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Special Features of the Interaction of Pyridine and Quinoline Derivatives, and Related Compounds with Triphenylphosphine

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Abstract—Using pyridine, quinoline, and related compounds as examples, it has been shown that their interaction with triphenylphosphine occurs via different pathways. Reaction of triphenylphosphine with *N*-vinylisonicotinic acid chloride leads to the mixture of 1,2-bis(triphenylphosphoniumchlorido)ethane and 4-carboxy-2-(triphenylphosphoniumchloridoethyl)pyridine. In the case of α-(*N*-2-carboxyquinolinylbromido)-β-bromopropionic acid, the reaction with triphenylphosphine proceeds via phosphine attack on the oxygen atom with elimination of quinaldinic acid, and subsequent nucleophilic substitution with the formation of 3-(triphenylphosphoniumbromido)propionic acid bromide.

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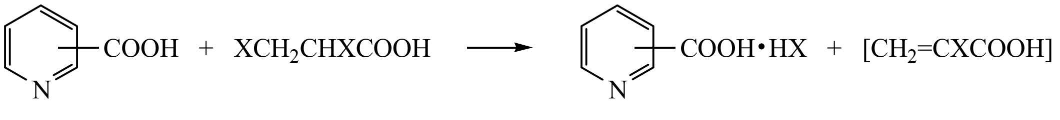
It is known that vinyl phosphonium and vinyl sulfonium salts are capable of reaction with nucleophiles to form compounds bearing the β-substituted ethyl group. Similar reactions of vinylammonium salts have not been described in the literature. The inactivity of vinylammonium salts in such reactions has been explained by *d*-orbital resonance [1], that is, by stabilization of the intermediate α-carboanions by its mesomeric form, impossible in the case of vinylammonium salts.

$$R^1_3\overset{+}{P}\overset{-}{C}HR^2 \rightleftarrows R^1_3P{=}CHR^2$$

Our studies of the nucleophilic addition to vinylammonium salts have shown that apart from *d*-orbital effect the electron acceptor ability of the cation may be an important factor.

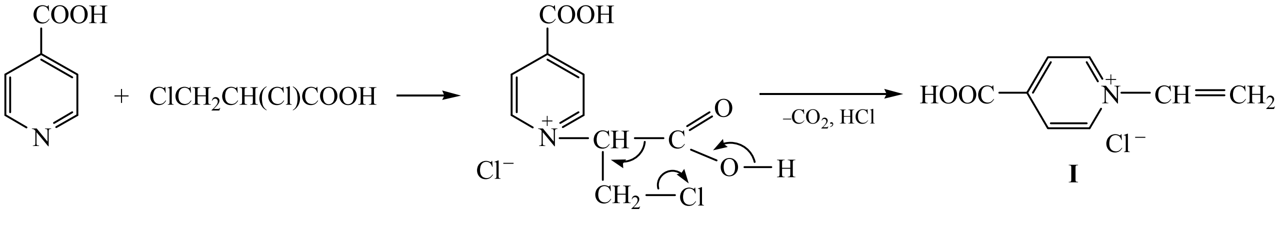
In the extension of our work, we attempted to carry out such reactions with the substrates bearing pyridine ring fragments.

We failed to prepare salts of *N*-vinyl-substituted nicotinic and picolinic acid. In the reactions of these acids with 2,3-dichloro- or 2,3-dibromopropionic acid in boiling acetonitrile as well as in ether the corresponding hydrohalides were obtained in high yields.



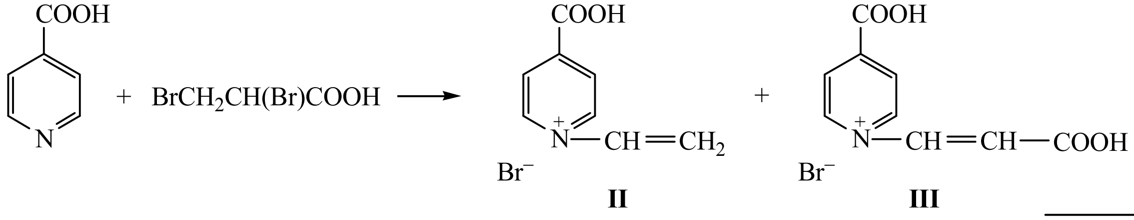
X = Cl, Br.

However, in the reaction of 2,3-dichloropropionic acid with isonicotinic acid in boiling acetonitrile the salt of *N*-vinyl-substituted isonicotinic acid was the sole product. The reaction proceeded as nucleophilic substitution, decarboxylation, and halogen anionization [2].



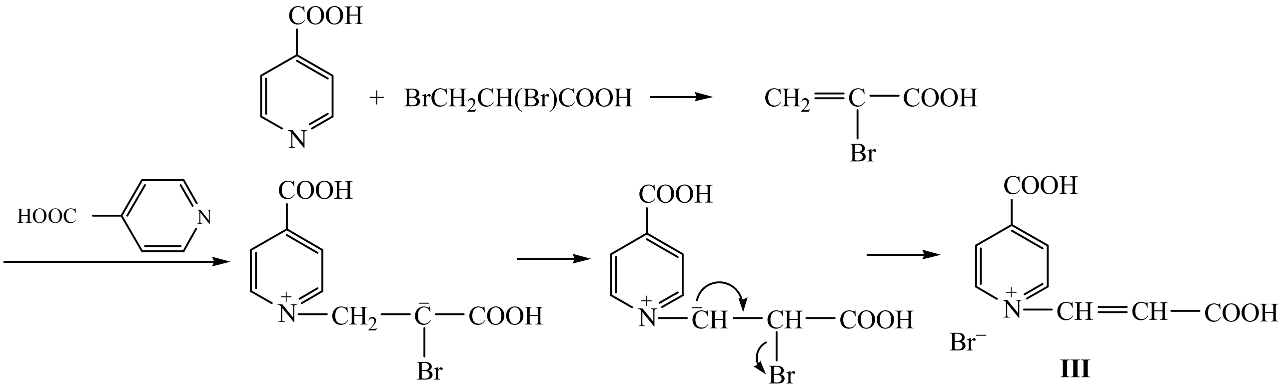
I

In the case of 2,3-dibromopropionic acid, along with the *N*-vinylisonicotinic acid salt **II**, the compound **III** was formed as a minor product (**II**:**III** ratio was 3:1).



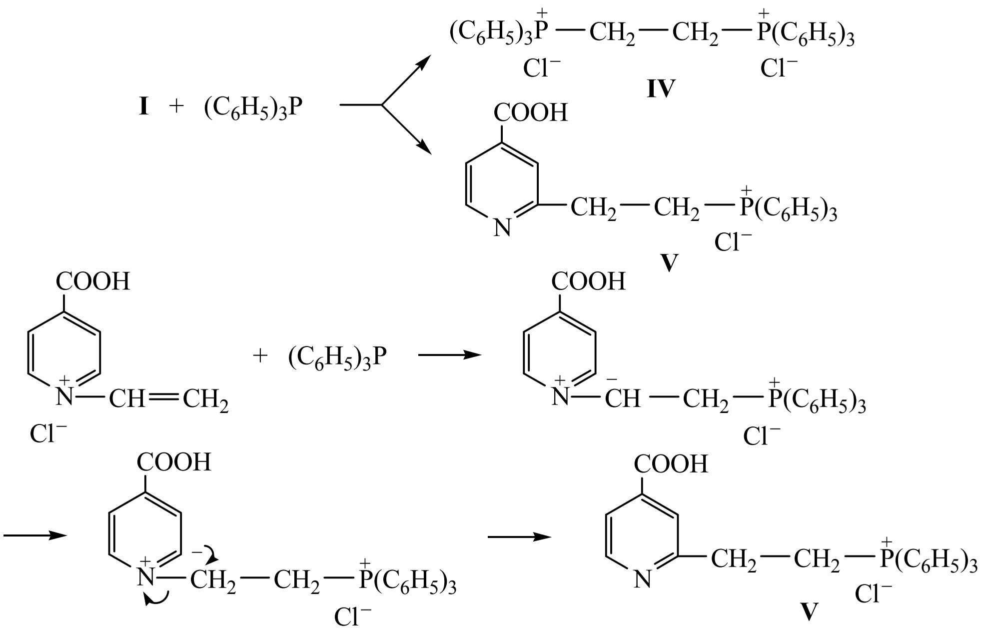
II **III**

In this case, similar to pyridine reaction [3], two reaction pathways occurred simultaneously. The formation of **III** included dehydrobromination with subsequent interaction of the formed α-bromoacrylic acid with isonicotinic acid.



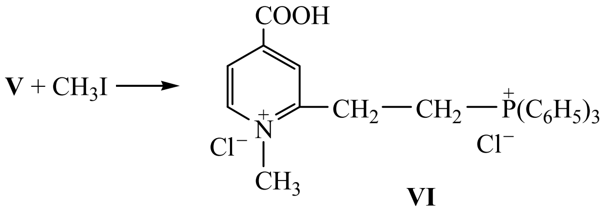
III

The reaction of salt **I** with triphenylphosphine occurred with the formation of 1,2-bis-(triphenylphosphoniumchlorido)ethane (**IV**). The product of Stevens rearrangement **V** [3] was also isolated that formed according to the following scheme.



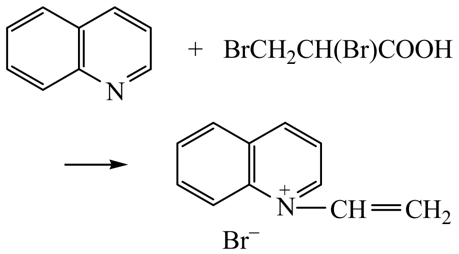
IV **V** **V**

The data obtained showed that in this case high electron acceptor ability of the onium cation favored the anionization the α-hydrogen of pyridine ring. The structure of **V**, besides NMR (^{1}H and ^{31}P) data was confirmed by iodomethylation of the obtained mixture.



VI

Attempts to prepare salts of *N*-vinyl-substituted quino-line, 8-oxyquinoline, and carboxyquinoline with 2,3-dichloro-propionic acid or 2,3-dibromo-propioniic acid failed; the only products were hydrohalides of the starting quinolines.

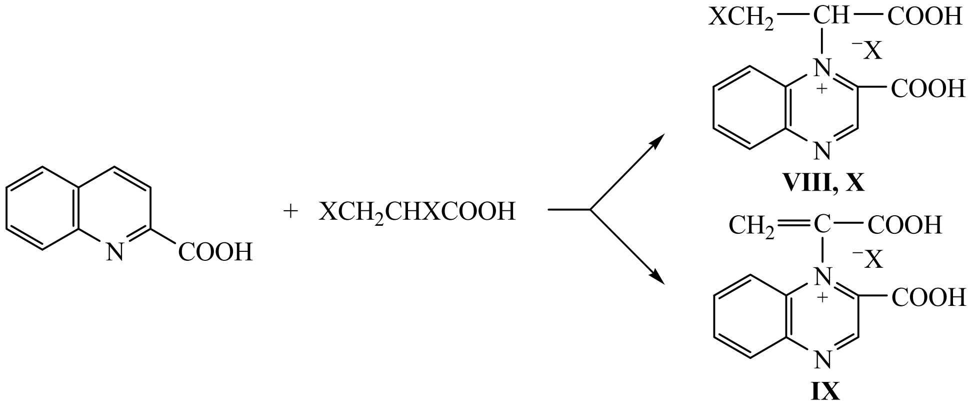


VII

We were able to prepare *N*-vinylquinolinic salt **VII** in a low yield (~15%) in the reaction of quinoline with 2,3-dibromopropionic acid in ether.

This salt, however, did not react with triphenylphosphine.

As a continuation we studied the interaction of quinaldinic acid with 2,3-dichloropropionic acid and 2,3-dibromopropionic acid. After boiling 2,3-dichloropropionic acid with quinaldine in acetonitrile, a mixture of **VIII** and **IX** in the ratio of 3:1 was obtained.

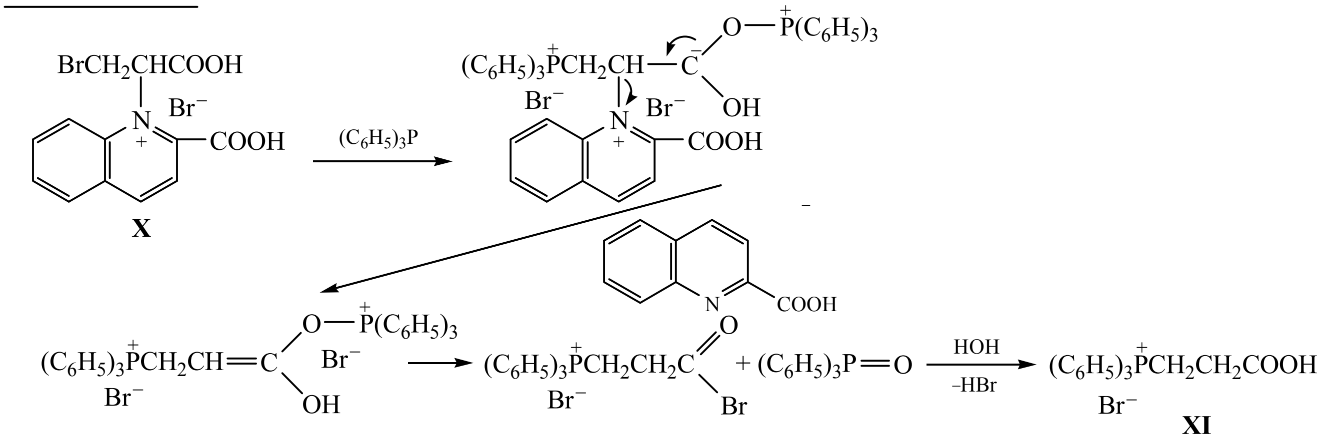


VIII, X

IX

X = Cl (**VIII, IX**), Br (**X**).

The result of interaction of salt **X** with triphenylphosphine in boiling acetonitrile was unexpected. Instead of dehydrobromination or nucleophilic substitution products, 3-(triphenylphosphiniumbromido)propionic acid was isolated from the acetonitrile solution by ether precipitation. The reaction



X

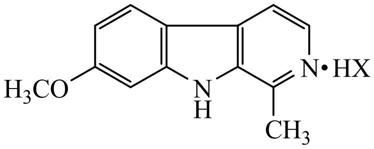
XI

likely proceeded as a phosphine attack on the oxygen atom with quinaldinic acid elimination and subsequent nucleophilic substitution of the bromide with the formation of 3-(triphenylphosphiniumbromido)propionyl bromide.

Triphenylphosphine oxide was isolated from the filtrate after the removal of the solvents.

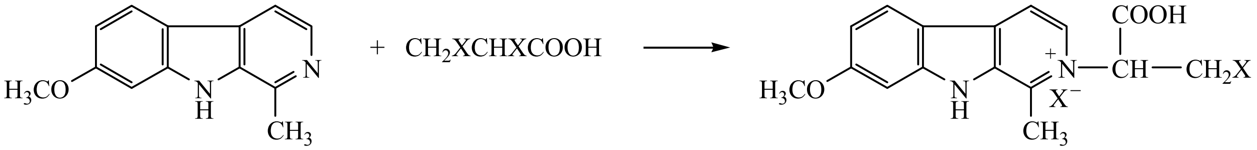
The reaction was studied of 2,3-dihalopropionic acid with indole alkaloid harmine, containing nitrogen groups of different basicity. Systematic studies in this field may potentially lead to preparation of physiologically active compounds.

In the reaction of harmine with 2,3-dichloropropionic acid and 2,3-dibromopropionic acid in boiling acetonitrile harmine hydrohalides were obtained.



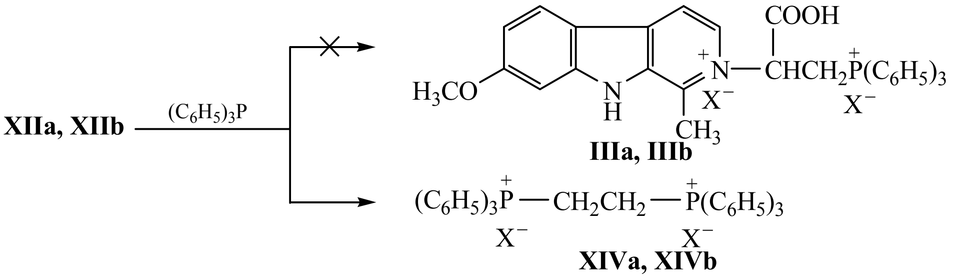
X = Cl, Br.

Similar reactions in ether gave compounds **XIIa**, **XIIb**.



XIIa, X = Cl; **XIIb**, X = Br.

We carried out the reactions of 2-harminium-halido-3-halopropionic acids (**XIIa**, **XIIb**) with triphenylphosphine. Theoretically, the formation of either mixed phosphonium-ammonium salts (**XIIIa**, **XIIIb**), or their transformation products, 1,2-bis(triphenylphosphoniumhalido)ethanes (**XIVa**, **XIVb**) could be anticipated.



X = Cl (**XIIIa, XIVa**), Br (**XIIIb, XIVb**).

EXPERIMENTAL

NMR spectra were recorded on a Varian Mercury-300 (300 MHz) spectrometer at 303 K. Chemical shifts are given relative to TMS internal reference.

Interaction of 2,3-dichloropropionic acid with isonicotinic acid. A mixture of 1.43 g (0.01 mol) of 2,3-dichloropropionic acid and 1.23 g (0.01 mol) of isonicotinic acid in 10 ml of acetonitrile was boiled during 40 h. The formed precipitate was filtered off, washed with acetonitrile, and dried in a vacuum. Yield 1.7 g (94%) of *N*-vinylisonicotinic acid salt **I**, mp 270°C. ^{1}H NMR spectrum (DMSO-d_6–CCl$_4$, 1:3), δ, ppm (*J*, Hz): 5.19 d.d (1H, *J* 13.3, 9.2), 5.35 d.d (1H, *J* 9.2, 4.3), 5.60 d.d (1H, *J* 13.3, 4.3), 8.51 m (2H, Pyr), 9.61 m (2H, Pyr), 13.60 br.s (2H, COOH). Found, %: C 52.02; H 3.98; N 7.61. $C_8H_8NO_2Cl$. Calculated, %: C 51.75; H 4.31; N 7.54.

Interaction of 2,3-dibromopropionic acid with isonicotinic acid. A mixture of 2.32 g (0.01 mol) of 2,3-dibromopropionic acid and 1.23 g (0.01 mol) of isonicotinic acid in 10 ml of acetonitrile was boiled during 40 h. The formed precipitate was filtered off, washed with acetonitrile, and dried in a vacuum. Yield 1.9 g of the mixture **II**, **III** in the ratio of 1:3 (according to ^{1}H NMR spectrum). ^{1}H NMR spectrum of the salt **II** corresponded to that shown above. ^{1}H NMR spectrum of the salt **III** (DMSO-d_6–CCl_4, 1:3), δ, ppm (*J*, Hz): 7.20 d (1H, =CHCOOH, *J* 13.0), 8.50 m (3H, Pyr, =CHN$^+$), 9.62 m (2H, Pyr), 12.00 br.s (2H, COOH).

Interaction of triphenylphosphine with *N*-vinylisonicotinic acid hydrochloride (I). A mixture of 1.15 g (0.005 mol) of N-vinylisonicotinic acid hydrochloride (**I**) and 2.62 g (0.01 mol) of triphenylphosphine in 7 ml of acetonitrile was boiled for 40 h. After filtration of the reaction mixture and treatment with ether, 1.4 g of the mixture of salts was obtained [^{1}H NMR data: 0.6 g (45%) of **IV** and 0.8 g (62.5%) of **V**]. ^{1}H NMR spectrum and ^{31}P NMR spectrum of the salt **IV** corresponded to the literature data [3]. ^{1}H NMR spectrum of **V** (DMSO-d_6–CCl_4, 1:3), δ, ppm, 2.63 m (2H, CH_2), 3.88 m (2H, CH_2), 7.65–8.00 m (18H, Ph, Pyr). ^{31}P NMR spectrum: δ_P 31.30 ppm.

Interaction of the mixture of salts IV, V with methyl iodide. Triple amount of methyl iodide (acetonitrile solution) was added at room temperature to 0.5 g of the mixture of **IV** and **V**. After 1 day of incubation, the mixture was poured into ether. The formed crystals were filtered off, washed with ether, and dried in a vacuum. Yield 0.56 g of mixture of **IV**, **V**, and **VI** in the ratio of 4:0.5:5 (according to ^{1}H and ^{31}P NMR spectra). ^{1}H NMR spectrum of **VI** (DMSO-d_6–CCl_4, 1:3), δ, ppm: 3.10 m (2H, CH_2), 3.65 s (3H, Me), 4.00 m (2H, CH_2), 7.60 m (18H, Ph, Pyr). ^{31}P NMR spectrum: δ_P 29.90 ppm.

Interaction of 2,3-dichloropropionic acid with quinaldinic acid. A mixture of 0.72 g (0.005 mol) of 2,3-dichloropropionic acid and 0.86 g (0.005 mol) of quinaldinic acid in 10 ml of acetonitrile was boiled during 20 h. The formed precipitate was filtered off, washed with acetonitrile, and dried in a vacuum. Yield 0.3 g (30%) of quinaldinic acid hydrochloride. From the acetonitrile solution, after ether treatment, a mixture of salts **VIII** and **IX** was obtained, in the ratio of 3:1 (according to ^{1}H NMR spectrum). ^{1}H NMR spectrum of **VIII** (DMSO-d_6–CCl_4, 1:3), δ, ppm (*J*, Hz): 3.72 d.d (1H, J_1 9.7, J_2 4.7), 3.87 d.d (1H, J_1 10.7, J_2 9.7), 4.43 d.d (1H, J_1 10.7, J_2 4.7), 7.66 d.d.d (1H, C_6H_4, J_1 8.2, J_2 5.9, J_3 1.1), 7.80 d.d.d (1H, C_6H_4, J_1 8.5, J_2 5.4, J_3 1.5), 7.98 d.d (1H, C_6H_4, J_1 8.2, J_2 1.5), 8.18 d.d (1H, C_6H_4, J_1 8.5, J_2 1.1), 8.12 d (1H, C_5H_2N, *J* 8.5), 8.43 d (1H, C_5H_2N, *J* 8.5), 11.00 br.s (2H, COOH). ^{1}H NMR spectrum of **IX** (DMSO-d_6–CCl_4, 1:3), δ, ppm (*J*, Hz): 6.00 and 6.45 s (2H, =CH_2), 7.66 d.d.d (1H, C_6H_4, J_1 8.2, J_2 5.9, J_3 1.1), 7.80 d.d.d (1H, C_6H_4, J_1 8.5, J_2 5.4, J_3 1.5), 7.98 d.d (1H, C_6H_4, J_1 8.2, J_2 1.5), 8.18 d.d (1H, C_6H_4, J_1 8.5, J_2 1.1), 8.12 d (1H, C_5H_2N, *J* 8.5), 8.43 d (1H, C_5H_2N, *J* 8.5), 11.00 br.s (2H, COOH).

Interaction of 2,3-dibromopropionic acid with quinaldinic acid. A mixture of 2.32 g (0.01 mol) of 2,3-dibromopropionic acid and 1.73 g (0.01 mol) of quinaldinic acid in 15 ml of acetonitrile was boiled during 20 h. The formed precipitate was filtered off, washed with acetonitrile, and dried in a vacuum. Yield 0.55 g (21.5%) of quinaldinic acid hydrobromide. After treating similarly to the previous reaction, 2.82 g (69.6%) of salt **X** was obtained, mp 170°C. Found, %: C 39.64; H 3.02; N 3.76. $C_{13}H_{11}O_4 \cdot NBr_2$. Calculated, %: C 39.49; H 2.78; N 3.54.

Interaction of X with triphenylphosphine. A mixture of 1 g (0.0025 mol) of salt **X** and 1.31 g (0.005 mol) of triphenylphosphine was boiled in acetonitrile for 20 h. After filtering off 0.42 g (98%) of the formed quinaldinic acid, the filtrate was poured into ether, the precipitate was filtered off, washed with ether, and dried in a vacuum. Yield 0.5 g (50%) of 3-(triphenylphosphiniumbromido)propionic acid **XI,** mp 190°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1:3) δ, ppm (*J*, Hz): 2.62 d.d (2H, $\underline{C}H_2COOH$, *J* 11.1, 7.7), 3.68 d.d (2H, CH_2P, *J* 13.5, 7.7), 7.71–7.92 m (15H, Ph_3P), 12.55 br.s (1H, COOH). ^{31}P NMR spectrum: δ_P 30.16 ppm. Found, %: C 80.84; H 4.90; Br 19.41; P 7.61. $C_{21}H_{20}BrO_2P$. Calculated, %: C 60.72; H 4.82; Br 19.28; P 7.47. After removal of the solvents, 0.35 g (50%) of triphenylphosphine oxide, mp 154°C, was obtained.

Interaction of 2,3-dihalopropionic acids with harmine. A mixture of 0.01 mol of 2,3-dichloropropionic and 2,3-dibromopropionic acid with 0.01 mol of harmine in 150 ml of ether was boiled during 30 h. The precipitate was filtered off, washed with ether, and dried in a vacuum. Yield, respectively, 2.1 g (60%) of salt **XIIa,** mp 275°C and 2.63 g (59%) of salt **XIIb**, mp 265°C. ^{1}H NMR spectrum of the mixture (DMSO-d_6–CCl_4, 1:3), δ, ppm (*J*, Hz): 2.87 s (3H, CH_3), 3.84 d.d (1H, J_1 11.2, J_2 5.9), 3.99 d.d (1H, $CH\underline{CH_2}$, J_1 11.2, J_2 6.8), 3.92 s (3H, OCH_3), 4.44 d.d (1H, $CH\underline{CH_2}$, J_1 6.8, J_2 5.9), 6.81 d.d (1H_{arom}, J_1 8.7, J_2 2.2), 7.02 d (1H_{arom}, *J* 2.2), 7.84 d (1H_{arom}, *J* 5.6), 7.96 d (1H_{arom}, *J* 8.7), 8.16 d (1H_{arom}, *J* 5.6), 9.54 br.s (1H, COOH), 11.75 br.s (1H, NH). Found, % (**XIIa**): C 54.12; H 4.56; N 7.96. $C_{16}H_{16}O_3N_2Cl_2$. Calculated, %: C 54.09; H 4.51; N 7.90. Found, % (**XIIb**): C 43.35; H 3.69; N 6.9. $C_{16}H_{16}O_3N_2Br_2$. Calculated, %: C 43.24; H 3.60; N 6.31.

Interaction of salts XIIa, XIIb with triphenylphosphine. A mixture of 0.00226 mol of salts **XIIa**, **XIIb** and 0.0045 mol of triphenylphosphine in 7 ml of acetonitrile was boiled during 20 h. After filtering off harmine, the treatment of acetonitrile solution with ether afforded 0.55 g (43.3%) of 1,2-bis(triphenylphosphoniumchlorido)ethane **XIVa**, mp 265°C and 0.72 g (48.0%) of 1,2-bis(triphenylphosphoniumbromido)ethane **XIVb**, mp 244°C. ^{1}H NMR spectrum of the mixture (DMSO-d_6–CCl_4, 1:3), δ, ppm (*J*, Hz): 4.31 d (4H, $2P^+CH_2$, *J* 4.5), 7.70 d (12H, C_6H_5, *J* 7.80), 7.86 d (6H, C_6H_5, *J* 7.40), 7.91–7.99 m (12H, C_6H_5). NMR ^{31}P: δ_P 31.60 ppm.

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