Dipolar Additions with 1-(4,6-Dimethylpyrimidin-2-yl)- and 1-(4,6-Dimethoxy-*s*-triazin-2-yl)-3-oxidopyridinium Betaines

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Cycloaddition to 1-(4,6-dimethylpyrimidin-2-yl)- and 1-(4,6-dimethoxy-*s*-triazin-2-yl)-3-oxidopyridinium betaines across the 2,6-positions of the pyridine rings with indene, acenaphthylene and ethyl cinnamate gave substituted 8-aza[3.2.1]bicyclooct-3-en-2-ones, whereas the [6π + 4π] cycloaddition reaction with 6,6-dimethylfulvene gave a tricyclo[6.3.1.0^{2,6}]dodeca-2,(6),4,9-trien-11-one. Structural and configurational assignments of the cycloadducts were deduced from ^{1}H nmr and ir spectral data.

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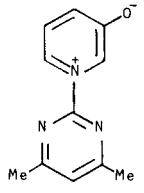
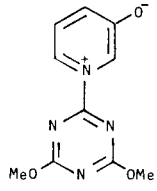
Katritzky (1) has demonstrated that 1-substituted 3-oxidopyridinium betaines have substantial 1,3-dipolar character and will react with 2π-, 4π- and 6π-dipolarophiles to give cycloadducts, which are of considerable interest as synthetic intermediates. In earlier publications (2,3) Katritzky examined the cycloaddition reactions of 1-(4,6-dimethylpyrimidin-2-yl)- and 1-(4,6-dimethoxy-*s*-triazin-2-yl)-3-oxidopyridinium betaines, **1a** and **1b**, with simple monosubstituted alkenes. We have extended his work and we now report the cycloaddition of **1a** and **1b** with indene, acenaphthylene, ethyl cinnamate to give the correspondingly substituted 8-heteroaryl-8-aza[3.2.1]-bicyclooct-3-en-2-ones and with 6,6-dimethylfulvene to give the substituted 12-azatricyclo[6.3.1.0^{2,6}]dodeca-2(6),4,9-trien-11-one.



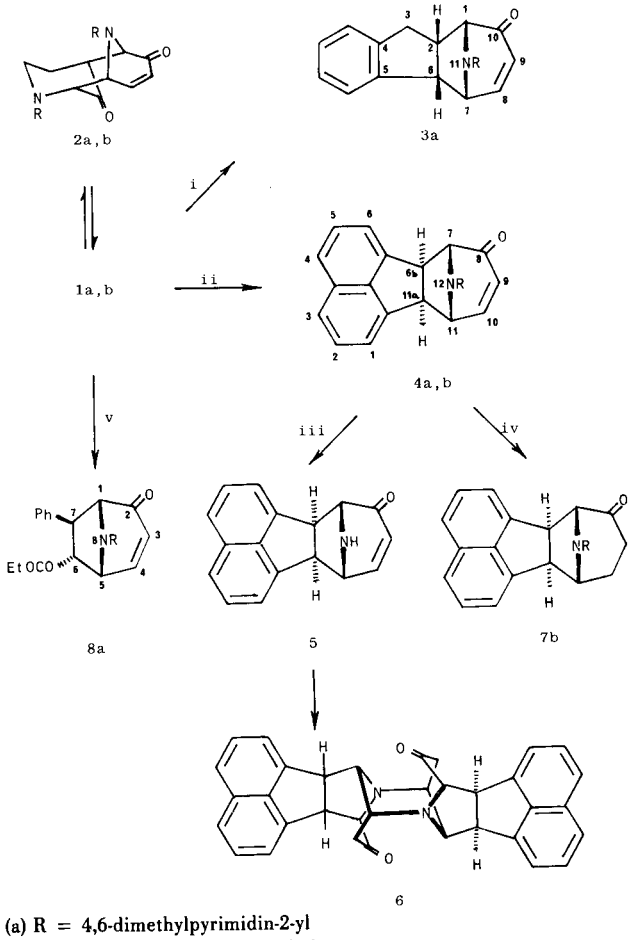
1a



1b

Cycloaddition Reactions with 2π-Addends.

1-(4,6-Dimethylpyrimidin-2-yl)- (**1a**) and 1-(4,6-dimethoxy-*s*-triazin-2-yl)- (**1b**) -3-oxidopyridinium betaines exist as stable crystalline dimers (**2a** and **2b**) (2,4), which are convenient sources of the nascent betaines by thermal retro-cycloaddition (5). In the presence of indene the pyrimidinyl pyridinium betaine (**1a**) was trapped to give the benzotricyclo[5.3.1.0^{2,6}]undec-8-en-10-one (**3a**) as the only product in 50% yield. The observed regiospecificity of this reaction is compatible with the previously reported (2,3) formation of the 6-*endo*-phenyl cycloadducts from the reactions of styrene with **1a** and **1b**, but is in contrast with the analogous reaction of indene with 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-3-oxidopytridinium betaine in which the two possible *endo* regioisomers were obtained in low yield (*ca.* 15%) (6). The structure of **3a** was fully confirmed by elemental analysis and spectral data. Infrared absorption at 1680 and 1604 cm^{-1} indicated the presence of the α,β-unsaturated carbonyl group. The chemical shift and multiplicity of the H-1 signal, which appeared as a double doublet at 5.70 ppm due to the coupling with *exo*-2-H (J =



(a) R = 4,6-dimethylpyrimidin-2-yl
(b) R = 4,6-dimethoxy-*s*-triazin-2-yl
i indene, ii acenaphthylene, iii HCl:H$_2$O, iv H$_2$/Pd/C, v ethyl cinnamate.

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7 Hz) and the long-range W-coupling with H-9 (J = 1.5 Hz), and the "triplet" signal at 5.24 ppm for H-7, resulting from comparable values of $J_{7,8}$ (5.5 Hz) and $J_{7,exo\text{-}6}$ (6 Hz), confirmed both the regiospecific addition of the indene and the *endo*-configuration of the adduct. The mass spectrum of **3a** showed the presence of the molecular ion peak at m/e 317 with the major fragmentation pathway resulting from an initial retro-cycloaddition regenerating indene and the betaine. Subsequent fragmentation of the betaine was similar to that described previously for pyridinium betaines (7).

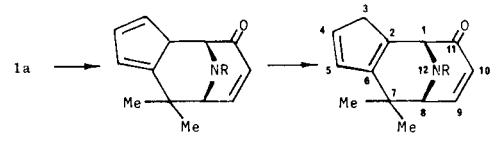
In contrast with the *endo*-addition of indene, the [2π + 4π] cycloaddition of the strained alkene, acenaphthylene, to **1a** and **1b** gave, exclusively, the *exo*-acenaphthyleno compounds **4a** and **4b** in high yield (90%). These observations are consistent with the expected steric control of the cycloaddition reactions, but are in contrast with the earlier reported cycloadditions of acenaphthylene with other 1-substituted-3-oxidopyridinium betaines in which both the *exo*- and *endo*-cycloadducts were isolated in low yields (3-20%) (6). Both cycloadducts **4a** and **4b** exhibit the expected absorption near 1680 and 1610 cm^{-1} for the α,β-unsaturated carbonyl system and, although the ^1H nmr spectra of **4a** and **4b** showed a similar pattern to that observed for **3a**, the coupling constants for the H-7 and H-11 signals, which appeared as a fine doublet ($J_{7,9}$ = 1.5 Hz; $J_{7,6b} \cong 0$ Hz) and a doublet ($J_{10,11}$ = 6 Hz; $J_{11,11a} \cong 0$ Hz), respectively, for both compounds established the *exo*-configuration of the aromatic system. It was noted that, although the acenaphthylene adducts were thermally stable at atmospheric pressure, and that the molecular ions appeared as the base peaks in the mass spectra of both compounds, retrocycloaddition occurred when the compounds were sublimed at *ca.* 1 mm of Hg. It is significant that the principal fragmentation mode for both **4a** and **4b** was the retrocycloaddition, similar to that observed for the indene derivative. This fragmentation could be induced thermally as well by electron impact.

In view of their high yields, **4a** and **4b** appeared ideal precursors for the formation of fused tropones (1). However, as noted earlier with cycloadducts derived from other 1-heteroaryl-3-oxidopyridinium betaines (*cf.* reference 6), methylation of **4b** with a range of reagents failed to give the 12-methylammonium salt, due to the strong resonance interaction of the 12-aza group with the triazinyl ring. Removal of the triazinyl substituent by refluxing with hydrochloric acid gave cyanuric acid (2) and a colorless crystalline product, mp > 310°, the infrared spectrum of which exhibited a band at 1710 cm^{-1}, characteristic of a saturated carbonyl group. Mass spectral analysis indicated the hydrolysis product to be dimeric in nature, formed *via* a Michael type addition between the enantiomers of the initially formed product **5**. By analogy with previous work (2), the *trans* structure with the chair conformation of the piperazine ring is assigned to the dimeric product **6**. In order to prevent dimerisation of the hydrolysis product, **4b** was initially hydrogenated to give the saturated cyclic ketone **7b**. However, although **7b** was obtained in high yield, all attempts to remove the 12-substituent from **7b** and to quaternize the imino group failed unexpectantly (*cf.* reference 2).

Although the cycloaddition of styrene to **1a** and **1b** has been shown previously (2,3) to be regio- and stereo-specific to give exclusively the 6-*endo*-phenyl adducts, the analogous reaction of methyl acrylate with a range of 1-substituted-3-oxidopyridinium betaines has been found to be regiospecific but not stereospecific (1). The ratio of the 6-*exo*- and 6-*endo*-carboxylic esters depends upon the 1-substituent of the betaine. We have examined the cycloaddition reaction of ethyl cinnamate with **1a** and found it gave predominantly a single cycloadduct (50%) which, on the basis of the chemical shifts and coupling constants for the ^1H nmr signals for H-1 (5.35 ppm; $J_{1,3}$ = 1.0 Hz; $J_{1,7\text{-}endo}$ = 1.5 Hz), H-5 (5.57 ppm; $J_{4,5}$ = 3 Hz; $J_{5,6\text{-}exo}$ = 4.5 Hz), H-6-*exo* (3.64 ppm; $J_{6\text{-}exo,5}$ = 4.5 Hz; $J_{6\text{-}exo,7\text{-}endo}$ = 5.0 Hz) and H-7-*endo* (3.21 ppm; $J_{7\text{-}endo,1}$ = 1.5 Hz; $J_{7\text{-}endo,6\text{-}exo}$ = 5.0 Hz), has been assigned the 7-*exo*-phenyl-6-*endo*-carboxylic ester structure **8a**. Two minor products (< 10%), which could not be isolated in a pure form, were also detected; one of which is tentatively assigned the 7-*endo*-phenyl-6-*exo*-carboxylic ester structure on the basis of the ^1H nmr spectral data obtained from an impure sample. The high regio- and stereospecificity of this reaction is consistent with it being a HOMO (betaine) controlled reaction in which secondary orbital overlap between the ester group and the pyridinium ring is more important than steric or dipole-dipole interaction (*cf.* reference 2). Further work to examine the effect of the *N*-substituent of the betaine system upon the stereospecificity of the cycloaddition with ethyl cinnamate is currently under investigation (8).

Cycloaddition Reactions with 6π-Addends.

Predictably, 6,6-dimethylfulvene behaves as a 6π electron addend (1,3) and reacted readily with **1a** to give the cycloadduct **10**, which is produced *via* a rapid 1,5-sigmatropic hydrogen shift from the initially formed adduct **9**. The structure was confirmed by the ^1H nmr signals at 3.02 and 6.30 ppm characteristic of the



9 10

R = 4,6-dimethylpyrimidin-2-yl

methylene and =CH- protons of the cyclopentadiene ring (3), together with signals at 6.00 (s), 5.84 (d), 7.04 (dd) and 5.60 ppm (d), assigned to the protons at the 1-, 10-, 9- and 8-positions, respectively.

EXPERIMENTAL

The spectra were recorded with a Perkin-Elmer 257 ir spectrometer, Varian HA-100 and Perkin-Elmer R12 nmr spectrometers and a Hitachi-Perkin-Elmer RMU-6E mass spectrometer. All compounds were purified by preparative tlc on Kieselgel PF 254 and elemental analyses were performed by Mr. A. Saunders in the microanalytical laboratory at the University of East Anglia.

1(*RS*),2(*SR*),6(*RS*),7(*RS*)-11-Aza-11-(4,6-dimethylpyrimidin-2-yl)-4,5-benzotricyclo[5.3.1.$0^{2,6}$]undec-8-en-10-one (**3a**).

The dimeric compound **1a** (0.5 g) was heated in refluxing ethanol (25 ml) for 30 minutes and indene (1 g) was added and the solution heated under reflux for a further 12 hours. The solvent was removed under reduced pressure and the residual yellow oil was purified by preparative tlc (chloroform:petroleum ether, bp 60-80°, 1:1) to give the *endo*-indene derivative **3a** (0.39 g, 50%), as yellow needles (chloroform), mp 160-160.5°; ^{1}H nmr (deuteriochloroform): δ 2.28 (s, pyrimidinyl 4,6-CH_3), 2.74 (d, 3-CH_2), 3.12 (dd, 6-*exo*-CH), 3.78 (m, 2-*exo*-CH), 5.24 (t, 7-CH), 5.58 (dd, 9-CH), 5.70 (dd, 1-CH), 6.39 (s, pyrimidinyl 5-CH), 6.70 (dd, 8-CH) and 7.40 ppm (m, aryl CH); M^+ = 317 amu.

Anal. Calcd. for $C_{20}H_{19}N_3O$: C, 75.7; H, 6.0; N, 13.2. Found: C, 75.4; H, 6.1; N, 12.8.

6b(*SR*),7(*RS*),11(*RS*),11a(*RS*)-Tetrahydro-12-(4,6-dimethylpyrimidin-2-yl)-7,11-iminocyclohept[*a*]acenaphthylene-8-one (**4a**).

The dimer **1a** (0.5 g) in ethanol (25 ml) was heated under reflux for 30 minutes and acenaphthylene (1.5 g) in ethanol (20 ml) was added. The solution was refluxed for 10 hours. The solvent was removed under reduced pressure to give a yellow solid, which upon recrystallisation from toluene gave the *exo*-adduct **4a** (0.79 g, 90%), mp 270-271°; ^{1}H nmr (deuteriochloroform): δ 2.30 (s, pyrimidinyl 4,6-CH_3), 4.47 (d, 11a-*endo*-CH), 4.57 (d, 6b-*endo*-CH), 5.70 (d, 11-CH), 6.20 (dd, 9-CH), 6.38 (d, 7-CH), 6.40 (s, pyrimidinyl 5-CH) and 7.55 ppm (m, 10-CH and aryl CH); M = 353 amu.

Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 78.2; H, 5.4; N, 11.9. Found: C, 78.2; H, 5.4; N, 11.5.

6b(*SR*),7(*RS*),11(*RS*),11a(*RS*)-Tetrahydro-12-(4,6-dimethoxy-*s*-triazin-2-yl)-7,11-iminohept[*a*]acenaphthylen-8-one (**4b**).

The dimer **1b** (2.5 g) was initially converted into the monomeric betaine by heating in butan-1-ol (50 ml) for 30 minutes. Acenaphthylene (1.5 g) in butan-1-ol (25 ml) was added and the solution heated under reflux for 24 hours. The solvent was removed under reduced pressure to give the *exo*-adduct **4b** (3.71 g, 90%), as pale yellow crystals, mp 214-215° (benzene); ^{1}H nmr: δ 3.88 (s, OCH_3), 4.17 (d, 11a-*endo*-CH), 4.26 (d, 6b-*endo*-CH), 5.40 (d, 11-CH), 5.95 (dd, 9-CH), 6.15 (d, 7-CH), 7.20 (dd, 10-CH) and 7.48 ppm (m, aryl CH); M^+ = 386 amu.

Anal. Cacld for $C_{22}H_{18}N_4O_3$ + C_6H_6: C, 72.4; H, 5.2; N, 12.1. Found: C, 72.4; H, 5.1; N, 11.8.

Hydrolysis of **4b**.

The cycloadduct **4b** (2 g) in ethanol (5 ml), concentrated hydrochloric acid (10 ml) and water (10 ml) was refluxed for 2.5 hours. On cooling, cyanuric acid crystallised and was collected. The filtrate was evaporated under reduced pressure and the residue diluted with ice-water, neutralised with sodium bicarbonate and extracted wtih hot chloroform. The extracts were dried (magnesium sulfate), evaporated and the residue crystallised from ethanol to give the 8,7-16,15-bis-acenaphthyleno derivative of 2,10-diazapentacyclo[9.5.0.$0^{2,14}$.$0^{3,9}$.$0^{6,10}$]hexadecan-5,13-dione **6** (0.39 g, 30%) as colorless crystals from ethanol, mp > 310°; M^+ = 494 amu.

Anal. Calcd. for $C_{34}H_{26}N_2O_2$: C, 82.5; H, 5.3; N, 5.7. Found: C, 82.1; H, 5.2; N, 5.9.

Catalytic Hydrogenation of **4b**.

The cycloadduct **4b** (2 g) in ethanol (100 ml) was hydrogenated over Pd-C (10%, 0.5 g) at 30 lb/in^2 for 3 hours. The catalyst was removed by filtration and the filtrate evaporated. The residue was recrystallised from ethanol to give 6b(*SR*),7(*RS*),9,10,11(*RS*),11a(*RS*)hexahydro-12-(4,6-dimethoxy-*s*-triazin-2-yl)-7,11-iminocyclohept[*a*]acenaphthylen-8-one **7b** (1.8 g, 90%), mp 290-291°; M^+ = 388 amu.

Anal. Calcd. for $C_{22}H_{20}N_4O_3$: C, 68.0; H, 5.15; N, 14.4. Found: C, 68.2; H, 5.4; N, 14.3.

8-(4,6-Dimethylpyrimidin-2-yl)-8-azabicyclo-6-*endo*-ethoxycarbonyl-7-*exo*-phenyl[3.2.1]oct-3-en-2-one (**8a**).

The dimer **2a** (0.5 g) was heated in ethanol (25 ml) for 30 minutes and an excess of ethyl cinnamate (10 ml) was added. Heating was continued for a further 24 hours and the yellow residue, obtained after removal of all volatile material under reduced pressure, was purified by preparative tlc (chloroform) to give the 7-*exo*-phenyl-6-*endo*-carboxylic ester **8a** (0.25 g, 50%) as a viscous oil, which failed to solidify; ^{1}H nmr (deuteriochloroform): δ 1.23 (t, CH_3CH_2), 2.26 (s, pyrimidinyl 4,6-CH_3), 3.21 (dd, 7-*endo*-CH), 3.64 (t, 6-*exo*-CH), 4.14 (q, CH_3CH_2), 5.35 (d, 1-CH), 5.57 (t, 5-CH), 5.93 (dd, 3-CH), 6.35 (s, pyrimidinyl 5-CH), 6.80 (dd, 4-CH) and 7.25 ppm (m, phenyl); M = 377 amu.

Anal. Calcd. for $C_{22}H_{23}N_3O_3$: C, 70.0; H, 6.1; N, 11.1. Found: C, 70.3; H, 6.1; N, 10.8.

1(*RS*),8(*RS*)-7,7-Dimethyl-12-(4,6-dimethylpyrimidin-2-yl)-12-azatricyclo[6.3.1.$0^{2,6}$]dodeca-2(6),4,9-trien-11-one (**10**).

The dimer **2a** (0.5 g) in ethanol (25 ml) was heated under reflux for 30 minutes and 6,6-dimethylfulvene (1.0 g) was added. The solution was refluxed for a further 24 hours and the solvent was then removed under reduced pressure to give a solid, which was purified by preparative tlc (chloroform:petroleum ether, bp 60-80°, 1:3) to give the cycloadduct **10** (0.3 g, 41%), as pale yellow needles from ethanol, mp 149-150°; ^{1}H nmr (deuteriochloroform): δ 1.20 (s, 7-CH_3), 1.26 (s, 7-CH_3), 2.25 (s, pyrimidinyl 4,6-CH_3), 3.02 (d, 3-CH_2), 5.60 (d, 8-CH), 5.84 (d, 10-CH), 6.00 (s, 1-CH), 6.30 (m, 4-CH and 5-CH), 6.40 (s, pyrimidinyl 5-CH) and 7.04 ppm (dd, 9-CH).

Anal. Calcd. for $C_{19}H_{21}N_3O$ + C_2H_5OH: C, 71.4; H, 7.7; N, 11.9. Found: 71.6; H, 7.2; N, 12.3.

REFERENCES AND NOTES

(1) N. Dennis, A. R. Katritzky and Y. Takeuchi, *Angew. Chem., Int. Ed. Engl.*, **15**, 1 (1976); A. R. Katritzky and N. Dennis in "New Trends in Heterocyclic Chemistry", R. B. Mitra, N. R. Ayyanger, V. N. Gogte, R. M. Acheson and N. Cromwell, eds., Elsevier, New York, N. Y., 1979, p.290.

(2) N. Dennis, A. R. Katritzky, G. J. Saboungi and L. Turker, *J. Chem. Soc., Perkin Trans. I*, 1930 (1977).

(3) N. Dennis, B. Ibrahim and A. R. Katritzky, *ibid.*, 2307 (1976).

(4) N. Dennis, B. Ibrahim and A. R. Katritzky, *ibid.*, 2296 (1976).

(5) A. R. Katritzky, B. El-Osta, G. Musumarra and C. Ogretir, *J. Chem. Research, (M)*, 4074; *(S)* 322 (1978).

(6) A. R. Katritzky, A. Boonyarakvanich and N. Dennis, *J. Chem. Soc., Perkin Trans. I*, 343 (1980).

(7) N. Dennis, B. Ibrahim and A. R. Katritzky, *Org. Mass Spectrom.*, **11**, 814 (1976).

(8) R. A. Jones, A. H. Moustafa and A. Shalaby, unpublished work.