# Alkylation of Quinolines with Trialkyl Phosphates.   Part 2.[1]   Mechanistic Studies

By **Judit Frank** * and **Zoltán Mészáros**, Chinoin Pharmaceutical and Chemical Works, Ltd., 1325-Budapest, P.O.B. 110, Hungary
Tamás Kömives, Attila F. Márton, and **Ferenc Dutka,** Central Research Institute for Chemistry, of the Hungarian Academy of Sciences, 1525-Budapest, P.O.B. 17, Hungary

The mechanism of alkylation of 4-quinolone (3) by trialkyl phosphates has been studied by preparative, kinetic, and isotopic methods, as well as by u.v. spectrophotometry. In a kinetically controlled process the transient initial formation of 4-methoxyquinoline (4a) was established; this was subsequently transformed by trimethyl phosphate to a quaternary N-methyl-4-methoxyquinolinium salt (6a). The latter catalyses the transformation of (4a) by intermolecular O→N methyl transfer to the more stable N-methyl-4-quinolone (5a). The end product is a mixture of (5a) and (6a). Their ratio is shifted at higher temperature in favour of (6a). This is due partly to differences in the temperature dependence of the individual reactions and partly to alkylation of (5a) by trimethyl phosphate at higher temperature. A mechanism for the alkylation reaction is proposed.

In the course of the synthesis of analogues of the efficient antibacterial oxolinic acid [2] we found that trialkyl phosphates are excellent reagents for the N-alkylation of 4-substituted quinolines (1).[1]   Alkylation was carried out

(1)

(2)
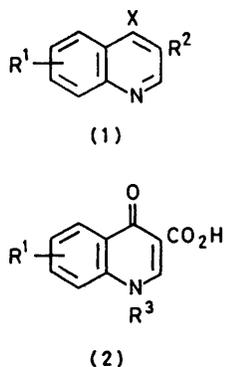
R^1 = H, 6,7-CH_2O_2, 6-$C_{10}H_{21}O$, 7-EtO, 6,7-$(EtO)_2$
R^2 = CO_2Et, CN
R^3 = Me, Et
R^4 = OH, Cl

at the boiling point of the reagent followed by hydrolyis to give from both the 4-hydroxy- and 4-chloro-compounds N-alkyl-4-oxoquinoline-3-carboxylic acids (2) in 90—95% yield.[3,4]

Trialkyl phosphates, which are non-toxic, water miscible, and inexpensive, are suitable reagents not only for laboratory scale but also for industrial alkylations.

The fact that both 4-chloro- and 4-hydroxy-quinolines led to the same product (2) and that good yields of (2) could only be obtained when alkylation was followed by hydrolysis, directed our attention to the mechanism of the alkylation step.   Though alkylation of N-heterocycles with alkyl phosphates has been reported in several recent papers [5] mechanistic aspects have not been discussed so far.

As a model alkylation, that of 4-quinolone (3) with trimethyl phosphate (TMP) was selected.   The similar

behaviour of analogous trialkyl phosphates has been checked.

RESULTS AND DISCUSSION

The fundamental problem concerning the mechanism of alkylation was whether N-methyl-4-quinolone (5a) was formed directly or via an intermediate.   4-Quinolone (3) is a bifunctional nucleophile which may react with electrophiles both at nitrogen and oxygen.   In TMP both phosphorus and carbon atoms are electrophilic and on attack of a nucleophile may undergo either O–P or O–C cleavage.   There is no unequivocal correlation known between the nature of the nucleophile and its point of attack, although with strong nucleophiles O–P cleavage and with weak nucleophiles rather O–C cleavage is common.[6]   Considering the nucleophilic character of reaction centres in (3) and the structure of the products, O–C bond cleavage can be assumed in the alkylation process.

Earlier we have shown [7] that the tautomeric equilibrium of 4-quinolone (3) is dependent on solvent polarity.

A   B

(3)

Scheme 1
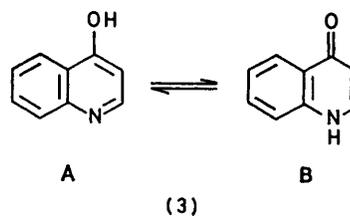
By comparison of the u.v. spectra of 4-quinolone (3) and its fixed forms (4a) and (5a) we established that in the highly polar TMP (3) was, as expected, exclusively in the keto-form (3B).

The oxide oxygen of polar trialkyl phosphates is a good acceptor for mobile protons [8] and it forms a hydrogen bond with the NH-proton of (3B), thus fixing the position of the hydrogen atom [9a] on the nitrogen.   This,
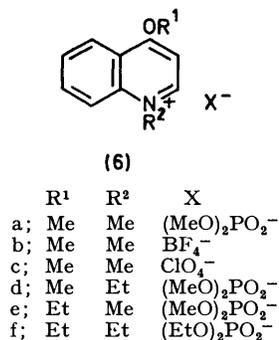
at the same time, enhances O-alkylation by another TMP molecule.

In fact we found that, when following the reaction of (3B) with TMP by t.l.c. and u.v. spectrophotometry, in the range of 90—200 °C 4-methoxyquinoline (4a) was formed in an initial phase and then (4a) gradually disappeared.

(4)   (5)

a : R = Me

b : R = Et
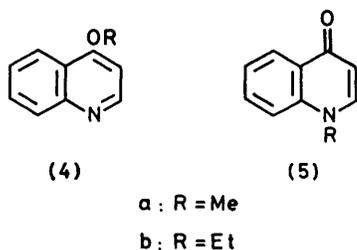
Thermal or catalytic rearrangement of imidates to the more stable amides is a known process [9b] and the interconversion of (4) and (5), as vinylogues, may be envisaged.

Therefore we studied the behaviour of (4a) and found that (a) (4a) is thermally stable. No isomerization could be detected on heating (4a) in aprotic solvents (dimethylformamide, dimethyl sulphoxide, hexamethylphosphoric triamide, and propylene carbonate) at 130 °C for 4 h; (b) isomerization in solvents in the presence of one molar equivalent of TMP was slow; (c) in TMP as a solvent (4a) is transformed at 90 °C into (5a) and a quaternary salt, probably (6a) (Scheme 3). The

(6)

	R^1	R^2	X
a;	Me	Me	(MeO)$_2$PO$_2^-$
b;	Me	Me	BF$_4^-$
c;	Me	Me	ClO$_4^-$
d;	Me	Et	(MeO)$_2$PO$_2^-$
e;	Et	Me	(MeO)$_2$PO$_2^-$
f;	Et	Et	(EtO)$_2$PO$_2^-$

latter was separated and identified as a tetrafluoroborate (6b) and perchlorate (6c). The ratio (5a) : (6a) was 75 : 25 at 100 °C and 60 : 40 at 190 °C. Transformation of (4a) was complete at both temperatures.

Concentration *vs.* time plots, as determined by u.v. spectrophotometry, are shown in Figure 1. Induction periods on the curves of (4a) and (5a) indicate autocatalysis or the formation of an intermediate.

The quaternary salt (6) formed according to Schemes 3 and 4 as a common alkylated derivative of both (4a) and (5a) may catalyse the imidate–amide transformation.[9b] In fact we found that in propylene carbonate (at 90, 110, and 130 °C) (4a) was quantitatively transformed into (5a) in the presence of (6b), whereas the concentration of (6b) remained unchanged.

Participation of (6) was confirmed by separate experi-

ments with N-[^{14}C]methyl-4-methoxyquinolinium tetrafluoroborate (6b') in propylene carbonate. At the end of the reaction the label accumulated in the N-methyl-4-quinolone (5a') (Scheme 2).

Since (6b) is recovered, catalytic amounts of it are sufficient. The reverse, *i.e.* $N \rightarrow O$ methyl transfer, was not observed either in our experiments or with pyridine analogues.[9b]

These results explain the induction periods of the curves for (4a) and (5a) in Figure 1. For (4a) this is a consequence of autocatalysis, for (5a) it is due to the formation of an intermediate. Salt (6) is the precursor in the formation of (5). Accordingly, when (6b) was
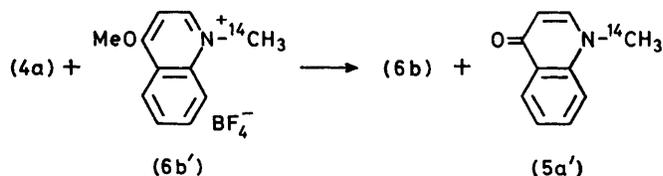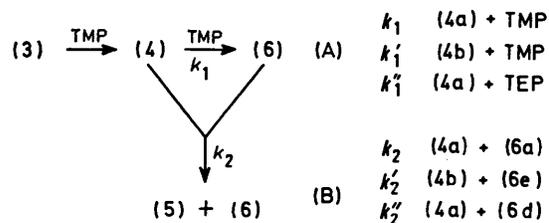

Scheme 2

added to the system at the beginning of the reaction, formation of (5a) followed a simple saturation curve. Besides being a catalyst and an intermediate, (6) is also an end product. The formation of a quaternary salt in imidate–amide rearrangements catalysed by the alkylating agent has been assumed earlier;[10] although its catalytic effect has been studied in detail,[9b] our experiments demonstrate their formation directly.

Thus N-methylation of (4a) in TMP proceeds in two ways: with TMP (k_1) and with the salt (6a) (k_2) (Scheme 3).

Formation of (6a) is preferred if $k_1 > k_2$ and, in turn, the proportion of (5a) increases if $k_2 > k_1$.

The product ratio can thus be influenced by the activity of the alkylating agent. Rate values for the formation of (6a) (k_1 4.0×10^{-7} l mol^{-1} s^{-1}) and (5a) (k_2 1.0×10^{-4} l mol^{-1} s^{-1}) in TMP at 90 °C show that as an alkylating agent (6) is three orders of magnitude more active than TMP. Nevertheless, owing to the higher concentration of TMP the proportion of (5a) and

Scheme 3

(6a) in the end product is comparable. This also explains why in other solvents (4a) rearranges at a measurable rate only in the presence of a large excess of TMP.

Further support for the proposed mechanism was lent by the close agreement of the rate constants k_2 (Scheme 3) in TMP and propylene carbonate (9.0 $\times$ 10^{-5} l mol^{-1} s^{-1} at 90 °C). The latter is a single S_N2 reaction.

The fact that under the same conditions 4-ethoxy-quinoline (4b) gave N-methyl-4-quinolone (5a) with TMP whereas 4-methoxyquinoline (4a) yielded with triethyl phosphate (TEP) a mixture of N-methyl- (5a) and N-ethyl-4-quinolone (5b) as well as the corresponding quaternary salts was also in accord with the above mechanism.

Considering reaction (A) in Scheme 3, rates for the ethoxy- (4b) and methoxy-compounds (4a) (k_1' and k_1) should not differ significantly since the Hammett constants of the C-4 substituents are close:[11] $\sigma_{p\text{-OMe}}$ —0.27 and $\sigma_{p\text{-OEt}}$ —0.24. For reaction (B), however, the transformation of (4b) is slower since it may also involve $O{\rightarrow}N$ ethyl transfer and, as it is characteristic for S_N2 reactions, $k_2/k_2' \geqq 10$. A similar ratio of rates was found with the rearrangement of N-methylbenzimidates catalysed by methyl and ethyl iodide.[10] Therefore the concentration of N-ethyl-4-ethoxyquinolinium salt (6f) formed along with (5a) is in this step much lower than that of the N-methyl-4-ethoxyquinolinium salt (6e) formed with rate k_1', and cannot compete later on with (6e) in the $O{\rightarrow}N$ transfer process. Consequently, the end product of the alkyl transfer reaction is mainly (5a) together with (6).

The reaction of (4a) in process (A) of Scheme 3 is slower with TEP (k_1'') than with TMP (k_1): according to what was noted above $k_1/k_1'' \geqq 10$ (S_N2 reaction). Reaction (B) is, in turn, faster (k_2'') than in the previous case (k_2') since instead of an ethyl group, a methyl group is transferred; thus $k_2'' > k_2'$ and $k_2'' \cong k_2$. Because of the relationships $k_1'' < k_1$ and $k_2'' > k_2'$ (6a) is formed faster, and reaction (B) is able to compete in the $O{\rightarrow}N$ transfer with the N-ethyl-4-methoxyquinolinium salt (6d); in this way (5a) is formed as well as (5b).

Similarly, ethyl toluene-p-sulphonate with (4a) gives rise to a mixture of (5a) and (5b) but with methyl toluene-p-sulphonate (4b) yields only (5a) (besides the quaternary salts).

It is a reasonable assumption that (4a) would react in the same way when it is formed as an intermediate from (3) and TMP.

In agreement with this, the change of concentration of (4a) and (5a), as followed by u.v. spectrophotometry, is the same as shown in Figure 1, and further the end product is a mixture of (5a) and (6a). The latter was isolated and identified by conversion into (6b) and (6c). The product ratio is temperature dependent: at higher temperatures formation of (6a) is preferred due to the different temperature dependence of k_1 and k_2 and to methylation of (5a) by TMP at higher temperatures (>150 °C) (Scheme 4).

$$(5a) \xrightarrow[>150°\text{ C}]{\text{TMP}} (6a)$$

SCHEME 4
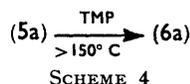
This is in accordance with the finding[12] that the carbonyl group of the analogous N-methyl-4-pyridone is highly polarized ($0.5e$ charge is localized at the oxygen). O-Alkylation is, therefore, preferred over N-alkylation.

The conversion of (5a) into (6a) demonstrates that (6) is the common alkylated form of (4) and (5) and is in accord with the preferred alkylation at oxygen of the tautomeric form (3B). Since its rate is negligible at 90 °C, it does not affect kinetic measurements carried out at this temperature.

The mechanism of the TMP alkylation of 4-quinolone suggested by preparative experiments, u.v. spectrophotometry, tracer studies and kinetic measurements is summarized in Scheme 3.

In the formation of (6a) from (3B), determined by isotopic dilution method, the induction period implies the presence of an intermediate. This is, in fact, (4a) which was confirmed by the formation of (6a) from (4a) itself without an induction period (Figure 1).

Although according to Kornblum's rule[13] direct alkylation of the nitrogen would be expected, in a kinetically favoured charge-controlled process O-alkylation occurs followed by a transformation to the thermodynamically more stable N-methyl-4-quinolone.

Based on our experience with reactions involving TMP and TEP it seems probable that other simple alkyl phosphates react by a similar mechanism.

We found that alkylation of 4-pyridone with TMP and TEP was, in every respect, analogous to that of 4-quinolone, indicating that N-alkylation of the two heterocycles proceeded by the same mechanism.

The primary formation of (4a) and the character of (6a) excluded alternative mechanisms involving the tautomeric form (3A). The following possibilities may be considered: (a) O-methylation of the 4-hydroxy-form (3A) is improbable because of the acidity of the phenolic hydroxyl; (b) though quaternization of a cyclic tertiary nitrogen by TMP is feasible,[14,15] N-methylation and subsequent deprotonation or covalent association of the anion with C-4 could not give a quaternary salt as one of the end products; (c) C-4 methoxylation by O–P bond cleavage is unlikely because sufficient activation at C-4 would require a positive charge as a consequence of prior quaternization at the ring nitrogen.[16] In this case, however, (4a) could not be primary product.
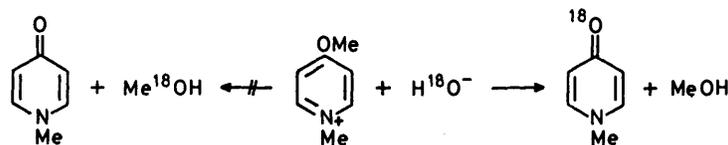
Methylation of (3B) in TMP gives after hydrolysis only (5a) because under such conditions the quaternary salt (6a) is rapidly converted into (5a).[17] The mechanism of this hydrolysis was established by alkaline hydrolysis of (7) with ^{18}O-labelled alkali (Scheme 5).[16] The main

(7)
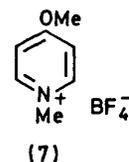
process is the elimination of the methoxy-group while O-methyl cleavage is insignificant.

Kinetic Measurements.—The reaction between (4a) and TMP was studied at 90 °C at concentrations of 0.05, 0.10, 0.20, 0.30, 0.40, and 0.50 M. Samples taken at intervals were diluted with methanol to ca. 10^{-4}M, and measured

by u.v. spectrophotometry. From the curves differential spectra were calculated and from these the concentrations of 4-methoxyquinoline (4a), N-methyl-4-methoxyquinolinium salt (6a) and N-methyl-4-quinolone (5a) at time t (Figure 1) were obtained.

Thus, knowing the concentration of TMP the ratio of rate constants can be determined. k_1 Can be obtained from the tangent drawn to point $t = 0$ of the curve of (4a) in Figure 1 and therefore k_2 also can be calculated. Data pertinent to solutions of low concentration

SCHEME 5

For reactions in Scheme 3 relations (1)—(3) hold:

$$- \frac{d[(4a)]}{dt} = k_1[(4a)][TMP] + k_2[(4a)][(6a)] \quad (1)$$

$$\frac{d[(6a)]}{dt} = k_1[(4a)][TMP] \quad (2)$$

$$\frac{d[(5a)]}{dt} = k_2[(4a)][(6a)] \quad (3)$$

The process is zero order for TMP (present also as solvent); from this, after solving the kinetic differential equations relations (4) and (5) hold:

$$[(5a)]_t = \frac{k_2}{2k_1[TMP]} [(6a)]_t^2 \quad (4)$$

$$[(4a)]_o - [(4a)]_t = [(6a)]_t + \frac{k_2}{2k_1[TMP]} [(6a)]_t^2 \quad (5)$$

These equations are transformed to a linear form by dividing both sides by $[(6a)]_t$ representing thus two

FIGURE 1 Absorbance–time plots for the reaction of 4-methoxyquinoline (4a) with TMP at 90 °C; formation of (5a) N-methyl-4-quinolone and (6a) N-methyl-4-methoxyquinolinium salt

straight lines (Figure 2) with intercepts 0 and 1 (i and ii) respectively, and of the same slope [see relation (6)].

(<0.40M) are unsuited for evaluation due to the considerable relative error of the spectrophotometric

$$m = \frac{k_2}{2k_1[TMP]} \quad (6)$$

determination of (6a); solutions of 0.40 and 0.50M concentration can be evaluated graphically.
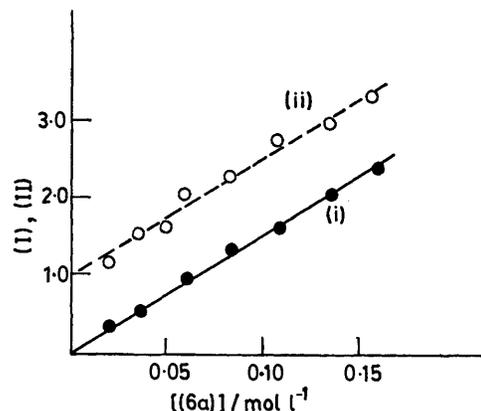

FIGURE 2 Graphical evaluation of kinetic data of the reaction of 4-methoxyquinoline (4a) and TMP at 90 °C

$$(I) = \frac{[(5a)]_t}{[(6a)]_t}; \quad (II) = \frac{[(4a)]_o - [(4a)]_t}{[(6a)]_t}$$

EXPERIMENTAL

U.v. spectra were recorded with Specord UV-VIS (Carl Zeiss, Jena) and Unicam SP 800 instruments. T.l.c.: method (A) (for alkylation of heterocycles) on Kieselgel H; solvent: ether–ethanol (1 : 1) containing 2% acetic acid; indicators (a) u.v. fluorescence, (b) iodine vapour; R_F-values: 4-quinolone (3) 0.61; 4-methoxyquinoline (4a) 0.48; N-methyl-4-quinolone (5a) 0.31; quinolinium salts (6) 0. Spots were scratched out and identified by u.v. spectroscopy. Method (B) (for experiments with picric acid and 4-nitrophenol): on neutral alumina (Woelm); solvent: benzene–pyridine (9 : 1); indicator: iodine vapour (light spots on dark background).

Materials.—4-Pyridone (Aldrich) was redistilled (b.p. 240 °C/12 mmHg); 4-quinolone (Koch–Light) was recrystallized from ethyl acetate (m.p. 201 °C); TMP (Fluka, b.p. 198—199 °C) and TEP (Merck, Schuchardt, b.p. 215—216 °C) were fractionally distilled; 4-nitroanisole (Aldrich) and 2,4,6-trinitroanisole (Aldrich) were recrystallized from ethanol (m.p. 54 and 68 °C respectively); picric acid (Merck) and 4-nitrophenol (Fluka) were used without further purification.
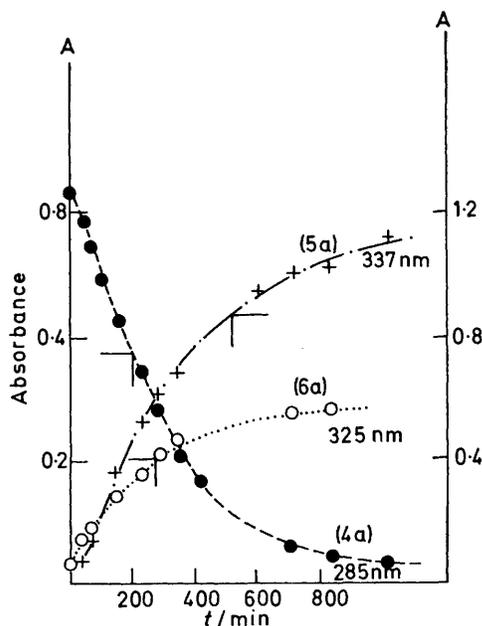
4-Methoxypyridine [18] (b.p. 80—82 °C/15 mmHg, lit.,[19] b.p. 190 °C), N-methyl-4-pyridone (m.p. 91—92 °C, lit.,[20] 92—93 °C), N-methyl-4-methoxypyridinium fluoroborate (7) (m.p. 55—57 °C; lit.,[20] 56—58 °C), 4-methoxyquinoline (4a) (m.p. 39—40 °C, lit.,[18] 39—40 °C), 4-ethoxyquinoline (4b) (b.p. 113—116 °C/1 mmHg, lit.,[21] 112—114 °C), N-ethyl-4-quinolone (5b) (m.p. 99—101 °C, lit.,[21] 100—101 °C), 4-chloroquinoline (m.p. 34—35 °C, lit.,[22] 34—35 °C), 2,4,6-trinitrophenetole (m.p. 76—77 °C, lit.,[23] 78 °C), N-methyl-4-methoxyquinolinium iodide (m.p. 131—133 °C, lit.,[17] 132—133 °C), and N-methyl-4-methoxyquinolinium perchlorate (6c) (m.p. 251—253 °C, lit.,[24] 250—252 °C) were prepared by literature methods.

N-Methyl-4-quinolone (5a). This compound was prepared by the above general method. The crude product was dissolved in ethyl acetate–chloroform (1 : 1) precipitated with cyclohexane, and recrystallized from ethyl acetate, m.p. 151—153 °C (lit.,[18] 152—153 °C).

N-Methyl-4-methoxyquinolinium fluoroborate (6b). To an aqueous solution of N-methyl-4-methoxyquinolinium iodide (2.5 g) aqueous fluoroboric acid (40%, 3 ml) was added. The precipitate was filtered off and washed with aqueous $Na_2S_2O_3$ and water. The crude product (1.14 g, m.p. 230—240 °C) was recrystallized from water and then from methanol to give colourless crystals (0.55 g), m.p. 244—246 °C (Found: C, 50.5; H, 4.7; N, 6.6 Calc. for $C_{11}H_{12}$-BF_4NO: C, 50.6; H, 4.6; N, 6.6%).

Thermal Stability of 4-Methoxyquinoline (4a).—There was no change in the u.v. spectrum of (4a) after it had been heated at 0.5 mol l⁻¹ concentration for 4 h at 130 °C in dimethylformamide, dimethyl sulphoxide, hexamethylphosphoric triamide, and propylene carbonate. 4-Methoxypyridine behaved similarly.

Reaction of 4-Methoxyquinoline (4a) with TMP.—Compound (4a) was heated in TMP (0.5 mol l⁻¹) at 190 °C. T.l.c. of a sample taken after 10 min still showed the presence of (4a). After 30 min (a) according to t.l.c. (4a) had already disappeared; (b) the u.v. spectrum in methanol was identical with that of a 6 : 4 mixture of (5a) and (6b), the presence of (4a) not being detected in the spectrum; (c) the product obtained by adding to a sample (1 ml) dissolved in ether (50 ml) and ethanol (5 ml) perchloric acid (2 ml) was identified as (6c) after recrystallization (from methanol) by its m.p. and u.v. spectrum; (d) the product obtained by adding to another sample (1 ml) dissolved in ether (50 ml) and ethanol (5 ml) aqueous fluoroboric acid (40%, 2 ml) was identified as (6b) after recrystallization (from methanol) by its m.p. and u.v. spectrum.

Reaction of 4-Methoxypyridine and TMP.—Under the same conditions as those described above this reaction afforded the N-methyl-4-methoxypyridinium salt [isolated as the fluoroborate (7), m.p. 55—57 °C] and N-methyl-4-pyridone (m.p. 91—92 °C) in a similar ratio. 4-Methoxypyridine could not be detected.

Reaction of 4-Ethoxyquinoline (4b) and TMP.—This reaction carried out at 190 °C for 30 min gave according to t.l.c. only N-methyl-4-quinolone (5b); that of 4-methoxyquinoline (4a) and TEP at 210 °C for 30 min only N-methyl-(5a) and N-ethyl-4-quinolone (5b).

Reaction of 4-Quinolone (3) with TMP.—4-Quinolone was heated in TMP (0.5 mol l⁻¹) at 190 °C and samples were analysed as described above. After 5 min much 4-methoxyquinoline (4a) and traces of N-methyl-4-quinolone (5a) were detected by t.l.c. Later the amount of 4-methoxyquinoline (4a) increased further subsequently decreasing after 25 min;

the concentration of N-methyl-4-quinolone (5a) increased continuously until the end of the reaction. After 2 h N-methyl-4-quinolone (4a) and N-methyl-4-methoxyquinolinium salt [identified as the fluoroborate (6b)] were detected, but no 4-methoxyquinoline (4a).

Thermal Stability of N-Methyl-4-methoxyquinolinium Fluoroborate (6b).—No change in the u.v. spectrum was observed when a 0.2 mol l⁻¹ solution of TMP in propylene carbonate was refluxed for 4 h.

The same was found for the corresponding pyridinium salt.

Isomerization of 4-Methoxyquinoline (4a) with N-Methyl-4-methoxyquinolinium Fluoroborate (6b).—On heating equimolar quantities (0.1 mol l⁻¹) of the reactants in propylene carbonate at 130 °C for 30 min, (4a) disappeared and besides (6b) N-methyl-4-quinolone (5a) was detected by u.v. spectrophotometry.

Experiments with the pyridine analogue gave the same result.

Methylation of N-Methyl-4-quinolone (5a) with TMP.—Compound (5a) (0.25 g) was heated in TMP (2.5 ml) for 3 h at 200 °C. After cooling, aqueous perchloric acid (60%, 0.5 ml), ether, and some ethanol were added to the solution and the mixture was stored overnight in a refrigerator. The product (0.216 g) was separated and recrystallized from ethanol to give N-methyl-4-methoxyquinolinium perchlorate (6c) (0.164 g), m.p. 248—251 °C (lit.,[24] 250—252 °C) identified also by its u.v. spectrum.

Under the same conditions N-methyl-4-pyridone reacted in the same way.

Isotope Studies.—Compound (4a) was converted into N-[¹⁴C]methyl-4-methoxyquinolinium iodide with [¹⁴C]methyl iodide [25] prepared from [¹⁴C]methanol [26] and isolated as the fluoroborate (6b) (specific activity 3.82/μCi/mmol).

Equimolar amounts of (6b′) and (4a) were allowed to react for 3 h at 150 °C in propylene carbonate (0.05 mol l⁻¹). To the cooled solution ethanol (15 ml), aqueous fluoroboric acid (40%, 1 ml) and ether (150 ml) were added and the mixture was stored overnight in a refrigerator. The precipitate was separated, recrystallized (from methanol), and identified as (6b′); specific activity 0.380/μCi/mmol.

Isotope dilution analyses. A solution of (4a) in TMP (0.5 mol l⁻¹) was kept at 130 °C. To 1-ml samples taken at intervals 0.1 molar ethanolic solutions of (6b′) of known specific activity (0.5 ml) were added and the fluoroborate salt recovered as described above [cf. reaction of (4a) with TMP (d)]. The m.p.s, the u.v. spectra, and the specific activities of each of the samples were determined. The concentration of (6a) formed in the reaction was calculated in the usual way.[27]

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