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**SYNTHESIS AND REACTIONS OF  $\beta$ -SUBSTITUTED DERIVATIVES OF FURAN\***

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The 1,4-cycloaddition reaction of 4-phenyl-1,3-oxazole to 2-propinyl benzoate and dimethyl butinedioate afforded the respective 3-furylmethyl benzoate (*I*) and 3,4-bis(methoxycarbonyl)-furan (*II*). These compounds served for the synthesis of 3-chloromethylfuran and 3,4-bis(chloromethyl)furan, which afforded *via* Wittig reaction 3-( $\beta$ -arylvinyl)furans *III* (aryl = 5-nitro-2-furyl (*IIIa*), 5-nitro-2-thienyl (*IIIb*), 1-methyl-4-nitro-2-pyrrolyl (*IIIc*), and 4-nitrophenyl (*IIIe*)) and 3,4-bis( $\beta$ -arylvinyl)furans *IV* (aryl = 5-nitrofuryl (*IVa*), 5-nitro-2-thienyl (*IVc*), and 4-nitrophenyl (*IVd*)). According to spectral evidence ( $^1\text{H}$  NMR, IR, UV spectra), compound *IIIa* and *IIIb* originated as *E* isomers, whilst the remaining products are a mixture of *E* and *Z* isomers; some couples were succeeded to separate.

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In principal, two methods can be used to prepare  $\beta$ -substituted derivatives of furan: cyclization of 1,4-dicarbonyl compounds and 1,4-cycloaddition; the latter is of progressive interest. 1,4-Furandicarboxylates were synthesized, in addition to the Alder–Rickert pressure reaction<sup>1</sup>, by cyclization of formyl butanedioate<sup>2</sup> or by a *retro* Diels–Alder reaction of butinedioates with 4-methyloxazole<sup>3</sup>. The suitable dienone for the synthesis of  $\beta$ -derivatives of furan was found to be 4-phenyloxazole well reacting also with inactivated dienophiles<sup>4,5</sup>.

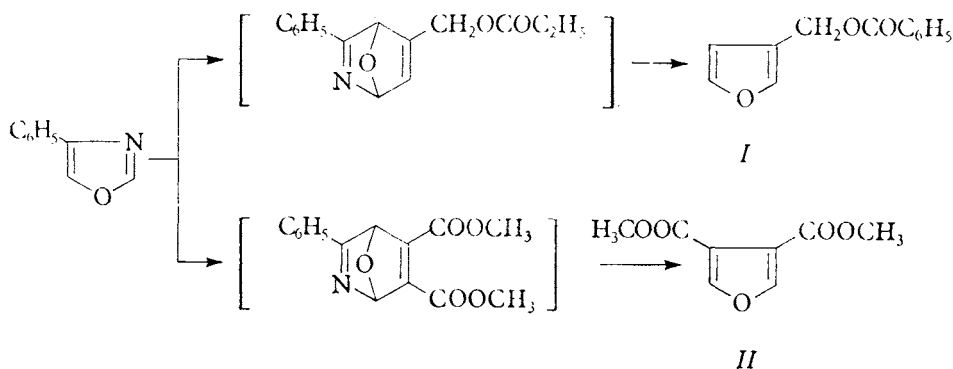
This paper presents the synthesis of 3-furylmethyl benzoate (*I*) and dimethyl 3,4-furandicarboxylate (*II*), both synthesized according to Scheme 1. The primarily formed adduct could not be isolated under conditions given in the experimental part. Syntheses of the new product *I* and the known product *II* (ref.<sup>6</sup>) are, however, advantageous considering the starting material used and the pressure-free conditions. Wittig reaction with these compounds furnished the corresponding 3-( $\beta$ -arylvinyl)-furans *III* and 3,4-bis( $\beta$ -arylvinyl)furans *IV* aimed to compare their biological activity with that of the  $\alpha$ -analogues.

3-Furylmethanol was obtained either by an alkaline hydrolysis of 3-furylmethyl benzoate or by a reduction of 3-furancarboxylic acid by lithium hydridoaluminate.

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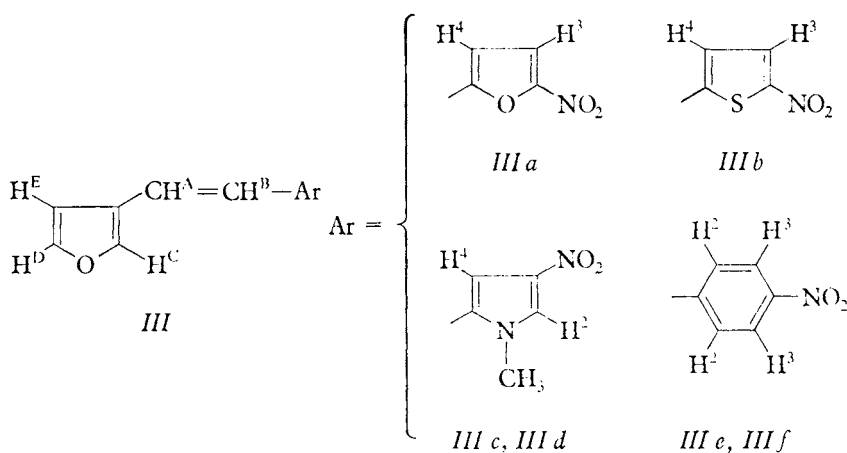
\* Part CLXXXV in the series Furan Derivatives; Part CLXXXIV: This Journal 50, 459 (1985).

This acid was advantageously prepared according to<sup>6,11</sup> from furantetracarboxylic acid by a modified decarboxylation, although  $\gamma$ -butyrolactone<sup>7,8</sup>, ester *II* (refs<sup>2,9,10</sup>) and method<sup>10</sup> could also be used. 3-Furylmethyltriphenylphosphonium chloride was obtained from 3-chloromethylfuran<sup>11</sup> and triphenylphosphine. Derivatives *IV* were synthesized from ester *II* by analogous reactions. Of various basic reagents



SCHEME 1

(NaOH, RONA recommended for  $\alpha$ -analogues<sup>12</sup>) needed for generation of ylides from  $\beta$ -furanphosphonium salts the most suitable was lithium ethoxide in dimethylformamide<sup>13</sup>. Yields of this reaction are by far higher with monosubstituted derivatives *III* in contrast to disubstituted derivatives *IV* (Table I) which are photochemically unstable. Course of the Wittig reaction was monitored by thin-layer chromatography; it was found that only one geometric isomer (*IIIa*, *IIIb*) resulted from the reaction of 3-furylmethyltriphenylphosphonium chloride with 5-nitro-2-furaldehyde



or 5-nitro-2-thienylaldehyde. *IIIa* and *IIIb* had *E* configuration, *IIIc* and *IIId* formed from 1-methyl-4-nitro-2-pyrrolaldehyde and *IIIe*, *IIIf* from 4-nitrobenzaldehyde were a mixture of *E* and *Z* isomers with *E* isomers in predomination. Reaction conditions (90°C, dimethylformamide, LiOC<sub>2</sub>H<sub>5</sub>) backed the lower reactivity of the ylide in question when compared with that of the  $\alpha$ -analogue<sup>12</sup>.

The structure of all compounds was adduced from <sup>1</sup>H NMR, IR, and UV spectra. The UV spectra of compounds *IIIc*–*IIIf* contain only one complex band

TABLE I  
Compounds *III* and *IV*

Compound	Formula (M.w.)	Isomer	M.p., °C <sup>a</sup> (yield, %)	Calculated/Found			$\lambda_{\max}$ , nm <sup>b</sup> (log $\epsilon$ , m <sup>2</sup> mol <sup>-1</sup> )
				% C	% H	% N	
<i>IIIa</i>	C <sub>10</sub> H <sub>7</sub> NO <sub>4</sub> (205·1)	<i>E</i>	111 (61·5)	58·50	3·43	6·82	251 (3·33)
				58·37	3·30	6·68	282 (3·30)
							399 (3·48)
<i>IIIb</i>	C <sub>10</sub> H <sub>7</sub> NO <sub>3</sub> S (221·3)	<i>E</i>	110–112 (59)	54·29	3·18	6·32	272 (3·07)
				54·60	3·09	6·25	407 (3·40)
<i>IIIc</i>	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub> (218·2)	<i>E</i>	146 (37)	60·54	4·61	12·83	292 (3·40)
				60·61	4·67	12·90	
<i>IIId</i>	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub> (218·2)	<i>Z</i>	53–54 (24)	60·54	4·61	12·83	283 (3·22)
				60·47	4·70	13·00	
<i>IIIe</i>	C <sub>12</sub> H <sub>9</sub> NO <sub>3</sub> (215·2)	<i>E</i>	108 (36)	66·97	5·61	6·50	354 (3·34)
				66·58	5·54	6·65	
<i>IIIf</i>	C <sub>12</sub> H <sub>9</sub> NO <sub>3</sub> (215·2)	<i>Z</i>	46 (21·5)	66·97	5·61	6·50	339 (2·92)
				66·83	5·70	6·41	
<i>IVa</i>	C <sub>16</sub> H <sub>10</sub> N <sub>2</sub> O <sub>7</sub> (341·9)	<i>(E, E)</i>	173–175 (10)	56·20	2·95	8·18	212 (2·98)
				56·28	2·73	7·94	240 (3·03)
							388 (3·23)
<i>IVb</i>	C <sub>16</sub> H <sub>10</sub> N <sub>2</sub> O <sub>7</sub> (341·9)	—	98–105 (7)	56·20	2·94	8·18	212 (3·22)
				56·47	2·80	7·99	257 (3·10)
<i>IVc</i>	C <sub>16</sub> H <sub>10</sub> N <sub>2</sub> O <sub>5</sub> S <sub>2</sub> (374·0)	—	201–205 (16)	51·38	2·69	7·52	211 (3·08)
				51·60	2·73	7·30	285 (3·12)
							388 (3·23)
<i>IVd</i>	C <sub>20</sub> H <sub>14</sub> N <sub>2</sub> O <sub>5</sub> (362·3)	—	140–147 (15)	66·30	3·89	7·73	207 (2·77)
				66·43	3·92	7·82	227 (2·67)
							352 (2·71)

<sup>a</sup> Derivatives *IV* melt with decomposition; <sup>b</sup> the UV spectra of *IVa* and *IVb* contain additional bands at 274 (3·04) and 320 nm (3·20), respectively.

at 283–354 nm, corresponding to electronic transitions of the entire conjugated system. Spectra of compounds *IIIa* and *IIIb* (*E* isomers) reveal, in addition to the K band at 399 and 407 nm, respectively, further bands (*cf.* Table I). The IR spectra show absorption bands due to vibrations of characteristic groups as follows:  $\tilde{\nu}(\text{NO}_2)_s$  at 1310–1350  $\text{cm}^{-1}$ ,  $\tilde{\nu}(\text{NO}_2)_{as}$  at 1503–1520  $\text{cm}^{-1}$ ,  $\tilde{\nu}(\text{C}=\text{C})$  at 1625–1645  $\text{cm}^{-1}$ ; the out-of-plane vibrations of *E*-vinyl protons  $\delta(\text{C}-\text{H})$  appear at 950–965  $\text{cm}^{-1}$ . All derivatives *III* show, moreover, a characteristic  $\gamma(\text{C}-\text{H})$  band at 850 to 865  $\text{cm}^{-1}$  characteristic of furans. Configuration at the double bond of 3-furyl-ethene derivatives also evidenced the coupling constants in the  $^1\text{H}$  NMR spectra:  $J_{AB}$  for *E* isomers equals 16 Hz, that for *Z* isomers 12 Hz (Table II). Reduction of the ester *II* to 3,4-bis(hydroxymethyl)furan, required for the synthesis of *IV*, proceeded with lithium hydridoaluminate in ether; the complex was decomposed with hot ethanol<sup>14</sup>. 3,4-Bis(chloromethyl)furan prepared by conversion of the diol with thionyl chloride (yield 59%, *ref.*<sup>15</sup>) afforded with triphenylphosphine furan-3,4-bis(methylenetriphenyl)phosphonium chloride<sup>13</sup> in a 80% yield. 3,4-Bis( $\beta$ -aryl-vinyl)furans *IVa-IVd* (Table I) can exist in three configurations: (*E,E*)-*IVA*, (*Z,Z*)-*IVB* and (*Z,E*)-*IVC*.

Reaction of 3,4-bis(chloromethyl)furan with the respective aldehydes afforded always a mixture of geometric isomers. A pure geometric isomer *IVA* was the only one of *IVA* to *IVC* which was succeeded to separate from the reaction mixture with 5-nitro-2-furaldehyde; its spectral data entitled to ascribe the structure (*E,E*)-3,4-

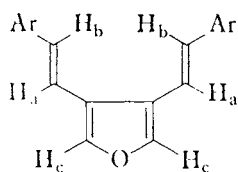
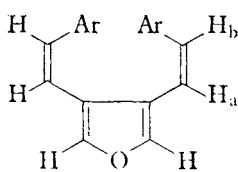
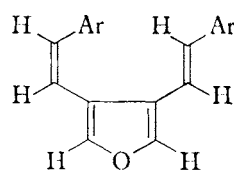
TABLE II

$^1\text{H}$  NMR Chemical shift values ( $\delta$ , ppm) of compounds *III*

Compound	Olefinic <sup>a</sup>		Furan <sup>a</sup>			Ar <sup>a</sup>		
	H <sup>A</sup>	H <sup>B</sup>	H <sup>C</sup>	H <sup>D</sup>	H <sup>E</sup>	H <sup>2</sup>	H <sup>3</sup>	H <sup>4</sup>
<i>IIIa</i>	6.68 d	7.19 d	7.64 t	7.45 t	6.63 t	—	7.34 d	6.46 d
<i>IIIb</i>	6.83 d	7.20 d	7.61 t	7.44 m	6.63 dd	—	7.81 d	6.93 d
<i>IIIc</i>	6.86 d	7.06 d	7.75 t	7.55 t	6.86 t	7.74 d	—	6.91 d
<i>III d</i>	6.11 d	6.56 d	7.45 t	7.30 t	6.15 t	7.49 d	—	6.73 q
<i>IIIe</i>	6.98 d	7.15 d	7.48 t	7.44 t	6.54 t	7.59 d	8.18 m	—
<i>III f</i>	6.54 s	6.54 s	7.43 t	7.28 t	6.09 t	7.58 d	8.18 m	—

<sup>a</sup> Coupling constants:  $J_{AB} = 16$  Hz for *IIIa,b,c*;  $J_{AB} = 12$  Hz for *III d*;  $J_{CE} = 0.5$  Hz for *IIIa,b*;  $J_{CE} = 0.7$  Hz for *IIIc,d,e*;  $J_{CE} = 1$  Hz for *III f*;  $J_{CD} = 1$  Hz for *IIIa,b,c*;  $J_{CD} = 1.6$  Hz for *III d*;  $J_{CD} = 1.7$  Hz for *IIIe,f*;  $J_{DE} = 1.6$  Hz for *IIIa*;  $J_{DE} = 1.5$  Hz for *IIIb*;  $J_{DE} = 1.7$  Hz for *IIIc,d,e,f*;  $J_{3,4} = 4$  Hz for *IIIa*;  $J_{3,4} = 4.2$  Hz for *IIIb*;  $J_{2,4} = 2$  Hz for *IIIc,d*;  $J_{2,3} = 9$  Hz for *IIIe,f*;  $\delta_{\text{NCH}_3} = 3.83$ , s for *IIIc*;  $\delta_{\text{NCH}_3} = 3.55$ , s for *III d*.

-bis(5-nitro-2-furylvinyl)furan to *IVa* (Table I). The  $^1\text{H}$  NMR spectrum of this compound displays two doublets of protons at  $\delta$  6.94 and 7.47 ppm ( $J_{a,b} = 16.7$  Hz) corresponding to the *E* arrangement of ethylene protons. Chemical shifts of  $\text{H}^3$  and  $\text{H}^4$  protons in positions 3 and 4 of the furan backbone appeared at  $\delta$  7.57 and 6.89 ppm ( $J = 3.7$  Hz). Since the molecule of this isomer is ideally symmetric, protons  $\text{H}_c$  in positions 2 and 5 of the furan ring occurred as a two-proton singlet at  $\delta$  8.11 ppm. The IR spectrum of this compound is indicative of furan ring vibrations at 870 and  $1010\text{ cm}^{-1}$ ,  $\tilde{\nu}(=\text{CH})$  at  $1480$  and  $1600\text{ cm}^{-1}$ ,  $\tilde{\nu}(\text{C}=\text{C})$  at  $1630\text{ cm}^{-1}$ ,  $\tilde{\nu}(\text{NO}_2)_s$  and  $\tilde{\nu}(\text{NO}_2)_{as}$  at  $1340$  and  $1515\text{ cm}^{-1}$ , respectively; the band at  $970\text{ cm}^{-1}$  evidences the *E* arrangement of ethylene protons. Compound *IVb* (m.p.  $98-105^\circ\text{C}$ , Table I), constituting the first fraction upon chromatography on silica gel column is, according

*IV A*, (*E*), (*E*)*IV B*, (*Z*), (*Z*)*IV C*, (*Z*), (*E*)

to spectral data either a mixture of geometric isomers *IVA* and *IVB*, or an isomer related to *IVC*. The  $^1\text{H}$  NMR spectrum of thiophene derivative *IVc* shows signals at  $\delta$  6.60 and 6.31 ppm ( $J_{a,b} = 12$  Hz) due to a *Z* arrangement of protons at the ethylene double bond. Two multiplets at  $\delta$  6.81–7.06 ppm and  $\delta$  7.60–7.81 ppm cummulate the thiophene proton signals, *E*-protons of the ethylene bond and those in positions 2 and 5 of the furan ring. Due to a very poor solubility of this compound the double resonance experiment could not be employed for proton assignment. The *E* arrangement of protons at the double bond was proved by the split band in the IR spectrum at  $960$  and  $970\text{ cm}^{-1}$ . The  $^1\text{H}$  NMR spectrum of *IVd* discloses two doublets of olefinic  $\text{H}_a$  and  $\text{H}_b$  protons at  $\delta$  5.79 and 7.14 ppm ( $J_{a,b} = 16.8$  Hz, *E* configuration) and two doublets of protons at  $\delta$  6.32 and 6.52 ppm ( $J_{a,b} = 11.5$  Hz) in a *Z* arrangement. The (*E,E*) to (*Z,Z*) ratio of protons is approximately 3 : 1 and therefore, a mixture of *IVA* and *IVB* with prevailing *E* isomer has to be involved. This conclusion is also backed by the split absorption band in the IR spectrum at  $960$  and  $970\text{ cm}^{-1}$ . The UV spectra of compounds *IVa* are characteristic of three or four absorption maxima at 207–212, 227–257, 274–320, and 352–400 nm. Comparison of the K band of pure *E* isomers (*IIIa* 399 nm, *IVa* 388 nm) shows that extension of the conjugated system by 5-nitro-2-furylvinyl grouping in the second  $\beta$ -position of furan does not result in a bathochromic, but does in a hypsochromic shift (11 nm) what can be associated with a symmetric distribution of the charge in derivative *IVa*. The K band in the spectrum of *IVa* corresponds to absorption of a 5-nitro-2-furylvinyl grouping

and one double bond of the central furan ring, whereas that in *IIIc* is due to electronic transitions of the entire system of the molecule. This is in line with the UV spectral data of 5-nitro-2-furylpolyenes<sup>16</sup>. The attempt to isomerize compounds *IVa* and *IVc* failed, because their methanolic solution underwent photochemical reaction in the sunlight and consequently, the K bands disappeared and new ones appeared in the 270–290 nm region. The band at 252 nm of compound *IV* disappeared in the light and two new ones appeared at 320 and 390 nm.

## EXPERIMENTAL

Melting points were determined on a micro hot-stage, the IR spectra were measured with a UR-20 (Zeiss, Jena) spectrophotometer in saturated chloroform solutions, the UV spectra of methanolic  $3-5 \cdot 10^{-5} \text{ mol l}^{-1}$  solutions were recorded with a Specord UV VIS apparatus in a 1-cm cell with a  $\pm 1 \text{ nm}$  reading accuracy. The <sup>1</sup>H NMR spectra of deuteriochloroform solutions taken with a Tesla BS 487 B instrument operating at 80 MHz are relative to tetramethylsilane.

### 3-Furylmethyl Benzoate (*I*)

A mixture consisting of 4-phenyl-1,3-oxazole (10 g, 70 mmol), 2-propinyl benzoate (12 g, 75 mmol), hydroquinone (0.4 g), and sodium carbonate (0.6 g) was successively heated with stirring in a nitrogen atmosphere and kept at 200–210°C for 8 h. The oily product was poured into water and extracted with ethyl acetate; the organic layer was washed with water, sodium carbonate solution, dried and distilled. B.p. 95–97°C/0.1 kPa, yield 4.5 g (31%). For C<sub>12</sub>H<sub>10</sub>O<sub>3</sub> (202.2) calculated: 71.21% C, 4.94% H; found: 70.63% C, 4.96% H. IR spectrum (cm<sup>-1</sup>): 860 ( $\gamma$ (C—H)), 1 020 ( $\tilde{\nu}$ (C—O—C)), 1 500 ( $\tilde{\nu}$ (C=C)), 1 720 ( $\tilde{\nu}$ (C=O)); UV spectrum,  $\lambda_{\text{max}}$  (log  $\epsilon$ , m<sup>2</sup> · mol<sup>-1</sup>): 228 (3.32), 278 (2.27); <sup>1</sup>H NMR spectrum ( $\delta$ , ppm): 5.17 (s, CH<sub>2</sub>), 7.48–7.50 (m, H<sub>2</sub>), 6.45–6.80 (m, H<sub>5</sub> and protons of the aromatic ring).

### 3,4-Bis(methoxycarbonyl)furan (*II*)

4-Phenyl-1,3-oxazole (14.5 g, 0.1 mol), dimethyl butinedioate (14.2 g, 0.1 mol), and hydroquinone (0.2 g) were heated at 205–210°C under nitrogen for 7 h. The product was distilled off under diminished pressure to give 14 g (76%), b.p. 98°C/0.2 kPa, m.p. 45°C (ref.<sup>6</sup> 46°C). IR spectrum (cm<sup>-1</sup>): 830 ( $\gamma$ (C—H)), 960, 1 070 ( $\tilde{\nu}$ (C—O—C)), 1 540 ( $\tilde{\nu}$ (C=C)), 1 730 ( $\tilde{\nu}$ (C=O)); UV spectrum,  $\lambda_{\text{max}}$  (log  $\epsilon$ , m<sup>2</sup> · mol<sup>-1</sup>): 238 (2.54); <sup>1</sup>H NMR spectrum ( $\delta$ , ppm): 3.85 (s, CH<sub>3</sub>), 7.93 (s, H<sub>2</sub>), 7.93 (s, H<sub>5</sub>).

### 3-( $\beta$ -Arylviny)furans *IIIa–IIIf* and 3,4-Bis( $\beta$ -vinylyl)furans *IVa–IVd*

*III*: A solution of lithium (37 mg) in ethanol (10 ml) was added to 3-furylmethyltriphenylphosphonium chloride (2.0 g, 5 mmol) and the respective aldehyde (5 mmol) dissolved in dimethylformamide (60 ml) and heated to 90°C. The mixture was stirred under nitrogen at 90°C for 4 h, cooled and poured into water (500 ml). The product was taken in ether, the extract was dried with sodium sulfate, the solvent was evaporated and the residue was either crystallized from n-hexane–benzene 10 : 1, or separated by column chromatography. Compounds *IIIc*, *IIIa*, *IIIe*, and *IIIf* were separated by column chromatography on silica gel (40  $\times$  3.5 cm); the isomers of the first two compounds were eluted with light petroleum–benzene 10 : 1, the remaining isomers with light petroleum–benzene 1 : 4.

*IV*: Lithium (69 mg, 10 mmol) dissolved in ethanol (30 ml) and the respective aldehyde (10 mmol) in dimethylformamide (30 ml) were added in a nitrogen atmosphere during 5 h to furan-3,4-bis(methylenetriphenyl)phosphonium chloride (3.45 g, 5 mmol) dissolved in dimethylformamide (20 ml) and heated to 90°C. The mixture was cooled, poured into water (500 ml) and taken in benzene. The organic layer was concentrated and chromatographically separated. Because of the photochemical instability, compounds *IV* were separated in the dark taking 60 g silica gel per 1 g of the product and using benzene as eluent. The individual fractions from the column were rechromatographed on silica gel-coated plates with chloroform-benzene 1 : 1 as eluent.

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