HIGH-PRESSURE INITIATED SYNTHESIS OF DOMINICALURES 1 AND 2 BY THE BAYLIS–HILLMAN METHOD

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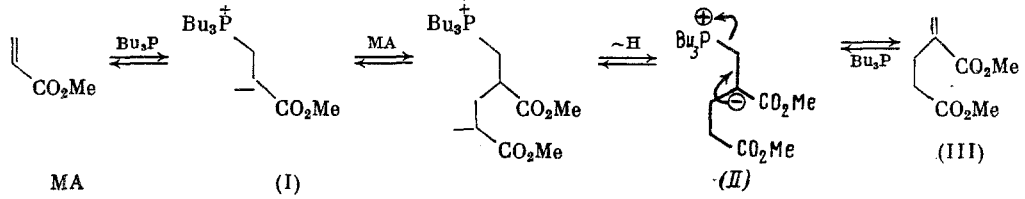
The dimerization of methyl acrylate to dimethyl α-methyleneglutarate by the action of tributylphosphine in the absence of a solvent was investigated. Methyl α-methylene-β-hydroxypentanoate was obtained with a moderate yield by the condensation of propionaldehyde with methyl acrylate catalyzed by triphenylphosphine or 1,4-diazabicyclo[2.2.2]octane and initiated by high pressure. In the last of these data a three-stage stereospecific synthesis of dominicalures 1 and 2 (components of the aggregation pheromone of the grain beetle) was realized from sec-amyl acrylate and propionaldehyde or isobutyraldehyde.

The condensation of acrylates with aldehydes catalyzed by a weakly nucleophilic base such as 1,4-diazabicyclo[2.2.2]octane (DABO) (the Baylis–Hillman reaction [1]) provides the simplest method for the production of the α-hydroxyalkyl derivatives of the initial esters [2]. The substitution of DABO by other tertiary amines and also by phosphines [3, 4], like the substitution of aldehydes by simple ketones, in this slowly occurring reaction proved substantially less effective [2], although marked acceleration by high pressure was demonstrated in the last case [5]. In the light of these data in the present work we studied the behavior of certain acrylates and, in particular, of methyl acrylate (MA) itself in the presence of propionaldehyde. This led finally to the development of a simple method for the synthesis of dominicalures 1 and 2 which are components of the aggregation pheromone of the grain beetle Rhizopertha dominica [6].

According to existing data, the dimerization of acrylates into α-methyleneglutaric esters which are of independent interest takes place with moderate yields during the action of various aliphatic phosphines, including tributylphosphine, in acetonitrile or dioxane [7] or of the complex of tricyclohexylphosphine with carbon disulfide in pyridine [8]. In contrast to the related reaction for acrylonitrile and vinyl ketones [9], we were unable to realize this reaction by the action of DABO in various solvents. It was found, however, that in their absence catalytic amounts of tributylphosphine at ~25°C give rise to rapid polymerization of the MA. This could be suppressed by a reduction in the temperature of the reaction mixture to −10°C followed by an increase to 0°C. As a result with 10 mole-equivalents of phosphine we obtained dimethyl α-methyleneglutarate (III) with a yield of more than 60% (Table 1). Compound (III) is evidently formed as a result of a series of reversible transformations, including the initial formation of the Michael adduct (I) and dissociation into the zwitterionic intermediate (II) in the final stage.



Unlike tributylphosphine, the less basic triphenylphosphine which is nucleophilic to the same degree is clearly less active in the formation of the zwitterion of type (I). In fact, according to existing data for ethyl acrylate [10], a minimal yield (2-3%) of the

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TABLE 1. Transformation of MA into the α-Methyleneglutarate (III) Catalyzed by Phosphines

Phosphine	Amount of catalyst, mole %	Reaction conditions			Yield of products (III), %
		T, °C	time, h	P, MPa	
Bu_3P	10	25	0,2	0,1	2–3
Bu_3P	10	0	1	0,1	62
Ph_3P	30	25	48	0,1	2–3
Ph_3P	30	50	8	0,1	2–3
Ph_3P	30	50	4	500	50
Ph_3P	6	50	4	500	50
Ph_3P	1	50	4	500	21
Ph_3P	15	50	4	1400	2–3

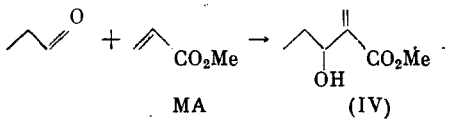
TABLE 2. Condensation of Methyl Acrylate with Propionaldehyde

Molar ratio EtCHO/MA	Catalyst	Amount of catalyst in relation to methyl acrylate, mole %	Reaction conditions			Yield of product (IV), %
			T, °C	time, h	P, MPa	
1,1	Bu_3P	10	−30	0,5	0,1	2–3
1,1	Ph_3P	20	25	48	0,1	2–3
1,5	Ph_3P	20	25	4	500	12
1,05	Ph_3P	20	50	2	500	13
1,0	Ph_3P	6	50	4	500	13
1,2	Ph_3P	10	50	4	500	14
1,05	Ph_3P	20	50	2	500	18
1,05	Et_3N	10	50	4	500	13
1.1	DABO	15	25	4	500	56

glutarate (III) was detected after prolonged treatment of MA with 30 mole-equivalents of triphenylphosphine in the range of 25-50°C (Table 1) and it was shown that a forced temperature regime and/or increase in the amount of phosphine only accelerated the polymerization of the MA.

The effectiveness of the investigated bimolecular process at the first stage could be increased sharply by the use of a high-pressure technique. Here the maximum yield [50% of the dimer (III)] was obtained at 500 MPa and 50°C in the presence of 5-30 mole% of triphenylphosphine after 4 h (Table 1). Increase in the pressure to 1400 MPa, like increase in the triphenylphosphine concentration, was accompanied in all cases by accelerated polymerization of the MA with a simultaneous reduction in the yield of the product (III).

In light of the data set out above we studied the condensation of some acrylates with aldehydes by the Baylis–Hillman method and primarily the readily polymerized methyl acrylate with propionaldehyde in order to seek the optimum conditions for this reaction and, above all, to reduce its extremely long duration [2]. In all cases the obtained results indicated low activity for the phosphines and also for tertiary amines of the Et_3N type at atmospheric and higher pressures (Table 2). An acceptable yield (56%) of the condensation product (IV) was recorded when 15 mole % of DABP was used at 500 MPa and 25°C for only 4 h. This agrees with previously published data on the acceleration of related transformations by high pressure [5].

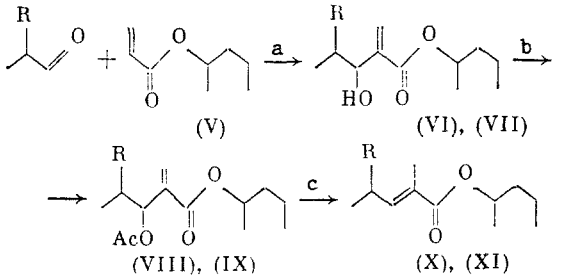


MA (IV)

The structure of the unsaturated hydroxy ester (IV) prepared in this way was confirmed by comparison of its physicochemical characteristics with those obtained earlier for this compound [11].

In light of the data set out above we developed a short (see [6, 12, 13]) stereocontrolled synthesis of the pheromones of the grain beetle by a unified scheme starting from sec-

amyl acrylate (V), which is less susceptible to polymerization than methyl acrylate, and propionaldehyde or isobutyraldehyde.



R = H (VI), (VIII), (X); R = Me (VII), (IX), (XI); a: DABO, 500 MPa, 50°, 4 h (> 72%); b: AcCl, Py (~ 90%); c: $LiBHEt_3$, THF, −50° (~ 90%).

Their condensation in the presence of ~15 mole % of DABO at 500 MPa and 50°C led after 4 h to the corresponding hydroxy esters (VI) and (VII) with an identical yield of 72%. The yield is, however, reduced by almost half when the reaction temperature is reduced to ~25°C. Hydride reduction of the acetates (VIII) and (IX) corresponding to the indicated alcohols under conditions [14] securing reaction according to the S_N2' scheme gives the dominicalures 1 (X) and 2 (XI) almost quantitatively with stereochemical purity E > 99% (PMR). The physicochemical characteristics obtained for them (bp, n_D, PMR) agree fully with published data for these pheromones [6, 12, 13]. The structures of the previously unknown compounds (VI)-(IX) were confirmed by the data from their spectral and elemental analyses. Altogether the overall yield of the dominicalures (X) and (XI) exceeded 50%, calculated on the initial acrylate (V).

EXPERIMENTAL

The IR spectra were recorded in chloroform on a UR-20 instrument. The UV spectra of alcohol solutions were recorded on a "Specord UV-VIS" spectrophotometer. The PMR spectra of solutions in deuterochloroform were measured with reference to TMS on a "Bruker WM-250" spectrometer. The mass spectra were obtained at 70 eV on a "Varian MAT CH-6" instrument. Gas-liquid chromatography was performed on an LKhM-80 chromatograph (3 m × 3 mm column, 15% Carbowax 20M on chromaton N-AW-HMDS). Thin-layer chromatography was performed on plates with a fixed layer of Silufol silica gel in the 1:1 hexane–ether system.

Dimerization of Methyl Acrylate to Dimethyl α-Methyleneglutarate (III) (Table 1). A. At Atmospheric Pressure. To 2 ml (22 mmoles) of methyl acrylate, while stirring in an atmosphere of argon, we added 0.45 g (2.2 mmoles) of tributylphosphine or 1.73 g (6.6 mmoles) of triphenylphosphine. The mixture was kept until no further changes occurred according to TLC (in the second case tributylphosphine was added at −10°C and the mixture was stirred at 0°C for 1 h), the unreacted methyl acrylate was evaporated, and the residue was chromatographed on 50 g of silica gel. By gradient elution from hexane to 15% ether in hexane we obtained the diester (III) in the form of a colorless liquid [8]; R_f 0.35, bp 71°C (2 mm Hg). PMR spectrum (δ, ppm, J, Hz): 2.46 and 2.58t (4H, CH_2, J = 7.5), 3.61 and 3.70s (6H, CH_3), 5.54 and 6.12s (2H, $H_2C{=}C$).

B. At High Pressure. A mixture of methyl acrylate and triphenylphosphine was kept in a 3-ml Teflon tube at 50°C and 500 or 1400 MPa for 4 h. After the usual treatment the diester (III) was obtained.

Methyl 2-Methylene-3-hydroxypentanoate (IV) (Table 2). A mixture of propionaldehyde, methyl acrylate, and catalyst was kept in a 3-ml Teflon tube at 25-50°C and 500 MPa for 2-4 h. It was then evaporated, and chromatography of the residue on silica gel with gradient elution from hexane to ether (to 40% of the latter) gave the hydroxy ester (IV) in the form of a colorless liquid [11]; R_f 0.25, bp 53°C (2 mm Hg). PMR spectrum (δ, ppm, J, Hz): 0.92t (3H, CH_3, J = 7.5), 1.65m (2H, HC^4), 3.74s (3H, OCH_3), 4.31 br.t (1H, HC^3, J = 7), 5.78 and 6.21s (2H, $H_2C{=}C$).

sec-Amyl Acrylate (V). To a stirred solution of 7.78 g (88.4 mmoles) of 2-pentanol, 0.5 ml of HMPTA, and 5 mg of triphenylmethane in 100 ml of ether at −40°C in an atmosphere of argon we added dropwise a 1.2 M solution of butyllithium in pentane until a stable pink color appeared in the mixture (70-75 ml, 88-90 mmoles). The mixture was treated with 8.4 g (92.8 mmoles) of acryloyl chloride at −40°C over 30 min. The reaction mass was heated

to 25°C over 30 min and diluted with ether and with water. The organic layer was neutralized with 5% hydrochloric acid, dried with sodium sulfate, and evaporated, and the residue was distilled. We obtained 8.92 g (71%) of (V) in the form of a colorless liquid [15]; bp 52°C (20 mm Hg). PMR spectrum (δ, ppm, J. Hz): 0.90t (3H, CH_3, J = 7), 1.23d (3H, CH_3, J = 7), 1.3-1.7m (4H, CH_2), 4.98m (1H, HC), 5.78d (1H, HC=CCO_2, J = 10), 6.08d.d (1H , $HCCO_2$, J = 17 and 10), 6.37d (1H, HC=CCO_2, J = 17).

1-Methylbutyl 2-Methylene-3-hydroxypentanoate (VI). A mixture of 1.58 g (11.1 mmoles) of (V), 0.77 g (13.3 mmoles) of propanol and 0.19 g (1.7 mmoles) of DABO was kept in a Teflon tube with a volume of ~3 ml at 50°C and 500 MPa and was then chromatographed on 150 g of silica gel. Gradient elution from hexane to ether (to 20% of the latter) gave (in order of elution) 0.11 g of the unreacted (V) and 1.61 g (72%) of (VI) in the form of a colorless liquid; bp 68°C (2 mm Hg), n_D^{18} 1.4473. IR spectrum (ν, cm^{-1}): 790, 820, 850, 905, 960, 1015, 1050, 1100, 1120, 1180, 1230, 1250, 1320, 1380, 1460, 1700, 2360, 2895, 2950, 3020, 3535. UV spectrum (λ_{max}, nm): 203 (ε 7000). PMR spectrum (δ, ppm, J, Hz): 0.91t (3H, CH_3, J = 7), 0.94t (3H, CH_3, J = 7), 1.26d (3CH, CH_3, J = 7), 1.3-1.8m (6H, CH_2), 2.75d (1H, OH, J = 7), 4.31br.q (1H, HC^3, J = 7), 5.12m (1H, CH), 5.75 and 6.19s (2H, C_2C=C). Mass spectrum, m/z (relative intensity, %): M^+ 200 (5), 172 (15), 171 (50), 157 (15), 155 (15), 153 (20), 149 (40), 144 (15), 143 (15), 142 (15), 141 (15), 131 (20), 130 (100), 129 (30), 127 (25), 123 (15), 114 (20), 113 (75), 112 (100), 111 (50). Found, %: C, 66.03; H, 10.08%. $C_{11}H_{20}O_3$. Calculated, %: C, 65.97; H, 10.07%.

Acetate (VIII). The product was a colorless liquid and the yield was 88%; bp 70°C (2 mm Hg), n_D^{18} 1.4388. IR spectrum (ν, cm^{-1}): 875, 965, 1000, 1040, 1070, 1090, 1175, 1210, 1220, 1370, 1460, 1605, 1730, 2345, 2970, 3000. UV spectrum (λ_{max}, nm): 201 (ε 9500). PMR spectrum (δ, ppm, J, Hz): 0.8-1.0m (6H, CH_3), 1.25d (3H, CH_3, J = 7), 1.3-1.8m (6H, CH_2), 2.08s (3H, CH_3CO), 5.01m (1H, CH), 5.58 br.t (1H, HC^3, J = 7), 5.72 and 6.27s (2H, H_2C=C). Mass spectrum, m/z (relative intensity, %): 202 (5), 200 (10), 199 (10), 171 (10), 155 (50), 149 (15), 143 (15), 142 (10), 130 (15), 129 (50), 125 (15), 113 (50), 112 (100), 111 (30), 107 (10), 101 (30), 97 (15), 96 (20), 95 (50). Found, %: C, 64.64; H, 9.19%. $C_{13}H_{22}O_4$. Calculated, %: C, 64.44; H, 9.15%.

1-Methylbutyl 4-Methyl-2-methylene-3-hydroxypentanoate (VII). Similarly, from 1.7 g (12 mmoles) of (V), 1.03 g (14.3 mmoles) of isobutanol and 0.2 g (1.8 mmoles) of DABO we obtained 1.85 g (72%) of (VII); bp 72°C (2 mm Hg), n_D^{18} 1.4482. IR spectrum (ν, cm^{-1}): 790, 820, 855, 890, 960, 1030, 1115, 1180, 1224, 1270, 1320, 1385, 1465, 1625, 1700, 2890, 2940, 2960, 3020, 3605. UV spectrum (λ_{max}, nm): 203 (ε 7550). PMR spectrum (δ, ppm, J, Hz): 0.8-1.0m (9H, CH_3), 1.25d (3H, CH_3, J = 7), 1.3-1.8m (4H, CH_2), 1.91m (1H, HC^4), 2.79d (1H, OH, J = 7), 4.04 br.t (1H, HC^3, J = 7), 5.00m (1H, CH), 5.70 and 6.20s (2H, H_2C=C). Mass spectrum, m/z (relative intensity, %): M^+ 214 (5), 199 (5), 185 (10), 173 (80), 172 (70), 171 (100), 157 (20), 154 (20), 153 (50), 145 (80), 144 (100), 143 (75), 129 (70), 128 (80), 127 (100), 126 (100), 125 (50). Found, %: C, 67.33; H, 10.42%. $C_{12}H_{22}O_3$. Calculated, %: C, 67.26; H, 10.35%.

Acetate (IX). The product was a colorless liquid and the yield was 90%; bp 78°C (1 mm Hg), n_D^{18} 1.4408. IR spectrum (ν, cm^{-1}): 780, 790, 815, 960, 990, 1025, 1095, 1120, 1175, 1205, 1225, 1245, 1295, 1370, 1465, 1630, 1730, 2320, 2870, 2935, 2970, 3015. UV spectrum (λ_{max}, nm): 201 (ε 8250). PMR spectrum (δ, ppm, J, Hz): 0.8-1.0m (9H, CH_3), 1.27d (3H, CH_3, J = 7), 1.3-1.7m (4H, CH_2), 2.05m (1H, HC^4), 2.08s (3H, CH_3CO), 5.01m (1H, CH), 5.47d (1H, CH^3, J = 7), 5.68 and 6.29s (2H, H_2C=C). Mass spectrum, m/z (relative intensity, %): 216 (5), 214 (20), 213 (15), 200 (10), 199 (10), 186 (50), 185 (15), 172 (10), 171 (50), 170 (30), 169 (100), 168 (15), 153 (15), 145 (30), 144 (100), 143 (100), 129 (30), 128 (50), 127 (100), 126 (100), 125 (75). Found, %: C, 65.77; H, 9.56%. $C_{14}H_{24}O_4$. Calculated, %: C, 65.60; H, 9.44%.

Dominicalure 1 (X). To a stirred solution of 0.2 g (0.8 mmole) of (VIII) in 3 ml of THF at −50°C in an atmosphere of argon over 10 min we added 0.9 ml of a 1 M solution of $LiBHEt_3$ (0.9 mmole) in THF. The reaction mass was stirred at −50°C for 0.5 h and was then poured into an iced saturated solution of ammonium chloride and extracted with pentane. The extract was washed with a saturated solution of sodium chloride and dried with magnesium sulfate. The residue (0.3 g) was chromatographed on 30 g of silica gel. Gradient elution from hexane to ether (to 3% of the latter) gave 0.13 g (86%) of (X) in the form of a colorless liquid [6, 12, 13]; bp 60°C (3 mm Hg), n_D^{20} 1.4410. PMR spectrum (δ, ppm, J, Hz): 0.89t (3H, CH_3, J = 7), 1.02t (3H, CH_3, J = 7), 1.21d (3H, CH_3, J = 7), 1.3-1.7m

(4H, CH_2), 1.79 br.s (3H, $CH_3C{\equiv}C$), 2.15 quint (2H, HC^4, J = 7), 4.94m (1H, CH), 6.69 br.t (1H, HC^3, J = 7).

Dominicalure 2 (XI). Similarly, from 0.32 g (1.2 mmoles) of (IX) in 3 ml of THF and 1.37 ml of a 1 M solution of $LiBHEt_3$ (1.37 mmoles) in THF we obtained 0.22 g (89%) of (XI) in the form of a colorless liquid [6, 12, 13]; bp 65°C (2 mm Hg), n_D^{20} 1.4405. PMR spectrum (δ, ppm, J, Hz): 0.92t (3H, CH_3, J = 7), 1.02d (6H, CH_3, J = 7), 1.23d (3H, CH_3, J = 7), 1.3-1.7m (4H, CH_2), 1.83 br.s (3H, $CH_3C{\equiv}C$), 2.62m (1H, HC^4), 4.97m (1H, CH), 6.54d (1H, HC^3, J = 10).

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