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Features of the Reaction of 2,3-Dihalopropanoic Acids with Pyridines and Nucleophilic Addition to *N*-Vinylpyridinium Salts

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Abstract—The example of vinylpyridinium salts to establish for the first time the possibility of nucleophilic addition to the vinyl group in quaternary ammonium salts, which provides evidence against the concept that such reactions involve d orbitals. The nucleophilic addition reaction was accomplished with triphenylphosphine and pyridine. In the latter case, the suggested reaction scheme was confirmed by the observation of the Wittig reaction under the action of carbon dioxide and the Stevens reaggangement involving the double bond of the pyridinium ring and migrating 2-phosphonioethyl group. Procedures for preparing the starting vinylpyridinium salts. Reaction schemes were siggested.

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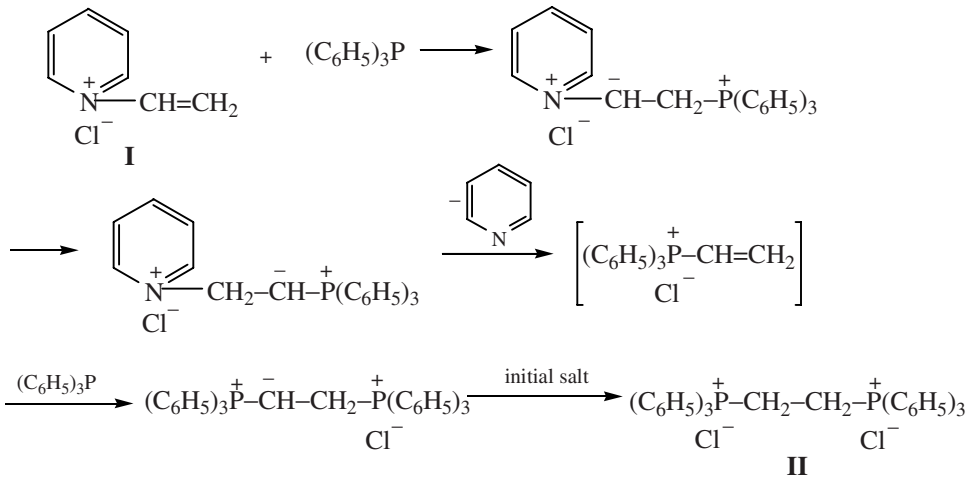
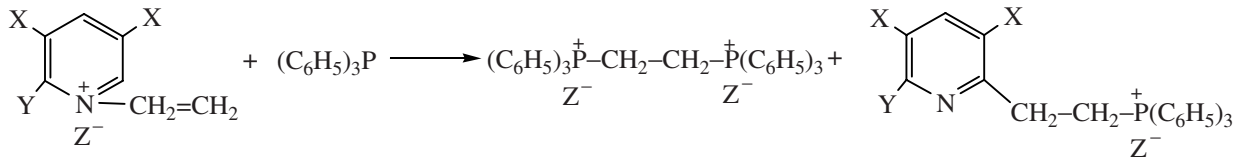
We previously established [1] that vinylpyridinium chloride (**I**) reacts with triphenylphoshine in boiling acetonitrile to form ethylenebis(triphenylphosphonium) dichloride (**II**). A scheme of the reaction was suggested, involving nucleophilic addition of the phosphine followed by anion exchange, β-cleavage, and addition of a further phosphine molecule to the resulting triphenylphsophonium chloride.



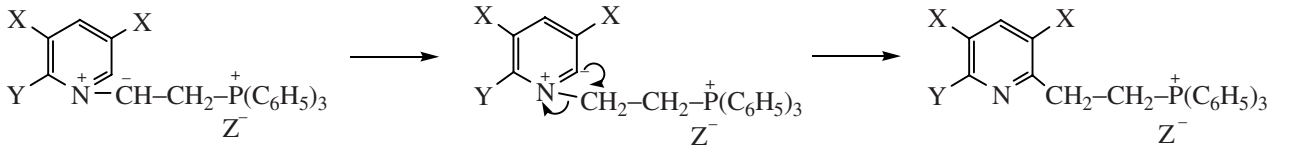
Proceeding with this research we found that 3,5-dibromo-1-vinylpyridinium halides **III** and **IIIa** form [2-(3,5-dihalopyridin-2-yl)ethyl]triphenylphosphonium halides **V** and **Va**, along with ethylenebis(triphenylphosphonium) dihalides **II** and **IIa** (**II** : **V** and **IIa** : **Va** ratios ~1 : 1). With 2-methyl-1-vinylpyridinium chloride (**IV**), [2-(6-methylpyridine-2-yl)ethyl]triphenylphosphonium chloride (**VI**) is formed along product **II** (**II** : **VI** ratio 16 : 3).



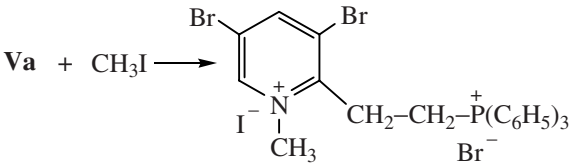
III, IIIa, IV **II, IIa** **V, Va, VI**

II, Z = Cl; **IIa**, Z = Br; **III, V**, X = Br, Y = H, Z = Cl; **IIIa, Va**, X = Z = Br, Y = H; **IV, VI**, X = H, Y = CH_3, Z = Cl.

Products **V, VI** are probably formed via anion exchange in the initially formed ammonium ylides followed by the Stevens rearrangement involving the double bond of the pyridinium ring.



The structure of compound **Va** was confirmed by ^{1}H NMR data, as well as the iodomethylation of the mixture obtained from compound **IIIa** and triphenylphosphine, which provided a mixture of compounds **IIa, Va**, and **VII** in a 4 : 1 : 4 ratio.



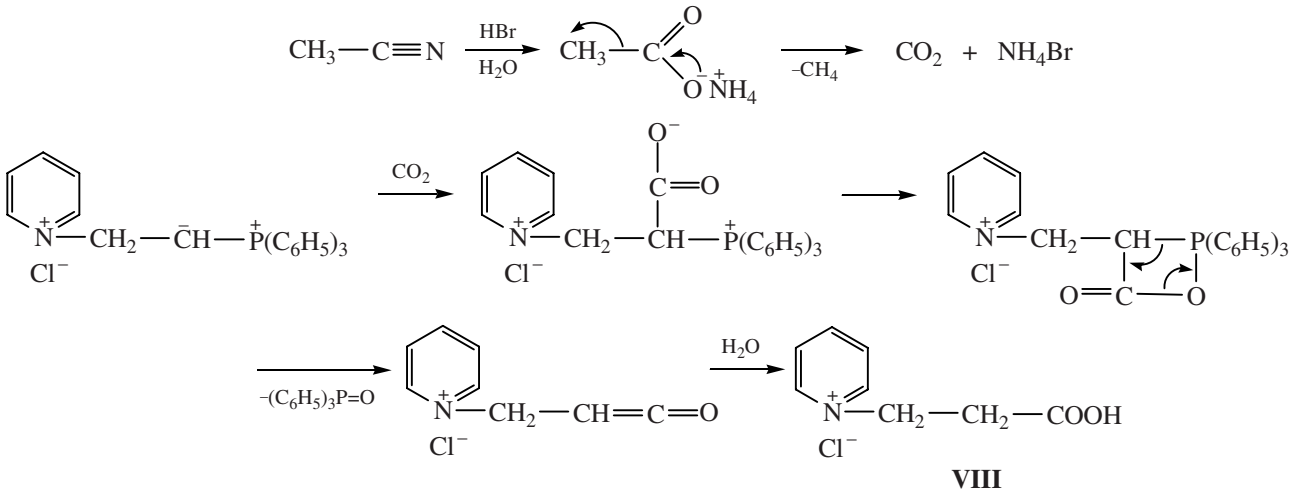
VII

We found that salt **II** is also formed by the reaction of compound **I** with triphenylphosphine in the presence of HBr in aqueous medium.

The reaction of salt **I** with triphenylphosphine in a mixture of acetonitrile and HBr unexpectedly gave acid **VIII** (isolated yield 44%) formed, probably, by Scheme 1.

As seen from the scheme, the intermediate ylide undergoes the Wittig reaction under the action of CO_2 formed by hydrolysis of acetonitrile and subsequent decarboxylation. Evidence for the decarboxylation of acetate ion in such conditions was provided by the formation of calcium carbonate in reactions of acetonitrile with HBr in the presence of calcium salts. The formation of acid **VIII** in the reaction of triphenylphosphine with salt **I**, like the Stevens rearrangement observed with compounds **III, IIIa**, and **IV**, provides conclusive evidence for the suggested

Scheme 1.



VIII

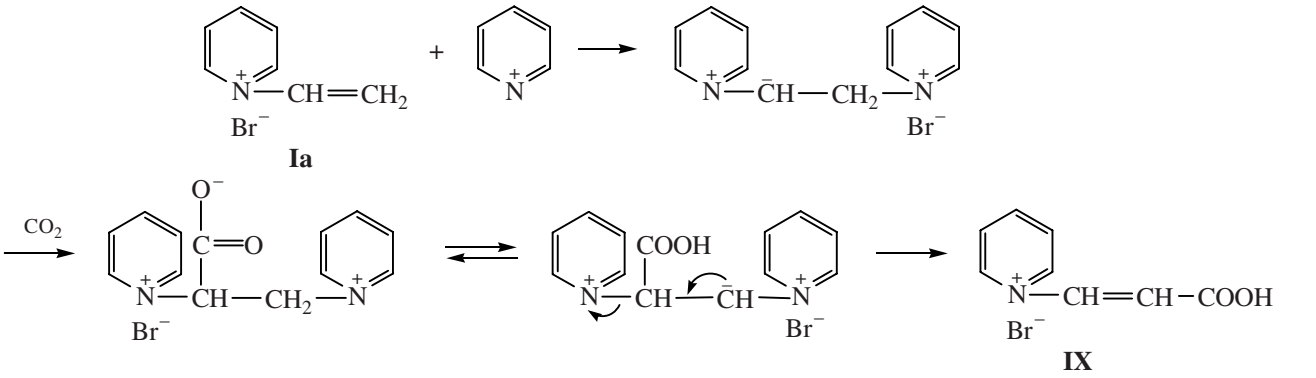
reaction scheme involving nucleophilic addition into the β-position of the vinyl group and ylide formation.

We made an attempt to react triphenylphosphine with salt **I** in the presence of benzaldehyde. However, the reaction gave phosphonium salt **II** as a single product, and unreacted salt **I** was recovered. These results are probably explained by a lower electrophilicity of benzaldehyde compared to CO_2, which makes β-cleavage more competitive.

Vinylphosphonium and vinylsulfonium salts are known to readily react with nucleophiles to form compounds with a β-substituted ethyl group. Reliable information concerning similar reactions of vinylammonium salts is lacking from the literature. The inertness of vinylammonium salts in these reactions has been explained in [2] in terms of "*d*-orbital resonance," i.e. the stabilization of intermediate α-carbanions in the measomeric ylene, which takes place in phosphonium and sulfonium salts and is impossible in vinylphosphonium salts.

$$R_3P{-}CH{-}R' \rightleftharpoons R_3P{=}CH{-}R'.$$

Our present results provide the first reliable example of nucleophilic addition to vinylammonium salts. Interesting data were obtained when salt **Ia** was reacted with pyridine in boiling acetonitrile. The reaction gave acetoxyvinylphosphonium bromide **IX** in a yield of ~36%. The reaction is mpst likely to follow a nucleophilic addition scheme. The ylide formed is stabilized by reaction with CO_2 followed by β-cleavage.



Ia

IX

However, theoretically, the reaction may take an alternative route to form, under the action pf pyridine, a C-betaine which than stabilizes by reacting with CO_2.

The tendency of pyridine to formation of betaine structures is well known. A lot of pyridinium ylides and imines were reported [3, 4]. The reaction of pyridine with dimethyl acetylenedicaroxylate, involving C-betaine formation, was described [5]. In this respect pyridine differs from aliphatic tertiary amines, since in the latter case such structures are almost as unstable as in phosphorus compounds. It is supposed that phosphonium betaines are stabilized due to *d* orbitals, whereas the stability factor in pyridinium salts is the electron-acceptor nature of pyridine.

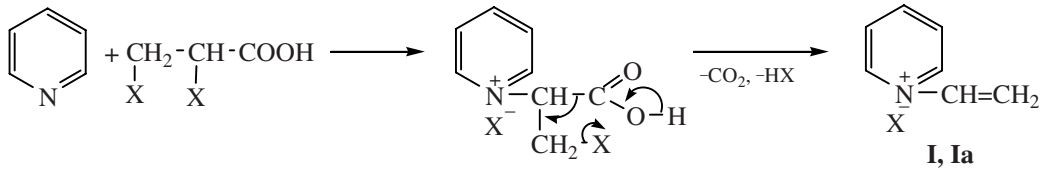
We also reacted vinylpyridinium salts with di- and triethylamines. As a result, the corresponding amine hydrochlorides were isolated in yields of 50 and 52% for compound **I** and nearly quantitative yields for compounds **III** and **IIIa**. The reaction was accompanied by strong tarring. Presumably, the reaction involves amine attack on the α position of the pyridinium ring and subsequent cleavage of the latter, as observed by Krohnke [6] in the reaction of vinylpyridinium salts with potash in acetone.

We previously prepared vinylpyridinium salts by the reaction of pyridine with 2,3-dihalopropanoic acids in boiling acetonitrile [7]. Compounds **III** and **IIIa** were prepared in a similar way [1]. On repeated study we found that the reaction with the bromine analog gives acetoxyvinylpyridinium bromide **IX** as a minor product. The **Ia** : **IX** ratio is 15 : 2. In the reaction with 2,3-dibromopropanoic acid at room temperature the fraction of acid **IX** unexpectedly proved to be much greater (**Ia** : **IX** ~6 : 5).

The formation of products of **I** and **Ia** from 2,3-dihalopropanoic acids was previously explained in terms of a scheme involving nucleophilic substitution

followed by decarboxylation and hydrogen halide release, probably, by a synchronous mechanism [1, 7] (Scheme 2).

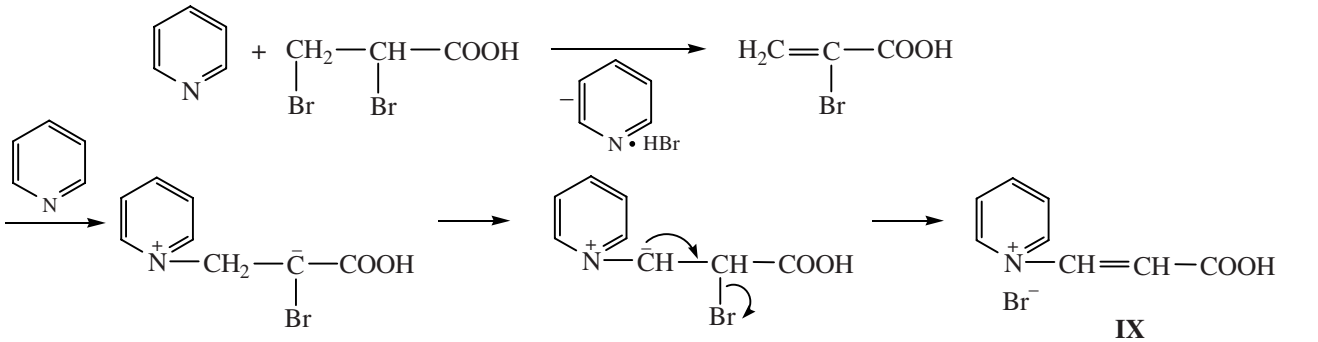
Scheme 2.



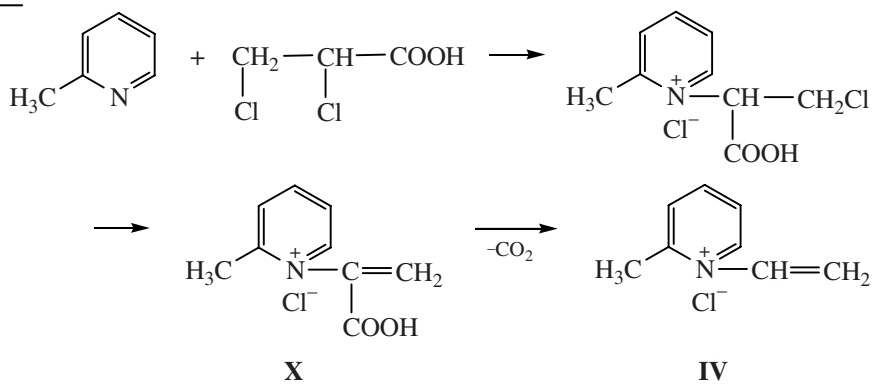
I, X = Cl; **Ia**, X = Br.

A special experiment showed that pyridine fails to react with salt **Ia** at room temperature. Consequently, our results in experiments with 2,3-dibromopropanoic acid suggest two independent reaction routes. The first we described above and the second involves preliminary dehydrobromination followed by reaction of the resulting α-bromoacrylic acid with pyridine, like in a similar reaction with triphenylphosphine [8] (Scheme 3).

Scheme 3.



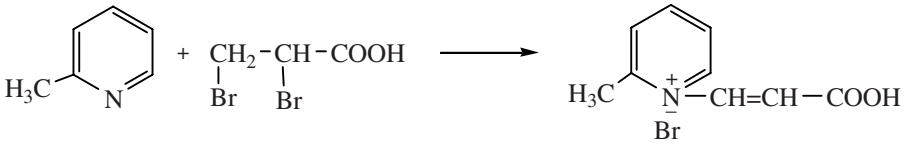
2,3-Dichloropropanoic acid was reacted with picoline in pyridine under reflux under conditions used for the preparation of vinylpyridinium salts to isolate salt **IV** in a yield of 6.4%. The precipitate comprised a mixture of salt **IV**, acid **X**, and picoline hydrochloride in a 1:1:1 ratio.



The same reaction with 2,3-dibromopropanoic acid gave acid **XI** as a single product (yield 50%) (Scheme 4).

Attempted synthesis of *N*-vinylquinolinium salt by reacting quinoline with 2,3-dibromopropanoic acid failed. The only product was quinoline hydrobromide

Scheme 4.



XI

isolated in nearly quantitative yield. Such a difference in the behavior of quinoline and pyridine is probably explained by steric reasons.

EXPERIMENTAL

The ^{1}H and ^{31}P NMR spectra were measured on a Varian MERCURY-300 instrument at 300 MHz, internal reference TMS.

Reaction of triphenylphosphine with salts III and IIIa. *a.* A mixture of 0.1 g of salt **III** and 0.18 g of triphenylphosphine in 5 ml of acetonitrile was heated under reflux for 32 h. The reaction mixture was filtered, and the acetonitrile filtrate was treated with ether to isolate 0.1 g of a mixture of salts, containing, according to the ^{1}H NMR spectrum, 0.052 g (26.0%) of product **II** and 0.048 g (25.0%) of product **V**. The ^{1}H and ^{31}P spectra of salt **II** are consistent with those reported in [1]. ^{1}H NMR spectrum of salt **V** (DMSO-d_6 + CCl_4, 1:3), δ, ppm: 2.55–2.65 m (2H, CH_2); 3.80–3.90 m (2H, P^+CH_2); 7.60–8.00 m (17H, Ph and Py). ^{31}P NMR spectrum: δ_P 30.18 ppm.

b. The reaction was performed similarly. From 0.52 g of salt **IIIa** and 0.78 g of triphenylphosphine in 7 ml of acetonitrile we obtained 0.5 g of a mixture of salts comprising, according to the ^{1}H NMR spectrum, 0.29 g (27.2%) of product **IIa** and 0.21 g (23.0%) of product **Va**. The ^{1}H and ^{31}P NMR spectra of the salts are similar to those obtained in the above experiment.

Reaction of salt IV with triphenylphosphine. A mixture of 0.20 g of salt **IV** and 0.67 g of triphenylphosphine in 5 ml of acetonitrile was heated under reflux for 34 h. The acetonitrile filtrate was poured into ether, and the precipitate that formed was filtered off, washed with ether, and dried in a vacuum to obtain 0.20 g of a mixture of products **II, VI**, and **IV** in a 16 : 3 : 2 ratio (^{1}H NMR data). The ^{1}H and ^{31}P NMR spectra of salt **II** are consistent with those reported in [1]. ^{1}H NMR spectrum of salt **VI** (DMSO-d_6 + CCl_4, 1 : 3), δ, ppm: 2.70 m (2H, CH_2); 3.00 s (3H, Me); 3.90 m (2H, P^+CH_2); 7.60–8.00 m (15H, Ph); 8.15 d (^{1}H, *J* 7.5 Hz, Pim-H-picoline); 8.25 d.d (1H, $J_1 = J_2$ 7.5 Hz, *p*-H-picoline); 8.65 d (1H, *J* 6.3 Hz, picoline *m*-H). ^{31}P NMR spectrum: δ_P 30.30 ppm.

^{1}H NMR spectrum of salt **IV** (DMSO-d_6 + CCl_4, 1 : 3), δ, ppm: 3.00 s (3H, Me); 5.00–5.40 m (3H, $CH{=}CH_2$); 8.00 d.d (1H, ^3J 1 7.5, $^3J_2$ 6.3 Hz, picoline *m*-H); 8.15 d (1H, ^3J 7.5 Hz, picoline *m*-H); 8.60 d.d (1H, $^3J_1 = {}^3J_2$ 7.5 Hz, *p*-H-picoline), 9.20 d (1H, $^3J_2$ 6.3 Hz, *o*-H-picoline).

Reaction of the mixture of salts, obtained from compound IIIa and triphenylphosphine, with methyl iodide. To 0.10 g of the mixture, a triple molar excess of methyl iodide in acetonitrile was added at room temperature. A day after, the reaction mixture was poured into ether, the crystal that formed were filtered off, washed with ether, and poured into ether to obtain 0.11 g of a mixture of products **IIa, Va**, and **VII** in a 4 : 1 : 4 ratio (^{1}H NMR data). ^{1}H NMR spectrum of salt **VII** (DMSO-d_6 + CCl_4, 1:3), δ, ppm: 2.70–2.80 m (2H, CH_2); 3.60 s (3H, Me); 3.90–4.00 m (2H, P^+CH_2); 7.40–7.60 m (17H, Ph and Py). ^{31}P NMR spectrum: δ_P 29.90 ppm.

Reaction of salt I with triphenylphosphine in aqueous hydrogen bromide. A mixture of 0.35 g of salt **I**, 0.65 g of triphenylphosphine, and 0.45 ml of 46% HBr in 6 ml of water was heated at 75–80°C for 20 h. Extraction with chloroform and reprecipitation with ether gave 10 g (11.23%) of compound **II**, mp 262°C. The ^{1}H and ^{31}P NMR spectra are consistent with those reported in [1].

Reaction of salt I with triphenylphosphine in aqueous hydrogen bromide in the presence of acetonitrile. A mixture of 0.35 g of salt **I**, 0.65 g of triphenylphosphine, and 0.48 g of 42% aqueous HBr in 10 ml of acetonitrile was heated under reflux for 20 h. The precipitate that formed was filtered off, washed with acetonitrile, and dried in a vacuum to obtain 0.176 g (44.0%) of acid **VIII**, mp > 270°C. ^{1}H NMR spectrum (DMSO-d_6 + CCl_4, 1:3), δ, ppm: 3.20 t (2H, ^3J 7.1 Hz, CH_2COOH); 5.00 t (2H, ^3J 7.1 Hz, N^+CH_2); 8.20 d.d (2H, $^3J_1$ 7.5 Hz, $^3J_2$ 6.3, pyridine *m*-H); 8.70 d.d (1H, $^3J_1 = {}^3J_2$ 7.5 Hz, pyridine *p*-H); 9.38 d (2H, ^3J 6.3 Hz, pyridine *o*-H); 12.20–12.60 br (1H, COOH).

Found, %: C 51.28; H 5.40; Cl 18.85; N 7.51. $C_8H_{10}ClNO_2$. Calculated, %: C 51.20; H 5.33; Cl 18.93; N 7.46.

Reaction of salt I with triphenylphosphine in aqueous hydrogen bromide in the presence of benzaldehyde and acetonitrile. A mixture of 0.47 g of salt **I**, 0.78 g of triphenylphosphine, 0.30 g of benzaldehyde, and 0.57 g of 42% aqueous HBr in 7 ml of acetonitrile was heated under reflux for 14–15 h. Unreacted starting salt was filtered off and washed with acetonitrile. The acetonitrile filtrate was poured into ether, and the precipitate that formed was filtered off, washed with acetonitrile, and dried in a vacuum to obtain 0.41 g (22.0%) of compound **II**, mp >262°C. The ^{1}H and ^{31}P NMR spectra are consistent with those reported in [1].

Reaction of salt Ia with pyridine. A mixture of 0.75 g of salt **Ia** and 0.32 g of pyridine in 10 ml of acetonitrile was heated under reflux for 40 h. The precipitate that formed was filtered off, washed with acetonitrile, and dried in a vacuum to obtain 0.35 g (38.0%) of product **IX**, mp 200–201°C. ^{1}H NMR spectrum (DMSO-d_6 + CCl_4, 1 : 3), δ, ppm: 7.10 d (1H, =CH, J 14.0 Hz); 8.30 d.d (2H, H^2, J_1 7.8, J_2 6.4 Hz); 8.55 d.d (1H, =CH, J 14.0 Hz); 8.80 t.t (1H, H^3, J_1 7.8, J_2 1.2 Hz); 9.42 d.d (2H, H^1, J_1 6.4, J_2 1.1 Hz). Found, %: C 41.78; H 3.41; Br 34.81; N 6.14. $C_8H_8BrNO_2$. Calculated, %: C 41.73; H 3.47; Br 34.78; N 6.08.

Reaction of 2,3-dibromopropanoic acid with pyridine. *a*. *Under reflux*. A mixture of 1.16 g of 2,3-dibromopropanoic acid and 0.395 g of pyridine in 5 ml of acetonitrile was heated under reflux for 13 h. The precipitate that formed was filtered off, washed with acetonitrile, and dried in a vacuum to obtain 0.85 g of a mixture of salts **Ia** and **IX** in a 15 : 2 ratio (^{1}H NMR data). The ^{1}H NMR spectra are the same as given above.

b. *At room temperature*. The same reaction was performed at room temperature. The reaction mixture was treated as above to obtain 0.81 g of a mixture of products **Ia** and **IX** in a 6 : 5 ratio (^{1}H NMR data). The ^{1}H NMR spectra are the same as given above.

Reaction of 2,3-dichloropropanoic acid with picoline. A mixture of 5.72 g of 2,3-dichloropropanoic acid and 3.72 g of picoline in 6 ml of acetonitrile was heated under reflux for 60 h. The precipitate that formed was filtered off, washed with acetonitrile, and dried in a vacuum to obtain 0.70 g of a mixture of products **IV, X**, and picoline hydrochloride in a 1 : 1 : 1 ratio (^{1}H NMR data). The 1H spectra of salt **IV** are the same as given above. ^{1}H NMR spectrum of salt **X** (DMSO-d_6 + CCl_4, 1:3), δ, ppm: 2.80 s (3H, Me); 5.95 and 6.45 s (2H, =CH_2); 7.75 d.d (1H, J_1 7.5, J_2 6.3 Hz, picoline *p*-H); 8.00 d (1H, J 7.5 Hz, picoline *m*-H); 8.20 d.d (1H, J_1 7.5, J_2 6.3 Hz, picoline *m*-H); 8.70 d (1H, J 7.5 Hz, picoline *o*-H).

The acetonitrile filtrate was poured into ether. An oily precipitate formed and was filtered off, thoroughly washed with ether, and dried in a vacuum to obtain 0.40 g (6.43%) of product **IX**, mp 181–182°C. The ^{1}H NMR spectra are the same as given above.

Reaction of 2,3-dibromopropanoic acid with picoline. A mixture of 4.35 g of 2,3-dibromopropanoic acid and 1.74 g of picoline in 6–7 ml of acetonitrile was heated under reflux for 6 h. The precipitate that formed was filtered off, washed with acetonitrile, and dried in a vacuum to obtain 2.20 g (50.0%) of salt **XI**, mp 250–255°C. ^{1}H NMR spectrum (DMSO-d_6 + CCl_4, 1 : 3), δ, ppm: 2.80 s (3H, Me); 6.80 d (1H, ^3J 13.0, =C*H*COOH); 8.00–8.20 m (3H, N$^+$–CH=, picoline *m*-H); 8.60 d.d (1H, $^3J_1$ = $^3J_2$ 7.5 Hz, picoline *p*-H); 9.18 d (1H, ^3J 6.3 Hz, picoline *o*-H); 13.50 br (1H, COOH).

The acetonitrile filtrate was poured into ether. A precipitate formed and was filtered off, thoroughly washed with ether, and dried in a vacuum to obtain 1.51 g (50.0%) of picoline hydrobromide, mp 45–50°C.

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