

Reactions of 3-Substituted 1,2-Epoxypropanes with Pyridinium Salts. *N*-Alkylpyridinium Salts and Their Synthetic Potential

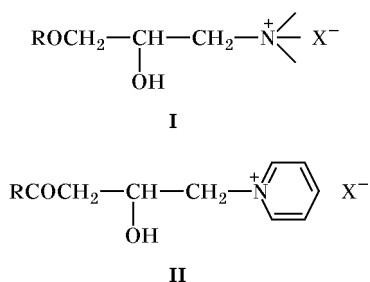
A. N. Karaseva, V. F. Mironov, V. V. Karlin, A. I. Kononov,
O. V. Tsepaeva, and E. R. Yunusov

Arbuzov Institute of Organic and Physical Chemistry, Kazan Research Center, Russian Academy of Sciences,
Kazan, Tatarstan, Russia

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Abstract—1-Chloro-2,3-epoxypropane and 2,3-epoxypropyl carboxylates react with pyridinium carboxylates and phosphonates, yielding *N*-alkylated pyridinium salts.

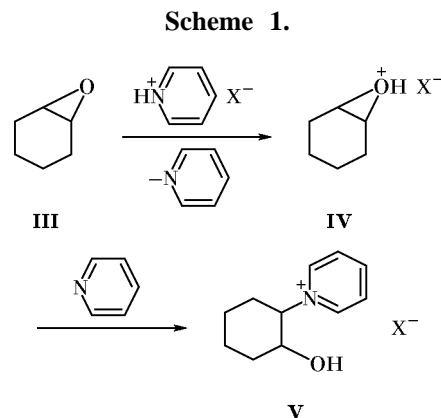
2-Hydroxy-3-ammoniopropyl alkyl (or aryl) ethers and esters of the general formula **I** exhibit diverse pharmacological activity and are widely used in medicine. Pyridiniopropyl ethers and esters **II** are structural analogs of **I**, which combine hydroxypropyl and pyridinium salt fragments and are promising from the viewpoint of searching for new pharmacologically active compounds.



The present communication describes the synthesis of compounds **II** starting from 1-chloro-2,3-epoxypropane and 2,3-epoxypropyl carboxylates. Hayes *et al.* [1] reported on the preparation of pyridinium salts on the basis of epoxy derivatives [1]. *N*-(2-Hydroxycyclohexyl)pyridinium salts **V** were obtained from 1,2-epoxycyclohexane (**III**) and pyridium perchlorates and *p*-toluenesulfonates. It was presumed that the reaction involves intermediate formation of oxonium ion like **IV** (Scheme 1).

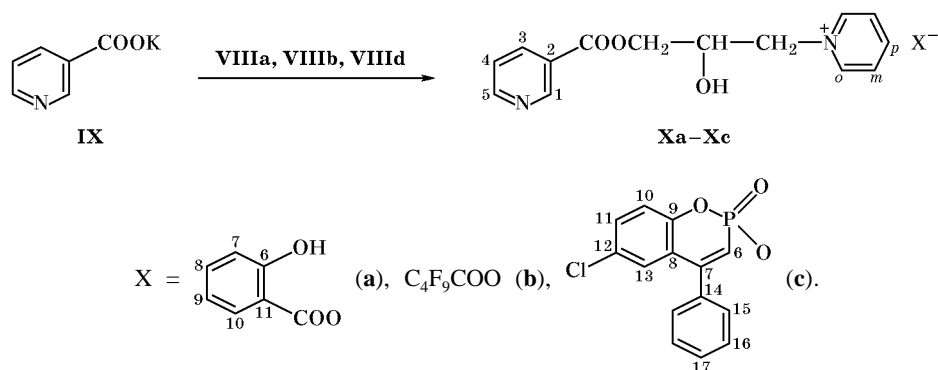
We have studied the possibility of involving in this reaction substituted epoxy derivatives and pyridine salts with substituted carboxylic and phosphonic acids in order to extend its synthetic potential.

As substrates we used 1-chloro-2,3-epoxypropane (**VI**) and 2,3-epoxypropyl carboxylates, and the reagents were pyridine salts with 2-hydroxybenzoic, perfluoropentanoic, and α -hydroxyphenylacetic (mandelic) acids and 6-chloro-2-hydroxy-4-phenyl-2*H*-1,2 λ^5 -benzoxaphosphinine 2-oxide (compounds **VIIa–VIIId**).

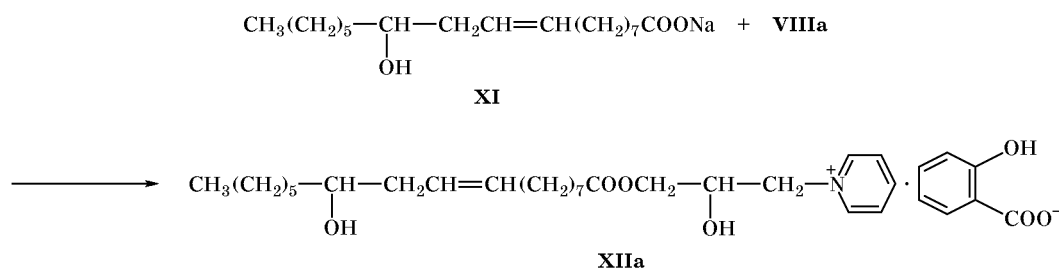


Variation of the reaction conditions showed that the optimal temperature of the reaction of pyridinium salts **VIIa–VIIId** with chloromethyloxirane **VI** is 18–20°C. In this case longer reaction time is compensated by the absence of by-products which could be formed at elevated temperature, and the yield of target products **VIIIa–VIIId** is nearly quantitative (Scheme 2). The structure of salts **VIIIa–VIIId** was proved by IR spectroscopy. The IR spectra of **VIIIa–VIIId** contained bands typical of hydroxy group and pyridinium ring (see Experimental).

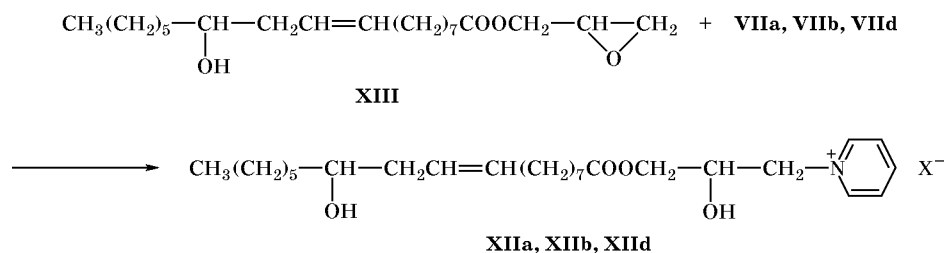
Scheme 3.



Scheme 4.



Scheme 5.



mixtures was observed. Starting from ester **XIII** and pyridinium salts **VIIa**, **VIIb**, and **VIIId**, we obtained 3-pyridiniopropyl (*Z*)-12-hydroxy-9-octadecenoates **XIIa**, **XIIb**, and **XIIId** (Scheme 5). Their structure was confirmed by the data of elemental analysis and IR spectroscopy.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples prepared as films between KBr plates. The ¹³C and ¹³C-¹H NMR spectra were obtained on a Bruker MSL-400 instrument operating at 100.6 MHz in methanol-*d*₄ at 35°C. The reaction mixtures and products were analyzed by TLC on Silufol plates (Czechia, Kavalier) using MeOH-AcOH (1:3) as eluent; spots were visualized under UV light and with iodine vapor.

Pyridinium salts **VIIa**–**VIIc** were prepared by heating equimolar amounts of pyridine and the corresponding acid in dry diethyl ether. 2,3-Epoxypropyl (*Z*)-12-hydroxy-9-octadecenoate (**XIII**) was prepared by the procedure reported in [6].

Reaction of 1-chloro-2,3-epoxypropane (VI) with pyridinium 2-hydroxybenzoate (VIIa). A mixture of 1.8 ml (19.5 mmol) of chloromethyloxirane **VI** and 5 g (23 mmol) of salt **VIIa** in 5 ml of pyridine was kept for 2 days at 20°C until it became homogeneous. The solvent was distilled off under reduced pressure to obtain 6.7 g of 1-(3-chloro-2-hydroxypropyl)pyridinium 2-hydroxybenzoate (**VIIIa**) as an oily substance. *R*_f 0.44. IR spectrum, ν, cm⁻¹: 665, 685, 710, 725, 1100, 1130, 1145, 1163, 1193, 1220, 1255, 1300, 1330, 1386, 1460, 1489; 1590, 1612, 1632, 1675, 1720 sh (C=N, C=C, COO⁻); 2730–2800, 2860–2880, 2930, 2970, 3020–3030 sh, 3060–3070,

Table 2. ^{13}C - $\{^1\text{H}\}$ and ^{13}C NMR spectra of 1-(2-hydroxy-3-nicotinoyloxypropyl)pyridinium 2-hydroxybenzoate (**Xa**)

| Atom | Chemical shifts δ_{C} , ppm | Coupling constants $J_{\text{C,H}}$, Hz |
|--------------------------------|---|--|
| C ¹ | 150.86 s (d.d.d) | 181.3 (HC ¹), 11.3(HC ⁵ HC ¹), 5.5 (HC ³ CC ¹) |
| C ² | 132.21 s (m) or 126.96 s (br.d.d) | ^a |
| C ³ | 138.46 s (d.d.d) | 165.9 (HC ³), 5.5 (HC ¹ CC ³), 6.3 (HC ⁵ CC ³) |
| C ⁴ | 124.41 s (br.d.d) | 166.6 (HC ⁴), 7.8–7.9 (HC ⁵ C ⁴) |
| C ⁵ | 151.73 br.s (d.d.d.d) | 179.6 (HC ⁵), 11.0 (HC ¹ HC ⁵), 7.3 (HC ³ CC ⁵), 3.6–3.7 (HC ⁴ C ⁵) |
| C ^o | 146.40 br.s (br.d.m) | 190.7–191.2 (HC ^o) |
| C ^m | 128.70 br.s (br.d.m) | 175.0 (HC ^m), 7.4 (HC ^m CC ^m), 3.2 (HC ^o C ^m) |
| C ^p | 146.66 br.s (br.d.t) | 172.2 (HC ^p), 6.2 (HC ^o CC ^p) |
| C ⁹ | 162.34 s (br.d.d) | 7.8–8.0 (HC ¹³ CC ⁹), 7.8–8.0 (HC ¹³ CC ⁹) |
| C ¹⁰ | 119.57 s (m) | – |
| C ¹¹ | 131.35 s (d.d) | 158.3 (HC ¹¹), 8.7–8.8 (HC ¹³ CC ¹¹) |
| C ¹² | 118.78 s (d.d) | 161.3 (HC ¹²), 8.1 (HC ¹⁴ CC ¹²) |
| C ¹³ | 133.35 s (d.d) | 158.0 (HC ¹³), 9.1–9.2 (HC ¹¹ CC ¹³) |
| C ¹⁴ | 117.05 s (d.d) | 159.7 (HC ¹⁴), 8.1–8.2 (HC ¹² CC ¹⁴) |
| OCH ₂ | 67.13 s (br.t) | 149.5 (HC) |
| CHOH | 69.16 s (br.d) | 146.5 (HC) |
| CH ₂ N ⁺ | 64.99 s (br.t) | 145.3 (HC) |
| COO ⁻ | 175.06 s (br.m) | – |
| COO | 165.85 s (br.m) | – |

^a Superposition with a component of the C¹¹ signal; $J = 6.6$ (HC¹²CC¹⁰), 6.6 Hz (HC¹⁴CC¹⁰).

3080, 3080–3090, 3140 (=C–H); 3160–3230 (OH). Found, %: C 57.75; H 4.98; N 4.05. C₁₅H₁₆ClNO₄. Calculated, %: C 58.15; H 5.4; N 4.52.

Salts **VIIIb**–**VIIIc** were synthesized in a similar way. The products were oily substances.

1-(3-Chloro-2-hydroxypropyl)pyridinium perfluoropentanoate (VIIIb) was synthesized from 2.69 g (29.1 mmol) of chloromethyloxirane **VI** and 10 g (29.2 mmol) of salt **VIIIb**. Yield 11.36 g. R_f 0.37. IR spectrum, ν , cm⁻¹: 690, 715, 745, 775, 809, 870, 885, 912, 1025 (C₅H₅N), 1060, 1135 (C–OH), 1160, 1190–1210 (C₅H₅N, CF), 1215 (CF), 1240–1245, 1300, 1345 (C–OH), 1389, 1435, 1450, 1495 (C₅H₅N), 1590, 1660 (C=N, C=C), 1680–1695 (COO⁻), 3050–3100 (=C–H), 3230 (OH).

1-(3-Chloro-2-hydroxypropyl)pyridinium α -hydroxyphenylacetate (VIIIc) was synthesized from 7 ml (75.7 mmol) of chloromethyloxirane **VI** and 20 g (86.5 mmol) of salt **VIIIc**. Yield 20.6 g. IR spectrum, ν , cm⁻¹: 685, 705, 740, 765, 1030, 1065, 1095–1100, 1120, 1175–1190, 1210–1225, 1265, 1310, 1340–1360, 1455, 1495; 1580, 1610–1620, 1632 sh (C=N, C=C), 1741 (COO⁻), 2700–2750, 2850–2950, 2970, 3035, 3065, 3090–3100 (=C–H); 3150–3250 (OH). Found, %: C 58.64; H 4.99; N 4.14. C₁₆H₁₈ClNO₄. Calculated, %: C 58.94; H 5.01; N 4.17.

1-(3-Chloro-2-hydroxypropyl)pyridinium 6-chloro-2-oxo-4-phenyl-2H-1,2 λ ⁵-benzoxaphosphinin-2-olate (VIIId) was synthesized from 0.6 ml (6.49 mmol) of chloromethyloxirane **VI** and 2.5 g (6.72 mmol) of salt **VIIIc**. Yield 3.1 g. R_f 0.67. IR spectrum, ν , cm⁻¹: 536, 570, 615, 650, 675, 688, 705, 725, 750, 765, 810, 825, 870, 950; 1035, 1075, 1120, 1155, 1195 sh, 1210–1240, 1230, 1270 sh (POC, C–OH, P=O); 1340 (C–OH); 1380, 1400, 1450, 1490 (δ C–H); 1550, 1590, 1640 (C=N, C=C, COO), 2670–2700, 2720–2760, 3040–3200 (=C–H), 3300–3350 (OH). Found, %: N 2.84; P 6.17. C₂₂H₂₀Cl₂NO₄P. Calculated, %: N 3.01; P 6.68.

Reaction of potassium 3-pyridinecarboxylate (IX) with pyridinium salt (VIIIa). A mixture of 1 g (6.2 mmol) of potassium salt **IX**, 1.92 g (6.2 mmol) of pyridinium salt **VIIIa**, and 20 ml of DMF was heated for 5 h at 70°C. The solvent was distilled off under reduced pressure (12 mm), the residue was dissolved in methanol heated to 50°C, the precipitate of potassium chloride was filtered off, and the filtrate was evaporated under reduced pressure to isolate 1.91 g of 1-(2-hydroxy-3-nicotinoyloxypropyl)pyridinium 2-hydroxybenzoate (**Xa**) as an oily substance. R_f 0.28. IR spectrum, ν , cm⁻¹: 745, 765, 1035, 1260, 1285–1290, 1330, 1460, 1490; 1592, 1617, 1631, 1670 (C=N, C=C, COO⁻), 1730 (C=O); 2830–2840,

Table 3. ^{13}C - $\{^1\text{H}\}$ and ^{13}C NMR spectra of 1-(2-hydroxy-3-nicotinoyloxypropyl)pyridinium 6-chloro-2-oxo-4-phenyl-2*H*-1,2,λ⁵-benzoxaphosphinine-2-olate (**Xc**)

| Atom | Chemical shifts δ_{C} , ppm | Coupling constants J , Hz |
|--------------------------------|---|---|
| C ¹ | 150.94 br.s (d.d.d) | 182.0 (HC ¹), 11.0–11.5 (HC ⁵ HC ¹), 5.5 (HC ³ CC ¹) |
| C ² | 127.59 br.s (br.m) | – |
| C ³ | 138.32 br.s (br.d.d.d) | 166.6 (HC ³), 5.9–6.0 (HC ¹ CC ³), 5.9–6.0 (HC ⁵ CC ³) |
| C ⁴ | 124.83 s (br.d.d) | 166.5 (HC ⁴), 7.8 (HC ⁵ C ⁴) |
| C ⁵ | 151.16 br.s (br.d.d.d) | 179.9 (HC ⁵), 12.0 (HC ¹ HC ⁵), 7.3 (HC ³ CC ⁵) |
| C ^o | 146.54 br.s (br.d.m) | 190.1 (HC ^o) |
| C ^m | 128.73 s (br.d.d.d) | 175.0 (HC ^m), 7.0–8.0 (HC ^m CC ^m), 3.5 (HC ^o C ^m) |
| C ^p | 146.54 br.s (br.d.m) | 172.0 (HC ^p), 5.9 (HC ^o CC ^p) |
| C ⁶ | 122.50 br.d (br.d.d) | 165.9 (PC), 158.6 (HC) |
| C ⁷ | 149.02 br.s (br.m) | – |
| C ⁸ | 126.09 br.d (br.d.d.d) | 15.8 (PCCC ⁸), 8.3 (HC ⁶ CC ⁸), 5.4 (HC ¹⁰ CC ⁸) |
| C ⁹ | 152.86 br.d (br.m) | 6.6 (POC ⁹) |
| C ¹⁰ | 121.76 br.d (d.d) | 165.0 (HC ¹⁰), 6.4 (POCC ¹⁰) |
| C ¹¹ | 130.24 s (d.d) | 167.7 (HC ¹¹), 6.3 (HC ¹³ CC ¹¹) |
| C ¹² | 127.67 s (d.d.d) | 11.8 (HC ¹⁰ CC ¹²), 3.5 (HC ¹¹ C ¹²), 3.5 (HC ¹³ C ¹²) |
| C ¹³ | 128.58 s (d.d) | 164.3 (HC ¹³), 5.5 (HC ¹¹ CC ¹³) |
| C ¹⁴ | 140.44 br.d (br.d.d.t) | 16.7 (POCC ¹⁴), 7.5 (HC ¹⁶ CC ¹⁴), 6.0 (HC ⁶ CC ¹⁴) |
| C ¹⁵ | 129.27 s (br.d.d.d) | 159.7 (HC ¹⁵), 6.8–6.9 (HC ¹⁵ CC ¹⁵), 6.8–6.9 (HC ¹⁷ CC ¹⁵) |
| C ¹⁶ | 129.49 s (d.d.d) | 161.6 (HC ¹⁶), 7.5 (HC ¹⁶ CC ¹⁶), 1.8 (HCC) |
| C ¹⁷ | 129.31 s (d.t) | 161.2 (HC ¹⁷), 7.7 (HC ¹⁵ CC ¹⁷) |
| OCH ₂ | 65.34 br.s (br.t) | 146.4–147.0 (HC) |
| CHOH | 71.66 s (br.d) | 144.7 (HC) |
| CH ₂ N ⁺ | 64.0 s (br.t) | 143.2–144.0 (HC) |
| COO | 166.27 br.s (br.m) | – |

2940–2950, 3030–3040 sh, 3070, 3090–3100, 3140 (C–H); 3300–3350 (OH). Found, %: C 63.26; H 4.98; N 6.27. C₂₁H₂₀N₂O₆. Calculated, %: C 63.63; H 5.05; N 7.07.

Following the above procedure, the reaction of 1.47 g (9.13 mmol) of potassium salt **IX** with 4.23 g (9.13 mmol) of pyridinium salt **VIII d** gave 5.03 g of 1-(2-hydroxy-3-nicotinoyloxypropyl)pyridinium 6-chloro-2-oxo-4-phenyl-2*H*-1,2,λ⁵-benzoxaphosphinine-2-olate (**Xc**) as an oily substance. R_f 0.21. IR spectrum, ν , cm⁻¹: 540, 570, 675, 690, 705, 725, 745, 755, 810, 830, 880, 950, 1030, 1080–1090, 1120, 1140–1152, 1220–1245, 1282 (P=O), 1336, 1386, 1425, 1444, 1473, 1495, 1505 sh, 1551, 1592, 1610 sh, 1628, 1660–1673, 1730, 2750–2780, 2870, 2930, 2960, 2980, 3015, 3030–3040, 3060–3070, 3090, 3200, 3350 sh. Found, %: C 57.38; H 4.89; N 5.69; Cl 6.98. C₂₄H₂₄ClN₂O₆P. Calculated, %: C 57.31; H 4.77; N 5.57; Cl 7.06.

Likewise, from 6 g (37.27 mmol) of potassium salt **IX** and 16.23 g (37.27 mmol) of pyridinium salt **VIII b** in 140 ml of DMF we obtained 18.5 g of

1-(2-hydroxy-3-nicotinoyloxypropyl)pyridinium pentafluoropentanoate (**Xb**) as an oily substance. R_f 0.29. IR spectrum, ν , cm⁻¹: 505, 534, 565, 660, 686, 705–710, 740, 765, 800, 884, 1030, 1133, 1195–1205, 1210, 1230–1240, 1280, 1340, 1380, 1420, 1490, 1586, 1600–1610, 1631, 1669–1683, 1720, 1860–2870, 2925–2980, 3040, 3060–3070, 3080–3090, 3220–3260 (OH). Found, %: C 43.89; H 3.11. C₁₉H₁₅F₉N₂O₅. Calculated, %: C 43.67; H 2.87.

Reaction of compound VIIIa with sodium (Z)-12-hydroxy-9-octadecenoate (XI). A mixture of 0.87 g (2.97 mmol) of compound **VIII a** and 1 g (2.97 mmol) of salt **XI** in 10 ml of DMF was heated for 3 h at 70°C. It was then poured into water, and the product was extracted into 1-butanol. The extract was evaporated under reduced pressure (12 mm) to obtain 1.87 g of 1-[2-hydroxy-3-[(Z)-12-hydroxy-9-octadecenoyloxy]propyl]pyridinium 2-hydroxybenzoate (**XII a**) as an oily substance. R_f 0.31. IR spectrum, ν , cm⁻¹: 670, 680, 705–710, 760, 855, 865, 1040, 1090, 1145, 1164, 1190 (C–OH, aliph.), 1220, 1250–1260 (C–OH, arom.), 1295–1310, 1330–1345,

1385, 1410 sh, 1420 sh, 1465, 1485, 1565–1580 sh, 1590, 1615, 1630, 1680 (C=C, COO⁻), 1710, 1725–1740 (C=O), 3020–3140 (=C–H), 2600–2800, 3200–3300 (OH). Found, %: C 69.03; H 8.43. C₃₃H₄₉NO₇. Calculated, %: C 69.33; H 8.63.

Reaction of 2,3-epoxypropyl (Z)-12-hydroxy-9-octadecenoate (XIII) with salt VIIa. A mixture of 1 g (2.79 mmol) of ester XIII and 0.47 g (2.79 mmol) of salt VIIa in 10 ml of pyridine was kept for 2 days at 20°C (until the reaction was complete according to the TLC data). The solvent was distilled off under reduced pressure (12 mm) to obtain 1.45 g of oily pyridinium salt XIIa.

1-[2-Hydroxy-3-[(Z)-12-hydroxy-9-octadecenoyloxy]propyl]pyridinium perfluoropentanoate (XIIf) was obtained in a similar way from 2 g (5.83 mmol) of salt VIIb and 2.09 g (5.83 mmol) of ester XIII. Yield 3.97 g. Oily substance, R_f 0.18. IR spectrum, ν, cm⁻¹: 690, 720, 730, 750, 760, 780, 812, 870, 887, 1030, 1060, 1135 (C–OH), 1160–1170, 1190–1210 (C–F), 1215, 1235–1245 (C–F), 1300, 1345 (C–OH), 1382, 1480, 1493, 1585, 1640, 1680 sh, 1690 (C=C, COO), 1730–1740 (C=O); 3010–3020, 3070, 3095, 3140 (=C–H); 3350 (OH). Found, %: C 52.05; H 6.17. C₃₀H₄₄F₉NO₆. Calculated, %: C 52.55; H 6.47.

1-[2-Hydroxy-3-[(Z)-12-hydroxy-9-octadecenoyloxy]propyl]pyridinium 6-chloro-2-oxo-4-phenyl-2H-1,2λ⁵-benzoxaphosphinin-2-olate (XIId) was synthesized in a similar way from 2 g (5.36 mmol) of salt VIId and 1.92 g (5.36 mmol) of ester XIII. Yield 3.43 g. Oily substance, R_f 0.67. IR spectrum, ν, cm⁻¹:

1082 (C–OH, POC); 1120, 1166, 1170–1190, 1230–1240, 1250 sh, 1280 (POC, POO), 1340, 1400, 1460, 1472, 1495; 1555, 1580, 1595, 1607, 1640 (C=C), 1740 (C=O); 3015–3040, 3075, 3090–3100, 3130–3140 (=C–H), 3230–3240 (OH). Found, %: C 63.98; H 7.17. C₄₀H₅₃ClNO₇P. Calculated, %: C 64.18; N 7.78.

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