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The cycloaddition chemistry of 3-oxidopyraziniums. Dimerisation of 1-(4-methoxybenzyl)-5,6-dimethyl-3-oxidopyrazinium

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Dedicated to the great chemists Alan R. Katritzky and Charles W. Rees

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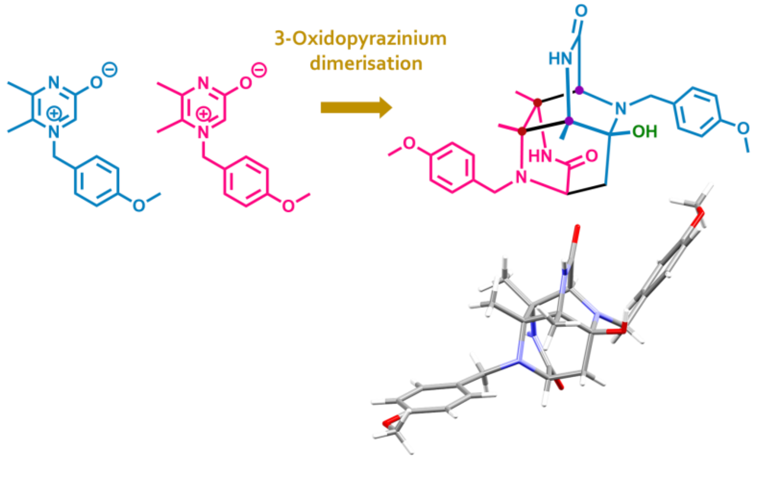
Abstract

3-Oxidopyraziniums are accessed from 2(1*H*)-pyrazinones via N-alkylation and then exposure of the resulting pyrazinium salts to mild base at room temperature. 3-Oxidopyraziniums react with acrylates in a 1,3-dipolar cyclisation producing 3,8-diazabicyclo[3.2.1]octanes. 1-(4-methoxybenzyl)-5,6-dimethyl-3-oxidopyrazinium ($C_{14}H_{16}N_2O_2$) dimerises at room temperature, forming a tetracyclic alcohol $C_{28}H_{34}N_4O_5$, the structure of which was elucidated using spectroscopic and X-ray analyses.

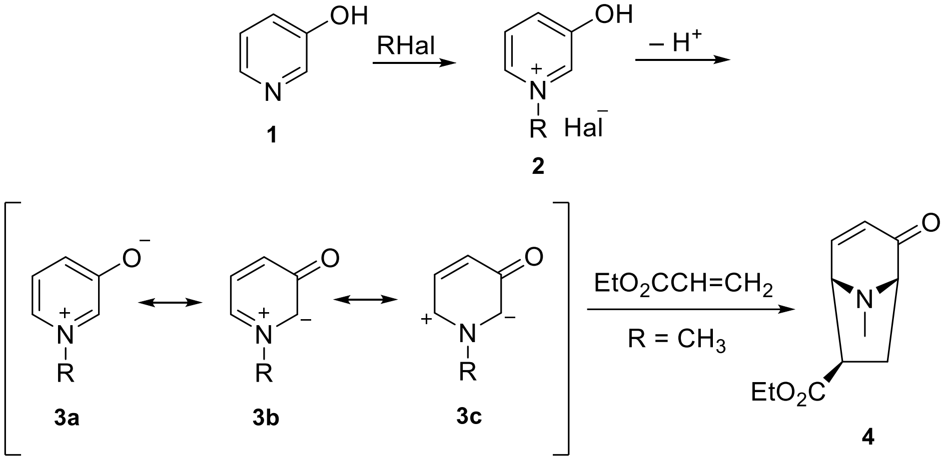


Keywords: 3-Oxidopyridiniums, 2(1*H*)-pyrazinone, 3-oxidopyraziniums, dipolar cycloadditions

Introduction

Alan Katritzky's extensive contributions to the systematic development of heterocyclic chemistry are no better illustrated than by his studies of the structures and reaction chemistry of zwitterions **3**,[1] neutral species, which were termed '3-oxidopyridiniums', thus **3** is 1-methyl-3-oxidopyridinium (R = Me) (*Chemical Abstracts* uses the term '3-hydroxy-1-methylpyridinium, inner salt') (Scheme 1). These isolable species were accessed via quaternisation of 3-hydroxypyridine **1** with an alkyl halide, giving 3-hydroxypyridinium salts **2**, and then O-deprotonation under mild conditions.

It was shown that 3-oxidopyridiniums act as dipoles in cycloaddition reactions with alkenes, across C-2 and C-6, thus, for example, 1-methyl-3-oxidopyridinium (**3**) (R=Me), with ethyl acrylate, produces ethyl 8-methyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6-carboxylate (**4**) (Scheme 1). Note that the regioselectivity of combination follows that implied by the polar resonance structure **3b**, taken with the polarisation of the acrylate C=C double bond.[1]

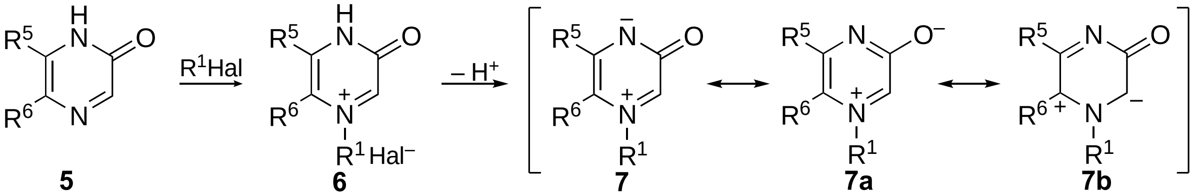


Scheme 1. Main resonance contributors to 3-oxidopyridiniums and reaction of 1-methyl-3-oxidopyridinium **3** (R=Me) with ethyl acrylate.

Results and Discussion

Synthesis and structure of 3-oxidopyraziniums

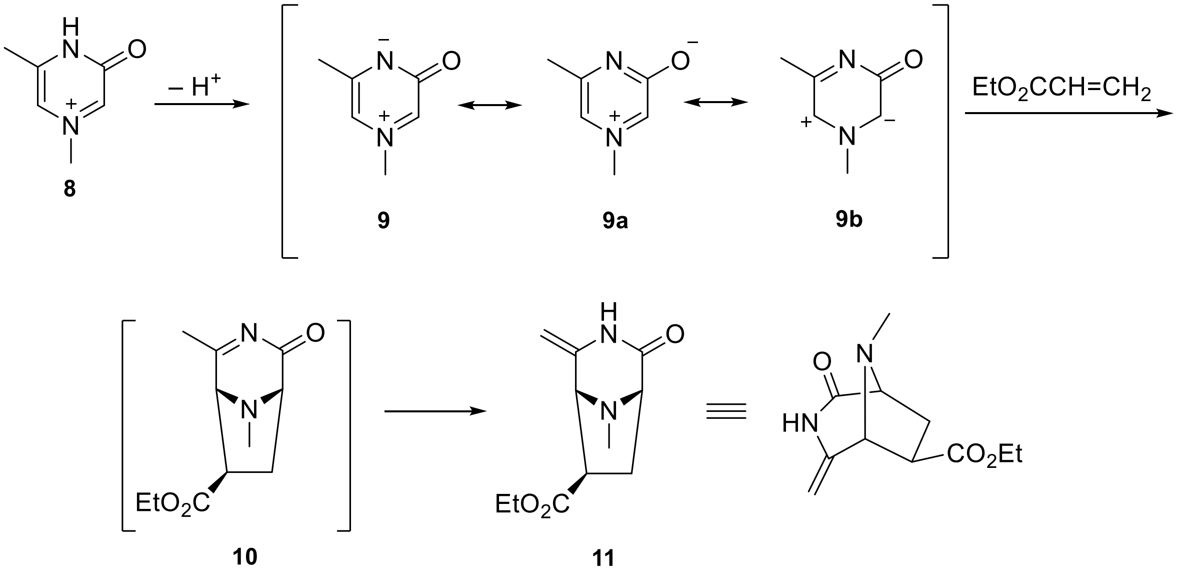
It occurred to us that comparable zwitterions and thence comparable cycloadditions might be possible in an analogous pyrazine series. 3-Oxidopyraziniums **7** (*Chemical Abstracts* uses the term '3,4-dihydro-3-oxopyrazinium, inner salt'), which were not known at the time, would need a synthesis route different from that used to produce 3-oxidopyridiniums. This requirement was satisfied by accessing 3-oxidopyraziniums **7** from 2(1*H*)-pyrazinones **5**.[2] We showed that regioselective quaternisation of the imine nitrogen (N-4) of a 2(1*H*)-pyrazinone **5** gives pyrazinium salts **6**, and that N-deprotonation of these reveals a 3-oxidopyrazinium **7**.



Scheme 2. Main resonance contributors to 3-oxidopyraziniums **7** and synthesis from 2(1*H*)-pyrazinones **5.**

Dipolar cycloadditions of 3-oxidopyraziniums

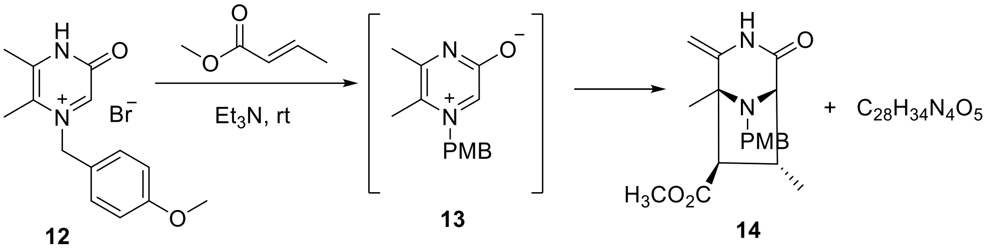
The 3-oxidopyraziniums **7** reacted, as we had hoped, with dipolarophiles across C-2 and C-6.[3,4] Scheme 3 shows the reaction of 1,5-dimethyl-3-oxidopyrazinium (**9**), in a typical dipolar cycloaddition with ethyl acrylate, producing ethyl 8-methyl-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-carboxylate (**11**). The anticipated direct adduct **10** was not seen in this, or other analogous situations; clearly the isomer with an enamide unit and an exocyclic methylene is thermodynamically preferred; **11** is simply a tautomer of **10**.



Scheme 3. Synthesis of 1,5-dimethyl-3-oxidopyrazinium (**9**) and its reaction with ethyl acrylate.

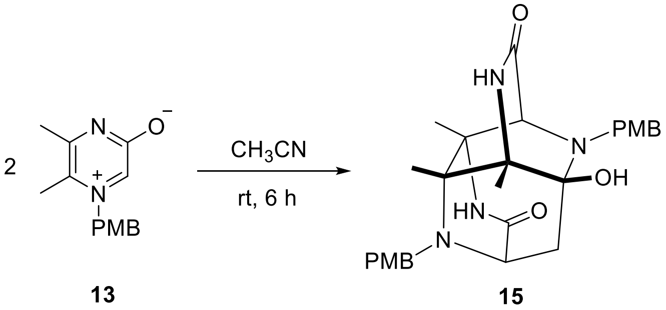
In our further work,[5] we found that it is not necessary to isolate the 3-oxidopyrazinium. Thus, reactions were carried out more conveniently by generation of the ylide in situ, at room temperature, in the presence of the dipolarophile, by addition of triethylamine as base to the pyrazinium salt, **8** in this case. We also found that using *para*-methoxybenzyl on the nitrogen, improved the solubility of these polar compounds, and additionally might eventually provide a means to deprotect the nitrogen, therefore we have used this N-substituent in our subsequent experiments.

When we came to examine the reaction of methyl crotonate with 1-(4-methoxybenzyl)-5,6-dimethyl-3-oxidopyrazinium (**13**), derived from 1-(4-methoxybenzyl)-5,6-dimethylpyrazinone bromide (**12**), a minor product was isolated in 29% yield, in addition to the expected cycloadduct **14** (51%).[5] The HRMS spectrum of this byproduct showed three major peaks at *m/z* 507.2596, 529.2419 and 545.2174 which corresponded to $[M+H]^+$, $[M+Na]^+$ and $[M+K]^+$, respectively, of a compound with molecular formula $C_{28}H_{34}N_4O_5$. Compared to that of the starting ylide, $C_{14}H_{16}N_2O_2$, it seemed that two molecules had combined to produce a 'dimer', with the incorporation of an equivalent of water.



Scheme 4. Cycloaddition between 3-oxidopyrazinium **13** and methyl crotonate.

Since methyl crotonate was not presumably involved in the formation of this byproduct, **13** was stirred at room temperature in the absence of this dipolarophile (Scheme 5). After 6 hours of reaction, as shown by TLC and NMR analysis, all the starting ylide **13** was converted into the byproduct $C_{28}H_{34}N_4O_5$, obtained in the cycloaddition reaction. The structure of this byproduct was unambiguously elucidated by single-crystal X-ray diffraction (Figure 1). It proved to be compound **15** (72% yield), a complex fused polycyclic structure with a tertiary alcohol (Scheme 5).



Scheme 5. Dimerization of 3-oxidopyrazinium **13**.

The ^{1}H-NMR spectra of **15** showed three methyl signals, the most downfield (1.43 ppm) corresponding to the bridgehead 8a-CH_3 (Figure 1). The signal of the quaternary C-8 appeared at a higher chemical shift (84.9 ppm) than the rest of non-aromatic carbon atoms, because it is functionalized with both an alcohol and an amine. In the ^{1}H-^{13}C HMBC spectrum, C-8 correlated with the methylene protons H-7 which appeared at 1.90 and 2.26 ppm as two doublet of doublets due to their mutual coupling and the coupling with H-6 at 3.18 ppm. The bridgehead H-3 was a singlet with important HMBC correlations with 4-CH_3 and the quaternary carbons C-4a and C-8.

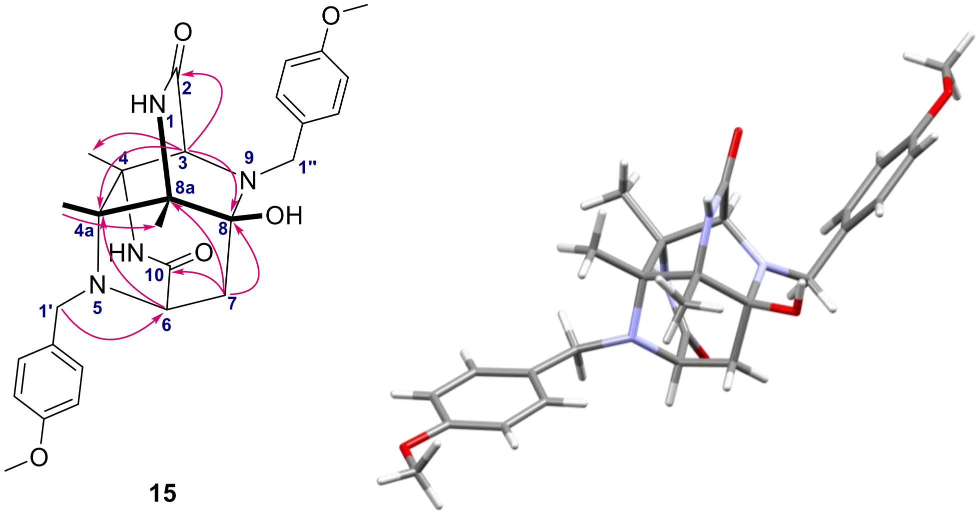


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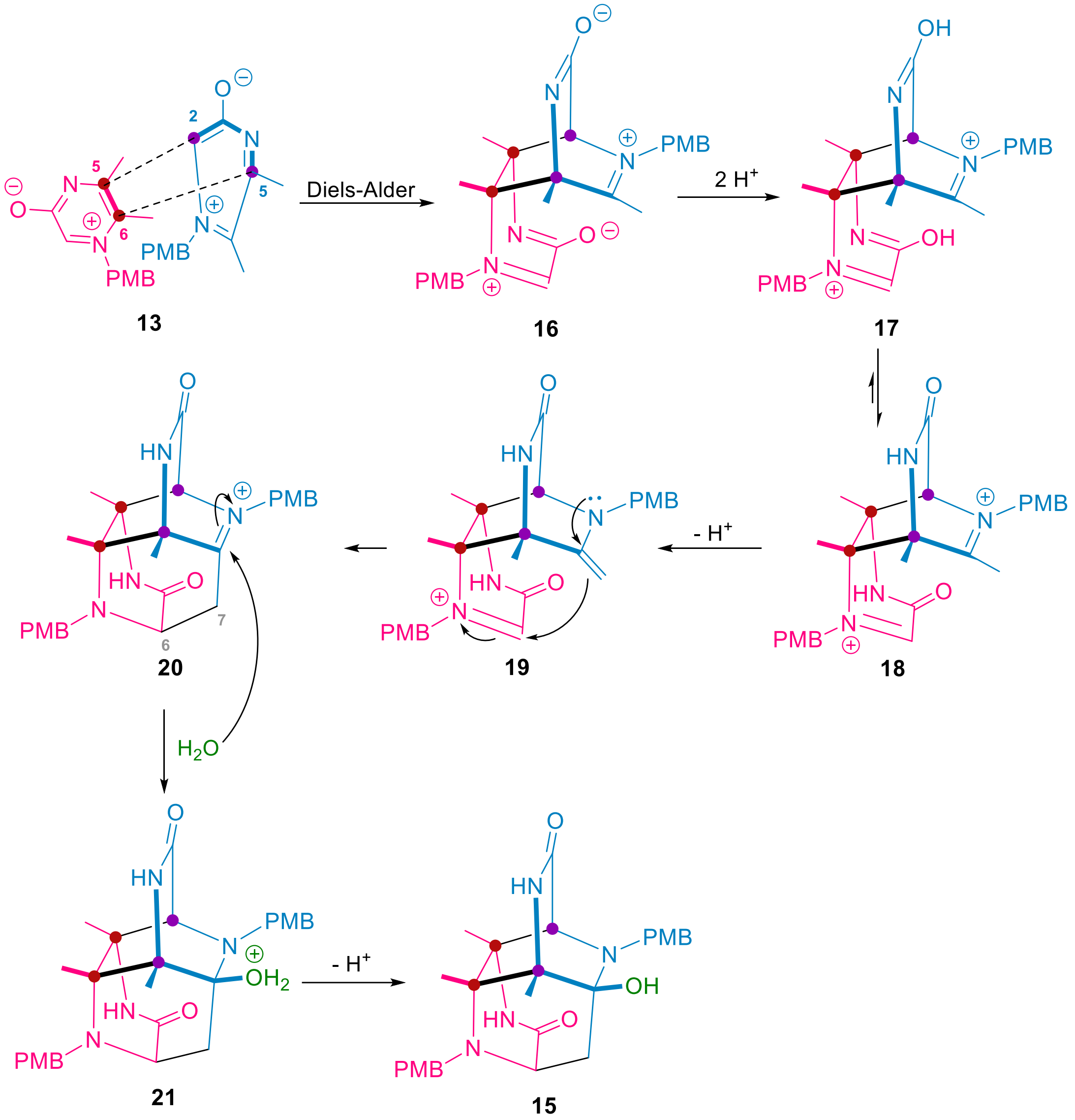
Figure 1. Selected key ^{1}H-^{13}C HMBC correlations and capped-stick representation of the X-ray crystal structure of **15**.

The structural elucidation of **15** demonstrated that it resulted from two equivalents of **13** together with a water equivalent. A feasible mechanism for the formation of this dimer is represented in Scheme 6. The key step of this mechanism is an aza-Diels-Alder reaction between two molecules of the 3-oxidopyrazinium **13**. Protonation of the resulting cycloadduct **16** would afford **17**, that could tautomerize to **18**. Deprotonation of the α-CH_3 of the iminium group would yield to **19**. This intermediate could cyclize through the nucleophilic attack of the enamine to the electrophilic iminium group, leading to the formation of the bond C-6–C-7 and resulting in the polycyclic intermediate **20**. Finally, the addition of H_2O to the iminium group of **20** and subsequent deprotonation of **21** would yield the hemiaminal group in **15**.



Scheme 6. Proposed mechanism of formation of the dimer **15** from **13**.

Conclusions

It seems that the tetracyclic system present in **15** has not been reported previously and, thus, these results show how other such poly-heterocycles could be obtained utilizing 3-oxidopyrazinium chemistry. In work on 3-oxidopyridiniums,[1] dimers were seen when the N-substituent was strongly electron-withdrawing, but these bear no structural relationship to that of **15**. Thus, the structure **15**, arising from this work, is novel and its proposed mode of formation intriguing. Once, again the pioneering studies of the Katritzky group have led, albeit indirectly, to new heterocyclic knowledge.

Experimental Section

General methods. Anhydrous CH_3CN and CH_2Cl_2 were obtained from MBraun SPS-800 (Garching, Germany) solvent purification system. Thin layer chromatography (TLC) analyses were performed on precoated TLC plates, silica gel 60 F_{254} (Merck) and detection was done with UV light (254 nm). Flash chromatography purifications were performed on silica gel 60 (0.040-0.063 mm, Merck). NMR experiments were recorded in the Serveis Tècnics de Recerca de la Universitat de Girona (STR-UdG) with an Ultrashield Avance III 400 (9.4 T) spectrometer from Bruker (^1H, 400 MHz; ^{13}C, 100 MHz), equipped with an RT BBI probe and a temperature control unit (BCU Xtreme) or with an Ultrashield ASCEND Nanobay 400 (9.4T) from Bruker (^1H, 400 MHz; ^{13}C, 100 MHz). Structural assignments were made with additional information from COSY, HSQC, and HMBC experiments. NMR spectra were processed and analysed using TopSpin 3.6.2. Chemical shifts were reported as δ (ppm) directly calibrated with the solvent signal. IR spectra were recorded with a Cary 630 FT-IR spectrophotometer (Agilent Technologies) equipped with a Golden Gate Single Reflection, ATR MK-II system. For the acquisition, the instrument was controlled with the MicroLabPC software, and spectra were analysed with ResolutionsPro 5.2.0. ESI-MS analyses were performed with an Esquire 6000 ESI Bruker ion Trap LC/MS instrument equipped with an electrospray ion source (STR-UdG) operating in both positive and negative ion modes. Samples (5 µL) were introduced into the mass spectrometer ion source directly through a 1200 Series Agilent HPLC autosampler. The mobile phase, CH_3CN/H_2O (80:20), was delivered by an Agilent 1200 Series HPLC pump at a flow rate of 100 µL/min. Nitrogen was employed as both drying and nebulizing gas. HRMS were recorded under conditions of ESI with a Bruker MicroTOF-Q II instrument using a hybrid quadrupole time-of-flight mass spectrometer (STR-UdG). Samples were introduced into the mass spectrometer ion source by direct infusion through a syringe pump and were externally calibrated using sodium formate. Single-crystal X-ray diffraction (XRD) data was acquired on a Bruker D8 Quest Eco diffractometer (STR-UdG) equipped with a graphite-monochromated molybdenum Kα radiation (λ = 0.71073 Å) and a Photon II area detector. The melting point (mp) of the compounds was determined with a Melting Point SMP10 (Stuart) instrument and their values are expressed in degrees Celsius (°C).

Synthesis of 5,6-dimethyl-2(1*H*)-pyrazinone. In a 250 mL round-bottom flask, glycinamide hydrochloride (2.5 g, 22.6 mmol, 1 equiv) was dissolved in MeOH (40 mL) and the solution cooled to –30 to –40 °C. Aq NaOH 12.5 M (56.5 mmol, 2.5 equiv) was added and the mixture stirred for 10 min. After that, a solution of butane-2,3-dione (2.4 mL, 27.2 mmol, 1.2 equiv) in MeOH (10 mL), previously cooled, was added dropwise and the mixture was maintained at –30 °C for 30 min and then at rt for 3 h. The formation of the 2(1*H*)-pyrazinone was monitored by TLC and once it was complete, concentrated HCl was added to the crude reaction mixture followed by neutralization with a saturated aq solution of $NaHCO_3$. MeOH was evaporated under reduced pressure and the remaining aq. solution extracted with $CHCl_3$ (3 × 50 mL). The organic extract was dried over anhydrous $MgSO_4$, filtered and evaporated to give 5,6-dimethyl-2(1*H*)-pyrazinone. Recrystallization of the crude product from acetone afforded 5,6-dimethyl-2(1*H*)-pyrazinone as a pale pink solid (1.21 g, 43% yield).
MW ($C_6H_8N_2O$): 124.1 g/mol. **TLC** ($CHCl_3/CH_3OH/AcOH$ 8:6:0.5): R_f = 0.63; **mp**: 194-196 °C.
FT-IR (ATR) ν (cm^{-1}): 3271 (N–H), 2855 (C–H), 1683 (C=O), 1607 (N–C=O).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.29 (s, 3H, 6-CH_3), 2.32 (s, 3H, 5-CH_3), 8.01 (s, 1H, H-3), 13.90 (br, H-1).
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 17.1 (5-CH_3), 19.3 (6-CH_3), 132.4 (C-5), 134.5 (C-6), 144.4 (CH, C-3), 159.2 (C-2).

ESI-MS (*m/z*): 125.1 [M+H]$^+$, 147.0 [M+Na]$^+$; **ESI-HRMS** (*m/z*) calcd. for $C_6H_8N_2ONa$ [M+Na]$^+$ 147.0529, found 147.0537; calcd. for $(C_6H_8N_2O)_2Na$ [2M+Na]$^+$ 271.1165, found 271.1169.

Synthesis of 1-(4-methoxybenzyl)-5,6-dimethyl-3-oxo-3,4-dihydropyrazin-1-ium bromide (12). In a round-bottom flask, 5,6-dimethyl-2(1*H*)-pyrazinone (1.18 g, 9.52 mmol, 1 equiv) was dissolved in anhydrous CH_3CN under N_2 and, subsequently, *p*-methoxybenzyl bromide (3.83 g, 19.04 mmol, 2 equiv) was added. The mixture was heated at reflux for 6 h and then stirred at rt for 18 h, until completion as evidenced by TLC. Once finished, the solvent was evaporated under reduced pressure and the residue was purified by reversed-phase chromatography. Elution with H_2O/CH_3CN (85:15) afforded 1-(4-methoxybenzyl)-5,6-dimethyl-3-oxo-3,4-dihydropyrazin-1-ium bromide (**12**) (2.33 g, 75% yield) as a pale brown solid.

MW ($C_{14}H_{17}N_2O_2Br$): 325.2 g/mol. **TLC** ($CHCl_3/CH_3OH$ 9:1): $R_f = 0.14$; **mp**: 108-112 °C.

FT-IR (ATR) ν (cm^{-1}): 3338 (N–H), 2917 (C–H), 1673 (C=O), 1606 (Ar), 1510 (N–C=O), 1247 and 1176 (C–O).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.58 (s, 3H, 5-CH_3), 2.59 (s, 3H, 6-CH_3), 3.75 (s, 3H, 5′-OCH_3), 5.72 (s, 2H, H-1′), 6.89 (d, *J* 8.4 Hz, 2H, H-4′), 7.30 (d, *J* 8.4 Hz, 2H, H-3′), 8.23 (s, 1H, H-2).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 15.2 (6-CH_3), 21.6 (5-CH_3), 55.4 (5′-OCH_3), 62.9 (CH_2, C-1′), 115.2 (2CH, C-4′), 121.7 (C-2′), 128.9 (CH, C-2), 130.8 (2CH, C-3′), 133.6 (C-6), 155.6 (C-5), 159.4 (C-3), 160.8 (C-5′).

ESI-MS *(m/z)*: 121.0 $[CH_3O\text{-}C_6H_4\text{-}CH_2]^+$, 245.1 [M]$^+$, 267.1 [M–H+Na]$^+$; **ESI-HRMS** *(m/z)*: calcd. for $C_{14}H_{16}N_2O_2Na$ [M–H+Na]$^+$ 267.1104, found 267.1116; calcd. for $(C_{14}H_{16}N_2O_2)_2Na$ [2M–2H+Na]$^+$ 511.2316, found 511.2327.

Synthesis of methyl 8-(4-methoxybenzyl)-5,7-dimethyl-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-carboxylate (14). To a suspension of 1-(4-methoxybenzyl)-5,6-dimethyl-3-oxo-3,4-dihydropyrazin-1-ium bromide **12** (107 mg, 0.33 mmol, 1 equiv) in anhydrous CH_3CN (2 mL), triethylamine (1.5 equiv) was added dropwise, and the mixture was stirred at room temperature under nitrogen. After 10 min, the formation of an orange transparent solution evidenced the formation of the 3-oxidopyrazinium **13**. Then, methyl crotonate (54 µL, 0.50 mmol, 1.5 equiv) was added dropwise to the ylide and the resulting mixture was stirred under nitrogen at room temperature for 6 h. The progress of the reaction was monitored by TLC. Once the reaction was complete, the solvent was removed under reduced pressure. Purification of the residue by flash chromatography eluting with CH_2Cl_2/CH_3OH (99:1) afforded **14** (58 mg, 51% yield) as a colourless solid.

MW ($C_{19}H_{24}N_2O_4$): 344.4 g/mol; **TLC** ($CHCl_3/CH_3OH$ 9:1): $R_f = 0.70$; **HPLC** (λ = 220 nm) t_R = 6.49 min (98% purity); **mp**: 179-182 °C.

FT-IR (ATR) ν (cm^{-1}): 2951 (C–H), 1733 and 1680 (C=O), 1509 (Ar), 1165 (C–O).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.04 (d, *J* 7.2 Hz, 3H, 7-CH_3), 1.36 (s, 3H, 5-CH_3), 2.60 (d, *J* 7.2 Hz, 1H, H-6), 2.95 (sext, *J* 7.2 Hz, 1H, H-7), 3.26 (d, *J* 13.6 Hz, 1H, H-1′), 3.38 (dd, *J* 7.2 Hz, *J′* = 1.2 Hz, 1H, H-1), 3.72 (d, *J* 13.6 Hz, 1H, H-1′), 3.76 (s, 3H, CO_2CH_3), 3.79 (s, 3H, 5′-OCH_3), 4.19 (d, *J* 1.6 Hz, 1H, H-9), 4.31 (d, *J* 1.6 Hz, 1H, H-9), 6.83 (d, *J* 8.6 Hz, 2H, H-4′), 7.22 (d, *J* 8.6 Hz, 2H, H-3′), 8.04 (s, 1H, H-3).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 15.0 (7-CH_3), 17.7 (5-CH_3), 38.7 (CH, C-7), 49.4 (CH_2, C-1′), 52.1 (CO_2CH_3), 55.4 (5′-OCH_3), 60.9 (CH, C-6), 64.0 (C-5), 67.7 (CH, C-1), 90.0 (CH_2, C-9), 113.9 (2CH, C-4′), 129.8 (2CH, C-3′), 130.3 (C-2′), 146.8 (C-4), 158.9 (C-5′), 170.3 (C-2), 173.2 (CO_2CH_3).

ESI-MS (*m/z*): 345.1 [M+H]$^+$. **ESI-HRMS** (*m/z*) calcd. for $C_{19}H_{24}N_2O_4Na$ [M+Na]$^+$ 367.1628, found 367.1625; calcd. for $(C_{19}H_{24}N_2O_4)_2Na$ [2M+Na]$^+$ 711.3364, found 711.3327.

Dimerisation of the 3-oxidopyrazinium 13. Synthesis of 15. To a suspension of 1-(4-methoxybenzyl)-5,6-dimethyl-3-oxo-3,4-dihydropyrazin-1-ium bromide (**12**) (42.0 mg, 0.12 mmol) in anhydrous CH_3CN (0.8 mL), triethylamine (24 µL, 0.18 mmol, 1.5 equiv) was added dropwise, and the mixture was stirred at room temperature under nitrogen for 6 h. The progress of the reaction was monitored by TLC. Once the reaction was

complete, the solvent was removed under reduced pressure. Final purification by flash chromatography eluting with CH_2Cl_2/CH_3OH (98:2) afforded the polycyclic compound **15** (21.5 mg, 72% yield) as brown solid. Suitable crystals for XRD were obtained by slow evaporation of a $CHCl_3$ solution.
MW ($C_{28}H_{34}N_4O_5$): 506.6 g/mol; **TLC** ($CHCl_3/CH_3OH$ 9:1): $R_f = 0.51$.
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.13 (s, 3H, 4-CH_3), 1.27 (s, 3H, 4a-CH_3), 1.43 (s, 3H, 8a-CH_3), 1.90 (dd, *J* 13.2 Hz, *J'* = 5.6 Hz, 1H, H-7), 2.26 (dd, *J* 13.2 Hz, *J'* = 2.4 Hz, 1H, H-7), 2.50 (s, 1H, H-3), 3.18 (dd, *J* 5.6 Hz, *J'* = 2.4 Hz, 1H, H-6), 3.42 (d, *J* 13.6 Hz, 1H, H-1'), 3.66 (d, *J* 13.6 Hz, 1H, H-1''), 3.73 (s, 3H, 5'-OCH_3), 3.74 (s, 3H, 5''-OCH_3), 3.93 (d, *J* 13.6 Hz, 1H, H-1''), 3.99 (d, *J* 13.6 Hz, 1H, H-1'), 6.79 (d, *J* 8.8 Hz, 4H, H-4' and H-4''), 7.11-7.16 (m, 4H, H-3' and H-3'').
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 14.2 (8a-CH_3), 18.3 (4a-CH_3), 23.8 (4-CH_3), 38.0 (CH_2, C-7), 49.7 (CH_2, C-1''), 52.7 (CH_2, C-1'), 55.1 (5'-OCH_3), 55.2 (5''-OCH_3), 57.2 (CH, C-6), 60.4 (C-4), 61.7 (C-4a), 63.9 (C-8a), 66.2 (CH, C-3), 84.9 (C-8), 113.7 and 113.8 (4CH, C-4' and C-4''), 129.2 (2CH, C-3'), 130.3 (2CH, C-3''), 130.5 (C-2''), 131.4 (C-2'), 158.7 (2C, C-5' and C-5''), 173.6 (C-2), 178.6 (C-10).
(+)-ESI-MS (*m/z*): 507.2 $[M+H]^+$; **(–)-ESI-MS** (*m/z*): 505.0 $[M-H]^-$; 551.0 $[M+HCOO]^-$ **ESI-HRMS** (*m/z*) calcd. for $C_{28}H_{35}N_4O_5$ $[M+H]^+$ 507.2602, found 507.2596; calcd. for $C_{28}H_{34}N_4O_5Na$ $[M+Na]^+$ 529.2421, found 529.2419; calcd. for $C_{28}H_{34}N_4O_5K$ $[M+K]^+$ 545.2161, found 545.2174.

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Supplementary Material

Spectroscopic data (NMR, ESI-MS, HRMS, FT-IR, XRD) of synthesized compounds are available in the supplementary material file associated with this manuscript.
CCDC 2353346 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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