SYNTHESIS AND SAPONIFICATION OF ETHYL ESTERS OF *cis*- AND *trans*-β-4-ALKOXYBENZOYL-β- AND -α-BROMOACRYLIC ACIDS*

V.ZIKÁN, M.SEMONSKÝ, H.ŠKVOROVÁ, B.KAKÁČ, J.HOLUBEK and H.VESELÁ

Research Institute of Pharmacy and Biochemistry, 130 60 Prague 3

Received December 18th, 1975

Wittig's method was used for synthesizing the ethyl esters of β-4-pentoxybenzoyl- and β-4-methoxybenzoyl-β-bromoacrylic acid (*V*, *XI*) which represent mixtures of 70–75% *trans* and 25–30% *cis*: Br, H isomers. Saponification, using a mixture of dilute sulfuric and acetic acids, of ester *V* yielded β-4-pentoxybenzoyl-β-bromoacrylic acid (*VIII*), a mixture of *cis* with some 10% *trans*: Br, H isomer; that of ester *XI* yielded *cis*-β-4-methoxybenzoyl-β-bromoacrylic acid (*XII*). When a mixture of hydrobromic and acetic acids was used, ester *V* yielded a mixture of substances from which *threo*-β-4-pentoxybenzoyl-α,β-dibromopropionic acid (*VI*) and *trans*-β-4-pentoxybenzoylacrylic acid (*VII*) were isolated. The methyl ester of *cis*-β-4-pentoxybenzoyl-β-bromoacrylic acid (*IX*) was prepared in a reaction of diazomethane with the *cis* acid. Wittig's method was used to synthesize the ethyl ester of β-4-pentoxybenzoyl-α-bromoacrylic acid (*XIII*), a mixture of 79% *trans* and 21% *cis*: Br, H isomers. Saponification of ester *XIII* yielded the *trans* acid *XIV*. None of *V*, *IX*, *XI*, *XIII* and *XIV* displayed an appreciable antineoplastic effect in mice and rats with transplanted tumours.

In connection with studying the properties of *cis*-β-4-pentoxybenzoyl-β-bromoacrylic acid (*cis*: Br, H) (ref.[1]) which is antineoplastically active against experimental tumours in animals upon oral application, as well as in the context of examining the cytostatically active *cis*-β-4-methoxybenzoyl-β-bromoacrylic acid** the preparations of some novel derivatives of the above acids was taken up here.

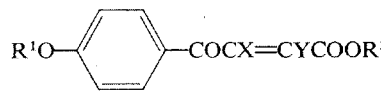
To prepare the *trans* isomers of the esters Wittig's reaction was used. The starting 4-pentoxy-ω-bromoacetophenone (*I*) was obtained by bromination of 4-pentoxyacetophenone in dioxane and diethyl ether. Its reaction with triphenylphosphine led to triphenyl(4-pentoxybenzoyl)methylphosphonium bromide (*II*) which was converted to triphenyl(4-pentoxybenzoyl)methylenephosphorane (*III*) and this was then brominated to triphenyl(4-pentoxybenzoyl)bromomethylenephosphorane (*IV*). Compound *IV* reacted with the ethyl ester of glyoxylic acid to the ethyl ester of β-4-pentoxy-

* Part LVII in the series Substances with Antineoplastic Activity; Part LVI: This Journal *40*, 2883 (1975).

** The sodium salt of *cis*-β-4-methoxybenzoyl-β-bromoacrylic (*cis*: Br, H) acid is an active component of the cytostatic Cytembena-Spofa.

benzoyl-β-bromoacrylic acid (*V*). The ^{1}H-NMR spectrum of ester *V* showed the product to be a mixture of about 70–75% *trans* and 25–30% *cis* isomers. Saponification of ester *V* by boiling in a mixture of hydrobromic and acetic acids resulted in a product which was chromatographed on a column of silica gel and resolved into *threo*-β-4-pentoxybenzoyl-α,β-dibromopropionic acid (*VI*) and *trans*-β-4-pentoxybenzoylacrylic acid (*VII*). Boiling of ethyl ester *V* with a mixture of dilute sulfuric and acetic acids yielded β-4-pentoxybenzoyl-β-bromoacrylic acid (*VIII*) which is, according to ^{1}H-NMR spectra, a mixture of the *cis* with some 10% *trans* isomer.

For a comparison with analogous 4-methoxybenzoyl compounds, triphenyl-(4-methoxybenzoyl)bromomethylenephosphorane (*X*) was prepared. This was condensed with the ethyl ester of glyoxylic acid to the ethyl ester of β-4-methoxybenzoyl--β-bromoacrylic acid (*XI*) which is a mixture of 70–75% *trans* and 25–30% *cis* isomers, like ester *V*. Boiling of ester *XI* with dilute sulfuric and acetic acids yielded *cis*-β-4-methoxybenzoyl-β-bromoacrylic acid (*XII*) which is identical with the authentic sample[2]. To check the configuration of the *cis* isomers present in ester *V* or in acid *VIII*, authentic *cis*-β-4-pentoxybenzoyl-β-bromoacrylic acid[1] was methylated with diazomethane to a homogeneous methyl ester of *cis*-β-4-pentoxybenzoyl-β-bromoacrylic acid (*IX*). Comparison of the chemical shifts of (=C*H*) in the ^{1}H-NMR spectra yielded the corresponding values for the *cis*: Br, H isomers found in compounds *V* and *VIII*, as well as in compounds *XI* and *XII*.



	R¹	X	Y	R²
V	C_5H_{11}	Br	H	C_2H_5
VIII	C_5H_{11}	Br	H	H
IX	C_5H_{11}	Br	H	CH_3
XI	CH_3	Br	H	C_2H_5
XII	CH_3	Br	H	H
XIII	C_5H_{11}	H	Br	C_2H_5
XIV	C_5H_{11}	H	Br	H

In further work we were interested in a comparison of the antineoplastic activity of β-4-pentoxybenzoyl-β-bromoacrylic acid and of its α-analogue, *i.e.* β-4-pentoxybenzoyl-α-bromoacrylic acid. Condensation with triphenylethoxycarbonylbromomethylenephosphorane with 4-pentoxyphenylglyoxal yielded the ethyl ester of β-4-pentoxybenzoyl-α-bromoacrylic acid (*XIII*) which, according to the chemical shifts of (=CH), is a mixture of 79% *trans* and 21% *cis* isomers. Boiling of ethyl ester *XIII* with dilute acetic and sulfuric acids yielded *trans*-β-4-pentoxybenzoyl-α-bromo-

acrylic acid (*XIV*). Saponification of ester *XIII* led to the formation of an energetically more stable acid *XIV*; in the series of β-bromo derivatives, esters *V* and *XI* were saponified to the *cis* isomer, or to the *cis* isomer with a small amount of the *trans* isomer of acid *XII* or *VIII*.

Compounds *V*, *IX*, *XI*, *XIII*, *XIV* were orientatively evaluated for antineoplastic activity in female mice of strain H with transplantable tumours: Crocker's solid sarcome 180 (S 180), mammary adenocarcinome (HK) and ascitic sarcome 37 (S 37); further in Wistar rats with Yoshida's transplantable ascitic sarcome (Y). The compounds were applied in daily doses of 100 and 200 mg/kg *p.o.* in an aqueous suspension and in an olive oil suspension, on the 8th day after transplantation in the case of solid tumours in a total of 10 daily doses, and on the day after transplantation, in a total of 8 daily doses in the case of the S 37 tumour and in 5 doses in the case of the Y tumour. The size of the tumours and the survival of the control group of animals is taken as 100%. Compound *V*, in a daily dose of 200 mg/kg resulted in a survival increase by 20% in the case of the S 180 tumour while it had no effect on tumour size. In the case of the S 37 tumour, application of *XI* in a daily dose of 200 mg/kg, inhibited tumour growth by 27%, application of *IX* in a daily dose of 100 mg/kg by 23%, without any effect on survival. In the case of *IX* and *XIII*, at daily doses of 100 mg/kg, the survival period of treated animals with the Y tumour was increased by 35 and 31%, respectively; with *XIV* at a daily dose of 200 mg/kg, by 34%. Detailed information on the results of the testing will be published elsewhere.

EXPERIMENTAL

The melting points of the compounds shown here were determined in a capillary and are not corrected. Compounds 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 checked by thin-layer chromatography on Silufol UV_{254} in benzene with 1% acetic acid for *VII*, *XII*, or in benzene with 5% acetic acid for *XIV*; benzene with methanol (7 : 3) for *III*, *IV*, *X*; benzene for *I*, *V*, *XI*, *XIII*. The IR spectra were recorded in an Infrascan (Hilger and Watts) spectrophotometer, in a chloroform solution (*c* 5%, 0·1 mm NaCl cuvette), or in the form of KBr pellets. The ^{1}H-NMR spectra were recorded in a Tesla 487 C spectrometer (80 MHz, $CDCl_3$ or hexadeuteriodimethyl sulfoxide, *c* 8—10%; tetramethylsilane as standard).

4-Pentoxy-ω-bromoacetophenone (*I*)

Bromine (58·2 g, 0·36 mol) was added dropwise at 20°C and under stirring to a solution of 75 g (0·36 mol) 4-pentoxyacetophenone[3] in 90 ml dioxane and 140 ml ether and the mixture was stirred for 45 min. After adding 90 ml ether and 90 ml water the mixture was shaken and the organic layer separated. After drying (Na_2SO_4) and filtration the solvents were distilled in water-pump vacuum. The viscous residue was dried at 40°C/3 Torr (51·2 g, 50%) and recrystallized from cyclohexane; 35·1 g, m.p. 33°C. For $C_{13}H_{17}BrO_2$ (285·2) calculated: 54·75% C, 6·01% H, 28·02% Br; found: 54·62% C, 5·95% H, 27·92% Br.

Triphenyl(4-pentoxybenzoyl)methylphosphonium Bromide (*II*)

A solution of 29 g (0·11 mol) triphenylphosphine in 165 ml benzene was added to a solution of 31 g (0·1 mol) 4-pentoxy-ω-bromoacetophenone (*I*) in 165 ml benzene at 20°C and the mixture was stirred for 5 min and then left to stand for 3 h at 0°C. Filtration produced 35·4 g (60%) pro-

duct melting at 70—72°C which crystallized from aqueous ethanol to a m.p. of 87—89°C. For $C_{31}H_{32}BrO_2P$ (547·5) calculated: 68·00% C, 5·89% H, 14·59% Br; found: 68·36% C, 5·98% H, 14·47% Br.

Triphenyl(4-pentoxybenzoyl)methylenephosphorane (*III*)

A solution of 0·64 g (0·028 mol) sodium in 25 ml ethanol was added dropwise under stirring over a period of 10 min at 20°C to a suspension of 10 g (0·018 mol) triphenyl(4-pentoxybenzoyl) methylphosphonium bromide (*II*) in 25 ml ethanol. 150 ml chloroform was added dropwise to the mixture under stirring and after 10 min the precipitated sodium bromide was filtered off and the filtrate freed of solvents by distillation in water-pump vacuum. The residue (8·5 g, 100%) was crystallized from ethyl acetate. A total of 6 g product melting at 178—180°C was obtained. For $C_{31}H_{31}O_2P$ (466·5) calculated: 79·80% C, 6·70% H, 6·64% P; found: 79·45% C, 7·01% H, 6·68% P.

Triphenyl(4-pentoxybenzoyl)bromomethylenephosphorane (*IV*)

A solution of 3·34 g bromine (0·021 mol) in 20 ml tetrachloromethane was added dropwise under stirring over a period of 10 min at —70°C to a solution of 9·32 g (0·02 mol) triphenyl(4-pentoxybenzoyl)methylenephosphorane (*III*) in 60 ml dichloromethane. The mixture was stirred for 10 min under cooling and for 1 h at room temperature, freed of solvents by distillation in water-pump vacuum and the residue (14 g) was dissolved under stirring at 20°C in 50 ml of a mixture of acetone and water (4 : 3). The solution was filtered, alkalified with 1M-NaOH to phenolphthalein, diluted with 50 ml water and left to stand overnight at 0°C. The filtered product was dried in a vacuum desiccator; 9·3 g (85%), m.p. 120—122°C, and recrystallized from aqueous acetone, m.p. 122—124°C. For $C_{31}H_{30}BrO_2P$ (545·4) calculated: 14·65% Br, 5·68% P; found: 14·52% Br, 5·66% P.

Ethyl Ester of β-4-Pentoxybenzoyl-β-bromoacrylic Acid (*V*) (mixture of about 70—75% *trans* and 25—30% *cis*: Br, H)

A solution of 0·75 g (0·0073 mol) ethyl ester of glyoxylic acid[4] in 30 ml benzene was added to a solution of 4 g (0·0073 mol) triphenyl(4-pentoxybenzoyl)bromomethylenephosphorane (*IV*) in 100 ml benzene and the mixture was refluxed for 4 h in an atmosphere of nitrogen. After standing overnight at 20°C the solvent was distilled in water-pump vacuum and the residue (5·26 g) was purified by chromatography on a column of silica gel (80 g), using benzene for elution. The front fractions were pooled, filtered and, after distillation of benzene in water-pump vacuum, the oily residue was dried at 40°C/0·5 Torr; 2·44 g (90%), n_D^{20} 1·5550. For $C_{17}H_{21}BrO_4$ (369·2) calculated: 55·29% C, 5·73% H, 21·64% Br; found: 55·23% C, 5·69% H, 21·45% Br. ^{1}H-NMR spectrum ($CDCl_3$): δ 6·75 (s (=CH) *trans*-isomer 70—75%), 6·56 (s, (=CH) *cis*-isomer 25—30%). IR spectrum ($CHCl_3$): 1720 (ester), 1665 (conjugated C=O), 1597, 1572 (conjugated C=O, aromatic vibrations), 1509, 826 cm^{-1} (*p*-substituted aromatic ring).

Saponification of the Ethyl Ester of β-4-Pentoxybenzoyl-β-bromoacrylic Acid (*V*)

A. Mixture of 5·56 g (0·015 mol) ethyl ester of β-4-pentoxybenzoyl-β-bromoacrylic acid (*V*), 93 ml glacial acetic acid and 18·7 ml 46% hydrobromic acid was refluxed for 1 h, cooled, diluted with 500 ml water and extracted with 5 × 250 ml ether. Pooled ether fractions were extracted with 2 × 50 ml water, dried (Na_2SO_4) and the filtrate was freed of solvents by distillation

in watter-pump vacuum. The residue was dried at 40°C/1 Torr (6·24 g) and separated by chromatography on a column of silica gel (70 g) using benzene, or benzene plus 1% methanol, for elution.

The combined front fractions (3·1 g) were crystallized from a mixture of benzene and cyclohexane to β-4-pentoxybenzoyl-α,β-dibromopropionic acid (*threo* — *VI*), m.p. 149—150°C. For $C_{15}H_{18}Br_2O_4$ (422·1) calculated: 42·67% C, 4·29% H, 37·86% Br; found: 42·78% C, 4·18% H, 37·46% Br. IR spectrum (KBr): 845 (*para*-substituted aromatic ring) 960 (—COOH), 1180 (aromatic ether), 1510, 1580, 1605 (Ar), 1675 (Ar—CO), 1715 (nonconjugated COOH), 2845, 2912 (CH_3, CH_2). ^{1}H-NMR spectrum hexadeuteriodimethyl sulfoxide: δ 8·12, 7·08 (ABq, J = = 8·0 Hz, 4 H, aromatic protons); 5·90 (d, J = 11·0 Hz, 1 H, ArCOOH); 4·76 (d, J = 11·0 Hz, 1 H, BrCH—CO); 4·10 (t, J = 6·0 Hz, 2 H, $ArOCH_2$); 1·2—1·9 (m, 6 H, $(CH_2)_3$), 0·92 (t, 3 H).

Homogeneous fractions were pooled from the slower-moving components (1·1 g) and crystallized from a mixture of benzene and cyclohexane to *trans*-β-4-pentoxybenzoylacrylic acid (*VII*), m.p. 131—133°C. For $C_{15}H_{18}O_4$ (262·3) calculated: 68·68% C, 6·92% H; found: 68·22% C, 6·87% H. IR spectrum (KBr): 1180 (aromatic ether), 840, 1512, 1600 (*para*-substituted aromatic ring), 1260 (CO), 1620 (conjugated C=C), 1668 (Ar—CO), 1695 (conjugated COOH), 2870, 2940 (CH_3, CH_2). ^{1}H-NMR spectrum hexadeuteriodimethyl sulfoxide: δ 8·02; 7·06 (ABq, J = = 8·0 Hz, 4 H, aromatic protons); 7·88 (d, J = 15·0 Hz, 1 H, ArCOCH=); 6·65 (d, J = 15·0 Hz, 1 H, =CHCOOH); 4·08 (t, J = 6·0 Hz, 2 H, $ArOCH_2$); 1·20—1·90 (m, 6 H, $(CH_2)_3$); 0·92 (t, 3 H).

B. A mixture of 2 g (0·0054 mol) ethyl ester of β-4-pentoxybenzoyl-β-bromoacrylic acid (70—75% *trans* and 25—30% *cis*, *V*) 35 ml glacial acetic acid and 10 ml dilute sulfuric acid (1 : 2) was refluxed for 1 h, diluted with 200 ml water and extracted with 5 × 100 ml ether. The pooled ether fractions were extracted with 2 × 30 ml water, dried (Na_2SO_4) and ether was distilled in water-pump vacuum. The residue (1·8 g, 97%) was recrystallized from cyclohexane; 1 g product, melting at 90—95°C. For $C_{15}H_{17}BrO_4$ (341·2) calculated: 52·80% C, 5·02% H, 23·42% Br; found: 53·24% C, 5·18% H, 23·19% Br. ^{1}H-NMR spectrum ($CDCl_3$): δ 6·50 (s, (=CH) *cis* isomer c. 90%); 6·75 (s, (=CH) *trans* isomer c. 10%).

Methyl Ester of β-4-Pentoxybenzoyl-β-bromoacrylic Acid (*cis*: Br, H) (*IX*)

A solution of 2·7 g (0·064 mol) diazomethane in 250 ml ether was added dropwise at 0°C to a solution of 21·9 g (0·064 mol) *cis*-β-4-pentoxybenzoyl-β-bromoacrylic acid[1] in 250 ml ether. The mixture was kept for 1 h at 0°C and left to stand overnight at 20°C. Ether was distilled off in water-pump vacuum and the residue was purified by chromatography on a column of silica gel (50 g) using benzene for elution. The yield was 21·9 g (96%) oil which was dried at 40°C/0·1 Torr; n_D^{20} 1·5610. For $C_{16}H_{19}BrO_4$ (355·2) calculated: 54·09% C, 5·39% H, 22·49% Br; found: 54·12% C, 5·32% H, 22·55% Br. ^{1}H-NMR spectrum ($CDCl_3$): δ 6·61 (s, (=CH) *cis* isomer).

Triphenyl(4-methoxybenzoyl)bromomethylenephosphorane (*X*)

A solution of 3·34 g (0·021 mol) bromine in 20 ml tetrachloromethane was added under stirring over a period of 10 min at —70°C to a solution of 8·2 g (0·02 mol) triphenyl(4-methoxybenzoyl)-methylenephosphorane[5] in 60 ml dichloromethane. The mixture was stirred for 30 min at room temperature and the solvents were distilled off under water-pump vacuum. The residue (13·4 g) was dissolved at 20°C in 600 ml of a mixture of acetone and water (4 : 3), the filtrate was alkalified with 1M-NaOH to phenolphthalein and the mixture was diluted with 600 ml water and left to stand overnight at 0°C. The precipitate was filtered (8 g, 82%). The product was purified for

analysis by crystallization from aqueous acetone, m.p. 162–163°C. For $C_{27}H_{22}BrO_2P$ (489·3) calculated: 6·33% P; found: 6·15% P.

Ethyl Ester of β-4-Methoxybenzoyl-β-bromoacrylic Acid (*XI*) (mixture of about 70–75% *trans* and 25–30% *cis*)

A solution of 0·83 g (0·008 mol) ethyl ester of glyoxylic acid[4] in 30 ml benzene was added to a solution of 4 g (0·008 mol) triphenyl(4-methoxybenzoyl)bromomethylenephosphorane (*X*) in 100 ml benzene and the mixture was refluxed for 4 h in an atmosphere of nitrogen and left to stand overnight at room temperature. The solvent was distilled off in water-pump vacuum and the residue (5·46 g) was resolved by chromatography on a column of silica gel (80 g) using benzene for elution. The combined front fraction were filtered, benzene was distilled off under water-pump vacuum and the oily residue was dried at 35°C/0·2 Torr; 2·4 g (93%), n_D^{20} 1·5827. For $C_{13}H_{13}BrO_4$ (313·1) calculated: 49·86% C, 4·18% H, 25·52% Br; found: 50·15% C, 4·17% H, 25·27% Br. IR spectrum ($CHCl_3$): 1720 (ester), 1665 (conjugated CO), 1596, 1571 (conjugated —C=C— and aromatic) 1508, 825 cm^{-1} (*para*-substituted aromatic ring). ^{1}H-NMR spectrum ($CDCl_3$): δ 6·80 (s, (=C<u>H</u>) *trans* isomer 70–75%); 6·63 (s, (=C<u>H</u>) *cis* isomer 25–30%).

β-4-Methoxybenzoyl-β-bromoacrylic Acid (*cis XII*)

A mixture of 3·4 g (0·011 mol) ethyl ester of β-4-methoxybenzoyl-β-bromoacrylic acid (70–75% *trans* and 25–30% *cis* isomers, *XI*) 55 ml glacial acetic acid and 14 ml dilute sulfuric acid (1 : 2) was refluxed for 1 h, the mixture was diluted with 340 ml water and extracted with 5 × 150 ml ether. The pooled ether fractions were extracted with 2 × 75 ml water, dried (Na_2SO_4) and ether was distilled off under water-pump vacuum. The residue (3 g, 97%) was purified by chromatography on a column of silica gel (60 g) using benzene and 1% ethanol for elution. The corresponding fractions were pooled (2·6 g) and recrystallized from benzene, m.p. 141–143°C. For $C_{11}H_9BrO_4$ (285·1) calculated: 46·34% C, 3·18% H, 28·03% Br; found: 46·77% C, 3·23% H, 28·18% Br. ^{1}H-NMR spectrum hexadeuteriodimethylsulfoxide: δ 6·69 (s, (=C<u>H</u>) *cis* isomer).

Ethyl Ester of β-4-Pentoxybenzoyl-α-bromoacrylic Acid (*XIII*) (mixture of 79% *trans* and 21% *cis*: Br, H)

A filtered solution of 10·1 g (0·042 mol) monohydrate of 4-pentoxyphenylglyoxal[6] in 200 ml benzene was added to a solution of 18 g (0·042 mol) triphenylethoxycarbonylbromomethylenephosphorane[7] in 400 ml benzene. The mixture was refluxed for 4 h in an atmosphere of nitrogen, left to stand for 24 h at 20°C and the solvent removed by distillation under water-pump vacuum. The residue (28 g) was resolved by chromatography on a column of silica gel (100 g), using benzene for elution. The homogeneous front fractions were pooled, benzene was removed by distillation under water-pump vacuum and the residue (15 g, 96·4%) was dried at 40°C/0·1 Torr; n_D^{20} 1·5555. For $C_{17}H_{21}BrO_4$ (369·2) calculated: 55·29% C, 5·73% H, 21·64% Br; found: 55·58% C, 5·76% H, 21·77% Br. NMR spectrum ($CDCl_3$): δ 8·05 (s, 79% *trans*, Ar—CO—CH=); 7·31 (s, 21% *cis* Ar—COCH=); 7·85; 6·88 (ABq, J = 8·0 Hz, 4 H, aromatic protons); 4·40 (q, J = 7.OHz, 2 H, OCH_2CH_3). 4·00 (q, J = 6·0 Hz, 2 H, $ArOCH_2$); 1·40–1·80 (m, 6 H, $(CH_2)_3$); 1·38 (t, *trans*, OCH_2CH_3); 1·12 (t, *cis*, OCH_2CH_3); 0·90 (t, 3 H, CH_3).

trans-β-4-Pentoxybenzoyl-α-bromoacrylic Acid (*XIV*)

A mixture of 2 g (0·0054 mol) ethyl ester of β-4-pentoxybenzoyl-α-bromoacrylic acid (mixture of 79% *trans* and 21% *cis* isomers, *XIII*), 35 ml glacial acetic acid and 10 ml dilute sulfuric acid

(1 : 2) was refluxed for 1 h, diluted with 200 ml water and extracted with 5 × 100 ml ether. The ether fractions were pooled, extracted with 2 × 30 ml water, dried (Na_2SO_4) and ether was removed by distillation under water-pump vacuum. The residue, 1·88 g (98%), m.p. 85—86°C, was crystallized for analysis from cyclohexane, m.p. 87—89°C. For $C_{15}H_{17}BrO_4$ (341·2) calculated: 52·80% C, 5·02% H, 23·42% Br; found: 53·21% C, 5·17% H, 23·42% Br. ^{1}H-NMR spectrum ($CDCl_3$): δ 8·20 (s, (=C<u>H</u>) *trans* isomer).

The analyses were done in the analytical department of this Institute by Mrs J. Komancová, Mrs V. Šmídová and Mr M. Čech under the direction of Dr J. Körbl.

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Translated by A. Kotyk.