Reactions of 1,3-bis(ω-bromoalkyl)-6-methyluracils with 2-(dialkylamino)ethylphosphonates and 2-(dialkylamino)ethyl phosphates

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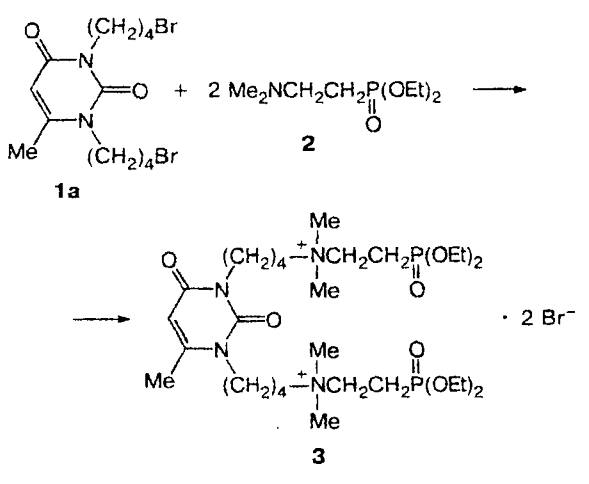
1,3-Bis(4-bromobutyl)-6-methyluracil reacts with diethyl 2-(dimethylamino)ethylphosphonate to form a bisquaternary ammonium salt, whereas the reaction of 1,3-bis-(6-bromohexyl)-6-methyluracil with diethyl 2-(diethylamino)ethyl phosphate gives 1,3-bis-[(6-diethoxyphosphoryloxy)hexyl]-6-methyluracil and 1,1,4,4-tetraethylpiperazinium dibromide.

Key words: 1,3-bis(ω-bromoalkyl)-6-methyluracil, diethyl 2-(dimethylamino)ethylphosphonate, diethyl 2-(diethylamino)ethyl phosphate, 1,3-bis{4-[2-(diethoxyphosphoryl)-ethyl]dimethylammoniobutyl}-6-methyluracil dibromide, 1,3-bis[6-(diethoxyphosphoryloxy)-hexyl]-6-methyluracil.

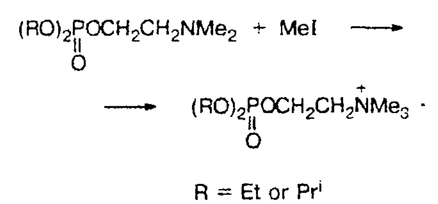
As part of continuing studies of procedures for the preparation of tetraalkylammonium derivatives based on 6-methyluracil[1] and procedures for the synthesis of nonglycoside analogs of pyrimidine nucleotides containing the phosphoryl group at a specified distance from the N atom of the pyrimidine ring,[2,3] we studied the reactions of 1,3-bis(ω-bromoalkyl)-6-methyluracils (**1a,b**) with 2-(dialkylamino)ethylphosphonate and 2-(dialkylamino)ethyl phosphate. As expected, 1,3-bis(4-bromobutyl)-6-methyluracil (**1a**) reacted with diethyl 2-(dimethylamino)ethylphosphonate (**2**) to form a bisquaternary ammonium salt (**3**) (Scheme 1).

Scheme 1



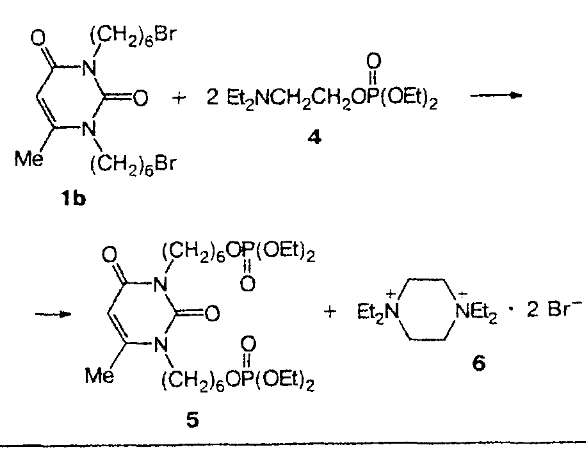
It is known that dialkyl 2-(dimethylamino)ethyl phosphates are alkylated with MeI to form the corresponding ammonium salts[4] (Scheme 2).

Scheme 2



One would expect that the reaction of 1,3-bis(ω-bromoalkyl)-6-methyluracil **1** with aminoethyl phosphates will also afford the corresponding ammonium derivatives. However, the reaction of 1,3-bis(6-bromohexyl)-6-methyluracil (**1b**) with diethyl 2-(diethylamino)ethyl phosphate (**4**) in boiling ethyl methyl ketone afforded 1,3-bis[6-(diethoxyphosphoryloxy)hexyl]-6-methyluracil (**5**) and 1,1,4,4-tetraethylpiperazinium dibromide (**6**) (Scheme 3).

Scheme 3



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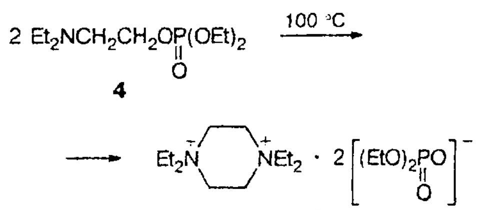
To elucidate whether this reaction pathway has a general character, we performed the reaction of aminoethyl phosphate **4** with bromoheptane (**7**) under analogous conditions. As a result, we obtained diethyl heptyl phosphate (**8**) and piperazinium salt **6**.

Consequently, such reaction pathway as trans-esterification of the initial phosphate **4** is most likely attributable to the fact that diethyl aminoethyl phosphate **4** exists at high temperature as 1,1,4,4-tetraethylpiperazinium bis(diethyl phosphate) (**9**)[5] (Scheme 4).

Scheme 4



Therefore, it can be suggested that alkylating agents **1b** and **7** react with salt **9** rather than with aminoethyl phosphate **4** resulting in compounds **5**, **6**, and **8**.

The ^{31}P NMR and IR spectra of compounds **3**, **5**, and **8** do not contradict the suggested structures.

Experimental

The IR spectra were recorded on a Specord-75 IR spectrometer in a thin film or as Nujol mulls between KBr plates in the region of 400—4000 cm^{-1}.

The ^{31}P NMR spectra were measured on a KGU-4 instrument (10.2 MHz, 85% H_3PO_4 as the internal standard).

The starting compounds, *viz.*, diethyl 2-(diethylamino)ethyl phosphate,[5] diethyl 2-(dimethylamino)ethylphosphonate,[6] and 1,3-bis(ω-bromoalkyl)-6-methyluracils (**1a,b**),[7] were prepared according to known procedures. Their physicochemical constants coincided with the published data.

1,3-Bis{4-[2-(diethoxyphosphoryl)ethyl]dimethylammoniobutyl}-6-methyluracil dibromide (3). A solution of diethyl 2-(dimethylamino)ethylphosphonate (**2**) (2.09 g, 0.01 mol) and 1,3-bis(4-bromobutyl)-6-methyluracil (**1a**) (1.98 g, 0.005 mol) in ethyl methyl ketone (30 mL) was refluxed for 12 h. The oil that formed was separated. This oil crystallized upon addition of ether. The crystals were filtered off, thoroughly washed with ether, and dried *in vacuo* (0.02 Torr) at 35—45 °C. Water- and ethanol-soluble compound **3** was obtained in a yield of 3.28 g (81%), m.p. > 102 °C (decomp.). Found (%): C, 42.84; H, 7.26; Br, 19.45; N, 6.89; P, 7.66. $C_{29}H_{60}Br_2N_4O_8P_2$. Calculated (%): C, 42.75; H, 7.42; Br, 19.62; N, 6.87; P, 7.60. IR, ν/cm^{-1}: 1065 (P—O—C); 1255 (P=O); 1660, 1715 (C=O). ^{31}P NMR, δ: 30.

Reaction of 1,3-bis(6-bromohexyl)-6-methyluracil (1b) with diethyl 2-(diethylamino)ethyl phosphate (4). A solution of bromide **1b** (4.52 g, 0.01 mol) and phosphate **4** (5.06 g, 0.02 mol) in ethyl methyl ketone (35 mL) was refluxed for 30 h. The crystals that precipitated were filtered off (filtrate A) and washed with ether. Product **6** was obtained in a yield of 3.4 g (94%), m.p. > 308 °C (decomp.) (*cf.* Ref. 8). Found (%): C, 40.27; H, 8.02; Br, 44.18; N, 7.61. $C_{12}H_{28}Br_2N_2$. Calculated (%): C, 40.01; H, 7.83; Br, 44.37; N, 7.77. Filtrate A was concentrated *in vacuo* (10 Torr). The residue was diluted with benzene (30 mL) and filtered. After removal of the benzene, the residue was kept at 90 °C (0.005 Torr) for 30 min. Phosphate **5** was obtained as a pale-brown viscous oil in a yield of 4.31 g (72%). Found (%): C, 50.02; H, 8.21; N, 4.56; P, 10.64. $C_{25}H_{48}N_2O_{10}P_2$. Calculated (%): C, 50.16; H, 8.08; N, 4.68; P, 10.35. IR, ν/cm^{-1}: 1050 (P—O—C); 1280 (P=O); 1675, 1710 (C=O). ^{31}P NMR, δ: 2.

Reaction of bromoheptane (7) with phosphate 4. A solution of phosphate **4** (1.48 g, 5.8 mmol) and bromide **7** (1.04 g, 5.8 mmol) in ethyl methyl ketone (30 mL) was refluxed for 35 h. The reaction products were isolated as described above. Product **6** was obtained in a yield of 0.93 g (89%). Phosphate **8** was obtained as a pale-yellow viscous oil in a yield of 3.7 g (94%). Found (%): C, 52.19; H, 9.76; P, 12.45. $C_{11}H_{25}O_4P$. Calculated (%): C, 52.37; H, 9.99; P, 12.28. IR, ν/cm^{-1}: 1055 (P—O—C); 1280 (P=O). ^{31}P NMR, δ: 2.

References

1. V. S. Reznik, K. A. Anikienko, V. K. Kurochkin, V. D. Akamsin, I. V. Galyametdinova, and E. N. Bychikhin, *Dokl. Akad. Nauk SSSR*, 1998, **362**, 68 [*Dokl. Chem.*, 1998 (Engl. Transl.)].
2. V. S. Reznik and Yu. S. Shvetsov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1970, 2254 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1970, **19** (Engl. Transl.)].
3. V. S. Reznik, Yu. S. Shvetsov, V. S. Bakulin, and I. Sh. Salikhov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1975, 1397 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1975, **24** (Engl. Transl.)].
4. L. E. Tammelin, *Acta Chem. Scand.*, 1957, **11**, 1340.
5. J. I. G. Cadogan and L. C. Tomas, *J. Chem. Soc.*, 1960, 2248.
6. A. N. Pudovik and G. M. Denisova, *Zh. Obshch. Khim.*, 1953, **23**, 263 [*J. Gen. Chem. USSR*, 1953, **23** (Engl. Transl.)].
7. V. S. Reznik, I. Sh. Salikhov, Yu. S. Shvetsov, A. N. Shirshov, V. S. Bakulin, and B. E. Ivanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1977, 880 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1977, **26** (Engl. Transl.)].
8. K. H. Meyer and H. Hopff, *Chem. Ber.*, 1921, **54**, 2274.

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