

Polybromoaromatic Compounds: IX.* Reactions of Polybromobenzyl Bromides with Enolates Derived from Some Dicarboxyl Compounds**

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Abstract—The reaction of polybromobenzyl bromides $RC_6Br_4CH_2Br$ ($R = Br, OCH_3$) with diethyl malonate sodium salt in ethanol and dimethylformamide leads to formation of diethyl 2-(polybromobenzyl)malonates, whereas in aqueous ethanol ethyl polybromobenzyl malonates are formed. The same polybromobenzyl bromides react with an equimolar amount of ethyl acetoacetate sodium salt or acetylacetonate sodium salt to give C-alkylation products; with excess sodium enolates ethyl 3-(polybromophenyl)propionates and 4-(polybromophenyl)-2-butanones are formed, respectively.

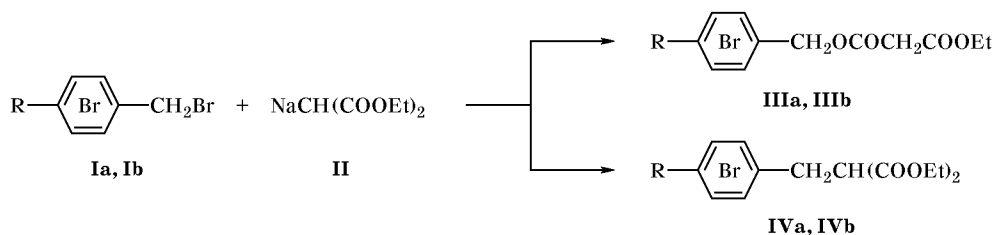
Benzyl bromides are known to react with diethyl malonate in the presence of bases to give exclusively C-alkylation products [2]. However, we found [3] that the reaction of pentabromobenzyl bromide (**Ia**) with diethyl malonate sodium salt (**II**) in ethanol leads to formation of ethyl pentabromobenzyl malonate (**IIIa**), whereas the reaction between the same compounds in toluene and dimethylformamide yields diethyl pentabromobenzylmalonate (**IVa**). The reasons for the different reaction pathways were unclear.

The present communication reports on the results of a more detailed study of the reactions of penta-

bromobenzyl bromide (**Ia**) and 2,3,5,6-tetrabromo-4-methoxybenzyl bromide (**Ib**) with sodium enolates derived from some β -dicarboxyl compounds (diethyl malonate, ethyl acetoacetate, and acetylacetonate) in ethanol and dimethylformamide. The reactions were carried out with a 2–3-fold excess of the dicarboxyl compound (Table 1). The progress of reactions was monitored, and the final products were identified, by GLC, TLC, and ¹H NMR spectroscopy using authentic samples (Table 2).

The reaction of pentabromobenzyl bromide (**Ia**) with diethyl malonate sodium salt (**II**) in ethanol at

Scheme 1.



R = Br (a), OMe (b).

* For communication VIII, see [1].

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Table 1. Reactions of polybromobenzyl bromides with sodium enolates derived from β -dicarbonyl compounds

Run no.	Substrate no.	Reagent no.	Solvent	Bromide–reagent ratio	Time, h	Temperature, °C	Product (fraction, %), yield, %
1	Ia	II	EtOH	1:1.4	4	78	IVa (>98), 72; Va (traces)
2	Ia	II	96% EtOH	1:1.63	4.4	78	IIIa (>97), 92; Va (traces), VIa (traces)
3	Ia	II	DMF	1:1.07	0.5	100	IVa , 82
4	Ib	II	EtOH	1:1.4	3.5	78	IVb , 75
5	Ib	II	96% EtOH	1:1.05	8	78	IIIb (>98), 85; Vb (traces)
6	Ib	II	DMF	1:1.05	0.25	100	IVb , 75
7	Ia	VIIa	EtOH	1:1.04	4	78	Ia (traces); Va (traces), VIIIa (>97), 82
8	Ia	VIIa	EtOH	1:1.23	3.5	78	VIIIa (65); IXa (35)
9	Ia	VIIa	EtOH	1:2.5	5.5	78	IXa (>98), 93; IXc (traces)
10	Ia	VIIa	96% EtOH	1:1.22	4	78	Va ; VIIIa ; IXa ; IXc
11	Ia	VIIa	DMF	1:1.05	1	100	VIIIa (>98), 86; IXc (traces)
12	Ib	VIIa	EtOH	1:1.05	3.3	78	VIIIb (>98), 70; IXb (traces)
13	Ib	VIIa	EtOH	1:2.5	1.5	78	IXb (>98), 74; VIIIb (traces)
14	Ia	VIIIb	EtOH	1:1.05	4	78	Ia (4); Va (2); VIIIc (46); IXc (48)
15	Ia	VIIIb	EtOH	1:2.5	3	78	IXc , 93.2
16	Ia	VIIIb	96% EtOH	1:1.2	4.5	78	Ia (5); Va (12); VIa (14); VIIIc (52); IXc (17)
17	Ia	VIIIb	Toluene	1:1.1	31	110	Ia (54); VIIIc (46), 20
18	Ib	VIIIb	EtOH	1:1.05	4.5	78	Ib (traces); Vb (traces), VIIIb (>96), 74; IXd (traces)
19	Ib	VIIIb	EtOH	1:2.5	2	78	VIIIb (40); IXd (60)
20	Ib	VIIIb	EtOH	1:2.5	6	78	IXd (>98), 85; VIIIb (traces)

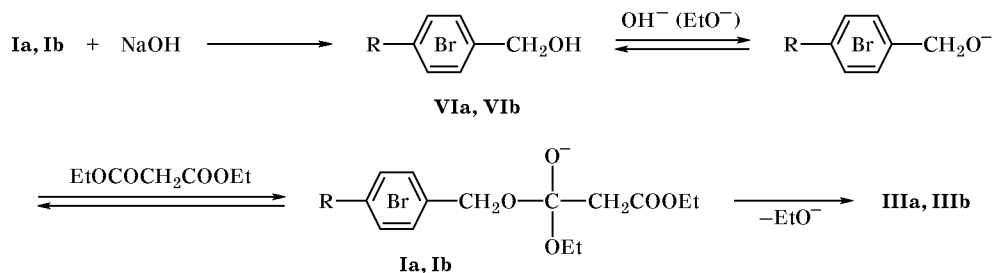
78°C was not selective, and the product composition strongly depended on the concentration of water in the solvent (Scheme 1). C-Alkylation product **IVa** was formed as the major one when the reaction was carried out in anhydrous ethanol. In addition, traces of ethyl pentabromobenzyl ether (**Va**) were detected. Even such a small concentration of water as 0.1–0.2% in ethanol gives rise to formation of compound **IIIa** which becomes the major product in 96% ethanol. In this case, traces of pentabromobenzyl alcohol (**VIa**) were also detected.

2,3,5,6-Tetrabromo-4-methoxybenzyl bromide (**Ib**) behaves similarly in the reaction with sodium salt **II** in ethanol (Table 1, run nos. 4 and 5). It should be noted that bromides **Ia** and **Ib** react with diethyl malonate sodium salt (**II**) in anhydrous dimethyl-

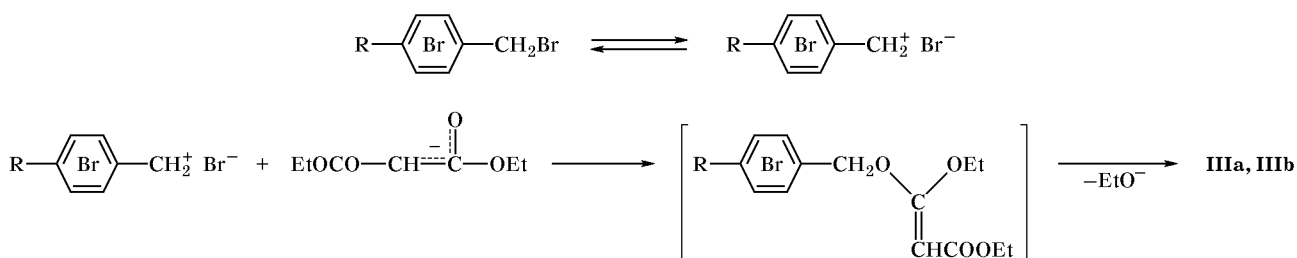
formamide to give exclusively C-alkylation products **IVa** and **IVb**. The reaction in dimethylformamide is much faster than in ethanol (it is complete in 0.25 to 0.5 h at 100°C).

It could be presumed that in aqueous ethanol sodium hydroxide formed via exchange reaction promotes hydrolysis of benzyl bromides **Ia** and **Ib** to the corresponding benzyl alcohols **VIa** and **VIb** which then react with excess NaOH (or EtONa) to give alkoxides. The latter can be involved in transesterification of diethyl malonate according to Scheme 2. However, by special experiments we showed that such reaction pathway does not occur. In the reaction of alcohol **VIa** with excess diethyl malonate in ethanol in the presence of sodium hydroxide or ethoxide, other conditions being the same, we did not detect

Scheme 2.



Scheme 3.



even trace amount of malonate **IIIa** over a period of 4 h; only unreacted pentabromobenzyl alcohol (**VIa**) was isolated. Moreover, we found that bromide **Ia** in 96% ethanol in the presence of NaOH is converted exclusively into ether **Va**; only traces of alcohol **VIa** were detected in the reaction mixture.

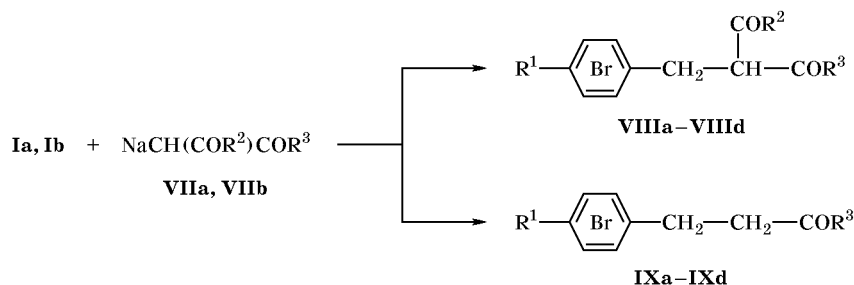
Obviously, the reactions in anhydrous ethanol and dimethylformamide follow $\text{S}_{\text{N}}2$ mechanism, resulting in C-alkylation of diethyl malonate, whereas in aqueous ethanol ionization of benzyl bromides **Ia** and **Ib** is possible. The subsequent attack by ambident nucleophile **II** in which the greatest negative charge is localized on the oxygen atom leads to formation of unstable intermediate O-alkylation product ($\text{S}_{\text{N}}1$ -like process, Scheme 3). An analogous scheme for formation of transesterification products via O-alkylation of sodium salt derived from methyl *O*-(tetrahydropyran-2-yl)amygdalic acid in DMSO at 80°C was proposed in [4]. It should be noted that products of intramolecular O-alkylation of cyanoacetic, malonic, and acetoacetic acid β -bromoethyl esters by the action of sodium hydride in THF were isolated for the first time by Parker [5] and were identified as substituted ketene acetals.

The reactions of bromides **Ia** and **Ib** with ethyl acetoacetate sodium salt (**VIIa**) at a ratio of 1:1 gave exclusively the corresponding C-alkylation products, ethyl 3-oxo-2-(polybromobenzyl)butanoates **VIIIa** and **VIIIb** (Scheme 4). By reaction of **Ia** with a slight excess (1:1.2) of enolate **VIIa** we obtained a mixture of ester **VIIIa** and ethyl 3-(pentabromophenyl)propio-

nate (**IXa**) (Table 1, run no. 8). The latter becomes the major product when the reaction is carried out with more than twofold excess of **VIIa** (Table 1, run no. 9). Analogous products are formed in the reaction of sodium salt **VIIa** with bromide **Ib** (Table 1, runs nos. 12 and 13). Under the same conditions, the reaction of **Ia** with an equimolar amount of acetylacetone sodium salt (**VIIb**) leads to formation of a mixture of the C-alkylation product and 4-(pentabromophenyl)-2-butanone (**IXc**) (Table 1, run no. 14); some amount of unchanged bromide **Ia** is also present in the reaction mixture. The reaction with excess sodium salt **VIIb** yields ketone **IXc** as the major product (Table 1, run no. 15). Pure 3-(pentabromobenzyl)-2,5-pentanedione (**VIIIc**) was obtained in 20% yield by slow reaction of bromide **Ia** with compound **VIIb** in toluene at 110°C (the conversion of **Ia** was $\sim 50\%$; Table 1, run no. 17). Bromide **Ib** reacted with an equimolar amount of **VIIb** to give mainly dione **VIIId**, whereas butanone **IXc** was the major product in the reaction of **Ib** with more than twofold excess of sodium salt **VIIb**.

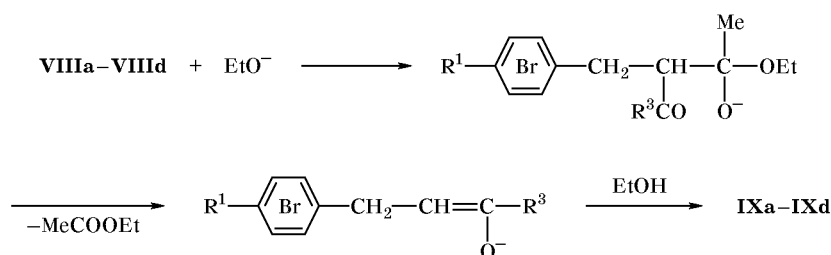
Presumably, ketones **IXc** and **IXd** and esters **IXa** and **IXb** are formed by cleavage of the primary C-alkylation products **VIIIa–VIIId** in the presence of excess sodium ethoxide (Scheme 5). This assumption was proved by special experiments. It should be noted that dione **VIIId** is more stable than **VIIIc**. The latter undergoes cleavage immediately following its formation, while complete transformation of compound **VIIId** into **IXd** requires high concentration of EtONa

Scheme 4.



VII, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{OEt}$ (a); $\text{R}^2 = \text{R}^3 = \text{Me}$ (b); VIII, IX, $\text{R}^1 = \text{Br}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{OEt}$ (a); $\text{R}^1 = \text{OMe}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{OEt}$ (b); $\text{R}^1 = \text{Br}$, $\text{R}^2 = \text{R}^3 = \text{Me}$ (c); $\text{R}^1 = \text{OMe}$, $\text{R}^2 = \text{R}^3 = \text{Me}$ (d).

Scheme 5.



and considerable time (Table 1; runs. nos. 14, 15, 19, and 20).

The structure of the C-alkylation products of dicarbonyl compounds was additionally proved by their alkaline and acid hydrolysis to the corresponding ketones and carboxylic acids. The reactions under study can be used as the basis of convenient preparative procedures for synthesis of β -polybromophenyl derivatives of carboxylic acids, esters, and ketones, which attract interest as starting compounds in the synthesis of biologically active substances.

EXPERIMENTAL

The ^1H NMR spectra were recorded on Tesla BS-467 (60 MHz), Bruker AM-200 (200 MHz), and Varian VXR (300 MHz) instruments in CCl_4 and CDCl_3 using HMDS as internal reference. The IR spectra were obtained on a UR-20 spectrometer from samples dispersed in mineral oil. Chromatographic analysis was performed on a Chrom-42 instrument using glass columns 3000×3.5 and 1500×3.5 mm; stationary phases 5% of SE-30 on Chromaton N-AW-HMDS (0.16–0.20 mm) and 3% of OV-17 on Chromaton N-Super (0.16–0.20 mm); oven temperature 220–260°C; thermoionic detector; carrier gas nitrogen. The purity of the initial compounds and final products was checked by GLC. All individual com-

pounds contained no less than 97.5–98.5% of the main substance. Polybromobenzyl alcohols VIa and VIb [1] and bromides Ia [6] and Ib [7] were synthesized by known procedures.

Reaction of polybromobenzyl bromides Ia and Ib with sodium salts of β -dicarbonyl compounds.

A mixture of ethanol, sodium ethoxide, and a 2–3-fold excess of β -dicarbonyl compound was heated for 10 min, bromide Ia or Ib was added, and the mixture was heated under reflux until the latter disappeared (TLC on Silufol plates, eluent toluene). Excess solvent was distilled off, the residue was treated with water, and the precipitate was filtered off, washed with water, dried, and analyzed by GLC, TLC, and ^1H NMR spectroscopy. Individual products were isolated by recrystallization from ethanol. When the reaction was performed in dimethylformamide and toluene, diethyl malonate sodium salt was prepared by dissolving metallic sodium in a 3-fold amount of diethyl malonate.

During GLC analysis (200–260°C) malonates IVa and IVb and butanoates VIIIa and VIIIb partially decomposed to give propionates IXa and IXb and ketones IXc and IXd, respectively. Therefore, in some cases quantitative analysis of the products was performed by ^1H NMR spectroscopy using CDCl_3 or CCl_4 as solvent; the following signals were used as

Table 2. Melting points, ^1H NMR spectra, and elemental analyses of polybromoaromatic compounds **IIIa**, **IIIb**, **IVa**, **IVb**, **VIIIa–VIIId**, and **IXa–IXd**

Comp. no.	mp, ^a °C	^1H NMR spectrum, δ , ppm	Found, %		Formula	Calculated, %	
			C	H		C	H
IIIa	149–150	(300 MHz, CDCl_3): 1.26 t (3H, CH_3), 3.42 s (2H, CH_2), 4.20 q (2H, CH_2 , $J = 7.1$ Hz), 5.67 s (2H, CH_2Ar)	23.25	1.61	$\text{C}_{12}\text{H}_9\text{Br}_5\text{O}_4$	23.37	1.47
IIIb	104–105	(60 MHz, CCl_4): 1.20 t (3H, CH_3), 3.22 s (2H, CH_2), 3.82 s (3H, OCH_3), 4.09 q (2H, CH_2 , $J = 7$ Hz), 5.50 s (2H, CH_2Ar)	27.63	2.04	$\text{C}_{13}\text{H}_{12}\text{Br}_4\text{O}_5$	27.50	2.13
IVa	104–105	(200 MHz, CDCl_3), 1.24 t (6H 2CH_3), 3.71–3.91 m (3H, CHCH_2), 4.21 q (4H, 2CH_2 , $J = 7.2$ Hz) (300 MHz, CDCl_3): 1.26 t (6H, 2CH_3 , $J = 7.2$ Hz), 3.75 t (1H, CH , $J = 5.9$ Hz), 3.88 d (2H, CH_2 , $J = 5.9$ Hz), 4.19 q (4H, 2CH_2 , $J = 7.2$ Hz)	25.92	2.01	$\text{C}_{14}\text{H}_{13}\text{Br}_5\text{O}_4$	26.08	2.03
IVb	83	(60 MHz, CCl_4): 1.15 t (6H, 2CH_3), 3.48–3.72 m (3H, CHCH_2), 3.80 s (3H, OCH_3), 4.08 q (4H, 2CH_2 , $J = 7.2$ Hz)	30.41	2.73	$\text{C}_{15}\text{H}_{16}\text{Br}_4\text{O}_5$	30.23	2.71
VIIIa	123–124	(200 MHz, CDCl_3): 1.23 t (3H, CH_3), 2.28 s (3H, CH_3CO), 3.73–3.90 m (3H, CHCH_2), 4.19 q (2H, CH_2 , $J = 7.2$ Hz)	25.77	1.94	$\text{C}_{13}\text{H}_{11}\text{Br}_5\text{O}_3$	25.40	1.80
VIIIb	100–101	(60 MHz, CCl_4): 1.12 t (3H, CH_3), 2.12 s (3H, CH_3CO), 3.53–3.72 m (3H, CHCH_2), 3.78 s (3H, OCH_3), 4.06 q (4H, 2CH_2 , $J = 7.5$ Hz)	29.78	2.63	$\text{C}_{14}\text{H}_{14}\text{Br}_4\text{O}_4$	29.72	2.49
VIIIc	190	(300 MHz, CDCl_3): 2.22 s (6H, $2\text{CH}_3\text{CO}$), 3.79 d (2H, CH_2Ar), 3.96 t (1H, CH , $J = 6.7$ Hz)	24.00	1.70	$\text{C}_{12}\text{H}_9\text{Br}_5\text{O}_2$	24.65	1.55
VIII d	143–144	(60 MHz, CCl_4): 2.07 s (6H, $2\text{CH}_3\text{CO}$), 3.57–3.72 m (3H, CHCH_2), 3.80 s (3H, OCH_3)	28.95	2.51	$\text{C}_{13}\text{H}_{12}\text{Br}_4\text{O}_3$	29.14	2.26
IXa	121	(200 MHz, CDCl_3): 1.30 t (3H, CH_3), 2.54–2.62 m (2H, CH_2CO), 3.53–3.62 m (2H, CH_2Ar), 4.19 q (2H, CH_2 , $J = 7.2$ Hz) (300 MHz, CDCl_3): 1.28 t (3H, CH_3 , $J = 7.2$ Hz), 2.57 t (2H, CH_2CO , $J = 8.5$ Hz), 3.56 t (2H, CH_2Ar , $J = 8.5$ Hz), 4.19 q (2H, CH_2 , $J = 7.2$ Hz)	23.55	1.64	$\text{C}_{11}\text{H}_9\text{Br}_5\text{O}_2$	23.07	1.58
IXb	127	(60 MHz, CCl_4): 1.22 t (3H, CH_3), 2.18–2.63 m (2H, CH_2CO), 3.22–3.71 m (2H, CH_2Ar), 3.80 s (3H, OCH_3), 4.06 q (2H, CH_2 , $J = 7.4$ Hz)	27.48	2.13	$\text{C}_{12}\text{H}_{12}\text{Br}_4\text{O}_3$	27.51	2.31
IXc	152–153	(300 MHz, CDCl_3): 2.21 s (3H, CH_3SO), 2.69 t (2H, CH_2CO), 3.47 t (2H, CH_2Ar , $J = 8.3$ Hz)	22.40	1.23	$\text{C}_{10}\text{H}_7\text{Br}_5\text{O}$	22.13	1.30
IXd	148–149	(60 MHz, CCl_4): 2.07 s (3H, CH_3), 2.25–2.62 m (2H, CH_2CO), 3.12–3.51 m (2H, CH_2Ar), 3.77 s (3H, OCH_3)	26.60	2.13	$\text{C}_{11}\text{H}_{10}\text{Br}_4\text{O}_2$	26.76	2.04

^a From ethanol.

reference: malonates **IIIa**, **IIIb**: ArCH₂; **IVa**, **IVb**: CHCH₂; **VIIIa**, **VIIIb**: CH₃CO; **IXa**, **IXb**: CH₂CO; the error in determination was 3–4%.

Ethyl pentabromobenzyl ether (Va). *a.* Metallic sodium, 2.6 mmol, was dissolved in 40 ml of anhydrous ethanol, 1.9 mmol of bromide **Ia** was added, and the mixture was heated for 2 h. It was then treated with water, and the precipitate was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 95%. Colorless crystals, mp 124–125°C. ¹H NMR spectrum (60 MHz, CCl₄), δ, ppm: 1.17 t (3H, CH₃), 3.37 q (2H, CH₂, *J* = 7.2 Hz), 4.83 s (2H, CH₂C₆Br₅). Found, %: C 20.35; H 1.14. C₉H₇Br₅O. Calculated, %: C 20.58; H 1.33.

b. A mixture of 100 ml of 96% ethanol, 5.78 mmol of NaOH, and 3.54 mmol of bromide **Ia** was heated for 4.5 h under reflux. The mixture was treated as described above in *a.* Yield 92%.

Ethyl 2,3,5,6-tetrabromo-4-methoxybenzyl ether (Vb) was synthesized from bromide **Ib** by the procedure described above for ether **Va** (method *a.*) Yield 65%. Colorless crystals, mp 75–76°C. ¹H NMR spectrum (60 MHz, CCl₄), δ, ppm: 1.13 t (3H, CH₃), 3.36 q (2H, CH₂, *J* = 7 Hz), 3.78 s (3H, OCH₃), 4.83 s (2H, CH₂C₆Br₄OCH₃). Found, %: C 24.81; H 2.38. C₁₀H₁₀Br₄O₂. Calculated, %: C 24.93; H 2.09.

Reaction of ethyl 3-oxo-2-(pentabromobenzyl)butanoate (VIIIa) with sodium ethoxide. A mixture of 30 ml of anhydrous ethanol, 0.81 mmol of ester **VIIIa**, and 1.03 mmol of sodium ethoxide was heated for 1 h under reflux. It was then treated with water, and the precipitate was filtered off, washed with water, dried, and recrystallized from ethanol. We thus obtained 74% of ester **IXa**.

Hydrolysis of ethyl 3-oxo-2-(pentabromobenzyl)butanoate (VIIIa). *a.* A mixture of 6.5 mmol of ester **VIIIa** and 60 ml of an alcoholic solution of sodium hydroxide (50 ml of 96% ethanol and 10 ml of 30% aqueous NaOH) was heated for 1 h under reflux and evaporated. The residue was treated with dilute hydrochloric acid, and the precipitate was washed with water and recrystallized from ethanol to obtain 3-(pentabromophenyl)propionic acid as a colorless crystalline substance. Yield 71%, mp 219–220°C. IR spectrum, ν, cm⁻¹: 3200 (OH), 1700 s (CO). Found,

%: C 19.85; H 0.93. C₉H₅Br₅O₂. Calculated, %: C 19.42; H 0.92.

b. A mixture of 16.3 mmol of ester **VIIIa** and 0.7 l of 0.5 N aqueous potassium hydroxide was heated for 6 h under reflux. The undissolved material was separated, washed with water, and recrystallized from dioxane to obtain 4-pentabromophenyl-2-butanone (**IXc**) in 84% yield. The alkaline filtrate was acidified with dilute hydrochloric acid to isolate 0.4 g (4.4%) of 3-(pentabromophenyl)propionic acid.

c. A mixture of 12.5 mmol of compound **VIIIa** and 200 ml of 40% H₂SO₄ was heated for 9 h under reflux. The precipitate was filtered off, washed with water, dried, and recrystallized from ethanol. The product was ketone **IXc**. Yield 70%.

Hydrolysis of ethyl (pentabromophenyl)propionate (IXa). A mixture of 60 ml of ethanol, 50 ml of 10% aqueous sodium hydroxide, and 2.1 mmol of ester **IXa** was heated for 0.5 h under reflux. The mixture was treated with water and acidified with dilute hydrochloric acid, and the precipitate was filtered off, washed with water, and dried. Recrystallization from ethanol gave 74% of 3-(pentabromophenyl)propionic acid.

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