

Cycloaddition products of 3-oxido-1-phenylpyridinium and 1-cyanoacenaphthylene

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Cycloaddition of 3-oxido-1-phenylpyridinium **8a** to 1-cyanoacenaphthylene **9a** affords three isomeric adducts (**13**, **14** and **15**). Structures for these compounds resulted from a comparative NMR study, as well as an X-ray crystallographic determination of isomer **15**. Attempts to eliminate HCN from compounds **13–15** resulted only in cycloreversion to 1-cyanoacenaphthylene.

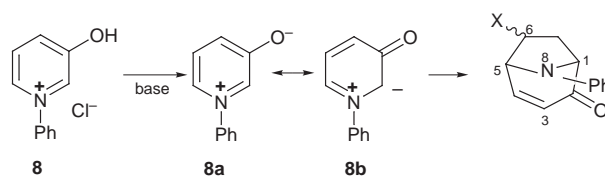
Introduction

Imerubrine **1**¹ and grandirubrine **2**²—isolated in 1975 and 1980, respectively, from the tropical American genus *Abuta* (Menispermaceae)—were for many years the only known members of a class of naturally occurring tropoloisoquinoline alkaloids.

Recently, other members of the class, namely isoimerubrine **3**, pareirubrines A and B (**4** and **5**) and pareitropone **6**³ have been isolated. Banwell and his group⁴ have reported the total synthesis of compounds **1** and **2**, and subsequently, Boger and

a potential pathway to compound **7**, the simple carbocyclic analog of these alkaloids.

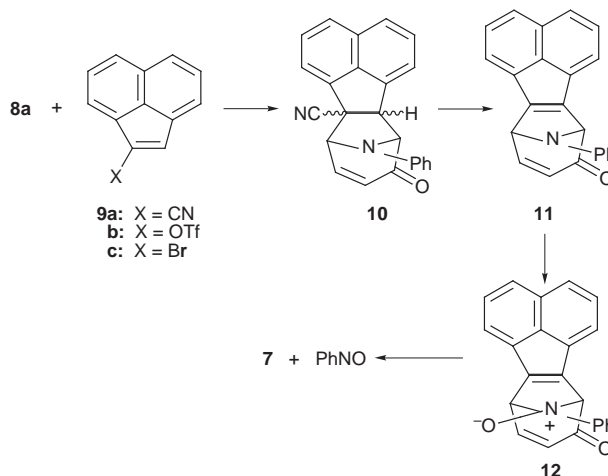
The reaction of 3-oxido-1-phenylpyridinium **8a** (prepared *in situ* from reaction of 3-hydroxy-1-phenylpyridinium chloride **8** and triethylamine), with 2π -electron dipolarophiles to form 8-azabicyclo[3.2.1]oct-3-en-2-ones as cycloadducts, has been studied in depth by Katritzky and his co-workers (Scheme 1).⁶



Scheme 1

Various dipolarophiles (e.g. styrene, acrylonitrile, diethyl maleate and phenylacetylene) and pyridinium salts have been employed. Hofmann degradation of the quaternized cycloadducts usually produces tropones.⁷

One of our approaches to the acenaphthenotropone system was based on the electronically directed dipolar addition of the pyridinium dipole **8a** to the nitrile **9a** (Scheme 2). We



Scheme 2

Takahashi⁵ have synthesized compounds **1**, **2** and **3**. These are the only total syntheses of the tropoloisoquinoline alkaloids that have so far been reported. In our efforts to develop an alternate route to the tropoloisoquinoline system, we explored

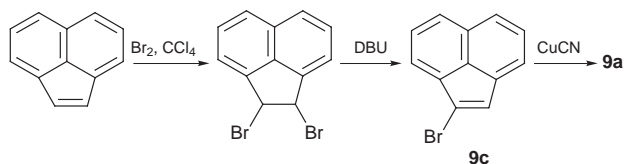
anticipated that treatment of the resultant enone **10** with a strong protic base would result in elimination of hydrogen cyanide to form **11**. The compound **11** could then be oxidized to an unstable *N*-oxide **12**, which could collapse to nitrosobenzene and the desired tropone skeleton. There are many cases of analogous aromatization *via* oxidation of a bridged nitrogen

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and, in fact, we have found this reaction to be very useful in some of our own previous work.⁸

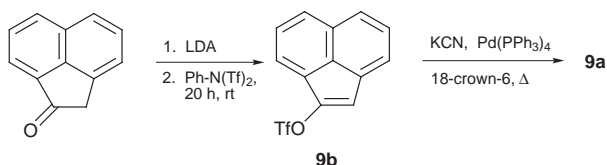
Results and discussion

Acenaphthylene-1-carbonitrile **9a** was obtained from readily available acenaphthylene in 50% yield, by the bromination–dehydrobromination and halide exchange sequence outlined in Scheme 3.^{9,10}



Scheme 3

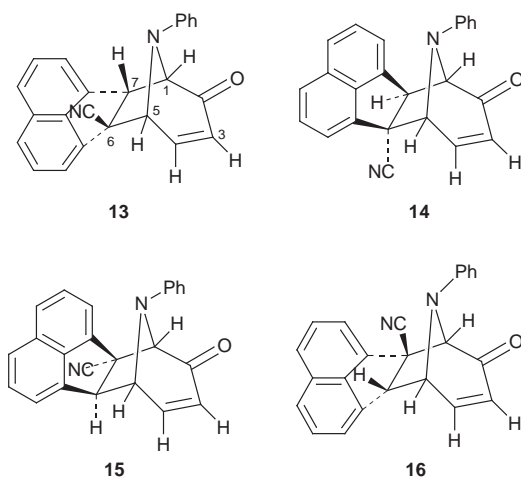
We also obtained **9a** by conversion of acenaphthenone to the unsaturated triflate **9b** using *N*-phenyltrifluoromethanesulfonamide¹¹ followed by treatment with LiCN according to the method of Piers (Scheme 4).¹² In our hands, the triflate was



Scheme 4

obtained in 73% yield and conversion to the nitrile required use of KCN, 18-crown-6 and catalytic amounts of tetrakis-(triphenylphosphine)palladium. The overall yield from acenaphthenone using this pathway, however, was only 38%.

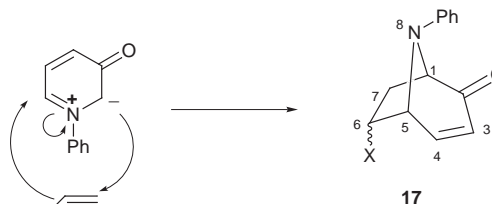
The dipolarophile **9a**, on refluxing with 3-hydroxy-1-phenylpyridinium chloride (1.07 molar equivs.) and triethylamine (1.6 molar equivs.) for eighteen hours, produced the corresponding cycloadducts **13**, **14** and **15** as a mixture in the ratio 1:8:3. In our hands, none of the compound **16** was isolated.



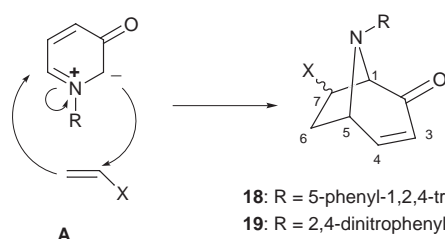
For addition at the 2,6-position of the dipole, the usual mode of reaction is as shown in Scheme 5, to produce the 6-substituted adduct **17**. In their study of peri-, site-, regio- and stereo-selectivity of these reactions,¹³ Katritzky and his group indicate that 6-substituted regioisomers **17** are favored for monosubstituted ethylenes. Only very few instances of addition to produce 7-substituted compounds of the type **15** have been found. These instances include formation of compounds **18–21**^{6a,14–16} and arise by reaction in the manner

Table 1 Typical coupling constants for protons of cycloadducts

Protons	<i>J</i> /Hz	Protons	<i>J</i> /Hz
1,3	0–1.5	6- <i>exo</i> , 6- <i>endo</i>	13.0
1,7- <i>endo</i>	0–1.0	6- <i>endo</i> , 7- <i>endo</i>	9.5–10.0
1,7- <i>exo</i>	7.5–8.5	6- <i>endo</i> , 7- <i>exo</i>	4.0
3,4	9.5–10.0	6- <i>exo</i> , 7- <i>exo</i>	9.0–11.0
4,5	5.0–6.0	6- <i>exo</i> , 7- <i>endo</i>	6.0–7.0
5,6- <i>endo</i>	0.0	7- <i>endo</i> , 7- <i>exo</i>	14.0–14.5
5,6- <i>exo</i>	5.8–7.0		



Scheme 5



18: R = 5-phenyl-1,2,4-triazin-3-yl, X = CN

19: R = 2,4-dinitrophenyl, X = CN

20: R = Me, X = CO₂Me

21: R = -N=CHPh, X = CN

shown in **A**, indicating that activation of the dipolarophile by electron-withdrawing groups is not a requirement for reaction. Compounds **13** and **14** are the *endo*- and *exo*-adducts, respectively, of the cycloaddition according to the normal mode of reaction shown in Scheme 5. Compound **15** is the *exo*-adduct of the reaction in the less common mode shown as **A**.

Katritzky and his group compared the proton NMR spectra of *exo*- and *endo*-isomers of many of these cycloadducts.^{6a,6c,14} Table 1 above shows the characteristic coupling constants observed.

The proton NMR data for our new adducts are shown in Table 2. Structural assignments were confirmed by double-resonance experiments. We were able to confirm the stereochemistry of our products by comparison of coupling constants, and by decoupling experiments. The structure of **15** was unambiguously established by single crystal X-ray determination as the *exo*-adduct of cycloaddition in the less common mode **A** (Fig. 1). The data immediately disqualifies adduct **16**, since, on referring to the values listed in Table 1, H-5 here should be a double doublet, coupled to H-6-*exo* and to H-4 with *J* values of ~6–7 and ~5–6 Hz respectively. None of the products showed this feature. The *endo*-adduct **13** had the resonance due to H-1 as its distinguishing feature. This showed up as a double doublet with coupling due to H-3 (*J* value ~1 Hz) and to H-7-*exo* (*J* value of ~8 Hz).

In the NMR spectrum of **15**, H-1 appears as a broadened singlet, with fine splitting due to H-3. This was confirmed by irradiation at δ 6.22. H-3 appears as a double doublet coupled with H-4 and H-1, and H-4 appears as part of a two hydrogen multiplet in the aromatic region, which signal is distinguished on irradiation at δ 6.22 and 4.86. H-5 appears as a doublet (coupling with H-4) and H-6 as a singlet at δ 4.69. As shown in Table 2, the NMR spectra of compounds **14** and **15** are very similar. With single crystal X-ray establishing the structure of **15**, the structure of **14** was thus confirmed, by elimination, to be the *exo*-adduct of cycloaddition according to the normal mode (Scheme 5).

Table 2 Proton NMR spectral data for cycloadducts **13–15**, **22** and **23**

Compound	Chemical shifts (δ) (multiplicity, J /Hz)					
	H-1 ^a	H-3	H-4	H-5	H-6	H-7
13	5.10 (dd, ~1, 7)	5.28 (dd, ~1, 9.5)	6.32 (dd, 5, 9.5)	5.38 (d, 5)	—	5.32 (d, 7)
14	4.54 (s)	6.31 (dd, 1, 10)	7.57 (m with arom. H's)	5.08 (d, 5)	—	4.55 (s)
15	4.73 (bs)	6.22 (dd, 1, 10)	7.48 (m with arom. H's)	4.86 (d, 5)	4.69 (s)	—
22	4.97m	5.27 (dd, 1.5, 9)	6.49 (dd, 5, 9)	5.18 (dd, 5, 7)	4.87 (t, ~7)	4.97m
23	4.57 (d, ~1)	6.05 (dd, 1, 9)	7.44 (m with arom. H's)	4.86 (d, 5)	4.34 (d, 7)	4.21 (d, 7)

^a Numbering of protons (see **13**) is non-systematic. Used to coincide with positions described in Table 1, which we use for comparison.

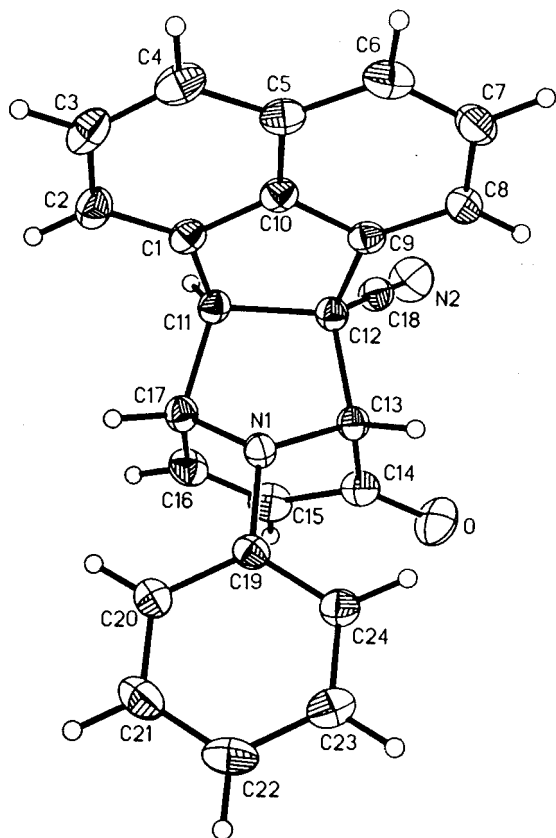


Fig. 1 Molecular structure of **15** showing the crystallographic numbering system used

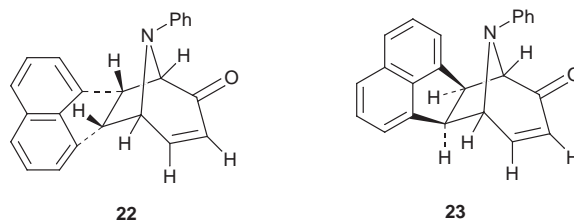
The proton NMR spectrum of the *endo*-adduct **13** (acenaphthylene ring down) is different from that of the *exo*-adduct **14** in characteristic ways.

- In **13**, H-1 appears as a double doublet with J values of 7 and 1.7 Hz being due to coupling with H-7-*exo* and H-3, respectively, whereas in **14**, H-1 appears as a singlet.
- In **13**, H-7 appears as a doublet coupled to H-1, whereas in **14**, H-7 appears as a singlet.
- Signals corresponding to H-3 and H-4 appear at δ 5.28 and 6.32 respectively in the spectrum of compound **13**. In the spectra of **14** and **15**, the signals for these protons appear at δ ~6.31 and ~7.57, respectively. This is no doubt due to the fact that in the case of **13**, the protons H-3 and H-4 reside within the shielding zone of the acenaphthylene ring system.

Unfortunately, our attempts at removal of HCN from these adducts using potassium *tert*-butoxide or methoxide, were unsuccessful. Heating the cycloadduct in triethylamine resulted only in partial (35%) conversion to the nitrile **9a**, evidence of thermally induced retro-1,3-dipolar cycloaddition.^{6d,17} 1,3-Dipolar additions are also known to be reversible photo-

chemically,¹⁸ and by electron impact.¹⁹ The lack of molecular ions in the mass spectra of adducts **13–15** (obtained *via* electron-impact techniques), and the appearance of base peaks at m/z 177 (corresponding to M^+ for 1-cyanoacenaphthylene **9a**), provides further indication of the facility with which the undesired cycloreversion takes place.

We also attempted the cycloaddition reaction using acenaphthylene-1-yl trifluoromethanesulfonate **9b**, 1-bromoacenaphthylene **9c** and acenaphthylene, as the dipolarophiles. Compounds **9b** and **9c** both proved unreactive, whereas acenaphthylene produced a 17% yield of the cycloadduct as a 1:1 mixture of two isomers (**22** and **23**) after 23 hours at reflux. Starting material (82%) was recovered from the reaction.



Again, examination of the NMR data of the adducts led to the establishment of their structures. Double-resonance experiments were used to confirm the assignments of protons. Note the shielding of H-3 and H-4 in compound **22** as compared with **23** (δ 5.27 and 6.49 as against δ 6.05 and 7.44), and the signal for H-5 appearing as a double doublet with $J = 5$ and 7.2 Hz (coupled with H-4 and H-6 respectively), which was ready evidence of **22** being the *endo*-adduct. (From Table 1, $J_{5,6-endo} = 0$.) All other signals were in accordance with these assignments.

Experimental

General

All mps are uncorrected. NMR spectra (Bruker 360 MHz spectrometer) were determined in $CDCl_3$ solution and the resonances are reported in δ units downfield from TMS. Elemental analyses were carried out by Atlantic Microlabs, Atlanta, Georgia.

Acenaphthylene-1-carbonitrile **9a**

A mixture of 1-bromoacenaphthylene (25 g, 108 mmol) and CuCN (17.5 g, 195 mmol) in *N,N*-dimethylacetamide (105 cm³) was heated at reflux for 2 h. The mixture was diluted with CH_2Cl_2 (~800 cm³) whereupon CuBr precipitated. This was filtered, and the filter cake washed with CH_2Cl_2 . The CH_2Cl_2 solution was then washed with water (3 \times 150 cm³), dried (Na_2SO_4) and concentrated to give a maroon-red liquid which was purified by flash chromatography (SiO_2 , hexane- CH_2Cl_2 5:1) to give the desired nitrile as a yellow solid (12.02 g, 63%), mp 51–52 °C (lit.,⁹ mp 53 °C).

Cycloadducts 13, 14 and 15

A mixture of the nitrile **9a** (12.02 g, 67.91 mmol) and 3-hydroxy-1-phenylpyridinium chloride **8** (15 g, 72.46 mmol) in acetonitrile (280 cm³) was heated at reflux with stirring, in an atmosphere of nitrogen, for 30 min. Triethylamine (15 cm³, 108.7 mmol) was then added to the mixture and heating continued at reflux for a further 18 h after which the solvent was removed *in vacuo*. The resultant solid was dissolved in CH₂Cl₂, washed with water, and the CH₂Cl₂ solution dried (Na₂SO₄) and concentrated to yield a very dark oil. Flash chromatography (SiO₂, hexane–CH₂Cl₂ 2:1) afforded the starting nitrile **9a** (7.84 g, 65%). Gradually increasing the polarity of the solvent system to hexane–CH₂Cl₂ 1:1, produced a mixture of compounds **13** and **14** (3.75 g), and a second band containing compound **15** as major product.

Recrystallization of the first batch (3.75 g) of product from CH₂Cl₂–MeOH produced **13** as fluffy yellow needles (0.27 g, 1.1%), mp 178 °C; *m/z* (relative intensity) 177 (100), 171 (10), 150 (26) (Found: C, 82.6; H, 4.6; N, 8.0. Calc. for C₂₄H₁₆N₂O: C, 82.7; H, 4.6; N, 8.0%).

The mother liquor was concentrated and recrystallized from MeOH to give **14** as a yellow powder (2.01 g, 8.5%), mp 146 °C; *m/z* (relative intensity) 177 (100), 171 (70), 150 (65) (Found: C, 82.55; H, 4.6; N, 8.0. Calc. for C₂₄H₁₆N₂O: C, 82.7; H, 4.6; N, 8.0%).

The second band was further purified by chromatography (SiO₂, hexane–EtOAc 2:1) and compound **15** was obtained as yellow crystals (0.83 g, 3.5%), mp 168–169 °C; *m/z* (relative intensity) 177 (100), 171 (60), 150 (80) (Found: C, 82.8; H, 4.6; N, 8.0. Calc. for C₂₄H₁₆N₂O: C, 82.7; H, 4.6; N, 8.0%).

X-Ray data collection, structure determination and refinement for 15

A yellow single crystal of **15** was mounted on a fiber and transferred to the Siemens SMART CCD area detector diffractometer system. The crystal was cooled to –100 °C during data collection by using a stream of cold nitrogen gas. Compound **15** crystallizes in the monoclinic space group *Cc* with *a* = 19.351(12), *b* = 10.069(6), *c* = 8.966(6) Å, β = 91.91(1)°, *V* = 1746.2(2) Å³, μ = 0.082 mm^{–1}, and ρ_{calc} = 1.325 Mg m^{–3} for *Z* = 4. Graphite monochromated Mo-K α radiation (λ = 0.7107 Å) was utilized to collect 5400 reflections within the θ range 2.11 to 27.88°. Of the total reflections collected, 3352 were unique (*R*_{int} = 0.0196) and 3142 were considered observed [*I* > 2 σ (*I*)]. The geometrically constrained hydrogen atoms were placed in calculated positions and allowed to ride on the bonded atom with *B* = 1.2 × U_{eqv} (*C*). Refinement of non-hydrogen atoms was carried out with anisotropic temperature factors. Structure solution and refinement was accomplished using SHELXTL, Ver. 5 and led to final residuals of *R*₁ = 0.0350 and *wR*₂ = 0.0776 based on 245 parameters refined against all data. The final minimum and maximum residuals in the final difference Fourier map were 0.242 and –0.150 e Å^{–3}.

Cycloadducts 22 and 23

Acenaphthylene (1 g, 6.6 mmol) and 3-hydroxy-1-phenylpyridinium chloride **8** (1.36 g, 6.6 mmol) in acetonitrile (25 cm³) were heated at reflux, in an atmosphere of nitrogen, for 30 min. Triethylamine (1.1 cm³, 7.92 mmol) was then slowly added to the mixture, and heating continued at reflux for a further 23 h. The black solution was concentrated and the residue diluted with CH₂Cl₂, and filtered. The CH₂Cl₂ solution

was concentrated and chromatographed (SiO₂, hexane) to yield acenaphthylene (0.82 g, 82%). Increasing the polarity of the solvent to hexane–EtOAc 3:1 produced the cycloadducts **22** and **23** as a mixture, a dark brown oil (0.37 g).

Further chromatography of the oil (SiO₂, hexane–EtOAc 10:1) yielded both compounds **22** and **23** as yellow crystals.

Compound **22** (148 mg, 6.9%), mp 186–188 °C; *m/z* (relative intensity) 323 (0.5), 171 (9), 152 (100); (HRMS calcd. for C₂₃H₁₇NO: 323.1310; found: 323.1307).

Compound **23** (165 mg, 7.7%), mp 159–160 °C; *m/z* (relative intensity) 323 (0.5), 171 (11), 152 (100); (HRMS calcd. for C₂₃H₁₇NO: 323.1310; found: 323.1302).

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