THE DIFFERENTIAL REACTIVITY OF 5- AND 3-METHYL GROUPS IN THE REACTION OF 4-SUBSTITUTED 2,3,5-TRIMETHYLISOXAZOLIUM SALTS WITH AROMATIC ALDEHYDES.

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Abstract – 2,3,5-Trimethylisoxazolium salts with electron-withdrawing groups at C-4 react with aromatic aldehydes to give 3- and/or 5-arylidene derivatives resulting from the condensation at CH_3-3 and/or CH_3-5. The differential reactivity of 3- and 5-methyl groups is markedly influenced by the nature of the substituent at C-4 and varies in the same order as its kinetic acidity which was estimated from studies on deuteriodeprotonation. The influence of inductive, resonance and steric effects due to the 4-substituents on the course of the reaction is shown.

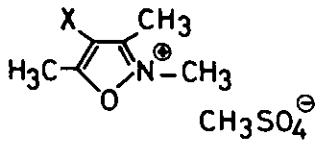
INTRODUCTION

3,5-Dimethylisoxazoles substituted in the 4-position by electron-withdrawing groups condense with aromatic aldehydes, in the presence of bases, exclusively at the methyl group in 5-position to give 5- arylidene derivatives[1]. The strength of the necessary base depends on the nature of the groups attached at C-4. In the case of 3,5-dimethyl-4-nitroisoxazole, derivatives at the 5-methyl group (never at 3-positio) have also been obtained not only with aromatic aldehydes but also with their anils, with N,N-diarylformamidines and p-nitrosodimethylaniline[1]. It also undergoes Michael-type reactions with benzalacetophenone and acridine[1].

5-Alkylisoxazolium salts are deprotonated even more readily than the corresponding isoxazoles and can undergo condensation reactions under the influence of comparatively weak bases. In these compounds, however, deprotonation of 3-alkyl and 5-alkyl compete and the ratio of the deprotonation depends on the nature of the base[1]. Furthermore, α-deprotonation of the N-alkyl and 3-alkyl groups of N-alkylisoxazolium salts takes place also competitively[1].

More recently we found[2] that 5-unsubstituted 3-alkylisoxazolium salts do not condense with aromatic aldehydes, in the presence of bases, but undergo ring cleavage leading to β-iminoesters *via* a ketene intermediate.

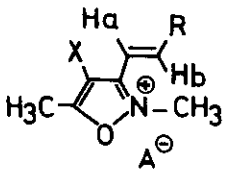
Taking this into consideration, the behavior of 2,3,5-trimethylisoxazolium salts with electron-withdrawing groups at C-4 toward oxo compounds is impossible to predict. In this paper, the differential reactivity of the methyl groups at C-3 and C-5 of some isoxazolium salts (Ia-e) is studied in function with the inductive, resonance and steric effect of the substituent at C-4.

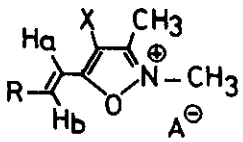


Ia, X=NO_2 Id, X= CN
Ib, X= Cl Ie, X= COC_6H_5
Ic, X= $COCH_3$

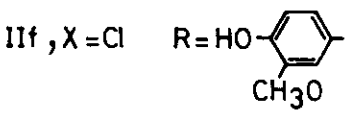
RESULTS AND DISCUSSION

4-Substituted 2,3,5-trimethylisoxazolium methosulfates (Ia-d) react with aromatic aldehydes in the presence of bases and lead to only one product of monocondensation (II or III) or to a mixture of monocondensated products (II and III) (table 1).

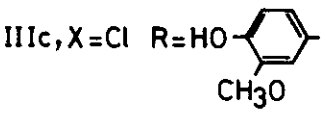


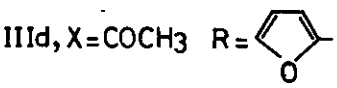


IIa, X=NO_2 R=C_6H_5
IIb, X=NO_2 R=$C_6H_5CH=CH$
IIc, X=NO_2 R=$p(CH_3)_2NC_6H_4$
IId, X= Cl R=C_6H_5
IIe, X= Cl R=$C_6H_5CH=CH$



IIIa, X= Cl R=C_6H_5
IIIb, X= Cl R=$C_6H_5CH=CH$





IIIe, X=$COCH_3$ R=$C_6H_5CH=CH$
IIIf, X=$COCH_3$ R=$p(CH_3)_2NC_6H_4$
IIIg, X= CN R=C_6H_5

IIa-c, $A^{\ominus} = SO_4^{\ominus}$
IId-f, IIIa-g, $A^{\ominus} = F_4B^{\ominus}$

Ia-d do not react with aliphatic aldehydes or ketones. 2,3,5-Trimethyl-4-benzoylisoxazolium (Ie) methosulfate or perchlorate was proven to be totally inactive toward oxo compounds in all possible conditions. Ia is also inactive toward p-nitrobenzaldehyde.

The nature of the arylidene derivatives obtained in each case, the utilized base and the conditions of the reactions are listed in table 1.

The high reactivity of the 2,3,5-trimethyl-4-nitroisoxazolium methosulfate (Ia) requires the use of ethanol as the base; pyridine and piperidine cause the cleavage of the ring and the polymerization of the resulting products. In the remaining cases pyridine has proven to be the most satisfactory base; secondary amines cause

Table 1

The reaction of 4-substituted 2,3,5-trimethylisoxazolium *methosulfates with aromatic aldehydes*

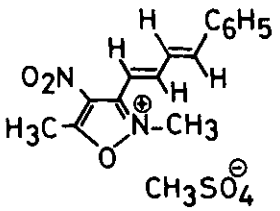
4-Subst.	R-CHO	Base	Time (min.)	Products[a] II(%)	III (%)
NO_2	C_6H_5CHO	C_2H_5OH	120	IIa (36)	-
NO_2	$C_6H_5CH=CHCHO$	C_2H_5OH	60	IIb (67)[b]	-
NO_2	$p(CH_3)_2NC_6H_4CHO$	C_2H_5OH	1	IIc (80)	-
Cl	C_6H_5CHO	C_5H_5N	180	IId (36)	IIIa (9)
Cl	$C_6H_5CH=CHCHO$	C_5H_5N	120	IIe (18)	IIIb (18)
Cl	Vanillin	C_5H_5N	120	IIf (10)	IIIc (5)
$COCH_3$	Furfural	C_5H_5N	60	-	IIId (85)
$COCH_3$	$C_6H_5CH=CHCHO$	C_5H_5N	120	-	IIIe (68)
$COCH_3$	$p(CH_3)_2NC_6H_4CHO$	C_5H_5N	180	-	IIIf (11)
CN	C_6H_5CHO	C_5H_5N	60	-	IIIg (42)

[a] IIa-c were isolated as sulfates; IId-f and IIIa-g were isolated as tetrafluoroborates.

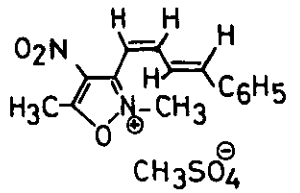
[b] Yield corresponding to the mixture of geometric isomers ZE-IIb and EE-IIb, isolated in the ratio 1:3 respectively.

the partial degradation of the ring and the final yields decrease notably. The behavior of Ie is remarkable because pyridine does not seem strong enough for the reaction to be effective whereas piperidine degrades the ring.

In the reaction of Ia with cinnamaldehyde, two geometric isomers (EZ-IIb and EE-IIb) in relative proportions 1:3 have been isolated. EZ-IIb spontaneously transform itself into EE-IIb. The conversion is complete after being subjected to room temperature for eigth months.



EE-IIb



ZE-IIb

Since the reactivity of Ia-e toward aromatic aldehydes in the presence of bases must depend on the ease with which the respective carbanions are generated in CH_3-3 or CH_3-5, the study of the hydrogen-deuterium exchange of Ia-d when treated with D_2O should shed some light on the relative reactivity of the methyl groups. Ia-d exchange regioselectively in the methyl groups at C-3 and/or C-5 depending on the nature of the group attached at C-4 (table 2). Reaction of these salts with aldehydes occurs only at the methyl group in which the hydrogen-deuterium exchange takes place. Deuteriodeprotonation reactions have been followed by ^{1}H-NMR spectroscopy in order to determine the influence of the substituent at C-4 upon the kinetic acidity of the 3- and 5-methyl groups. The expected signal for the N-CH_3 protons remains unchanged and no evidence for hydrogen exchange was found. However, the 3- and/or 5-methyl groups underwent exchange at rates which depend on the substituent at C-4. The variation of the intensities of the ^{1}H-NMR absorption bands associated with the 3- and 5-methyl groups, when time and temperature were held constant are shown in table 2.

Table 2

Hydrogen-deuterium exchange rates for 3- and 5-methyl groups of 4-substituted 2,3,5-trimethylisoxazolium salts[a]

4-Subst.	Time (min.)	t (ºC)	NMR signals final intensities (%)[b]		
			N-CH_3	CH_3-5	CH_3-3
NO_2	5[c]	20[c]	100	98	0
Cl	40	100	100	10	11
$COCH_3$	40	100	100	11	94
CN	40	100	100	3	90
COC_6H_5	40	100	100	98	100

[a] In D_2O. Basic catalized exchange sharply reduces the exposure to deuterium oxide.

[b] Referred to the initial intensities.

[c] The high reactivity of Ia does not permit exchange experiences to be carried in the same conditions as Ib-e.

The nature of the compounds obtained in the preceding reactions and the results of the experiments of hydrogen-deuterium exchange suggest that the influence of the electron-withdrawing substituents at C-4 upon the reactivity of the 3- and 5-methyl groups depens on the inductive, resonance and steric effects of these substituents. With regard to the influence that the resonance effects have on the reactivity of the 5-methyl group, the steric hindrance of the groups attached at C-4 is of consi-

derable importance. Thus, introduction of a bulky substituent at C-4 (nitro, benzoyl) can result in the non-planarity of the substituent and the isoxazole ring as well as the non-planarity of the members of the ring[3]. In the first case, the action of the substituent at C-4 upon the 5-methyl group decreases and can be negligible. In the second case, the activation of the 5-methyl group due to the positively charged nitrogen is also very small or non-existent.

The inductive effect of the nitro group, especially strong (the constants of Taft[4] are σ_I = 0.65, σ_R = 0.47) and the steric factors which were mentioned before ($-E_S$ = 2.52) determine the preferential increase of the reactivity of the 3-methyl group of Ia due to the sum of the factor σ_I plus the influence of the charged heterocyclic nucleus.

On the other hand, the moderate steric exigencies of the chlorine atom (σ_I = 0.46, σ_R = -0.23, $-E_S$ = 0.97) do not cause an appreciable distorsion of the ring and both methyl groups of Ib are activated by the positively charged nitrogen and the inductive effect of the chlorine atom.

The acetyl and cyano groups (σ_I = 0.28, σ_R = 0.47 and σ_I = 0.56, σ_R = 0.33, respectively), less bulky, increase the acidity of the 5-methyl group because their resonance effect -M is added to the one which originates in the ring[5]. The small hindrance of the cyano group ($-E_S$ = 0.51) derived from its lineal geometry should cause the acidity of the 5-methyl group of Id to be superior to the acidity of the same methyl group of Ic (table 2) in spite of their differences in the resonance constants.

The strong steric distorsion in Ie due to the hindrance of the benzoyl group can be the origin of the non-reactivity of this compound toward the studied bases. The lack of planarity between the benzoyl group and the ring in Ie can also be deduced from its IR carbonylic absorption (1687 cm^{-1}) which is higher than the expected for a diaryl ketone.

Ketones fail to react with Ia-d and do not seem to show enough electrophilic cha - racter. Nevertheless, the readily condensation of these salts with aromatic aldehydes (but not with the aliphatic ones) suggests that these reactions are subjected to thermodynamic control. Aromatic aldehydes with electron-withdrawing groups as p-nitrobenzaldehyde seem to unstabilize the positively charged heterocyclic nucleus and Ia does not condense with the mentioned aldehyde. The absence of dicondensed compounds in all the studied reactions (even when working with an excess of aldehyde) must be attributed to the decrease in the acidity of the remaining methyl group when an arylidene group is introduced in the 3- or 5-position.

EXPERIMENTAL

All mp are uncorrected. Diethyl ether, toluene and ethanol were dried. 4-Nitro-3,5-dimethylisoxazole[6], 4-chloro-3,5-dimethylisoxazole[7], 4-benzoyl-3,5-dimethylisoxazole[8], 4-cyano-3,5-dimethylisoxazole[9] and 4-acetyl-3,5-dimethylisoxazole[10] were prepared by established procedures. IR spectra were recorded on a Pye-Unicam SP-1100 spectrometer equipped with NaCl optics. A Pye-Unicam SP-1700 was used to obtain UV spectra. ^{1}H-NMR spectra were determined at 60 MHz on a Varian T-60A spectrometer using Cl_3CD-$(CD_3)_2SO$ solutions and TMS as standard reference; chemical shifts were measured in the δ scale.

Quaternization of 4-substituted 3,5-dimethylisoxazole derivatives (general procedure). A mixture of 4-substituted 3,5-dimethylisoxazole and redistilled dimethyl sulfate (molar ratio 1:1.1) in toluene (100 ml) was refluxed for 11 h. On cooling the product solidified to a yellow-brown glass. This was decanted from the toluene layer, repeatedly extracted with ether and used directly. It could be crystallized by trituration with ether, but purification was difficult because the methosulfate was exceedingly hygroscopic; yield, 85-95%. The structure of the isoxazolium salts resulting from the above reaction has been elucidated througt their ^{1}H NMR spectroscopic characteristics (table 3). Ia-e show IR ring stretching bands in the 1635 - 1615 cm^{-1} range.

Table 3

NMR chemical shifts for 4-substituted 2,3,5-trimethylisoxazolium methosulfates (δ, 60 MHz, Cl_3CD - $(CD_3)_2SO$)

4-Subst.	CH_3-3	CH_3-5	N-CH_3	SO_4CH_3
COC_6H_5 [a]	2.60	2.75	4.20	3.75
NO_2	3.00	3.15	4.40	3.80
Cl	2.65	2.70	4.30	3.80
$COCH_3$ [b]	2.70	2.80	4.20	3.80
CN	2.80	2.90	4.20	3.80

[a] COC_6H_5, 7.5-7.9; [b] $COCH_3$, 2.45.

Reaction of Ia-e with aromatic aldehydes in the presence of bases (general procedure). An ethanol solution of the aldehyde (50 mM) and the required organic base (30 mM) was added to a strirred solution of Ia-e (25 mM) in 60 ml of ethanol and the mixture was refluxed during a determinated number of hours (table 1). When the isoxazolium salt used was the 4-nitro derivative (Ia), coloured crystals from the ethanol solution were collected by cooling at 0ºC, recrystallized from water and proven to be, in each case, IIa-c. After evaporation of the ethanol (reactions in which Ib-d are involved) the crude product was dissolved in a small amount of water, extracted with ether and added to a saturated solution of sodium tetrafluoborate in water to which a little of tetrafluoboric acid had been added (pH = 2-3) and the precipitated fluoborate salt was filtered off, washed with water, dried and recrystallized from water to give, in each case, IId-f or IIIa-g. Separation of the mixture of geometric isomers EE-IIb and ZE-IIb could be achieved by fractional recrystallization (ethanol). The reaction of Ib with aromatic aldehydes led to a mixture of 3- and 5-monocondensated products (table 1) which could not be seperated due to the analogy in their chemical properties. Quantitative estimations of these mixtures (IId-IIIa, IIe-IIIb and IIf-IIIc) were achieved by ^{1}H NMR.

Physical and spectroscopic data of II and III are given below.

2,5-Dimethyl-4-nitro-3-styrylisoxazolium sulfate (IIa): yellow crystals from water, mp 190ºC (d). Anal. Calcd. for $(C_{13}H_{13}O_3N_2)_2SO_4$: C, 53.22; H, 4.43; N, 9.55. Found:

C, 52.96; H, 4.37; N, 9.71. IR (nujol): 1635, 1605, 1570, 1350, 985, 770, 700 cm^{-1}. ^1H NMR (Cl_3CD-$(CD_3)_2SO$): 2.90 (3H, s, CH_3-5), 4.25 (3H, s, N-CH_3), 7.10-7.70 (6H, m, H_a and aromatic protons), 7.90 (1H, d, J=15 Hz, H_b).

2,5-Dimethyl-4-nitro-3-(4-phenyl-1,3-butadienyl)isoxazolium sulfate (EE-IIb, trans-trans): red crystals (water), mp 175-176º (d). Anal. Calcd. for $(C_{15}H_{15}O_3N_2)_2SO_4$: C, 56.42; H, 4.70; N, 8.77. Found: C, 56.67; H, 4.68; N 8.82. UV: λ_{max}(EtOH-H_2O) 215 (ϵ=20500) and 408 (ϵ=25000). IR (nujol): 1620, 1600, 1560, 995, 770, 700 cm^{-1}. ^1H NMR (Cl_3CD-$(CD_3)_2SO$): 2.85 (3H, s, CH_3-5), 4.20 (3H, s, N-CH_3), 7.00-7.60 (9H, m, olefinic and aromatic protons).

2,5-Dimethyl-4-nitro-3-(4-phenyl-1,3-butadienyl)isoxazolium sulfate (ZE-IIb, cis-trans): orange crystals (water), mp 194º (d). Anal. Calcd. for $(C_{15}H_{15}O_3N_2)_2SO_4$: C, 56.42; H, 4.70; N, 8.77. Found: C, 56.63; H, 4.76; N, 8.88. UV: λ_{max}(EtOH-H_2O) 208 (ϵ=18000) and 401 (ϵ=21000). IR (nujol): 1620, 1600, 1560, 1000, 770, 740, 710 cm^{-1}. ^1H NMR (Cl_3CD-$(CD_3)_2SO$): 2.90 (3H, s, CH_3-5), 4.20 (3H, s, N-CH_3), 6.90-7.40 (9H, m, olefinic and aromatic protons).

2,5-Dimethyl-4-nitro-3-(2-p-dimethylaminophenylethenyl)isoxazolium sulfate (IIc): violet crystals from water, mp 196º (d). Anal. Calcd. for $(C_{15}H_{18}O_3N_2)_2SO_4$: C, 53.57; H, 5.35; N, 12.50. Found: C, 53.79; H, 5.41; N, 12.81. IR (nujol): 1610, 1600, 1575, 1365, 995, 825 cm^{-1}. ^1H NMR (Cl_3CD-$(CD_3)SO$): 2.85 (3H, s, CH_3-5), 3.20 (6H, s, $(CH_3)_2N$), 4.25 (3H, s, N-CH_3), 6.80 (2H, d, J=8 Hz, β-aromatic protons), 7.05 (1H, d, J=15 Hz, H_a), 7.45 (2H, d, J=8 Hz, α-aromatic protons), 7.75 (1H, d, J=15 Hz, H_b).

Mixture of 2,5-dimethyl-4-chloro-3-styrylisoxazolium tetrafluoroborate (IId) and 2,3-dimethyl-4-chloro-5-styrylisoxazolium tetrafluoroborate (IIIa) (molar ratio 4:1): yellowish crystals from water, mp 156-163º. Anal. Calcd. for $C_{13}H_{13}ONClF_4B$: C, 48.55; H, 4.04; N, 4.36. Found: C, 48.49; H, 4.10; N, 4.29. IR (nujol): 1640, 1600, 980, 770, 740, 710 cm^{-1}. ^1H NMR (Cl_3CD-$(CD_3)_2SO$): 2.50 (3H, s, IId CH_3-5), 2.60 (3H, s, IIIa CH_3-3), 4.25 (6H, s, IId and IIIa N-CH_3), 6.95 (2H, d, J=15 Hz, IId and IIa H_a), 7.20-7.60 (10 H, m, IId and IIIa aromatic protons), 7.85 (2H, d, J=15 Hz, IId and IIIa H_b).

Mixture of 2,5-dimethyl-4-chloro-3-(4-phenyl-1,3-butadienyl)isoxazolium tetrafloroborate (IIe) and 2,3-dimethyl-4-chloro-5-(4-phenyl-1,3-butadienyl)isoxazolium tetrafluoroborate (IIIb) (molar ratio 1:1): yellow crystals from water, mp 170-176º. Anal. Calcd. for $C_{15}H_{15}ONClF_4B$: C, 51.82; H, 4.32; N, 4.03. Found: C, 51.59; H, 4.11; N, 3.88. IR (nujol): 1630, 1600, 1000, 780, 740, 710 cm^{-1}. ^1H NMR (Cl_3CD-$(CD_3)_2SO$): 2.55 (3H, s, IIe CH_3-5), 2.65 (3H, s, IIIb CH_3-3), 4.30 (6H, s, IIe and IIIb N-CH_3), 6.60-7.50 (18H, m, IIe and IIIb aromatic and olefinic protons).

Mixture of 2,5-dimethyl-4-chloro-3- 2-(4-hydroxy-3-methoxyphenyl)ethenyl isoxazolium tetrafluoroborate (IIf) and 2,3-dimethyl-4-chloro-5- 2-(4-hydroxy-3-methoxyphenyl)ethenyl isoxazolium tetrafluoroborate (IIIc) (molar ratio 2:1): yellowish crystals from water, mp 181-187º. Anal. Calcd. for $C_{14}H_{15}O_3NClF_4B$: C, 45.73; H, 4.08; N, 3.81. Found: C, 46.05; H, 4.27; N, 3.91. IR (nujol): 3460, 1650, 1615, 985, 820 cm^{-1}. ^1H NMR (Cl_3CD-$(CD_3)_2SO$): 2.55 (3H, s, IIf CH_3-5), 2.65 (3H, s, IIIc CH_3-3), 3.85 (6H, s, IIf and IIIc O-CH_3), 4.30 (6H, s, IIf and IIIc N-CH_3), 6.60-7.25 (8H, m, IIf and IIIc aromatic and H_a protons), 7.45 (1H, d, J=15 Hz, IIIc H_b), 7.90 (1H, d, J=14 Hz, IIf H_b).

2,3-Dimethyl-4-acetyl-5-(2- -furylethenyl)isoxazolium tetrafluoroborate (IIId): yellow crystals from water, mp 134-135º. Anal. Calcd. for $C_{13}H_{14}O_3NF_4B$: C, 48.93; H, 4.39; N, 4.39. Found: C, 49.01; H, 4.36; N, 4.54. IR (nujol): 1695, 1625, 1570, 960 cm^{-1}. ^1H NMR (Cl_3D-$(CD_3)_2SO$): 2.60 (3H, s $COCH_3$), 2.80 (3H, s, CH_3-3), 4.25 (3H, s, N-CH_3), 6.50 (1H, dd, J=2 Hz and 3 Hz, 4-furylic proton), 6.95 (1H, d, J=3 Hz, 3-furylic proton), 7.10 (1H, d, J=15 Hz, H_a), 7.60 (1H, d, J=15 Hz, H_b), 7.65 (1H, d, J=2 Hz, 5-furylic proton).

2,3-Dimethyl-4-acetyl-5-(4-phenyl-1,3-butadienyl)isoxazolium tetrafluoroborate (IIIe): orange crystals from water, mp 173-175º. Anal. Calcd. for $C_{17}H_{18}O_2NF_4B$: C, 57.49; H, 5.07; N, 3.94. Found: C, 57.19; H, 4.78; N, 3.73. IR (nujol): 1695, 1605, 1590, 980, 770, 690 cm^{-1}. ^1H NMR (Cl_3CD-$(CD_3)_2SO$): 2.60 (3H, s, $COCH_3$), 2.80 (3H, s, CH_3-3), 4.20 (3H, s, N-CH_3), 7.00-7.50 (9H, m, aromatic and olefinic protons).

2,2-Dimethyl-4-acetyl-5-(2-p-dimethylaminophenylethenyl)isoxazolium tetrafluoroborate (IIIf): violet crystals from water, mp 148-150º. Anal. Calcd. for $C_{17}H_{21}O_2N_2F_4B$: C, 54.86; H, 5.65; N, 7.53. Found: C, 54.58; H, 5.60; N, 7.50. IR (nujol): 1690, 1600, 985, 840 cm^{-1}. ^1H NMR (Cl_3CD-$(CD_3)_2SO$): 2.60 (3H, s, $COCH_3$), 2.75 (3H, s, CH_3-3), 3.10 (6H, s, $(CH_3)_2N$), 4.20 (3H, s, N-CH_3), 6.55 (2H, d, J=8 Hz, β-aromatic protons), 7.05 (1H, d, J=15 Hz, H_a), 7.40 (2H, d, J=8 Hz, α-aromatic protons), 7.60 (1H, d, J=15 Hz, H_b).

2,3-Dimethyl-4-cyano-5-styrylisoxazolium tetrafluoroborate (IIIg): yellow crystals from water, mp 171º. Anal. Calcd. for $C_{14}H_{13}ON_2F_4B$: C, 53.87; H, 4.17; N, 8.98. Found: C, 53.60; H, 3.90; N, 8.68. IR (nujol): 2215, 1635, 1600, 900, 760, 695 cm^{-1}. ^1H NMR (Cl_3CD-$(CD_3)_2SO$): 2.80 (3H, s, CH_3-3), 4.20 (3H, s, N-CH_3), 7.05 (1H, d, J=14 Hz, H_a), 7.05-7.60 (5H, m, aromatic protons), 7.80 (1H, d, J=14 Hz, H_b).

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