On the Mechanism of the Alkylation of Quinoline and Naphthyridine Derivatives

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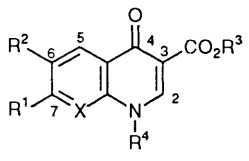
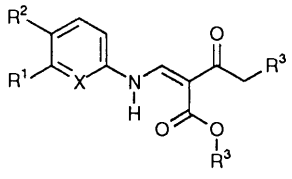
Ethylation studies on substituted 3-ethoxycarbonyl-4-oxo-quinolines and -naphthyridines as well as of the potassium salts of their enolates has revealed that the pathway suggested by Frank *et al.* for the alkylation of 4-quinolone with $(Et_3O)PO$, *i.e.*, thermal rearrangement of an *O*- to *N*-alkyl product cannot be extended to this class of compound since no *O*-alkylated intermediates could be detected. The mechanism of the alkylation was revised and the site of attack was rationalised using Klopman's theorem and Pearson's HSAB (hard–soft acid–base) theory based on AM1 level semiempirical calculations. Our results suggest a nucleophile enolate intermediate, the alkylation of which can only lead to the *N*-alkylated product. In accordance with our calculations, the reactive enolates of the title compounds could be selectively transformed into the corresponding *N*-alkylated products. The selective formation of the *N*-alkylated product was explained by an analysis of the total charge distribution and frontier orbitals. The conclusions can be generalised for other alkylations.

Prompted by recognition of the antibacterial activity of substituted 4-oxoquinoline- and -naphthyridine-carboxylic acids[1] [*e.g.*, nalidixic acid (**1a**), oxolinic acid (**1b**) and norfloxacin (**1c**)] a large number of analogues have been synthesised.[2,3] The biological activity seems to be associated with an alkyl group at the nitrogen of the pyridinone moiety. This can be introduced by *N*-alkylation of the pyridinones, *e.g.*, of **2a**, **2b** or **2c**, but surprisingly none of the open-chain precursors (**4a**, **4b**, **4c**) could be alkylated. Alkylation at





	X	R^1	R^2	R^3	R^4
1a	N	CH_3	H	H	CH_3CH_2
1b	CH	O–CH_2–O		H	CH_3CH_2
1c	CH	piperazinyl	F	H	CH_3CH_2
2a	N	CH_3	H	CH_3CH_2	H
2b	CH	O–CH_2–O		CH_3CH_2	H
2c	CH	Cl	F	CH_3CH_2	H
3a	N	CH_3	H	CH_3CH_2	CH_3CH_2
3b	CH	O–CH_2–O		CH_3CH_2	CH_3CH_2
3c	CH	Cl	F	CH_3CH_2	CH_3CH_2

	X	R^1	R^2	R^3
4a	N	CH_3	H	CH_3CH_2
4b	CH	O–CH_2O		CH_3CH_2
4c	CH	Cl	F	CH_3CH_2

nitrogen[4] succeded only after the ring-closure of **4**. Pyridinones are bifunctional nucleophiles that can react with electrophiles both at nitrogen and oxygen. In a study aimed at the selective preparation of *N*-alkylated products[5] it was found that treatment with diazoethane yielded mainly the *O*-alkylated product,[6] while from the alkylations with ethyl iodide,[7,8] dimethyl sulfate[9] and triethyl phosphate[10–12] the *N*-alkylated product could be isolated. The mechanism of this alkylation has been investigated by Frank *et al.*[13] As a model, alkylation of 4-quinolone with trimethyl phosphate was selected. At 190 °C the *O*-alkylated compound was formed first, which isomerised thermally to the *N*-alkylated product.

Table 1 Total energies and heats of formation for keto (**2**) and enol forms (**5**)

	H_f/kcal mol^{-1}		E_{tot}/eV	
	2	**5**	**2**	**5**
a	−71.36	−73.67	−3076.34	−3076.44
b	−135.58	−143.51	−3623.75	−3624.09
c	−125.40	−132.41	−3686.98	−3687.27

Following technological experiments on the ethylation of compounds **2**, TLC revealed that the *N*-alkylated derivatives **3** were formed directly *via* the enolate anion **6** (see later) and that *O*-alkylated products could not be isolated at all. Since this conflicted with the proposal by Frank *et al.*, we undertook a theoretical investigation on the mechanism of alkylation of substituted 3-ethoxycarbonyl-4-oxo-quinolines and -naphthyridines. Alkylation was modelled by ethylation with ethyl iodide, diethyl sulfate and triethyl phosphate. Our results demonstrate that conclusions obtained with 4-quinoline cannot be extended to the corresponding 3-ethoxycarbonyl compounds.

As a result of an infrared study on 4-hydroxy-1,5-naphthyridine in solution and in the solid state by Bailey and Hercules the tautomeric behaviour of quinolones and hydroxynaphthyridines is now well-known.[14] Further, Frank *et al.* have shown that the tautomeric equilibria of 4-quinolones is dependent on solvent polarity. The keto form predominates in polar solvents, in the gas phase and in the solid state,[15] while, in non-polar solvents, the enol form is in excess.[16]

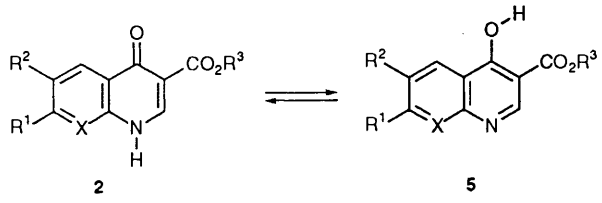
With the 3-alkoxycarbonyl analogues, however, it is the enol form which is more stable in the gas phase. The gas phase predominance of the enol tautomer (**3**) in the case of 3-ethoxycarbonyl-4-oxoquinolines and naphthyridines was also proved by our calculations (Table 1). Although in polar solvents the keto form (**2**) is preferred, the enol form is also present in a small concentration.

Table 2 LUMO energies for ethylating agents

	E_{LUMO}/eV
Ethyl iodide	0.4500
Diethyl sulfate	−2.2012
Triethyl phosphate	−1.2165

Table 3 HOMO energies, HOMO p_z coefficients and total electron densities at nitrogen and oxygen in the pyridinone ring of **2**, **5** the nucleophilic anion **6** and in the aliphatic chain of **4**

		p_z coeff. in HOMO		Total electron density	
	E_{HOMO}/eV	N	O	N	O
2a	−9.25	0.4654	0.3455	5.2285	6.2886
2b	−8.91	0.3884	0.2818	5.2346	6.2890
2c	−9.23	0.4473	0.2871	5.2365	6.2778
5a	−9.71	0.4089	0.2942	5.1368	6.2452
5b	−9.19	0.2475	0.1976	5.1631	6.2440
5c	−9.44	0.3313	0.2219	5.1559	6.2409
6a	−4.49	0.4670	0.3838	5.2604	6.4050
6b	−4.41	0.4533	0.3714	5.2855	6.4049
6c	−4.58	0.4598	0.3953	5.2843	6.3953
4a	−9.13	0.5180	0.1852	5.2363	6.3330
4b	−9.05	0.4615	0.1641	5.2336	6.3296
4c	−9.34	0.5269	0.1730	5.2380	6.3276



Calculations.—Alkylation is a bimolecular nucleophilic substitution for which both FMO[17] and HSAB[18] theory is applicable. According to Klopman's theorem[19] for chemical reactivity, *N*-ethylation should be an orbital-controlled reaction, because of the soft electrophilic character of ethylating agents. The large difference between the LUMO energies of the ethylating agents (Table 2) and the HOMO energies of **2** and **5** (Table 3) suggests that perturbation of these orbitals is small.

The likelihood of a charge-controlled reaction on nitrogen is small. Basicity and electron density at nitrogen in **2** and **5** are insufficient to form an energetically preferred interaction with the ethylating agent. The low electron density, caused by the overlapping of the nonbonding p_z orbital with the aromatic ring and the electron-deficient double bond, prevents the charge-controlled reaction at the nitrogen atom.

Calculation of the HOMO energies and coefficients for anions **6a**, **6b** and **6c** (Table 3) showed that the difference between the LUMO energies of the alkylating agents and the HOMO energies of the nucleophilic anions decreases, whereby the perturbation increases. The preferred orbital-controlled reaction between anion **6**, a soft nucleophile and the ethylating agent, a soft electrophile, should be very fast and result in an *N*-alkylated product. In accordance with the observed selectivity, the p_z coefficient at nitrogen in anion **6** is larger than that on oxygen. A charge-controlled reaction, in turn should lead to *O*-alkylated products in accordance with the total charge distribution in anion **6** (Table 3).

Experimental

The molecular orbital energies and coefficients were calculated by AMPAC 1.0[20] on the AM1 semiempirical level from pre-optimised structures from MMX(87)[21] molecular mechanics calculations on an IBM 80486DX computer.

Ethylation experiments are described in detail for compounds in the **a** series. For series **b** and **c** reaction conditions were similar. IR spectra were measured on an M80-SPECORD instrument for KBr tablets. ^{1}H NMR spectra were measured on a Bruker AM-400 and the ^{13}C NMR spectra on a JEOL FX-100 FT-NMR spectrometer for solutions in [$^2H_6$]Me_2SO. TLC was carried out on Kieselgel 60 F_{254} plates using benzene–acetone–acetic acid 80:20:10 as the eluent. R_f values for **2a**, **3a** and **7a** are 0.26, 0.48, 0.55, respectively.

Ethyl 7-methyl-4-oxo-1,8-naphthyridine-3-carboxylate[22] (**2a**), ethyl 6,7-methylenedioxy-4-oxoquinoline-3-carboxylate[23] (**2b**), ethyl 7-chloro-6-fluoro-4-oxoquinoline-3-carboxylate[23] (**2c**), ethyl 7-methyl-4-methoxy-1,8-naphthyridine-3-carboxylate[22] (**7a**), ethyl 6,7-methylenedioxy-4-methoxyquinoline-3-carboxylate[23] (**7b**) and ethyl 7-chloro-6-fluoro-4-methoxyqinoline-3-carboxylate[23] (**7c**) were prepared by literature methods.

Reaction of Ethyl 7-Methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate[22] (**2a**) *and Ethyl Iodide.*—(*a*) *In the presence of triethylamine.* A solution of **2a** (5.0 g, 21.5 mmol), triethylamine (3.0 cm^3, 21.66 mmol) and ethyl iodide (2.0 cm^3, 24.8 mmol) in 50 cm^3 of dimethylformamide (DMF) was heated at 120 °C for 2 h. The solvent was removed under reduced pressure and the residue was quenched with water. The precipitate was filtered off and dried to give ethyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyiridine-3-carboxylate (**3a**) as a solid [4.9 g, 87%, m.p. 118 °C (lit.,[23] 122–123)].

(*b*) *In the presence of* K_2CO_3. To a solution of **2a** (5.0 g, 21.5 mmol) and ethyl iodide (2.0 cm^3, 24.8 mmol) in 50 cm^3 of DMF was added K_2CO_3 (4.0 g, 29.0 mmol) and the mixture was heated at 120 °C for 30 min. The solvent was removed under reduced pressure and the residue was quenched with 80 cm^3 of water. The precipitate was filtered off and dried to give **3a** as a solid [5.3 g, 94%, m.p. 118 °C (lit.,[23] 122–123)].

Reaction of Ethyl 7-Methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate[22] (**2a**) *and Diethyl Sulfate.*—(*a*) *In the presence of triethylamine.* A solution of **2a** (5.0 g, 21.5 mmol), triethylamine (3.0 cm^3, 21.6 mmol) and diethyl sulfate (4.0 cm^3, 30.5 mmol) in 50 cm^3 of DMF was heated at 120 °C for 2 h and gave, after the usual work-up, **3a** as a solid (5.0 g, 89%).

(*b*) *In the presence of* K_2CO_3. A solution of **2a** (5.0 g, 21.5 mmol), K_2CO_3 (4.0 g, 29.0 mmol) and diethyl sulfate (4.0 cm^3, 30.5 mmol) was heated at 85 °C for 15 min and gave after the usual work-up, **3a** as a solid (5.5 g, 98%).

Reaction of Ethyl 7-Methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate[22] (**2a**) *and Triethyl Phosphate.* (*a*) *In the presence of* K_2CO_3. A solution of **2a** (5.0 g, 21.5 mmol), K_2CO_3 (1.6 g, 11.9 mmol) and triethyl phosphate (6.0 cm^3; 35.6 mmol) in 5 cm^3 light petroleum was heated at 190 °C for 15 min and gave after the usual work-up **3a** as a solid (5.4 g, 96%).

(*b*) *Without added base.* **2a** (5.0 g, 21.5 mmol) and triethyl phosphate (15.0 cm^3, 89 mmol) was heated at 190 °C for 30 min and gave after the usual work-up **3a** which was transformed directly into nalidixic acid (2.9 g, 53%).

Preparation of **6a**.—A solution of **2a** (5.0 g, 21.5 mmol) and K_2CO_3 (1.5 g, 11.0 mmol) in 50 cm^3 of DMF was heated under reflux for 1 h. The mixture was cooled to 10 °C and filtered to give **6a** as a solid (5.0 g, 85%). A sample was recrystallized from hot DMF for spectral analysis; δ_H(400 MHz; [$^2H_6$]Me_2SO)

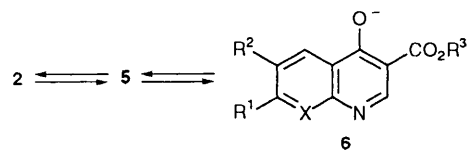
1.26 (3 H, t, CH_3CH_2), 2.53 (3 H, s, 7-CH_3), 4.14 (2 H, q, OCH_2), 7.07 (1 H, d, J = 8 Hz, 6-H), 8.34 (1 H, d, J = 8 Hz, 5-H) and 8.76 (1 H, s, 2-H); δ_C(100 MHz; [$^2H_6$]Me_2SO) 14.8 (CH_3C), 24.7 (7-CH_3), 58.2 (OCH_2), 107.6 (C-3), 117.8 (C-6), 121.3, (C-8a), 134.7 (C-5), 142.6 (C-7), 156.9 (C-2), 159.7 (C-4a) and 174.4 (C-4).

Results and Discussion

In accordance with the results of our calculations, at room temperature the *N*-alkylated products should be formed in an orbital-controlled reaction, while the *O*-alkylated isomers should arise from a charge-controlled reaction under kinetic control. *N*-Alkylation is most unlikely because of the large difference between frontier orbital energies. 3-Alkoxycarbonyl-4-oxoquinolines and naphthyridines (**2a**, **2b** and **2c**) can be easily deprotonated with potassium carbonate to form potassium salts (**6a**, **6b** and **6c** respectively).[4] The structure of nucleophilic anion **6a** was established by IR and ^1H and ^{13}C NMR spectroscopy. The main feature of its IR spectrum was the disappearance of the ν_{NH} band from the region 3300–3500 cm^{-1}. Comparison of the ^1H and ^{13}C NMR spectra of **6a** and **2a** showed that the NH signal had disappeared from the proton spectrum, but intensity ratio and multiplicity of other peaks were unchanged. The assignment of the ^1H and ^{13}C NMR spectra of the compounds was based on substituent effects[25] and on the APT (attached proton test) technique.

The characteristic chemical shift differences observed were compared with the charge distribution in the two compounds calculated by the AM1 method (Table 3). Although the computational results have only qualitative importance, the tendency of the charge in the electron density is in accordance with the changes in the chemical shift values (Table 4). The calculated electron density at H-2 increased by 0.0400 on forming the anion **6a**. Since an increase in the electron density generally results in a smaller chemical shift we would expect a shielding effect at this proton instead of the observed deshielding by 0.28 ppm. On the other hand we have to consider that, with the loss of the NH proton in **6a**, a negative charge distributed over the whole ring would lend an aromatic character to the pyridinone ring. This results in an aromatic ring current which increases the chemical shifts of the attached protons. ^{13}C chemical shifts of the ring carbons, in turn, reflect the charge distribution in the ring, because the ring current has no influence on them. Thus the changes of the electron density at C-2, C-3, C-4 and C=O (ester) are in a good agreement with ^{13}C chemical shifts. For the C=O (ester) we have to consider the ring current effect, too. Concerning C-4a and C-8a NMR data are not interpretable by the present computations. It seems, that the AM1 method is unable to handle the relation with the pyridine ring.

Aromatisation of the pyridinone ring also results in changes in the IR spectrum of **6a**. The $\nu_{C=C}$ bands at 1590 and 1620 cm^{-1} are shifted to 1560 and 1580 cm^{-1}, respectively, in accordance with the formation of the delocalized π-system. It is assumed that deprotonation sequesters the coexisting enol form (**5**) resulting in the complete transformation of the keto form (**2**) into the nucleophilic anion (**6**).



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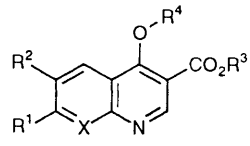
At room temperature the reaction was complete only in the presence of more than equimolar base. An excess of base was necessary to shift the tautomeric equilibrium. Note that at higher temperature this equilibrium was shifted by evolution of CO_2 and therefore a slight excess of base secured a high yield. In none of our experiments were *O*-alkylated products detected by TLC. When the reaction was repeated in the absence of base, as described by Frank *et al.*,[13] reaction time increased. It is our opinion that deprotonation of **5** to the nucleophilic anion **6** would be slower because of a weak H-bonding interaction between the OH proton and the P=O and C=O oxygens of triethyl phosphate and the pyridinones.

Frank and co-workers[13] found an *O*-ethylated isomer (**7**) in the reaction mixture that can be regarded as the charge-controlled product. At high temperature (190 °C) the strongly polarised triethyl phosphate can act as a hard electrophilic carbocation,[26] reacting in a charge-controlled reaction. Formation of **7** was not observed, because of its complete rearrangement to *N*-alkylated **3** at 160 °C.[27]



	X	R^1	R^2	R^3	R^4
7a	N	CH_3	H	CH_3CH_2	CH_3CH_2
7b	CH	O–CH_2–O		CH_3CH_2	CH_3CH_2
7c	CH	Cl	F	CH_3CH_2	CH_3CH_2

Comparison of the total energies and heats of formation of *N*- and *O*-alkylated products (**3** and **7**, respectively) in the gas phase shows that the *N*-alkylated isomers are not always more stable (Table 5) and the differences are too small to justify an explanation of the observed selectivity on the base of thermodynamic control. According to Hammond's principle[28] the transition state should be reactant-like and similar to **6**, therefore the charge-controlled term of the Klopman equation should be small.

The open-chain compounds (**4**) which are precursors of **2** could not be ethylated even at temperatures as high as 200 °C, although according to the mechanistic proposal by Frank *et al.* alkylation of such compounds should be possible. Considering nothing other than the comparison of the HOMO p_z coefficients and total charge distribution in **2** and **4** (Table 3) an ethylating agent could attack both molecules in an orbital-controlled reaction, but in our view it is the nucleophilic anion

Table 4 Differences in electron densities [d(**6a**) − d(**2a**)] and NMR chemical shifts [δ(**6a**) − δ(**2a**)]

Atom	d(**6a**) − d(**2a**)	δ(**6a**) − δ(**2a**)
H-2	+0.0400	+0.28
C-2	+0.0345	−5.1
C-3	+0.1312	−2.6
C-4	−0.0063	+2.5
C (ester CO)	−0.0235	+3.7

Table 5 Heats of formation and total energies (E_{tot}) for *N*- (**3**) and *O*-alkylated (**7**) products

	H_f/kcal mol^{-1}	E_{tot}/eV
3a	−71.22	−3387.41
3b	−134.88	−3934.80
3c	−125.06	−3998.04
7a	−64.69	−3387.13
7b	−134.91	−3934.80
7c	−123.77	−3997.98

formed from the enol tautomer that reacts with the alkylating agent in the presence of base. In compound **4**, however, there is no possibility for tautomerization, and therefore the nucleophilic anion cannot be formed, thus alkylation is prevented.

In summary, we have shown that the necessary condition for *N*-alkylation is the formation of an anion (**6**) with high HOMO energy by deprotonation of 3-alkoxycarbonyl-4-oxoquinolines and -naphthyridines (**2**). The structure of the nucleophilic anion **6a** was established by IR and ^{1}H and ^{13}C NMR spectroscopy. The orbital-controlled reaction of **6** results in *N*-alkylated products (**3**) selectively, because according to the HOMO p_z-coefficients the reactive centre towards soft electrophiles is the nitrogen atom. Other *N*-aryl enamines, such as **4**, where deprotonation was impossible, could not be alkylated.

Acknowledgements

The authors are grateful to the *Pro Renovanda Cultura Hungariae* Foundation for financial assistance and to Prof. M. Nógrádi for helpful discussions.

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Paper 3/03920J
Received 6th July 1993
Accepted 17th November 1993