 g (35%) of pure *VIIId* m.p. 89–90°C (benzene–petroleum ether). ^{1}H NMR (C^2HCl_3): 0·84 d, 6 H (J = 7 Hz, —CH—$(CH_3)_2$); 2·06 m, 1 H (—CH—$(CH_3)_2$); 2·2 m, 2 H (—CO—CH_2); 3·08 d, 2 H (J = 7 Hz, —CO—CH_2—$CHAr_2$); 4·58 t, 1 H (Ar—CH—Ar); 7·24 m, 8 H (Ar—H). For $C_{19}H_{20}Cl_2O$ (335·1) calculated: 68·10% C, 5·98% H, 20·95% Cl; found: 68·10% C, 6·15% H, 20·35% Cl; found: 68·10% C, 6·15% H, 20·35% Cl.

Spectral Data for the Alkylated β-Ketoesters *VIIa*, *VIIb*, and *VIIc* and for the Ketones *VIIIa*, *VIIIb*, and *VIIIc*

VIIa: 74%; m.p. 118–120°C. ^{1}H NMR (C^2HCl_3): 1·10 t, 3 H (J = 7 Hz, —COO—CH_2—CH_3); 2·15 s, 3 H (—CO—CH_3); 4·05 q, 2 H (—COO—CH_2—CH_3); 4·46 d, 1 H (J = 12 Hz, —CH—COOC_2H_5); 4·83 d, 1 H (Ar—CH—Ar); 7·23 s, 8 H (Ar—H).

VIIb: 64%; m.p. 120–121°C. ^{1}H NMR (C^2HCl_3): 0·9 t, 3 H (J = 7 Hz, —CO—CH_2—CH_3); 1·04 t, 3 H (J = 7 Hz, —COO—CH_2—CH_3); 2·42 q, 2 H (—CO—CH_2—CH_3); 4·02 q, 2 H (—COO—CH_2—CH_3); 4·45 d, 1 H (J = 12 Hz, —CH—$COOC_2H_5$); 4·82 d, 1 H (Ar—CH—Ar); 7·24 m, 8 H (Ar—H).

VIIc: 61%; m.p. 121–123°C; IR spectrum (cm^{-1}): 1 745 and 1 705.

VIIIa: 46%; m.p. 92°C. For $C_{16}H_{14}Cl_2O$ (293·2) calculated: 65·75% C, 4·79% H, 23·97% Cl; found: 65·60% C, 4·68% H, 23·58% Cl. ^{1}H NMR (C^2HCl_3): 2·2 s, 3 H (—CO—CH_3); 3·2 d, 2 H (J = 7 Hz, —CO—CH_2); 4·6 t, 1 H (Ar—CH—Ar); 7·25 m, 8 H (Ar—H).

VIIIb: 44%; m.p. 91–92°C. For $C_{17}H_{16}Cl_2O$ (307·2) calculated: 66·66% C, 5·22% H, 22·87% Cl; found: 66·50% C, 5·13% H, 22·60% Cl. ^{1}H NMR (C^2HCl_3): 0·98 t, 3 H (J = 7 Hz, —CO—CH_2—CH_3); 2·36 q, 2 H (—CO—CH_2—CH_3); 3·12 d, 2 H (J = 7 Hz, —CO—CH_2—CH); 4·58 d, 1 H (Ar—CH—Ar); 7·22 m, 8 H (Ar—H).

VIIIc: 38% m.p. 92–93°C. For $C_{18}H_{18}Cl_2O$ (321·2) calculated: 67·5% C, 5·62% H, 21·87% Cl; found: 67·83% C, 5·81% H, 21·39% Cl. ^{1}H NMR (C^2HCl_3): 0·95 t, 3 H (J = 7 Hz, —CO—$(CH_2)_2$—CH_3); 1·5 m, 2 H (—CO—CH_2—CH_2—CH_3); 2·32 t, 2 H (—CO—CH_2—CH_2); 3·08 d, 2 H (J = 7 Hz, —CO—CH_2—CH); 4·6 t, 1 H (Ar—CH—Ar); 7·2 m, 8 H (Ar—H).

Bis(*p*-methoxycarbonylphenyl)methanol (*IX*)

Bis(*p*-methoxycarbonylphenyl)bromomethane (*II*) (3·0 g) was hydrolyzed by refluxing with wet dioxan (5%) for 12 h. The reaction mixture was diluted with water and extracted with ether. The extract was repeatedly washed with water, dried and ether removed to furnish the alcohol *IX* (2·1 g). This was chromatographed over silicagel column, elution with petroleum ether–chloroform (50 : 50) gave 0·83 g (34%) of pure *IX*, m.p. 123°C (chloroform–petroleum ether). IR spectrum (cm^{-1}): 3 500, 1 730, and 1 700; ^{1}H NMR (C^2HCl_3): 2·94 d, 1 H (J = 3 Hz, Ar—CH—OH); 3·92 s, 2 × 3 H (Ar—$COOCH_3$); 5·94 d, 1 H (Ar—CH—Ar); 7·44 d, 4 H (J = 8 Hz, Ar—H *ortho* to side chain) and 8·0 d, 4 H (Ar—H *ortho* to —$COOCH_3$). For $C_{17}H_{16}O_5$ (300·3) calculated: 68·00% C, 5·33% H; found: 67·87% C, 5·12% H.

Bis(methoxycarbonylphenyl)methyl Isovalerate (*X*)

To the stirred solution of alcohol *IX* (0·3 g) and dry pyridine (0·2 ml) in chloroform (10 ml) isovaleryl chloride (0·2 ml) was added and it was stirred for 6 h. The reaction mixture upon dilution with water was extracted with ether. The ether extract was washed with water, dried and ether removed to give 0·29 g (76%) of the isovalerate *X*, m.p. 89–90°C (chloroform–petroleum ether). ^{1}H NMR (C^2HCl_3): 0·91 d, 6 H (J = 7 Hz, —CH—$(CH_3)_2$); 2·3 m, 3 H (—CH_2—CH—$(CH_3)_2$); 3·9 s, 2 × 3 H (Ar—$COOCH_3$); 6·8 s, 1 H (Ar—CH—Ar); 7·3 d, 4 H (J = 8 Hz, Ar—H *meta* to —$COOCH_3$) and 7·9 d, 4 H (Ar—H *ortho* to —$COOCH_3$).

Bis(*p*-methoxycarbonylphenyl)methyl Trichloroacetate (*XI*)

To the stirred solution of alcohol *IX* (0·3 g) and dry pyridine (0·3 ml) in chloroform (15 ml) trichloroacetyl chloride (0·2 ml) was added and the mixture was stirred for 6 h. The work-up as described in the earlier case yielded the 0·27 g (61%) of trichloroacetate *XI*, m.p. 110–111°C (chloroform–petroleum ether). IR spectrum (cm^{-1}): 1 750 and 1 720; ^{1}H NMR (C^2HCl_3): 3·9 s, 2 × 3 H (Ar—$COOCH_3$); 6·8 s, 1 H (Ar—CH—Ar), 7·3 d, 4 H (J = 8 Hz, Ar—H *ortho* to side chain) and 7·85 d, 4 H (Ar—H *ortho* to —$COOCH_3$). For $C_{19}H_{15}O_6Cl_3$ (445·6) calculated: 53·25% C, 3·37% H, 23·86% Cl; found: 53·15% C, 3·17% H, 24·49% Cl.

Bis(*p*-chlorophenyl)methyl Isovalerate (*XIII*)

This was prepared from alcohol *XII* (1·26 g, 0·005 mol), dry pyridine (1 ml, 0·012 mol) and isovaleryl chloride (1·2 g, 0·01 mol) in chloroform (10 ml), as described in the earlier cases. The workup furnished the isovalerate *XIII* (1·53 g). This was chromatographed over neutral alumina when elution with petroleum ether gave pure isovalerate (0·780 g, 47%). IR spectrum (cm^{-1}): 1 740 (ester - C=O); ^1H NMR (C^2HCl_3): 0·92 d, 6 H ($J = 7$ Hz, —CH—$(CH_3)_2$); 2·28 m, 3 H (CH_2—CH—$(CH_3)_2$); 6·82 s, 1 H (Ar—CH—Ar); 7·3 m, 8 H ($J = 2$ Hz, Ar—H).

Bis(*p*-chlorophenyl)methyl Citronellyl Ether (*XIV*)

To sodium hydride (0·2 g, prewashed with dry benzene) covered with dry ether–dry dimethyl sulphoxide (2 : 1, 15 ml), the alcohol *XII* (0·840 g, 0·003 mol) was added. The reaction mixture was stirred for about 15 minutes and citronellyl bromide (0·84 g, 0·004 mol) in dry ether–dry dimethyl sulphoxide (2 : 1, 6 ml) was added. The reaction mixture was stirred at room temperature for 24 h. It was decomposed by pouring into ice–water and was extracted with ether. The ether extract was washed with water repeatedly, dried and ether removed to give impure ether *XIV* (1·15 g). This was chromatographed over silicagel (30 g). Elution with petroleum ether gave pure *XIV* (0·410 g, 32%) as a colorless liquid. IR spectrum (cm^{-1}): 1 580, 1 480, 1 070, 1 000, and 800; ^1H NMR (CCl_4): 0·88 d, 3 H ($J = 7$ Hz, —CH—CH_3); 1·6 and 1·7 broad singlets, 3 H each (isopropylidene methyl groups); 1·94 m, 2 H (allylic methylene); 3·2 t, 2 H ($J = 7$ Hz, —O—CH_2—CH_2); 4·9 m, 1 H (olefinic H); 5·1 s, 1 H (Ar_2—CH—O); 7·05 m, 8 H (Ar—H). The other protons appeared as complex multiplets. For $C_{23}H_{28}OCl_2$ (391·3) calculated: 70·76% C, 7·17% H, 17·94% Cl; found 70·38% C, 6·92% H, 17·38% Cl.

2-Phenyl-4-hexanone (*XVa*)

To a stirred solution of Grignard's reagent prepared from magnesium (4 g) and methyl iodide (13 ml) in dry ether (80 ml) cooled to 0°C Cu_2Cl_2 powder (0·8 g) was added. To the resulting solution styryl ethyl ketone[15] (13 g) in dry ether (40 ml) was added dropwise during 1 h. During the addition of ketone, more Cu_2Cl_2 (0·8 g) was added in three lots. The reaction mixture was stirred at room temperature for 8 h and refluxed on water bath for 1 h. It was again cooled to 0°C and decomposed by addition of ice-cold HCl (1 : 1, 50 ml). The ether layer was separated and aqueous layer extracted with ether. The ether extract was successively washed with water, aqueous sodium thiosulphate and dried. Removal of ether gave *XVa* (11·5 g). The product was purified by distillation under vacuum, b.p. 112—117°C/10 mm (8·8 g, 62%). IR spectrum (cm^{-1}): 1 718; ^1H NMR (C^2HCl_3): 1·0 t, 3 H ($J = 7$ Hz, —CO—CH_2—CH_3); 1·28 d, 3 H ($J = 7$ Hz, Ar—CH—CH_3); 2·34 q, 2 H (—CO—CH_2—CH_3); 2·70 two doublets, 2 H ($J = 6·5$ Hz and 8 Hz, —CO—CH_2—CHAr); 3·34 q, 1 H (Ar—CH—CH_3); 7·24 m, 5 H (Ar—H).

Aryl Alkyl Ketones *XVb*, *XVc*, and *XVd*

These were prepared from the corresponding styryl alkyl ketones by 1,4-Grignard addition of methyl iodide by the procedure described for *XVa*.

XVb: 66%; b.p. 110—113°C/8 mm; ^1H NMR (C^2HCl_3): 0·85 t, 3 H ($J = 7$ Hz, —CH_2—CH_3); 1·28 d, 3 H ($J = 7$ Hz, Ar—CH—CH_3); 1·54 sextet, 2 H (—CO—CH_2—CH_2); 2·30 t, 2 H (—CO—CH_2—CH_2); 2·68 m, 2 H (Ar—CH—CH_2); 3·33 sextet, 1 H (Ar—CH—CH_3); 7·20 s, 5 H (Ar—H).

XVc: 61%; b.p. 131–136°C/15 mm; ^{1}H NMR (C^2HCl_3): 0·86 t, 3 H (J = 7 Hz, —CH_2—CH_3); 1·26 d, 3 H (J = 7 Hz, Ar—CH—CH_3); 1·2 to 1·6 complex multiplet, 4 H (aliphatic methylenes); 2·32 t, 2 H (—CO—CH_2—CH_2); 2·68 two doublets, 2 H (J = 6·5 and 8 Hz, Ar—CH—CH_2); 3·34 sextet, 1 H (Ar—CH—CH_3); 7·3 m, 5 H (Ar—H).

XVd: 52%; b.p. 102–106°C/8 mm; ^{1}H NMR (CCl_4): 0·84 d, 6 H (J = 7 Hz, —CH—$(CH_3)_2$); 1·27 d, 3 H (J = 7 Hz, Ar—CH—CH_3), 2·1 m, 3 H (—CH_2—CH—$(CH_3)_2$); 2·6 m, 2 H (—CO—CH_2); 3·2 sextet, 1 H (Ar—CH—CH_3); 7·1 m, 5 H (Ar—H).

2-(*p*-Methoxycarbonylphenyl)hexan-4-one (*XVIa*)

To a stirred solution of oxalyl chloride (5 ml) and anhydrous aluminium chloride (7·0 g) in dry CS_2 (20 ml) the ketone *XVa* (2·0 g in 10 ml of CS_2) was added dropwise, at 0°C during 1/2 h. The reaction mixture was stirred at 0°C for 2 h and at room temperature for 2 h. This was again cooled to 0°C and dry methanol (20 ml) was added with stirring. The reaction mixture was further stirred at room temperature for 4 h and decomposed with ice-cold hydrochloric acid. This was extracted with ether and ether extract washed with water, aqueous Na_2CO_3, dried and ether removed to give ester *XVIa* (0·59 g, 23%). This was purified by preparative TLC (0·31 g). IR spectrum (cm^{-1}): 1 725; ^{1}H NMR (C^2HCl_3): 1·0 t, 3 H (J = 7 Hz, —CO—CH_2—CH_3); 1·28 d, 3 H (J = 7 Hz, Ar—CH—CH_3); 2·32 q, 2 H (—CO—CH_2—CH_3); 2·7 m, 2 H (—CO—CH_2—CH—Ar); 3·42 sextet, 1 H (Ar—CH—CH_3); 3·92 s, 3 H (Ar—$COOCH_3$); 7·28 d, 2 H (J = 8 Hz, Ar—H *ortho* to side chain) and 8·0 d, 2 H (Ar—H *ortho* to —$COOCH_3$). For $C_{14}H_{18}O_3$ (234·2) calculated: 71·79% C, 7·69% H; found 71·53% C, 7·48% H.

Ar-Juvabione and Its Analogs *XVIb*, *XVIc*, and *XVId*

These were prepared by methoxycarbonylation of the corresponding aryl-alkyl ketones with oxalyl chloride–aluminium chloride according to the procedure reported for *XVIa*.

XVIb: 20%, IR (cm^{-1}): 1 728 (ester and ketone —C=O); for $C_{15}H_{20}O_3$ (248·2) calculated: 72·58% C, 8·06% H; found: 72·26% C, 7·86% H. ^{1}H NMR (CCl_4): 0·85 t, 3 H (J = 7 Hz, —CO—$(CH_2)_2$—CH_3); 1·22 d, 3 H (J = 7 Hz, Ar—CH—CH_3); 1·35 q, 2 H (—CO—CH_2—CH_2); 2·05 t, 2 H (—CO—CH_2); 2·42 d, 2 H (J = 7 Hz, —CO—CH_2—CH); 3·21 m, 1 H (Ar—CH—CH_3); 3·9 s, 3 H (Ar—$COOCH_3$); 7·18 d, 2 H (J = 8 Hz, Ar—H *meta* to —$COOCH_3$) and 8·05 d, 2 H (Ar—H *ortho* to —$COOCH_3$).

XVIc: 23%, IR (cm^{-1}): 1 725 (broad C=O). For $C_{16}H_{22}O_3$ (262·2) calculated: 73·28% C, 8·39% H; found 73·13% C, 8·14% H. ^{1}H NMR (C^2HCl_3): 0·86 t, 3 H (J = 7 Hz, —CH_2—CH_3); 1·28 d, 3 H (J = 7 Hz, Ar—CH—CH_3); 1·1 to 1·7 complex multiplet, 4 H (aliphatic methylenes); 2·32 t, 2 H (—CO—CH_2—CH_2); 2·70 two doublets, 2 H (J = 6 Hz and 8 Hz, Ar—CH—CH_2); 3·4 sextet, 1 H (Ar—CH—CH_3); 3·9 s, 3 H (Ar—$COOCH_3$); 7·30 d, 2 H (J = 8 Hz, Ar—H *meta* to —$COOCH_3$) and 8·0 d, 2 H (Ar—H *ortho* to —$COOCH_3$).

XVId: 21%, IR (cm^{-1}): 1 720. For $C_{16}H_{22}O_3$ (262·2) calculated: 73·28% C, 8·39% H; found 73·23% C, 8·21% H. ^{1}H NMR (CCl_4): 0·83 d, 6 H (J = 7 Hz, —CH—$(CH_3)_3$); 1·27 d, 3 H (J = 7 Hz, Ar—CH—CH_3); 2·1 m, 3 H (—CH_2—CH—$(CH_3)_2$); 2·5 m, 2 H (—CO—CH_2 nearer to phenyl); 3·27 m, 1 H (Ar—CH—CH_3); 3·83 s, 3 H (Ar—$COOCH_3$); 7·2 d, 2 H (J = 8 Hz, Ar—H *meta* to —$COOCH_3$) and 7·86 d, 2 H (J = 8 Hz, Ar—H *ortho* to —$COOCH_3$).

1-(*p*-Methoxycarbonylphenyl)ethyl Trichloroacetate (*XX*)

To a stirred solution of (*p*-methoxycarbonylphenyl)ethanol[16] (*XVIII*) (0·9 g, 0·005 mol) and dry pyridine (0·9 g, 0·01 mol) in chloroform (10 ml) trichloroacetyl chloride (0·9 ml, 0·008 mol) was

added in two portions and the reactions mixture was stirred further for 6 h. The routine workup yielded the trichloroacetate *XX* (1·52 g) as a liquid. This was purified by chromatography over neutral alumina, elution with petroleum ether gave pure *XX* (0·89 g, 55%). IR spectrum (cm^{-1}): 1 770 and 1 725; ^1H NMR (C^2HCl_3): 1·7 d, 3 H ($J = 7$ Hz, Ar—CH—CH_3); 3·94 s, 3 H (Ar—$COOCH_3$); 6·04 q, 1 H (Ar—CH—CH_3); 7·50 d, 2 H ($J = 8$ Hz, Ar—H *meta* to —$COOCH_3$) and 8·1 d, 2 H (Ar—H *ortho* to —$COOCH_3$). For $C_{12}H_{11}O_4Cl_3$ (325·6) calculated: 44·44% C, 3·39% H, 32·40% Cl; found: 44·24% C, 3·12% H, 31·98% Cl.

1-(*p*-Methoxycarbonylphenyl)ethyl Isovalerate (*XIX*)

This was prepared from alcohol *XVIII* (0·9 g) and isovaleryl chloride (1·0 ml) as reported in the earlier case. The work-up furnished desired isovalerate *XIX* (1·43 g), the chromatographic purification of which over neutral alumina gave pure isovalerate (0·68 g, 52%). IR spectrum (cm^{-1}): 1 740 and 1 725; ^1H NMR (C^2HCl_3): 0·95 d, 6 H ($J = 7$ Hz, —CH—$(CH_3)_2$); 1·54 d, 3 H ($J = 7$ Hz, Ar—CH—CH_3); 2·24 m, 3 H (CH_2—CH—$(CH_3)_2$); 3·94 s, 3 H (Ar—$COOCH_3$); 5·94 q, 1 H (Ar—CH—CH_3); 7·45 d, 2 H ($J = 8$ Hz, Ar—H *meta* to —$COOCH_3$) and 8·06 d, 2 H (Ar—H *ortho* to —$COCH_3$). For $C_{15}H_{20}O_4$ (264·2) calculated: 68·18% C, 7·57% H; found 67·96% C, 7·32% H.

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