REACTION OF β-4-ALKOXYBENZOYL-β(α)-BROMOACRYLIC ACIDS AND OF THEIR ESTERS WITH SODIUM METHYLATE AND ETHYLATE*

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Reaction of methyl-β-4-pentoxybenzoyl-β-bromoacrylate with sodium methylate in methanol resulted in β-4-pentoxybenzoyl-α,α-dimethoxypropionic acid (*I*) and its methyl ester *II*, β-4-pentoxybenzoyl-α-hydroxyacrylic acid (*VI*) and its methyl ester *VII*. Reaction of ethyl-β-4-pentoxybenzoyl-α-bromoacrylate with sodium ethylate in ethanol yielded β-4-pentoxybenzoyl-α,α-diethoxypropionic acid (*III*) and its ethyl ester *IV*. Acid *III* also was obtained in the reaction of methyl-β-4-pentoxybenzoyl-β-bromoacrylate with sodium ethylate in ethanol. Reaction of sodium β-4-pentoxybenzoyl-β-bromoacrylate with sodium ethylate in ethanol yielded acid *VI* and its ethyl ester *VIII*. An analogous reaction of sodium β-4-methoxybenzoyl-β-bromoacrylate with sodium ethylate in ethanol yielded β-4-methoxybenzoyl-α,α-diethoxypropionic acid (*V*), β-4-methoxybenzoyl-α-hydroxyacrylic acid (*IX*) and its ethyl ester *X*. Acid hydrolysis of *I*—*IV*, *VII*, *VIII* yielded acid *VI*, hydrolysis of *V* and *X* yielded acid *IX*. Acid *VI* was converted to ethyl ester *VIII*. The structure of *I*—*X* was confirmed by spectral analysis. In an orientative testing for antineoplastic activity *in vivo*, *I*, *III* and *VIII* inhibited the growth of some transplantable tumours and extended the survival of treated animals.

In the context of studying the derivatives of cytostatically active β-4-pentoxybenzoyl-β-bromoacrylic acid[1] and of β-4-methoxybenzoyl-β-bromoacrylic acid[2] we took up the reactions of these acids and of their esters with sodium methylate and ethylate.

Methyl-β-4-pentoxybenzoyl-β-bromoacrylate[3] reacted with sodium methylate in boiling methanol to a mixture of products, the number and relative proportion of which differed depending on the amount of alcoholate used and on the type of treatment of the reaction mixture. Using 1 equivalent of sodium methylate and, shaking the aqueous extract of the reaction mixture residue with ether resulted in a 72% yield of methyl-β-4-pentoxybenzoyl-α,α-dimethoxypropionate (*II*); β-4-pentoxybenzoyl-α-hydroxyacrylic acid *VI* was obtained in a 21% yield from the acidified aqueous fraction. Using 2 equivalents of sodium methylate and the same method of treatment, acidification of the aqueous fractions yielded 79% of methyl-β-4-pentoxybenzoyl-α-hydroxyacrylate (*VII*). Processing of this reaction mixture in the absence

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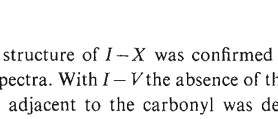
of water yielded besides 23% ester *II* also 59% of the sodium salt of β-4-pentoxybenzoyl-α,α-dimethoxypropionic acid (*I*). When using less than 1 equivalent of sodium methylate some *I*, *II*, *VI* and *VII* were formed but only in an amount proportional to the amount of methylate used, along with nonreacted starting methyl ester of β-4--pentoxybenzoyl-β-bromoacrylic acid. It is assumed that due to the methylate a dehydrobromination in position α,β of the starting ester and a subsequent addition of methanol to the triple bond takes place, giving rise to an α,α-dialkoxy-compound. An analogous addition of alcohol to a triple bond was observed *e.g.* by Bowden and coworkers[4] who exposed 1-phenyl-1-oxo-2-propine in ethanol to sodium ethylate and obtained 1,1-diethoxy-3-phenyl-3-propane; the course of this addition to the α-position agrees with the finding of Jones and coworkers[5] who obtained methyl--β-benzoyl-α-anilinoacrylate in a reaction of methyl-β-benzoylpropiolate with aniline; further acid hydrolysis of the product yielded β-benzoyl-α-hydroxyacrylic acid. The results permit one to draw the conclusion that the primarily formed ester *II* is converted (depending on reaction conditions) to acid *I* by saponification, to ester *VII* by hydrolysis while acid *I* and ester *VII* are further hydrolyzed to acid *VI*. An analogous instability of diacetals of keto acids was observed by Reimer and Kamerling[6] with the diacetal of methyl-4-*p*-methoxyphenyl-2-oxo-3-butenoate which, while quite resistant to alkaline treatment, is readily hydrolyzed in an acid aqueous medium to 4-*p*-methoxyphenyl-2-oxo-3-butenoic acid. Compounds *I*, *II* and *VII* were converted to acid *VI* by boiling in aqueous dioxane in the presence of a small amount of sulfuric acid. In a boiling solution of 1–2 molar equivalents of sodium ethylate in ethanol both *I* and *VI* are stable; when using 10 molar equivalents of sodium ethylate in ethanol, acid *VI* gave rise to a small amount of ethyl ester *VIII*. β-4-Pentoxybenzoyl-α,α-diethoxypropionic acid (*III*) was obtained in a 43% yield analogously to acid *I*, *i.e.* in a reaction of methyl-β-4-pentoxybenzoyl-β-bromoacrylate with 2 molar equivalents of sodium ethylate in ethanol. Ethyl ester *VIII* and acid *VI* were also obtained in a reaction of β-4-pentoxybenzoyl-β-bromoacrylic acid or of its sodium salt with a large excess of sodium ethylate in ethanol at a raised temperature.

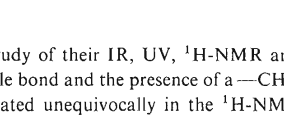
For the sake of comparison was studied the reaction using ethyl-β-4-pentoxybenzoyl -α-bromoacrylate as the starting compound. The reaction of this ester with two molar equivalents of sodium ethylate in boiling ethanol yielded some 15% ethyl--β-4-pentoxybenzoyl-α,α-diethoxypropionate (*IV*) plus a major amount (84%) of acid *III* which was identical with the compound obtained by an analogous reaction of methyl β-4-pentoxybenzoyl-β-bromoacrylate. It may be assumed that the reaction course is the same with both starting derivatives of α-bromo- and β-bromoacrylic acids. The ethyl ester *VIII*, like compounds *III* and *IV*, are converted to acid *VI* by boiling in an acid aqueous solutions. Acid *VI* is esterified to ester *VIII* by boiling with ethanol in the presence of sulfuric acid.

In further work we studied the reaction of β-4-methoxybenzoyl-β-bromoacrylic acid with sodium ethylate in ethanol. This reaction, too, proceeds by an analogous

mechanism and it was possible to isolate from the reaction mixture the following compounds: acid *V* (52%), β-4-methoxybenzoyl-α-hydroxyacrylic acid *IX* (10·8%) and ethyl β-4-methoxybenzoyl-α-hydroxyacrylate *X* (3·6%). Acid hydrolysis of *V* produced acid *IX* (ref.[7]). The reaction of sodium ethylate with β-4-methoxybenzoyl-β-bromoacrylic acid was studied by Nicholson[8] who also observed the formation of acid *V*.



I, $R^1 = C_5H_{11}$, $R^2 = R^3 = CH_3$, $R^4 = H$
II, $R^1 = C_5H_{11}$, $R^2 = R^3 = R^4 = CH_3$
III, $R^1 = C_5H_{11}$, $R^2 = R^3 = C_2H_5$, $R^4 = H$
IV, $R^1 = C_5H_{11}$, $R^2 = R^3 = R^4 = C_2H_5$
V, $R^1 = CH_3$, $R^2 = R^3 = C_2H_5$, $R^4 = H$



VI, $R^1 = C_5H_{11}$, $R^2 = H$
VII, $R^1 = C_5H_{11}$, $R^2 = CH_3$
VIII, $R^1 = C_5H_{11}$, $R^2 = C_2H_5$
IX, $R^1 = CH_3$, $R^2 = H$
X, $R^1 = CH_3$, $R^2 = C_2H_5$

The structure of *I*–*X* was confirmed by a study of their IR, UV, ^{1}H-NMR and mass spectra. With *I*–*V* the absence of the double bond and the presence of a —CH_2—-group adjacent to the carbonyl was demonstrated unequivocally in the ^{1}H-NMR spectrum (a singlet at 3·68–3·62 ppm, corresponding to two protons). For determining the positions of OR^2 and OR^3 substituents in compounds *I*–*V* mass spectra were used. In the case of *II*, the molecular ion found at 338 correspond to the suggested structure by its elementary composition $C_{18}H_{26}O_6$ and by the presence of an intense fragment at *m/e* 133; in its doublet the principal signal has the composition $C_5H_9O_4$ and of the fragment at *m/e* 233 ($C_{14}H_{17}O_3$) which is formed from *m/e* 248. It follows that both methoxy groups are situated at the α-carbon with respect to the carboxyl. A similar fragmentation is found in the ethoxy derivative *IV*. In the case of *V* there were intense fragments at 251 ($C_{14}H_{19}O_4$), and 161 ($C_7H_{13}O_4$) and further at 147 ($C_9H_7O_2$), 177 ($C_{10}H_9O_3$) and 206 ($C_{12}H_{14}O_3$), the last three of which convincingly support the substitution with two ethoxy groups at the α-carbon with respect to the carboxyl. Analogous results were obtained from the mass spectrum of *I* and *III*. Study of IR spectra of acids *I*, *III* and *V* displayed a substantial shift of ν(COOH) toward higher wavenumbers (1780 cm^{-1}) which is due to the presence of two alkoxy groups at the α-carbon. The same shift was found in the case of methoxy and ethoxy substituents. In the case of esters *II* and *IV* the maximum of the valence vibration band of the ester carbonyl is shifted toward higher wavenumbers (1755 cm^{-1}) even if to a lesser degree than with the acids. A convincing proof of the α-position of the hydroxy group in compounds *VI*–*X* was obtained from IR as well as UV spectrophotometry. The absorption curve of ethanol

solutions of these compounds displays in the region of 200–400 nm a relatively low maximum at 230–240 nm and a high maximum as 330–340 nm which indicate, in agreement with the literature[5], that the hydroxyl is placed at the α-carbon. This is in agreement with the IR spectra of *VI–X*; the relatively broad and high vibration band of the conjugated keto group does not lie at 1 680–1 690 cm^{-1}, like with *I–V*, but is shifted up to 1 600 cm^{-1} where it merges with the absorption bands of the *para*-substituted aromatic rings. This behaviour is characteristic for α,β-unsaturated β-hydroxy ketones where this shift is brought about by the inner chelate being formed —C(=O)—CH=C(—O)—. This has the other consequence that the absorption of the hydroxyl

O·····H—O

is displayed in the IR spectrum merely by a broad absorption band at 2800–3000 cm^{-1}; in the NMR spectrum the signal belonging to the hydroxyl proton is missing altogether.

Compounds *I*, *III*, *V*, *VI* and *VIII* were orientatively evaluated for antineoplastic activity in H strain mice with transplanted tumours: Crocker solid sarcome 180 (S 180), gland adenocarcinome (HK), ascitic carcinome 37 (S 37); further in Wistar rats with a Yoshida transplantable ascitic sarcome (Y). The compounds were administered *per os* in daily doses of 50 and 100 mg/kg, or 200 mg/kg in the case of *I* and *III*, in an aqueous suspension. In animals with solid tumours the compounds were applied beginning on the 7th day after transplantation of tumour cells, in a total of ten daily doses; in animals with the ascitic tumour on the 1st day after transplantation, in a total of 5 daily doses. In the case of rats with a Y tumour, the effect of the compounds on survival only was studied. Tumour size or the survival of control animals were taken as 100%. Compound *I*, applied in a daily dose of 100 mg/kg, inhibited the growth of HK tumours by 30%, with a survival extension by 41%; compound *III*, in a daily dose of 200 mg/kg, inhibited tumour growth by 30% with a survival extension of 30%; in the case of *VIII*, an application of 100 mg/kg inhibited tumour growth by 41% without any effect on survival. A significant extension of survival of animals bearing the S 180 tumour (by 37%) was achieved by *VIII* in a daily dose of 50 mg/kg, tumour growth being inhibited by 16%. Survival of animals with the Y tumour was improved by 23% after *VIII* in a daily dose of 100 mg/kg. Details on the biological evaluation will be published elsewhere.

EXPERIMENTAL

The melting points of compounds reported in this paper were determined in a capillary and are not corrected. Compounds for analysis, unless stated otherwise, were dried at 0·1 Torr at a temperature raised in proportion to their melting point. The purity of the compounds was followed by chromatography on a thin layer of Silufol UV_{254} using benzene with 3% acetic acid, and by paper chromatography using benzene with cyclohexane (1 : 9) as the mobile phase and dimethylformamide with phosphoric acid as the stationary phase. Detection was done by UV light

at 254 and 366 nm. The UV spectra were recorded in the form of 0·001% solutions in ethanol in 10 mm quartz cuvettes in an Optica Milano CF 4R apparatus. The IR spectra were recorded in the form of 5% solutions in chloroform in 0·1 mm NaCl cuvettes or in the form of KBr pellets (2 mg/600 mg KBr) in an Infrascan (Hilger and Watts) spectrophotometer. The ^{1}H-NMR spectra were measured in 8—10% solutions in a Tesla BS 487C spectrometer.

Reaction of Methyl β-4-Pentoxybenzoyl-β-bromoacrylate with Sodium Methylate in Methanol

A. *Using* 1 *molar equivalent of sodium methylate*: 3·55 g (0·01 mol) methyl β-4-pentoxybenzoyl-β-bromoacrylate was refluxed for 1 h with a solution of 0·01 mol sodium methylate in 100 ml methanol. The methanol was distilled in water-pump vacuum and the residue was extracted with a mixture of 25 ml water and 50 ml ether; the aqueous solution was shaken with 2 . 50 ml ether, the organic fractions were pooled, dried with Na_2SO_4 and the ether removed from the filtrate by distillation in water-pump vacuum. The oily residue (2·44 g; 72%) was chromatographed on a column of silica gel (50 g) using benzene for elution. The homogeneous fractions were pooled (2 g; 59%) and dried for analysis at 60°C/0·1 Torr; they form a colourless oil, n_D^{20} 1·5171, methyl β-4-pentoxybenzoyl-α,α-dimethoxypropionate (*II*). For $C_{18}H_{26}O_6$ (338·4) calculated: 63·88% C, 7·74% H; found; 64·15% C, 7·85% H. UV spectrum: maximum at 281 nm, log ε = = 4·29. IR spectrum ($CHCl_3$): 1 753 cm^{-1} (ester), 1 673 cm^{-1} (ArCO), 1 508 and 835 cm^{-1} (*para*-subst. aromatic part.) ^{1}H-NMR-spectrum ($CDCl_3$): δ 7·89 and 6·88 (ABq, J = 9·0 Hz, aromatic H, 4 H); δ 3·99 (t, J = 6·0 Hz, $ArOCH_2$, 2 H); δ 3·75 (s, —OCH_3 ester, 3 H); δ 3·62 (s, $ArCOCH_2$, 2 H); δ 3·30 (s, —OCH_3 ether, 6 H); δ 1·10—2·00 (m, aliphatic CH_2, 6 H); δ 0·90 (t, aliphatic CH_3, 3 H).

The aqueous fraction was acidified with dilute sulfuric acid (1 : 3) and extracted with 4 . 50 ml ether. The combined ether fractions were dried with Na_2SO_4, the ether removed from the filtrate by distillation and the residue was recrystallized from a mixture of benzene and hexane; 0·6 g (21·5%), m.p. 116—117°C. β-4-Pentoxybenzoyl-α-hydroxyacrylic acid (*VI*) was recrystallized for analysis from benzene, m.p. 117—118°C. For $C_{15}H_{18}O_5$ (278·3) calculated: 64·73% C, 6·51% H; found: 64·86% C, 6·88% H. UV spectrum: maximum at 332 nm, (log ε 4·35) and of 230 nm, (log ε 3·89). IR spectrum (KBr): 1 712 cm^{-1} (—COOH), 1 605 cm^{-1} (ArCO···HO—), 1 512 and 833 cm^{-1} (*para*-substituted aromatic ring). ^{1}H-NMR spectrum(hexadeuteriodimethyl sulfoxide): δ 7·96 and 6·96 (ABq, J = 9·0 Hz, aromatic H, 4 H); δ 6·98 (s, olefinic H, 1 H); δ 3·99 (t, J = = 6·0 Hz, $ArOCH_2$, 2 H); δ 1·10—2·00 (m, aliphatic H, 6 H); δ 0·83 (t, aliphatic CH_3, 3 H).

B. *Using* 2 *molar equivalents of sodium methylate*: 3·55 g (0·01 mol) methyl β-4-pentoxybenzoyl-β-bromoacrylate was refluxed with 0·02 mol sodium methylate in 100 ml methanol for 1 h. The methanol was distilled in water-pump vacuum and the residue was extracted with a mixture of 30 ml water and 75 ml ether. The aqueous fraction was separated, acidified with dilute sulfuric acid (1 : 3) and shaken with 4 . 50 ml ether; the ether extracts were pooled, dried with Na_2SO_4 and the ether was removed by distillation under water-pump vacuum. The residue (3·22 g) was chromatographed on a column of silica gel (50 g) using benzene for elution. The homogeneous front fractions were pooled (2·32 g, 79·3%) and recrystallized from a mixture of benzene and hexane. The yield was 2·11 g methyl β-4-pentoxybenzoyl-α-hydroxyacrylate (*VII*); m.p. 56—58°C. For $C_{16}H_{20}O_5$ (292·3) calculated: 65·73% C, 6·89% H; found: 65·91% C, 6·88% H. UV spectrum: maximum at 337 nm (log ε = 4·34) and at 232 nm (log ε 3·89). IR spectrum (KBr): 1 753 cm^{-1} (ester), 1 603 cm^{-1} (ArCO···H—O—), 1 520 and 830 cm^{-1} (*para*-substituted aromatic). ^{1}H-NMR spectrum ($CDCl_3$): δ 8·00 and 6·95 (ABq, J = 9·0 Hz, aromatic H, 4 H); δ 7·02 (s, olefinic H, 1 H); δ 4·03 (t, J = 6·0 Hz, $ArOCH_2$, 2 H); δ 3·95 (s, —OCH_3 ester, 3 H); δ 1·10—2·00 (m, aliphatic CH_2, 6 H); δ 0·95 (t, aliphatic CH_3, 3 H).

C. *Using 2 molar equivalents of methylate, processed in the absence of water*: 25·9 g (0·073 mol) methyl β-4-pentoxybenzoyl-β-bromoacrylate was refluxed with 0·145 mol sodium methylate (prepared from 3·35 g sodium) in 600 ml methanol for 1 h. Methanol was removed by distillation in water-pump vacuum, the residue was heated with 60 ml benzene and the undissolved inorganic fraction was filtered. The filtrate was chromatographed on a column of silica gel (80 g) using benzene for elution (or benzene plus 10% methanol for the tail fractions). The homogeneous front fractions were pooled and the oily product (5·7 g; 23%) chromatographed on a column of silica gel using benzene for elution. The oily product, n_D^{20} 1·5174, corresponds to ester *II* obtained under (*A*). The homogeneous tail fractions from the first chromatography were pooled (14·9 g; 59·2%) and recrystallized from benzene. A total of 9 g sodium β-4-pentoxybenzoyl--α,α-dimethoxypropionate was obtained, melting at 153°C. For analysis it was recrystallized from a mixture of benzene–methanol–hexane: m.p. 154—155°C. For $C_{17}H_{23}NaO_6$ (346·4) calculated: 58·94% C, 6·69% H, 6·64% Na; found: 58·48% C, 6·60% H, 6·66% Na.

β-4-Pentoxybenzoyl-α,α-dimethoxypropionic acid (*I*) was obtained from the sodium salt practically quantitatively by shaking with a mixture of 10% sulfuric acid with ether at 0°C. The ether was dried with Na_2SO_4, the ether was removed by distillation in water-pump vacuum and the residue was recrystallized from a mixture of benzene with hexane; m.p. 87—89°C. For $C_{17}H_{24}O_6$ (324·4) calculated: 62·95% C, 7·45% H; found: 63·05% C, 7·61% H. UV spectrum: maximum at 280 nm ($\log \varepsilon$ 4·28). IR spectrum ($CHCl_3$): 1 782 cm^{-1} (—COOH), 1 680 cm^{-1} (ArCO), 1 512 and 835 cm^{-1} (*para*-substituted aromatic ring). ^{1}H-NMR spectrum ($CDCl_3$): δ 9·50 (bs, —COOH, 1 H); δ 7·89 and 6·88 (ABq, J = 9·0 Hz, aromatic H, 4 H); δ 4·00 (t, J = = 6·0 Hz, $ArOCH_2$, 2 H); δ 3·65 (s, $ArCOCH_2$, 2 H); δ 3·28 (s, —OCH_3 ether, 6 H); δ 1·10 to 2·00 (m, aliphatic CH_2, 6 H); δ 0·90 (t, aliphatic CH_3, 3 H).

Reaction of Ethyl β-4-Pentoxybenzoyl-α-bromoacrylate with Sodium Ethylate in Ethanol

9·25 g (0·025 mol) ethyl β-4-pentoxybenzoyl-α-bromoacrylate was refluxed with a solution of 0·05 mol sodium ethylate in 150 ml ethanol for 1 h. Ethanol was distilled under water-pump vacuum and the residue extracted with a mixture of 125 ml water and 250 ml ether. The ether fraction was extracted with 20 ml 5% $NaHCO_3$ and 2 . 10 ml water, dried with Na_2SO_4 and the ether distilled under water-pump vacuum. The oily residue (1·4 g, 15%) was chromatographed on a column of silica gel (25 g) using benzene for elution; the pooled homogeneous fractions (1·2 g) of ethyl β-4-pentoxybenzoyl-α,α-diethoxypropionate (*IV*) were dried at 50°C/0·1 Torr; n_D^{20} 1·5047. For $C_{21}H_{32}O_6$ (380·4) calculated: 66·28% C, 8·47% H; found: 66·43% C, 8·30% H. UV spectrum: maximum at 281 nm ($\log \varepsilon$ 4·28). IR spectrum ($CHCl_3$): 1 757 cm^{-1} (ester), 1 681 cm^{-1} (ArCO), 1 518 and 848 cm^{-1} (*para*-substituted aromatic rings). ^{1}H-NMR spectrum ($CDCl_3$): δ 7·78 and 6·95 (ABq, J = 9·0 Hz, aromatic H, 4 H); δ 4·20 (q, J = 7·0 Hz, —CH_2—, ester, 2 H); δ 3·97 (t, J = 6·0 Hz, $ArOCH_2$, 2 H); δ 3·60 (s, $ArCOCH_2$, 2 H); δ 3·52 (q, J = 7·0 Hz, —CH_2—, ether, 4 H); δ 1·10—2·00 (m, aliphatic CH_2, 6 H); δ 1·26 (t, J = 7·0 Hz, —CH_3, ester, 3 H); δ 1·17 (t, J = 7·0 Hz, —CH_3, ether, 6 H); δ 0·90 (t, aliphatic CH_3, 3 H).

The aqueous fraction was acidified at 0°C with dilute sulfuric acid (1 : 3) and extracted with 3 . 50 ml ether. The combined ether fractions were dried with Na_2SO_4, the ether removed by distillation under water-pump vacuum and the residue (7·4 g) was recrystallized from cyclohexane; 6·6 g (75·2%), m.p. 75—78°C. β-4-Pentoxybenzoyl-α,α-diethoxypropionic acid (*III*) was crystallized for analysis from cyclohexane, m.p. 79—82°C. For $C_{19}H_{28}O_6$ (352·4) calculated: 64·75%C, 8·00% H; found: 64·91% C, 7·94% H. UV spectrum: maximum at 279 nm ($\log \varepsilon$ 4·26). IR spectrum ($CHCl_3$): 1 782 cm^{-1} (—COOH), 1 682 cm^{-1} (ArCO), 1 518 and 840 cm^{-1} (*para*-substituted aromatic ring). ^{1}H-NMR spectrum ($CDCl_3$): δ 8·80 (bs, —COOH, 1 H); δ 7·88 and 6·88 (ABq, J = 9·0 Hz, aromatic H, 4 H); δ 4·00 (t, J = 6·0 Hz, $ArOCH_2$, 2 H); δ 3·68 (s, $ArCOCH_2$,

2 H); δ 3·52 (q, J = 7·0 Hz, —CH_2—, ether, 4 H); δ 1·10—2·00 (m, aliphatic CH_2, 6 H); δ 1·20 (t, J = 7·0 Hz, —CH_3, ether, 6H); δ 0·88 (t, aliphatic CH_3, 3 H).

Reaction of Methyl β-4-Pentoxybenzoyl-β-bromoacrylate with Sodium Ethylate in Ethanol

3·55 g (0·01 mol) methyl β-4-pentoxybenzoyl-β-bromoacrylate was refluxed with 0·02 mol sodium ethylate in 100 ml ethanol for 1 h. The ethanol was distilled under water-pump vacuum, the residue (4·2 g) was heated with 50 ml benzene and the nondissolved inorganic fraction was filtered. The filtrate was chromatographed on a column of silica gel (35 g) using benzene or benzene with 10%, ethanol for elution. The homogeneous tail fractions were pooled (1·61 g) and extracted with a mixture of 40 ml 10% sulfuric acid and 250 ml ether at 0°C. The aqueous fraction was extracted with 100 ml ether and the combined ether extracts were dried with Na_2SO_4 and the ether was removed by distillation under water-pump vacuum. The residue (1·55 g, 43%) was crystallized from cyclohexane to yield acid *III*.

Reaction of Sodium β-4-Pentoxybenzoyl-β-bromoacrylate with 10 Equivalents of Sodium Ethylate in Ethanol

18·2 g (0·05 mol) sodium β-4-pentoxybenzoyl-β-bromoacrylate was introduced into a solution of 0·5 mol sodium ethylate in 750 ml ethanol and the mixture was stirred for 4 h at 65°C. The residue was dissolved in 500 ml water, acidified with sulfuric acid (1 : 2) at 0°C to Congo red and extracted with ether (4 . 150 ml). The pooled ether extracts were dried with Na_2SO_4, the ether was evaporated in water-pump vacuum and the residue (16·7 g) was chromatographed on a column fo silica gel (60 g) using chloroform or chloroform with 10% ethanol for elution. The homogeneous front fractions were combined and recrystallized from hexane; 7·5 g (50%), m.p. 40—41°C. Ethyl β-4-pentoxybenzoyl-α-hydroxyacrylate (*VIII*) was crystallized for analysis from hexane, m.p. 40—41°C. For $C_{17}H_{22}O_5$ (306·3) calculated: 66·25% C, 7·24% H; found: 66·54% C, 7·17% H. UV spectrum: maximum at 339 nm ($\log \varepsilon$ 4·34) and at 231 nm ($\log \varepsilon$ 3·88). IR spectrum ($CHCl_3$): 1730 cm^{-1} (ester), 1600 cm^{-1} (ArCO···H—O—), 1514 and 828 cm^{-1} (*para*-substituted aromatic rings).

^{1}H-NMR spectrum ($CDCl_3$): δ 8·01 and 6·96 (ABq, J = 9·0 Hz, aromatic H, 4 H); δ 7·05 (s, olefinic H, 1 H); δ 4·35 (q, J = 7·0 Hz, —CH_2, ester, 2 H); δ 4·00 (t, J = 6·0 Hz, $ArOCH_2$, 2 H); δ 1·10—2·00 (m, aliphatic CH_2, 6 H); δ 1·37 (t, J = 7·0 Hz, —CH_3, ester, 3 H), δ 0·90 (t, aliphatic CH_3, 3 H). The corresponding tail fractions from elution chromatography were combined and recrystallized from chloroform. The yield of crude *VI* was 1·95 g (13%, m.p. 108—110°C).

Reaction of β-4-Methoxybenzoyl-β-bromoacrylic Acid with Sodium Ethylate

A solution of 14·3 g (0·05 mol) β-4-methoxybenzoyl-β-bromo-acrylic acid in 200 ml ethanol was stirred at 20°C, poured into a solution of 0·1 mol sodium ethylate in 300 ml ethanol and the mixture was stirred for 4 h at 65°C. The ethanol was distilled under water-pump vacuum, the residue was dissolved in 250 ml water and acidified with dilute sulfuric acid (1 : 2) to Congo red under cooling with ice. The mixture was shaken with ether (7 . 200 ml) and the ether fractions after drying with Na_2SO_4 were freed of ether by distillation under water-pump vacuum. The residue (14 g) was chromatographed on a column of silica gel (60 g) using chloroform or chloroform with 10% ethanol for elution. The corresponding homogeneous front fractions were pooled (0·9 g) and recrystallized from a mixture of benzene with hexane. A total of 0·45 g (3·6%) ethyl

β-4-methoxybenzoyl-α-hydroxyacrylate (*X*) was obtained; m.p. 41—42°C; this was recrystallized for analysis from the same solvent; m.p. 45—47°C. For $C_{13}H_{14}O_5$ (250·2) calculated: 62·39% C, 5·64% H; found: 62·19% C, 5·74% H. UV spectrum: maxima at 335 nm (log ε 4·33) and at 241 nm, (log ε 3·87). IR spectrum ($CHCl_3$): 1728 cm^{-1} (ester), 1601 cm^{-1} (ArCO···H—O—), 1512 and 828 cm^{-1} (*para*-substituted aromatic rings). ^{1}H-NMR spectrum ($CDCl_3$): δ 7·90 and 6·86 (ABq, J = 9·0 Hz, aromatic rings H, 4 H); δ 6·91 (s, olef. H, 1 H); δ 4·30 (q, J = 7·0 Hz, —CH_2—, ester, 2 H); δ 3·76 (s, $ArOCH_3$, 3 H); δ 1·36 (t, J = 7·0 Hz, —CH_3, ester, 3 H).

The pooled corresponding middle fractions (9·7 g) were recrystallized from ethanol, 7·62 g (52%), m.p. 122—125°C. The β-4-methoxybenzoyl-α,α-diethoxypropionic acid (*V*) obtained was crystallized for analysis from ethanol, m.p. 128—129°C. For $C_{15}H_{20}O_6$ (296·3) calculated: 60·79% C, 6·80% H; found: 60·59% C, 7·03% H. UV spectrum: maximum at 279 nm (log ε 4·26). IR spectrum ($CHCl_3$): 1782 cm^{-1} (—COOH), 1680 cm^{-1} (ArCO), 1512 and 830 cm^{-1} (*para*-substituted aromatic rings). ^{1}H-NMR spectrum ($CDCl_3$): δ 9·35 (bs, —COOH, 1 H); δ 7·88 and 6·86 (ABq, J = 9·0 Hz, aromatic H, 4 H); δ 3·78 (s, $ArOCH_3$, 3 H); δ 3·64 (s, $ArCOCH_2$, 2 H); δ 3·50 (q, J = 7·0 Hz, —CH_2—, ether, 4 H); δ 1·20 (t, J = 7·0 Hz, —CH_3—, ether, 6 H). The combined tail fractions (3·5 g) were crystallized from ethanol to 1·20 g (10·8%) β-4-methoxybenzoyl-α-hydroxyacrylic acid (*IX*), m.p. 162—164°C (ref.[7] reports 162·5°C for anisoylpyruvic acid with 1 H_2O). For $C_{11}H_{10}O_5$ (222·2) calculated: 59·48% C, 4·54% H; found: 59·72% C, 4·43% H. UV spectrum: maxima at 332 nm, (log ε 4·33) and at 232 nm (log ε 3·88). IR spectrum (KBr): 1740 cm^{-1} (—COOH), 1602 cm^{-1} (ArCO···H—O—), 1516 and 824 cm^{-1} (*para*-substituted aromatic rings). ^{1}H-NMR spectrum (hexadeuteriodimethylsulfoxide): δ 9·20 (bs, COOH, 1 H); δ 8·00 and 7·01 (ABq, J = 9·0 Hz, aromatic H, 4 H); δ 6·99 (s, olefinic H, 1 H); δ 3·79 (s, $ArOCH_3$, 3 H).

Hydrolysis of β-4-Pentoxybenzoyl-α,α-diethoxypropionic Acid (*III*)

A mixture of 1·0 g (0·028 mol) acid *III*, 50 ml 50% aqueous dioxane and 3 drops of sulfuric acid was refluxed for 2 h. After standing overnight at 5°C, the precipitated acid *VI* was filtered (0·58 g, 73·5%, m.p. 110—115°C) and recrystallized from benzene: 0·44 g, m.p. 117—118°C. The same procedure was used for hydrolyzing *I*, *II*, *IV*, *VII*, and *VIII* which yielded a crude product which was recrystallized (possibly after silica gel chromatography with benzene or benzene plus 5% ethanol for elution) to homogeneous *VI*.

Hydrolysis of *V* and *X* was carried out analogously, obtaining a crude product which was purified to result in acid *IX*.

Esterification of β-4-Pentoxybenzoyl-α-hydroxyacrylic Acid (*VI*)

A mixture of 1·0 g (0·035 mol) acid *VI*, 100 ml ethanol and 3 drops of sulfuric acid was refluxed for 2 h. Ethanol was distilled under water-pump vacuum, the residue was extracted with 100 ml ether, the solution filtered and evaporated to dryness. The residue was dissolved in benzene and chromatographed on a column of silica gel (25 g) using the same solvent for elution. Individual front fractions were combined (1 g) and recrystallized from hexane; a total of 0·83 g (76%) ester *VIII* was obtained (m.p. 40°C).

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