# *N*-Alkylation of Thymine and Uracil with Trialkyl Phosphates

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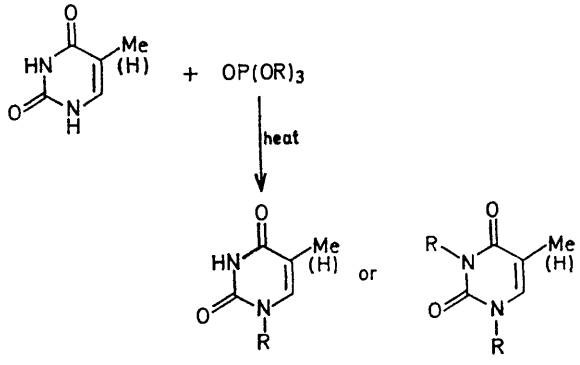
Treatment of thymine and uracil under appropriate conditions with trimethyl, triethyl, or tri-n-butyl phosphate has given 1-methylthymine (80%), 1,3-dimethylthymine (87%), 1-ethylthymine (80%), 1-n-butylthymine (40%), 1-methyluracil (80%), 1,3-dimethyluracil (75%), and 1-ethyluracil (35%).

OF many methods available for *N*-alkylation of pyrimidines,[1] those that appear to have the most general application involve the reactions of alkyl halides with thymine,[2] with 2,4-dialkoxypyrimidines,[3] and with 2,4-bis(trimethylsiloxy)pyrimidine,[4] giving the corresponding 1-alkyl and 1,3-dialkyl derivatives. Recently, Wong and Fuchs obtained 1,3-dimethyluracil in addition to several *N*- and *O*-methyluracils from the reaction of uracil with diazomethane.[5]

We describe here a new method for alkylation of thymine and uracil with trialkyl phosphates (see Scheme). The general procedure consists of heating the heterocycle with a trialkyl phosphate in the presence or absence of a solvent, and isolating the products by crystallization from the reaction mixture.

This method brought about substitution at the 1- or at both the 1- and 3-positions of pyrimidines, depending on the quantity and the nature of the phosphate used. No 3-alkyl derivative was isolated. Thus, when trimethyl phosphate reacted with 1 equiv. of thymine, 1-methylthymine was produced in high yield, whereas with an excess of trimethyl phosphate 1,3-dimethylthymine was isolated almost quantitatively. Uracil




SCHEME

behaved in a similar fashion towards trimethyl phosphate, affording 1-methyl- or 1,3-dimethyl-uracil in high yield. On the other hand, alkylation with triethyl and tri-n-butyl phosphate occurred more slowly

[1] W. W. Zorbach and R. S. Tipson, 'Synthetic Procedures in Nucleic Acid Chemistry,' Interscience, New York, 1968.
[2] G. Shaw and R. N. Warrener, *J. Chem. Soc.*, 1959, 50.
[3] G. E. Hilbert and T. B. Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 2001.
[4] E. Wittenburg, *Chem. Ber.*, 1966, **99**, 2380.
[5] J. L. Wong and D. S. Fuchs, *J. Org. Chem.*, 1971, **36**, 848.

than methylation, and generated only the corresponding 1-alkyl derivatives. In all these reactions, thymine underwent alkylation more easily than uracil. This may perhaps be due to the higher solubility of the former.

The alkylation reactions reported here may be capable of extension to *N*-alkylation of amides and imides; trialkyl phosphates have long been known as alkylating reagents for amines.[6] Investigation in this direction is continuing.

## EXPERIMENTAL

U.v. and i.r. spectra were measured with Hitachi EPS-3T and Jasco IR-G spectrometers, respectively. Commercially available uracil, thymine, and trimethyl, triethyl, and tri-n-butyl phosphates were used without further purification.

*Alkylation of Thymine.*—1-*Methylthymine.* Thymine (1·0 g, 7·9 mmol), trimethyl phosphate (1·12 g, 8·0 mmol), and naphthalene (4·0 g) were refluxed with stirring for 4·5 h. The cooled mixture was washed with ether to remove naphthalene. A solution of the residue in water was neutralized with sodium hydrogen carbonate and extracted with chloroform. Evaporation of the extracts afforded 1-methylthymine (0·85 g, 80%), m.p. 281—282° (from water) (lit.,[7] 280—282°), $\lambda_{max.}$ ($H_2O$) 272 nm (ε 9900), $\nu_{max.}$ (KBr) 3110w, 2950m, 2800m, 1640s, 1475m, 1410m, 1320m, 1200m, 1055m, 888m, and 680m $cm^{-1}$.

1,3-*Dimethylthymine.* Thymine (1·0 g, 7·9 mmol) was refluxed in trimethyl phosphate (6·0 g, 42·8 mmol) for 2·5 h. A low-boiling substance was removed under reduced pressure and the residue was washed with n-hexane. A solution of the solid remaining in chloroform (20 ml) was washed with aqueous sodium hydrogen carbonate, then evaporated to afford 1,3-dimethylthymine (1·07 g, 87%), m.p. 153—155° (lit.,[7] 155°), $\lambda_{max.}$ ($H_2O$) 271 nm (ε 8700), $\nu_{max.}$ (KBr) 3050w, 2950w, 1685s, 1645s, 1620s, 1445m, 1330m, 1180m, 1040m, 915m, and 750m $cm^{-1}$.

1-*Ethylthymine.* Treatment of thymine (1·0 g, 7·9 mmol) with triethyl phosphate (6·0 g, 33·0 mmol) as in the preparation of 1-methylthymine afforded 1-ethylthymine (0·97 g, 80%) after refluxing at 215° for 5 h; m.p. 222—223° (from tetrahydrofuran–ether) (lit.,[8] 223°), $\lambda_{max.}$ ($H_2O$) 273·5 nm (ε 7500), $\nu_{max.}$ (KBr) 3150w, 3030w, 1685s, 1650s, 1475s, 1350m, 1265m, 1080w, 860w, 765w, and 690m $cm^{-1}$.

1-*n-Butylthymine.* Thymine (1·0 g, 7·9 mmol) and tri-n-butyl phosphate (9·5 g, 36·0 mmol) were refluxed with stirring at 230° for 4 h. Excess of phosphate was removed under reduced pressure and the residue was mixed with chloroform. The undissolved thymine (0·3 g, 30%) was removed, and the solution was neutralized with aqueous sodium hydrogen carbonate and evaporated to leave 1-n-butylthymine (0·6 g, 40%), m.p. 138—139° (from water) (lit.,[9] 135—138°), $\lambda_{max.}$ (MeOH) 272·0 nm (ε 8800), $\nu_{max.}$ (KBr) 3000m, 1695s, 1645s, 1470m, 1415m, 1350m, 1210w, 908w, and 665m $cm^{-1}$.

*Alkylation of Uracil.*—1-*Methyluracil.* Uracil (1·0 g, 8·9 mmol) was treated with trimethyl phosphate (2·1 g, 15·0 mmol) in dimethylformamide (5 ml) at 140° for 9 h. The cooled mixture was washed with ether. A solution of the remaining solid in water was neutralized with sodium hydrogen carbonate. Undissolved uracil (0·1 g, 10%) was removed and the solution was evaporated. The residue was taken up in anhydrous ethanol and the solution was evaporated to give 1-methyluracil (0·9 g, 80%), m.p. 233—234° (from water–ethanol) (lit.,[10] 233—234°), $\lambda_{max.}$ ($H_2O$) 268 nm (ε 10,700), $\nu_{max.}$ (KBr) 3030w, 1660s, 1490m, 1420m, 1380m, 1335m, 1145w, 865m, 805m, and 760m $cm^{-1}$.

1,3-*Dimethyluracil.* A similar reaction of uracil (1·0 g, 8·9 mmol) with trimethyl phosphate (5·0 g, 35·7 mmol) at 210° for 2·5 h afforded 1,3-dimethyluracil (0·9 g, 75%), m.p. 120—121° (from ethanol–ether) (lit.,[11] 120—121°), $\lambda_{max.}$ ($H_2O$) 276 nm (ε 11,000), $\nu_{max.}$ (KBr) 3100w, 1650s, 1480m, 1340m, 1230w, 1140m, 815m, and 765m $cm^{-1}$.

1-*Ethyluracil.* Uracil (1·3 g, 11·6 mmol) and triethyl phosphate (4·0 g, 22·0 mmol) were heated at 215° for 3 h. Chloroform (30 ml) was added to the cooled mixture. Undissolved uracil (0·58 g, 45%) was removed and the solution was concentrated to about 10 ml and chromatographed on alumina (1·5 × 30 cm). Elution with methanol–ethyl acetate (1 : 4) gave 1-ethyluracil (0·56 g, 34%), m.p. 145—146° (from ether–tetrahydrofuran) (lit.,[3] 147·5°), $\lambda_{max.}$ ($H_2O$) 268·0 nm (ε 10,900), $\nu_{max.}$ (KBr) 3050m, 1710m, 1680s, 1650m, 1470m, 1430m, 1390w, 1275m, 1160w, and 850w $cm^{-1}$.

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