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

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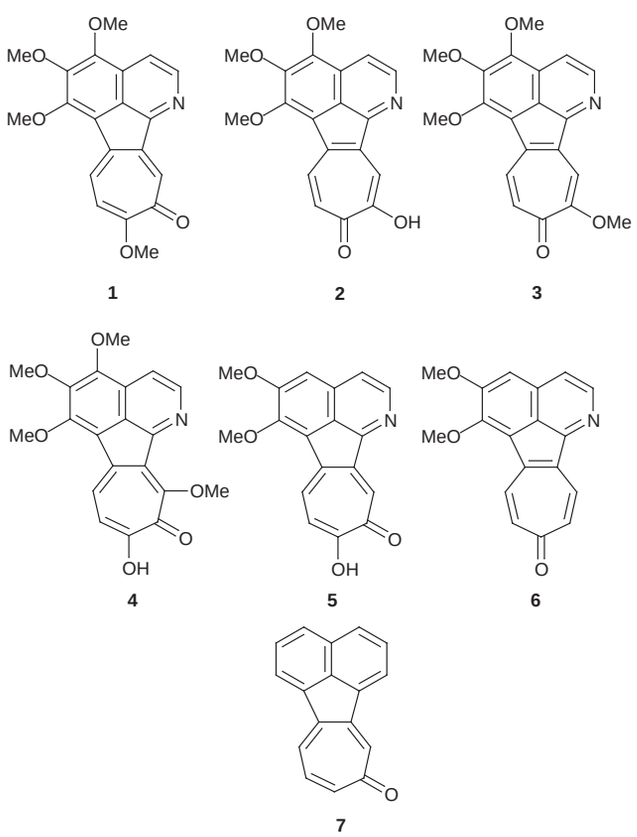
Cycloaddition of 3-oxido-1-phenylpyridinium 8a to 1-cyanoacenaphthylene 9a affords three isomeric adducts (13, 14 and 15). Structures for these compounds resulted from a comparative NMR study, as well as an X-ray crystallographic determination of isomer 15. Attempts to eliminate HCN from compounds 13–15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

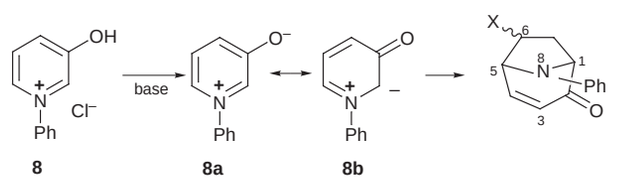
Introduction

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 group[4] have reported the total synthesis of compounds **1** and **2**, and subsequently, Boger and Takahashi[5] 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 a potential pathway to compound **7**, the simple carbocyclic analog of these alkaloids.



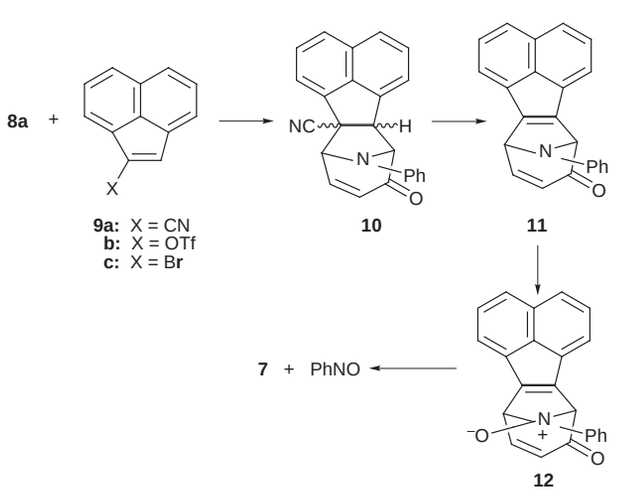
The reaction of 3-oxido-1-phenylpyridinium **8a** (prepared *in situ* from reaction of 3-hydroxy-1-phenylpyridinium chloride **8** and triethylamine), with 2π-electron dipolarophiles to form 8-azabicyclo[3.2.1]oct-3-en-2-ones as cycloadducts, has been studied in depth by Katritzky and his co-workers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



Scheme 2

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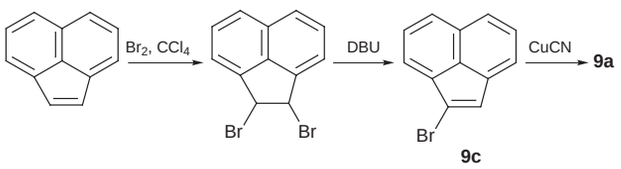
and, in fact, we have found this reaction to be very useful in some of our own previous work.[8]

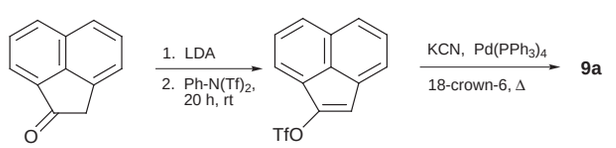
Results and discussion

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

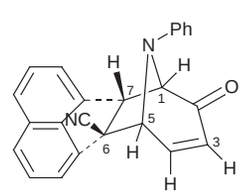
We also obtained **9a** by conversion of acenaphthenone to the unsaturated triflate **9b** using *N*-phenyltrifluoromethanesulfonamide[11] followed by treatment with LiCN according to the method of Piers (Scheme 4).[12] In our hands, the triflate was



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.



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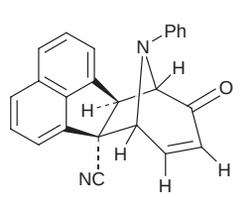

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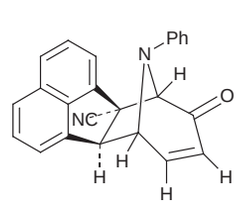

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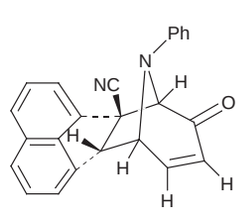

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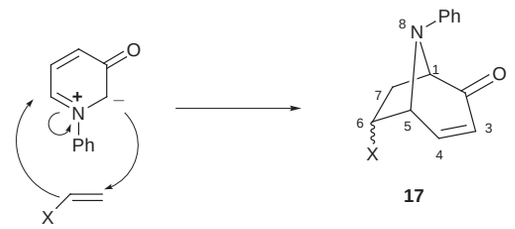
For addition at the 2,6-position of the dipole, the usual mode of reaction is as shown in Scheme 5, to produce the 6-substituted adduct **17**. In their study of peri-, site-, regio- and stereo-selectivity of these reactions,[13] Katritzky and his group indicate that 6-substituted regioisomers **17** 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	*J*/Hz	Protons	*J*/Hz
1,3	0–1.5	6-*exo*, 6-*endo*	13.0
1,7-*endo*	0–1.0	6-*endo*, 7-*endo*	9.5–10.0
1,7-*exo*	7.5–8.5	6-*endo*, 7-*exo*	4.0
3,4	9.5–10.0	6-*exo*, 7-*exo*	9.0–11.0
4,5	5.0–6.0	6-*exo*, 7-*endo*	6.0–7.0
5,6-*endo*	0.0	7-*endo*, 7-*exo*	14.0–14.5
5,6-*exo*	5.8–7.0		



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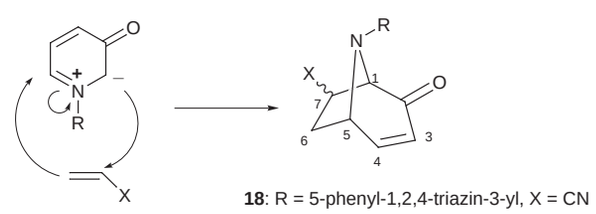
Scheme 5



18: R = 5-phenyl-1,2,4-triazin-3-yl, X = CN
19: R = 2,4-dinitrophenyl, X = CN
20: R = Me, X = CO_2Me
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**

	Chemical shifts (δ) (multiplicity, J/Hz)					
Compound	**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.

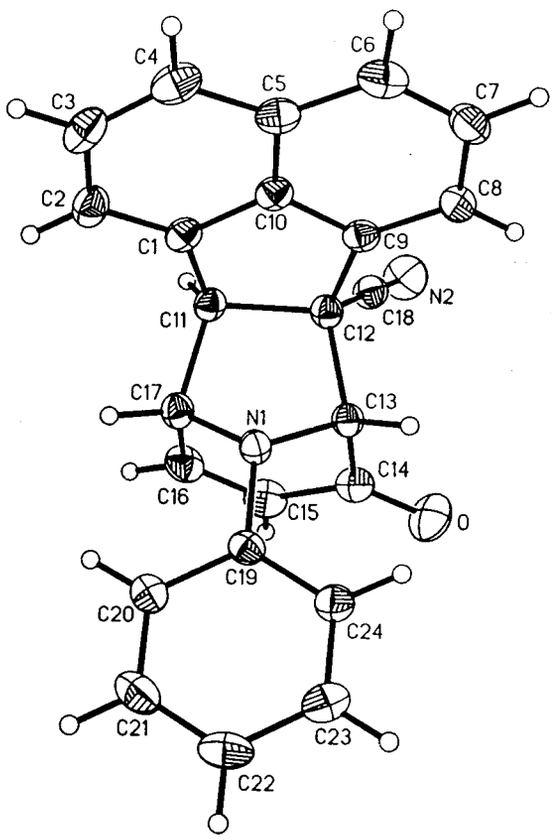


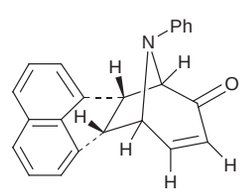
Fig. 1 Molecular structure of **15** showing the crystallographic numbering system used

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

a) 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.
b) In **13**, H-7 appears as a doublet coupled to H-1, whereas in **14**, H-7 appears as a singlet.
c) 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 photochemically,[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 acenaphthylen-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.



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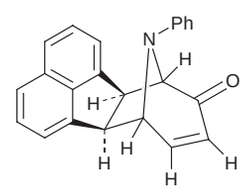

23

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, $J_{5,6\text{-}endo} = 0$.) 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 cm^3) was heated at reflux for 2 h. The mixture was diluted with CH_2Cl_2 (~800 cm^3) 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 × 150 cm^3), 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 cm^3) was heated at reflux with stirring, in an atmosphere of nitrogen, for 30 min. Triethylamine (15 cm^3, 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 CH_2Cl_2, washed with water, and the CH_2Cl_2 solution dried (Na_2SO_4) and concentrated to yield a very dark oil. Flash chromatography (SiO_2, hexane–CH_2Cl_2 2:1) afforded the starting nitrile **9a** (7.84 g, 65%). Gradually increasing the polarity of the solvent system to hexane–CH_2Cl_2 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 CH_2Cl_2–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 $C_{24}H_{16}N_2O$: 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 $C_{24}H_{16}N_2O$: C, 82.7; H, 4.6; N, 8.0%).

The second band was further purified by chromatography (SiO_2, 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 $C_{24}H_{16}N_2O$: 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, $\beta = 91.91(1)°$, $V = 1746.2(2)$ $Å^3$, $\mu = 0.082$ mm^{-1}, and $\rho_{calc} = 1.325$ Mg m^{-3} for $Z = 4$. Graphite monochromated Mo-Kα radiation ($\lambda = 0.7107$ 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 [$I > 2\sigma(I)$]. The geometrically constrained hydrogen atoms were placed in calculated positions and allowed to ride on the bonded atom with $B = 1.2 \times$ Ueqv (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 cm^3) were heated at reflux, in an atmosphere of nitrogen, for 30 min. Triethylamine (1.1 cm^3, 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 CH_2Cl_2, and filtered. The CH_2Cl_2 solution was concentrated and chromatographed (SiO_2, 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 (SiO_2, 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 $C_{23}H_{17}NO$: 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 $C_{23}H_{17}NO$: 323.1310; found: 323.1302).

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