

Carboxylate Phosphobetaines based on Tertiary Phosphines and Unsaturated Dicarboxylic Acids

Yu. V. Bakhtiyarova^a, R. I. Sagdieva^a, I. V. Galkina^a, V. I. Galkin^a, R. A. Cherkasov^a,
D. B. Krivolapov^b, A. T. Gubaidullin^b, and I. A. Litvinov^b

^aButlerov Chemical Institute at Kazan State University, Kazan, 420008 Russia

e-mail: Julia.Bakhtiyarova@ksu.ru

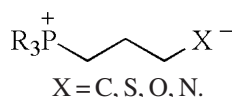
^bInstitute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences, Kazan, Russia

Received December 19, 2005

Abstract—By reaction of triorganylphosphines with unsaturated dicarboxylic acids adducts of betaine structure were synthesized whose stability depended on the character of substituents at phosphorus and on the structure of acid. The betaine obtained from phosphines and maleic and fumaric acids readily underwent decarboxylation into the corresponding monoacyl phosphonium derivatives. The structure of the latter was established by means of X-ray crystallography. The adduct prepared from phosphines and itaconic acid was stabilized by intramolecular hydrogen bond between the acylate anionic center and the "second" carboxy group.

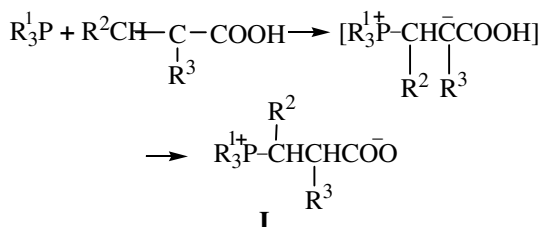
DOI: 10.1134/S1070428007020091

Phosphobetaines are internal phosphonium salts where the cationic phosphonium and anionic centers are linked by a system of covalent bonds.



These substances frequently arise as intermediates in many reactions of organophosphorus compounds; they are besides analogs of a certain kind of organic amino acids, and they are endowed with a wide range of chemical [1] and biological properties [2, 3].

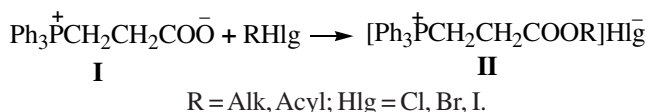
We formerly systematically investigated synthetic procedures for preparation, structures, and reactivity of phosphobetaines **I** obtained by addition of tertiary phosphines to unsaturated monocarboxylic acids. [4–6].



R¹ = Ph, Bu; R² = H, Ph, *i*-CH₃OC₆H₄; R³ = H, Me.

It was established that proton-donor reagents and solvents play an important part in stabilization of phosphobetaine structures with separated charges.

Betaines **I** readily undergo alkylation and acylation with haloalkyles and acyl halides to give the corresponding phosphonium salts **II**.



Phosphonium salts in contrast to betaine proper do not require proton-donor reagents to stabilize their crystal structure.

In the present article we report on the results of studying reactions between tertiary phosphines (triphenyl-, methyl-diphenyl-, and tributylphosphines) with unsaturated dicarboxylic acids (maleic, fumaric, and itaconic) whose second carboxy group we hope to be able to function as an internal proton-donor center facilitating the stabilization of the arising betaines.

Maleic acid reacted with triphenylphosphine under mild conditions in ethyl ether solution giving an adduct insoluble in organic solvents [mp 67–72°C (decomp.)] that represents according to IR spectrum dicarboxylate betaine **III**.

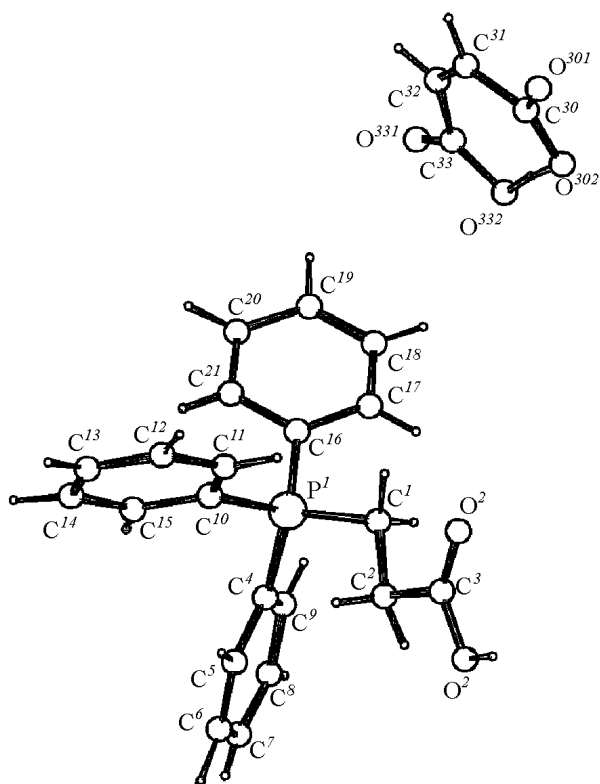
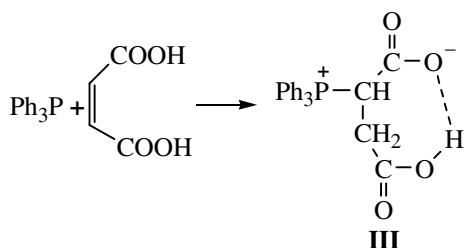


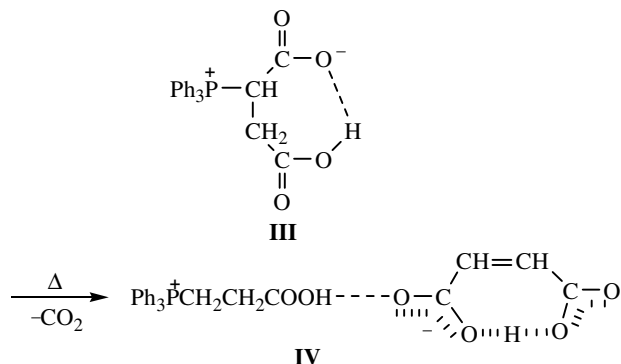
Fig. 1. Molecular structure of β -carboxyethyltriphenylphosphonium maleate (IV).

Betaine **III** is unstable and at heating or short storage easily suffers decarboxylation to form a phosphonium salt **IV** which may be regarded as a product of betaine **I** protonation with a molecule of maleic acid.



The decomposition pathway of betaine **III** resulting in phosphonium salt **IV** we proved by a special experiment: the heating of a sample of zwitter-ion **III** at 70°C for 1 h led to its quantitative decarboxylation. The high basicity of the “anionic moiety” of betaine **I** caused virtually complete proton transfer from the molecule of maleic acid. Thus forming β -carboxyethyltriphenylphosphonium cation and maleate anion are bound by a strong hydrogen bond. A similar bond in the maleate anion ensured its cyclization. These features of an uncommon structure of new quasiphosphonium salt **IV** were unambiguously revealed by X-ray diffraction analysis (Fig.1). Inasmuch

as salt **IV** unlike betaine **III** is well soluble in organic solvents, its IR and NMR spectra also proved this structure (see EXPERIMENTAL).



Asymmetrical part of the unit cell of the crystal of salt **IV** is formed by an ion pair of phosphonium cation and monoanion of maleic acid. The phosphorus atom coordination is a common one for a four-coordinated phosphonium atom. The bond distances and bond angles are consistent with the values found in the alkylation products of phosphobetaine **I** [7]. Conformation of the fragment $P^1C^1C^2C^3$ is close to transoid [torsion angle φ 156.2(2)°], of the fragment $C^1C^2C^3O^1$, to eclipsed one [torsion angle φ -24.7(4)°]. The CO distances in the molecule correspond to a double and an ordinary bonds (Table 1). As a result of deprotonation of the acid in one of the carboxy groups the CO bond lengths are equalized like in betaine **I** (Table 1). In the crystal intermolecular hydrogen bonds $O^2-H\cdots O^{301}$ ($3/2 - x, 1/2 + y, 3/2 - z$) were found linking the anion to the cation. Parameters of the hydrogen bonds are as follows: O^2-H^2 1.07(3), $H^2\cdots O^{301}$ 2.37(3), $O^2\cdots O^{301}$ 3.422(3) Å, angle $O^2H^2\cdots O^{301}$ 167(2)° (Fig. 2). Besides in the anion an intramolecular hydrogen bond $O-H\cdots O$ is present with the following parameters: $O^{332}-H^{332}$ 1.15(2), $H^{332}\cdots O^{302}$ 1.27(3), $O^{332}-H^{332}\cdots O^{302}$ 2.420(3) Å, angle 175(2)°.

The similarity of the crystal structures of triphenyl- β -carboxyethylphosphonium maleate and alkylation products of phosphobetaine [7] is also seen in the packing of the molecules: channels are formed parallel to $0a$ axis where the acid anions are located (Fig. 3).

The complete proton transfer from maleic acid to betaine **I** ($R^1 = Ph, R^2 = R^3 = H$) in adduct **IV** resulted in its inertness in previously studied reactions of alkylation with haloalkyles.

Triphenylphosphine reacted with fumaric acid only at heating in acetonitrile. Under these conditions we failed to isolate or detect the intermediate containing the initial dicarboxylic acid. Only betaine **I** was obtained stabilized

by an aceto-nitrile molecule. Its structure was confirmed by IR and NMR spectroscopy, and also by X-ray crystallography (Fig. 4).

Phosphonium salts are prone to include in the unit cell a molecule of solvent [7]. We established that in the unit cell of phosphobetaine **I** was present a molecule of acetonitrile. The geometry of a phosphorus atom in the phosphobetaine is usual, The conformation of the fragment $P^1C^1C^2C^3$ is transoid [torsion angle φ 171.7(2)°], of the fragment $C^1C^2C^3O^1$ is close to eclipsed [torsion angle φ 31.1(4)°]. The lengths of CO bonds in the molecule are equalized and are the same within the experimental accuracy.

Reaction of methyldiphenyl- and tributylphosphines with maleic acid occurred in the same manner as with triphenyl-phosphine with preliminary formation of

Table 1. Selected geometrical parameters of compounds **I** and **IV**

Bond	<i>d</i> , Å	
	I	IV
P^1-C^1	1.793(2)	1.810(3)
P^1-C^4	1.789(2)	1.795(2)
P^1-C^{10}	1.784(3)	1.796(2)
P^1-C^{16}	1.788(3)	1.792(2)
C^1-C^2	1.523(4)	1.535(4)
C^2-C^3	1.495(3)	1.543(4)
O^1-C^3	1.200(3)	1.220(5)
O^2-C^3	1.300(3)	1.241(5)
$O^{301}-C^{30}$	1.247(3)	
$O^{302}-C^{30}$	1.249(3)	
$O^{331}-C^{33}$	1.207(3)	
$O^{332}-C^{33}$	1.303(3)	

Bond angle	ω , deg	
	I	IV
$C^1P^1C^4$	110.5(1)	109.5(1)
$C^1P^1C^{10}$	109.0(1)	111.1(1)
$C^1P^1C^{16}$	108.9(1)	109.1(1)
$C^4P^1C^{10}$	107.8(1)	107.5(1)
$C^4P^1C^{16}$	109.9(1)	110.7(1)
$C^{10}P^1C^{16}$	110.8(1)	109.0(1)
$P^1C^1C^2$	113.8(2)	112.2(2)
$C^1C^2C^3$	113.0(2)	112.7(3)
$O^1C^3O^2$	124.3(2)	124.4(3)
$O^1C^3C^2$	124.1(2)	118.7(3)
$O^2C^3C^2$	111.5(2)	116.9(3)

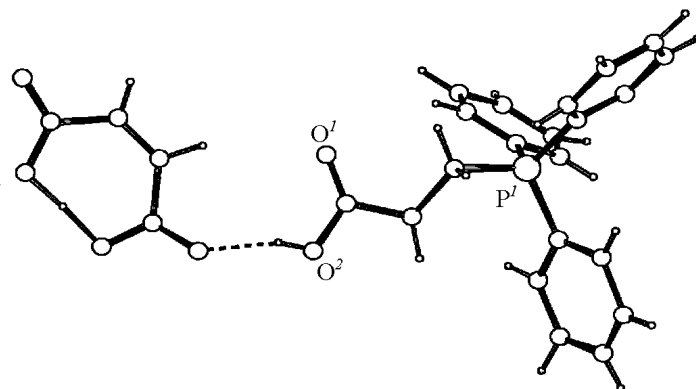


Fig. 2. Hydrogen bonds in the crystal of b-carboxyethyl-triphenylphosphonium maleate (**IV**).

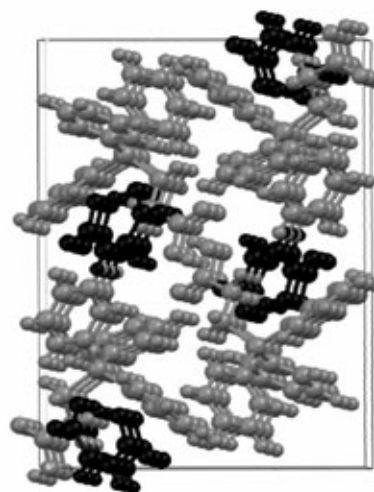


Fig. 3. Packing in the crystal of compound **IV**. Projection along $0a$ axis.

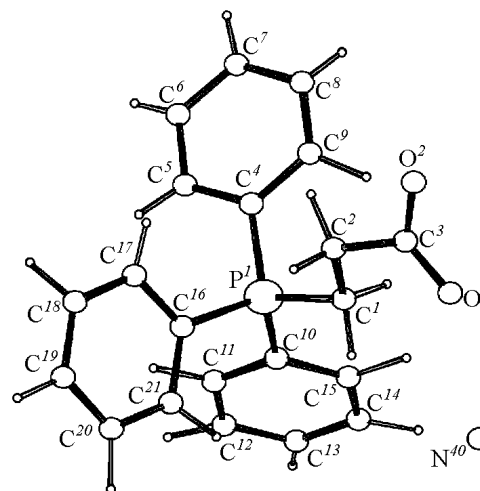
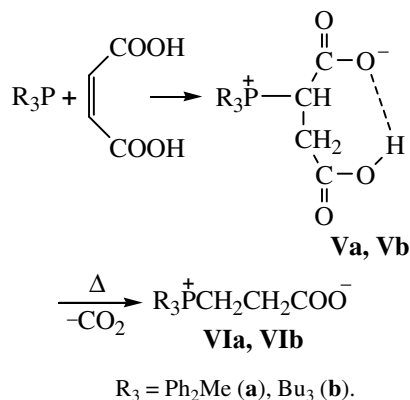


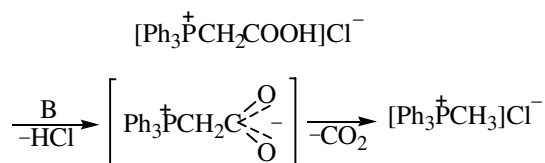
Fig. 4. Molecular structure of phosphobetaine **I** obtained by reaction of triphenylphosphine and fumaric acid.

dicarboxylate betaines **Va** and **Vb** which already under the reaction condition suffer decarboxylation into phosphobetaines **VIa** and **VIb**.



The analysis of stability of adducts formed from triorganylphosphines and unsaturated dicarboxylic acids showed that the geminal position of the phosphonium cation and acylate anion results in destabilization of the betaine structure promoting decarboxylation and leading to appearance of more thermodynamically favorable zwitter-ion with a β -location of its anionic and cationic parts. Apparently, this spreading of charges alongside with the betaine stabilization by proton-donor solvent molecules or by specially added acidic substances serves as a factor of stabilization for the structure of bipolar ions.

This conclusion is well consistent with published data [8] on failed attempts to obtain triphenylphosphonium methylcarboxylate by reaction of triphenylphosphine with chloroacetic acid. Here also decarboxylation occurred giving triphenylmethylphosphonium chloride.

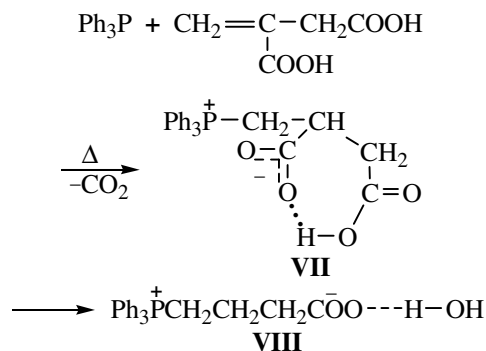


To support these assumptions we involved into the reaction with the tertiary phosphine itaconic acid hoping that these reaction products unlike analogous products obtained from fumaric and maleic acids would be more stable for in the arising betaines the nearest carboxy group should be located not in the α -, but in the β -position with respect to the phosphonium center.

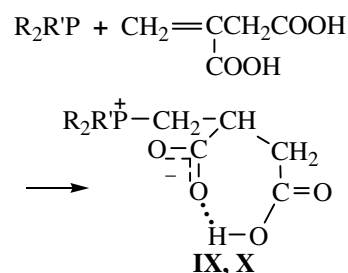
The reaction between triphenylphosphine and itaconic acid occurs with the formation of a single crystalline compound **VII** [δ_p 23.9 ppm, mp 58–60°C (decomp.)]. Its IR spectrum contains absorption bands of both carboxy

centers: that of the carboxy group at 1700 cm^{-1} , and that of carboxylate anion in the region 1600 cm^{-1} .

However also in this case the bipolar adduct **VII**, although more stable than betaines based on maleic and fumaric acids, still is not very heat-resistant. Its melting or boiling in chloroform is accompanied with clear signs of decomposition with CO_2 liberation. In a special experiment we performed its decarboxylation leading to a product of its thermal decomposition, phosphobetaine **VIII** (δ_p 22.45 ppm, mp 53–57°C) that was readily hydrated with the air moisture giving the corresponding phosphonium salt. Its IR spectrum lacks the absorption band of the carboxylate anion, and the strong band at 1720 cm^{-1} corresponds to the absorption of a single carboxy group.



Methyldiphenylphosphine reacted with the itaconic acid leading to the formation of a single crystalline substance, betaine **IX** [δ_p 24.5 ppm, mp 132°C (decomp.)].



R = Ph, R' = Me (**IX**); R, R' = Bu (**X**).

In its IR spectrum absorption bands appeared both from the carboxy group in the region 1700 cm^{-1} and from the carboxylate anion in its characteristic region 1600 cm^{-1} . According to elemental analysis compound **IX** is a stable dicarboxylate phosphonium betaine. Analogous reaction of tributylphosphine with itaconic acid gave rise to dicarboxylate phosphobetaine **X** (δ_p 34.0 ppm),

yellowish oily substance. Also in this case the IR spectrum contained the absorption bands of carboxylate anion at 1600 cm^{-1} and of carboxy group at 1720 cm^{-1} .

Thus the investigation performed showed the essential features of behavior inherent to the unsaturated dicarboxylic acids in phosphobetaines formation originating from the thermodynamical instability of the structures with the α -position of phosphonium and carboxylate sites.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer Specord M80 in the frequency range $700\text{--}3600\text{ cm}^{-1}$ from thin films or mulls in mineral oil between KBr plates. ^1H and ^{31}P spectra were registered from solutions in CDCl_3 on a spectrometer Varian Unity-300 at operating frequencies 300 (^1H , internal reference HMDS) and 121.64 MHz (^{31}P , external reference H_3PO_4).

X-ray diffraction study on single crystals of compounds **I** and **IV** was carried out at 20°C on an automatic four-circle diffractometer Enraf-Nonius CAD-4 using $\lambda\text{MoK}\alpha$ -radiation, $\lambda 0.71073\text{ \AA}$ (graphite monochromator, variable scanning rate, $1\text{--}16.4\text{ deg/min}$ by θ , Table 2). Unit cell parameters were estimated from 25 reflections. The stability of crystals in the course of the experiment was checked every 2 h by measuring three reference reflections, the crystal orientation was controlled by measuring two reflections after every 200 reflections. The structures were solved by the direct method using SIR software [7]. All calculations were carried out applying software package MolEN [9] on a computer DEC Alpha Station 200.

3-Triphenylphosphoniopropanoate (I). To a solution of 2.110 g of triphenylphosphine in 5 ml of acetonitrile was added dropwise at stirring 0.935 g of a solution of fumaric acid. The reaction mixture was boiled on a water bath at 70°C for 18 h , and the solution turned brown. The solvent was removed in a vacuum, the crystal substance was washed with ether, the crystals were filtered off and dried in a vacuum to obtain 1.614 g (60%) of colorless crystals of compound **I** including acetonitrile molecules, mp $145\text{--}148^\circ\text{C}$, $\delta_{\text{p}} 25\text{ ppm}$, $\nu_{\text{COO}^-} 1605\text{ cm}^{-1}$. The structure was proved by X-ray diffraction study, (Fig. 4).

2-(Triphenylphosphonio)hydrosuccinate (III). Into a solution of 3.094 g of triphenylphosphine in 5 ml of anhydrous ether at constant stirring was added dropwise

Table 2. Parameters of crystals of compounds **I** and **IV**, and conditions of X-ray crystallographic experiments

Parameter	I	IV
Crystal system	monoclinic	
Empirical formula	$\text{C}_{21}\text{H}_{19}\text{O}_2\text{P}$ $\text{C}_2\text{H}_3\text{N}$	$\text{C}_{21}\text{H}_{20}\text{O}_2\text{P}^+$ $\text{C}_4\text{H}_2\text{O}_4^-$
Molecular weight	375.39	450.4
Space group	$P2_1/n$	
Parameters of unit cell, \AA		
<i>a</i>		
<i>b</i>	9.151(2),	9.671(2),
<i>c</i>	12.759(2),	18.537(6),
β	16.375(4)	13.327(2),
	$98.54(3)^\circ$	$105.82(2)^\circ$
Volume, \AA^3	1891.23	2298.55
<i>Z</i>	4	
Density (calc), g/cm^3	1.32	1.42
Extinction coefficient, μ, cm^{-1}	1.6	20.97
θ_{max} , deg	26.30	22.76
Reflections measured	4277	3247
Number of observed reflections with $I > 3\sigma(I)$	2023	2200
Scanning type	$\omega/2\theta$	
Accounting for extinction	empirical	
Conditions of revealing and refining of hydrogen atoms	Revealed from difference of electron density, not refined	Revealed from difference of electron density, refined isotropically
Final values of divergence factors	$R 0.049$, $R_w 0.057$	$R 0.034$, $R_w 0.046$
Number of reflections used in refining	2023	2200
Number of refined parameters	244	381

an ether solution of 1.372 g of maleic acid. After 15 min a colorless precipitate of betaine **III** separated and was filtered off, mp $67\text{--}73^\circ\text{C}$ (decomp.). Compound **III** is insoluble in organic solvents, unstable to heat, and readily decomposed with CO_2 liberation even at short storage; the decomposition product was soluble in acetonitrile.

Thermal decomposition of betaine III. At 70°C was heated on a water bath 3.045 g of betaine **III** for 1 h in a flask equipped with a gas-outlet tube. The reaction mixture was dissolved in 5 ml of acetonitrile, to a solution anhydrous ether was added. The separated colorless precipitate was filtered off, washed with ether, and dried

in a vacuum. We isolated 2.441 g (67%) of colorless crystals of **(2-carboxyethyl)triphenyl-phosphonium hydromaleate (IV)**, mp 144–148°C, δ_p 21 ppm, ν_{COO^-} 1600 cm^{-1} . The liberated gas was passed through a solution of calcium hydroxide. A white precipitate of calcium carbonate separated, The structure of compound **IV** was proved by ^1H and ^{31}P NMR spectroscopy, and also by X-ray diffraction study, (Fig. 1).

3-(Methyldiphenylphosphonio)propanoate (VIa). To a solution of 0.539 g of methyldiphenylphosphine in 5 ml of acetonitrile at constant stirring was added dropwise a solution of 0.341 g of maleic acid in 5 ml of acetonitrile, the reaction mixture was kept at room temperature for several hours, the solvent was removed in a vacuum. The formed colorless crystals of **2-(methyldiphenylphosphonio)hydrosuccinate (Va)** are insoluble in organic solvents and are stable only under a layer of solvent. Compound **Va** is unstable in air and easily suffered decarboxylation to phosphobetaine **VIa**, oily substance, ν_{COO^-} 1615 cm^{-1} , δ_p 24.9 ppm

3-(Tributylphosphonio)propanoate (VIb). To a solution of 3.062 g of tributylphosphine in 5 ml of anhydrous ether at constant stirring was added dropwise a solution of 1.761 g of maleic acid. The reaction mixture was kept for 1 month. First in the course of the reaction formed **2-(tributyl-phosphonio)hydrosuccinate (Vb)**, δ_p 56 ppm, that under the reaction conditions easily suffered decarboxylation into betaine **VIb**, δ_p 35 ppm. In the IR spectrum of betaine **VIb** appear absorption bands both of carboxylate anion at 1600 cm^{-1} and of carboxy group involved in a hydrogen bond ($\nu_{\text{C=O}}$ 1720, ν_{OH} 800–3200 cm^{-1}).

2-(Triphenylphosphoniomethyl)hydrosuccinate (VII). To a solution of 0.901 g of triphenylphosphine in 5 ml of acetonitrile was added dropwise at stirring a solution of 0.472 g of itaconic acid in 5 ml of acetonitrile. The reaction mixture was kept for 24 h. The solvent was removed in a vacuum, the crystalline residue was washed with ether, filtered off, and dried in a vacuum to obtain 0.863 g (64%) of colorless crystals, mp 58–60°C (decomp.), δ_p 23.92 ppm, ν_{COO^-} 1605, ν_{COOH} 1720 cm^{-1} . Betaine **VII** is stable in air, well soluble in polar solvents.

Decomposition of betaine (VII). To 70°C was heated on a water bath 0.450 g of betaine **VII** for 15 min in a flask equipped with a gas-outlet tube. The reaction

mixture was dissolved in 5 ml of acetonitrile, to a solution anhydrous ether was added. The separated colorless precipitate was filtered off, washed with ether, and dried in a vacuum. We isolated 0.280 g (70%) of **4-(triphenylphosphonio)butanoate (VIII)**, mp 55°C, δ_p 24 ppm, ν_{COOH} 1720 cm^{-1} . On passing the liberated gas through the calcium hydroxide solution white precipitate of calcium carbonate was obtained.

2-(Methyldiphenylphosphoniomethyl)hydro-succinate (IX). To a solution of 0.512 g of methyldiphenylphosphine in 5 ml of acetonitrile was added dropwise a solution of 0.335 g of itaconic acid in 5 ml of acetonitrile. On storage of the solution at room temperature after several days a fine colorless precipitate separated that was washed with ethyl ether, filtered off, and dried in a vacuum. We obtained 0.549 g (65%) of betaine **IX** that was stable in air, insoluble in most organic solvents, soluble in DMF. mp 132°C, ν_{COO^-} 1600 cm^{-1} , ν_{COOH} 1700 cm^{-1} , δ_p 24.5 ppm. Found, %: C 65.39; H 5.72; P 8.98. $\text{C}_{18}\text{H}_{19}\text{O}_4\text{P}$. Calculated, %: C 65.45; H 5.76; P 9.39.

2-(Tributylphosphoniomethyl)hydrosuccinate (X). To a solution of 1.510 g of tributylphosphine in 5 ml of acetonitrile was added a solution of 1.080 g of itaconic acid in 5 ml of acetonitrile. The reaction mixture was kept for 24 h at room temperature. The solvent was removed in a vacuum. We obtained betaine **X** as an oily yellowish substance. ^{31}P NMR spectrum: δ 34 ppm. IR spectrum, cm^{-1} : 1730 (ν_{COOH}), 1600 (ν_{COO^-}).

The study was carried out under a financial support of the program of the Ministry of Education and Science of the Russian Federation “Universities of Russia, fundamental research” and of joint program of the Ministry of Education and Science of the Russian Federation and CRDF “Basic Research & Higher Education” (grant no. REC-007).

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