[$\pi 2_s + \pi 4_s$] DIMERISATION OF 1-(SACCHARIN-1-YL) PYRIDINIUM-3-OXIDE AND ITS DIPOLAR ADDITIONS WITH 2π-1,3-DIPOLAROPHILES.

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Abstract

1-(Saccharin-1-yl)pyridinium-3-oxide reacted as[4n] π–electrocyclic component across the 2,6-positions of the pyridine ring with 2π– electron addends to give substituted-2-oxo-8-azabicyclo[3.2.1] oct-3-enes.Structural and configuratioinal assignments were deduced from ^{1}H NMR, IR, and mass spectral analyses.

Introduction

MO calculations(1) indicated and experimental data (2) have confirmed that pyridinium-3-oxides, which are substituted at the 1-position by π-electron-deficient aryl or in particular heteroaryl groups are more reactive in their cycloaddition reactions with dipolarophiles than are 1-alkylpyridinium-3-oxides. The relative reactivities of the 1-heteroaryl betaines can be expressed in terms of their HOMO and LUMO energy levels and CNDO/2 calculations(3) show that the cycloaddition reactions of the betaines with π-electron-deficient dipolarophiles are HOMO (betaine) controlled (Sustmann Type I) , whilst those reactions with π-electron-rich dipolarophiles are LUMO (betaine) controlled (Sustmann Type III). In reactions involving conjugated alkenes both HOMO(betaine)-LUMO (dipolarophile) and LUMO (betaine)-HOMO (dipolarophile) interactions are important (Sustmann Type II). Recently, we have reported the synthesis of 1-(saccharin-1-yl) pyridinium-3-oxide (4) 4. ASED-MO calculations (12) show that the 1-saccharinyl substituent at position-1 in pyridinium-3-oxide has a marked lowering in the LUMO level, making the HOMO-LUMO energy separation within the betaine 4, 1.099 eV, which is comparable with that reported for the highly reactive 1-(phenyl),1-(2-pyridyl) 1-(4-pyridyl), 1-(5-nitro-2-pyridyl), 1-(4,6-dimethylpyrimidinyl), and 1-(s, triazinyl) betaines (2,3), even though, 4 failed to dimerise at room temperature. The calculated structure for 1-(saccharin-1-yl) pyridinium-3-oxide (4) shows that the saccharinyl ring rotates around the C_1-N bond by an angle 19°. Presumably, this deviation from coplanarity prevents the approach of the betaine molecules to form the parallel double layer transition state at room temperature. Simi-

lar observation was noted before with the highly reactive 1-(2,4-dinitrophenyl) pyridinium-3-oxide (5). Now, we wish to report herein, the dimeristion of 1-(saccharin-1-yl) pyridinium 3-oxide 4 at elevated temperature and its dipolar additions with numerous 2π-electron-deficient and conjugated 1,3-dipolarophiles.

Results and Discussion

The 3-hydroxy-1-(saccharin-1-yl) pyridinium chloride 2 was prepared by a standard procedure from pyridin-3-ol and pseudo-saccharine chloride 1 in dry THF. when the quaternisatin process was conducted in alcohol, the corresponding ethers 3 were isolated in almost quantitative yield (4). The following pathways were suggested for the formation of the ether 3, Alcoholysis takes place with pseudosaccarin chloride 1 or with the preformed pyridium hydrochloride 2. The calculations (4) show that the C-1 in either pscudosaccharin chloride 1 or 3-hydroxy-1-(saccharin-1-yl) pyridinium chloride 2 is more electron-deficient center, and is mostly contributed to the LUMO which controlled the reactivity of both compounds as soft electrophiles reacting readily with alcohols. This was supported by recrystallisation of 3-hydroxy-1-(saccharin-1-yl)pyridium hydrochloride 2 with ethanol, which resulted in the formation of the corresponding ether from m.p and mixed m.p experiments (cf. Scheme1).

The 3-hydroxy-1-(saccharin-1-yl) pyridinium chloride 2 was converted into the betaine 4 upon treatment with triethylamine in 1,2-dichloroethane as a bright yellow oil. IR spectrum of 4 lacks the νOH group characteristic of pyridin-3-ol, instead it displayed the characteristic absorption of the quaternary ammonium cation at 2700-2500 cm^{-1} besides the skeletal vibrations of the pyridinium-3-oxide at 1550 cm^{-1} . It was observed that, on standing the betaine 4 for long time , it was able to detect the presence of the corresponding dimer 5 from the I.R. spectrum, which displayed the saturated and unsaturated carbonyl groups at 1730 and 1680 cm^{-1} respectively. So, heating a suspension of 2 in 1,2-dichloroethane in the presence of triethylamine (pH≈ 8-8.5) for 1 hr at 60-70°C, afforded a deep yellow solid, identified as 3,12-bis-(saccharin-1-yl)-3,12-diazatricyclo[5.3.1.$1^{2,6}$]undeca-4,8-diene-10,11-dione 5 from elemental and spectral evidence. IR:1730 (saturated,C=O), 1680 (α,β–unsaturated C=O) ; 1645 (enamine) ; 1630 (conjugated, C=C), 1605-1540 cm^{-1} (ring vibrations). ^{1}H NMR: δ 6.0(1-H, d, $J_{1,2}$= 2.5 Hz) 5.1 (2-H, dd, $J_{2,1}$ = 2.5 Hz, $J_{2,6}$ = 2.5 Hz ; 7.3) (4-H, d, $J_{4,5}$ = 8 Hz) ; 5.78 (5-H, dd, $J_{5,4}$ = 8 Hz, $J_{5,6}$ = 6 Hz) ; 3.55 (6-H, double triplet, $J_{6,2}$ = 2.5 Hz, $J_{6,5}$ = 6 Hz, $J_{6,7}$ = 2.5 Hz) ; 5.97 (7-H, dd, $J_{7,6}$ = 2.5 Hz, $J_{7,8}$ = 5.5 Hz) ; 7.45 (8-H, dd, $J_{8,9}$ = 9 Hz, $J_{8,7}$ = 5.5 Hz) ; 6.32 (9-H, dd. $J_{9,8}$ = 9 Hz, $J_{9,1}$ = 2.0 Hz) ; and 7.6-7.8 (m, phenyl, 8H). When ^{1}H NMR was carried out in $CDCl_3$ with drops of trifluoroacetic acid the spectrum is for the 3-hydroxy 1-(saccharin-1-yl) pyridinium cation which indicated that retrocycloaddition was induced by protonation (Scheme 1).

The mass spectrum of 5 displayed the betaine 2 which supports the retrocycloadditin in the ionisation chamber . As the dimerisation process has taken place at elevated temperature, presumably, at

which the saccharinyl ring be coplaner with the pyridinium cation which minimises the steric effect and facilitates the formation of the double layer transition state leading to the dimer 5

Cycloaddition reactions with 2π-electron addends

Betaine 4 reacted readily with numerous 2π-1,3-dipolarophiles. All cycloaddition reactions were conducted either by preparation of the betaine 4 in the presence of the dipolarophile or by the convenient thermal regeneration of the monomeric betaine 4 from the dimer 5

(i) With 2π-electron-deficient monoenes:

The betaine 4 failed to give the expected cycloadduct with maleic anhydride. Instead, when the reaction was carried out in refluxing tetrahydrofuran, the maleate salt of the 3-hydroxy - pyridinium cation 6 was produced, whilst the fumarate salt 7 was obtained when the reaction was conducted in refluxing dioxane. It is apparent that hydrolysis of the anhydride occurs and that, at the higher temperature, the more stable fumarate anion is formed. The reaction products were identified by their ^{1}H NMR and IR spectra, by satisfactory elemental analysis and by mixed m.p experiments with authentic salts, which were produced by direct reaction of the betaine 4 with maleic and fumaric acid respectively. Similar observations have been reported previously for the reaction of 1-substituted pyridinium-3-oxides with maleic anhydride (7,8). In contrast, the betaine 4 reacted regiospecifically with other 2π-electron-deficient mono and disubstituted alkenes to give the 6-substituted-2-oxo-8-azabicyclo[3.2.1]oct-3-ene derivatives 8-16. The reaction with acrylonitrile gave both the endo- and exo-6-carbonitriles 8a and 8b. This observation parallels that recorded for the corresponding cycloaddition reactions with 1-phenyl, 1-(2-pyridyl) and 1-(s-triazinyl) (9) pyridinium-3-oxides, but it is in contrast with the reactions of the 1-(4-pyridyl) (9) and 1-(pyridazin-1-yl) (7) analogues, which gave the 6-endo-carbonitriles to the virtual exclusion of 6-exo-stereoisomers. Confirmation of the structure of (8a and 8b) was provided by ^{1}H NMR, IR and mass spectral evidence. The appearance of the key 5-H proton signal as an apparent triplet in fact it is a double doublet at δ 4.98 resulting from a 6 Hz coupling with 4-H and 5 Hz coupling with 6-exo-H. established the endo-configuration of the 6-carbonitrile group. It is also displayed a doublet at δ 5.1, resulting from a 6 Hz coupling with 4-H and a negligible $J_{5,6\text{-endo}}$ coupling. The IR spectrum revealed the characteristic absorption of conjugated carbonyl at 1690, conjugated olefinic double bond at 1630, and aromatic ring vibrations at 1610-1550 cm^{-1} . The cyano group displayed a stretching frequency at 2235 cm^{-1}. The mass spectrum of 8 confirmed the molecular ion at m/z 281 in which it displayed the betaine at m/z 228 as the base peak which is indicative of the retrocycloaddition. Analogous treatment of the betaine 4 with methyl acrylate gave the 6-endo- and 6-exo- carboxylic ester (9a and 9b). Again, the assignment of the 6-endo- configuration was provided by the appearance of the 5-H signal in the ^{1}H NMR spectrum as an apparent triplet at δ 5.15, J5,4 = 6 Hz, $J_{5,6}$-exo = 5.5 Hz , whereas the corresponding signal for the exo isomer appeared as a doublet at δ 4.78 due to negligible $J_{5,6}$-endo coupling, $J_{5,4}$=6 Hz.

The IR spectrum confirmed the presence of the ester carbonyl at 1725 and the α,β-unsaturated ketone at 1690 cm^{-1}. Reaction of the betaine 2 with allyl alcohol gave both 6-endo-and 6-exo- stereoisomers 12 a and 12 b. Endo, cycloaddition leads to the formation of the tricyclic cycloadduct 13 as a major product (45%) via an intrarmolecular Michael addition of the hydroxyl group to the enone moiety in 12 a . Confirmation of the structure of 13 was provided by the position of the carbonyl stretching frequency at 1725 cm^{-1}, showing the presence of a saturated cyclic ketone. This contrasts with the lower frequency of 1690 cm^{-1}, characteristic of the α,β-–unsaturated ketone group. Ring closure of this type has been noted previously (7). The structure of the 6-exo- hydroxymethyl-2-oxo-8-(saccharin-1-yl)-8-azabicyclo[3.2.1]oct-3-ene 12 b (minor isomer 20%) was established from IR and ^1H NMR spectra. The IR spectrum exhibited νOH at 3500-3200 (br), ν C=O (conjugated) at 1690 and νC=C (conjugated) at 1635 cm^{-1} . The ^1H NMR spectrum revealed 5-H as a doublet at δ 5.3 $J_{5,4}$ = 6 Hz (cf. Table 1).

(ii) With conjugated olefins

The cycloaddition of styrene with the betaine 4 followed the pattern reported for the corresponding reaction with other 1-heteroarylpyridinium-3-oxides (2), to yield the endo-6-phenyl-8-(1-saccharin-1-yl)-2-oxo-8-azabicyclo[3.3.1]oct-3-ene 10 which was characterized by the apparent triplet splitting of the 5-H signal (cf. Table 1). The regio- and stereospecificity of the cycloaddition reaction was maintained in the formation of endo-6-(4-pyridyl)-8-(1-saccharin-1-yl)-2-oxo-8-azabicyclo[3.2.1]oct-3-ene 11 from the reaction of 4-vinylpyridine with the betaine 4. The endo- configuration of 11 was confirmed by the appearance of the 5-H signal in the ^1H NMR spectrum as an apparent triplet (cf. Table 1)

(iii) With Disubstituted monoenes

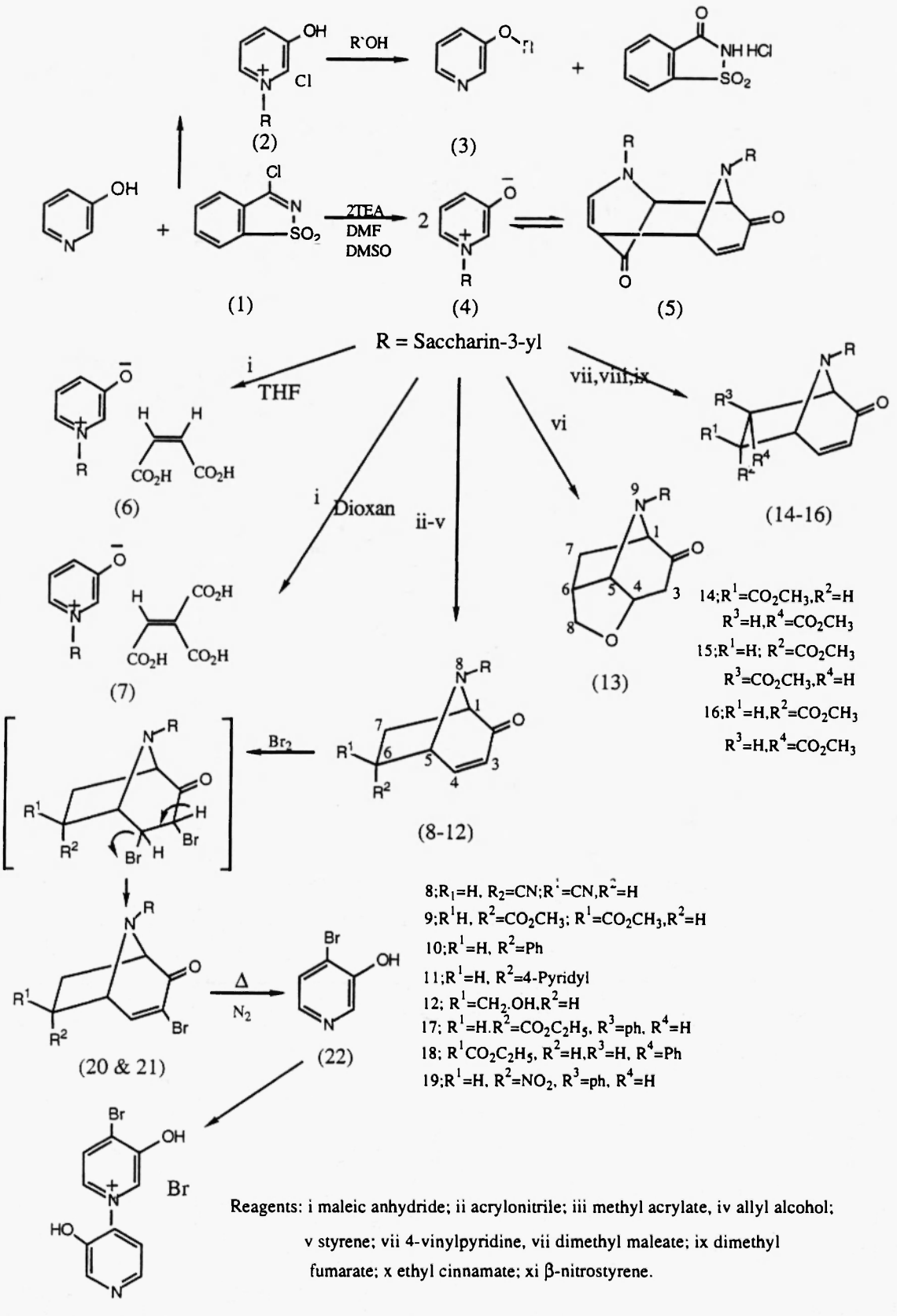
Dimethyl maleate reacted with either the isolated betaine 4 or the betaine 4 prepared in situ with triethylamine, to produce unexpectedly the fumarate cycloadduct,dimethyl 8-(1-saccharin-1-yl)-2-oxo-8-azabicyclo[3.2.1]oct-3-en-6-exo , 7-endo- carboxylate 14. Confirmation of the structure of 14 was provided by IR, and ^1H NMR spectra.IR revealed the carbonyl absorptions at 1730 and 1720 cm^{-1}, assignable for two carbonyl ester located in different environments, and the conjugated carbonyl at 1690 cm^{-1}. ^1H NMR displayed the 5-H proton as a doublet at δ 5.4 ($J_{5,4}$ = 5.5 Hz, $J_{5.6\text{-endo}}$ = negligible), whilst 1-H proton appeared at δ 4.85 as a double doublet ($J_{1,3}$ = 1.5 Hz, $J_{1.7\text{-exo-}}$ =10 Hz). On the other hand , when the betaine 4 was allowed to react with dimethyl fumarate under similar conditions the counter isomer, was isolated and identified as dimethyl 6-endo-7-exo-carboxylate 15 based on ^1H NMR spectrum, 5-H signal appeared as an apparent triplet at δ 5.3 ($J_{5,4}$ = 5 Hz, $J_{5,6\text{-exo}}$ = 6 Hz) whilst 1-H signal displayed a doublet at δ 4.7 ($J_{1,3}$ = 1.5 Hz , $J_{1.7\text{-endo-}}$ small to be neglected). The isolation of the fumarate cycloadduct 14 as the sole product and no maleate counter isomer being detected even by ^1H NMR spectrum of the product 14 indicates that the

reaction is apparently non-stereospecific which is contrary to the most acceptable concerted mechanism proposed by Hüisgen (13) and later by Katritzky (2) for 1,3-dipolar cycloadditions. Two possible pathways are possible for the formation of 14: (a) Isomerisation of dimethyl maleate prior to addition under the condition of the reaction or (b) Isomerisation of the intially formed kinetically controlled maleate cycloadduct 16 to the thermodynamically stable fumarate isomer due to steric consideration.. Dimethyl maleate is known to isomerise partially to the fumarate isomer on heating in the presence of triethylamine. However, owing to the isolation of the fumarate cycloadduct 14 as the sole product, the first pathway has been excluded. So, the apparent nonstereospecificity of the cycloaddition may be rationalised via an initial addition of the dimethyl maleate to the betaine 4 to give the kinetically controlled maleate cycloadduct 16 which is transformed to the thermodynamically stable fumarate cycloadduct 14 through epimerisation at C-6 depending upon whether the maleate adduct has the endo- or exo- configuration. We are inclined that the initially formed maleate adduct has the endo-configuration of the two ester groups in which the steric interaction may promote the possible epimerisation at C-6. This would be in agreement with the isolation of the fumarate counter- isomer 15. The isolation of the fumarate counterisomer 15 which has the 6-endo and 7-exo-carboxylic ester supports the initial formation of the endo- maleate cycloadduct 16. followed by, epimerisation at C-6 to give 14. Analogous treatment of the betaine 4 with ethyl cinnamate afforded two cycloadducts 17 and 18. The major product 17 was identified as 6-endo-ethoxycarbonyl-7-exo-phenyl-2-oxo-8-(saccharin-1-yl)-8-azabicyclo[3.2.1]oct-3-ene from IR spectrum which exhibited 1720 (-$COOC_2H_5$); 1690 (α,β-unsaturated, C=O) ; 1630 (conjugated,C=C) 1610 -1550 cm^{-1} (ring vibrations), and ^1H NMR spectrum which assigned the endo-onfiguration at C-6 and the exo-configuration at C-7. 1-H displayed a doublet at δ 4.98 due to its long-range W-type coupling with 3-H, $J_{1,3}$=1.5 Hz, and the negligible coupling with 7-H-endo.. 5-H appeared as an apparent triplet at δ 5.55 due to comparable coupling with 4-H and 6-H-exo- $J_{5,4}$ = 6 Hz, $J_{5,6\text{-exo}}$= 5.5Hz. The minor product 18 was identified on the basis of IR and ^1H NMR spectral evidence. IR: 1725 ($COOC_2H_5$) ; 1695 (α,β–saturated, C=O) ; 1610-1580 cm^{-1} (ring vibrations). ^1H NMR : δ 5.0 (1-H, dd, $J_{1,3}$ = 1.5 Hz, $J_{1,7\text{-exo}}$ =10 Hz) and 5.35 (5-H,d, $J_{5,4}$ = 5.5 Hz, $J_{5,6\text{-endo}}$= negligible) . In a previous work we have reported the lower reactivity of the β-–nitrostyrene with some 1-substituted pyridinium-3-oxides (10). However, β-Nitrostyrene reacted with the betaiane 4 to give low yield 20% of the 2,6-cycloadduct which was identified as endo-6-nitro-7-exo-phenyl-2-oxo-8-(saccharin-1-yl)-8-azabicyclo[3.2.1]oct-3-ene 19. IR spectrum of 19 confirmed the presence of the conjugated carbonyl absorption at 1690 cm^{-1} besides the characteristic absorption of the nitro group at 1505 (asym. stretch) and 1350 cm^{-1} (sym. stretch.) The endo-configuration of the nitro group at C-6 and exo-configuration of the phenyl group at C-7 were established from the signals of the key 1-H and 5-H protons. 1-H displayed a doublet at δ 5.25 due to its coupling with 3-H (W-type) $J_{1,3}$ = 2.0 Hz,

$J_{1,7\text{-endo}}$ = negligible) ; and 5-H appeared as an apparent triplet at δ 5.55 ($J_{5,4}$ = 6 Hz ; $J_{5,6\text{-endo}}$ = 5 Hz). The isolation of the 2,6-cycloadducts in substantial amounts and the reversibility of the cycloaddution process make such type of compounds as valuable synthetic intermediates. Thus , bromination of the cycloadducts 8 and 9 afforded directly the corresponding 3-bromo derivatives 20 and 21. Structural and configurational assignments were established from elemental and spectral evidence. The elemental analyses of the isolated compounds fit on monobromo-derivatives, 20 and 21 which indicated that bromination has taken place followed by a subsequent dehydrobromination. IR spectra of 20 and 21 exhibited a higher stretching frequencies for the α,β-unsaturated carbonyl group at 1710 cm^{-1} due to the adjacent electronegative bromine. ^1H NMR spectra confirmed the 3-bromo derivative as 1-H proton displayed a singlet at 5.18 and 4-H proton appeared as a doublet at δ 7.35 $J_{4,5}$= 6 Hz. Sublimation of the 3-bromo cycloadducts 20 and 21 in air of nitrogen at elevated temperature (180°, 1mm Hg), afforded on the cold finger a yellowish solid which on the basis of elemental and spectral evidence was identified as 4-bromo-3-hydroxy-1-(pyridin-3-ol)pyridinium bromide 23. IR: 3200-2500 br. (OH) ; and 1610-1550 (ring vibrations). ^1H NMR displayed down-field pyridine protons as a complex multiplit in the region δ 7.8-8.9, The isolation of 23 indicated that the retrocycloaddition process resulted in an initial formation of 4-bromopyridin-3-ol 22 which underwent a subsequent bromide displacement to give 23. (Scheme 1).

Regio- and stereo-selectivity of the cycloaddition reactions of 1-(saccharin-1-yl) pyridinium-3-oxide with 2 π-electron addends.

The only products isolated from the addition of 2 π-electron addends to the betaine 4 were found to be highly regioselective in favour of the 6-substituted isomer as previously found for pyridinium-3-oxides (2). Reactions of conjugated olefins, styrene, 4-vinylpyridine with the betaine 4 yielded exclusively the 6-endo- adducts i.e. regio- and stereo- specific. This is in accord with PMO-FMO theory for $[_\pi 2_s + _\pi 4_s]$ processes which should proceed preferentially via the endo- transition state (2,3) .



Reagents: i maleic anhydride; ii acrylonitrile; iii methyl acrylate, iv allyl alcohol; v styrene; vii 4-vinylpyridine, vii dimethyl maleate; ix dimethyl fumarate; x ethyl cinnamate; xi β-nitrostyrene.

Scheme 1

Table 1. ^{1}H-NMR spectra of cycloadducts derived from mono-and disubstituted alkenes in $CDCL_3$

δ*	8	9	10	11	12	13**	14	15	17	18	19
1	4.35[c]	4.65[c]	4.95[c]	4.88[c]	4.30[c]	4.56[f]	4.82[c]	4.35[c]	4.75[b]	5.1[c]	4.78[b]
3	6.30[c]	6.45[c]	6.30[c]	6.10[c]	6.25[c]	4.10[f]	6.2[c]	6.30[c]	6.18[c]	6.15[c]	6.55[c]
4	7.30[c]	7.15[c]	7.25[c]	7.10[c]	7.05[c]	4.55[g]	7.0[c]	7.30[c]	7.1[c]	7.2[c]	7.3[c]
5	a) 5.20[c]	a) 5.38[c]	5.55[c]	5.78[c]	5.53[c]	5.48	5.35[c]	a) 5.20[c]	5.57[c]	5.45[b]	5.78[c]
	b) 4.87[b]	b) 4.98[b]	----	----	----	----	----	b) 4.87[b]	----	----	----
6-endo	----	----	----	----	3.50[d]	----	3.55[c]	----	----	3.75[b]	----
6-exo	3.40[d]	4.10[d]	4.68[d]	4.60[d]	----	4.87[c]	----	3.40[d]	3.7[c]	----	4.55[c]
7-endo	2.20[c]	2.25[c]	2.35[c]	2.30[c]	2.45[e]	----	2.35[b]	2.20[c]	2.55[b]	----	2.6[b]
7-exo	3.05[c]	2.80[c]	3.33[e]	3.10[c]	3.00[c]	2.50[f]	----	3.05[e]	----	3.15[c]	----
8	----	----	----	----	----	4.65[c]	----	----	----	----	----
ph	7-7.60[c]	7.5-80[c]	7.4-7.9[c]	7.3-7.9[c]	7.3-7.7[c]	7.3-7.8[c]	7.3-7.6[c]	7.3-7.6[c]	7.4-7.8[c]	7.4-7.75[c]	7.5-7.8[c]
4-pyridyl	----	----	----	8.3-8.5[c]	----	----	----	----	----	----	----
CO_2CH_3	----	3.75[a]	----	----	----	----	2.3[a],2.5[a]	2.35[a],2.4[a]	----	----	----
$CO_2CH_2CH_3$	----	----	----	----	----	----	----	----	1.2,t,CH_3	4.35,q,CH_2	----
CH_2OH	----	----	----	----	4.15[a]	----	----	----	----	----	----

Coupling Constants (Hz).

1,3	1.5	1.4	1.5	1.0	1.5	2.5 (1,3a) 4.5 (1,3b)	1.5	1.0	1.8	1.5	1.5
1,7-exo	10 0	9.5	8.0	10.0	8.0	8.0	8.0	-----	-----	-----	8.0
3,4	10 0	10.0	10.0	10 0	10 0	10 (4,3a) 8 (4,3b)	10.0	10 0	9.8	9.5	9 0
4,5	6 0	6 0	6.5	6.0	6.0	6.0	6 0	5.5	6	6	6
5,6-exo	5.5	5.5	-----	5.5	5.5	6.0	-----	6	5.5	-----	5.5
5,6-endo	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
6-endo, 7-endo	9.8	9 8	10.0	9.5	9.8	10	10	-----	-----	-----	-----
6-exo, 7-endo	6 5	6.3	6.5	7 2	7 1	6.8	-----	8.1	8.0	-----	7
6-exo, 7-exo	8.0	10 0	9.8	10 0	10 0	9.5	-----	-----	10 0	-----	-----
7-endo, 7-exo	14.0	13.8	14.0	14.0	13 8	13 8	-----	-----	-----	-----	-----
1,7-endo	1.3	1.4	1.5	1.5	1.5	1.4	1.3	1.3	1.0	-----	-----
6-endo, 7-exo	-----	-----	----	-----	-----	-----	8	-----	-----	-----	8

* In p.p.m relative to Me_4 Si as internal standard. a singlet; b doublet; c double doublet; d three doublets; e multiplet; f quartet of doublet; g double triplets; t triplet; q quartet.

** For the tricycic aduuct 13, numbering is non-systematic, for comarison only.

The high regio- and stereo- selectivity of these reactions is consistent with it being HOMO (betaine) controlled reactions (Sustmann Type I) in which secondary orbital overlap between the aryl group and the pyridinium ring is more important than steric and dipole-dipole interactions (3). Stereoselectivity is however lost in the addition of the betaine 4 to acrylonitrile, methyl acrylate, allyl alcohol, dimethyl maleate, dimethyl fumarate, ethyl cinnamate and β-nitrostyrene. Presumably, the secondary orbital overlap leading to the endo- product is weak in these cases, while steric and dipole-dipole interactions are considerably stronger and lead to the formation of the exo- counterisomers in substantial amounts. However, epimerisation, at C-6 in the endo- cycloadducts are suggested, owing to the long reaction time at elevated temperatures and in the presence of the organic base, triethylamine. It was shown that, substantial amounts of the dimer 5 have been isolated from most of the cycloaddition reactions. ASED - MO calculations (4) show that , the HOMO - LUMO energy separation within the betaine 4 is 1.099 eV, which was found to be comparable with that values for HOMO (betaine) - LUMO (dipolarophile, $\overset{==}{}$ x) calculated by the same method (14) which make competitive processes possible (HB-LD 0.90324, x = CN) ; (HB-LD 1.13524, x = CO_2CH_3) ; (HB-LD 1.90324, x = CH_2.OH) ; (HB-LD 0.91824, $\dot{x}\backsim$ C_6H_5) ; (HB-LD 0.60424, x = 4-pyridyl).

Experimental

Infrared spectra were measured using PYE-Unicam SP 300 infrared spectrophotometer (νmax in cm^{-1}), ^1H NMR spectra in $CDCl_3$ on a Varian EM-390 spectrometer using TMS as an internal reference (Chemical shift, δ in ppm). The m.p.s were determined on a GallenKamp melting-point apparatus and are uncorrected. Unless otherwise stated, light petroleum refers to the fraction having b.p 60-80°C. All compounds were purified by a column of alumina Brockmann grade activity II (BDH). Elemental analyses were performed by microanalytical laboratory, University of Ain Shams, Cairo, Egypt. The substrate, 3-hydroxy-1-(saccharin-1-yl)pyridinium hydrochloride 2 was prepared by quaternisation of pyridin-3-ol with pseudo-saccharin chloride1 1 (4) in dry tetrahydrofuran or dry acetonitrile as a solvent. m.p 224-226° (lit . (4) 224-226°).

3,12-Bis-(1-Saccharin-1-yl)-3,12-diazatricyclo[5.3.1.$1^{2,8}$] undeca-5,9-diene-10,11-dione 5.

To a stirred suspension of 3-hydroxy-1-(saccharin-3-yl)-pyridinium chloride 2 (2.0g, 0.0067 mol.) in 1,2 dichloroethane (25 ml), triethylamine (2 ml) was added dropwise in 1/2 h. Triethylamine hydrochloride was filtered off, and the filtrate was heated under reflex for 1 hr. Evaporation of the solvent under reduced pressure resulted in the formation of a reddish yellow Semi-solid, which on trituration with little cold distilled water gave a yellow solid, recrystallisation from THF gave 3,12-bis-(1-saccharin-3-yl)-3,12-diazatricyclo[5.3.1.$1^{2,8}$]undeca-5,9-diene-10,11-dione 5 as yellow crystals, (1,2 g, 0.0023 mol.),m.p 191-2° (yield, 68%). νmax ($CHBr_3$): 1720 (non-conjugated C=O). 1680 (α,β-unsaturated C=O) ; 1650 (enamine) ; and 1630 (conjugated C = C) , 1605-1550 cm^{-1} (ring vibrations). (Found: C,55.67 ; H,3.38 ; N,10.98 ; S,12.55 $C_{12}H_{16}N_4O_6S_2$ requires C,55.38, H,3.07, N,10.76 ; S,12.30%).

Cycloaddition reactions of 1-(saccharin-1-yl)pyridinium-3-oxide with 2π-electron addends.

Method A: The 3-hydroxy-1-(saccharin-1-yl) pyridinium chloride 2 (0.006 mol.) , triethylamine (2 ml), were heated under reflex with an excess of the 2π-dipolarophile (Ca. 0.3 mol.) in the presence of hydroquinone (0.02 g) for 24 h.. Volatile materials were removed under reduced pressure using rotatory evaporator to give a colored viscous material which was purified over a column of alumina as indicated in the individual experiment. Method B: The dimer 5 (0.003 mol) in dry THF (25 ml) was heated under reflex with the appropriate dipolarophile (Ca.0.3 mol) in the presence of hydroquinone (0.02g) for 24 h. The solvent and volatile materials were removed under reduced pressure and the products were isolated by the same procedure as in method A.

Isomeric 2-oxo-8-(Saccharin-1-yl)-8-azabicyclo[3.2.1]oct-3-en-6-endo -8 a and 6-exo-carbonitrile 8 b

The cycloadducts 8a and 8b were prepared by method A, using acrylonitrile. Elution from a column of alumina using chloroform- light petroleum (1:1) afforded an inseparable mixture of 8a and 8b which showed two spots on TLC plate with very closed Rf values. (yield 70%). IR: νmax (neat) 2240 (ν C= N), 1690 (α,β–unsaturated C = O), 1640 (conjugated, C = C) 1610-1550 cm^{-1} (ring vibrations). m/z 313 [M^+]. (Found: C,57.85 ; H,3.60 ; N,13.70 $C_{15}H_{11}N_3O_3S$. requires: C,57.50 ; H,3.51 ; N,13.42%).Further elution with chloroform and 10% ethanol gave the dimer 5 m.p 191-2° (yield, 10%). νmax (neat) 1720 (non conjugated, = O) and 1680 cm^{-1} (conjugated, C = O).

Isomeric Mehtyl-2-oxo-8-(saccharin-1-yl)-8-azabicyclo[3.2.1]oct-3-en-6-endo- 9 a and 6-exo-carboxylate 9 b.

An inseparable mixture of the 6-endo- and 6-exo- carboxylic esters 9a and 9b, showing two spots with closed Rf values on TLC plate was prepared by method B using methylacrylate. Purification of the crude product over a column of alumina using ethyl acetate-light petroleum(1:2) yielded a yellow viscous oil (yield,65%).IR:νmax (neat): 1725 (ester, C = O) ; 1690 (α,β-unsaturated, C = O); 1635 (conjugated, C = C); and 1605-1560 cm^{-1} (ring vibrations). (Found : C,55.88 ; H,4.35 ; N,8.27. $C_{16}H_{14}N_2O_5S$. requires: C,55.49 ; H,4.04 ; N,8.09%). m/z 346 [M^+].

Endo-5-oxa-9-(saccharin-1-yl)-2-oxo-9-azatricyclo [5.2.1.$0^{4,8}$] decane 13, and Exo-6-hydroxy methyl-2-oxo-8-(saccharin-1-yl)-8-azabicyclo [3.2.1] oct-3-ene 12.

The tricyclic adduct 13 was isolated from the reaction of betaine 4 and allyl alcohol by method A which was isolated from a column of alumina using chloroform-light petroleum (1:1) as yellowish white crystals m.p 281-3°C (yield, 40%), IR: νmax ($CHBr_3$) 1725 (non-conjugated ,C=O) , and 1605-1530 cm^{-1} (ring vibrations). C,56.78 ; H,4,66 ; N,9.01 $C_{15}H_4N_2O_4S$. requires: C,56.60 ; H,4.40 ; N,8.80%). Further elution with ethyl acetate gave 6-exo-hydroxymethyl-2-oxo-8-(saccharin-1-yl)-8-azabicyclo[3.2.1]oct-3-ene (12), as yellow needles from ethyl acetate m.p 200 -202°(yield, 28%). IR:νmax ($CHBr_3$) 3450-3280 (ν OH), 1690 (α,β-unsaturated,C=O), 1640 (conjugated, C=O), 1605-1540 cm^{-1} (ring vibrations). (Found : C,56.35 ; H,4.26 ; N,8.99 $C_{15}H_{14}N_2O_4S$. requires: C,56.60 ; H,4.40 ; N,8.80%).

Endo-6-phenyl-2-oxo-8-(saccharin-1-yl)-8-azabicyclo[3.2.1]oct-3-ene 10.

The endo-6-phenyl cycloadduct 10 was prepared by method (A) using the betaine 4 and styrene. Purification with a column of alumina using chloroform - light petroleum (1:1), afforded a yellow solid, which was recrystallised from ethanol to give yellow needles m.p 170-2°C (yield , 45%) . IR: νmax ($CHBr_3$) 1690 (α,β-unsaturated, C=O) ; 1630 (conj. C=C) and 1615 - 1550 cm^{-1} (ring vibrations). (Found : C, 65.58 ; H,4.37 ; N,8.01 $C_{20}H_{16}N_2O_3S$ requires C,65.93 ; H,4.39 ; N,7.69.

Endo-6-(4-pyridyl)-2-oxo-8-(saccharin-1-)yl-8-azabicyclo [3.2.1] oct-3-ene 11.

The 6-endo-(4-pyridyl) cycloadduct 11 was prepared by method (A) using the betaine 4 and 4-vinylpyridine. Purification with a column of alumina using chloroform - light petroleum (1:1) , and recrystallisation from ethanol gave yellow crystals, m.p 185-7°C (yield , 55%). IR: νmax ($CHBr_3$) , 1695 (α,β-unsaturated, C=O); 1635 (conjugated, C=C);and 1620-1550 cm^{-1} (ring vibrations). (Found: C,62.85 ; H,4.41 ; N,11.82 $C_{19}H_5N_3O_3S$ requires: C,62.46 ; H,4.10 ; N,11.50%). m/z 365 [M^+].

Dimethyl-2-oxo-8-(saccharin-1-yl)-8-azabicyclo[3.2.1] oct-3-en-6-exo-7-endo-dicarboxylate 14 ,and 6-endo-7-exo-dicarboxylate 15.

The cycloadduct 14 was prepared by method A, using dimethyl maleate. The organic layer was separated and dried over anhydrous sodium sulphate. Solvents were evaporated under vacuum. The residual viscous material was boiled, with diethyl ether for 30 min. to remove the excess of dimethyl maleate. The crude semi-solid material left was purified over a column of alumina using ethyl acetate-light petroleum (2:1) to give yellow needles after evaporation of the solvents , recrystallisation from ethyl acetate gave dimethyl-2-oxo-8-(saccharin-1-yl)8-azabicyclo[3.2.1]oct-3-en-6-exo-,7-endo-dicarboxylate 14 m.p 178 -180°C (yield 54%). IR: νmax ($CHBr_3$) 1730 & 1725 (ester , C=O) , 1695 (α,β-unsaturated , C=O) ; 1630 (conjugated , C=C) ; and 1605-1540 cm^{-1} (ring vibrations). (Found : C,53.81 ; H,4.08 ; N,7.18 $C_{18}H_6N_2O_7S$ requires: C,53.46 ; H,3.96 ; N,6.93%).
Dimethyl fumarate reacted with the betaine 4 under similar conditions to give the counter isomer, 6-endo-7-exo-dicarboxylic ester cycloadduct 15 as yellow crystals from ethyl acetate m.p 167-169°C (yield, 45%). IR: νmax ($CHBr_3$) 1735, 1728 (ester, C=O); 1690 (α,β-unsaturated, C=O), 1635 (conjugated, C=C); and 1605-1560 cm^{-1} (ring vibrations). (Found : C,53.21 ; H,3.68 ; N,6.88%).

Endo-6-Ethoxycarbonyl-7-exo-phenyl-2-oxo-8-(saccharin-1-yl)-8-azabicyclo[3.2.1]oct-3-ene 17 and Exo-6-Ethoxy carbonyl -7-endo-phenyl-2-oxo-8-(saccharin-1-yl)-8-azabicyclo[3.2.1]-oct-3-ene 18

The reaction was carried out as in the preceding experiment. The material left was treated similarly and then passed through a column of alumina using light-petroleum at first to remove the residual ethyl cinnamate, then eluted with ethyl acetate-light petroleum (2:1) which gave after removal of the solvents, a yellow solid, recrystallisation from ethyl acetate gave 17 as yellow crystals, m.p 210-2°C (yield, 35%). IR:νmax ($CHBr_3$)1735 (ester,C=O); 1695 (α,β-unsaturated, C=O); 1635 (conjugated, C=C) , and 1605-1550 cm^{-1} (ring vibrations). (Found : C,63.64 ; H,4.23 ; N,6.78 $C_{23}H_{20}N_2O_5S$.

requires: C,63.30 ; H,4.58 ; N,6.42%). Further elution with ethyl acetate gave 6-exo-ethyoxycarbonyl-7-endo-phenyl isomer 18 as yellow plates, m.p 185-6°C (yield, 10%). IR: νmax ($CHBr_3$), 1730 (ester, C=O), 1695 (α,β-unsaturated, C=O);1635 (conjugated, C=C); and 1610-1550 cm^{-1} (ring vibrations). (Found : C,63.32 ; H,4.72 ;N,6.67%).

Endo 6-nirtro-7-exo-phenyl-2-oxo-8-(saccharin-1-yl)-8-azabicyclo [3.2.1] oct-3-ene 19.

A mixture of the dimer 5 (0.003 mol.), β-nitrostyrene (1.5 g. , 0.01 mol) , hydroquinone (0.02 g.) in chlorobenzene (25 ml) and dry THF (25 ml) , was heated under reflux while stirring for 72 h. Evaporation of the solvents under reduced pressure afforded a deep brown viscous material. Purification through a column of alumina using ethyl acetate - light petroleum (1:4) to remove the residual β-nitrostyrene , followed by ethyl acetate. Yellow crystals of 19, were isolated, m.p 210-211°C (yield 18%). IR: νmax ($CHBr_3$) 1695 (α,β-unsaturated , C=O) ;1640 (conjugated , C=C) , 1530 & 1370 (νNO_2 , assym. and sym.) ; and 1605-1580 cm^{-1} (ring vibrations). (Found: C,62.48 ; H,3.10 ; N,9.81. $C_{23}H_{15}N_3O_5S$ requires: C,62.02; H,3.37 ; N,9.43%).

3-Hydroxy-1-(saccharin-1-yl) pyridinium maleate 6.

The betaine 4 (0.006 mol.) and maleic anhydride (0.01 mol.) were heated under reflux while stirring in THF (25 ml) for 16 h. Repeated recrystallisation from ethanol gave 3-hydroxy-1-(saccharin-1-yl) pyridinium maleate 6 as buff crystals (yield,70%) m.p 190-2°. IR: νmax ($CHBr_3$) 3250-2550 (br.) (νOH), 1610-1500 cm^{-1} (ring vibrations), 1710-1660 br. nonionised and ionized car boxylic groups. ^1H NMR: δ 6.3 (s, maleate protons ; 7.3-8.8 (m, phenyl and pyridine protons, 8H). Authentic specimen was prepared by the reaction of the betaine 4 and maleic acid under similar conditions m.p and mixed m.p undepressed, 190-2°. (Found : C,51.50 ; H,3.27 ; N,7.10. $C_{16}H_{12}N_2O_7S$ requires: C,51.06 ; H,3.19 ; N,7.44%).

3-Hydroxy-1-(saccharin-1-yl) pyridinium fumarate 7.

The reaction of the betaine 4 with maleic anhydride was repeated in boiling dioxan, a pale yellow solid was separated and recrystallised from ethanol to give pale yellow plates m.p 230-2°C (80% yield). IR: νmax (CHBr3) 3300-2500 (br.) (νOH) , 1610-1550 (ring vibrations) ; and 1715-1660 cm^{-1} (ionized and unionized carboxyl groups). ^1H NMR: δ 6.8, (S, fumarate protons) 7.4-8.8 (m, phenyl and pyridine protons, 8H) authentic specimen prepared from the reaction of the betaine 4 with fumaric acid under similar conditions, m.p and mixed m.p experiments 230-2°C.(Found: C,50.90 ; H,2.98 ; N,7.15. $C_{16}H_{12}N_2O_7S$ requires: C,51.06 ; H,3.19 ; N,7.44%).

3-Bromo-2-oxo-8-(1-saccharin-1-yl)-8-azabicyclo[3.2.1]-octa-3-en-6-carbonitrile 20. and 6-methyl carboxylate 21.

To a solution of the mixed cycloadduct 8 and/or 9 (19 (0.01 mol.) , in dichloromethane (80 ml) , bromine (0.7 ml , 1.37 x 10-2 mol.) , in dichloromethane (20 ml) was added dropwise while stirring at room temperature. The mixture was stirred for further 4 h., and more bromine (0.7 ml) in dichloromethane (20 ml) was then added. After 8 h., the solution was decanted and the orange viscous oil was

triturated with hot light-petroleum. The orange oil was dissolved in chloroform (150 ml) ; this solution was washed with 10% aqueous sodium bicarbonate , separated , and dried over anhydrous sodium sulphate. Evaporation of the chloroform afforded a viscous orange oil (70%). (20): IR: νmax (neat) 2235 (CN) ; 1710 (α,β-unsaturated, C=O). (Found: C,45.57 ; H,2.88 ; N,11.14; S,8.48, Br,20.88. $C_{15}H_{10}BrN_3O_3S$ requires: C,45.91 ; H,2.55 ; N,10.71 ; S,8.16 ; Br , 20.40%).

21:IR: νmax (neat) 2235 (νC≡N);1705. α,β-unsaturated, C=O). (Found: C,45.49; H,2.88;N,6.24; S,7.88; Br,19.02 $C_{16}H_{13}BrN_2O_5S$ requires:C,45.17; H,3.05;N,6.58; S,7.52; Br,18.82%).

4-bromo-3-hydroxy-1-(pyridin-3-ol) pyridinium bromide 23

Sublimation of the 3-bromo-cycloadducts 20 and/or (21) (1.49, 3.92 x 10^{-2} mol) at 140 ° (1 mm Hg) , under nitrogen atmosphere , gave on the cold finger,4-bromo-3-hydroxy-1-(pyridin-3-ol) pyridinium bromide 23 recrystallised from ethanol as yellowish white needles m.p 290-4° with decomposition. (0.3 g, yield 26%). IR: νmax ($CHBr_3$) 3200-2200 br. (νOH) , 1610-1500 (ring vibrations). ^{1}H NMR (D_2O) 7.73 (2-H, d, J = 7 Hz) ; 8.62 (2H, d, J = 7 Hz) ; 8.6 (1H, d, H-2, J = 1.5 Hz) and 8.7 (1H, d, H-2, J = 1.5 Hz). (Found : C,33.95; H,2.55 ; N,8.47 ; Br,46.55 $C_{10}H_8Br_2N_2O_2$ requires: C,34.48 ; H,2.29 ; N,8.04 ; Br,45.97%).

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