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Monoethyl esters of 2-quinolylmethylphosphonic acid (**3**) and 8-quinolylmethylphosphonic acid (**6**) have been prepared. The corresponding diethyl esters **1** and **4**, and sodium salts of monoesters **2** and **5**, respectively, have also been isolated. The properties of the monoethyl esters of 8- and 2-quinolylmethylphosphonic acid are very different. While the former was isolated as the hydrochloride, the latter did not form such a salt. Molecular weight determination indicated a dimeric structure of the monoester **3**, and spectroscopic measurements confirmed the association presumably owing to the hydrogen bonding between the P=O and P-OH groups.

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The preparation of certain quinolylmethylphosphonic acids and their neutral esters have been reported (1-4). However no attempt has been made to synthesize quinolylmethyl derivatives of phosphonic acid monoesters and the corresponding sodium salts of these monoesters. Since some monoalkyl esters of α-anilinobenzylphosphonic acid (5-8) as well as their phenylazo analogues (9,10) have found applications as extractants and complex-forming agents for metals, the present investigation has been undertaken as a continuation of our efforts to prepare new potential metal complexing agents. Monoesters of quinolylmethylphosphonic acids were chosen because of the possibility of chelate formation involving the phosphonic acid group, the metal, and the ring nitrogen.

In this report we wish to describe the synthesis and spectral properties of 2- and 8-quinolylmethylphosphonates (**1-6**) and free 8-quinolylmethylphosphonic acid (**7**). We are interested mainly in the monoethyl esters. However, the corresponding intermediates were also analysed. The physical properties and the results of the elemental analysis of the new organophosphorus compounds are given in Table I. Their spectroscopic data are listed in Table II.

Results and Discussion.

Neutral esters **1** (11) and **4** were prepared by the Michaelis-Becker method. Condensation of diethyl sodium phosphite with 2-chloromethylquinoline and 8-bromomethylquinoline, respectively, afforded diethyl esters as colorless liquids which were miscible with most organic solvents. The proton magnetic resonance spectra of esters **1** and **4** show that two ethyl ester groups are equivalent. Thus, their relative position should be identical with respect to the quinoline ring. This is shown in Figure 1 in which the phosphorus atom is represented with a tetrahedron (full line) and, below it,

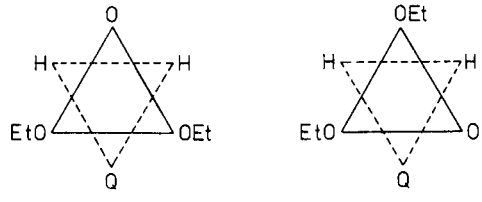
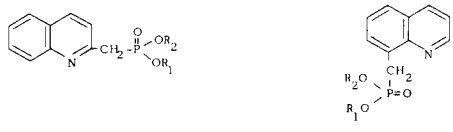



Figure 1

the α-carbon atom of the methylene group, so that the C-P bond is perpendicular to the plane of the paper.





1, $R_1 = R_2 = CH_2CH_3$
2, $R_1 = CH_2CH_3$; $R_2 = Na$
3, $R_1 = CH_2CH_3$; $R_2 = H$

4, $R_1 = R_2 = CH_2CH_3$
5, $R_1 = CH_2CH_3$; $R_2 = Na$
6, $R_1 = CH_2CH_3$; $R_2 = H$
7, $R_1 = R_2 = H$

When refluxed with an excess of alcoholic sodium hydroxide both of diesters did not exibit any significant rupture of the C-P bond. The corresponding sodium salts **2** and **5** were obtained as white solids. Although they are very hygroscopic compounds, after drying *in vacuo* they were obtained anhydrous.

These sodium salts were converted to the free monoesters **3** and **6** by acidification with dilute hydrochloric acid. Although essentially the same reaction was applied to prepare both monoesters, they exibit great differences in their properties. While the monoethyl ester of 8-quinolylmethylphosphonic acid was isolated as the hydrochloride with water of crystallization, the monoethyl ester of 2-quinolylmethylphosphonic acid failed to form the

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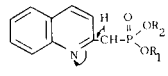
same type of salt. In quinoline derivatives, as in pyridine analogues, the basic electron pair of nitrogen is the first site attacked by electrophiles and this creates a positive quinolinium ion. In 2-quinolylmethylphosphonates the presence of the acidic methylene group in the α-position of the quinoline ring decreases the basic character of nitrogen and increases the resistence to the electrophilic attack. The following enolization is possible.



Molecular weight determination showed that monoester **3** is a dimer in chloroform solution. From the infrared spectra it may be concluded that it is also associated in the solid state due to the bonding between phosphoryl and acidic hydroxyl groups. It was impossible to determine the molecular weight of monoester **6** due to its insufficient solubility. Infrared studies however have shown that hydrogen bonding exists presumably in this monoester too. In the $^1$H nmr spectra of monoesters the position of the OH resonance at low applied field confirmed this association. Since monoester **3** has a lower field signal at δ 12.03 ppm, than monoester **6** at δ 7.75 ppm, it is evident that the stronger hydrogen bonding exists in the former monoester.

Furthermore it has been observed that in monoesters as well as in the free phosphonic acid **7** proton from P-OH group does not show the spin-spin coupling with phosphorus. The lack of doublet arises either from a rapid exchange of the proton between the two oxygens or from an equal distribution between them. In either case, the phosphoryl oxygen and the OH group would be equivalent.

Infrared spectral studies can give us also details about the nature of the prepared quinolylmethylphosphonates. The main and characteristic absorption bands associated with typical functional groups are given in Table II. The bands that appear to be a lesser importance for identification of compounds are omitted.

In neutral esters **1** and **4** stretching bands of the phosphoryl group lie between 1260-1240 cm$^{-1}$. In the corresponding monoesters this frequency is shifted to lower energy by 20-30 cm$^{-1}$. It is well known that in acidic phosphorus compounds the phosphoryl group is particularly reactive with strong donor properties (12). It easily forms hydrogen bonds, which result in a considerable shift to longer frequencies.

Monoesters **3** and **6** as well as free phosphonic acid **7** do not show any evidence of the OH stretching at about 3500 cm$^{-1}$ characteristic for the free OH group. They give instead three typical bands in the 2800-1600 cm$^{-1}$ region, that are associated with the hydrogen bonded P(O)OH group (13).

The highest band represents the stretching of the OH group bonded to the phosphoryl group, the second one is a combination band of the P-OH stretching and PO-H deformation, and the lowest band is also a combination band involving the P=O vibration. These bands are found in the monoester **3** and phosphonic acid **7**, while in the monoester **6** only the band at 1660 cm$^{-1}$ can be noticed. The other two bands are masked by the absorption due to $NH^+$ ion.

Table I

Physical Constants of Quinolylmethylphosphonates

| Compound No. | M.p. (°C) or B.p. (°C/mm) | Yield % | Molecular Formula | Elemental Analysis % Calcd./Found | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | P | Cl | Na | $H_2O$ |
| **1** (a) | 154-156 ($4 \times 10^{-2}$) | 94 | $C_{14}H_{18}NO_3P$ | 60.21<br>60.03 | 6.50<br>6.70 | 5.02<br>5.20 | 11.09<br>10.96 | —<br>— | —<br>— | —<br>— |
| **2** | 263-266 | 68 | $C_{12}H_{13}NO_3P{\cdot}Na$ | 52.75<br>52.40 | 4.79<br>5.10 | 5.13<br>4.93 | 11.34<br>11.28 | —<br>— | 8.42<br>8.13 | —<br>— |
| **3** | 156-157 | 59 | $C_{12}H_{14}NO_3P$ | 57.37<br>57.25 | 5.62<br>5.73 | 5.58<br>5.44 | 12.33<br>12.24 | —<br>— | —<br>— | —<br>— |
| **4** | 142-144 ($5 \times 10^{-3}$) | 78 | $C_{14}H_{18}NO_3P$ | 60.21<br>59.98 | 6.50<br>6.76 | 5.02<br>5.29 | 11.09<br>10.85 | —<br>— | —<br>— | —<br>— |
| **5** | 228-230 | 51 | $C_{12}H_{13}NO_3P{\cdot}Na$ | 52.75<br>52.44 | 4.79<br>5.15 | 5.13<br>4.98 | 11.34<br>11.18 | —<br>— | 8.42<br>8.41 | —<br>— |
| **6** | 126-128 (b) | 66 | $C_{12}H_{14}NO_3P{\cdot}HCl{\cdot}H_2O$ | 47.15<br>46.99 | 5.61<br>5.58 | 4.58<br>4.62 | 10.13<br>10.34 | 11.60<br>11.80 | —<br>— | 5.89<br>6.06 |
| **7** | 185-187 | 61 | $C_{10}H_{10}NO_3P$ | 53.82<br>53.75 | 4.52<br>4.40 | 6.28<br>6.12 | 13.88<br>13.65 | —<br>— | —<br>— | —<br>— |

(a) Preparation of this compound was described in reference 4, reported b.p. 130-132°/($5 \times 10^{-2}$). (b) Melting with decomposition.

Table II

Spectral Analyses of Quinolylmethylphosphonates

| Compound No. | | |
|---|---|---|
| 1 | (film): $\nu$ 1250 (s, P=O), 1055, 1025 (vs, P-OC) | (carbon tetrachloride): 8.1-7.3 (m, 6H, aromatic), 4.29-3.75 (m, 4H, $POCH_2$, J = 7 Hz), 3.5 (d, 2H, $PCH_2$, J = 22 Hz), 1.18 (t, 6H, $CH_3$, J = 7 Hz) |
| 2 | (potassium bromide): $\nu$ 1220, 1192 (m, s, asym $PO_2^-$), 1060 (br vs, sym $PO_2^-$, P-OC) | (deuterium oxide): 8.1-7.3 (m, 6H, aromatic), 4.25-3.6 (m, 2H, $POCH_2$, J = 7 Hz), 3.4 (d, 2H, $PCH_2$, J = 21 Hz), 1.12 (t, 3H, $CH_3$, J = 7 Hz) |
| 3 | (nujol): $\nu$ 2500, 2080, 1660 (br m, PO-H), 1230, 1202 (s, P=O), 1070, 1045, 1025 (vs, P-OC, P-OH) | (deuteriochloroform): 12.03 (br s, 1H, OH), 8.40-7.35 (m, 6H, aromatic), 4.4-3.9 (m, 2H, $POCH_2$, J = 7 Hz), 3.78 (d, 2H, $PCH_2$, J = 21 Hz), 1.3 (t, 3H, $CH_3$, J = 7 Hz) |
| 4 | (film): $\nu$ 1260, 1240 (sh, br s, P=O), 1045, 1020 (s, vs, P-OC) | (carbon tetrachloride): 8.85 (m, 1H, aromatic $H_2$), 8.2-7.15 (m, 5H, aromatic), 4.2-3.65 (m, 6H, $PCH_2$, $POCH_2$), 1.1 (t, 6H, $CH_3$, J = 7 Hz) |
| 5 | (potassium bromide): $\nu$ 1225, 1200 (br s, asym $PO_2^-$), 1055 (br vs, sym $PO_2^-$, P-OC) | (deuterium oxide): 8.75 (m, 1H, aromatic $H_2$), 8.25-7.25 (m, 5H, aromatic), 4.2-3.45 (m, 4H, $POCH_2$, $PCH_2$), 1.15 (t, 3H, $CH_3$, J = 7 Hz) |
| 6 | (potassium bromide): $\nu$ 1800 (br m, $NH^+$, P-OH), 1645 (m, P-OH), 1235 (br vs, P=O), 1037, 994 (br vs, P-OC, P-OH) | (DMSO-$d_6$): 9.2-7.6 (m, 7H, aromatic), 7.75 (s, 2H, OH, $NH^+$), 4.15-3.55 (m, 4H, $POCH_2$, $PCH_2$), 1.1 (t, 3H, $CH_3$, J = 7 Hz) |
| 7 | (nujol): $\nu$ 1270, 1210 (s, m, P=O), 1090-980 (br s, P-OC, P-OH) | (DMSO-$d_6$): 8.9 (m, 1H, aromatic $H_2$), 8.5-7.4 (m, 5H, aromatic), 5.34 (s, 2H, OH), 3.76 (d, 2H, $PCH_2$, J = 22 Hz) |

(a) The assignments for absorption are expressed in wave numbers ($cm^{-1}$). Abbreviations: s = strong, vs = very strong, m = medium, sh = shoulder, br = broad, asym = asymmetric, sym = symmetric. (b) Chemical shifts are reported as $\delta$ values in parts per million (ppm), and coupling constants are in Hz. The spin multiplicities are indicated by abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad signal.

## EXPERIMENTAL

Melting points were determined in capillary tubes on an electrothermal apparatus and are uncorrected. Infrared spectra were recorded on potassium bromide pellets and nujol mulls using a Perkin-Elmer 257 spectrometer. Nuclear magnetic resonance spectra were determined on Varian A-60A spectrometer using tetramethylsilane as an internal reference. Ultraviolet spectra were obtained with a Perkin-Elmer 124 spectrophotometer. Molecular weights were determined by ebullioscopic method. Pentaacetylglucose (B. D. H. microanalytical reagent) was used as a standard reagent. Thermogravimetric measurements were performed using the Cahn RG electromicro balance with a heating rate of 2°/minute in an atmosphere of static air. Elemental analyses were carried out by the Microanalytical Laboratory of the Institute Rudjer Bošković.

Diethyl phosphite was purchased from Eastman Organic Co. and was freshly distilled. 2-Chloromethylquinoline was prepared by direct chlorination of 2-methylquinoline (14). Modified Skraup method was used for preparation of 8-methylquinoline from *o*-toluidine, glycerol and sodium salt of *m*-nitrobenzenesulfonic acid (15,16). 8-Bromomethylquinoline was prepared by bromination of 8-methylquinoline with *N*-bromosuccinimide (17, 18). All other reagents and solvents were reagent grade purity products.

Diethyl 2-Quinolylmethylphosphonate (**1**) (4).

To a solution of 14.5 g. (0.11 mole) of diethylphosphite in dry benzene (120 ml.) was added portionwise 2.3 g. (0.11 mole) of elemental sodium under vigorous stirring. The mixture was refluxed until complete dissolution of metal. Immediately after, 18.5 g. (0.11 mole) of 2-chloromethylquinoline dissolved in 100 ml. of dry benzene was added dropwise, and the mixture was refluxed for 2 hours. After cooling the benzene solution was washed twice with 30 ml. of water and dried over anhydrous magnesium sulfate. Benzene was removed by evaporation at reduced pressure giving an oily residue. Following distillation *in vacuo*, compound **1** was obtained as a colorless liquid.

Sodium Monoethyl 2-Quinolylmethylphosphonate (**2**).

A mixture of 10 g. (0.036 mole) of diethyl 2-quinolylmethylphosphonate (**1**) and 0.30 g. (0.072 mole) of sodium hydroxide in 60 ml. of ethanol was heated under reflux for 25 hours. The excess of the base was precipitated as sodium carbonate by introducing carbon dioxide into the ethanolic solution. The precipitate was filtered. After purification with charcoal, the solvent was removed *in vacuo* to dryness. Water (100 ml.) was added to the residue, and the solution was washed three times with 10 ml. of chloroform. The solvent was evaporated *in vacuo*, and the resultant sodium salt was purified by crystallization in ethanol.

Monoethyl 2-Quinolylmethylphosphonate (**3**).

The solution of 17.2 g. (0.060 mole) of sodium monoethyl 2-quinolylmethylphosphonate (**2**) in 50 ml. of water was acidified with 10% hydrochloric acid to *p*H 3.5. The solvent was removed *in vacuo* to dryness at room temperature. Chloroform (100 ml.)

was added to the residue, and the crude sodium chloride was filtered off. The filtrate was evaporated and, upon the addition of petroleum ether (40-70°) and subsequent cooling at room temperature, the monoester **3** as a crystalline white solid was obtained. Recrystallization from chloroform afforded an analytical sample; uv (water): λ max 244 nm (log ε, 4.40), 316 nm (log ε, 3.87); (chloroform): 244 nm (log ε, 4.07), 317 nm (log ε, 370); mol. wt. (chloroform): Calcd. for dimer: 502.4. Found: 495.5.

Diethyl 8-Quinolylmethylphosphonate (**4**).

A solution of 24.0 g. (0.108 mole) of 8-bromomethylquinoline in 150 ml. of dry benzene was added dropwise with stirring to a solution of diethyl sodium phosphite (0.162 mole) in 90 ml. of dry benzene. The mixture was refluxed for 3 hours, cooled to room temperature, washed three times with 100 ml. of water, and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the colorless diethyl ester **4** was isolated by distillation at reduced pressure from the oily residue.

Sodium Monoethyl 8-Quinolylmethylphosphonate (**5**).

In a fashion similar to that used for compound **2**, 5.0 g. (0.018 mole) of diethyl 8-quinolylmethylphosphonate (**4**) was subjected to alkaline hydrolysis with 0.15 g. (0.036 mole) of sodium hydroxide in ethanol. The isolation and purification of sodium salt **5** was carried out as described previously for compound **2**. Although both sodium quinolylmethylphosphonates **2** and **5** were hygroscopic compounds, after drying *in vacuo* they were obtained anhydrous.

Monoethyl 8-Quinolylmethylphosphonate Hydrochloride (**6**).

The solution of 6.4 g. (0.0234 mole) of sodium 8-quinolylmethylphosphonate (**5**) in 25 ml. of water was acidified with 10% hydrochloric acid to *p*H 2. After addition of acetone, the mixture was allowed to stand at 0° for a few hours. The solid mass thus obtained was washed with acetone, dried, and recrystallized several times from absolute ethanol. Monoethyl 8-quinolylmethylphosphonate was isolated as hydrochloride; uv (water): λ max 243 nm (log ε, 4.51), 317 nm (log ε, 3.74).

8-Quinolylmethylphosphonic Acid (**7**).

Hydrochloride of monoethyl-8-quinolylmethylphosphonate (**6**) (2.4 g., 0.0081 mole) was refluxed with 6 ml. of hydrochloric acid 1:1 for two hours, cooled, and the reaction mixture was neutralized with 3 *M* sodium hydroxide to *p*H 5. After standing overnight at 0° a solid product formed and crystallized from absolute ethanol.

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(11) The preparation of this diester was described in reference 4. We found that the boiling point of the cited compound was considerably higher than the value reported (see Table I). Since no spectral data were given, we examined its ir and $^1$H nmr spectra.

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