The Chemical Properties of 1-Substituted 4-Oxopyrimidinium Cations

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Received June 11, 1996

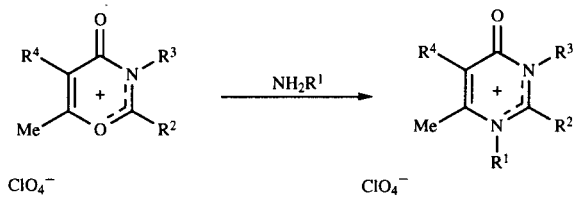
Some theoretical aspects of electrophilic properties of 4-pyrimidinium cations are discussed. The reactivity towards a series of *C*-, *H*-, *N*- and *O*-nucleophiles is studied.

J. Heterocyclic Chem., **34**, 161 (1997).

Introduction.

1,2,3,4-Tetrahydro-4-oxopyrimidines are rarely dealt with in heterocyclic chemistry. Two examples are the synthesis of N^3-H and N^3-phenyl-2-alkyl-2,6-diphenyl-4-oxo-1,2,3,4-tetrahydropyrimidines by cycloaddition of inactivated 2-aza-1,3-dienes with isocyanates [1] and the preparation of 2-*tert*-butyl-1-methyloxycarbonyl-4-oxo-1,2,3,4-tetrahydropyrimidine in a reaction of asparagine and *tert*-butyraldehyde, followed by carbamoylation and oxidative decarboxylation [2].

In our research on 4-oxopyrimidinium salts **2** [3], we found that the electrophilic properties of these compounds, prepared from the corresponding 4-oxo-1,3-oxazinium salts [4] **1** by treatment with an amine, can be used to synthesize their corresponding 1,2,3,4-tetrahydro-4-oxopyrimidines. In this article we report on the reaction of N^1-substituted pyrimidinium perchlorates with *C*-, *H*-, *N*- and *O*-nucleophiles.



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2a R^1 = Ph, R^2 = Me, R^3 = H, R^4 = Ph
2b R^1 = Bn, R^2 = Me, R^3 = H, R^4 = Ph
2c R^1 = R^2 = Me, R^3 = H, R^4 = Ph
2d R^1 = *p*-CH_3OPh, R^2 = Me, R^3 = H, R^4 = Ph
2e R^1 = *p*-HOPh, R^2 = Me, R^3 = *o*-CH_3OPh, R^4 = H
2f R^1 = Ph, R^2 = Me, R^3 = H, R^4 = *p*-FPh

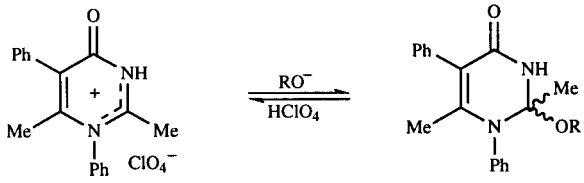
Results.

4-Oxopyrimidinium perchlorate **2a** reacted with alcoholates or phenolates giving rise to 2-alkoxy- or 2-aryloxy-4-oxo-1,2,3,4-tetrahydropyrimidines **3a-d** (Table 1).

Table 1
2-Alkoxy(aryloxy)-4-oxo-1,2,3,4-tetrahydropyrimidines

Compound	R	Mp °C	Yield %	ir, ν (cm^{-1}) NH	C=O	C=C	C-O
3a [a]	CH_3	78	92	3400	1630	1580 1530	1100
3b [b]	$C(CH_3)_3$	75	72	3400	1640	1580 1520	1100
3c [c]	Ph	73	83	3400	1645	1595 1540	1100
3d [d]	*p*-CH_3OPh	99	63	3400	1625	1580 1530	1100

[a] ^{1}H nmr (deuteriochloroform): δ 1.67 (s, 3H, 2-CH_3), 2.07 (s, 3H, 6-CH_3), 4.7 (s, 3H, OCH_3), 7.25 (s, 5H, phenyl), 7.5 (s, 5H, *N*-phenyl). [b] ^{1}H nmr (DMSO-d_6): δ 1.85 (s, 3H, 2-CH_3), 2.2 (s, 3H, 6-CH_3), 3.72 (s, 9H, $C(CH_3)_3$), 7.37-7.77 (m, 10H, phenyl). [c] ^{1}H nmr (deuteriochloroform): δ 1.7 (s, 3H, 2-CH_3), 2.05 (s, 3H, 6-CH_3), 6.87-7.51 (m, 15H, phenyl). [d] ^{1}H nmr (deuterioacetone): δ 1.65 (s, 3H, 2-CH_3), 1.95 (s, 3H, 6-CH_3), 3.57 (s, 3H, OCH_3), 6.66-7.57 (m, 14H, phenyl).



2a **3a-d**

2-Alkoxy- and 2-aryloxy-4-oxo-1,2,3,4-tetrahydropyrimidines **3a-d** lost their alkoxy- or phenoxy function by treatment with perchloric acid, giving rise to starting pyrimidinium salt **2a** in quantitative yield.

Treatment of pyrimidinium perchlorates **2** with amines such as triethylamine, diethylamine and benzylamine showed an analogous reaction. The resulting 2-amino-4-oxo-1,2,3,4-tetrahydropyrimidines **4a-f** were isolated as perchlorate salts (Tables 2-4). This addition worked with N^3-H as well as with N^3-aryl pyrimidinium ions.

As with the alcoholate and phenolate adducts, the reaction was reversible. Compounds **4a-f** afforded the starting

Table 2

2-Amino-4-oxo-1,2,3,4-tetrahydropyrimidines

Compound	R^1	R^3	R^4	R^5	R^6	R^7	Mp °C	Yield %
4a	*p*-HOPh	*o*-CH_3OPh	H	C_2H_5	C_2H_5	C_2H_5	84	81
4b	*p*-HOPh	H	Ph	C_2H_5	C_2H_5	C_2H_5	234	49
4c	*p*-HOPh	H	Ph	C_2H_5	C_2H_5	H	206	86
4d	*p*-HOPh	*o*-CH_3OPh	H	C_2H_5	C_2H_5	H	75	89
4e	Ph	H	Ph	$CH_2C_6H_5$	H	H	105	80
4f	*p*-HOPh	*o*-CH_3OPh	H	$CH_2C_6H_5$	H	H	63	88

Table 3

Spectra and Analysis of 2-Amino-4-oxo-1,2,3,4-tetrahydropyrimidines

Compound	ir, ν (cm^{-1})			Molecular Formula	Analysis (%) Calcd./Found		
	C=O	C=C	ClO_4		C	H	N
4a	1745	1660	1100	$C_{25}H_{34}N_3ClO_7$	57.65	5.99	6.93
		1595			(57.36)	(6.50)	(6.69)
4b	1720	1625	1100	$C_{24}H_{32}N_3ClO_6$	58.40	6.69	6.73
		1580			(58.41)	(6.49)	(7.09)
4c	1715	1640	1120	$C_{22}H_{28}N_3ClO_6$	57.02	6.37	7.52
		1570			(56.77)	(6.02)	(7.52)
4d	1740	1660	1100	$C_{23}H_{30}N_3ClO_7$	55.80	5.82	7.04
		1600			(55.75)	(6.06)	(7.07)
4e	1720	1620	1120	$C_{25}H_{26}N_3ClO_5$	62.28	5.67	7.50
		1580			(62.11)	(5.38)	(7.24)
4f	1740	1660	1100	$C_{26}H_{28}N_3ClO_7$	58.50	5.28	6.74
		1610			(58.92)	(5.29)	(6.70)

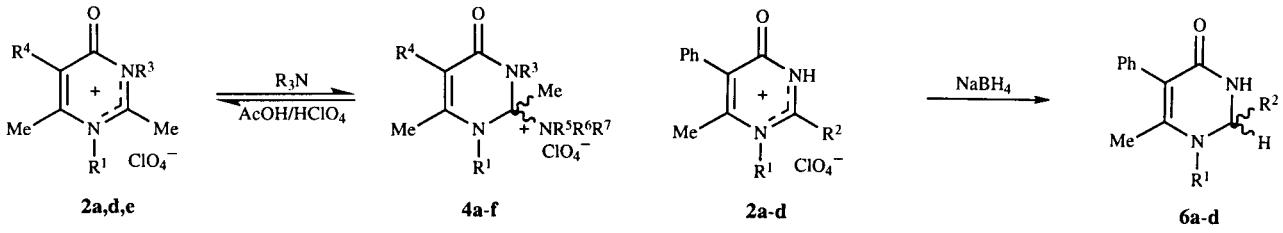
Table 4

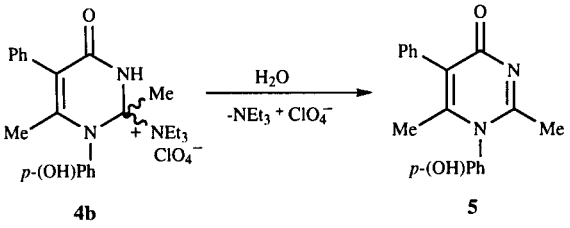
^{1}H NMR Spectra of the Adducts with Amines (CF_3COOH)

Compound	δ ppm
4a	0.9 (t, J = 7 Hz, 9H, CH_2CH_3), 1.85 (s, 3H, 2-CH_3), 2.0 (s, 3H, 6-CH_3), 2.46 (q, J = 7 Hz, 6H, CH_2CH_3), 3.5 (s, 3H, OCH_3), 6.60-7.25 (m, 8H, phenyl)
4b	0.95 (t, J = 7 Hz, 9H, CH_2CH_3), 1.63 (s, 3H, 2-CH_3), 2.22 (s, 3H, 6-CH_3), 2.90 (q, J = 7 Hz, 6H, CH_2CH_3), 6.75-7.12 (m, 8H, phenyl)
4c	1.01 (t, J = 7.1 Hz, 6H, CH_2CH_3), 1.67 (s, 3H, 6-CH_3), 2.30 (s, 3H, 2-CH_3), 2.90 (q, J = 7.1 Hz, 6H, CH_2CH_3), 6.65-7.05 (m, 9H, phenyl)
4d	0.85 (t, J = 7.1 Hz, 6H, CH_2CH_3), 1.55 (s, 3H, 2-CH_3), 2.25 (s, 3H, 6-CH_3), 2.85 (q, J = 7.1 Hz, 4H, CH_2CH_3), 3.4 (s, 3H, OCH_3), 6.70-7.15 (m, 8H, phenyl)
4e	1.61 (s, 3H, 2-CH_3), 2.20 (s, 3H, 6-CH_3), 3.95 (AB-q, 2H, CH_2PH), 6.85-7.37 (m, 15H, phenyl)
4f [a]	1.97 (s, 3H, 2-CH_3), 2.09 (s, 3H, 6-CH_3), 3.77 (s, 2H, CH_2Ph), 3.82 (s, 3H, OCH_3), 4.95 (s, 1H, 5-H), 6.75-7.7 (m, 13H, phenyl)

[a] Deuterioacetone.

Compound **2a** did not react with alcohols, even under boiling conditions. Corresponding non-cationic 4-pyrimidones were obtained by treatment with hydroxyl ions; the intermediate hydroxyl adduct however could not be isolated.





perchlorates on treatment with acetic acid. As illustrated with **4b** the amine adducts decomposed in water into the 4-pyrimidone **5**.

Reduction of the $C(2)=N(3)$ double bond was performed by reaction with sodium borohydride in acetonitrile. The use of the hydride ion as attacking nucleophile on C(2) of **2a-d** resulted in 4-oxo-1,2,3,4-tetrahydropyrimidines **6a-d** (Tables 5-7).

Table 5
1,2,3,4-Tetrahydro-4-oxopyrimidines

Compound	R	R^1	R^2	R^3	R^4	Mp °C	Yield %
6a	H	CH_3	CH_3	H	Ph	----	87
6b	H	Bn	CH_3	H	Ph	205	60
6c	H	Ph	CH_3	H	Ph	195	99
6d	H	*p*-CH_3OPh	C_2H_5	H	Ph	83	34
8a	CH_3	Ph	CH_3	H	Ph	236	53
8b	CH_3	*p*-OHPh	CH_3	*o*-CH_3OPh	H	208	55
8c	Bn	Ph	CH_3	H	Ph	167	40
8d	C_2H_5	*p*-CH_3OPh	CH_3	H	Ph	150	32
8e	CH_3	Bn	CH_3	H	*p*-*F*Ph	160	39

Table 6
Spectra and Analysis of the 2-Alkyl-4-oxo-1,2,3,4-tetrahydropyrimidines

Compound	ir, ν (cm^{-1})			Molecular Formula	Analysis (%) Calcd./Found	
	NHv.	C=O	C=C		C	H
6a	3150	1630	1580	$C_{13}H_{16}N_2O$	71.58 (72.22)	7.55 (7.40)
6b	3160	1635	1605 1560	$C_{19}H_{20}N_2O$	78.20 (78.08)	6.61 (6.85)
6c	3160	1655	1595 1575	$C_{18}H_{18}N_2O$	77.61 (77.69)	6.06 (6.47)
6d	3160	1640	1605 1580	$C_{20}H_{22}N_2O_2$	73.35 (74.53)	6.74 (6.83)
8a [a]	3190	1642	1585 1575	$C_{19}H_{20}N_2O$	78.20 (78.08)	6.90 (6.85)
8b [b]	3110	1616	1580	$C_{20}H_{22}N_2O_3$	71.06 (71.01)	6.48 (6.85)
8c [c]	3035	1655	1599 1580	$C_{25}H_{24}N_2O$	81.98 (81.52)	6.95 (6.52)
8d	3100	1630	1585 1565	$C_{21}H_{24}N_2O_2$	75.34 (75.00)	7.13 (7.14)
8e [d]		1620	1595	$C_{20}H_{21}N_2FO$	74.12 (74.05)	8.55 (8.64)

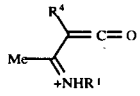
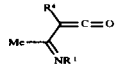
[a] ms: (EI) m/z 292 (23), 277 (24), 236 (40), 235 (57), 118 (100), 77 (44). [b] ms: (EI) m/z 338 (81), 323 (15), 175 (27), 148 (55), 134 (28), 77 (18). [c] ms: (EI) m/z 277 (100), 236 (15), 118 (41), 91 (38), 77 (35). [d] ms: (EI) m/z 324 (27), 309 (10), 268 (55), 91 (100).

Table 7

^{1}H NMR Spectra of the 2-Alkyl-4-oxo-1,2,3,4-tetrahydropyrimidines ($CDCl_3$)

Compound	δ ppm
6a	1.27 (d, J = 6.1 Hz, 3H, 2-CH_3), 1.70 (s, 3H, 6-CH_3), 2.80 (s, 3H, N-CH_3), 4.52 (q, J = 2.4 Hz, 1H, CH), 6.82 (d, 1H, J = 3 Hz, NH), 7.11 (s, 5H, phenyl)
6b	1.37 (d, J = 6 Hz, 3H, 2-CH_3), 1.77 (s, 3H, 6-CH_3), 4.67 (q, J = 2.4 Hz, 1H, CH), 5.11 (AB-q, J = 5.4 Hz, 2H, CH_2Ph), 6.75 (d, J = 3 Hz, 1H), 6.91-7.48 (m, 10H, phenyl)
6c	1.45 (d, J = 6.1 Hz, 3H, 2-CH_3), 1.6 (s, 3H, 6-CH_3), 5.03 (m, 1H, CH), 6.80-7.55 (m, 10H, phenyl)
6d	0.87 (t, J = 6.2 Hz, 3H, 2-CH_2CH_3), 1.53 (s, 3H, 6-CH_3), 1.76 (q, J = 6.2 Hz, 2-CH_2CH_3), 3.68 (s, 3H, OCH_3), 4.53 (t, 1H, CH), 6.76 (d, J = 3 Hz, 1H), 6.87 (AB-q, J = 8 Hz, 4H, *p*-phenyl), 7.18 (s, 5H, phenyl)
8a	1.46 (s, 6H, 2,2-diCH_3), 1.52 (s, 3H, 6-CH_3), 6.07 (s, 1H, NH), 7.17-7.38 (m, 10H, phenyl)
8b	1.32 (s, 3H, 2-CH_3), 1.67 (s, 3H, 2-CH_3), 1.87 (s, 3H, 6-CH_3), 4.0 (s, 3H, OCH_3), 5.23 (s, 1H, 5-CH), 7.32 (m, 8H, phenyl)
8c	1.11 (s, 3H, 2-CH_3), 1.61 (s, 3H, 6-CH_3), 3.37 (s, 2H, CH_2Ph), 6.08 (s, 1H, NH), 7.19-7.41 (m, 15H, phenyl)
8d	1.06 (t, J = 8 Hz, 3H, 2-CH_2-CH_3), 1.13 (s, 3H, 2-CH_3), 1.61 (s, 3H, 6-CH_3), 2.20 (q, J = 8 Hz, 2H, 2-CH_2CH_3), 3.72 (s, 3H, OCH_3), 6.82-7.30 (m, 9H, phenyl)
8e	1.50 (s, 6H, 2,2-diCH_3), 1.79 (s, 3H, 6-CH_3), 4.53 (s, 2H, CH_2Ph), 6.98 (t, J = 8.6 Hz, 2H, FCCH), 7.17-7.36 (m, 7H, phenyl)

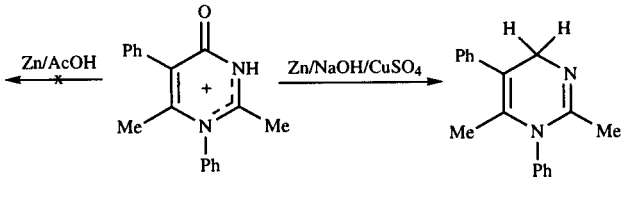
Table 8

Compound	MS method	$[M]^+$ or $[M+H]^+$	$[M\text{-}Me]^+$ or $[M\text{-}CH_2Ph]^+$	 (RDA)	 (RDA)	$MeC{\equiv}\overset{+}{N}R$	$[R^1]^+$
8a	EI	292 (23)	277 (24)	236 (41)	235 (57)	118 (100)	77 (45)
	FAB	293 (37)	----	236 (23)	----	----	----
	ms/ms	293 (100)	----	236 (80)	----	----	----
8c	EI	----	277 (100)	236 (16)	235 (12)	118 (40)	91 (38) [b]
	FAB	369 (62)	277 (100)	236 (82)	----	118 (32)	91 (17) [b]
	ms/ms	369 (100)	----	236 (100)	----	----	----
8e	EI	324 (25)	309 (10)	268 (55)	267 (21)	132 (10)	91 (100) [b]
	FAB	325 (41)/327 (28)	309 (10)	268 (100)	----	----	91 (100) [b]
	ms/ms	325 (100)	----	268 (100)	----	----	----
2a	ms/ms	277 (100) [a]	277 (100)	236 (56)	----	118 (100)	----

[a] Molecular cation. [b] Most likely corresponding to tropylium ions.

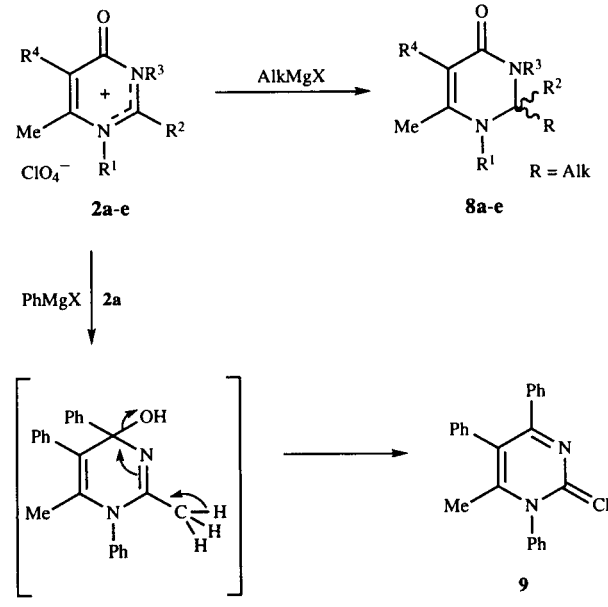
4-Oxopyridinium perchlorates **2** are also susceptible to reduction with other reducing agents. The carbonyl group of **2a** can be reduced in alkaline medium by treatment with zinc and a catalytic amount of copper sulphate [5]. In this case however 1,4-dihydropyrimidine **7** was obtained.

Using zinc in acetic acid no reaction occurred.



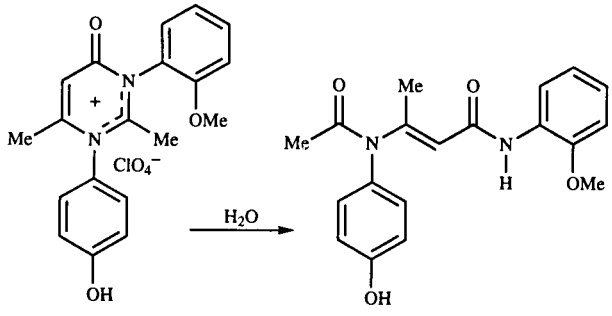
2a **7**

Finally we used Grignard reagents as nucleophiles. Alkyl Grignard reagents in ether solution reacted as *C*-nucleophiles at the 2-position of 4-oxopyrimidinium cations **2a-e** giving rise to 2,2-dialkyl-1,2,3,4-tetrahydro-4-oxopyrimidines **8a-e** (Tables 5-7). With aryl Grignard



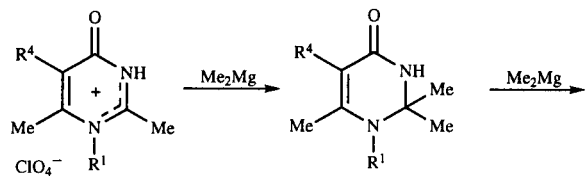
reagents we could not isolate type **8** compounds. We isolated from the reaction mixture 2-methenyl-1,2-dihydropyrimidine **9**. This compound resulted from an addition of the Grignard reagent at *C*(4) with formation of 4-aryl-4-hydroxy-1,4-dihydropyrimidines (not isolated) and subsequent dehydration into **9**.

In the case where the 4-oxopyrimidinium cation is N^3-aryl substituted, the Grignard reaction was accomplished smoothly with alkylmagnesium bromides. However no addition was observed with an aryl Grignard. We isolated *N*-acyl-β-crotonamide **10**, resulting from a reaction of the cation with the ammonium chloride solution, added at the end of the reaction.

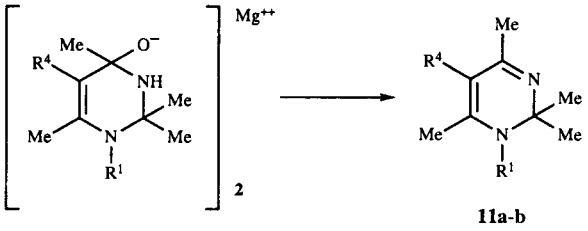


2 **10**

In an apolar, non-Lewis base, solvent such as benzene, we found that the initial attack on *C*(2) was followed by a second reaction on *C*(4) giving rise to 1,2-dihydropyrimidines **11a-b**. This behavior can probably be explained by an altered Grignard structure in benzene solution (Schenk equilibrium) [6].



2a, 2f



11a-b

The Grignard reaction performed on the non-cationic counterparts gave rise to the same compounds but the compounds obtained were more difficult to purify.

Spectral Data of 4-Oxo-1,2,3,4-tetrahydropyrimidines.

The ir, ^{1}H nmr and mass spectral data are summarized in Tables 1,3,4,6-8.

The mass spectral behavior of some 4-oxo-1,2,3,4-tetrahydropyrimidines of the **8** series was studied in more detail in order to evaluate whether informative structure fragmentation could be found. The mass spectral data are summarized in Table 8. Because EI did not always yield $M^{+\bullet}$ ions due to the thermolabile character of the compound, FAB spectra were also examined. In order to obtain structural information, product ion spectra of FAB generated $(M+H)^+$ ions were recorded using low-energy collisional activation.

Table 9
Total Energies, Charges and Coefficients (C_{ip}) (square) of the LUMO on *C*(2) and *C*(4) of 2,6-Dimethyl-4-oxo-1,5-diphenylpyrimidinium Perchlorate (**2a**)

	Method		
	AM1	MINDO3	MINDO
Energy (eV)	-3262.20614	-3219.28428	-3266.75843
Charge *N*(1)	-0.0404	0.0560	-0.0911
Charge *C*(2)	0.2315	0.2516	0.2967
Charge *N*(3)	-0.2481	-0.1134	-0.2572
Charge *C*(4)	0.3121	0.5935	0.3416
Charge *C*(5)	-0.0455	-0.0746	-0.0140
Charge *C*(6)	0.0094	0.0577	0.0099
HOMO energy (eV)	-12.037	-11.511	-12.069
LUMO energy (eV)	-4.943	-4.094	-5.163
Coefficients of LUMO *C*(2)			
S	0.00758	0.02368	0.00416
Px	0.00473	0.00098	0.00597
Py	0.01371	0.00893	0.01452
Pz	0.36784	0.22543	0.39488
Coefficients of LUMO *C*(4)			
S	0.00286	0.00573	0.00172
Px	0.00080	0.00314	0.00072
Py	0.00298	0.00058	0.00286
Pz	0.00042	0.01102	0.00012

The EI was found to result in $(M\text{-}CH_3)^+$ ions and abundant fragment ions which can be explained by retro Diels Alder type reactions. The EI fragmentation of compounds **8a**, **c**, **e** is summarized below.

Upon FAB $(M+H)^+$ ions are formed as well as ions at m/z 236 (**8a**,**8c**) or m/z 268 (**8c**), which can be explained by protonation at N(1) and retro Diels Alder fragmentation. The low-energy product ion spectra obtained for the $(M+H)^+$ ions indicate that this retro Diels Alder is a very favorable fragmentation route.

For compound **8c** it is worth noting that FAB results in fragment ions at m/z 277 and m/z 118, of which the ions at m/p 277 correspond to the molecular cations of **2a**. These results indicate that $(M+H)^+$ ions of **8c** fragment by loss of methylbenzene, resulting in a stable cation in which the positive change is delocalized as in the molecular cation of **2a**. The product ion spectrum obtained on the molecular cations of **2a** (m/z 277) reveals that the ions at m/z 236 and m/z 118 can be formed directly from these precursor ions.

Discussion.

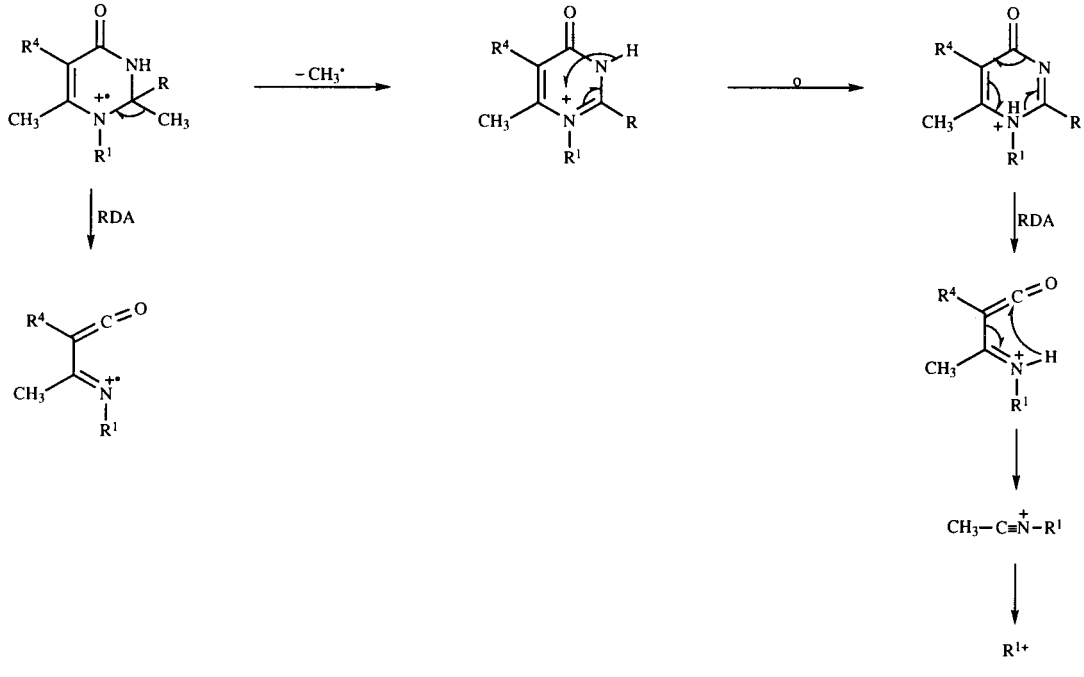
To understand the course of the above reported reactions, we found it useful to consider some theoretical aspects of the chemical properties of 4-oxopyrimidinium cations. The pyrimidinium cations contain two nitrogen atoms, each providing one pair of electrons to the ring. Other examples of heterocycles with two pyrrole *NH*-like nitrogens are 1,4-dihydro-1,4-diazocine and pyrrolo[2,1-*b*]imidazole [7,8].

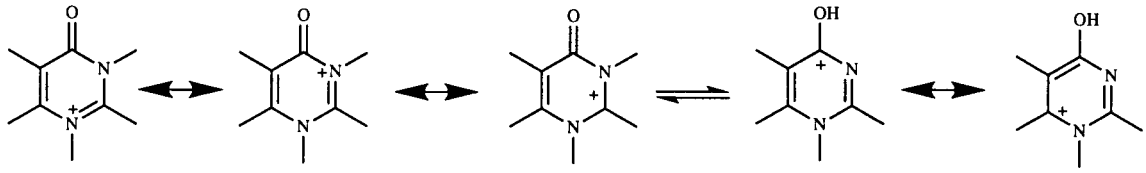
To determine the charge and coefficients of LUMO, we performed semiempirical calculations (MOPAC 93.00; AM1, MINDO3 and MNDO) on 2,6-dimethyl-4-oxo-1,5-diphenylpyrimidinium perchlorate **2a**. Total energies, charges and coefficients of the LUMO on *C*(2) and *C*(4), are given in Table 9. The three methods used (AM1, MINDO3 and MNDO) gave comparable results.

Molecular mechanical geometry optimization was performed with MM+. The heterocyclic nucleus of 2,6-dimethyl-4-oxo-1,5-diphenylpyrimidinium cation turned out not to be coplanar with the aromatic parts. All heterocyclic atoms are in a single plane. The dihedral angles around *C*(2) are slightly sp^2-hybridized.

Correlation of reactivity with charge distribution. The charge distribution was obtained from this ground state. It is obvious from Table 9 that the positive charge is not localized at the heteroatom, but that delocalization to *C*(4), *C*(2) and *C*(6) takes place. The decrease of the positive charge on the heteroatom indicates a more important contribution from the carbonium structures, compared with the Kekulé structures.

Correlation of reactivity with C_{ip}. Predictions based upon the calculated atomic charges gave however opposite results, compared with our own experiments. Indeed, in the pyrimidinium cation **2a**, the most positive atomic charge is found on *C*(4) followed by *C*(2) and finally *C*(6). This is totally inconsistent with our experimental data where *C*(2) has been found to be the most attractive site for a nucleophilic attack. The reactivity at *C*(2) can however be explained when we take into account the





Kekulé structures Carbonium structures

coefficients of the atomic orbitals C_{ip}. The square of the coefficients C_{ip} show the probability of the presence of an electron on the corresponding orbital.

From Table 9, it is clear that the coefficient C_{ip} (square) of LUMO $C(2)$ P_z is by far the most "empty" place for attack by a nucleophile compared with $C(4)$. This is in full agreement with our experimental results and shows that charges are not relevant for reactions with nucleophiles.

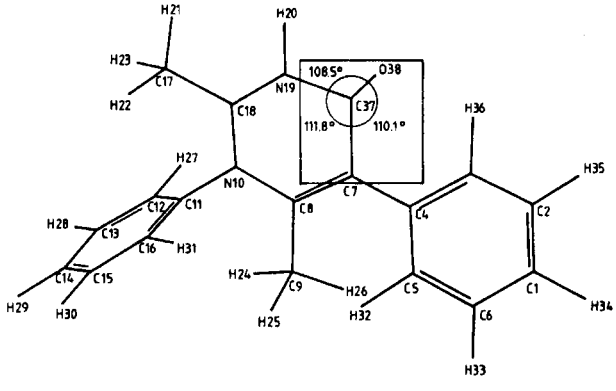
Correlation of reactivity with molecular electrostatic potential. The electrostatic potential $V(r)$ created around a molecule by its nuclei and electrons is indeed an interesting property for the determination of the molecular reactive behavior [9,10].

This electrostatic potential is only one of the contributions of the energy involved in an interaction between two molecules. Nevertheless, it has been useful as an indicator of the most negative sites a molecule to which an approaching electrophile is initially attracted. The electrostatic potential has been used to a limited extent for analyzing nucleophilic processes because positive potentials are not necessarily indicative of affinity for nucleophiles. The positive charges of atomic nuclei create indeed strongly positive potentials [11] and disturb the negative contributions of the dispersed electrons.

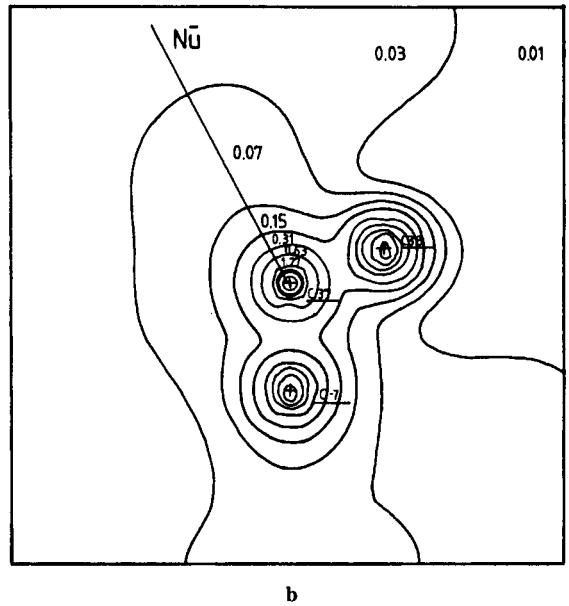
P. Politzer *et al.* [12] have developed a procedure where electrostatic potentials could be applied successfully to nucleophilic reactions. This is indeed possible if the potential is calculated for the molecule in a state of distorted geometry, in which the approach of the nucleophile is prepared. Comparison with the potential in the non-distorted geometry might indicate the apperance of sites favorable to nucleophilic attack.

In order to test whether electrostatic potential considerations will permit a correct choice between the two possible sites of nucleophilic attack in 4-oxopyrimidinium cation on $C(4)$ and $C(2)$, we have computed the potential around each of the carbons, first in their equilibrium undistorted states and then after the same degree of distortion (Figure 1a and 2a).

This distortion moves in each case the attached oxygen or $C(2)$-methyl out of the molecular plane until all bond angles around the carbon were tetrahedral. The vicinity of the fourth tetrahedral direction is then the region of inter-

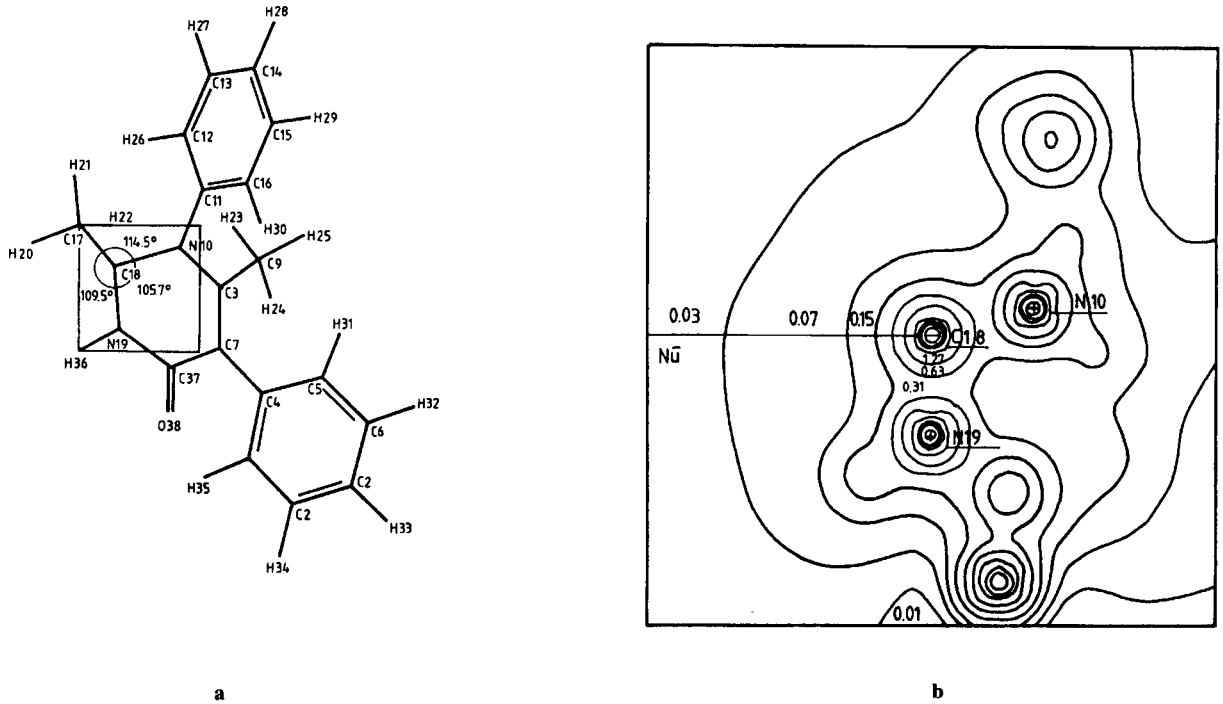


a



b

Figure 1. Structure and electrostatic potential of 2,6-dimethyl-4-oxo-1,5-diphenylpyrimidinium cation **2a**, distorted at $C(4)$ (The computer drawing shows $C(4)$ as $C37$).



a b

Figure 2. Structure and electrostatic potential of 2,6-dimethyl-4-oxo-1,5-diphenylpyrimidinium cation **2a**, distorted at *C*(2) (The computer drawing shows *C*(2) as *C*18).

est, since it is the likely channel of approach for a nucleophile.

The electrostatic potentials of the undistorted carbons do not suggest a preference for nucleophilic attack at the carbonyle site.

The potential of the distorted carbonyl carbon, *C*(4), shows clearly a positive channel in the fourth tetrahedral direction (Figure 1b), defining an attractive path of approach for a nucleophile.

Distortion of *C*(2), on the other hand, produces a competitive positive pathway to this carbon (Figure 2b). In the latter case the positive pathway is however larger than for distortion at *C*(4). Thus the proposed procedure correctly predicts that *C*(2) is the most probable site for a nucleophilic attack on the 4-oxopyrimidinium cation.

The electrostatic potential used in this work were calculated by using electronic density functions obtained from ab initio with self-consistent-field calculations using a 6-31G* basis set [13,14].

For the *C*(4) distorted structure (the oxygen atom is behind the molecular plane), depicted in Figure 1a, we have evaluated the potential in the same molecular plane, passing through the *O*-*C*(4)*C*(5) atoms (Figure 1b, the conversion factor 1 a.u. = 627.46 Kcal/mol). For the *C*(2) distorted structure (the 2-methyl group is behind the molecular plane), depicted in Figure 2a, we have evaluated the potential in the equivalent molecular plane passing through the *N*(1)-*C*(2)-*N*(3) atoms (Figure 2b).

We can conclude that charges are not relevant for reactions of 4-oxopyrimidinium cations with nucleophiles. The square of the expansion coefficients and electrostatic potential are in full agreement with our experimental results.

EXPERIMENTAL

The ^{1}H nmr spectra were recorded at room temperature on a Bruker AM 360 MHz spectrometer or a Varian EM360 A 60 MHz spectrometer with tetramethylsilane as an internal standard. Spectral data are reported in parts per millions (δ) relative to TMS.

The ir spectra were recorded in suspension with Nujol or in potassium bromide discs on an Acculab 4 spectrometer respectively. Spectral data are reported in cm^{-1} (ν).

The FAB spectra and the electron impact (EI) mass spectral analyses were performed on a VG 70-SEQ hybrid mass spectrometer of EBqQ configuration. Mass spectra were recorded under control of the VG 11-250J data system by repetitive scanning of MS-1 over the m/z 20-500 mass range, using a scan time of 2s decade^{-1}. The FAB spectra were obtained using *m*-nitrobenzyl alcohol as a liquid matrix. Product ion spectra of $(M+H)^+$ ions were obtained by selecting the ions using the EB part of the instrument, applying low-energy (50 eV) collisional activation with argon in the quadrupole gas cell at a pressure of 5.10^{-6} mbar and subsequent mass analysis using the quadrupole mass analyzer.

Melting points were determined with an Electrothermal digital apparatus or a capillary melting point apparatus.

2-Methoxy-2,6-dimethyl-4-oxo-1,5-diphenyl-1,2,3,4-tetrahydropyrimidine (**3a**).

To a solution of sodium (0.018 g, 0.8 mmole) in methanol (2 ml) was added 4-oxopyrimidinium perchlorate (**2a**) (0.3 g, 0.8 mmole) and the mixture was stirred for 30 minutes at room temperature. The mixture was diluted with water and cooled. The precipitate was filtered and crystallized from ethanol (Table 1).

Compound **3b** was prepared in the same way using *tert*-butyl alcohol (Table 1).

2-(*p*-Methoxyphenyl)-2,6-dimethyl-4-oxo-1,5-diphenyl-1,2,3,4-tetrahydropyrimidine (**3d**).

To a solution of *p*-methoxyphenol (0.08 g, 0.8 mmole) in acetone (2 ml) was added sodium (0.018 g, 0.8 mmole) and 4-oxopyrimidinium perchlorate **2a** (0.3 g, 0.8 mmole). The mixture was stirred at room temperature for 1 hour and was diluted with water and cooled. The solid was collected and recrystallized from ethylacetate (Table 1).

Compound **3c** was prepared in the same way using phenol (Table 1).

N,N-Diethyl-*N*-[2,6-dimethyl-4-oxo-1-(*p*-hydroxyphenyl)-5-phenyl-1,2,3,4-tetrahydropyrimidinyl]-2-ammonium Perchlorate (**4a**).

To a suspension of 4-oxopyrimidinium perchlorate (**2a**) (0.38 g, 1 mmole) in benzene (5 ml) was added diethylamine (0.1 ml, 1 mmole). The mixture was stirred for 5 minutes and the product was filtered off and washed with dry ether (Tables 2-4).

Compounds **4b-e** were prepared in the same way (Tables 2-4).

N-Benzyl-*N*-[2,6-dimethyl-1,5-diphenyl-4-oxo-1,2,3,4-tetrahydropyrimidinyl]-2-ammonium Perchlorate (**4f**).

To a suspension of 4-oxopyrimidinium perchlorate (**2d**) (0.3 g, 0.8 mmole) in hexane (3 ml) was added benzylamine (0.09 ml, 0.8 mmole). The mixture was stirred for about 5 minutes, filtered and the precipitate was washed with dry ether (Tables 2-4).

General Procedure for Reduction of **2** with Sodium Borohydride for **6a-d**.

To a stirred suspension of sodium borohydride (0.16 g, 4.3 mmoles) in dried acetonitrile (5 ml) was added slowly pyrimidinium perchlorate **2** (2.5 mmoles). The mixture was stirred for 12 hours at room temperature and diluted with water (38 ml). The precipitate was filtered and recrystallized from ethanol (Tables 5-7).

2,6-Dimethyl-1,5-diphenyl-1,4-dihydropyrimidine (**7**).

To a stirred mixture of pyrimidine **2a** (0.54 g, 2 mmoles) and sodium hydroxide (10 ml, 10%) were added zinc powder (0.97 g, 15 mmoles) and a catalytic amount of copper sulfate. The mixture was heated to start the reaction, indicated by liberation of hydrogen, and stirred for 30 minutes. After cooling, water was added and the precipitate was collected, washed with water and recrystallized from 2-propanol, yield 30%; ir (potassium bromide): ν 1615, 1585, 1540 (C=C and C=N); ^{1}H nmr (deuteriochloroform): δ 1.71 (s, 3H, 6-CH_3), 2.1 (s, 3H, 2-CH_3), 4.76 (s, 2H, CH_2), 7.28 (s, 5H, phenyl), 7.52 (s, 5H, *N*-phenyl).

Anal. Calcd. for $C_{18}H_{18}N_2$: C, 82.44; H, 6.87; N, 10.68. Found: C, 82.26; H, 5.79; N, 10.14.

2-Alkyl-2,6-dimethyl-4-oxo-1,5-diphenyl-1,2,3,4-tetrahydropyrimidine (**8**).

General Procedure.

To a stirred mixture of magnesium turnings (1.47 g, 0.06 mole) in sodium-dried ether (50 ml) were added a crystal of iodine and a solution of methyl iodide (3.72 g, 0.06 mole) in dry ether (60 ml). The mixture was stirred for 1 hour and 4-oxopyrimidinium perchlorate **2a** (0.06 mole) was added. The mixture was stirred at room temperature for 1.5 hours and was neutralized with 10% ammonium chloride solution (150 ml). The organic layer was separated, washed with water and evaporated *in vacuo*. The residue was filtered and recrystallized from benzene (Tables 5-7).

2-Methenyl-6-methyl-1,4,5-triphenyl-1,2-dihydropyrimidine (**9**).

This compound was obtained in the same way (yield 12%), mp 175°; ir (potassium bromide): ν 1625, 1586, 1490; ^{1}H nmr (deuteriochloroform): δ 1.74 (3H, s, 6-CH_3); 7.11-7.59 (m, 17H, phenyl and C=CH_2); ms: (EI) m/z 336 (15) (M^+), 335 (26), 275 (100), 160 (22), 118 (96).

[*N*-Acetyl-*N*-(*p*-hydroxyphenyl)amino]croton(*o*-methoxy)anilide (**10**).

To a stirred mixture of magnesium turnings (0.23 g, 9.6 mmoles) in sodium dried ether (10 ml) were added a crystal of iodine and a solution of bromobenzene (1.0 ml, 9.6 mmoles) in dry ether (8 ml). The mixture was stirred at ambient temperature for 1 hour and **2e** (1 g, 2.4 mmoles) was added. The mixture was heated until boiling and stirred for 1.5 hours. After neutralization with 10% solution of ammonium chloride (23.5 ml), the organic layer was separated. The precipitate was filtered off and recrystallized from toluene, yield 0.7 g (86%), mp 89°; ir (nujol): ν 3315 (OH), 3120 (NH), 1680 ($COCH_3$), 1645 (C=O), 1635, 1600 and 1550 (C=C and C=N); ^{1}H nmr (DMSO-d_6): δ 2.07 and 2.15 (s, 3H, 2-CH_3 and $COCH_3$), 4.07 (s, 3H, OCH_3), 6.50 (1H, s, 5-C*H*), 6.97-8.25 (m, 9H, phenyl); ms: (EI) (m/z) 340 (M^+).

Anal. Calcd. for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.88. Found: C, 67.50; H, 6.21.

2,2,4,6-Tetramethyl-1,5-diphenyl-1,2-dihydropyrimidine (**11a**).

To a stirred mixture of magnesium turnings (0.19 g, 8 mmoles) in sodium dried ether (15 ml) were added a crystal of iodine and a solution of methyl iodide (0.49 ml, 8 mmoles) in dry ether (15 ml). The mixture was refluxed for 1 hour. Benzene (10 ml) was added, ether was evaporated under reduced pressure and **2a** (0.77 g, 2 mmoles) was added. The resulting mixture was refluxed for 30 minutes with stirring. After neutralization with a 10% solution of ammonium chloride (20 ml), the product was extracted with benzene (4 x 10 ml). The combined extracts were dried (sodium sulfate) and evaporated to afford pale-yellow crystals, yield 25% (0.15 g), mp 123-125°; ir (potassium bromide): ν 1615, 1575, 1525; ^{1}H nmr (deuteriochloroform): δ 1.22 (s, 6H, 2,2'-di-CH_3), 1.73 (s, 3H, 6-CH_3), 2.12 (s, 3H, 4-CH_3), 7.07-7.62 (m, 10H, phenyl).

2,2,4,6-Tetramethyl-5-(*p*-fluorophenyl)-1-(*p*-hydroxyphenyl)-1,2-dihydropyrimidine (**11b**).

This compound was prepared in the same way with a yield 36%, mp 189° dec; ir (potassium bromide): ν 1623, 1595, 1515; ^{1}H nmr (deuterioacetone): δ 1.52 (s, 3H, 2-CH_3), 1.57 (s, 3H, 2-CH_3), 1.81 (s, 3H, 4-CH_3), 2.12 (s, 3H, 6-CH_3), 7.01-7.41 (m, 8H, phenyl); ms: (FB$^+$) m/z 325 $[M+H]^{+\bullet}$ (100), 216 (35), 134 (100).

REFERENCES AND NOTES

[1] J. Barluenga, F. J. Gonzalez, V. Gotor and S. Fustero, *J. Chem. Soc., Perkin Trans. 1*, 1739 (1988).

[2] J. P. Konopelski, K. S. Cho and G. R. Negrete, *J. Org. Chem.*, **56**, 1355 (1991).

[3] I. Vedernikova, Yu. I. Ryabukhin, M I. Haitin and Yu. N. Simkina, *Bull. Soc. Chim. Belg.*, **6**, 487 (1991).

[4] G. N. Dorofeenko, Yu. I. Riabukhin and V. D. Karpenko, *Khim. Geterotsikl. Soed.*, **5**, 704 (1977).

[5] Advanced Organic Chemistry, Reactions, Mechanisms and Structure, J. March, ed, John Wiley and Sons, 1992, p 1233.

[6] Advanced Organic Chemistry, Reactions, Mechanisms and Structure, J. March, ed, John Wiley and Sons, 1992, p 183-4.

[7] H.-J. Altenbach, H. Stegelmeier, M. Wilhelm, B. Voss, J. Lex and E. Vogel, *Angew. Chem.*, **91**, **S**, 1023 (1979).

[8] M. Breuninger, B. Gallenkamp, K.-H. Muller, H. Fritz, H. Prinzbach, J. Daly and P. Schonholzer, *Angew. Chem.*, **91**, **S**, 1030 (1979).

[9] P. Politzer, P. R. Laurence and K. Jayasuriya, *Environmental Health Perspectives*, **61**, 191 (1985).

[10] E. Scrocco and J. Tomasi, *Adv. Quantum. Chem.*, **11**, 115 (1978).

[11] P. Politzer and R. G. Parr, *J. Chem. Phys.*, **61**, 4258 (1974).

[12] P. Politzer, S. J. Landry and T. Warnhelm, *J. Phys. Chem.*, **86**, 4767 (1982).

[13] R. Ditchfield, W. J. Hehre, J. A. Pople, *J. Chem. Phys.*, **54**, 724 (1971).

[14] W. J. Hehre, R. Ditchfield and J. A. Pople, *J. Chem. Phys.*, **56** 2257 (1972).